Volume 2 of 2

The development of a Quality Risk Management Solution designed to facilitate compliance with the risk-based Qualification, Validation & Change Control GMP requirements of the EU

Kevin O'Donnell, B.Sc., H. Dip. (Ed.), M.Sc.(Pharm. QA)

*For the Award of PhD*

Dublin Institute of Technology

Supervisors: Dr. Anne Greene, Dr. Barry Foley
School of Chemical & Pharmaceutical Sciences, Faculty of Science

December, 2007
Volume 2 of 2

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- Volume 1 contains the text of all of the Thesis Chapters, and one Appendix.


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Volume 2, Part I - The Quality Risk Management Methodology

Section 1

The twelve Principles underlying this Quality Risk Management methodology
**Principles underlying this Quality Risk Management Methodology**

<table>
<thead>
<tr>
<th>No.</th>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The <strong>scope and extent</strong> of qualification and <strong>validation</strong>, and the <strong>likely impact of changes</strong>, should be determined and managed on a risk basis.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Risk is the combination</strong> of the probability of occurrence of harm and the severity of that harm, and harm is considered to be damage to health, including the damage which can occur from loss of product quality or availability.</td>
</tr>
<tr>
<td>3</td>
<td>As a <strong>minimum</strong>, <strong>Quality Risk Management</strong> contains the following four <strong>components</strong>: Risk Assessment, Risk Control, Risk Communication and Risk Review, as defined and described in ICH Q9.</td>
</tr>
<tr>
<td>4</td>
<td>A consideration of &quot;<strong>what might go wrong</strong>&quot; is fundamental to the Quality Risk Management exercise.</td>
</tr>
<tr>
<td>5</td>
<td>There may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls/resources, but which may be <strong>controlled to an acceptable level</strong> with improved detection or other measures, as determined on a case-by-case basis.</td>
</tr>
<tr>
<td>6</td>
<td>Quality Risk Management is <strong>not an exact science</strong> and, while a scientific approach should form the basis of the Risk Management process, there may be <strong>uncertainties</strong> associated with the outcome of the Risk Management exercise.</td>
</tr>
<tr>
<td>7</td>
<td>Risk may be assessed <strong>qualitatively</strong> as well as <strong>quantitatively</strong>, and a good qualitative assessment of risk may be more valid than a poor quantitative assessment.</td>
</tr>
<tr>
<td>8</td>
<td>The main <strong>stakeholders</strong> associated with the application of Quality Risk Management within GMP and Regulatory Compliance environments are patients &amp; users of medicines, including healthcare professionals, as well as industry and regulators, and, while the concerns of all involved stakeholders should be taken into account in any Quality Risk Management exercise, protection of the patient is of prime importance, and therefore, Quality Risk Management should ultimately link to the protection of the <strong>patient</strong>.</td>
</tr>
<tr>
<td>9</td>
<td>In GMP environments, a <strong>high detectability</strong> of risk does not necessarily mean that the risk is eliminated or adequately controlled.</td>
</tr>
<tr>
<td>10</td>
<td>The implementation of Risk Control measures could, in itself, inadvertently introduce <strong>new risks</strong>, which will need to be managed.</td>
</tr>
<tr>
<td>11</td>
<td>Performing Quality Risk Management exercises can be improved through the use of <strong>multi-disciplinary</strong> teams.</td>
</tr>
<tr>
<td>12</td>
<td>A <strong>formal Quality Risk Management</strong> process may not always be necessary or appropriate in all situations, and the level of effort, rigor, formality and documentation associated with the Quality Risk Management process should be commensurate with the complexity and/or the criticality of the issue to be addressed.</td>
</tr>
</tbody>
</table>
Discussion on these Principles

As is evident, the above Principles are largely self-explanatory, but the following provides some background and explanatory information relating to each.

- Principle 1 is based on Annex 15 (Qualification and Validation) to the EU GMP Guide. It implies that, before validation master plans and qualification & validation protocols are finalised, risks associated with the items under study should be considered, resulting in the identification of risk-based critical parameters requiring qualification or validation. This Principle also implies that, before Change Control proposals are approved, the potential risks presented by the change should be identified, and a strategy determined for managing such risks.

- Principles 2, 3 & 4 reflect the guidance presented in ICH Q9 and other publications, such as ISO/IEC Guide No. 73, titled 'Risk Management - Vocabulary - Guidelines for use in standards'. The inclusion of loss of product availability in the definition of harm is considered important in GMP Risk Management activities, because the loss of product availability may adversely impact not only business, but also patients and users of medicinal products.

- Principle 5 reflects the author’s experience in applying Risk Management principles and tools to GMP situations – that sometimes, the probability of occurrence of harm, or the severity of that harm, just cannot be reduced to levels which render the risk acceptable with current or realistic resources, but that such risks can be controlled to an acceptable level by means of detection or other risk control measures.

- Principle 6 & 7 recognise that risk can be difficult to quantify, and that there may be uncertainties in the outcome of any Risk Management exercise. As discussed in ICH Q9, for example, different stakeholders may perceive different potential harms, or place a different probability on each harm occurring, or assign different severities to each harm, and this can lead to uncertainties. This principle implies that the Risk Management solution should be able to address such difficulties and uncertainties.

- Principle 8 requires that the Quality Risk Management methodology should help to formally identify who the stakeholders are for the item under study. This enables the concerns of those stakeholders to be taken into account, and for appropriate definitions of Severity to then be determined.

- Principle 9 is far reaching, and it renders this solution somewhat different to other Quality Risk Management tools with respect to how risk detectability is dealt with. Here, users may not automatically conclude that a high detectability for a negative event or its effects means that a risk is acceptable or adequately controlled. For example, the ability to detect glass in filled and stoppered vials may sometimes be high, but this detection control does not mean that the vial filling and sealing process is under adequate GMP control, if the incidence of glass in vials is relatively high.
- Principle 10, also based on ICH Q9, means that the Quality Risk Management solution must formally be able to identify and manage any new risks which may be introduced as part of Risk Control activities. New risks can be introduced, for example, when a new PAT-based sensor is installed in a drying vessel, to monitor a parameter such as water content. The material housing the sensor may be incompatible with the contents of the dryer, or it may not be adequately robust, giving rise to a risk of product contamination.

- Principle 11 recognises the benefit of using multi-disciplinary teamwork when performing Risk Management, and is certainly not a new concept. Well established tools such as FMEA & HACCP require the use of multi-disciplinary teams.

- Finally, Principle 12, again reflecting ICH Q9, recognises that much of what we do within CMP environments is risk-based, even if we do not call it that. This is important, because often, there may be no need to use a formal Quality Risk Management tool, when existing procedures may be adequate. This principle, in a subtle way, also recognises the fact that risk events can have multiple causes, with multiple associated risks, some less important than others. This can result in formal Quality Risk Management activities becoming costly and quite labour-intensive exercises, and should therefore be targeted at the most complex and/or critical issues.

*****
Volume 2, Part I - The Quality Risk Management Methodology

Section 2

Overview of the Ten-Step Process used by this Quality Risk Management methodology
The Ten-Step Quality Risk Management Process

Step 1: Document Specific Information on the Quality Risk Management Exercise being undertaken:
- Identify whether the exercise is a Prospective, Retrospective or a Change Control Quality Risk Management exercise.
- Define the Item under Study & the scope of the exercise. If possible, define a boundary for the Item under Study.
- Provide relevant background information so that the reason for the Quality Risk Management exercise is made clear.
- State any pertinent assumptions being made, especially those relating to Quaification & Validation, and document any significant uncertainties associated with the data being used in the exercise.

Step 2: Who’s Who? - Define the Risk Management Team:
- Identify the Quality Risk Management team leader, and other team members.
- The team should be multi-disciplinary, and include persons knowledgeable in the item under study.
- At least one person should have a firm understanding of the Quality Risk Management process, principles and methodology.
- If possible, there should be personnel on the team who have the necessary authority (or the means) to make key decisions regarding the implementation and funding of risk mitigation controls.

Step 3: Review the Default Definitions provided for Negative Event Probability, Severity and Detection:
- Review the default Probability, Severity and Detection definitions provided in this Quality Risk Management Tool. These are presented on a Laminated Card, which accompanies the tool worksheet.
- The team then decides whether the default definitions as provided are appropriate for the specific Quality Risk Management exercise at hand.
- This is where new or modified Probability, Severity and Detection definitions can be drawn up, if required. For example, the definitions for Probability of Occurrence can be made quantitative, or the Severity definitions can be altered to better reflect the concerns of any specific stakeholders.
- A Risk Table (or matrix) is used by this Quality Risk Management tool, and this is also shown on the Laminated Card.

Step 4: What might go wrong? – Identify & Screen Potential Negative Events:
- Review relevant documentation, records & data, and use brainstorming techniques to identify potential Negative Events for the Item under Study. (Note: Guidance on brainstorming is provided in the guidance presentation which is provided in the Training & User’s Manual on the methodology.)
- As this is a formal and rigorous Quality Risk Management methodology, only the highest priority/most important potential Negative Events should normally be selected for formal evaluation. To do this, the following approach may be used:
- Discuss and review all of the suggested potential negative events identified above, in terms of their expected consequences and their likelihood of occurrence.
- In this regard, the strength of evidence for the likelihood of occurrence of each potential negative event should be considered, and the severity of the consequences of each potential negative event should be discussed.
- The level of complexity associated with the each potential negative event, in terms of how the potential negative event might occur, should also be considered.
- At this stage, those potential negative events considered by the team to be the most important, in terms of their potential consequences and/or complexity, should be selected for formal onward processing in the remaining steps of the Quality Risk Management process. However, the likelihood of occurrence of each potential negative event should also be taken into account. If it is considered at Step 4 that a potential negative event has only a remote likelihood of occurring, then this potential negative event should not normally be selected for onward processing through the remaining steps of the process, unless there is good reason for doing so.
The decisions made in relation to the above evaluations and considerations should be documented.

In relation to dealing with any potential negative events not selected for onward processing through the remaining steps of the Quality Risk Management process, a record should be made of what these potential negative events were, and why they were not formally routed through the remaining steps of the process.

The team may decide that any potential risk associated with these potential negative events should be managed in a less formal manner than this methodology requires, and information in this regard should be documented.

Alternatively, the team may decide that these potential negative events should actually be processed through the remaining steps of this Quality Risk Management process at some later date, perhaps during the planned review of the exercise as part of Periodic Review activities. This should be documented in Step 10 of the worksheet.

Alternatively, the team may just recommend that these potential negative events be reviewed again at the next review of the exercise, to determine whether at that time they should be formally routed through the remaining steps of the process. Again, this should be documented in Step 10 of the worksheet.

Lastly, there may be no need to give any more consideration to those potential negative events at all, following the above evaluation at Step 4 of their expected consequences and their likelihoods of occurrence. This should be documented.

Step 5: Risk Evaluation – Is the risk Acceptable, Unacceptable or Intolerable?

- For each potential Negative Event, identify and document the potential negative consequences.
- Document and critically evaluate any currently in place back-up or redundancy controls for the potential Negative Event, and assign a Severity rating.
- Identify and document the cause(s) of each potential Negative Event.
- Document and critically evaluate any currently in place preventative controls for each cause, and assign a Probability of Occurrence rating to each cause.
- Using the Risk Table provided on the Laminated Card which accompanies the tool worksheet, estimate each risk associated with the potential Negative Event.
- This results in the classification of each risk as either Acceptable, Unacceptable or Intolerable.
- Risks deemed to be Acceptable progress directly to Step 8 of the worksheet; all other risks progress to Step 6.

Step 6: Risk Evaluation – Is the Risk Adequately Controlled?

- Document and critically evaluate any currently in place detection controls for each Unacceptable & Intolerable risk.
- Assign a Detection rating to these controls, and determine whether these controls give assurance that the risk is adequately controlled & that no further controls are required.
- Risks that are considered adequately controlled progress directly to Step 8. All other risks progress to Step 7.

Step 7: Risk Control:

- Identify and critically evaluate any new or improved back-up or redundancy controls which may be put in place for Unacceptable & Intolerable risks.
- With these controls in mind, assign a new Severity rating to the potential Negative Event.
- Identify and critically evaluate any new or improved preventative controls which may be put in place for the cause(s) of each Unacceptable & Intolerable risk.
- With these controls in mind, assign a new Probability of Occurrence rating to each cause.
- Using the Risk Table provided on the Laminated Card which accompanies the tool worksheet, re-estimate each risk.
- This results in the re-classification of each risk as either Acceptable, Unacceptable or Intolerable.
- Risks deemed to be Acceptable progress to Step 8 of the worksheet; all other risks continue through Step 7.
• Identify and critically evaluate any new or improved detection controls for each Unacceptable &
  Intolerable risk.
• Assign a Detection rating to these controls, and determine whether these controls give assurance that
  the risk is now adequately controlled & that no further controls are required.
• Risks that are considered adequately controlled progress to Step 8.
• For risks which are still not considered adequately controlled, Step 7 (Risk Control), should be
  repeated. (A re-design of the item under study may be necessary in order to eliminate the potential
  negative event.)

Step 8: Qualification and Validation:
• For each control listed on Worksheets No. 5, 6 & 7, identify the items (such as documentation,
  equipment, facilities, personnel resources, etc.), which are required for the control to be in place.
• Determine Critical Process Parameters, their limits, and any other acceptance criteria or required
  outcomes for each control.
• Determine any training and assessment of training requirements for each control.
• Determine any Qualification or Validation activities required for each control, and assign a
  Qualification and Validation status to each.

Step 9: Action Items:
• Document any action items arising out of the Quality Risk Management exercise, and assign
  responsibilities for each.
• These could be actions required to implement a control, or they could be Qualification or Validation
  exercises.

Step 10: Risk Communication & Continuous Improvement (Periodic Review) Activities:
• Identify and document any communication activities required for the risks identified during the
  exercise.
• Assign responsibilities and timelines for each communication.
• Define when the Quality Risk Management exercise should be reviewed as part of continuous
  improvement, and document any key areas or issues to be reviewed at that time.
• Close out the Quality Risk Management exercise.

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Volume 2, Part I - The Quality Risk Management Methodology

Section 3

The Worksheet used by this Quality Risk Management methodology
Step 1: Preliminary Information on the QRM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>Option 1*</th>
<th>Option 2</th>
<th>Option 3**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective QRM Exercise *</td>
<td>Retrospective QRM Exercise</td>
<td>Change Control QRM Exercise</td>
</tr>
<tr>
<td>The QRM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed.</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
<tr>
<td>Manufacturing Process ***</td>
<td></td>
<td>Documentation Management System</td>
</tr>
<tr>
<td>Cleaning &amp; Hygiene Process ***</td>
<td></td>
<td>HVAC System</td>
</tr>
<tr>
<td>Labelling &amp; Packaging Process ***</td>
<td></td>
<td>Building Management System</td>
</tr>
<tr>
<td>Training Programme</td>
<td></td>
<td>Distribution &amp; Recall System</td>
</tr>
<tr>
<td>Material Sampling Programme</td>
<td></td>
<td>Supplier Approval System</td>
</tr>
<tr>
<td>Pest Control Programme</td>
<td></td>
<td>Regulatory Compliance System</td>
</tr>
<tr>
<td>Stability Programme</td>
<td></td>
<td>Materials Management System</td>
</tr>
<tr>
<td>Preventative Maintenance Programme</td>
<td></td>
<td>Other - specify below in this box</td>
</tr>
<tr>
<td>Self-Inspection Programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complaints &amp; Recall Programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced Testing Programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Item of Laboratory Equipment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplier / Material</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*** incorporating the equipment used

If the QRM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g., a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

Notes:
* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
## Step 1 Cont'd - Preliminary Information on the QRM Exercise

### The Item Under Study

**What is the Item Under Study?**
- e.g. Manufacturing Process No. 1234
- e.g. Dispensing Room No. 3
- e.g. Upgrade to Room No. ABC
- e.g. New Purified Water System P2

**Boundary Details:**
If the Item under study has a boundary, state the boundary here. For example:
- a boundary could be a P&ID for a piece of equipment or a system
- it could be 2 points within a manufacturing process, within which the QRM exercise applies
- it could be part of a process, such as the drying & discharge stages in an API manufacturing process

**Process Map or Schematic:**
State the ref. no. of any map or other document which describes or maps the item under study. Note: Comprehensive data on the Item under Study should be assembled at this point, and this should be referenced here also.

**Other Document (if any) associated with Item Under Study:**
- e.g. Cleaning SOP No. 1234
- e.g. Change Control No. 2005/13

### Reason, Relevant Background Info & Pertinent Assumptions relating to this QRM Exercise

State the reason this for this QRM exercise, give any background info & state all pertinent assumptions which may be relevant.
Step 2: Who's Who … Define the Quality Risk Management Team*

<table>
<thead>
<tr>
<th>Name of QRM Team Leader/Facilitator:</th>
<th>Position / Area of Expertise (if any):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Team Member Name *</td>
<td>Position / Area of Expertise (if any)</td>
</tr>
</tbody>
</table>

*Note: the team should be multidisciplinary, and should include personnel from QA, and possibly from QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted). QA should always be represented unless otherwise justified.


**Carry out the following tasks, and complete this table by ticking the appropriate options:**

1. The QRM Team Leader should review with the QRM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this QRM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.
   - Accept the default Probability, Severity & Detection definitions shown on the Card.
   - **Do not Accept** these default definitions, and draw up new definitions.

3. If applicable, **Document** any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.
   - **Tick here if any new definitions are attached**
   - **Tick here if N/A**
Step 4: What Might Go Wrong …Identify & Screen Pot. Negative Events Here:

This involves compiling & reviewing data & brainstorming to identify & screen potential negative events for the item under study.

Data Review & Brainstorming Session No:  
Session Date:  

**Tick One:**
- Select and list below the most critical and/or complex Potential Negative Events which could be associated with the item under study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- If a Specific Pot. Neg Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference &amp; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No. 123</td>
<td>e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3 and 2005/6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are Released without a PIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Filling Process for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure Occurs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note: Info on any near miss incidents should always be considered</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference &amp; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
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<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference &amp; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Step 5: Risk Evaluation**

*Use a Separate Step 5 for each Pot. Neg. Event. Number the controls in the format A, B, C,... etc.*

<table>
<thead>
<tr>
<th>Pot. Neg. Event No.</th>
<th>Brief Description of this Pot. Neg. Event:</th>
</tr>
</thead>
</table>

List the Potential Negative Consequences of this Potential Negative Event, should it occur:

<table>
<thead>
<tr>
<th>Crit #</th>
<th>List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Pot. Neg. Event occur. (Note: Number each Control starting with A, B, C,... etc.)</th>
</tr>
</thead>
</table>

**S: Severity:** Rate the Severity of this Pot. Neg. Event, taking into account a critical evaluation of the usefulness of the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- [ ] Critical
- [ ] Moderate
- [ ] Minor

*Note: When there is more than one Potential Negative Consequence listed above, the S Rating assigned here should reflect the most serious of those consequences.*

<table>
<thead>
<tr>
<th>List the Possible Causes or Mechanisms for this Pot. Neg. Event to Occur No.</th>
<th>Current Preventative Controls in place: (List the controls for each individual Negative Event Cause or Mechanism)</th>
<th>P: Prob. of Occurrence of each cause / mechanism</th>
<th>Risk assoc. wt each cause or mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctl #</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: When assigning P ratings, take into account a critical evaluation of the usefulness of the Preventative controls identified*

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
### Step 6: Risk Evaluation Cont’d

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C, etc.

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Ctrl</th>
<th>Detection Controls</th>
<th>D Detection Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>List any controls currently in place which detect the Pot. Neg. Event or its consequences after the Negative Event has occurred:</td>
<td>Hi/Med/ Low/Zero</td>
<td>Is this Risk adequately controlled? – Yes / No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do these controls give assurance that the risk is adequately controlled &amp; that no further controls are required? Justify Below.</td>
</tr>
</tbody>
</table>

*Note: When assigning D ratings, take into account a critical evaluation of the usefulness of the Detection controls identified.*
### Step 7: Risk Control

*Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.*

<table>
<thead>
<tr>
<th>Pot. Neg. Event No:</th>
<th>State the Cause or Mechanism for the Pot. Neg. Event to Occur (from Step 5):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Col 1</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
</table>

*Note: When assigning a new P rating, take into account a critical evaluation of the usefulness of the new or improved controls identified here.*

<table>
<thead>
<tr>
<th>Col 1</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Pot. Neg. Event, should it occur?</th>
</tr>
</thead>
</table>

*Note: When assigning a new S rating, take into account a critical evaluation of the usefulness of the new or improved controls identified here.*

**New Risk Level =**

- [ ] Acceptable - go to Step 8
- [ ] Unacceptable / Intolerable – continue below

#### If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New Improved Detection Criteria to Detect this Pot. Neg. Event?</th>
<th>New D Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
</table>

*Note: When assigning a new D rating, take into account a critical evaluation of the usefulness of the new or improved controls identified here.*

- Is risk now adequately controlled? Yes / No
  - e.g. Do these controls now give assurance that the risk is adequately controlled & no further controls are required?
    - [ ] Yes: Go to Step 8
    - [ ] No: Repeat this Step
    - Justify Below:

Note: If any of the above new controls may introduce a new risk, complete a new Step 4.

---

### Table Structure

- **Step 7: Risk Control**
- **Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.**
- **Risk Reduction Measures**
  - What New or Improved Preventative Controls could prevent this Negative Event?
  - What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Pot. Neg. Event, should it occur?
- **New Risk Level**
  - Acceptable - go to Step 8
  - Unacceptable / Intolerable – continue below
- **If the Risk is still Unacceptable or Intolerable**
  - New Improved Detection Criteria to Detect this Pot. Neg. Event?
  - New D Rating
  - Risk Decision Point:
    - Is risk now adequately controlled? Yes / No
    - Do these controls now give assurance that the risk is adequately controlled & no further controls are required?
    - [ ] Yes: Go to Step 8
    - [ ] No: Repeat this Step
    - Justify Below:
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ Current □ Improved □ New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

These Items are Already In Place □
These Items are Not Already In Place □

Complete Either Part A or B below:

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control?

☐ Yes  ☐ No  If yes, specify these here:

Part B: Critical Process Parameters (CPPs)
Does this control have any associated CPP to be measured or monitored?

☐ Yes  ☐ No
If yes, list the CPP below, and state the Limits/Acceptance Criteria for the CPP

Qualification & Validation Requirements
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Q & V
What is the Status of this Qualification or Validation exercise?

☐ Completed
☐ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)

☐ New Qualification/Validation work needed  ☐ No New Qualification/Validation work needed
Step 9: Action Items

Identify all action items from the completed Qualification & Validation Worksheets

<table>
<thead>
<tr>
<th>Pot. Neg. Event Ref. No.</th>
<th>Give a full description of the Action Item here:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
</table>

Comments or Notes:
Step 10: What communications are required arising out of this QRM exercise, and when will this exercise be reviewed or revisited?

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method:</th>
<th>Responsible Group:</th>
<th>Target Date:</th>
</tr>
</thead>
</table>

**Risk Communication Activities**
List any communication activities required in order to communicate risks to key groups or stakeholders.

**Plan for Continuous Improvement – Periodic Review Activities:**

- Propose here a **Date** on which this QRM exercise will be reviewed/revisited:

**Proposed Review Date:**

- In this Section, record any difficulties, concerns or uncertainties that were experienced during the current QRM exercise, for specific follow up during the Periodic Review activity.
- Record also any recommendations which the team feel should be made to the reviewing team for the Periodic Review activity.
- Record any other actions which the team should consider performing during the Periodic Review activity.

Use additional pages if necessary.

**Other Comments or Notes:**
Volume 2, Part I - The Quality Risk Management Methodology

Section 4

The Laminated Card
used in conjunction with the Worksheet
Laminated Card for the Quality Risk Management Methodology

This Card shows the default Probability, Severity & Detection definitions for the QRM methodology. It also shows the Risk Table, with the risk acceptability criteria.

Important: The definitions shown for each P, S & D Level are default definitions; they can be modified as required. See Step 3 of the Worksheet for details.

<table>
<thead>
<tr>
<th>P</th>
<th>Probability of Occurrence</th>
<th>Levels for the Pot. Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>The Pot. Neg. Event is Likely to Occur</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>The Pot. Neg. Event May Occur</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>The Pot. Neg. Event is Unlikely to Occur</td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>The Pot. Neg. Event is Very Unlikely to Occur, or is Extremely Unlikely to occur</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S</th>
<th>Severity Levels for the Effects of the Pot. Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>The Effects are Severe - Very Significant GMP/MA Non-Compliance - Potential Patient Injury</td>
</tr>
<tr>
<td>Moderate</td>
<td>The Effects are Moderately Severe - Significant GMP/MA Non-Compliance - Potential Patient Impact</td>
</tr>
<tr>
<td>Minor</td>
<td>The Effects are Not Severe - Minor GMP/MA Non-Compliance - No Patient Impact</td>
</tr>
</tbody>
</table>

Risk = P x S

<table>
<thead>
<tr>
<th>Pot. Negative Event Prob</th>
<th>Minor Severity</th>
<th>Moderate Severity</th>
<th>Critical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Acceptable Risk</td>
<td>Unacceptable Risk</td>
<td>Unacceptable Risk</td>
</tr>
<tr>
<td>Medium</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
<td>Unacceptable Risk</td>
</tr>
<tr>
<td>Low</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
</tr>
<tr>
<td>Remote</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
</tr>
</tbody>
</table>

* Formal justification must be provided here

Risk Definitions:

- **Intolerable:**
  Work to eliminate the Pot. Negative Event, or build in systems or controls to ensure the effects of the Pot. Negative Event are not realised (e.g. via back-up or redundant controls).

- **Unacceptable:**
  Reduce the risk, or control the risk to an acceptable level.

- **Acceptable** - The risk is acceptable as is. No risk reduction or new controls are required.

Detection Control Ratings:

- **High** - the control will likely detect the Pot. Negative Event or its effects
- **Medium** - the control may detect the Pot. Negative Event or its effects
- **Low** - it is not likely that the control will detect the Pot. Negative Event or its effects
- **Zero** - no detection controls are in place
Volume 2, Part I - The Quality Risk Management Methodology

Section 5

The Recommended Training Strategy
for potential users of this Quality Risk Management methodology
The importance of training

Training is essential to the successful use of the tool.

- Some key features are not immediately obvious, and require training using examples and case studies
  - e.g. the classification of GMP controls in terms of how they relate to S, P & D
  - e.g. the identification of Potential Negative Events (PNEs)
  - e.g. what to do when conflicts arise during Brainstorming activities, etc.

Training takes between 1.5 and 4 days, depending who on whether it is training for Team Leaders or Team Participants.

- This is not considered excessive, given the importance of Quality Risk Management work and its benefits towards compliance

Before we look at the recommended Training Strategy for the tool, let’s review the structure of the Tool, and the Training & User’s Manual
The Structure of this Tool

The tool comprises of the following five elements:

- A Tool Worksheet
  - This is a structured, 10-step instructional template which gets completed as the QRM exercise progresses
  - It is designed to guide users through the 10-step process

- A Laminated Card for use with the Tool Worksheet
  - This gives the default definitions for P, S, D, & also the Risk Table

- A document providing an overview of the Tool’s Ten Steps
  - This gives a description of the purpose and key activities of each of the steps in the Quality Risk Management process

The Structure of this Tool Cont’d

- A document providing the twelve Principles underlying this Quality Risk Management Solution

- A copy of this presentation, providing a recommended Training Strategy for the tool

The above five components make up this Quality Risk Management Tool
The Training & User’s Manual

There is also a Training & User’s Manual for this tool, and training should be based on the components of this Training & User’s Manual:

- This is a package of documents containing various components
- It contains training materials for both trainers and trainees on the tool
- It contains practical guidance (Q&A) for users of the tool during actual Quality Risk Management exercises
- The Training & User’s Manual should be given to all trainees at the start of training, and it should always be available during actual Quality Risk Management exercises
  - It contains the following five components:

The Training & User’s Manual

1. A copy of an Introductory Presentation on the tool
   - This provides a general introduction to this Quality Risk Management solution
   - It describes the structure of the tool, its uses, key features, scope and uses, limitations and advantages
   - It provides an overview of the ten steps of the Quality Risk Management process used by this tool
   - It provides an overview of Quality Risk Management in general, and the key components of the Quality Risk Management process

2. A detailed Tool Guidance Presentation
   - This provides both general guidance on the tool, as well as specific and detailed guidance on key activities and issues which may arise when working through each step of the Quality Risk management process
   - For simplicity and ease of use, it is mainly structured as a Q&A-type document
3. A copy of a partially and fully completed Case Study on the tool which involves an area not in any way related to GMP

- The purpose of this Case Study is to facilitate the initial training on the tool in a manner which is non-technical from a GMP perspective

- This allows trainees to focus only on the tool and how it is used, not on GMP issues
  - Our research has shown that this greatly facilitates the training process

- The Case Study relates to the application of this Quality Risk Management methodology to a wedding
  - It is a humorous, simple exercise, to put people at ease at the start of their training. This is important given the vigorous and formal nature of the Quality Risk Management methodology.

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3. Cont'd

- Trainees work through the partially completed case study with the trainer, in order to complete the exercise and learn how the tool works

- This allows trainees to become familiar with the tool components (e.g. the worksheet, laminate card) and also the ten-step process before applying the tool to GMP areas

- This allows trainees to explore and resolve any practical issues or difficulties which may be encountered in a non-technical setting, before moving on to GMP-related applications of the methodology

- At the end, the team evaluates their results from completing the case study, with reference to a fully completed version of the Case Study which is also provided in this section of the Training & User's Manual, for reference
The Training & User's Manual

4. A series of practical and completed real-life GMP-related case studies on the tool

- These show, in practical terms, how this tool is used, and what the expected outputs of the tool are when applied to specific GMP and GMP-related activities

- Case Study: The application of this Quality Risk Management solution to a Paracetamol Oral Suspension Mixing & Filling Process at a Finished Product Manufacturer (This involved the use of Tool Version 3 to Case Study 1)

- Case Study: The application of this Quality Risk Management solution to a proposed Change Control (introduction of ICP-MS) at an API manufacturer

The Training & User's Manual

4. Cont’d

- Case Study: The application of this Quality Risk Management solution to a Product Recall Procedure at a Finished Product Manufacturer

- Case Study: The application of this Quality Risk Management solution to a proposed Change Control to introduce a new critical product contact material at an IMP (i.e. clinical trial product) Manufacturer
  - This Case Study is written in such a way that it can be continued during the training exercise.

- Case Study: The application of this Quality Risk Management solution to a non-GMP activity (A Market Compliance Programme at an EU Competent Authority)
The Training & User's Manual

5. Copies of three peer-reviewed research papers describing this Quality Risk Management methodology

- The first two research papers are useful for obtaining general and detailed information on this Quality Risk Management methodology.

- The third paper describes some of the strategies used by this methodology to address the problems of subjectivity and uncertainty that can be encountered during Quality Risk Management activities.
  - *Journal Validation Technology*, February 2007

Strategy for Training

Each company or organisation planning to use this Quality Risk Management solution should develop its own training programme for potential users of this methodology

- The type of training programme to be delivered, and the time spent on training activities will depend on several factors, including:
  - the purpose of the training (whether it is Team Leader training or Team Participant training)
  - the number of Tool Case Studies to be covered during the training
  - the degree of familiarity of the trainees on Quality Risk Management activities generally

- The extent of training required should thus be determined on a case by case basis, taking the above factors into account
Strategy for Training

A Note about Team Leader Training

- Team leaders should generally receive much more detailed and technically-advanced training than non-Team leaders (i.e. Team Participants)
- This is because Team Leaders are generally expected to be the team members with the highest level of knowledge and competency on the Quality Risk Management methodology
- It is not necessary for the Team Participants to attain this level of competency
- The training given to Team leaders should generally include more GMP-related case studies than that given to Team Participants
  - The actual number of case studies covered is at the discretion of the trainer, but at least three are recommended during the training of Team leaders, and at least one for non-Team Leaders

Strategy for Training

Training Activities

- A number of discrete, structured training activities have been developed
  - These activities make up the recommended training strategy on this Quality Risk Management methodology
  - These training activities are labelled A though G, and are described in the following slides
  - The individual training activities should be carried out in the order in which they are presented, taking into account the following considerations

- For individuals undergoing training to become Team Leaders of Quality Risk Management exercises, the trainees should undergo all of the training activities listed (Approx 30 hours in total)

- For those individuals undergoing training to become Team Participants in Quality Risk Management exercises, the trainees should undergo all of the activities listed except Activity G. In addition, the time spent on each training activity may be reduced when the training is not team leader training. (Approx 11 hours in total)
Strategy for Training

Recommended Training Activity A

- Before the formal training begins on this Quality Risk Management methodology, trainees should be requested to read and familiarise themselves with the contents of ICH Q9

- Confirmation of this self-training on ICH Q9 should be documented as a pre-requisite for the training on this specific Quality Risk Management methodology

- Any issues which were encountered during this self-training on ICH Q9 should be resolved by the Trainer of this Quality Risk Management methodology at the outset of training

- Expected Duration for this Training Activity: 2 hours

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策略 for Training

Recommended Training Activity B

- The Introductory Presentation on the tool should be presented to the trainees

- Any issues or questions should be discussed and resolved by the trainer during the presentation

- Expected Duration for this Training Activity: 1.5 hours
Strategy for Training

Recommended Training Activity C

- Trainees should be introduced to the following Tool components:
  - The principles underlying Quality Risk Management solution
  - The outline of each of the 10 Steps of the Quality Risk Management process used by this methodology
  - The Tool Worksheet
  - The Tool Laminated Card

- Any issues or questions should be discussed and resolved by the trainer

- Expected Duration for this Training Activity: 3 hours

Strategy for Training

Recommended Training Activity D

- A brief workshop should be run with the trainees on the Case Study provided in the Training & Users Manual which involves the application of this Quality Risk Management methodology to an area not in any way related to GMP - The Wedding Case Study

- This Case Study is designed to enable trainees to focus only on the tool and how it is used, not on any GMP issues

- It is a humorous, simple exercise, to put people at ease at the start of their training

- Trainees should work through the partially completed case study with the trainer, in order to complete the exercise and learn how the tool works in practice
Strategy for Training

Recommended Training Activity D, Continued

- This Case Study is designed to enable trainees to become familiar with the tool components (e.g., the worksheet, laminate card) and also the ten-step process before applying the tool to GMP areas

- It allows trainees to explore and resolve any practical issues or difficulties which may be encountered in a non-technical setting, before moving on to GMP-related applications of the methodology

- At the end, the team should evaluate their results from completing the case study, with reference to a fully completed version of the Case Study which is also provided in this section of the Training & User Manual, for reference

- Expected Duration for this Training Activity: 2 hours

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Strategy for Training

Recommended Training Activity E

- The Tool Guidance Presentation should be presented to the trainees
  - This contains comprehensive and technical Guidance, with several appendices
  - Any issues or questions should be discussed and resolved during the presentation
  - A copy of a blank Tool Worksheet and the Laminated Card are required when going through this presentation

Expected Duration for this Training Activity:

- For Team Leaders 1.5 Days (11 Hours – here, all aspects of the presentation & its seven appendices should be covered in detail)
- For Team Participants (1 hour – here, the presentation is only reviewed at a high level, and none of the Appendices are to be covered.
- The presentation is then used during exercises.)
Strategy for Training

Recommended Training Activity F

- The trainer should review in detail with the trainees one or more of the GMP-related Case Studies provided in the Training & Users Manual.
- This is in order for potential tool users to understand the practicalities of applying this Quality Risk Management methodology to specific GMP areas, activities and problems.
  - Any issues or questions should be discussed and resolved during this review.
  - It is imperative that there is interaction and discussion among the group during this review of the Case Studies.
  - Potential Team Leaders should be trained on at least three GMP-related Case Studies.
  - Team Participants should be trained on at least one GMP-related Case Study.
- The trainer should frequently refer the trainees to the Tool Guidance Presentation to demonstrate how the specific guidance provided in that presentation can facilitate the use of this methodology.

Expected Duration for this Training Activity: 2.5 hours per Case Study

---

Strategy for Training

Recommended Training Activity G (For Team Leaders Only)

- The trainer should request the trainees to review in their own time the two peer-reviewed research papers in the Training & Users Manual describing this Quality Risk Management methodology, and the third peer-reviewed research paper in the Training & Users Manual relating to subjectivity uncertainty issues.
  - Ref: Journal of GXP Compliance, July 2006
- The latter paper describes some of the strategies used by this Quality Risk Management methodology to address the problems of subjectivity and uncertainty which can be encountered during Quality Risk Management work.
  - Ref: Journal Validation Technology, February 2007

- Expected Duration for this Training Activity: 3 hours in total
Volume 2, Part II - The Training & User’s Manual

Section 6

Introductory Presentation
on this Quality Risk Management methodology
Introductory Presentation - An Overview of this 10 Step Approach to Quality Risk Management for Qualification, Validation & Change Control in GMP Environments

Kevin O'Donnell
GMP Inspector & Market Compliance Manager, IMB

This presentation provides...

An overview of this Quality Risk Management solution (tool), which is designed to facilitate risk-based Qualification, Validation & Change Control

- The Background to the development of this tool, & some early findings
- Some of the Key Features of this tool
- Basic Concepts, Definitions & General Quality Risk Management Considerations
- The Structure of this Tool
- Tool Training Requirements
- The Training & User's Manual for this Tool
- The Uses & Scope of this tool
- The potential Outputs of this Tool
- Some of the Tool's Limitations
- Some of the Advantages of using this Tool
Background to the Development of this Tool

- Irish Industry has often communicated to IMB Inspectors the need for additional regulatory guidance on Annex 15 to EU GMP Guide

  "A risk assessment approach should be used to determine the scope and extent of validation."

- "The likely impact of changes...should be evaluated, including risk analysis."

- We also identified Inspector-training needs at IMB
  - We are inspecting company Quality Risk Management programmes and activities, so we need a good technical understanding of the area ourselves, beyond the conceptual!

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Background cont’d

- 2004: IMB research project - to better understand Quality Risk Management for GMP environments at a practical level, so as to address Inspector Training needs & Industry requests for useful regulatory guidance on the risk-related requirements of Annex 15

- A Quality Risk Management tool evolved from this research... purely for demonstration and training purposes
  - It shows how to apply Quality Risk Management across a wide range of areas
  - It is based on certain defined underlying principles & design criteria
  - It is fully in line with ICH Q9 principles and guidance
  - Early version first presented at IMB Info Day for Industry in October, 2004
  - Jan 2005 - Partnership with Dublin Institute of Technology to further develop this tool
Some key early findings....

- Lack of a GMP-tailored and effective Quality Risk Management tool for meeting the broad risk-related requirements of Annex 15...
  - Several useful tools are available... but...
  - Often, a high level of modification is required before they can be used to determine the Scope & Extent of Qualification & Validation, & in Change Control...
    - e.g. FMECA, FTA, HACCP, HAZOP
    - Also, some good tools are quite narrow in scope...
      - e.g. ISPE’s Impact Assessment Method
      - e.g. GAMP 4
  - Also, some aspects of existing tools seemed problematic and needed further research, e.g.
    - how GMP controls were dealt with
    - the use of RPNs
    - and the way detection is dealt with

Some key early findings....

- Poorly designed tools can be highly subjective & their results can have a lot of uncertainty associated with them
  - This is a problem tackled throughout this research

- How GMP controls are handled and classified during Quality Risk Management exercises can greatly influence whether the process can really facilitate meaningful risk-based Qualification & Validation
  - we looked at this area closely
  - a tool was designed which is focussed on identifying and critically evaluating GMP controls which lead to true patient-focussed, risk-based Qualification & Validation, and Change Control
Some key early findings....

- Quality Risk Management tools can lack Robustness if not designed well
  - Robustness was a key consideration during the development of this tool

- Training is an important part of implementing Quality Risk Management within an organisation, but how should we do this?
  - Some useful strategies were developed for this

- Business vs. GMP risks - issues can arise about this during Quality Risk management exercises
  - So the tool must take account of this

Some of the Key Features of this Tool

This is a formal Quality Risk Management solution, or tool, and it does require training, and documentation...

In line with ICH Q9, it is intended for the most complex & most critical processes, systems, concerns, issues, problems etc....
- A formal Quality Risk Management tool need not be used all the time

Examples of Informal Risk Management approaches:
- Deviations Procedures, Warehouse Temperature Mapping, Change Control, A Validation Master Plan, Self-Inspection programme, etc.

Many of us actually do Quality Risk Management work without calling it that...
- Using a formal Quality Risk Management tool may not always be necessary
- The level of criticality and complexity of the item under study should be considered when choosing a Quality Risk Management tool (ICH Q9)
This tool is based upon a formal 10 step Quality Risk Management process, which is fully in line with ICH Q9.

The following three peer-reviewed published papers present the 10 step Quality Risk Management process in detail and give guidance on other aspects of the tool:

Peer-reviewed published papers


This tool was designed around a set of 12 underlying principles which is fully in line with ICH Q9

- The two aforementioned peer-reviewed published papers in the July 2006 issue of the Journal of GXP Compliance present the 12 underlying principles as well as a discussion of each

---

1. Define the RM exercise (e.g. Retrospective) & describe the Item Under Study
2. Assemble a Multi-Disciplinary Team for the exercise
3. Review & Agree definitions for P, S, D
4. Determine *What Might go Wrong*... i.e. Identify Potential Negative Events
5. Estimate & Evaluate each risk using Probability & Severity Levels
   *(A laminated card which accompanies the tool is used here)*
6. Evaluate Risks using Detection Levels
   *(The laminated card is also used here)*
7. Determine any new Risk Controls which are required
8. Determine all Qualification & Validation requirements, as well as the Q & V Status of each control
9. List & plan out all Action Items resulting from the exercise
10. Communicate Risks, and plan for Continuous Improvement via Periodic Review

*See the July 2006 Issue of the Journal of GXP Compliance for more details on these ten steps*
Key Features Cont'd

Qualification & Validation requirements are an integral part of this 10 step Quality Risk Management process

- There is thus a high focus on GMP Controls and on their Q & V status
- Risk-based Critical Process Parameters, Required Outcomes or Acceptance Criteria need to be identified for each control involved in risk mitigation and risk control
- The tool requires a critical evaluation of current and proposed GMP controls

Key Features cont’d

The tool does not seek to re-invent the wheel, and thus, it draws upon some good aspects of other Quality Risk Management methodologies...

- FMECA... but GMP controls are dealt with significantly differently, detection is dealt with differently, RPNs are not used, and Potential Negative Event terminology is used instead of Failure Mode terminology
  - A Negative Event is simply “what can go wrong” (ICH Q9 phrase)
- HACCP... but corrective actions are not predefined in this approach, and risks are characterised and classified in more detail here
- The GAMP 4 Risk Assessment Process... but detection is dealt with significantly differently, and GMP controls are given much more prominence
- Also, ISO 14971 (Risk Management for Medical Devices) was used as Guidance

See the July 2006 Issue of the Journal of GXP Compliance for more details on this aspect of this Quality Risk Management Tool
**Key Features cont’d**

*Tis is a Qualitative Quality Risk Management tool*

- Risk is estimated qualitatively on the basis of Risk = P x S
- Detection controls are not used to estimate the risk, unless they serve to prevent the negative event, or reduce the severity of the effects...
  - then they become Preventative “P” or Severity-related “S” controls

**True Detection controls are used after the Risk has been estimated and before the Risk Control step - Key difference between this tool and FMEA / FMECA**

*See the July 2006 Issue of the Journal of GXP Compliance for more details on this aspect of this RM Tool*  

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**Key Features cont’d**

*In this tool, a high detection rating does not automatically allow one to conclude that the risk is adequately controlled or is of a low priority*

- Step 6 of the Quality Risk Management process requires users to formally determine (with justification) if the risk is adequately controlled, by considering whether the detection controls give assurance that the risk is adequately controlled & that no further controls are required
  - This recognises that improper use of detection controls can cause problems during Quality Risk Management activities for GMP environments
  - Consider missing PILs in packs versus COS impurities in a dried lot of an API
    - Detection controls may be high in each case, but...
Key Features cont’d

- So, the tool does not allow users to assume that a high detectability addresses the risk in question
  - This is in line with the GMP QA principles of building in quality by design, rather than relying on QC end stage testing
  - This is why the tool has this critical decision point at Step 6
  - Key difference between this tool and GAMP 4, FMEA, FMECA

See July 2006 Issue of the Journal of GXP Compliance for more details on this aspect of this RM Tool

Key Features cont’d

- The July 2006 Issue of the Journal of GXP Compliance contains two articles which more fully describe the key features of this Quality Risk Management methodology
  - These articles are included in the Tool User Manual
Key Features cont’d

Elements have been specifically incorporated into the design of the tool to deal with the problems of subjectivity and uncertainty which can arise during Quality Risk Management exercises.

- A set of practical strategies have been developed in this regard.
- See the research paper published in the Journal of Validation Technology, February 2007, for further information in this regard.
- See all the Tool Guidance Presentation for guidance in this area.

Before we use the tool...

There are some Basic Risk Concepts, Definitions & General Quality Risk Management Considerations which are important for the correct use of this tool.

These are presented on the next few slides.
What is risk?

Many Definitions:

- It is widely accepted that the concept of risk has two components – Chance & Consequences:
  - How likely is the scenario to happen?
  - If it does happen, what are the consequences?

Key Considerations:

- The probability of occurrence of harm, (chance, possibility, uncertainty, etc.)
- The consequences or severity of that harm, (injury, cost, supply issues, etc.)

A Risk Definition

- The ICH Q9 definition of Risk is used in this tool
  - *Risk is the combination of the probability of occurrence of harm and the severity of that harm, and that harm is considered to be damage to health, including the damage which can occur from loss of product quality or availability.*
  
  - **Risk = Probability x Severity**
  - **Risk = P x S**

- Risk can be Quantified .. **Risk = (4 x 3) = 12**
- Risk can be Qualified … **Risk = (Remote x Major) = Acceptable**
### Probability Levels used in this tool

<table>
<thead>
<tr>
<th>Probability</th>
<th>This means the Negative Event ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>... is Likely to Occur</td>
</tr>
<tr>
<td>Medium</td>
<td>... May Occur</td>
</tr>
<tr>
<td>Low</td>
<td>... is Unlikely to Occur</td>
</tr>
<tr>
<td>Remote</td>
<td>... is Very Unlikely or Extremely Unlikely to Occur</td>
</tr>
</tbody>
</table>

*Note: These are the default probability levels for the tool. The tool allows the levels to be re-defined & made quantitative if need be.*

### Severity Levels used in this tool

<table>
<thead>
<tr>
<th>Severity</th>
<th>This means the effects of the Negative Event are, or may be,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>- Very Significant Non-Compliance with GMP or MA</td>
</tr>
<tr>
<td></td>
<td>- Potential Patient injury</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderately Severe</td>
</tr>
<tr>
<td></td>
<td>- Significant Non-Compliance with GMP or MA,</td>
</tr>
<tr>
<td></td>
<td>- Potential Patient Impact</td>
</tr>
<tr>
<td>Minor</td>
<td>Not Severe</td>
</tr>
<tr>
<td></td>
<td>- Minor Infringement of GMP or MA</td>
</tr>
<tr>
<td></td>
<td>- No expected Patient Impact</td>
</tr>
</tbody>
</table>

*Note: These are the default Severity levels for the tool. The tool allows the levels to be re-defined & made quantitative if need be.*
### Risk Table used in this tool

<table>
<thead>
<tr>
<th>Negative Event</th>
<th>Minor Severity</th>
<th>Moderate Severity</th>
<th>Critical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Unacceptable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Acceptable</td>
<td>Acceptable*</td>
<td>Unacceptable</td>
</tr>
<tr>
<td><strong>Remote</strong></td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable*</td>
</tr>
</tbody>
</table>

* This must be formally justified
Risk Acceptance Criteria Notes

- **Red Means...**
  - The Risk is Intolerable.
  - Eliminate the hazard or build in systems/controls to ensure the effects of the hazard are not realised (e.g. via redundant systems)

- **Amber Means...**
  - The Risk is Unacceptable.
  - The Risk must be Reduced or Controlled to an acceptable level.

- **Green Means...**
  - The Risk is Acceptable.
  - No Risk Reduction or New Controls are Required.

Detection Levels used in this tool

<table>
<thead>
<tr>
<th>Detection</th>
<th>This means that ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>The Control will likely Detect the Negative Event or its Effects</td>
</tr>
<tr>
<td>Medium</td>
<td>The Control may Detect the Negative Event or its Effects</td>
</tr>
<tr>
<td>Low</td>
<td>The Control will probably not Detect the Negative Event or its Effects</td>
</tr>
<tr>
<td>None</td>
<td>There is no detection control in place</td>
</tr>
</tbody>
</table>

*Note: These are the default levels for the tool. The tool allows the levels to be re-defined and made quantitative if need be.*
We often hear of Hazards & Failure Modes

- A **Hazard** is a potential source of harm
  - e.g. an untrained analyst performing dissolution testing

- A **Failure Mode** is a way in which a process can fail to provide the anticipated result
  - it is a term used in some risk assessment tools, e.g. FMEA
    - e.g. a malfunctioning pump feeding material to a nano-mill is a failure mode...
    - The feed rate may be critical to the particle size reduction result achieved, and this can directly impact upon the bioavailability of the API in the medicinal product.

"Negative Events" are used in this tool

- A negative event is simply "what might go wrong"
  - This is an ICH Q9 phrase
  - **Advantage**: A negative event is a broad concept, and is somewhat easier to understand than the terms failure mode and hazard
What is Risk Assessment?

Risk Assessment is a method which...

- identifies negative events in a process, system, programme, product, etc*
- estimates or calculates the risk associated with these negative events*
- assesses that risk by comparing it against predefined risk acceptability criteria**
  * This is often called Risk Analysis
  ** This is often called Risk Evaluation

*Risk Assessment tells us whether a risk is acceptable or not!

What is Risk Control?

- A process in which risks are reduced or maintained within specified levels. It occurs after Risk Assessment.
- Helps you determine what detection or other controls are already in place to maintain the risk within specified levels
- Helps you determine whether these controls give assurance that the risk is adequately controlled & no further controls required
- Helps you determine what additional actions or controls are needed to reduce the risk or maintain it within specified levels
Additional Controls could include:

- Eliminating the hazard... by designing it out of the process
- Designing in Redundancy / Contingency controls
- Building in new & improved Detection Mechanisms
- Improving Preventative Maintenance Activities
- Training operators to better detect the effects of the negative event

- Risk Control work can be used also to determine:
  - Any Critical Process Parameters and their specifications for the control inspection
  - Any required outcomes or other acceptance criteria for controls for which there are no clear CPPs
  - How controls will be monitored, and what level of Qualification & Validation is required, if any, for each control

What is Quality Risk Management?

- The combination of Risk Assessment & Risk Control, with mechanisms for Periodic Review and Risk Communication...

  - Periodic Review
    - This lets us use new info (e.g. market surveillance, deviations, process experience, near-miss events, etc.), to increase knowledge about hazards, and to improve the Risk Assessment

  - Risk Communication
    - is also necessary & helps promote a culture of risk awareness

- For GMP applications, Qualification & Validation should be considered in any Quality Risk Management process, hence this tool
Schematic Overview of this Quality Risk Management solution

- **Risk Assessment**: Negative event identified, risk estimated, decision re. risk acceptability made

- **Risk Control**: Risk Reduction or Risk Maintenance Controls Initiated until Risk is Acceptable or Adequately Controlled

- **Qualification & Validation**: requirements are determined & actioned

- **Risk Knowledge Is Communicated**

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This Quality Risk Management Approach

- **Steps 1-6**: Risk Assessment
  - Negative event identified, risk estimated, decision re. risk acceptability made

- **Step 7**: Risk Control
  - Risk Reduction or Risk Maintenance Controls Initiated until Risk is Acceptable or Adequately Controlled

- **Steps 8 & 9**: Qualification & Validation
  - requirements are determined & actioned

- **Step 10**: Risk Knowledge Is Communicated
Some General Considerations for Quality Risk Management in GMP Environments

Start Early!
• It is usually more difficult and more costly to make changes to a process, facility, system or product after the fact than early on.

Assemble comprehensive data on the Item Under Study, including a Process Map
• Having these data is of major benefit when doing Quality Risk Management work.
• Sometimes a Process Map is generated, but as this is often only a schematic of the process, more comprehensive data should be assembled for consideration and reference during the Quality Risk Management exercise.
  * See the July 2006 Issue of the Journal of GXP Compliance for more details in this regard.

General Considerations, Cont’d

Negative event identification is perhaps most crucial step, and a variety of approaches can be used here, e.g.:
• Brainstorming... within the right team of people... see the Tool Guidance presentation in the Tool User Manual for more information here (NB!)
• Seeking informed and science-based opinions
• Drawing up Cause & Effect (Fish-Bone) Diagrams
• Evaluating Data: e.g. Complaints, Near-miss incidents, Deviations, Rejects, Control Charts, etc.
• Using Fault Tree Analysis
General Considerations, Cont'd

When estimating risk, there are statistical tools available which can help to determine the *Probability of Occurrence* of a Negative Event, such as:

- Process Capability Analysis (CpK)
- Control Charts

General Considerations – Should we Quantify or Qualify Risk?

Most Risk Assessment methods require you to determine the Probability of Occurrence of a failure mode or hazard (negative event)
- But accurate Probability of Occurrence info can often be very difficult to establish!

Reasons:
- Probability relates not to the effects of the Negative Event, but to the probability of occurrence of the Negative Event itself or to its cause…
  - and this can be difficult to determine accurately
- Some Negative Events occur because of systematic or random errors...
  - and these can also be difficult to quantify
Should we Quantify vs Qualify Risk?

- As Severity & Probability are ‘ordinal’ scales, their magnitude is not meaningful
  - This means that a negative event with a Probability of Occurrence of 4 is more likely, but not necessarily twice as likely to occur as one with a Probability of 2
  - It is not mathematically permissible to multiply ‘ordinal’ scales.
  - Numerical operations such as (Risk = 3 x 4) or (RPN = 3 x 4 x 2) have questionable validity

- Word descriptors (e.g. high, medium, low) may be more valid than numerical descriptors, and may be preferable, because we will not then be tempted to multiply numbers to get a ‘magic’ Risk or RPN numbers

Quantify vs Qualify - Conclusion

- It is inadvisable to place too much faith in risk quantitation.
  - A good qualitative estimation may be better than a poor quantitative estimation
  - Strength of evidence is important to consider (See ICH Q9)
  - Risk assessment is not an exact science – imagination, expert opinion, etc., are often required

- Charles Dickens... highlighted the absurdity of misunderstanding risk numbers...
What the Dickens!!

- One day, in late December, he announced he couldn't ride the train anymore that year because
  "the average annual quota of railroad accidents had not been filled" and disaster was obviously imminent! 😁

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The Structure of this Tool

The tool comprises of the following five elements:

- A document stating the twelve Principles underlying this Quality Risk Management methodology, with a discussion of each also provided
- A document providing an overview of the Tool's Ten Steps
  - This gives a description of the purpose and key activities of each of the steps in the Quality Risk Management process
- A copy of the Tool Worksheet
  - This is a structured, 10-step instructional template which gets completed as the QRM exercise progresses
  - It is also designed to guide users through the 10-step process
- A copy of the Laminated Card for use with the Tool Worksheet
  - This gives the default definitions for P, S, D, & also the Risk Table
- A presentation providing a recommended Training Strategy for the potential users of this methodology
The importance of training

Training is essential to the successful use of the tool

- Some key features are not immediately obvious, and require training using examples and case studies
  - e.g. the classification of GMP controls in terms of how they relate to S, P & D
  - e.g. the identification of Potential Negative Events (PNEs)
  - e.g. what to do when conflicts arise during Brainstorming activities, etc.

Training takes approx. two to three days, and should not be skipped

- This is not considered excessive, given the importance of Quality Risk Management work and its benefits towards compliance
- Best to start with a simple, non GMP-related case study on the tool
  - This helps us focus on learning how to use the tool, before we start thinking about GMP issues

The importance of training

A Training Strategy has been developed for the tool

- This is based upon the components of the Training & Users Manual which accompanies the tool

- See the Training Strategy Presentation contained in the tool documentation for further information
The Training & User's Manual

The Training & User's Manual is a package of documents containing various components:

- It contains training materials for both trainers and trainees on the tool
- It contains practical guidance (Q&A) for users of the tool during actual Quality Risk Management exercises
- The Training & User's Manual should be given to all trainees at the start of training, and it should always be available during actual Quality Risk Management exercises
- It contains the following five components:

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1. A copy of an Introductory Presentation on the tool
   - This provides a general introduction to this Quality Risk Management solution
   - It describes the structure of the tool, its uses, key features, scope and uses, limitations and advantages
   - It provides an overview of the ten steps of the Quality Risk Management process used by this tool
   - It provides an overview of Quality Risk Management in general, and the key components of the Quality Risk Management process

2. A detailed Tool Guidance Presentation
   - This provides both general guidance on the tool, as well as specific and detailed guidance on key activities and issues which may arise when working through each step of the Quality Risk management process
   - For simplicity and ease of use, it is mainly structured as a Q&A-type document
A copy of a partially and fully completed Case Study on the tool which involves an area not in any way related to GMP

- The purpose of this Case Study is to facilitate the initial training on the tool in a manner which is non-technical from a GMP perspective
- This allows trainees to focus only on the tool and how it is used, not on GMP issues
  - Our research has shown that this greatly facilitates the training process
- The Case Study relates to the application of this Quality Risk Management methodology to a Wedding
  - It is a humorous, simple exercise, to put people at ease at the start of their training.
  - This is important given the vigorous and formal nature of the Quality Risk Management methodology

3. Cont’d

- Trainees work through the partially completed case study with the trainer, in order to complete the exercise and learn how the tool works
- This allows trainees to become familiar with the tool components (e.g. the worksheet, laminate card) and also the ten-step process before applying the tool to GMP areas
- This allows trainees to explore and resolve any practical issues or difficulties which may be encountered in a non-technical setting, before moving on to GMP-related applications of the methodology
- At the end, the team evaluates their results from completing the case study, with reference to a fully completed version of the Case Study which is also provided in this section of the Training & User’s Manual, for reference
The Training & User's Manual

4. A series of practical and completed real-life GMP-related case studies on the tool

- These show, in practical terms, how this tool is used, and what the expected outputs of the tool are when applied to specific GMP and GMP-related activities

- Case Study: The application of this Quality Risk Management solution to a Paracetamol Oral Suspension Mixing & Filling Process at a Finished Product Manufacturer (This involved the use of Tool Version 3 to Case Study 1)

- Case Study: The application of this Quality Risk Management solution to a proposed Change Control (introduction of ICP-MS) at an API manufacturer

The Training & User's Manual

4. Cont'd

- Case Study: The application of this Quality Risk Management solution to a Product Recall Procedure at a Finished Product Manufacturer

- Case Study: The application of this Quality Risk Management solution to a proposed Change Control to introduce a new critical product contact material at an IMP (i.e. clinical trial product) Manufacturer

- Case Study: The application of this Quality Risk Management solution to an area related to the GMP environment, but not GMP-regulated. (A Market Compliance Programme at an EU Competent Authority)
5. Copies of three peer-reviewed research papers describing this Quality Risk Management solution

- These papers are useful for general and detailed information on this Quality Risk Management solution, and describe some of the strategies used in this Quality Risk Management solution to address the problems of subjectivity and uncertainty which can be encountered during Quality Risk Management work
  - Journal of GXP Compliance, July 2006
  - Journal Validation Technology, February 2007

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Uses & Scope of the Tool

This tool is designed to apply Quality Risk Management to:

- Manufacturing, Cleaning & Packaging Processes
- GMP Systems, such as HVAC systems, Building Management systems, Distribution & Recall systems, Regulatory Compliance systems, etc.
- GMP Programmes, such as Stability Programmes, Pest Control Programmes, Supplier Approval Programmes, Self-inspection programmes, etc.

See Step 1 of the tool Worksheet for an overview of what the tool can be applied to

- It can be used Prospectively or Retrospectively
- It can be used for Change Controls
Uses & Scope cont’d

This tool is not intended to replace other useful tools & guidance documents...

- ISPE’s Impact Assessment method for determining Commissioning & Qualification requirements
- GAMP 4 Risk Assessment method for Computerised Systems Validation
- ICH Q2(R1) - Guidance for Analytical Method Validation

This tool is not intended to be an IMB requirement for Irish manufacturers

- IMB’s work here is for Inspectors’ research and learning
- & to give guidance to industry when requested on the practical application of Quality Risk Management in meeting the Annex 15 requirements
- IMB is not setting a new GMP requirement in the area of Quality Risk Management, and IMB does not require (or promote in any way) the tool to be used by Industry

Tool Inputs & Some Outputs

- Item Under Study
- RM Tool
- - Risks associated with this Item Under Study
- - Critical Process Parameters, or critical required outcomes of controls
- - Qualification & Validation Status of GMP controls
- - Qualification & Validation Requirements for the Item under Study
- - A critical evaluation of the usefulness of current controls
- - Risks associated with a Change Control & a strategy for dealing with such risks
- - A means of evaluating and justifying PAT initiatives
- - A strategy for communicating risks to stakeholders
Possible Limitations of the tool

- Not a universal Quality Risk Management solution which may be applied in all situations, across all areas.
  - e.g. while this approach provides a means of prioritising risks (and their required risk control activities), it does not provide a methodology for formal risk ranking or filtering activities
  - Therefore, when prioritising suppliers for auditing for example, this solution does not offer a good means of doing this
  - There are specific and better tools available for these purposes, and ICH Q9 gives information in this regard.

Possible Limitations of the tool

- This is a formal and rigorous methodology, involving a detailed Quality Risk Management process with ten discrete steps, and a tool worksheet which requires completion as the exercise progresses
- This means that documentation, effort and training are required in order for this tool to be used effectively
  - As a result, this tool has been specifically designed to evaluate only a small number of potential negative events – those considered to be the most critical and/or most complex
  - While this is a key strength behind this approach, it also limits the application of this tool to a degree
  - If a large number negative events are to be studied, a less-detailed cause and effect approach, a HACCP or an FMEA-based approach may be more appropriate
Possible advantages of the tool

- The tool is specifically designed for GMP applications, to facilitate risk-based Qualification & Validation programmes
- The tool is specifically designed to be in line with ICH Q9
- The tool is specifically designed to facilitate compliance with the risk-based Validation and Change Control requirements of Annex 15
- The tool is intended to help to increase process understanding, and it provides a proactive means to identify and control potential quality issues during manufacturing
- The tool can be used to help identify and justify PAT initiatives, as the tool can show how PAT-based monitoring of a process can reduce or control an important risk
- The tool is a ready-made, structured, science-based and transparent method for applying Quality Risk Management within GMP environments
  - Thus, it may give GMP inspectors assurance that potential risks are being dealt with adequately and in an open, documented way

Section 7

Detailed Guidance Presentation
on this Quality Risk Management methodology
Purpose of this Presentation:

This presentation gives Guidance to users of this Quality Risk Management tool

- Part 1 gives guidance on a number of practical issues which can arise during Quality Risk Management exercises.
  - This guidance needs to be considered by the Quality Risk Management team before using this Quality Risk Management tool

- Part 2 provides practical answers and specific guidance in relation to common questions and issues which may arise when executing the various steps of this 10 Step Quality Risk Management process
  - For simplicity, this Part is structured mainly in a Questions and Answers (Q&A) type format
How to use this Presentation:

This presentation is designed to serve both as training material on this Quality Risk Management solution, as well as step-by-step guidance to be consulted when actually using this Quality Risk Management tool.

- Trainees should review the content of Part 1 of this Guidance Presentation for general guidance on some key issues which are important before starting to train on the actual Tool Worksheet.

- Trainees should review the content of Part 2 of this Guidance Presentation for guidance when starting to train on the ten step Quality Risk Management process and the accompanying Tool Worksheet & Tool Laminated Card.

- When performing a Quality Risk Management exercise with this tool, each participant of the team should have a paper copy of these slides for reference, and when at a particular Step of the tool, the corresponding slides for that Step should be consulted for guidance.

Appendices to this Presentation:

There are several Appendices to this Presentation

- Appendix 1 provides detailed guidance for carrying out team-based activities (such as brainstorming) during Quality Risk Management exercises.

- Appendix 2 provides detailed guidance for how disagreements and differences of opinion are to be dealt with during team-based activities.

- Appendix 3 provides detailed guidance in relation to how human heuristics can affect brainstorming sessions, and how the adverse affects of such heuristics may be reduced during brainstorming and decision making.

- Appendix 4 provides information pertinent to assessing the strength of evidence for opinions and judgements that have been given during Quality Risk Management exercises by team participants and experts.
Appendices to this Presentation:

- Appendix 5 provides practical guidance on what information might be included when assembling comprehensive data on the item under study, as required in Step 1 of the Quality Risk Management process.

- Appendix 6 presents a Practical GMP-related Case Study which is useful for understanding several of the strategies which were developed during this research to overcome problems of subjectivity and uncertainty when identifying potential negative events and when performing Risk Assessment activities.
  
  - This Case Study is also a useful example of how Fault Tree Analysis may be used in conjunction with this Quality Risk Management methodology to help identify potential negative events and their likely causes.

- Appendix 7 presents guidance for dealing with Human Error issues, & how to avoid situations in which Human Error is wrongly identified as the cause of a Potential Negative Event.

Part I of this Presentation

Some Practical Issues to be considered before starting to use this Quality Risk Management Tool.
Topics Covered in Part 1

- Subjectivity and Uncertainty in Quality Risk Management
  - Reducing uncertainty and subjectivity in Brainstorming activities
  - Dealing with disagreements and differences of opinion
  - The role of heuristics in brainstorming
  - Strength of Evidence considerations
- Other General ways to reduce subjectivity & uncertainty
  - Issues concerning Definitions and Terminology
  - Rules governing this Quality Risk Management methodology.
  - Principles underlying the Quality Risk Management process used by this tool
  - The uses and limitations of this methodology
- Issues Relating to GMP Controls
- Tool Robustness Issues
- Tool Training Issues
- Business versus GMP Risk Issues

Subjectivity and Uncertainty issues
"Too subjective... too uncertain"

- Quality Risk Management (QRM) is by definition uncertain – the definition of Risk itself is based on probability, hence uncertainty!

- Important to remove as much subjectivity, inconsistency and guesswork from the process as possible, using science-based & systematic methods
  - improve confidence in the results
  - more meaningful and value-adding qualification and validation work
  - safer change controls, less chance of adverse and expensive consequences or additional work being required

- Key Questions:
  - where do subjectivity and uncertainty arise in QRM?
  - what can we do to reduce this subjectivity & uncertainty?

Areas of subjectivity & uncertainty

In formal QRM, the main areas of subjectivity & uncertainty include:

- Identifying Potential Negative Events (& their causes)
- Assigning probability of occurrences values to Potential Negative Events
- Estimating the severity of the effects of Potential Negative Events
- Calculating Risks associated with Potential Negative Events
- Assigning detection ratings to detection controls
- Selecting RPN cut-off values, if used. (Note: RPNs are not used here)
- Over-relying on quantitative approaches when the data are simply not available to have confidence in the results (Note: this is not a quantitative approach to QRM)
- Estimating the impact of Risk Control measures on risks which serve to reduce the risks
- Brainstorming activities for some or all of the above

In informal QRM, the main concern is probably whether risks have been even identified
Reducing uncertainty and subjectivity in Brainstorming activities

- Brainstorming is mainly used during Steps 4 through 7 of this Quality Risk Management process, and is a vital feature of this methodology.
- Brainstorming however is an activity that, if not carried out appropriately, may be hindered by problems of subjectivity and uncertainty, and disagreements in opinions and judgements may occur during brainstorming sessions.
  - It is important therefore to ensure that brainstorming activities are adequately structured and proceduralised.
  - Detailed guidance is provided in Appendix 1 to this Presentation for carrying out brainstorming sessions.
  - This guidance applies not only to brainstorming activities used to identify potential negative events, it also applies to any Brainstorming sessions used during the remaining Risk Assessment activities and during the Risk Control stages of the Quality Risk Management process.

Reducing uncertainty and subjectivity in Brainstorming activities

- How should disagreements and differences of opinion be dealt with during brainstorming sessions and in decision-making in general?
  - Detailed guidance has been developed in this regard
  - See Appendix 2
Reducing uncertainty and subjectivity in Brainstorming activities

We sometimes hear about the affect that heuristics can have in brainstorming. What are heuristics?

- Heuristics are cognitive behaviours, rather like "rules of thumb".
- They come into play when people make judgments in the presence of uncertainty.
- How these behaviours are manifested is still the subject of much research, but there is evidence in the literature that heuristics can be a source of significant bias and error in judgment.

- In activities such as Quality Risk Management, heuristics become important because there is usually some level of uncertainty associated with the judgments and decisions which are made during such exercises.
- Experimental psychology researchers such as Kahneman, Slovic and others have shown that heuristics can sometimes lead to biased outcomes and errors.

Some useful references for further reading:

Reducing uncertainty and subjectivity in Brainstorming activities

Are there different types of heuristics?
- Yes. The main heuristics which are likely to be important in relation to Quality Risk management exercises are:
  - The Heuristic of Availability
  - The Heuristic of Representativeness
  - The Heuristic of Anchoring and Adjustment

- Detailed information on heuristics has been compiled to explain what these heuristics are, and practical strategies have been developed in relation to addressing the problems of heuristics when using this tool.
  - See Appendix 3

Reducing uncertainty and subjectivity in Brainstorming activities

Problems of uncertainty and subjectivity
- During brainstorming sessions, it is important to address the problems of uncertainty and subjectivity in decision-making and judgement that can arise via the potential adverse effects of human heuristics

- But how can we do this?
  - See Appendix 3 - This provides detailed guidance for how the adverse affects of heuristics may be reduced during brainstorming (and in decision making in general) during Quality Risk Management exercises
Reducing uncertainty and subjectivity in Brainstorming activities

Other ways to reduce subjectivity and uncertainty

- When identifying Potential Negative Events at Step 4 of the Tool Process, use the detailed guidance presented in Appendices 1 & 2 for brainstorming and for dealing with differences of opinion and disagreements which may arise.

- Don’t ignore the obvious - review what has gone wrong in the past...
  - We know those issues were real and not subject to uncertainty in whether they could occur!
  - Near-miss incidents, Deviations, rejects, complaints, defects, problems, qualification & validation incidents, reasons for change controls, etc. are all useful sources of information in this regard.

- Consult with the right people, who may know more than you:
  - e.g. for equipment-related QRM exercises, the equipment vendor may have valuable knowledge about likely problems, rates of failure of components, etc.

Reducing uncertainty and subjectivity in Brainstorming activities

Always examine the Strength of Evidence

- When obtaining opinions and judgements during Quality Risk Management exercises, the Team Leader should always seek out and discuss the strength of evidence for each opinion or suggestion proposed.

- This adds rigor to the exercise, and it helps reduce the level of subjectivity and guesswork that can arise during the failure mode identification process.

- However, caution should be exercised when seeking strength of evidence from team participants.
  - See Appendix 4 for important information in this regard.
Reducing uncertainty and subjectivity in Brainstorming activities

In this regard, it is helpful to:

- Seek the opinions of actual users and operators of the item under Study:
  - A process operator may know very well what can go wrong with a process or activity, and he or she may be in a position to advise as to its potential frequency.

- Seek the opinions of those employees or others who are knowledgeable in the item under study:
  - For example, during equipment-related Quality Risk Management exercises, the vendor may have valuable knowledge about likely problems and potential rates of failure of components, etc.

- Think “what might go wrong”, but not in isolation...
  - Use process maps or flow diagrams to visually review the item under study – especially useful if the maps show human interventions & actions
  - Cause & Effect (Fishbone) Diagrams are also helpful in this regard

- Take into account the concerns of stakeholder groups when thinking about "what might go wrong"
  - e.g. If a change control is proposed to roll out a new labelling range and livery for one of our products, practicing pharmacists can often easily tell us about risks of dispensing or usage errors introduced by the change, even if the new labelling is fully compliant.

- Don’t discount the power of ‘imagination’ – see the 9/11 Commission Report for interesting reading here
Other general ways to reduce subjectivity & uncertainty...

- Review and agree the definitions & meanings of the terms used in this QRM process, and use this terminology consistently when working through the QRM exercise
  - The inconsistent use of terms such as Risk Analysis & Risk Assessment can lead to misunderstandings and confusion among users
    - Even the EU GMP Guide makes this mistake!
  - This Tool uses simple terminology, based on ICH Q9 where possible.
  - Terms such as “failure mode” can be difficult to understand, and are not in this methodology. The term ‘potential Negative Event’ is used instead.
  - This tool also uses self-explanatory headings where possible
    - e.g. instead of just using the term ‘Periodic Review’ at Step 10, the phrase ‘Plan for Continuous Improvement via Periodic Review activities’ is used instead at step 10.

General ways to reduce subjectivity & uncertainty, cont'd

- Follow the documented and structured process provided in the tool worksheet when using this tool
  - Worksheet-based approaches are helpful and lead to systematic outcomes, and also help reduce inconsistency in using the tool
General ways to reduce subjectivity & uncertainty, cont’d

- Comply with the simple rules that govern this Quality Risk Management methodology
  - There are several rules which govern this Quality Risk Management methodology
  - These are simple and science-based
  - They are built into the design of the Quality Risk Management process and the tool worksheet
  - At the outset of a Quality Risk Management exercise, the Team Leader should review these rules with the team
    - This is useful, as doing this can help to reduce the problems of subjectivity and uncertainty which can occur during Quality Risk Management exercises when its rules are not well understood
  - These rules are:

General ways to reduce subjectivity & uncertainty, cont’d

- Rules cont’d....
  - That risk is considered to be the combination of the probability of occurrence of harm and the severity of that harm. In other words, Risk = Probability x Severity
  - That, in GMP environments, harm is considered to be damage to health, including the damage which can occur from loss of product quality or availability. (The incorporation of product availability into this definition of harm is important, as otherwise, some risks which might lead to a loss of product availability but not quality may be seen as business-related only, and not as GMP-related, regardless of whether a GMP failure lead to the risk)
  - That Risks and Risk Priority Numbers (based on P x S x D) are not the same things, and should not be confused.
General ways to reduce subjectivity & uncertainty, cont'd

- Rules cont’d

  - That, even if a risk is deemed acceptable with current controls and that no new risk controls are required, qualification and validation requirements still need to be assessed and determined for those controls, and the qualification and validation status of those controls needs to be identified and documented.

  - That there may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls/resources, but which may be controlled to an acceptable level with improved detection or other measures.

  - That, in GMP environments, a high detectability of a risk does not necessarily mean that the risk is eliminated or adequately controlled.

General ways to reduce subjectivity & uncertainty, cont’d

- Remember and apply the basic principles that govern the Quality Risk Management process used by this tool

  - There are twelve basic principles upon which the tool is designed

  - These are also science-based, and many are based on ICH Q9 principles and guidelines

  - It is important that the team is familiar with these principles in order to avoid confusion and mis-understandings during Quality Risk Management exercises that can lead to problems of subjectivity and uncertainty

- See the Tool Folder for the list of Principles and for a discussion on each
General ways to reduce subjectivity & uncertainty, cont’d

- Ensure that all members of the team are clear on the uses and limitations of this Quality Risk Management methodology
- Using a tool for an application that it was not designed for will likely frustrate staff and lead to dubious results
- The Tool Introductory Presentation in the Training & User’s Manual gives useful information in this regard
- See also Step 1 of the tool worksheet for the areas to which the methodology may be applied
- See also the following research paper published in the Journal of GXP Compliance for further information on this aspect of the tool

Practical issues to be considered before starting to use the QRM Tool, cont’d

Issues Relating to GMP Controls
**Issues relating to GMP Controls**

When performing Quality Risk Management as an aid to Qualification, Validation and Change Control, it is important to use a QRM process which is focussed on clearly identifying GMP controls which are directly related to patient risk and product quality. This tool is designed specifically to address this issue.

- This is because, to achieve meaningful & cost-effective risk-based Qualification & Validation, the tool must be able to identify such controls, so that critical process parameters, or critical features or required outcomes can be determined for those controls.
  
  - ISPE’s White Paper of March 2005 provides a useful discussion in this regard.

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**Issues relating to GMP Controls**

There are many different types of GMP controls

- It is important to bear these in mind during Steps 5, 6 & 7
  
  * This is where we document both the currently-in-place controls, as well as any new/improved controls which may be required.

- It is important to note that some types of controls may be less effective than others, and may be affected by external factors and influences.
  
  * The effectiveness of visual inspection-based controls, for example, may be affected by who is performing the inspection, and by the conditions provided for the inspection. Stamatidis (2003) discusses how visual inspection-based controls may only be 79% effective in some cases.

- Examples of some types of Risk Controls that may be selected during Quality Risk Management exercises are as follows:
Issues relating to GMP Controls

Examples of GMP Risk Controls

- Eliminating the potential negative event, by re-designing the process or item in question
  - e.g. this can be done by replacing a component in the process with a component which does not have the same potential negative event
  - Here, it is important that any risk presented by the new component are assessed and managed.

- Isolating the item, process, area, etc., in which the potential negative event may occur, so that the impact of the effects of the potential negative event may be reduced and contained

- Ensuring that effective procedures and checking activities are in place to ensure that unwanted steps and actions are avoided

Issues relating to GMP Controls cont'd

- Training operators and other staff to comply with procedures and policies

- Designing in Redundancy / Contingency controls so that if the potential negative event occurs, there are controls in place which reduce or counteract the effects of the potential negative event

- For equipment-related potential negative events, improving Preventative Maintenance activities so that the probability of occurrence of the potential negative event may be reduced

- Where detection controls are important in controlling a risk, training operators to better detect the effects of the potential negative event
Issues relating to GMP Controls cont’d

- Adding fool-proof measures which cannot be by-passed via human error or the by accidental or deliberate non-compliance with procedures.
  - An example of such a control would be a requirement for an operator to confirm the volume of a solvent to be added to a vessel by re-entering the volume required into a computer system controlling the transfer of the solvent.

- Providing warning information to relevant people about the hazard or its potential effects.
  - An example here is a warning on the label of an injectable product not to use the product if particulates are observed in the solution

- Building in new & improved Detection Mechanisms, so that if the negative event or failure mode occurs, it, or its effects may be detected in an appropriate timeframe.

Issues relating to GMP Controls ...

- Classifying current controls in terms of how they influence Severity (S), Probability (P) & Detection (D), and then carefully considering these before any S, P & D ratings are assigned to a potential Negative Event is very useful
  
  - This is a key design feature of this tool via Steps 5, 6 & 7
  - (Note: Many tools do not require this, even most FMEA applications)
  
  - But doing this leads to greater confidence in the S, P & D ratings we assign
  
  - It gives the S, P & D ratings a greater scientific basis
Issues relating to GMP Controls ...

- But classifying controls in terms of how they relate to S, P or D can be difficult
  - Training is required, and this should not be overlooked.
  - Real life examples can help...
    - We have found that starting with something simple, in a non-GMP area, is best.
    - Then we move into a GMP example.

Exercise on classifying controls as S, P or D

- Item Under Study in this QRM Exercise: the kitchen in your home
- Potential Negative Event – your deep fat fryer goes on fire
- Possible Cause – unit was left switched on overnight and oil overheated

- List and classify any controls which might reduce the Severity (S) of the effects of the fire, or the probability (P) of it occurring, or which might detect the fire or its effects (D)
  - Smoke Detector
  - Fire blanket
  - Fire Extinguisher
  - Unplugging all appliances before going to bed at night
  - Closing all doors before going to bed at night
Exercise on classifying controls as S, P or D

- Item Under Study in this QRM Exercise: the kitchen in your home
- Potential Negative Event – Your deep fat fryer goes on fire
- Cause – unit was left switched on overnight and oil overheated

- List and classify any controls which might reduce the Severity (S) of the effects of the fire, or the probability (P) of it occurring, or which might detect the fire or its effects (D)
  - Smoke Detector (D)
  - Fire blanket (S)
  - Fire Extinguisher (S)
  - Unplugging all appliances before going to bed at night (P)
  - Closing all doors before going to bed at night (S)

The above simple exercise shows how different controls can be classified in terms of how they influence S, P & D. The idea here is that:

- We assign a Severity Rating to the failure mode after we evaluate the controls we have in place which reduce the Severity
- We assign a Probability Rating to each cause of the failure mode after we evaluate the controls in place which prevent each cause
  - We then estimate the Risk based on Risk = P x S
- We assign a Detection Rating for the risk after we evaluate how good our Detection controls are

- By doing this, we obtain more scientific S, P & D ratings

➢ So the level of the risk we estimate is now not based on guesswork
➢ It is supported by an informed evaluation of the components contributing to the risk and its control, by taking into account the controls in place
GMP Exercise on classifying controls

- Item Under Study in this QRM Exercise: a Factor VII concentrate for solution for infusion
- Potential Negative Event – particulates observed in the solution after reconstitution (many complaints received)
- Cause – coring of the vial stopper upon needle penetration during reconstitution

- Classify any controls which might reduce the Severity (S) of the effects of the Negative Event, and the probability (P) of it occurring, and which might detect it or its effects (D)
  - The PIL could require user to inspect solution prior to administration (D)
  - A filter needle could be supplied in the pack (S)
  - A more robust stopper could be developed less prone to coring (P)
  - Better reconstitution instructions relating to the angle of penetration of the needle into the rubber stopper
Tool Robustness Issues

QRM processes should be robust, so that they can be of use across several areas, not just, for example, Process Validation

- A key learning we have made is that the robustness of any proposed QRM tool should be evaluated and optimised before it is rolled out
  - Otherwise a QRM process may work well in one area, such as with a manufacturing process, but may fail miserably in other areas, e.g. with a packaging process, or a supplier approval programme.
  - This problem can especially arise if defining quantitative levels for probability of occurrence ratings
  - A solution here is to have a flexible tool which lets us define both qualitative and quantitative levels each time the QRM process is being used
    - This way, the levels chosen can be tailored and will be more applicable to the item under study
Tool Robustness Issues cont'd

- Also, a QRM process should be robust enough to deal with the different types of controls which will be encountered in GMP environments
  - In Qualification & Validation, for example, we normally define CPPs
  - But many controls are not so easily described in terms of CPPs
    - e.g. a supplier approval programme will be a relevant control when studying the risk associated with introducing a new starting material to the site
  - Yet such controls may have definite required outcomes, and may have clear qualification or validation requirements
    - e.g. a new starting material will need to meet certain pre-defined criteria, and the supplier may need to pass a formal qualification exercise
  - The QRM process should be able to cope with this fact
    - otherwise it is easy to neglect to identify some required qualification & validation exercises
    - The above considerations have been taken into account during the design and development of this Quality Risk Management methodology

Some Practical issues to be considered before starting to use the QRM Tool

Tool Training Issues
Training Issues

- Staff should be formally trained on the terminology used in the tool
  - The Introductory Tool Presentation, as well as the Tool Guidance Presentation, cover all of the tool terminology that is used in the Tool Worksheet and Laminated Card which may not be self-explanatory
  - Thus, these two presentations should be presented to the team before using the tool
  - In terms of general Quality Risk Management terminology, the team should be familiar with the full contents of ICH Q9, the terminology and definitions used therein.
    - This is because this QRM methodology and its terminology are directly based on that contained within ICH Q9.

Training Issues cont’d

- Staff need to be formally trained on the details of the Quality Risk Management process used by this tool
  - This should include a review with the QRM Team of the twelve principles underlying this methodology and the ten steps of the Quality Risk Management process. These are contained in the Tool folder.
  - Also, the team should be trained on the Tool Worksheet and the Laminated Card which give effect to the Quality Risk Management process
    - As part of this training, the team should review the structure and contents of the blank worksheet and laminated card, as well as the detailed GMP Case Studies which represent completed versions of the worksheet.
    - These Case Studies are contained in the Tool User’s Manual, and demonstrate at a practical level not only how the tool works for GMP applications, but also the kind of issues that can arise when executing the various steps of the tool.
Training Issues cont'd

For example:

- One issue that often arises during QRM work is that some risks just cannot be eliminated or reduced to an acceptable level with current or realistic controls or resources.

- It is important therefore for the team to know how the tool works in practice for such issues, before starting to use it in their own company.

* Consider the following situation:

Before Risk Control measures...

<table>
<thead>
<tr>
<th>Negative Event</th>
<th>Minor Severity</th>
<th>Moderate Severity</th>
<th>Critical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Probability</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Medium Prob.</td>
<td>Acceptable</td>
<td>Unacceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Low Prob.</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Remote Prob.</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

* Acceptable only with justification
After Risk Control measures...

<table>
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<td></td>
</tr>
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<td>Low Prob.</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Remote Prob.</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

* Acceptable only with Justification

Training Issues cont'd

- The QRM tool is designed to cope with such situations via the design of the Detection components of Steps 6 and 7 of the Tool Worksheet
  - Current or new/improved detection controls are documented, critically evaluated and rated in Steps 6 and 7
  - There is then a Risk Decision to be made, after the detection controls have been documented and rated
  - Here, the team must decide (with justification) if the unacceptable or intolerable risk can be adequately controlled with the detection controls in question
    - This involves assessing whether these controls give assurance that the risk is adequately controlled & no further controls are required
Training Issues cont’d

- The practical, GMP-related Case Studies in the Training & User’s Manual for the tool are designed to show how the tool is used at a practical level.
  - It is important during training to move beyond the conceptual, and these Case Studies are useful in this regard.
    - No use showing how the tool works in aerospace manufacturing!

- However, when training staff on a formal QRM tool, it can be a mistake to start with detailed GMP-related case studies.
  - This is because GMP people tend to only focus on the GMP issues rather than learning the ins and outs of the actual Tool.
  - So, it is useful to start with a simple Case Study, not related to GMP.
  - This should demonstrate how the tool works at a practical level, before moving on to GMP examples.
  - See the Training Presentation contained in the Tool Folder for a recommended and detailed training strategy on the tool.

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Some Practical issues to be considered before starting to use the QRM Tool

Business versus GMP Risk Issues
Business vs. GMP Risks

- During the development and testing of this tool, an interesting question came to light:
  - When risks are identified which affect product release, but which do not affect product quality, are these solely business risks, with nothing to do with GMP?

- Some argued that such risks should not be subject to GMP control, as they are business-related only, and are not related to GMP

- This may be true in some cases, but certainly not in all cases, and it is a dangerous principle to adopt when performing Quality Risk Management
  - Question? Are business risks and GMP risks different things?

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Business vs. GMP Risks

- Point for Consideration:
  - Loss of API or medicinal product availability can adversely impact upon patients and users of medicinal products

  - If a GMP issue or a GMP failure leads to the loss of API/product availability, then the resulting risk should be considered to be related to GMP

  - ICH Q9 defines risk as the combination of the probability of occurrence of harm and the severity of that harm, and it defines harm as damage to health, including the damage which can occur from loss of product quality or availability
Business vs. GMP Risks – what is your opinion?

Consider the following three cases:

- Batch release ceases due to MA non-compliance issues with the registered manufacturing process for the product
  - There may be no adverse impact on product quality
    ➢ Business or GMP Risk, or both?

- A problem is identified with a difficult bioassay at a biologicals API manufacturer, and testing ceases, & API batch release is impacted
  - No adverse impact on batches already tested and released to date
    ➢ Business or GMP Risk, or both?

- Shipping Drug Product batches pre-QP release, under quarantine
  - Two recent incidents in Ireland where such batches which were OOS were marketed in error
  - Recalls were requested
    ➢ Is this a GMP risk or a business risk? Or both?

Part II of this Presentation

Q&A and Guidance for each of the ten Steps of the Quality Risk Management Process used by this Tool
Guidance for Step 1 – Preliminary Info

What is Step 1 about?
- Step 1 is where we define the purpose of the QRM exercise, and here also we state what is being studied (e.g., a Manufacturing Process). Page 2 of Step 1 is where we scope out the QRM exercise, and it is where we state the reason for the exercise.

Selecting from the available three Options in Step 1
- Options 1 and 3 are similar in that they both relate to Change Controls, but Option 3 goes beyond looking merely at the Q & V requirements associated with a proposed Change, as it assesses the change control from a broader viewpoint… it asks “If we implement the proposed change, what risks does it present?”
- Option 1 & 2 cannot both be selected at one time.

Guidance for Step 1 – Preliminary Info

What could a Specific Issue or Problem look like in Step 1?
- This could be something such as glass in vials, a series of batch rejects due to high impurity levels, a product recall issue, etc.

What is meant by “Item Under Study” in Step 1?
- This is just the term used in the tool to refer to the subject of the Risk management exercise.
Guidance for Step 1 – Preliminary Info

Comprehensive data on the Item Under Study:

In Step 1, the item relating to “Process Map or Schematic”, what information is to be assembled in relation to the statement “Comprehensive data on the Item Under Study should also be assembled at this point, and referenced here”.

• See Appendix 5 for detailed guidance in this regard

Guidance for Step 1 – Preliminary Info

What kind of info do we record under “Reason & Relevant Background Info”?

• Under “Reason & Relevant Background Info” give as much useful info as possible on why we are doing this exercise. It can be useful here to think in terms of a Risk Question, or in terms of a Problem Description when completing this section.

• Also, here is where we should clearly state or reveal any pertinent assumptions which may be relevant to the QRM exercise.
  • For example, a pertinent assumption might be that all equipment used in a process has been qualified. This becomes very useful (and important) later on, when we get to Step 8, which is about Qualification & Validation.
  • Also for example, we could record the following here “It is assumed that all personnel have been successfully trained on the SOPs in question”, or that “all equipment will have been calibrated”.

Slide 59

Slide 60
Guidance for Step 1 – Preliminary Info

"Reason & Relevant Background Info" cont'd

- Note: Revealing and documenting any assumptions which are relevant helps us to have confidence in the output of the QRM exercise, and also, it helps to identify the limitations of the QRM exercise.

Guidance for Step 2 – The QRM Team

Who should be on the QRM Team?
- It is important to include knowledgeable people from the appropriate areas which are of relevance to the item under study in the Quality Risk Management exercise. (Ref: ICH Q9)
- Also, there should be at least one person from QA, because this is a quality-related activity and the input and buy-in of QA is beneficial
- There should be at least one person who is knowledgeable in the Quality Risk Management process and its methodology (Ref: ICH Q9)
- This person need not be the team leader, but the team leader should have sufficient knowledge in the process and methodology too

Why should the QRM Team be multi-disciplinary?
- Multi-disciplinary teams can offer diverse viewpoints, and will not be biased by group effects. Synergistic effects can be realised when teams are used.
- This is important especially if the QRM exercise will use the team to brainstorm to identify potential negative events.
Guidance for Step 2 – The QRM Team

How many people should be on the QRM Team?

- Obviously, the more people that are on the Quality Risk Management team, the greater the chance that disagreements and differences of opinion arise.
- This problem may be compounded by having both expert and non-expert people on the team, as experts might not appreciate the opinions of those who may not be as technically familiar with the item under study.
- The size of the team should ideally represent a balance between the need to ensure that the team is adequately multi-disciplinary in composition, that it has the necessary expertise in relation to the item under study, and that it is not too large.
- Teams with no fewer than three people and no more than six people appear to work reasonably well.
- Note: the Team Leader may act as facilitator for the exercise, rather than being active in performing the exercise.

Guidance for Step 2 – The QRM Team

Are there any other issues to be considered for QRM Teams?

- Yes. Each team member should have direct or indirect ownership of the Quality Risk Management exercise.
  - This should be taken into account when the team is being selected

- The team members should be familiar with the cognitive factors which can affect decision-making in teams
  - See Appendix 3 for specific guidance in relation to human heuristics and how the adverse effects of such heuristics may be reduced during brainstorming and decision making

- Each team member must be willing to contribute constructively to the exercise at hand, and to comply with the rules of team brainstorming activities
  - See Appendix 1 for specific guidance in relation to team activities
Team Ground-Rules

- There are certain ground rules for all team-based activities in this Quality Risk Management methodology.
- The Team Leader should review these with the team at the start of Team meetings. These are listed in Appendix 1.
- Some of these are:
  - All suggestions which are made during the brainstorming session are welcome and important.
  - Listening to others points of view is vital.
  - The Majority does not rule – As Stamatis (2003) points out, sometimes a single individual may be on the right track, with everyone else being wrong. (Ref: "Failure Mode and Effect Analysis: FMEA from Theory to Execution", 2nd edition, D. H. Stamatis, ASQ Quality Press, 2003, pp 97.)

Team Ground-Rules cont'd

- Creativity and imagination are welcome and encouraged.
- Differences of opinion are welcome, but these should be expressed in a constructive way.
- Opinions should be considered as hypotheses, so that they can be tested instead of argued against (Ref: Mosvick and Nelson, 1987*).
- Compromise is sometimes needed.
- Negative statements such as those listed below are not helpful and should be avoided: These include:
  - "We have never done it that way."
  - "We are not ready for that yet."
  - "We are doing all right without it."
  - "That is not our responsibility."
  - "That would not work around here anyway."

Guidance for Step 2 – The QRM Team

Team Ground-Rules cont'd
- Everyone is free to build upon someone else's ideas
- There is to be no qualification of the idea or suggestion until after it has been documented
- All team members are expected to participate and contribute to the discussion, and no one will be allowed to dominate. The Team Leader has a central role in ensuring that this occurs.
- "Contribute, not defend" should be a goal for all participants
- The Team Leader may prompt and drive the discussion when needed

Guidance for Step 3 – P, S & D Levels

The Laminated Card – Some general points to note
- The card shows the various levels for Probability, Severity, and Detection which the tool uses. These levels may not be changed.
- The card gives default definitions for each of these levels. These are simple and basic definitions, and there are purposely non-quantitative. They are qualitative definitions.
  - For example, a Medium probability is defined as one where "the negative event may occur".
- However, these qualitative definitions can be changed, especially where there are reliable data available which support the use of quantitative definitions. See next slide, and also, follow the instructions in Step 3 of the Tool Worksheet if you want to change the default qualitative definitions given on the laminated card.
- The laminated card also shows the Risk Table, and the associated risk acceptability criteria.
Guidance for Step 3 – P, S & D Levels

Modifying the S, P & S Definitions on the Laminated Card

- As noted on the previous slide, the definitions for P, S & D are qualitative, but they may be modified to suit the case at hand, allowing for quantitative definitions to be drawn up.
  - e.g. The definition for a high probability could be modified to mean that the negative event occurs in more than 50% of the time, or in more than 90% of the time, or most of the time, or every day, etc.
  - However, it is difficult to put numbers on P, S & D levels, and what works for one negative event may not for another, even within the same risk management exercise.
  - It is useful to use Process Capability Cpk values as ranges for quantitative probability ratings
    - see next slide for guidance values

Guidance for Step 3 – P, S & D Levels

Modifying the S, P & S Definitions on the Laminated Card

- Examples of Process Capability Cpk values that can be used as ranges for quantitative probability ratings
  - Remote Probability may be represented by a Cpk greater than or equal to 1.67
  - Low Probability may be represented by a Cpk between 1.33 and 1.66
  - Medium Probability may be represented by a Cpk between 1.01 and 1.32
  - High Probability may be represented by a Cpk less than or equal to 1.00
    - these are just guidance values

- Note also that when modifying the Severity level definitions, it is important to consider who the stakeholders for the item under study are. (See next slide.)
Guidance for Step 3 – Stakeholders

What is a Stakeholder?

- This is “any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk.” (Ref. ICH Q9)
- In the GMP area, the main stakeholders will usually be:
  - Patients, users of medicines, and animals (for Veterinary medicines) – these comprise the main stakeholder group for the purposes of this Quality Risk Management methodology, and all risks assessed via this methodology should ultimately link back to their protection
  - Healthcare Professionals of various types
  - Wider Society (this is more relevant for some medicines, such as vaccines, than for others, such as analgesics.)
  - The Company itself – this is because the company can be affected by GMP risks which are not adequately addressed.
  - Wider Industry
  - GMP Regulators

Guidance for Step 3 – Stakeholders

What is a Stakeholder cont’d?

- There may be other stakeholders too, e.g. supplier and customer companies, and these may need to be considered if new Severity Levels are being defined.
- The tool assumes that the above make up the main stakeholders of any GMP item under study:
What is a potential Negative Event?
• A Negative event is defined broadly as “something that can go wrong”.
• “What can go wrong” is a phrase borrowed from ICH Q9, and it has been found to be useful and easier to understand than the other terms such as “Failure Modes”.

Why do we select just three potential Negative Events?
• This is a formal QRM tool. It is designed to apply QRM to only the most critical and/or complex issues or problems. It is not intended to be used to address more minor issues which can be addressed by other, less formal, means.
• ICH Q9 (10/2004) states:
  • “The degree of rigor and formality... can be commensurate with the complexity with the complexity and/or criticality of the issue to be addressed”.
  • “It is not always appropriate nor necessary to use a formal QRM process.”
  • “The level of effort, formality & documentation of the quality QRM process should be commensurate with the level of risk...”

Guidance for Step 4 – Potential Negative Events...

Why do we select just three potential Negative Events... cont’ed?
• This is a formal and rigorous methodology, involving a detailed Quality Risk Management process with ten discrete steps, and a tool worksheet which requires completion as the exercise progresses.
• This means that documentation, effort and training are required in order for this tool to be used effectively.
  • As a result, this tool has been specifically designed to evaluate only a small number of potential negative events – those considered to be the most critical and/or most complex.
  • While this is a key strength behind this approach, it also limits the application of this tool to a degree.
  • If a large number negative events are to be studied, a less-detailed cause and effect approach, a HACCP or an FMEA-based approach may be more appropriate.
**Guidance for Step 4 – Potential Negative Events**

**Some General Considerations when Identifying Potential Negative Events**

- Quality Risk Management is not an exact science, and identifying potential negative events is a subjective task to a degree, especially when expert judgement and informed opinions are used.
  - There may be uncertainty associated with whether some suggested potential negative events could actually occur.
  - Each of the suggested potential negative events identified at Step 4 should be discussed and evaluated for their potential severity and probability of occurrence during Step 4, taking into account strength of evidence considerations. This should be documented, preferably on a flip chart.
  - Those potential negative events considered by the team to have the most important and serious consequences, or those that appear to be the most complex in terms of how they might occur, should be selected for forward processing through the tool, taking into account the likely probability of occurrence of the potential negative event. If it is agreed that a potential negative event has only a remote probability of occurring, it should not normally be selected for onward processing through the tool unless there is good reason for doing so.

**Guidance for Step 4 – Potential Negative Events**

**What about the 'left-over' Potential Negative Events at step 4**

- There may be some potential negative events left over at Step 4 that were not selected for onward processing through the remaining steps of the Quality Risk Management process.
  - These should be documented during step 4 of the process, with notes made in relation to why each was not selected for further assessment.
  - The notes made in relation to these potential negative events should be kept, and they should formally be reviewed during the Periodic Review activities, at Step 10 of the process.
  - The intention here is that the team performing the Periodic Review exercise should formally review these potential negative events, in light of new experience, to determine whether any of these potential negative events should now be selected for onward processing through the remaining steps of the Quality Risk Management process.
**Guidance for Step 4 – Potential Negative Events**

**Some General Considerations when Identifying Potential Negative Events**

- It is important to recognise that the item under study will likely have several stakeholder groups associated with it.
- Each stakeholder may have different concerns in relation to the item under study, and so they might perceive different consequences for the same negative event.
- These factors can influence what we decide are the potential negative events, and the team should bear the likely concerns of the various stakeholders in mind when at Step 4.
- Identifying potential negative events is thus a subjective task to a degree.

  - In all cases, protection of the patient/animal should be considered of prime importance, and this principle, (protection of the patient/animal), is a useful guide when we are working to identify potential negative events for onward study in the Quality Risk Management exercise.

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**Guidance for Step 4 – Potential Negative Events**

- Think “what might go wrong”, but not in isolation...
  - use process maps or flow diagrams to visually review the item under study – especially useful if the maps show human intervention

- Take into account the concerns of stakeholder groups when thinking about “what might go wrong”
  - e.g. if a change control is proposed to roll out a new labelling range and livery for one of our products, practicing pharmacists can often easily tell us about risks of dispensing or usage errors introduced by the change, even if the new labelling is fully compliant.

- Don’t discount the power of ‘imagination’ – see the 9/11 Commission Report for a good discussion in this regard
Guidance for Step 4 – Potential Negative Events

Some useful aides for identifying Potential Negative Events:

- Assemble and review background information & data. Review historical data to see what has been known to go wrong in the past. These data could include near-miss incident data, deviations data, complaints files, batch rejects, change controls in response to problems which arose, etc.

- Have a process map or flowchart for the item under study. This allows us to look over the process or item under study and identify where the critical and most complex activities may be.

- Fault Tree Analysis and Cause & Effect diagrams may be used to identify both the potential negative event and its likely causes which may be associated with an undesirable end state.
  - See Appendix 6 for a detailed case study in which Fault Tree Analysis was used in this regard

Guidance for Step 4 – Potential Negative Events

Some useful aides for identifying Potential Negative Events:

- It is useful to formally consider the following areas when identifying potential negative events
  - Equipment
  - People
  - Methods
  - Environment
  - Materials
  - Measurements
- This is because production processes typically involve all five components
- Fishbone (Ishikawa) analysis is useful here
  - This is a simple but structured technique which facilitates this work
Guidance for Step 4 – Potential Negative Events

Some useful aids for identifying Potential Negative Events:

- Encourage the use of informed opinions and expert judgement when thinking of “what might go wrong”.
  - For example, seek the opinions of those employees or stakeholders who are knowledgeable about the item under study.
  - An operator may know very well what can go wrong with a process or activity, and he or she can advise as to its frequency.
  - Scientific knowledge should always be used when identifying potential negative events.
  - Performing a theoretical analysis or a simulation exercise can also help identify “what might go wrong”.
  - Take into account the concerns of stakeholder groups when thinking “what might go wrong”.

Guidance for Steps 4 & 5 – Potential Negative Events and their Probabilities

- **Near-miss Incidents** - During brainstorming at Step 4 of the Quality Risk Management process, the Team Leader should encourage the team to think about near-miss incidents which may have occurred in relation to the item under study.

  Near-miss incidents can provide valuable and real information on potential negative events and their frequencies, but they are often not formally documented.

  To facilitate the use of near-miss data, it is necessary to formally encourage a culture of reporting near misses within the organisation, and to integrate such reporting as a formal element of the Quality System, similar perhaps to how deviations are reported. The Team Leader should be active in this regard.

  If near-miss information is available, it should formally be considered by the Team as a potential source of potential negative event and probability of occurrence information during Steps 4 & 5 of the Quality Risk Management process.
Some useful sides for identifying Potential Negative Events:

- Use brainstorming techniques
  - This can be an effective method to think of "what might go wrong", and it also encourages lateral thinking.
  - Brainstorming can be used for more than identifying potential negative events
- It can also be used to:
  - Identify the causes of potential negative events (Step 5)
  - Identify the controls which are in place (Steps 5 & 6)
  - Classify those controls as S, P or D controls (Steps 5, 6 & 7)
  - Evaluate each control before assigning the S, P or D ratings (Steps 5, 6 & 7)
  - Identify new or improved controls which may be required (Step 7)

Guidance for Step 4 – Potential Negative Events

- Brainstorming sessions however need to be organised in a manner which delivers the best from everyone involved and where guesswork is reduced to a minimum.
- See Appendix 1 for detailed guidance on brainstorming.
- See also the earlier slides in this presentation in relation to brainstorming.
Guidance for Step 4 – Potential Negative Events

Guidance for writing the actual Potential Negative Events in Step 4

* How we write what is the potential negative event in Step 4 of the Quality Risk Management process is important

* During brainstorming at Step 4, the team should formally review the potential effects of each proposed potential negative event at the time the potential negative event is proposed, to ensure that the potential negative events which are documented are not essentially the same as their effects.

  * Reason: A common problem that has been observed during this research using practical Quality Risk Management exercises (and also in GMP inspections) is that, during brainstorming sessions, there can sometimes be confusion between potential negative events and their effects.

  * This can have a significant and unexpected negative impact on the outcome of the Quality Risk Management exercise.

Guidance for Step 4 – Potential Negative Events

Writing the actual Potential Negative Events in Step 4 Cont’d

* Confusion between potential negative events, their causes and their effects can occur because a potential effect identified in one indenture level of the system under study may become a potential negative event at a higher indenture level. Also, potential negative events identified at one indenture level may become causes at a higher indenture level.

* To overcome the above, it has been found useful if the following questions are put to the Quality Risk Management team during brainstorming or other activities when potential negative events are being identified:

  * What can go wrong?

  * What are the effects or consequences of this going wrong?

  * Is the potential negative event, as proposed, the same as its effects? If the latter is the case, work to determine the true failure mode relating to these effects.

* These simple questions force the Quality Risk Management team to differentiate between potential negative events and the effects of such.

* Fault Tree Analysis is also useful in this regard. See Appendix 6 for a practical Case Study in relation to the above.
**Guidance for Step 4 – Potential Negative Events**

**Guidance for writing the actual Potential Negative Events in Step 4**

- How we write what is the negative event in Step 4 is important.
- A potential Negative Event should not be so broad in scope as to be unworkable. This can happen when the potential Negative Event is one with a very large number of causes.
  - For example, a potential negative event such as “OOS Batches” is too broad, because such a negative event could have hundreds of causes. This is not a practical use of the QRM tool.
  - Instead, potential Negative Events should be high level but specific and narrow enough in scope, so as to allow for a workable use of the tool.
  - “Batches OOS for Moisture” is an example of a more specific and workable potential Negative Event in a Risk Management exercise for an API manufacturing process.

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**Guidance for Step 4 – Potential Negative Events**

**Guidance for writing the actual Potential Negative Events in Step 4 Cont’d**

- As a guide, there should be no more than 5 causes identified for any potential Negative Event.
- If more than 5 causes are identified, the potential Negative Event is too broad, and it needs to be broken down into more specific potential Negative Events.

What can be done to ensure that potential negative events are not documented which are too broad and have too many potential causes?

- During brainstorming at Step 4, the team should briefly review the potential causes of each proposed potential negative event in order to determine the likely number of possible causes which are associated with this potential negative event.
- If more than 5 causes are identified, the potential Negative Event is too broad, and it needs to be broken down into more specific potential Negative Events.
- This will help ensure that all potential Negative Events which are formally processed through the remaining steps of the tool are at a level that is workable and manageable.
Guidance for Step 4 – Potential Negative Events

Given that there may be many levels within the item under study at which potential Negative Events may be identified, how is the correct level identified?

- There is no one correct indenture level within the item under study at which potential Negative Events may be identified.
- This is simply because, in complex systems, failure modes identified in one indenture level may be considered to be failure mode causes at a higher level.
- This can make it difficult to determine at which level to identify potential negative events. The following provides guidance in this area:
  - During brainstorming activities at Step 4 (and at Step 5), the team should ensure that any potential negative events documented during such sessions for the item or system under study are at an indenture level in the item or system that can provide causative events that lead to appropriate risk mitigation and control.
  - When potential negative events are documented at too high an indenture level, research has shown that this can limit the extent to which causative factors and their mitigating controls may be identified.
  - Thus, documenting the potential negative event at too high a level can adversely impact the outcome of the Quality Risk Management exercise.

Guidance for Step 4 – Potential Negative Events

Cont’d from previous slide

- When potential Failure Modes are documented at a lower indenture level in the item under study, research has shown that more meaningful causative factors may be identified, allowing for risk mitigating controls to be identified which are less reliant upon detection and more reliant upon prevention.

- See Appendix 6 for a practical case study in relation to the above points.
Guidance for Steps 5, 6 & 7

How should controls be labelled/numbered on the worksheets?
- When documenting a Control on a worksheet, it should be given a Letter, in the format A, B, C, ... .
- All controls on a worksheet should be labelled consecutively in this way
- When you start a new Worksheet, start off with Letter A again for the first control being documented on that Worksheet, and continue as above
- This helps to identify the control when we go to complete the Qualification & Validation worksheets in Step 8

Guidance for Step 5 ~ Risk Evaluation

Identifying the effects of a potential Negative Event
- It is important to think both locally and globally in this area
- Local effects include the effects the potential negative event may have for the patient or animal (being administered the medicinal product), on the healthcare professional involved in the use or administration of the product, and also on the item under study itself (e.g. the service, process, etc. of concern), and on the product generally
- More Global effects include the effects of the potential negative event on the wider population group using the product or service concerned, as well as on the company responsible for the product, (including its reputation and compliance status)

Rating the Severity of the effects of a potential Negative Event
- ICH states that “the evaluation of risk should ultimately link back to the protection of the patient.”
  - Therefore, we must always think of the potential patient (or animal) impact when assigning a Severity rating.
  - Severity ratings should reflect the worst effect of the potential negative effect, if there is more than one effect, but the mitigating controls in place for those effects should be taken into account too.
Guidance for Step 5 – Risk Evaluation

What kind of controls are “back-up” or “redundancy” controls?

- These are controls which can reduce or eliminate the Severity of the effects of the negative event, should that negative event occur.
- They do not prevent the negative event, but they can sometimes have an element of detection. They could also be viewed as “contingency” controls.
- The value of implementing such controls should always be considered, even when the risk is considered to be acceptable using the Risk Table provided with this methodology.
  - This is especially important for cases where the Severity rating is Critical and the Probability of Occurrence rating is Remote, resulting in a risk that it deemed Acceptable using the Risk Table.
  - Before deciding that such a risk is acceptable, the team should determine whether there are any controls that can be implemented which may serve to reduce the severity of the effects of the Potential Negative Event, even when the Critical rating will remain unchanged.

Guidance for Step 5 – Risk Evaluation

Examples of “back-up” or “redundancy” controls

- A simple example of a “back-up” or “redundancy” control is an in-process pH test on a reaction solution, following the addition of an acid to a vessel.
  - If not enough acid is added, there could be negative consequences for the quality of the batch.
  - To counteract this, a pH in-process test could be in place.
  - If for some reason, not enough acid was added to the batch, this pH control reduces the negative consequences, because it allows us to correct the negative event (by adding more acid) before we proceed with processing the batch.

Could “back-up” or “redundancy” controls also be called ‘Severity Controls’?

- Yes.
Guidance for Step 5 – Risk Evaluation

Other simple examples of "back-up" or "redundancy" controls:

- In the home, we might view a chip-pan fire as a negative event.
- There are various "back-up" or "redundancy" controls which could be in place for such a negative event:
  - Fire blanket
  - Fire extinguisher
  - We might ensure all doors are closed before going to bed at night
- These controls all relate to the Severity of the negative event, for they ensure that if the negative event does occur (i.e. the chip pan does go on fire), its effects are either reduced or eliminated.

- A spare pair of reading glasses is also a "back-up" or "redundancy" control.

Guidance for Step 5 – Risk Evaluation

Other simple examples of "back-up" or "redundancy" controls cont’d:

- The above controls do not relate to Probability, as they do not prevent the chip pan fire, and they are not Detection controls, as they do not detect the chip pan fire.
  - Getting rid of the chip pan as a cautionary measure would be a Probability control, because, of course, it serves to prevent a chip pan fire in the first place.
  - Or, we might ensure that all electrical appliances are unplugged before going to bed at night. This would be a Probability control, because it serves to prevent a chip pan fire in the first place.
  - Installing a smoke alarm would be a Detection D control, because it serves to detect the smoke and/or heat from a chip pan fire.
Guidance for Step 5 – Risk Evaluation

Other simple examples of “back-up” or “redundancy” controls:

- Consider toll motorways. Some toll motorways charge drivers for the actual distance travelled.

- For example, when using the New Jersey Turnpike in the USA, drivers collect a ticket from a machine when they first enter a toll booth on the motorway, and then, when exiting the motorway some miles later via another toll booth, they hand the ticket to a clerk, who inspects the ticket and requests the appropriate payment from the driver on the basis of the distance travelled.

- A potential negative event here might be that the ticket dispenser machine fails in some way.
  - This can result in long delays at the toll booths, slowing down traffic through the toll booths.

Guidance for Step 5 – Risk Evaluation

Other simple examples of “back-up” or “redundancy” controls cont’d:

- To address the risk of long traffic delays at the toll booths caused by failing ticket dispensers, most of the NJ Turnpike entry toll booths have two ticket dispensers for each lane, and these machines are right next to each other.
  - This is so that, when one ticket dispenser machine fails or runs out of tickets, the second dispenser is configured to issue the ticket to the driver.
  - The second ticket dispenser machine is an example of a “back-up” or “redundancy” control – it serves to eliminate the effects (delays at the entry toll booth) of the negative event.

- It does not prevent the the negative event, so it is not a Probability control

- It does not detect that the first machine failed – this job is done by the software running the first dispenser – so it is not a Detection control.
Guidance for Step 5 – Risk Evaluation

What to do if problems occur when assigning the S rating to the effects of a potential negative event:

- Sometimes there may be uncertainty about the severity of the effects of a negative event
  - For example, during brainstorming sessions, we may argue over whether the effects are Minor or Moderate
  - Also, it can be unclear as to how any current controls in place reduce the severity of the negative event in question.
  - If this occurs, the team should formally review and discuss the proposed effects of the negative event again and the Severity-related current controls (if any are in place), and then try to choose the most appropriate Severity Level.
  - If there is still disagreement on which Severity Level should be assigned, the formal approach as presented in Appendix 2 should be used.

- Alternatively, and for less serious cases, the less formal approach presented on the next slide may be used.

Guidance for Step 5 – Risk Evaluation

Alternative Approach.... if problems occur when assigning the S rating to the effects of a potential negative event:

- The Team may simply chose to agree on two adjacent Severity levels which most closely fit the effects of the negative event.
  - Then, the most conservative of the two levels should be assigned to the negative event.
  - For example: If this approach is used, the team might chose Moderate and Minor as the two severity levels which most closely fit the effects of the negative event, and, the Moderate Severity Level would be assigned to the negative event.
  - When this approach is used, this should be documented, because when the QRM exercise undergoes its periodic review at a later date (as discussed in Step 10), the Severity rating which was assigned can be revisited at that time as there may be more data available then.
Guidance for Step 5 – Risk Evaluation

Identifying the causes of Potential Negative Events:

- The relation between a Potential Negative Event and its causes is not usually a linear one
  - Thus there may be several or many causes for the one Potential Negative Event
  - This methodology requires the risk associated with each cause to be assessed and controlled
  - The level at which the Potential Negative Event is identified in the item under Study is important with respect to the number of causes it may have
    - See Appendix 6 & 7 for useful guidance in this regard
    - See also the earlier slides in this presentation for Step 4

Guidance for Step 5 – Risk Evaluation

Identifying the causes of Potential Negative Events:

- As mentioned earlier, production processes typically involve five main components
  - equipment, people, methods, environment, materials and measurements

- Thus, when the likely causes of potential negative events are being identified, it is useful to consider each of these areas in turn
  - Fishbone (Ishikawa) analysis facilitates such work
Guidance for Step 5 – Risk Evaluation

Beware of 'human error' causes for a potential negative event?

• When human error is suggested as the potential cause of the Potential Negative Event, exercise caution.
• Human error tends to be over-used when performing Quality Risk management exercises. It offers a quick answer, but it can be problematic!
  • It usually only addresses the symptoms, not the root cause
  • It blames someone, and this may or may not be the right person
• Before human error is assigned as a cause, the following should be answered yes:
  • Do the personnel performing the task know what is expected of them?
  • Do they know whether or not they are accomplishing what is expected of them?
  • Do they have a means of regulating their process?
• See Appendix 7 for more complete guidance on dealing with human error issues
  • This Appendix is partly based on the text “Failure Mode and Effect Analysis: FMEA from Theory to Execution”, 2nd edition, by D. H. Stamatis. 2003

Guidance for Step 5 – Risk Evaluation

There are many different types of causes which are useful to consider

• It is helpful to think about these when identifying the most likely cause(s)
• These include:
  • Poor design leading to hardware, software, process, product, service failure
  • Missing or Inadequate procedures in place
    • Procedures not easy to follow or understand
    • Steps in the wrong order
  • Wrong part, tool, material, component selected for an operation
  • Use of an unqualified supplier, item of equipment, material
  • Equipment operated outside its qualified operating range
  • Use of a non-validated process, procedure, method
  • Controls by-passed
  • Poor Preventative maintenance
  • Human error – e.g. display information misread by an operator
Guidance for Step 5 – Risk Evaluation

Types of causes cont’d

- Poor design leading to hardware, software, process, product, service failure
- Missing or Inadequate procedures in place
  - Procedures not easy to follow or understand
  - Steps in the wrong order
- Wrong part, tool, material, component selected for an operation
- Use of an unqualified supplier, item of equipment, material
- Equipment operated outside its qualified operating range
- Use of a non-validated process, procedure, method
- Controls by-passed
- Poor Preventive maintenance
- Human error – e.g. display information misread by an operator

Guidance for Step 5 – Risk Evaluation

Assigning Probability of Occurrence (P) Ratings:

- A P rating is assigned to each cause of a negative event.
- We can use the following to help us assign a probability rating:
  - Historical data, such as near-miss incident reports, complaints, quality defects, deviations, OOS batches, inspection and self-inspection deficiencies, change controls which were implemented as a result of a problem
  - Statistical tools, such as Control Charts and Process Capability analyses
  - Expert judgement and informed opinion
  - Listening to the opinions of those employees or stakeholders who are knowledgeable about the negative event can be very useful, because these people will probably have an informed opinion about the probability of occurrence
  - See Appendix 3 for important information on using opinions and judgement in this regard

- IMPORTANT: If reliable data are available on the probability of occurrence of a cause of a potential negative event, these data should be used over any estimated probability ratings derived from on expert judgement
**Guidance for Step 5 – Risk Evaluation**

What to do if problems arise when assigning the P rating to the cause of a potential negative event:

- Sometimes it can be difficult to decide on the Probability of Occurrence of a particular cause of a negative event, and there can be differences of opinion in this regard
  - this is because we may not have any quantitative data to go on...
  - or we just do not have enough data of any kind to go on
- Some QRM tools require that the highest Probability of Occurrence available to be chosen in these cases.
  - This is not scientifically sound, and it can lead to an overestimation of the Risk, which can then influence where we spend our available validation resources and effort.
- When we are uncertain about which P rating to assign, in the interests of caution, the formal approach as presented in Appendix 2 should be used.

- Alternatively, and for less serious cases, the less formal approach presented on the next slide may be used.

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**Guidance for Step 5 – Risk Evaluation**

Alternative Approach.... if problems occur when assigning the P rating to the cause of a potential negative event:

- The Team should agree on two adjacent Probability levels which are closest to the likely probability of concern
- Then, the highest of the two Probability levels should be selected
  - So, if the team chose Medium and Low as the two possible Probability levels which appear most appropriate, then the Medium Probability Level should be chosen.
- When this approach is used, this should be documented, because when the QRM exercise undergoes its periodic review at a later date (as discussed in Step 9), the Probability of Occurrence rating what was assigned can be revisited at that time as there may be more data available then.
Guidance for Step 6 – Detection

What is Step 6 about?
• Here, Detection controls are identified and critically evaluated for how they might control the risk from Step 5
• The team must decide (with justification) if the unacceptable or intolerable risk from Step 5 can be adequately controlled with the detection controls in Step 6
• This is called the Risk Decision Point:
  • It happens after the detection controls have been documented and rated
  • This involves deciding whether these controls give assurance that the risk is adequately controlled & no further controls are required

Guidance for Step 6 – Detection

Are Detection controls used to estimate the risk?
• No. Detection controls are not used to estimate the risk
• Risk is estimated on the basis of Risk = P x S

• Note however that sometimes a detection-type control serves to prevent the negative event from occurring, or it may reduce the severity of the effects of the negative event
  • If this is the case, the control may be regarded as either a Preventative control or a Severity-related control, and it would then be considered at Step 5 and used to estimate the risk
• True Detection controls are considered in Step 6, after the Risk has been estimated in Step 5, and before Risk Control activities, at Step 7
  - Key difference between this tool and FMEA / FMECA
  - See the July 2006 Issue of the Journal of GXP Compliance for more details on this aspect of this RM Tool
Guidance for Step 6 – Detection

In Step 6, a high detection rating does not automatically allow one to conclude that the risk is adequately controlled or is of a low priority

- Step 6 requires users to formally decide (with justification) if the risk is adequately controlled, by considering whether the detection controls give assurance that the risk is adequately controlled & that no further controls are required

- This recognises that the improper use of detection controls can cause problems during Quality Risk Management activities for GMP environments

  - Consider missing PILs in packs versus OOS impurities in a dried lot of an API
  - Detection controls may be high in each case, but...

Guidance for Step 6 – Detection

Step 6 does not allow users to assume that a high detectability addresses the risk in question

- This is in line with the GMP QA principles of building in quality by design, rather than relying on QC end stage testing

- This is why the tool has the key decision point at Step 6
  - Key difference between this tool and GAMP 4, FMEA, FMECA

See July 2006 Issue of the Journal of GXP Compliance for more details on this aspect of this RM Tool
Guidance for Step 7 – Risk Control

Useful Questions to ask during Risk Control activities to help identify controls

- Can the potential negative event or its causes be eliminated, e.g. by re-designing the process or item under study, perhaps by replacing a component in the process with a component which may not give rise the potential negative event? (Note that it will be important here that any risk presented by the new component will be assessed and managed.)

- Can we isolate that part of the item under study which may give rise to the potential negative event or its causes, so that the impact of the effects of the hazard may be reduced and contained?

- Can we put effective procedures and checking activities in place to ensure that unwanted steps and actions are avoided?

Guidance for Step 7 – Risk Control

Useful Questions to ask during Risk Control activities to help identify controls

- Can we improve training for operators and other staff to ensure compliance with procedures and policies?

- Can we design in Redundancy / Contingency controls so that, if the potential negative event occurs, there are control systems in place which reduce or counteract the effects of the potential negative event?
Guidance for Step 7 – Risk Control

Useful Questions to ask during Risk Control activities to help identify controls

- Are there any fool-proof controls we can install, which cannot be by-passed via human error or the by accidental or deliberate non-compliance with procedures? (An example of such a control would be a requirement for an operator to confirm the volume of a solvent to be added to a vessel, by re-entering the volume required into a computer system controlling the transfer of the solvent.)

- Is there warning information that can be provided to relevant people about the potential negative event, its causes or potential effects? (An example here would be a warning on the label of an injectable medicinal product to not use the product if particulates are observed in the solution.)

- Can we build in new or improved detection mechanisms, so that if the potential negative event occurs, it, or its effects, may be detected in an appropriate timeframe?

Guidance for Step 7 – Risk Control

Useful Questions to ask during Risk Control activities to help identify controls

- Where detection controls are important in controlling a risk, can we improve the training for operators so that they will more likely detect the potential negative event or its effects?

- For equipment-related potential negative events, can Preventative Maintenance activities be improved so that the probability of occurrence of the potential negative event may be reduced?
Guidance for Step 7 – Risk Control

Useful Questions to ask during Risk Control activities to help identify controls

- Sometimes, controls may be available that are effectively outside of the GMP remit, but which serve to control or mitigate risk. It is useful to ask if there are any such controls available when working to identify control options during Step 7.
- Consider a particulate contamination problem in a parenteral solution for infusion. This is a solution packaged in clear infusion bags.
- It is often common practice for healthcare professionals to inspect such products for particulates, cloudiness and aggregation prior to administration of the solution to a patient or animal. Clinics and hospitals often require this as good clinical practice, and document it in internal medication policies/guidelines. This is an example of a control that is not governed by GMP, but which is applicable to mitigating a risk caused by a GMP failure.
- Therefore, it can be useful to think outside of the GMP environment for controls that may be in place and which address a GMP-related risk. (This also applies during Steps 5 & 6 of the Quality Risk management process, when considering what controls may be in place already.)

Guidance for Step 7 – Risk Control

How Much Risk Control is Required?

- It can be tempting during Step 7 to go overboard on devising extensive new controls for every risk identified. But the tool does not require this.
  - See "Failure Mode and Effect analysis: FMEA from Theory to Execution, 2nd edition" by D. H. Stamatis, 2003, for a useful discussion in this regard.
- Step 7 of the tool only requires that unacceptable & intolerable risks are reduced to an acceptable level (by lowering the S and/or P ratings), or that they are controlled to an acceptable degree, via detection-based controls.
- Note: ICH Q9 states: "The level of effort, formality and documentation should be commensurate with the level of risk, and be based on scientific knowledge". This tool applies this principle of ICH Q9 by not insisting that controls are put in place beyond achieving the above.
- The Team Leader should be active in ensuring that any controls which are proposed during Step 7 are actually necessary to reduce or control the risk in question.
Guidance for Step 7 – Risk Control

Can the tool take account of PAT (Process analytical Technology) Controls?

- Yes. Step 7 is an ideal place for exploring whether PAT initiatives could be used to reduce a risk or control a risk to an acceptable level.
- Also, Step 7 is where such initiatives can be evaluated and justified.
- Therefore, during Step 7, and when appropriate, the team should ask itself: "Is there a PAT-type control which might be useful here?"

Guidance for Step 7 – Risk Control

Could a new or improved control documented in Step 7 introduce a new risk?

- Yes. Sometimes a control from Step 7 can introduce a new risk.
  - For example, a new control in a manufacturing process could involve adding a piece of monitoring equipment to a mixing vessel. This new item of equipment, if intended to be a product contact part, could present a risk to the product, depending on its design, composition, location, etc.
  - Another example involved a change in the livery of the packaging of an injectable medicinal product in Ireland during 2005/2006. This change resulted in colour changes on the packaging.
    - Shortly after the change was introduced, both the company and the IMB received reports of serious near-miss dispensing accidents with the product at one Irish hospital.
    - Patients were almost administered twice the prescribed dose before the error was noted. A lack of adequate differentiation between the strengths of the product was considered to be a contributing factor.
Guidance for Step 7 – Risk Control

Cont’d from previous slide

- Therefore, at the end of Step 7, each new or improved control or action which is recommended for implementation should be evaluated for its potential to introduce a new risk.
- This should be done by the QRM Leader prompting a discussion during Step 7 to evaluate each new or improved control from this viewpoint.
- If it is likely that a new risk could be introduced, then the team should identify the potential negative event associated with such a risk, and route this potential negative event through the QRM exercise, by entering it into Step 4 of the exercise.

Guidance for Step 7 – Risk Control

When considering what Risk Controls are required, consideration should be given to reducing system complexity and coupling in the item under study

- This is useful, especially after other reasonable risk control measures may have failed to reduce or control the risk to an acceptable level.
- This is actually a form of Risk Control in itself

Why is this useful?

- Normal Accident Theory suggests that, with complex and tightly coupled systems, accidents cannot simply be prevented through good organisational design and management.
- Here, accidents with such systems are simply inevitable.
  - But what is meant by systems that are complex and tightly coupled?
Guidance for Step 7 – Risk Control

What is meant by the terms ‘complex’ and ‘tightly coupled’?

Complex systems can be regarded as systems with:
- Design features such as branching and feedback loops
- Unfamiliar, unplanned or unexpected sequences which are not visible or not immediately comprehensible
- Opportunities for failures to jump across subsystem boundaries.

Tightly coupled systems can be regarded as having
- Time dependent processes that cannot wait;
- Rigidly ordered processes (as in Sequence A must follow B);
- Only one path has a successful outcome
- Very little slack in the system, as the system requires precise quantities of specific resources for successful operations.

Guidance for Step 7 – Risk Control

What to do if problems occur when assigning the S rating to the effects of a potential negative event during step 7:
- See the guidance on this question for Step 5

What to do if problems occur when assigning the P rating to the cause of a potential negative event during step 7:
- See the guidance on this question for Step 5
Guidance for Step 8 – Q & V

What is Step 8 for?

- Step 8 is mainly used to identify Qualification & Validation activities.
  - Each control from Steps 5, 6 & 7 is entered into a Step 8 worksheet and is evaluated to see whether it needs a Qualification & Validation exercise, and what its Qualification & Validation status is.
  - Step 8 is thus very powerful in this regard.

- Step 8 is also used to identify what items must be put in place to implement any new or improved controls identified in Step 7.
  - These items could be documentation, equipment, training, systems, etc.
  - It is also useful to consider how the control in question may be monitored; it statistical control can be established, it is recommended that process capability studies be performed on the control. The results of these studies should be documented in Step 8, and reviewed during Periodic Review activities, at Step 10.

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Guidance for Step 8 – Q & V

What is the difference between Part A & Part B in Step 8?

- Part A is about acceptance criteria and required outcomes for a control.
- Part B concerns Critical Process Parameters (CPPs) associated with a control.
  - A CPP can be defined as an attribute of a control step or control point in a process which is considered critical and which is measurable or verifiable.

- The reason we have both of these in the tool is that some controls do not have any CPPs associated with them, while others do.
  - Having both parts (A & B) is to enable the tool to address this difficulty.
  - See next slide for an example in this regard.
**Guidance for Step 8 – Q & V**

The difference between Part A & Part B in Step 8, cont’d:

- For example, a new control may be to provide better training to operators on a specific activity.
  - We do not normally think of training as having a CPP associated with it, but training can have acceptance criteria or required outcomes!
  - The training activity should be completed and documented, and each trainee should pass the training assessment exercise. These could be considered the required outcomes for this control.
- On the other hand, a control such as an in-process pH test would have an associated CPP
  - The CPP here is the pH itself - because this is a measurable and verifiable parameter
  - The CPP has limits or acceptance criteria - these might be that the pH must be between 4.0 & 4.6 pH units

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**Guidance for Step 8 – Q & V**

The difference between Part A & Part B in Step 8, cont’d:

- See the following peer-reviewed published paper from the July 2006 issue of the Journal of GXP Compliance for a discussion in this regard:
Guidance for Step 9 – Action Items

**Action Items should be prioritised based on the associated Risk**

- By the end of Step 6, we had identified what risks were Intolerable, Unacceptable, and Acceptable.
- Step 7 allowed us to identify new or improved control measures that will either reduce the risks to an acceptable level, or that will adequately control the risks so that their effects are not realised.
- Step 8 allowed us to identify miscellaneous items which were needed for the various controls to be put in place, as well as all Qualification & Validation work activities required.
- In Step 9, we identify and document all action items which arise from the completed Qualification & Validation Worksheets at Step 8.
  - These could be actions to implement a control, or they could be a Qualification or Validation Exercise.
  - We also have an opportunity to prioritise these work activities, so that the highest risks are dealt with first.
  - We also assign responsibilities and target completion dates for each action item.

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Guidance for Step 10

**What is Risk Communication?**

- Risk communication is considered to be the exchange of information about risk and its management.
  - ICH Q9 defines Risk Communication as “the sharing of information about risk and risk management between the decision makers and others.”
  - The Canadian Standards Association, whose Risk Management Standard gives perhaps the highest level of attention to Risk Communication activities of any Risk Management standard reviewed, defines Risk Communication as “any two-way communication between stakeholders about the existences, nature, severity, or acceptability of risks.”
Guidance for Step 10

When should Risk Communications occur?

- ICH Q9 states that “parties can communicate at any stage of the risk management process” and that “the output/result of the quality risk management process should be appropriately communicated and documented”.
- Such communications might include those “among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.
- The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality.”

Guidance for Step 10

With this tool, do we have to wait until the end of the QRМ exercise to carry out the Risk Communication activities?

- No, and there are times when earlier communications about the QRМ exercise can be beneficial in addressing potential problems of risk mis-perception.

- Research shows that problems of mis-perception can be reduced when stakeholders have had an opportunity to participate in the Risk Management process or in the item under study at an earlier time-point.

- In GMP environments, this can be difficult to achieve in practice, because of the highly confidential and controlled nature of API and medicinal product manufacturing. But, there may be opportunities in this area.

- For example.....
Guidance for Step 10

Cent'd from previous slide...

- For example, a company may proactively invite GMP inspectors in to review and discuss early parts or results of a Quality Risk Management exercise which is underway.
  - This could be to review the potential negative events which were identified during Step 4 of the QRM exercise, and which will be studied in detail during subsequent steps of the process.
  - In this way, the Inspector is then not surprised when he/she reads of the negative events and their associated risks when reviewing during a GMP Inspection the final report on the Quality Risk Management exercise.

- Note: The IMB Inspectorate is open to such invitations, if Inspector resources are available for such work.

Guidance for Step 10

Why should we communicate risks?

- Risk communication also demonstrates to stakeholders that risks are being effectively managed.
- Risk communication is an exercise worth doing, because it helps promote a culture of risk awareness in the company. Risk communication is an exercise worth doing, because it can actually help to reduce risks.
  - Research (by Kaplan and Garrick 1981) has demonstrated that risk awareness is an important safeguard that may actually help to reduce risks. The following simple example demonstrates this: When people are made aware about “a hole in the road around the corner”, the risk presented by the hole in the road is reduced than when people do not know about it.
  - The idea that making people aware of a risk can help reduce that risk is a concept that directly relates to risk communication activities during Quality Risk Management, and any action that serves to help reduce risk should be considered.
Guidance for Step 10

What Risks should be communicated?

- ICH Q9 states that "Communication need not be carried out for each and every risk acceptance."
- The QRM Team should use their judgement and decide which risks or issues need communicating.
- Some or all of the risks identified may need to be communicated, or other specific issues may need communicating.
  - For all risks identified during the QRM exercise, the Quality Risk Management team should formally review each risk and decide whether it, or a related issue, needs to be communicated.
  - A good rule of thumb is that a risk needs to be communicated to those who either could be affected by that risk or to those who are important in mitigating or controlling that risk.

Guidance for Step 10

What should be covered in risk communications?

- When communicating about a particular risk, the following should be included:
  - The likely source(s) or cause(s) of the risk
  - The estimated magnitude of that risk
  - Any important uncertainties and assumptions associated with this estimation
  - The level of acceptability of the risk before and after Risk Control measures
  - The Risk Control measures adopted, or to be adopted
  - For risks still unacceptable or intolerable following Risk Control measures, information on how the risk will be controlled
  - The procedure in place governing risk acceptance decisions
- ICH Q9 states that "The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality."
Guidance for Step 10

What is important for the content of risk communications?

- The content of the Risk Communication should be balanced and open, and not manipulated by bias or ulterior motives.
- It is important also to truthfully report the findings of the QRM exercise, without manipulation of the results or data to suit the desired outcome.
- There will usually be uncertainty associated with the outcomes of the QRM exercise. Any significant sources of uncertainty and any pertinent assumptions relating to the QRM process and its outcomes should be openly communicated.
- Conflicting, and alternate points of view should be openly discussed during the Risk Communication, if applicable.
  - It is recognised that the “fair and balanced inclusion of other, conflicting, points of view” can “shape how recipients feel about the [Risk Management] process.” (Ref: Vesper, 2006)
- The QRM Team Leader should ensure that the above considerations are complied with.

Guidance for Step 10

With whom should we communicate risks?

- The QRM Team should identify the stakeholders associated with the Quality Risk Management exercise, and it should then determine those Stakeholders to whom risk communications should be made during the Quality Risk Management exercise.
  - This helps to determine the audiences for the risk communication activities, the actual content of the risk communications, and the technical level at which the pitch the risk communication message
Guidance for Step 10

With whom should we communicate risks?

- Certain stakeholders will be interested in the outcome of such Quality Risk Management exercises, for example, Senior Management and other staff at the company concerned, customers purchasing or using the API or medicinal product or process of concern, and Regulatory staff such as GMP Inspectors and Assessors.
- The groups to whom the risk communications may need to be made could include:
  - Employees within the company who should be aware of a risk which has been identified by the QRM exercise in their own work area
  - Company Management personnel, including technical, administrative and financial managers, where relevant.
  - Healthcare Professionals, when considered necessary
  - Patient / Patient Representative Organisations, when considered necessary
  - GMP Inspectors and other Regulators, when considered necessary
  - Suppliers and Customers, when considered necessary

Guidance for Step 10

Should patients be included in the risk communication activities associated with this tool?

- Not usually, unless there is a specific reason to carry out such communications with patients or their representative organisations. It depends on the exercise at hand.
  - If the QRM exercise was performed as a result of a complaint from a patient or patient organisation, or if the item under study in the QRM exercise was subject of adverse media coverage, it may be necessary to communicate the results of the QRM exercise with patients or their representative organisations.
  - However, this application of Quality Risk Management in GMP environments is specifically for Qualification, Validation and Change Control purposes, and so is usually technically detailed and concerned with the specifics of GMP.
  - While patients are of course clear stakeholders of any process which produces, controls or regulates medicinal products, the outcomes from such Quality Risk Management exercises may not be of direct interest to patients or their representative organisations.
Guidance for Step 10

How might Risk Communications occur between industry and regulatory authorities?

- There are no specific mechanisms required.
  - ICH Q9 states that “Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.”

- The most appropriate mechanism should be selected, and is should especially meet the needs of the organisation who performed the QRM exercise.

- The intended audience should of course be considered, in terms of:
  - What information will they likely need to receive
  - How technically competent might they be in the area of concern, and in the QRM process used

Guidance for Step 10

Who should carry out the communication activities?

- This could be the QRM Team leader or another person familiar with the QRM exercise.

- The QRM Team Leader should ensure that the person or persons designated to communicate the outcomes of the Quality Risk Management exercise are credible, trustworthy, honest, and have the necessary level of expertise to field questions and to explain the Quality Risk Management process and its outcomes.
Guidance for Step 10

Should only “experts” carry out the Risk Communication activities?

- It is tempting to only appoint persons who are considered ‘experts’ in the item studied in the Quality Risk Management exercise to be the risk communicators.
- This may not always be beneficial however, and others may be better communicators for the audience at hand. Why?
  - Experts sometimes use terminology that is technically correct but which may overwhelm the lay stakeholder.
  - Even in GMP applications when the audience for the Risk Communication may comprise of technical people such as GMP inspectors, it is important to recognise that the people in the audience may not have the same degree of technical knowledge in the technology underpinning the item under study as the risk communicator.

Guidance for Step 10

Before communicating risks and the outcomes of QRM exercises

- It is important to determine the needs of the particular audience with respect to the Quality Risk Management exercise, and the level of information they may already have on the item under study.
  - This allows the Risk Communication message to be tailored accordingly.
  - GMP inspectors will likely be technically verse in the item under study, and many be highly interested in how the risks were arrived at, in the risk mitigation measures proposed, and in how compliance with the applicable GMPs is achieved.
  - Senior Management, on the other hand, while also concerned with those same things, may be less technically familiar with the details of the item under study, and will likely be highly interested in the cost implications of the recommendation arising from the Quality Risk Management exercise.
  - In this regard, it is beneficial for the audience if the QRM team presents an overview of the item under study and the technology supporting the item under study before presenting the results of the Quality Risk Management exercise.
Guidance for Step 10

Before communicating risks and the outcomes of QRM exercises

- The QRM Team should study all of the risks generated by the QRM exercise to determine whether particular risks might be mis-perceived by the people to whom the risk communication is targeted.
- For example, the risk associated with glass or other particulates in injectable medicinal products is one which could fall into Slovic’s high “dreadfulness” group of risks, as discussed in KOD’s PhD thesis. This risk could be also characterised as an involuntary risk, with perceived catastrophic consequences, in accordance with Litai’s risk factors.
  - This is a type of risk that research has shown to be subject to the problems of mis-perception.
  - Thus, it is important during any risk communication activity on such risks to clearly describe how the risk is controlled at a practical, detailed level in clear and definite terms.

Guidance for Step 10

What is the Periodic Review about?

- There are two stages to the Periodic Review activity
  - The first stage is to plan for the Periodic Review at Step 9 of the current QRM exercise
    - Here, we define what items in particular should be reviewed, if any, and we set the date for the actual review to occur
    - These items should include any potential negative events identified at step 4 of the process that were not selected during the current QRM exercise for formal routing through the remaining steps of the process
    - It is vital that the team also document any difficulties, concerns or uncertainties that were experienced during the current QRM exercise, for specific follow up during the Review
    - Any recommendations which the team feel should be made to the reviewing team for the review should be documented at this time also
      - These can be documented in Step 9 of the Worksheet, or in additional pages/documents
  - The second stage is to actually carry out the planned review at that later date
Guidance for Step 10

How should we document the above two Periodic Review activities?

- We document the first stage on Step 9 of the Worksheet for the current QRM exercise, attaching any other documents/pages as are necessary
  - Any difficulties, concerns or uncertainties that were experienced during the current QRM exercise, should be documented here for specific follow up during the Review
  - Any recommendations which the team feel should be made to the reviewing team for the review should be documented at this time also
  - The team may also decide a date by which the review should be carried out for these specific issues and concerns

- We document the second stage in a report, which is then appended to the original completed QRM exercise worksheet.
  - Note that a new worksheet may also have to be completed (either fully or partially) during the review, if some parts of the QRM exercise were repeated. This should also be appended to the original completed QRM exercise worksheet

Guidance for Step 10

What is the purpose of performing the planned review?

- It's purpose is partly to go back and revisit the previous QRM exercise at some pre-defined future date
  - This can be regarded as a continuous improvement exercise
- The Review is not necessarily a brand new QRM exercise on the same item
- Its purpose is rather to allow us to evaluate the previous QRM exercise in light of the passage of time, taking into account any new knowledge or experience gained with the item of interest
- It also lets us evaluate how well the previous QRM exercise reflects the current situation
  - This is so that we can determine whether the outcomes and conclusions from the previous exercise are still valid, or if they need modifying
- The periodic review activity is an opportunity to review, and to study in detail, any difficulties, concerns or uncertainties that were experienced during the previous QRM exercise
  - For example…
Guidance for Step 10

- For example:
  - The probability of occurrence of a specific cause of a potential negative event may have been in doubt or in dispute during the previous QRM exercise
    - This means that the Risk which was estimated in relation to the cause of that potential negative event would also have been in doubt
  - New data or evidence may be now available to better estimate this probability of occurrence
    - So it would be beneficial to now repeat that part (e.g. Step 5) of the QRM exercise, taking these new data or evidence into account
    - This allows us to obtain a more reliable probability of occurrence, and thus a more reliable risk estimate

Purpose of performing the planned review... cont’d?
- The Periodic Review exercise is also an opportunity to review the list of potential Negative Events that were considered during the previous QRM exercise
  - This allows us to determine how relevant those potential Negative Events still are, and whether any new potential Negative Events, not considered last time, should now be assessed using the tool
- For example, if the previous QRM exercise was performed on a new process, there may have been very little data to draw upon when identifying potential negative events, and when rating probabilities during that QRM exercise.
  - The passage of time now allows such data to be generated
  - The Periodic Review step allows us to make use of those data, as well as the experience, learning and knowledge gained
  - We might now know of new potential Negative Events that were not originally envisaged and which should be addressed now
  - We might also learn that some probability ratings assigned last time were way off the mark, and now need to be revised.
Guidance for Step 10

Purpose of performing the planned review... cont'd?

• During the Review, we can compile, evaluate and interpret new trend data (e.g. using Control Charts, CpK data, etc.) on the item so that our original decisions about potential negative events, severities and probabilities can be re-assessed
• We can assess whether the item under study or any key risk-mitigating control is still within its validated or qualified state
• We can assess the performance of the new or improved risk control measures that were implemented
• We can also identify if any required risk-mitigating controls were not actually implemented, and the reasons for this.

• Importantly, we can assess whether any of the new or improved risk control measures which were implemented via Step 7 of the previous QRM exercise led to any new negative events being introduced which were not considered at the time

Guidance for Step 10

How often should the Periodic Review be carried out?

• There is no definite time interval here.
• Performing the review annually is a good rule of thumb, unless there is reason to perform it sooner
  • There should be a mechanism in place for individuals to make recommendations in relation to items they feel should be reviewed during the next Review for the Item under Study
  • For example, the team may recommend that a particular risk or its associated risk control measures should be reviewed at an early time-point, perhaps three months from the date of the exercise. This may then determine the date for performing the review
• The frequency of the review may also be based on the type and number of risks identified during the QRM exercise, and on the extent of risk mitigation which was required during Step 7
Volume 2, Part II - The Training & User’s Manual

Section 7.1

Appendix 1 to the Detailed Guidance Presentation

titled

Practical guidance for carrying out team-based activities such as brainstorming during Quality Risk Management exercises
Appendix 1 to the Tool Guidance presentation

Guidance for carrying out team-based activities (such as brainstorming) during Quality Risk Management exercises

Purpose of this Appendix

Detailed guidance for team-based activities such as brainstorming during Quality Risk Management activities is necessary to ensure that brainstorming sessions generate useful results and that the problems of subjectivity and uncertainty which can be associated with brainstorming activities in Quality Risk Management may be addressed.

Background Information

Brainstorming is a widely used component of Quality Risk Management processes, and in this methodology, it is used especially during Steps 4 through 8. It is an effective method to determine not just “what might go wrong” with the Item under Study, but also the probability of such events occurring. It is also used throughout the Risk Assessment and Risk Control parts of the process, when estimates of risk are being arrived at, and when GMP control issues are being considered as a means of mitigating risk. It is therefore important that any factors which can introduce bias, error or uncertainty into brainstorming activities be counteracted.

Our research has found that brainstorming is often not formally or adequately proceduralised, and formal training is often not provided in this area to users of Quality Risk management methodologies. There is generally little guidance provided in the pharmaceutical literature or elsewhere on how to actually perform or to manage brainstorming sessions for GMP environments.\(^1\) As a result, brainstorming sessions can often be poorly structured, not science-based, and inconsistent in approach.

Researchers such as Morgan (1-3), Kahneman & Tversky (4, 5) and have shown that probability judgements made during expert elicitation and brainstorming activities are susceptible to problems of uncertainty, for example as a result of heuristic-based behaviours. In the widely accepted “subjectivist” school of probability, the probability of an event is “a measure of the person’s degree of belief” that it will occur (1). Experimental psychology research has found that in most cases, experts and laypersons do not carry fully formed probability values and distributions around in their heads. Rather, “they must synthesise or construct” them when an analyst asks for them (1). Therefore, brainstorming activities which are well designed and science-based present opportunities for reducing the uncertainty which arise when determining failure modes and their probabilities.

\(^1\) During 2005 and 2006, the author asked senior QA personnel within six multinational pharmaceutical manufacturing companies which used formal risk management methodologies as part of internal Quality Assurance activities, whether their procedures allowed for brainstorming as a means of identifying failure modes, faults or hazards, and if so, whether there were documented and detailed instructions in place for how such brainstorming was required to be carried out. In all cases, brainstorming could be used as a means of identifying failure modes, faults or hazards, and in all cases, there were no documented instructions in place for how such brainstorming was to be carried out.
Brainstorming activities should thus be clearly proceduralised, with in-built mechanisms or other design features which deal with disagreements. Note that these procedures apply to Steps 4 through 7 of the Quality Risk Management methodology.

This guidance in relation to carrying our brainstorming sessions during Quality Risk Management exercises is presented below:

**Guidance:**

- During brainstorming sessions, the person assigned as Team Leader for the Quality Risk Management exercise at hand is expected to facilitate the session, has authority for managing the session, and this must be understood and accepted by all participants.

- At the start of the brainstorming session, the Team Leader should describe the Item Under Study in the Quality Risk Management exercise at hand, so that all participants can become familiar with the Item Under Study.

- At the start of the brainstorming session, the Team Leader should give an overview of the Quality Risk Management process being used, and the Step of the Quality Risk Management process which the team is presently at.

- At the start of the brainstorming session, the Team Leader should give each participant the items listed below, and should confirm that each participant has reviewed these items during their training on the Quality Risk Management methodology:
  - A copy of the ten-step Quality Risk Management worksheet
  - A copy of the Laminated Card which accompanies the worksheet
  - A copy of the Principles underlying this Quality Risk Management methodology
  - A copy of the outline of the ten-step Quality Risk Management process used by this methodology

- A copy of the Tool Guidance presentation from the Training & User’s Manual should be available during the session, preferably on a screen for consulting during the actual exercise.

- A copy of the Process Map or Schematic on the Item under study, which was assembled during Step 1 of the Quality Risk Management exercise, should be available for review during the session. Also, all of the data compiled on the Item under Study for the exercise should be available for review during the session. It is the responsibility of the Team Leader to ensure that these items are prepared and ready, when required. These items should formally be reviewed with the team by the Team Leader.

- At the start of the brainstorming session, the Team Leader should review with the team the slides relating to brainstorming contained within the above Tool Guidance presentation.
• The Team Leader should state the ground-rules for the session

  o All suggestions which are made during the brainstorming session are welcome and important
  o Listening to others points of view is vital
  o The Majority does not rule – As Stamatis (7) points out, sometimes a single individual may be on the right track, with everyone else being wrong.
  o Creativity and imagination are welcome and encouraged
  o Differences of opinion are welcome, but these should be expressed in a constructive way.
  o It is useful to consider opinions as hypotheses, so that they can be tested instead of argued against (Mosvick and Nelson, 8)
  o Compromise is sometimes needed
  o Negative statements such as those listed below are not helpful and should be avoided: These include:
    ▪ “We have never done it that way.”
    ▪ “We are not ready for that yet”
    ▪ “We are doing all right without it.”
    ▪ “That is not our responsibility.”
    ▪ “That would not work around here anyway.”
  o Everyone is free to build upon someone else’s ideas
  o There is to be no qualification of the idea or suggestion until after it has been documented
  o All team members are expected to participate and contribute to the discussion, and no one will be allowed to dominate. The Team Leader has a central role in ensuring that this occurs.
  o “Contribute, not defend” should be a goal for all participants
  o The Team Leader may prompt and drive the discussion when needed

• During the brainstorming session, participants will be asked to jot down their ideas and suggestions for the questions of interest for about 2-3 minutes before any discussion occurs on that question.

• During the brainstorming session, the Team Leader should ensure that the session is designed so as to allow different people to express their views and thoughts in ways that suit them best. Thus, while some people may prefer thinking on their feet and then expressing their opinions verbally, others may prefer an opportunity during the session to think more quietly and then to write down their thoughts and opinions first. The Team leader should facilitate different ways for people to express themselves during the brainstorming session, and should be sensitive to the needs of all.

• The Team Leader shall lead a critical analysis and discussion on the ideas, comments and suggestions which were recorded by the participants, and shall record all ideas and points on the flip chart, making notes to reflect the nature of the discussion on each point. (A flip-chart and markers should be available, as well as writing materials for each team participant.)
- During the discussion stage, all GMP controls which were identified as being important for either risk control or reduction should be critically assessed for the contribution they may make to risk control or reduction activities. In addition, the feasibility of the control, as well as its estimated cost (if the control is a newly proposed one), should be discussed and assessed critically.

- At an appropriate stage during the brainstorming session, the Team Leader should stop the discussion and initiate decision-making for the question of interest. This could be which of the potential negative events which were suggested or proposed should be formally processed through the Quality Risk Management tool, or which GMP controls might usefully be employed to mitigate or to control a certain risk.

  - In relation to Step 4 of the process, when selecting the potential negative events for formal assessment in the remaining steps of the tool, in an ideal situation, all of the proposed or suggested potential negative events would be selected for formal assessment. However, given the rigorous nature of this Quality Risk Management methodology, and its design intent, it is often more appropriate and practical to select only the most important potential negative events for formal study. To do this, it is helpful to review and discuss during the brainstorming session the seriousness of the potential effects of the potential negative event. There is clearly a degree of subjectivity here.

**See also:**

- Appendix 2 - Guidance for how disagreements and differences of opinion are to be dealt with during brainstorming sessions
- Appendix 3 - Guidance in relation to human heuristics and how the adverse affects of such heuristics may be reduced during brainstorming and decision making

**References:**

*Note:* The above guidance is partly based on learnings gained by the author during a series of training sessions run by the company known as *Training Works Ltd.*, Monkstown Co. Dublin., at the Irish Medicines Board during the period June-August 2005. (Trainer: Ms. Vanessa Cole.)
Appendix 2 to the Detailed Guidance Presentation
titled

Practical guidance for how disagreements and differences of opinion are to be dealt with during team-based activities such as brainstorming
Appendix 2 to the Tool Guidance presentation

Guidance for how disagreements and differences of opinion are to be dealt with during brainstorming sessions

Purpose of this Appendix:

Prior to commencing brainstorming sessions during any step of the Quality Risk Management process, there should be documented mechanisms in place to deal with any disagreements and differences of opinion which may occur, and all team participants are made aware of these mechanisms.

This Appendix provides detailed mechanisms to deal with such disagreements and differences of opinion.

Background Information:

- If significant disagreements and differences of opinion arise during the brainstorming session, it is important that there are clear guidelines in place and understood by the participants for dealing with such issues. For example, there can be significant uncertainty associated with the likelihood of the cause of a failure mode occurring. As Morgan has pointed out (1), there can also be disagreements in this area between scientific experts in the item under study. The latter can be an important source of uncertainty during Quality Risk Management exercises, as there may frequently be more than one so-called expert on a Risk Management team.

- Obviously, the more people that are on the Quality Risk Management team, the greater the chance that disagreements and differences of opinion arise. This problem can be compounded by having both expert and non-expert people on the team, as experts might not appreciate the opinions of those who may not be that technically familiar with the item under study.

- One option, of course, is to limit the size of the team, and/or to limit the number of so-called ‘experts’ (with respect to the item under study) that are on the team. There is some justification for using just one expert (in the item under study) on a Quality Risk Management team. For example, within the EU, only one QP (who might reasonably be regarded as being an expert relative to the product being certified) is required to certify batches for release – there is no requirement to have more than one QP discuss or debate batch certification issues for each batch.

- The size of the team should ideally represent a balance between the need to ensure that the team is adequately multi-disciplinary in composition, that it has the necessary expertise in relation to the item under study, and that it is not too large.

- Disagreements between experts may occur for many reasons. For example, not only might experts differ in their technical interpretation of the same scientific evidence, such disagreements between experts may be exacerbated “by the fact
the people view the problem from very different perspectives (1).” As an example, Morgan discusses how different experts involved in dealing with the effects of air pollution, including “inhalation toxicologists, clinical practitioners, lung physiologists and epidemiologists”, all have “very different perspectives on the impact of specific air pollutants on health (1).” In addition, Morgan Granger explains how uncertainty can be introduced into decisions because people frequently hold “direct or indirect stakes in the outcome to the question, and thus, their judgements may be influenced by motivational bias, consciously or unconsciously (1).”

- Numerous approaches have been used to overcome the uncertainty which can arise when making decisions relating to probability values.

  - For example, as a precautionary measure, some quantitative Quality Risk Management applications assign the highest possible probability of occurrence value to events when the actually frequency of occurrence is not known, e.g. Stamatis, 2003 (2). This is not regarded by this author as a scientific approach, as the resulting risks or RPNs can be greatly over-estimated, and this can distort the outcome of Quality Risk Management exercises, leading towards risk mitigation and validation activities that have little scientific basis.

  - Other approaches sometimes involve combining the various opinions compiled during brainstorming sessions, perhaps by averaging or by assigning weights to the opinions of experts; e.g. McDermott et al., 1996 (3). A number of methods have been developed to assign such weights (1). Scoring procedures for evaluating the credibility of experts involved in providing opinions and judgements on question such as event probability have also long been developed. In some fields, a widely used scoring rule for probability estimates is the Brier score, developed in 1950 (4).

  - Other researchers such as Matheson and Winkler (1976) (5), have developed their own scoring approaches for evaluating assessors of continuous probability distributions.

  - Morgan has assessed the findings from many of the scoring tools that have been developed and reported that “the one consistent finding across all elicitation techniques that have been examined is a strong and consistent tendency to overconfidence” in the results of the scoring (1). Morgan also found that some scoring techniques were generally difficult to learn.

  - A third approach sometimes adopted is one in which the primary risk analyst (or perhaps the Risk Management team leader) considers each differing opinion on its merits, and then makes a “best judgement” call on the probability of the event (1).

  - There are merits with each of the above approaches, and at this time, no one approach has been shown to be the most effective.
The mechanisms to be used for dealing with disagreements and differences of opinion during brainstorming sessions:

- When there are disagreements or differences of opinion during brainstorming sessions when performing Quality Risk Management exercises, the following approach should be used:
  
  o The Team Leader should direct the team to take a step back and examine whether the differences are actually significant or not.

  o There can be occasions where the differences of opinion have no substantial effect on the outcome of the exercise, and it is important to recognise this.

  o When this is the case, (e.g. perhaps with probability values of Medium and Low for a Minor severity Negative Event), the Team Leader should lead discussion within the team in an effort to reach a consensus for the issue of concern.

  o It should not be too difficult to reach a consensus here, when it is pointed out that the agreed, compromised position will not materially affect one's position.

  o If a consensus cannot be reached, an average decision/judgement is clearly justified here, if it is possible to assign an average, and the Team Leader should average the opinions accordingly. If it is not possible to assign an average of the opinions, the closest option should be chosen, always erring on the side of caution.

  o However, as an extra safeguard feature of this Quality Risk Management tool, when there are such differences of opinion and disagreement on whether a risk is either Unacceptable or Intolerable, by virtue of, for example, differences of opinion in either probability or severity ratings, or both, this tool is designed to overcome the potential effects of this "uncertainty", so that the end result is not affected by the uncertainty in judgement. This is because the tool is designed to treat Unacceptable or Intolerable risks equally in terms of three key activities: 1) assessing the usefulness of any detection controls pertinent to the negative event or its effects (via Step 6 of the Process), 2) in requiring risk mitigation actions where detection controls do not serve to adequately control the risk, (via Step 7 of the process), and 3) in assessing the Qualification and Validation (Q&V) requirements for all controls - controls relating to both Unacceptable and Intolerable risks are equally assessed in Step 8 of the tool.

- When there are differences of opinion or disagreements during brainstorming sessions, and when these differing opinions do have a substantial effect on the outcome of the exercise, (e.g. where differing opinions result in a risk being judged to be either
Acceptable or Unacceptable), the opinions of the different persons on the team should not be combined to produce some average result. As Morgan suggests, such differences in opinion provide "important information about the problem that should not be quickly discarded (1)."

- In such cases, the team leader should make efforts to resolve the dispute. A strategy which may be used in this case is as follows:
  - The team leader should encourage the team to take a short 5 minute break from the brainstorming session, and reconvene soon after to discuss the issue of concern again. (In exceptional circumstances, a special meeting may be required to discuss the item under dispute.)
  - If possible, any non-team members (e.g. technical people in the company) who may have been consulted by the team and who were involved in offering an opinion for the item under disagreement should also be present (or available for consultation).
  - The team leader should formally get the different team members to provide their opinions again, and to discuss the issue under dispute among themselves again, without any formal intervention by the team leader. This is to allow for the possibility that the disagreement may be resolved on foot of these fresh offerings of opinions, and that a consensus opinion may be reached.
  - If this fails, the team leader should then formally intervene, and manage the issue from here.
  - Each differing opinion should be listed on a flip-chart by the Team Leader, and the Team Leader should then lead a discussion to formally evaluate the full set of evidence for each opinion and any assumptions underlying each position.
  - Here, each person should be asked to state why they do or do not place confidence in the different opinions, data and interpretations being put forward.
  - All pertinent and relevant assumptions should be discussed in order to determine which assumptions may particularly give rise to uncertainty in an opinion.
  - The main points from this discussion should be recorded.
  - If a consensus decision is still not reached following this more formal discussion and evaluation of the facts and opinions, the more conservative of the opinions (not their average) must be taken as the decision for the exercise. This is an up-regulation approach, designed to exercise caution in such circumstances.
o The Team Leader will record the decision as dictated by the approach above, but it must be recorded as a disputed decision, for example, "Risk = Unacceptable (Disputed)".

o The Team Leader should record as an action item in Step 9 of the Worksheet that the above disputed decision (and the issues surrounding it) must formally be reviewed during the Periodic Review phase of the Quality Risk Management process for this item under study.

o Where possible, and in addition to the above action item, the Team Leader should also record as an action in Step 9 of the Worksheet that scientific studies should be initiated following the Quality Risk Management exercise to better understand the issue of dispute. This could, for example, relate to performing scientific studies into the failure rate of an item of equipment for a specified reason or via a specified mechanism.

o The Team Leader will also record in Step 10 (Communication) of the Worksheet the fact that there was significant uncertainty relating to that particular decision, and that this fact should be communicated to the appropriate stakeholders groups.

References:

Practical guidance in relation to the potential adverse effects of human
cognitive heuristics on Quality Risk Management activities and on
decision-making in general
Appendix 3 to the Tool Guidance presentation

Guidance in relation to human heuristics and how the adverse affects of such heuristics may be reduced during brainstorming and decision making

Purpose of this Appendix:

This Appendix is to serve as an information resource in addressing the challenges which are presented by Human Heuristics during Brainstorming sessions.

Specifically, it aims to help ensure that brainstorming activities are designed to address the problems of uncertainty and subjectivity in decision-making and judgement, as a result of the potential adverse influences of human heuristic cognitive behaviours.

Background Information:

- There is a need to address the problems of subjectivity and uncertainty when identifying specific potential negative events and their probabilities of occurrence during brainstorming sessions. One way to do this is to design controls and features into brainstorming sessions which reduce the effect that human heuristics can have in contributing to uncertainty in judgements and opinions.

- Heuristics are cognitive behaviours which come into play when we make judgments in the presence of uncertainty. How these behaviours are manifested is still the subject of much research, but there is much evidence in the literature that heuristics are a source of significant bias and errors in judgment.

- In activities such as Quality Risk Management, heuristics become important, because there is usually some level of uncertainty associated with judgments and decisions which are made during Quality Risk Management exercises. Kahneman & Tversky (1, 2), Slovic (3, 4) and other researchers have shown that heuristics can sometimes lead to biased outcomes and errors. Three of the main heuristics are discussed below.

- **The Heuristic of Availability**: This heuristic affects how people estimate the probability of an event occurring. As Morgan explains, a person’s probability judgement is often determined by “the ease with which [people] can think of previous occurrences of the event”, or the ease with which they can imagine the event occurring (5). Research has shown that people find it easier to recall or imagine dramatic, uncommon events (such as deaths from botulism) over more mundane, common events (such as deaths from stroke). This can cause people to sometimes over-estimate the frequency of an event where recall or imagination are enhanced, and to under-estimate the frequency of an event where recall or imagination are difficult. In contrast, people tend to make reasonable estimates of event frequencies when their “experience and memory of observed events corresponds fairly well with actual frequencies (5).
• **The Heuristic of Representativeness**: This heuristic also affects how people estimate the probability of an event occurring. As Morgan explains, a person’s probability judgement is often influenced by one “expecting in the small behaviour that which one knows exists in the large”. (5) Thus, when tossing a coin six times, people tend to rate as more likely the sequence HTHTTH than either of the sequences HHTHT or HHHHTT, even though all three sequences are equally likely. This is because, from one’s larger experience, people know that the process of coin tossing is random, and the sequence HTHTTH looks more random than the other two. This phenomenon is sometimes referred to by what Kahneman and Tversky (1, 2) call “the belief in the law of small numbers”.

• **The Heuristic of Representativeness**: This heuristic affects how people estimate the probability of an event occurring in another way too. When this heuristic is in operation, people can pay too much attention to the specific details, while ignoring or paying insufficient attention to background information such as base rates. Research has shown that people tend to ignore or forget important probability-related information, when they have been given other specific information which is worthless to the question at hand (5).

• **The Heuristic of Anchoring and Adjustment**: Another heuristic that affects how people make decisions, such as when estimating the probability of an event occurring, is the heuristic of anchoring and adjustment. When this heuristic is in operation, people’s judgement can be heavily influenced by the first approximation of the value or quantity that they think of or hear. Experimental psychology research has show that the first approximation of the value or quantity that a person may think of or hears can become a natural starting point for that person’s thought process. This first approximation is termed an “anchor” in the person’s thought process, and this value is known to influence any subsequent adjusted values for the quantity in question that are estimated.

Research by Kahneman and Tversky has demonstrated that the value of this anchor is critical (1, 2). When adjustments of the initial value are made in an effort to arrive at a more accurate answer, for example with the availability of new or more information on the item under study, these adjusted values are usually biased towards the value of the anchor.

From the author’s experience, and from a detailed review of the literature, it is difficult to reduce the uncertainty which is associated with probability decisions as a result of the heuristic of anchoring and adjustment. This is because one’s thought processes, which are the principle means by which the effects of this heuristic are realised, cannot easily be controlled, and simply thinking of an initial probability value may play an important part in the operation of this heuristic. However, it is possible that some of the uncertainty which may be associated with probability and other decisions during brainstorming sessions as a result of this heuristic may be overcome.
Guidance for how the effects of such heuristics may be reduced during brainstorming sessions:

The Team Leader should use this guidance when leading and managing brainstorming sessions

- At the beginning of the brainstorming session, the Team Leader should briefly explain to the team the ways in which cognitive heuristics are thought to affect human judgement and decision-making. Researchers such as Morgan et al., have found this approach to be useful, and they promote explaining to those participating in such sessions to be told “what is known about the psychology of judgements made in the face of uncertainty (5).” The text above in relation to the heuristics of Availability, Representativeness and Anchoring & Adjustment may be helpful in this regard.

- With respect to the heuristic of availability, in order to reduce the uncertainty associated with probability decisions which are made during brainstorming sessions, the team leader should ask the team if there is anyone on the team who has had direct experience of the potential failure mode under discussion (or its causative factors). If that person is likely to have learned of the event whenever that event occurred in the past, and is he/she is also able to recall actual real examples of such events, then that person’s opinion on the probability of occurrence of the potential failure mode should be considered to be more reliable than that of others on the team, and that person’s opinion should be used when assigning a rating to the probability of that event, unless there is a substantial reason not to do so.

  - An example of such a person would be a long-standing supervisor on a carton packaging line who would have had direct experience of dealing with Patient Information Leaflet (PIL) handling problems on the line. If this person is likely to be able to recall the events when packs were packaged without PILs on the packaging line, then this person is likely to be a suitable person to judge the probability of such packaging problems for that line or for similar equipment.

  - If there is no one on the team who fits the above description, it may be possible to seek out a person within the company who is likely to fit this description, so that that person’s opinion of the probability can be sought.

  - If no one can be identified who fits this description, the procedure for brainstorming should require the team leader to document that the probability which is assigned is an estimate without reliable direct experience.

- With respect to the heuristic of representativeness, in order to reduce the uncertainty associated with probability decisions which are made during brainstorming sessions, the Team Leader should ensure that the team focuses its attention on the item under study, and is not too heavily influenced by the expected behaviour of the larger class of objects that may contain the item under study, unless there is good reason to do so.
To demonstrate this by way of an example, consider the problem of particulates which is sometimes observed with injectable medicinal products. One source of particulates is the coring of the rubber stopper closures on vials, when a lyophilised injectable powder product is reconstituted with a diluent which is added to the vial via a transfer needle. One's wider experience may suggest that coring problems of this nature are prevalent with all such products, and that particulates are to be expected. However, it is important to focus on the exact product of concern, not just on the broad category of product. The actual stopper and needle components used in this product, the reconstitution instructions stated in the product literature, and the presence of a filtered needle in the pack may all be important factors to consider when estimating and evaluating the risk posed by stopper coring problems with such a product.

• Again with respect to the *heuristic of representativeness*, in order to reduce the uncertainty associated with probability decisions which are made during brainstorming sessions, the Team Leader should ensure that the team focuses its attention on the relevant information at hand when assigning a probability value to an event. Other information which is at hand but which is irrelevant to the question of interest should be ignored.

• With respect to the *heuristic of anchoring and adjustment*, before any ratings or values for the probability, severity or detectability of a failure mode, its causes or its effects are discussed during the brainstorming session, the Team Leader should instruct the team that no initial probability, severity or detectability opinions are to be verbalised by anyone on the team, until each member of the team has a) had an opportunity to consider the facts for him or herself, b) formed their own initial opinion or judgement on the issue at hand, and c) written their opinion or judgement down. A round table discussion of the opinions or judgements can then occur. While this strategy will not likely overcome anchoring effects as a result of the initial value or opinion thought of or formulated by the individual in his/her own mind, it may help to reduce the effects caused by Anchoring and Adjustment, because each team member has a chance to form his or her own opinion or judgement before hearing that from other team participants.

References:


Section 7.4

Appendix 4 to the Detailed Guidance Presentation

titled

Practical guidance in relation to assessing the strength of evidence for opinions and judgements that have been given during Quality Risk Management exercises by team participants and subject matter experts
Appendix 4 to the Tool Guidance presentation

Information pertinent to assessing the strength of evidence for opinions and judgements that have been given during Quality Risk Management exercises by team participants (including experts)

Purpose of this Appendix:

During brainstorming at Steps 4 through 7 of the Quality Risk Management process, it is important that strength of evidence is considered when expert judgments and informed opinions are offered. This Appendix provides guidance in this regard.

Background Information:

It is considered good practice to obtain informed opinion and expert judgement when identifying potential failure modes, their probabilities, and when opinions are needed in general. As discussed by Morgan, (1), Lichtenstein et al. (2) have demonstrated that “the more information subjects have about an unknown quantity, the less likely they are to exhibit overconfidence” in making judgements. However, the value of using experts for obtaining reliable judgements is far from clear.

Research at Carnegie Mellon University by Mullen, as part of her doctoral thesis (3) on the Process of Probabilistic Estimation, demonstrated that acknowledged experts in an area of study are still susceptible to the same influences of cognitive heuristics, such as anchoring and adjustment, as lay people, though the extent to which they may be affected may not be as high. Other researchers, e.g. Goldberg (4), have shown that experts sometimes perform no better than lay people in making judgements relating to their area of expertise!

Three important factors were identified by Faust (5) in 1985 which appear to influence the ability of experts to make reliable judgements on uncertain quantities in an area of study. These are:

- The availability of a well developed science that provides established scientific theory for the area under study;
- The availability of precise measuring techniques in that area of study;
- The availability of pre-specified procedures and judgement guidelines for decision-making.

Morgan summarised that problems relating to human heuristics “appear more likely to arise in fields involving complex tasks, with limited empirically validated theory.” (1)

In this regard, the pharmaceutical GMP industry, while of course involved in complex activities, is an industry which should be less affected by such problems. This is because there is an increasing reliance placed upon science and scientific technologies during pharmaceutical manufacturing and control, it is procedure-driven, and there is an emphasis on validated measuring methods.
When obtaining opinions and judgements during Quality Risk Management exercises, it is important to seek and assess the strength of evidence for each opinion or suggestion proposed. This adds rigor to the exercise, and it helps reduce the level of subjectivity and guesswork that can arise during the failure mode identification process. In this regard, it is helpful to:

- Seek the opinions of actual users and operators of the Item under Study. A process operator may know very well what can go wrong with a process or activity, and he or she may be in a position to advise as to its potential frequency.

- Seek the opinions of those employees or others who are knowledgeable in the item under study. For example, during equipment-related Quality Risk Management exercises, the vendor may have valuable knowledge about likely problems and potential rates of failure of components, etc.

- Where possible, take into account the concerns of stakeholder groups when considering "what might go wrong" with an Item under study. For example, if a change is proposed to roll out a new labelling and livery design for a range of medicinal products, practising pharmacists may usefully advise about risks of dispensing or usage errors which may be introduced by the change, even if the new labelling is fully compliant with Marketing Authorisation labelling requirements.

Much research has been performed into how best to elicit opinions and judgements from experts and non-experts, and findings in this area are relevant to brainstorming activities during Quality Risk Management exercises. There is evidence that asking experts for carefully articulated justification and reasons for and against their judgements may improve the quality of those judgements, but again, the situation is still far from clear.

As discussed by Morgan, (1), research by Hoch et al, (6), have demonstrated that "subjects' probability judgements were greatly affected by being asked for reasons" for and against their judgements, and that their judgements "were influenced by the type of reason asked for first (1)" Hoch's work found that peoples' judgements were less affected by the type of justification questions asked of them when they were more experienced in the item under study than when than when less experienced (6). This work suggests that, during brainstorming sessions, one should exercise caution particularly when challenging non-expert subjects on their opinions by asking for reasons and justification for their opinions.

Morgan summarises the situation by stating that "there is some evidence that asking for carefully articulated justification and reasons for and against judgments may improve the quality of judgements, but more research is clearly needed in this area (1). As Morgan usefully pointed out, when opinions are being sought from experts and others, it is also important to encourage those involved to actually think, and to keep the basic and common dangers in mind (1). Also, participants should use common sense, and be flexible."
References:


Section 7.5

Appendix 5 to the Detailed Guidance Presentation

titled

*Practical guidance on what information might be included when assembling comprehensive data on the Item under Study during a Quality Risk Management exercise*
Appendix 5 to the Tool Guidance presentation

Guidance on what information might be included when assembling comprehensive data on the Item under Study, as required in Step 1

Purpose of this Appendix:

During Step 1 of the Quality Risk Management process, as an aid to future brainstorming sessions, comprehensive data should be assembled on the Item under Study as an aid to the Team performing the Quality Risk Management exercise.

This Appendix outlines what information may be required in this regard.

Background Information:

Some Quality Risk Management methodologies recommend that a map of the process under study be generated, which can then be used to determine where potential failures may occur in the process or item under study. This is very useful, but in our experience and from workshops we have carried out, process maps sometimes provide only very limited information, and can be of little value during Quality Risk Management exercises.

It is useful therefore to ensure that the procedures in place for Quality Risk Management exercises define in detail the data and documentation that should be assembled on the Item under Study. If a process map or flowchart of the Item under Study is to be used, it should be sufficiently detailed and descriptive if it is to be of value. We have found it helpful to extend the scope of what is normally considered a “Process Map”, so that more comprehensive information is assembled on the Item under Study.

Guidance:

This information can include:

- A listing of the steps in the process or in the Item under Study in which human intervention occurs, or is at its highest.

- A brief overview of the technology or science underpinning the Item under Study. For example, if the Item under Study is a fermentation process, it is useful to train team members on the principles of fermentation and how it generally works. In multi-disciplinary Quality Risk Management teams, some members may not be technically familiar with the technology behind the Item under Study.

- The actual (detailed) Master Batch Manufacturing Record or SOP(s) relating to the Item under Study, if applicable. For example, if the Item under Study is a supplier approval programme, the SOP in place for this activity should formally be part of the process map. (With highly complex and multi-step processes, it
may be more useful to use a schematic of the process or Item under Study, but the
detailed Master Batch Manufacturing Record or SOP(s) should still be readily
available.)

- If the Item under Study is a Change Control proposal, it is useful to document the
current process/procedure as well as the proposed process/procedure in outline or
flow chart format.

- A list of equipment as well as all ancillary equipment relating to the Item under
Study. For example, if the item under study is a manufacturing process, and if
sampling occurs on that process, sampling equipment and facilities should be
included in equipment lists.

- Copies of any ancillary SOPs or other documents which are required for the Item
under Study, such as SOPs for controlling room environments, for taking samples
from reactors, etc.

- The known Critical Process Controls for the Item under Study, as well as the in-
process tests, the finished product tests, and their specifications or limits.

- Copies of any validation reports (and their protocols) which relate to the Item
under Study.

- Copies of any qualification reports (and their protocols) which relate to the Item
under Study.

- Data and reports in relation to any Deviations, Complaints, Out of Specification
Results, Batch Rejects, Near-miss Incidents, Problems, Inspection and Internal
Audit observations that relate to the Item under Study.

- If the Item under Study is a medicinal product, a copy of the most recent Product
Quality Review generated for that medicinal product and its associated
manufacturing process.

- If the Item under Study is an active substance, a copy of the most recent Annual
Product Review generated for that active substance and its associated
manufacturing process.

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Section 7.6

Appendix 6 to the Detailed Guidance Presentation

titled

Practical GMP-related Case Study designed to help users understand several of the strategies that were developed during this research to overcome problems of subjectivity and uncertainty that were observed when identifying potential negative events and when performing Risk Assessment activities in general during this research
Appendix 6 to the Tool Guidance presentation

*Practical Case Study in relation to a Change Control proposal to install a Filter Dryer in an API Manufacturing Process*

**Purpose of this Appendix:**

This Appendix is designed as back-up information for several of the strategies which were developed during this research to overcome the problems of subjectivity and uncertainty when identifying potential negative events and when performing Risk Assessment activities.

This Case Study was generated from the findings of two workshops run with an early version of this Quality Risk Management methodology. This Case Study is of relevance here because a number of the issues discussed within the strategies for addressing problems of subjectivity and uncertainty are explained by making reference to this Case Study.

This Case Study involved the application of Version 1 of Quality Risk Management methodology to a Change Control proposal relating to the installation of a Filter Dryer in an API Manufacturing Process.

**The Case Study:**

Two workshops were run in which the Quality Risk Management methodology was applied to the above Filter Dryer change control proposal.

In the first workshop, “Low yield” of API material following drying was identified and documented in a brainstorming session as a potential failure mode. A number of potential causes were identified for this failure mode, including, breakage of, or damage to, the stainless steel mesh screen in the filter dryer. It was documented that this could result in a physical loss of filtered, solid API material through the screen.

When it came to recording the potential consequences, or effects, of this failure mode, the effects were recorded as “Yield loss, cGMP deviation, economic business effect - unable to meet customer demand”. Thus, the failure mode and one of the main effects of the failure mode were essentially the same - Low yield and Yield loss”.

As this workshop progressed, it was evident that selecting such a high level potential Failure Mode significantly limited the extent to which causative factors and their mitigating controls were identified, and documenting the failure mode in this manner impacted the outcome of the risk management exercise in quite a significant way. For example:

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1 As noted above, the author has also observed this confusion between failure modes and their potential effects during GMP inspections; for example, failure modes such as “out-of-specification batches” may be documented, with their effects listed as “non-compliant product”. This problem has also occurred in other workshops using different case studies.
• The potential cause(s) of the actual breakage of, or damage to, the mesh screen were not identified or discussed in any way. It is not unreasonable to expect causative factors at this indenture level to have been identified, and there was, for example, no discussion during the workshop on whether an incorrectly rated screen (from a pressure perspective) could have been a potential cause for the screen breakage.

• With respect to risk-mitigating controls, the following five risk-mitigating controls were documented in the Quality Risk Management exercise as being important for addressing the risk associated with this failure mode:

1. Monitor the pressure in the dryer during operation, as a significant pressure drop may indicate a screen failure.
2. Do a screen integrity check before first batch and after fifth batch.
3. Do a heavy metals test on the finished API in order to detect screen particles.
4. Visually inspect the mother liquor for presence of particulates.
5. Ensure the screen is on a regular Preventative Maintenance schedule.

An analysis of the above five controls shows the 80% of the controls are detection-related. The fifth control serves as a preventative measure that may reduce the probability of screen damage or breakage, but to what extent this was unknown. Thus, it is clear that the above controls were heavily skewed towards detection as the primary means of addressing the risk posed by the failure mode in question. This is likely a result of documenting the Failure Mode at such a high indenture level and in a manner that rendered it effectively equivalent to its main end effects. When this occurred, it meant that the causative factors identified were, by definition, quite high level also, and it was found that preventative controls were not as readily determined than with lower level causative events.

A second workshop was then run to investigate the impact on the results of the above Quality Risk Management exercise when more care and vigor were applied to the failure mode identification and documentation process. The strategies outlined below were adopted during this repeat case study, and a simple Fault Tree Analysis (FTA) approach was used during a brainstorming session to determine causative factors for the selected high-level fault.

The intent here was that causative events could be identified via more vigorous, but simple, procedures, and these could then be used to select potential failure modes and the causes of such failure modes.\footnote{FTA is useful when Failure Modes need to be identified during FMEA and FMECA-based Quality Risk Management exercises. When using FTA methodology, there can be many causative events identified at the same or at different indenture levels in the fault tree and these may contribute to the high level fault. All of these causative events could potentially be considered to be failure modes, and this presents a practical difficulty when FTA approaches are used to identify failure modes, as it can sometimes be difficult to determine where in the fault tree the failure mode(s) should be selected. We have found it useful to first select the causes of the failure mode, before identifying the corresponding failure mode from the fault tree. (The latter will normally be one level above the fault tree.) The causes of the failure mode can be chosen from the fault tree by examining which causative factors in the tree are most readily suitable for assigning meaningful and practical preventative, detection or other controls to. This is a simple approach, but it has been found by the authors to be useable and effective.} This approach ensured that the potential failure
modes that were identified and documented were adequately differentiated from the high level faults that they related to, in this case the high level fault being “Low Yield API Batches”, and that the causative events were at a sufficiently low indenture level to facilitate meaningful and preventative risk mitigation. Importantly, as a control between the two workshops, the high level fault selected in Workshop No. 2 was the same as the failure mode selected in the first workshop on this Change Control case study.

In this second workshop, the first causative event identified under the high level fault was “the stainless steel mesh screen in the filter breaks or is damaged”, and three subsequent causative events were then identified at the next indenture level below this one. These three subsequent causative events, each separated by “or” gates in the Fault Tree, were:

- The mesh screen in the dryer is not chemically resistant to the slurry material (including the solvent) being filter-dried.
- The drying process uses an incorrectly rated screen from a pressure perspective, and the screen is unable to withstand the pressure exerted upon it when the filter dryer is at maximum agitation speed and contains a maximum load.
- A wrong screen is installed in the filter dryer during set-up for this API manufacturing campaign.

The first causative event documented in the Fault Tree under the high level fault was selected as the potential failure mode, and in the indenture level below this in the Fault Tree, the three causative factors mentioned above were taken to be the potential causes of this particular failure mode. When the above failure mode, together with the associated three potential causes, was inputted into the risk management methodology under study here, substantially different and more useful results were obtained compared to those from the first workshop, even though the issue of concern was essentially the same – low yield API batches.

In the second workshop on the same case study, nine risk mitigating controls were identified this time, for the same low yield problem described in the first workshop. These were:

1. Identify the correct pressure rating for the screen by determining (either via developmental batches or engineering calculations) the pressures expected to be exerted upon the screen when the dryer is in operation at maximum agitation speed and at maximum load. Then, ensure that this screen is used in the drying process.
2. Monitor the pressure across the screen in the dryer during operation. A significant pressure drop may indicate a screen failure.
3. Have a second person verify that the correct screen was chosen during set up of the dryer for this campaign.
4. Determine whether the screen material is inert with respect to the material being screened, and ensure that an inert screen material is chosen for this process.
5. Do a screen integrity check before drying the first batch in the campaign and after every fifth batch in the campaign.
6. Do a heavy metals test on the finished API batches.
7. Visually inspect the mother liquor for the presence of gross particulates.
8. Ensure the screen is on a regular Preventative Maintenance schedule.
9. Measure the yield of dried API for each batch. This may detect any gross screen failure, as there will be physical loss of API to the mother liquor.

An analysis of these controls presents a number of important findings. Firstly, an extra four risk mitigating controls were identified for the same low yield problem when more vigorous and defined procedures were used for identifying and documenting failure modes, in accordance with the strategies listed below. This was an increase of 80% over the controls identified during the first workshop on this same case study for the same problem.

Secondly, in the repeat workshop, the risk mitigating controls that were identified were based much more on prevention rather than on detection. Four of the nine controls, numbered 1, 3, 4 and 8 above, were preventative in nature, as opposed to only one such control identified during the first workshop. Similar findings have been observed with other case studies when this approach was used.

When these preventative controls are considered, the subjectivity and uncertainty associated with assigning probability of occurrence values to the causes of the failure mode are reduced, even with this qualitative methodology, because we are not now merely guessing probability of occurrence values for the causes of failure modes. Rather, there is now a more scientific rationale behind any probability of occurrence values that are assigned.

**Notes:**

The above case study demonstrates that, in order to reduce some of the problems of subjectivity and uncertainty discussed above, it is of prime importance that potential failure modes are identified and documented in a scientific manner, using meaningful, consistent and systematic processes, especially when brainstorming sessions are used.

This is because, with failure mode-based methodologies, the risks that are generated, and the overall results obtained from the Quality Risk Management exercises, directly relate to, and are usually wholly dependent upon, the failure modes and their probabilities that are identified / determined and input into the methodology being used.

From the above practical case study (and other case studies) generated during this research, and as a result of the difficulties described above, it became evident that there was a need for more rigorous and clear guidance in the Quality Risk Management methodology in relation to the practicalities of identifying and documenting failure modes, their probabilities of occurrence, and their associated controls, particularly during brainstorming sessions.

As a result, a number of simple and easy-to-implement strategies were developed during this work for use when identifying and documenting failure modes, and for related activities during the Risk Assessment and Risk Control processes. These
strategies, which are designed to help reduce the level of guesswork, subjectivity and uncertainty associated with the Quality Risk Management exercises at hand, helped to increase confidence in the results of the exercises, and they served to facilitate more meaningful and value-adding Quality Risk Management exercises for qualification, validation and change control activities.

These strategies, as outlined below, are science-based. They are qualitative in nature, reflecting the qualitative nature of this Quality Risk Management methodology, and many are actually based on common-sense approaches. Often, however, such approaches have been overlooked, or have not been developed appropriately, by the current Quality Risk Management methodologies that are already available.

Section 7.7

Appendix 7 to the Detailed Guidance Presentation

titled

Practical guidance on dealing with human error issues, and how to avoid situations in which human error may wrongly be identified as the cause of a potential negative event
Appendix 7 to the Tool Guidance presentation

Guidance for dealing with Human Error issues, & how to avoid situations in which Human Error is wrongly identified as the cause of a Potential Negative Event

Introduction:

When identifying the causes of Potential Negative Events at Step 5 of the Quality Risk Management process, it is important to exercise caution before assigning human error as the cause. This is because, while in some cases human error may be the cause of a Potential Negative Event, in others, it may be more of a symptom than a cause, or human error may not have occurred at all.

It is important therefore that the team performing the Quality Risk Management exercise carefully assesses whether human error is at fault or not. The guidance provided here is designed to assist in this regard.

Note: This guidance is also useful when identifying controls in relation to Potential Negative Events at Steps 5, 6 & 7 of the Quality Risk Management process.

A symptom rather than a cause:

Human error may result from carelessness or lack of attention when executing a work activity. For example, a failure to comply with a defined work procedure as a result of operator carelessness is an example of human error. However, errors and problems may occur even when instructions, procedures or policies are correctly followed or complied with by staff. Errors may also occur when staff are careful and attentive in carrying out a work activity. While it may be easy to assign human error as the cause of many Potential Negative Events, human error usually represents the symptoms of failure, rather than its cause.

In the following situations, human error should normally not be assigned as the cause of a Potential Negative Event without clear justification:

- **Staff are provided with a manufacturing or other process that is not robust, non-capable, unstable or poorly designed:**
  - This can be the case, for example, when a manufacturing process has not been sufficiently validated, or when equipment has not been sufficiently qualified. It may also occur when work instructions, procedures or policies are poorly written or designed. It may also occur when the operator/equipment interface, or the operator/process interface, is poorly designed or difficult to work through.
  - *Potential negative events in a manufacturing process or work activity should not normally be attributed to human error without first exploring the role of the manufacturing or other process in the Potential Negative Event.*
- **Staff do not know what is expected of them:**
  - This can occur, for example, when staff do not receive the proper training. It can also occur when important changes have been made to the manufacturing or other process that have not been properly communicated to the operating staff.
  - *Potential negative events in a manufacturing process or work activity should not normally be attributed to human error without first exploring the role of training and change control in the Potential Negative Event.*

- **Staff do not know whether or not they are accomplishing what is expected of them:**
  - Where possible, staff should know (or have to means to determine) when a piece of work was executed correctly, and when it was not. This will allow staff to recognise sub-standard work or non-compliant work practices if they occur. In this regard, it is helpful if there are ways available to operating staff for measuring or knowing the quality of their own work, either when performing the work activity or after it is completed. For example, criteria or examples might usefully be provided to staff which show acceptable versus unacceptable work and work practices. Also, it is useful to give operators feedback on the quality of their work.
  - *Potential negative events in a manufacturing process or work activity should not normally be attributed to human error without first exploring whether staff lack the means to know or determine whether a piece of work was executed correctly.*

- **Staff do not have a means of adjusting or regulating their manufacturing process or other work activity:**
  - In a manufacturing environment, process and equipment variability can lead to variability in the output of the process, or in the quality of the product or service produced. Also, deviations from approved procedures or from expected outcomes may occur, for a variety of reasons. The unexpected may also occur. Thus, it is important that operating staff are given the means to adjust or regulate their process, (in accordance with approved procedures), so as to ensure that the process can be brought back into control in a timely manner. This helps to prevent errors before they occur.
  - *Potential negative events in a manufacturing process or work activity should not normally be attributed to human error without first exploring whether staff lack the means to adjust or regulate their manufacturing process, in accordance with approved procedures.*

If one or more of the above is the case, then it may be wrong to attribute the cause of the Potential Negative Event to human error. The real functional cause of the Potential Negative Event may relate to one of the above situations.
**Strategy for not identifying Human Error as the cause of a Potential Negative Event when the cause actually relates to something else:**

When considering the cause of a Potential Negative Event at Step 4 of the Quality Risk Management process for cases where the cause of that Potential Negative Event looks like human error, the team should consider the following questions before human error is assigned as the cause:

1. **Could the cause of the Potential Negative Event be process, procedural or training related? In this regard:**
   - Can the manufacturing process or other work activity be considered to be robust, capable, and stable?
   - Are there any indications that the design of the manufacturing process or other work activity is such that it may be contributing to, or actually causing, the Potential Negative Event? For example, is there evidence that the operator/equipment interface, or the operator/process interface may be the source of the error?
   - Are there up-to-date written procedures, instructions or policies in place for the work activity or process in which the Potential Negative Event might occur, and are these materials available at the location in which the activity or process occurs?
   - Have the staff received proper training for executing the required activity or process?
   - Do Change Control procedures ensure that the relevant staff are always informed (and given training, if necessary) when there is a change in procedures, instructions or policies in relation to the activity or process of interest?
   - Is a Supervisor or Manager available when staff are performing the activity or process of interest in order to assist staff if there are questions about how to execute the activity or process of interest correctly?

2. **Could the cause of the Potential Negative Event be related to a lack of staff empowerment in their own area of work? In this regard:**
   - Do operating staff have any means of measuring or knowing their own performance, either during the work activity or after they have completed it? For example, are there any criteria or examples provided for acceptable versus unacceptable work? Or, are operators routinely given feedback on the quality of their work?
   - Do operating staff have a means of adjusting or regulating their manufacturing process or other work activity to correct for any potential problems or non-conformances?

   - **If the answer is no to any of the above questions, the cause of the Potential Negative Event may not be human error, but may be related to one of the areas indicated above.**

   - **If the answer is yes to any of the above questions, the cause of the Potential Negative Event may be human error, and the team should explore ways in which this may be prevented.**

**Important Note:** When working to identify the root cause(s) of a failure or Potential Negative Event, it is important to recognise that the absolute or ‘true’ root cause is usually not identifiable. This is because the cause of any failure will likely have an associated causative event at a lower indenture level in the item under study. Root cause analysis could
conceivably proceed all the way down to the molecular or even sub-atomic level in the item under study, and this would be a waste of time and resource. It is more beneficial, therefore, to look for functional root causes. These are root causes that can be addressed with functional, realistic controls. See the Case Study presented in the author's Journal of Validation Technology paper of February 2007 for a real-life example of this.

Identifying Measures to prevent or detect Human Error at Step 7 of the Quality Risk Management process:

During risk control activities at Step 7 of the Quality Risk Management process, it can be tempting to simply identify re-training as the necessary control for the staff member who made the error. While this approach may have some merit, the team performing the Quality Risk Management exercise should also consider the fact that the staff member in question was already trained on the procedure in question, and unless that training can be improved in some way, it is not reasonable to assume that the same, or a similar, error will not recur. There are many approaches, other than training-related measures, that may be taken in an effort to prevent human error.

- At the one end of the spectrum is the use of employee reprimands, so that the employee fully understands the importance of following the required procedures, polices and work instructions carefully, attentively and fully, and the implications of not.

- At the other end of the spectrum is the fool-proofing approach. Here, the manufacturing process or other work activity is redesigned so as to make it impossible for such an error to recur. (This approach is similar to eliminating the hazard.)

In-between these two approaches are measures that can be taken to make it less likely that the human error in question will recur, or if it does recur, that it will be detected in time. While these measures may require design changes in the manufacturing process, the work activity or in the finished product without resulting in any fool-proof solution to the problem, they can represent a useful approach.

Consider, for example, the use of warning statements on the labels of a parenteral powder for reconstitution for injection product. In cases where a patient makes an error in reconstituting the powder, by perhaps not following the labelled instructions when piercing the rubber stopper on the product vial with the transfer needle, coring of the rubber stopper may occur, resulting in contamination of the powder with rubber particles. These can be harmful if injected. A warning statement on the labelling of the product advising patients to carefully inspect the solution before injecting, and not to inject the solution if any particulates are observed in the vial, can serve as a measure that detects the effects of the human error before harm occurs. (While this detection-based control is useful, a better option would be to modify the design of the product so that coring of the rubber stopper cannot occur.)

As another example of such measures, consider the design of operator-system interfaces such as Programmable Logic Controller (PLC) systems. These units are commonly used in pharmaceutical manufacturing environments to control and operate equipment trains, and to execute manufacturing process steps. Certain design elements can be built into the PLC interface in an effort to prevent human error when people use the interface to perform work activities. With regard to interfaces which display process controls and their related parameter information:
• The displayed controls should be arranged in the sequence in which they are used.
• The parameter values for controls should be positioned on the screen close to where the actual control is displayed. (For example, a control for adjusting the pH of a solution should ideally be in close proximity to the display of solution pH.)
• Critical control information should be displayed in the operator’s optimum viewing area.
• When a control has a directional movement associated with it, such as turning a handle clockwise to close a valve, the displayed direction should reflect the actual required movement.
• In general, screen displays should provide only the information necessary for operating the system, and the font size used for displaying critical control parameter information (such as text or numbers) should be optimised by taking into account the operator’s likely viewing distance.
• If the PLC unit provides for audio-based controls that may sound in the event of a parameter exceeding a certain threshold value, the audio signal or alarm that is activated should be of a frequency and amplitude that can easily be heard in the operating environment.

*Note: The design features stated above, and the general guidance presented above, are partly based on the 2003 text by Stamatis (1), which referenced the US Military Standard known as MIL-STD-1472c, and research by Woodson, published in 1981 (2).*

**References:**


*****
Volume 2, Part II - The Training & User’s Manual

Section 8

Wedding Case Study

Copy of a partially and fully completed Case Study on the methodology which involves an area not in any way related to GMP
Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>☑ Option 1*</th>
<th>☐ Option 2</th>
<th>☐ Option 3 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective RM Exercise *</td>
<td>Retrospective RM Exercise</td>
<td>Change Control RM Exercise</td>
</tr>
<tr>
<td>The RM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed...</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
</tbody>
</table>

☐ Manufacturing Process ***
☐ Cleaning & Hygiene Process ***
☐ Labelling & Packaging Process ***
☐ Training Programme
☐ Material Sampling Programme
☐ Pest Control Programme
☐ Stability Programme
☐ Preventative Maintenance Programme
☐ Self-Inspection Programme
☐ Complaints & Recall Programme
☐ Reduced Testing Programme
☐ Item of Laboratory Equipment
☐ Supplier / Material

*** incorporating the equipment used

☐ Documentation Management System
☐ HVAC System
☐ Building Management System
☐ Distribution System
☐ Supplier Approval System
☐ Regulatory Compliance System
☐ Materials Management System
☐ Other - specify below in this box:

Wedding of Jack & Jill, December 27th, 2005

☐ If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

Notes:
* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
### Step 1 Cont’d - Preliminary Information on the RM Exercise

#### The Item Under Study

<table>
<thead>
<tr>
<th>What is the Item Under Study?</th>
<th>The Wedding of Jack &amp; Jill, December 27th, 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
<td>The RM exercise will be confined to the wedding day itself</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
<td></td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
<td></td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
<td></td>
</tr>
</tbody>
</table>

#### Boundary Details:

If the Item under study has a boundary, state the boundary here. For example:
- a boundary could be a P&ID for a piece of equipment or a system
- it could be 2 points within a manufacturing process, within which the RM exercise applies
- it could be part of a process, such as the drying & discharge stages in an API manufacturing process

<table>
<thead>
<tr>
<th>Process Map or Schematic:</th>
<th>Wedding Book</th>
</tr>
</thead>
<tbody>
<tr>
<td>State the ref. no. of any map or other document which describes / maps the item under study:</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Other Document (if any) associated with Item Under Study:

- e.g. Cleaning SOP No. 123/4
- e.g. Change Control No. 2005/11

#### Reason & Relevant Background Info for this RM Exercise

State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant:

**Purpose:** To anticipate problems on the wedding day in advance, and to try to address them

**Assumptions:** There is one month to go before the wedding. All arrangements are in place, and there seems to be nothing left to organise!
Step 2: Who's Who ... Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader:</th>
<th>Jill (Bride)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position / Area of Expertise:</td>
<td>Good organiser and now considering a career in professional wedding planning!!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name:*</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jack</td>
<td>Future Husband</td>
</tr>
<tr>
<td>Tom</td>
<td>Best Man</td>
</tr>
<tr>
<td>Rachel</td>
<td>Bridesmaid</td>
</tr>
<tr>
<td>Fr. Tom</td>
<td>Priest</td>
</tr>
<tr>
<td>Marin</td>
<td>Good friend of the Bride’s and level headed individual</td>
</tr>
</tbody>
</table>

* Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

******************************************************************************

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

**Carry out the following tasks, and complete this table by ticking the appropriate options:**

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - **Accept** the default Probability, Severity & Detection definitions shown on the Card.
   - **Do Not Accept** these default definitions, and draw up new definitions.

3. If applicable, **Document** any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - **Tick** here if any new definitions are attached
   - **Tick** here if N/A
From Step 3:

<table>
<thead>
<tr>
<th></th>
<th>Amended Definitions for Severity Levels:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical</strong></td>
<td>The wedding is badly impacted, and we are very upset!</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>The wedding is definitely impacted, and while we wish the negative event didn’t happen, it’s not the end of the world.</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>The wedding is impacted only a little, in a minor way. Hardly anyone notices.</td>
</tr>
</tbody>
</table>
**Step 4: What Might Go Wrong ...Identify Potential Negative Events Here:**

This involves compiling & reviewing data & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: 1  Session Date: Nov 30 '05

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference or Notes</th>
</tr>
</thead>
</table>
| 1   | e.g. Cross Contamination Event occurs in Dryer Room No, 123  
     e.g. Glass in Vials of Product X  
     e.g. Packs of Product X are Released without a PIL  
     e.g. Hard, yellow particles observed in batches of API X  
     e.g. Loss of Sterility Assurance for Filling Process for Product X  
     e.g. Low Yield Batches of API X  
     e.g. BMS System Failure Occurs | e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6) |

<table>
<thead>
<tr>
<th>No.</th>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>The Band Fails to Show Up. No other entertainment was planned.</td>
<td>The band is coming from afar, and we don’t know them personally</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>The two families don’t get along and no one mixes.</td>
<td>N/A</td>
</tr>
<tr>
<td>No.</td>
<td>Potential Negative Event</td>
<td>Comment</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>There are long delays between arriving at the hotel and sitting down to dinner.</td>
<td>Hotel has guaranteed that the meal will be served in time. We checked with other couples who used this hotel and they confirmed this. No need to process this Potential Negative Event through the tool.</td>
</tr>
<tr>
<td>2</td>
<td>The two families don’t get along and no one mixes.</td>
<td>We have been to many weddings where this has happened! But, as we come from the same village, the families know each other very well and this is not a concern for us. No need to process this Potential Negative Event through the tool.</td>
</tr>
<tr>
<td>3</td>
<td>The Band Fails to Show Up.</td>
<td>The band is coming from afar, and we don’t know them personally. We do need to process this Potential Negative Event through the tool.</td>
</tr>
<tr>
<td>4</td>
<td>Bride fails to show up.</td>
<td>This is something we should not consider a Potential Negative Event, because for her, it may be the most positive thing she could do!! We do not need to process this Potential Negative Event through the tool.</td>
</tr>
<tr>
<td>5</td>
<td>There is terrible wet weather on the day of the wedding and the guests and wedding party get soaked.</td>
<td>There are no outdoor activities planned, except for the brief stop-over by the wedding party at the local castle for photos. Tom (Best Man) will get a sufficient number of umbrellas in case of inclemental rain. If the weather is very bad, we will cancel this stop-over, and just take the our photos at the hotel. We do not need to process this Potential Negative Event through the tool.</td>
</tr>
<tr>
<td>6</td>
<td>Wedding gifts get stolen from Bride’s empty house on the day/night of the wedding</td>
<td>We need to arrange a neighbour or relative to stay at the house that day and night. Bride will do this. We do not need to process this Potential Negative Event through the tool.</td>
</tr>
</tbody>
</table>
Step 5: Risk Evaluation
Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C..., etc.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Band Fails to Show Up</td>
</tr>
</tbody>
</table>

List the Potential Negative Consequences of this Negative Event, should it occur:

List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C..., etc.)

**S: Severity:** Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- [ ] Critical
- [ ] Moderate
- [ ] Minor

List the Possible Causes or Mechanisms for this Negative Event to Occur:

<table>
<thead>
<tr>
<th>No.</th>
<th>Possible Causes or Mechanisms</th>
<th>Current Preventative Controls in place:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The band’s van breaks down</td>
<td>None that we know of.</td>
</tr>
<tr>
<td>2</td>
<td>The Band get lost and cannot find the venue</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>The Band is double booked on the date in question and they don’t come to our wedding</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A member of the band gets sick and Band have to cancel, or a family member of a band member dies and Band have to cancel.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>P: Prob. of Occurrence of each cause / mechanism</th>
<th>Risk assoc. w/ each cause or mechanism Risk=P x S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low or Remote?</td>
<td>#</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
**Step 6: Risk Evaluation Cont’d**

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Ctrl</th>
<th>Detection Controls</th>
<th>D</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>#</td>
<td>List any controls currently in place which detect the Negative Event or its consequences after the Negative Event has occurred.</td>
<td></td>
<td>Is this Risk adequately controlled? – Yes/No</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>Visual control: We will of course know when the band doesn’t show up</td>
<td></td>
<td>I.e. Do these controls give assurance that the risk is adequately controlled &amp; that no further controls are required? Explain below</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hi/Med/Low/Zero</td>
<td></td>
</tr>
</tbody>
</table>

If No, Go to Step 7. If Yes, Go to Step 8.
Step 7: Risk Control

Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Risk No.</th>
<th>State the Cause or Mechanism for the Negative Event to Occur (from Step 5):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>The band’s van breaks down</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Note: We could ask the band to have their van serviced the day before the wedding, but who’s going to do that?! (Good example of an unrealistic control)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
</tr>
</thead>
</table>

New Risk Level = [ ] Acceptable - go to Step 8  [ ] Unacceptable / Intolerable - continue below

If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
</table>

Note: if any of the above new controls may introduce a new risk, complete a new Step 4
**Step 7: Risk Control**

*Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>1</th>
<th>State the Cause or Mechanism for the Negative Event to Occur (from Step 5):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No.</td>
<td>4</td>
<td>Band member gets sick, or a family bereavement occurs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Reduction Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ctrl #</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
<th>New S Security Rating for this Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mod.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor</td>
</tr>
</tbody>
</table>

**New Risk Level = ☐ Acceptable - go to Step 8 ☐ Unacceptable / Intolerable - continue below**

**If the Risk is still Unacceptable or Intolerable:**

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? <em>Yes/No</em> i.e. Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ No: Repeat this Step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment/Explanation</td>
</tr>
</tbody>
</table>

**Note:** if any of the above new controls may introduce a new risk, complete a new Step 4
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Worksheet Step No:</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ Current □ Improved □ New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

These Items are **Already In Place** □

These Items are **Not Already In Place** □

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No
If yes, specify these here:

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes □ No
If yes, list the CPP below and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

**O & V**

What is the Status of this Qualification or Validation exercise?
□ Completed □ Not Yet Completed □ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)
□ New Qualification/Validation work needed □ No New Qualification/Validation work needed
Step 9: Action Items

*Identify any action items from the completed Qualification & Validation Worksheets*

**Action Items**

These could be actions to implement a control, or they could be a Qualification or Validation Exercise.

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
</table>
| 1                       | Make arrangements with Groom’s workmate Bill about stand-by van:  
|                         | • Check that Bill is free on Dec 27th  
|                         | • That he is willing to be on stand-by that evening to go pick up band if they have trouble with their van  
|                         | • Check that Bill’s van is reliable by checking that it has a valid NCT Cert (Instantiate!?) | Groom | December 5th 2005 |
| 2                       |                                 |                             |                        |
| 3                       |                                 |                             |                        |
Step 10: What are the risks, and how are we managing them:

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method</th>
<th>Responsible Group</th>
<th>Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tell the Hotel Manager that there will now be a disco as well as a</td>
<td>Best Man</td>
<td>December 5th 2005</td>
</tr>
<tr>
<td></td>
<td>band arriving for the wedding... so that the DJ can be expected by</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>the Hotel Staff.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Periodic Review Activities:**

Propose here a Date on which this Risk Assessment will be Reviewed:

If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:

Let's review the arrangements made in response to the risks identified here on __________, just to make sure that everything is running according to plan.

Other Comments or Notes:
Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>✓ Option 1*</th>
<th>☐ Option 2</th>
<th>☐ Option 3 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective RM Exercise *</td>
<td>Retrospective RM Exercise</td>
<td>Change Control RM Exercise</td>
</tr>
</tbody>
</table>

- The RM tool is being used to help determine, prospectively, the scope and extent of Qualification & Validation required for a new, or to be changed...
- The tool is being used to help determine, retrospectively, the Qualification & Validation status of, and Qualification & Validation requirements for, a...
- The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...

☐ Manufacturing Process ***
☐ Cleaning & Hygiene Process ***
☐ Labelling & Packaging Process ***
☐ Training Programme
☐ Material Sampling Programme
☐ Pest Control Programme
☐ Stability Programme
☐ Preventative Maintenance Programme
☐ Self-Inspection Programme
☐ Complaints & Recall Programme
☐ Reduced Testing Programme
☐ Item of Laboratory Equipment
☐ Supplier / Material

*** incorporating the equipment used

☐ Documentation Management System
☐ HVAC System
☐ Building Management System
☐ Distribution System
☐ Supplier Approval System
☐ Regulatory Compliance System
☐ Materials Management System
☐ Other - specify below in this box:

Wedding of Jack & Jill, December 28th, 2005

☐ If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

Notes:
* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
Step 1 Cont'd - Preliminary Information on the RM Exercise

<table>
<thead>
<tr>
<th>The Item Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the Item Under Study?</strong></td>
</tr>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
</tr>
<tr>
<td><strong>The Wedding of Jack &amp; Jill, December 28th, 2005</strong></td>
</tr>
</tbody>
</table>

| **Boundary Details:** |
| If the Item under study has a boundary, state the boundary here. For example: |
| • a boundary could be a P&ID for a piece of equipment or a system |
| • it could be 2 points within a manufacturing process, within which the RM exercise applies |
| • it could be part of a process, such as the drying & discharge stages in an API manufacturing process |
| **The RM exercise will be confined to the wedding day itself** |

| **Process Map or Schematic:** |
| State the ref. no. of any map or other document which describes/ maps the item under study: |
| **Wedding Book** |

| **Other Document (if any) associated with Item Under Study:** |
| e.g. Cleaning SOP No. 123/4 |
| e.g. Change Control No. 2005/11 |
| **N/A** |

| **Reason & Relevant Background Info for this RM Exercise** |
| State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant: |

**Purpose:** To anticipate problems on the wedding day in advance, and to try to address them

**Assumptions:** There is one month to go before the wedding. All arrangements are in place, and there seems to be nothing left to organise!
Step 2: Who's Who … Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader:</th>
<th>Jill (Bride)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position/Area of Expertise:</td>
<td>Good organiser and now considering a career in professional wedding planning!!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name:*</th>
<th>Position/Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jack</td>
<td>Future Husband</td>
</tr>
<tr>
<td>Tom</td>
<td>Best Man</td>
</tr>
<tr>
<td>Rachel</td>
<td>Bridesmaid</td>
</tr>
<tr>
<td>Fr. Tom</td>
<td>Priest</td>
</tr>
<tr>
<td>Maria</td>
<td>Good friend of the Bride’s and level headed individual</td>
</tr>
</tbody>
</table>

* Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

Carry out the following tasks, and complete this table by ticking the appropriate options:

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - [ ] Accept the default Probability, Severity & Detection definitions shown on the Card.
   - [x] Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - [x] Tick here if any new definitions are attached
   - [ ] Tick here if N/A
From Step 3:

<table>
<thead>
<tr>
<th>Amended Definitions for Severity Levels:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical</strong></td>
</tr>
<tr>
<td>The wedding is badly impacted, we are very upset.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>The wedding is definitely impacted, and while we wish the negative event didn’t happen, it’s not the end of the world.</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>The wedding is impacted only a little, in a minor way. Hardly anyone notices.</td>
</tr>
</tbody>
</table>
### Step 4: What Might Go Wrong ... Identify Potential Negative Events Here:

This involves compiling & reviewing data & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: [ ]  Session Date: Nov 30 '05

#### Tick One:
- ✔ Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- ❑ If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No. 123</td>
<td>e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are Released without a PIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Filling Process for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure Occurs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The Band Fails to Show Up.</td>
<td>The band is coming from afar, and we don’t know them personally</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 There are long delays between arriving at the hotel and sitting down to dinner.</td>
<td>We have been to many weddings where this has happened!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 The two families don’t get along and no one mixes.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Step 5: Risk Evaluation

*Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C,... etc.*

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Band Fails to Show Up</td>
</tr>
</tbody>
</table>

List the **Potential Negative Consequences** of this Negative Event, should it occur:

There is no music at the reception... The wedding is dull... People don’t know what to do... Everyone leaves early or they go to the bar attached to the hotel where there is a better atmosphere...

List any **Current Back-up Systems / Redundancy Controls** which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C,... etc.):

None. We had not planned for any alternative entertainment, and we deliberately decided not to hire a disco because the band were going to play until late.

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C,... etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None. We had not planned for any alternative entertainment, and we deliberately decided not to hire a disco because the band were going to play until late.</td>
</tr>
</tbody>
</table>

**S: Severity:** Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- ☐ Critical
- ☐ Moderate
- ☐ Minor

It's not the end of the world... or is it? What would we do if this happened? It is definitely not Minor, but is it Critical or Moderate? Some of us feel it is Critical, others Moderate. See Tool Guidance! The Tool requires us to select Critical.

List the **Possible Causes or Mechanisms** for this Negative Event to Occur:

(1) The band’s van breaks down
(2) The Band get lost and cannot find the venue
(3) The Band is double booked on the date in question and they don’t come to our wedding
(4) A member of the band gets sick and Band have to cancel, or a family member of a band member dies and Band have to cancel.

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List the Possible Causes or Mechanisms for this Negative Event to Occur:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(List the controls for each individual Negative Event Cause or Mechanism)</td>
</tr>
<tr>
<td>1</td>
<td>The band’s van breaks down</td>
</tr>
<tr>
<td>2</td>
<td>The Band get lost and cannot find the venue</td>
</tr>
<tr>
<td>3</td>
<td>The Band is double booked on the date in question and they don’t come to our wedding</td>
</tr>
<tr>
<td>4</td>
<td>A member of the band gets sick and Band have to cancel, or a family member of a band member dies and Band have to cancel.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>Current Preventative Controls in place: (List the controls for each individual Negative Event Cause or Mechanism)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None that we know of.</td>
</tr>
<tr>
<td>A</td>
<td>We have given the band the directions in writing</td>
</tr>
<tr>
<td>B</td>
<td>We have written confirmation from our band of our booking on Dec 27th 2005. (Also, the band is said to be very reliable and have been recommended by friends.)</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>P: Prob. of Occurrence of each cause / mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low or Remote? Low</td>
</tr>
<tr>
<td></td>
<td>Remote</td>
</tr>
<tr>
<td></td>
<td>Remote</td>
</tr>
<tr>
<td></td>
<td>Low or Remote? Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>Risk assoc. with each cause or mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk = P x S</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unaccept.</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Acceptable</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Acceptable</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Unaccept.</td>
</tr>
</tbody>
</table>

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
### Step 6: Risk Evaluation Cont'd

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C.

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Ctrl #</th>
<th>Detection Controls</th>
<th>D Detection Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Visual control: We will of course know when the band doesn’t show up</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: This High detectability is really no use to us. It's after the fact.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>Same as above</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: Same as above.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Step 7: Risk Control

*Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No.</td>
<td>1</td>
</tr>
<tr>
<td>Unacceptable Risk</td>
<td>✔</td>
</tr>
<tr>
<td>Intolerable Risk</td>
<td>✗</td>
</tr>
<tr>
<td><strong>State the Cause or Mechanism for the Negative Event to Occur (from Step 5):</strong></td>
<td>The band's van breaks down</td>
</tr>
</tbody>
</table>

#### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Ctr #</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>None.</strong> No preventative measures are within our control. So the Probability stays the same, at Low.</td>
</tr>
<tr>
<td></td>
<td>• Note: We could ask the band to have their van serviced the day before the wedding, but who's going to do that?! (Good example of an unrealistic control!)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctr #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Have a back-up van:</strong> We can arrange for the band to show up 2 hours earlier than planned, at 7pm. Then, if their van breaks down and they fail to show at the allotted time, we will have time to go and get them in the back-up van! We will need to have certain arrangements in place in advance, but these can be arranged.</td>
</tr>
<tr>
<td></td>
<td>• With this control in place, the effects of the Negative event are counteracted. Severity is now considered <strong>Minor</strong>.</td>
</tr>
</tbody>
</table>

**New Risk Level:**
- ✔ Acceptable - go to Step 8
- ✗ Unacceptable / Intolerable - continue below

#### If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes / No; i.e., Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✔ Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✗ No: Repeat this step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment/Explanation:</td>
</tr>
</tbody>
</table>

**Note:** If any of the above new controls may introduce a new risk, complete a new Step 4
Step 7: Risk Control
Complete only for Unacceptable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No:</td>
<td>4</td>
</tr>
<tr>
<td>☐ Unacceptable Risk</td>
<td></td>
</tr>
<tr>
<td>☑ Intolerable Risk</td>
<td></td>
</tr>
</tbody>
</table>

State the Cause or Mechanism for the Negative Event to Occur (From Step 5):
Band member gets sick, or a family bereavement occurs.

### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Ctrl</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None. No preventative measures are within our control.</td>
</tr>
<tr>
<td></td>
<td>So the Probability stays the same, at Low.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arrange to have a disco at the venue, so that way, if something happens with the band, we still have music.</td>
</tr>
<tr>
<td></td>
<td>• With this control in place, the effects of the Negative event are counteracted.</td>
</tr>
<tr>
<td></td>
<td>Severity is now considered Minor.</td>
</tr>
</tbody>
</table>

New Risk Level = ☑ Acceptable - go to Step 8  ☐ Unacceptable / Intolerable - continue below

If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes / No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ No: Repeat this Step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment/Explanation:</td>
</tr>
</tbody>
</table>

Note: if any of the above new controls may introduce a new risk, complete a new Step 4.
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control: Yes Current □ Improved □ New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

We have given the band the directions to the venue in writing.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Letter to the band with the directions to the venue.

- These items are Already In Place □
- These items are Not Already In Place □

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? 

- Yes □ No □

If yes, specify these here:

Band to acknowledge receipt of the letter. They have done so.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? 

- Yes □ No □

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

**O & V**

What is the Status of this Qualification or Validation exercise?

- Completed □
- Not Yet Completed □
- N/A □

**Current Qualification or Validation Status of this Control:** (Tick one below)

- New Qualification/Validation work needed □
- No New Qualification/Validation work needed □
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>5</th>
<th>Control No. (A, B, C, ...)</th>
<th>B</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current ☑️</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Written confirmation of booking for December 27th, 2005.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Letter from bank confirming the date.

These Items are Already In Place ☑️
These Items are Not Already In Place ☐

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑️ Yes ☐ No

If yes, specify these here:

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? ☑️ Yes ☐ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

<table>
<thead>
<tr>
<th>O &amp; V</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the Status of this Qualification or Validation exercise?</td>
</tr>
<tr>
<td>☐ Completed</td>
</tr>
<tr>
<td>☐ Not Yet Completed</td>
</tr>
<tr>
<td>☑️ N/A</td>
</tr>
</tbody>
</table>

**Current Qualification or Validation Status of this Control:** (Tick one below)

☑️ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control:</th>
<th>☑ Current</th>
<th>☑ Improved</th>
<th>☐ New</th>
</tr>
</thead>
</table>

Brief Description of the Control:

Visual Detection control: We will easily detect if the band doesn’t show up.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Best man is in charge of arrangements with the band.
He is designated to meet them upon arrival.

These items are Already In Place ☑
These items are Not Already In Place ☐

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
If yes, specify these here:

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored?
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

☑ Yes ☐ No

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

☑ V

What is the Status of this Qualification or Validation exercise?
☑ Completed
☐ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
☑ New Qualification/Validation work needed ☑ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (A, B, C, etc.)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Have a back-up van: We will arrange for the band to show up at 7pm on the 27th. Then, if their van breaks down and they fail to show at this time, Best Man will have time to call them, see what’s wrong, and if need be, someone can go and get them in the back-up van!

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

A Back-up Van and a Driver. (Bill, a workmate of the Groom’s, can do this, as he has a van.) Need also the band’s mobile number, and we need to arrange for the band leader to call the best man if they have a problem.

These items are Already In Place: □
These Items are Not Already In Place: ✓

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ No
If yes, specify these here:

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? □ Yes
If yes, list the CPP below and state the Limits / Acceptance Criteria for the CPP

Bill’s availability at 7pm December 27th is critical. He must be available.

Bill’s Van is critical. It must be available and operating on the 27th.

Qualification & Validation Requirements
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- We need to qualify (or prove) Bill’s availability at 7pm December 27th 2005.
  - Groom to call him next week to make sure he is free then, and has nothing else on that day.

- Bill’s van must be qualified to give assurance that it will operate ok on 27th.
  - Groom to check that the van has an NCT Cert. (Discreetly!! 😊)

What is the Status of this Qualification or Validation exercise?
- □ Completed
- □ Not Yet Completed
- □ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
- ✓ New Qualification/Validation work needed
- □ No New Qualification/Validation work needed
**Step 8: Qualification & Validation**

*Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.*

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (A, B, C,...)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>□ Current □ Improved □ New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

*Disco at the venue:* this is so that if something happens with the band, we still have music.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

A DJ and Set of Disco Equipment

These items are **Already In Place** □
These items are **Not Already In Place** ✔

---

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No

*If yes, specify these here:*

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes □ No

*If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP*

**DJ’s talent is a CPP:** the DJ must be able to run a good disco.

**The Sound from the Disco Equipment is a CPP:** the equipment must be working & give good sound

---

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, **describe the Qualification or Validation exercise:**

We need to qualify (or prove) the DJ’s talent and his sound system
* • Bride and Bridesmaid will go out next Saturday night to where he is DJ’ing and check him out!
* • They will also determine that the music sounds good.

**Q & V**

*What is the Status of this Qualification or Validation exercise?*

□ Completed
✓ Not Completed
□ N/A

---

**Current Qualification or Validation Status of this Control:** *(Tick one below)*

☑ New Qualification/Validation work needed
□ No New Qualification/Validation work needed
**Step 9: Action Items**

*Identify any action items from the completed Qualification & Validation Worksheets*

**Action Items**

*These could be actions to implement a control, or they could be a Qualification or Validation Exercise.*

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
</table>
| 1                      | Make arrangements with Groom’s workmate Bill about stand-by van:  
  • Check that Bill is free on Dec 27th  
  • That he is willing to be on stand-by that evening to go pick up band if they have trouble with their van  
  • Check that Bill’s van is reliable by checking that it has a valid NCT Cert | Groom | December 5th 2005 |
| 1                      | Find a DJ who is free on December 27th 2005 | Bride | December 5th 2005 |
| 1                      | Determine if the DJ is any good, and that his sound system is okay. | Bride & Bridesmaid | December 8th 2005 |
| 1                      | If this DJ is okay, then book him for the 27th. If not okay, Bride & Bridesmaid to find an alternative DJ. | Bride & Bridesmaid | December 10th 2005 |

**Comments or Notes:**
Step 10: What are the risks, and how are we managing them:

**Risk Communication Activities**

*List any communication activities required in order to communicate risks to key groups or stakeholders.*

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method:</th>
<th>Responsible Group:</th>
<th>Target Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tell the Hotel Manager that there will now be a disco as well as a band arriving for the wedding... so that the DJ can be expected by the Hotel Staff.</td>
<td>Best Man</td>
<td>December 5th, 2005</td>
</tr>
<tr>
<td>2</td>
<td>Tell the band that there will now be a disco playing after them on the night of the wedding... this is so that they can ensure that the DJ has time and space to set up his gear early on in the evening.</td>
<td>Best Man</td>
<td>December 5th, 2005</td>
</tr>
</tbody>
</table>

**Periodic Review Activities:**

Propose here a Date on which this Risk Assessment will be Reviewed:

Proposed Review Date: December 20th, 2005

If there are useful Comments or Recommendations relating to the review of this Risk Management exercise, state those here:

Let’s review the arrangements made in response to the risks identified here on December 20th, just to make sure that everything is running according to plan.

**Other Comments or Notes:**

None

Section 9

GMP-related Case Studies

This Section contains a series of completed GMP-related Case Studies showing the practical application of this Quality Risk Management methodology

The following Case Studies are presented:

- **Section 9.1:** The application of this Quality Risk Management methodology to a Paracetamol Oral Suspension Mixing & Filling Process at a Finished Product Manufacturer

- **Section 9.2:** The application of this Quality Risk Management methodology to a proposed Change Control to introduce a new Critical Product-Contact Material at an Investigational Medicinal Product (i.e. clinical trial product) Manufacturer

- **Section 9.3:** The application of this Quality Risk Management methodology to a proposed Change Control (for the introduction of ICP-MS analysis) at an API manufacture:

- **Section 9.4:** The application of this Quality Risk Management methodology to a Product Recall Procedure at a Finished Product Manufacturer

- **Section 9.5:** The application of this Quality Risk Management methodology to an area not regulated by, but directly related to, GMP - A Quality Defect Investigation Programme at an EU Competent Authority

Section 9.1

Case Study:

The application of this Quality Risk Management methodology to a Paracetamol Oral Suspension Mixing & Filling Process at a Finished Product Manufacturer
Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>☑ Option 1*</th>
<th>☑ Option 2</th>
<th>☐ Option 3 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective RM Exercise *</td>
<td>Retrospective RM Exercise</td>
<td>Change Control RM Exercise</td>
</tr>
<tr>
<td>The tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed...</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
</tbody>
</table>

- Manufacturing Process ***
- Cleaning & Hygiene Process ***
- Labeling & Packaging Process ***
- Training Programme
- Material Sampling Programme
- Pest Control Programme
- Stability Programme
- Preventative Maintenance Programme
- Self-Inspection Programme
- Complaints & Recall Programme
- Reduced Testing Programme
- Item of Laboratory Equipment
- Supplier / Material

*** incorporating the equipment used.

If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

Problems have been observed with Mixer Vessel No. VS-04 over the last year, in which the mixer appeared to malfunction on a number of occasions when mixing & filling batches of Formulation 123 (Paracetamol Suspension BP for Paediatric Use, 100mg/5ml in HDPE Bottles). Mixing speed appeared variable, and haphazard. Several stoppages were recorded.

Notes:
* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
Step 1 Cont’d - Preliminary Information on the RM Exercise

<table>
<thead>
<tr>
<th>The Item Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the Item Under Study?</strong></td>
</tr>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
</tr>
</tbody>
</table>

| This vessel is used to hold and mix the paracetamol suspension prior to and during filling into bottles. |

| **Boundary Details:** |
| If the item under study has a boundary, state the boundary here. For example: |
| • a boundary could be a P&ID for a piece of equipment or a system |
| • it could be 2 points within a manufacturing process, within which the RM exercise applies |
| • it could be part of a process, such as the drying & discharge stages in an API manufacturing process |

| The RM exercise will be confined to the mixing stage of this process in Mixer Vessel No. VS-04. |

| **Process Map or Schematic:** |
| State the ref. no. of any map or other document which describes/maps the item under study: |

| This Mixing process is described in Product Development Report No. ABC, dated June 1st ’98. See p4 of this report for a schematic of the process. |

| **Other Document (if any) associated with Item Under Study:** |
| e.g. Cleaning SOP No. 123/4 |
| e.g. Change Control No. 2065/11 |

| Batch Production Record No. 123/23.4 for Formulation No. 123 (Paracetamol Suspension BP for Paediatric Use, 100mg/5ml in HDPE Bottles). |

| **Reason & Relevant Background Info for this RM Exercise** |
| *State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant.* |

**Purpose & Background Info:**

Mixer Vessel No. VS-04 appeared to malfunction on a number of occasions when mixing & filling batches of Formulation 123. Mixing speed appeared variable, and haphazard. Stoppages recorded. Several deviations were therefore raised in late 2004 and during 2005 for this mixing process.

Note that this mixer is used with several other suspension formulations, but mixer problems were only observed with Formulation 123. This is a high viscosity suspension.

As part of our Product Quality Review work for this product, it has been decided (Ref: Minutes of Plant Deviations Meeting of November 28th, 2005) to apply a Risk Management approach to help determine what, if any, new qualification and/or validation work is required for this mixing process.

**Assumptions:**

- This mixing process has been fully validated as part of the overall validation of the process (Ref: 2003 Process Validation Report for Formulation 123), and all equipment has been qualified.
- All analytical methods associated with this process have been validated.
### Step 2: Who's Who ... Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader:</th>
<th>Team Leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position / Area of Expertise:</td>
<td>Validation Manager</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name *</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. N. Other</td>
<td>Qualified Person</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Senior QC Analyst</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>PM &amp; Engineering</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Regulatory Affairs</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>QA</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Senior Production Operator</td>
</tr>
</tbody>
</table>

*Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)*

### Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

**Carry out the following tasks, and complete this table by ticking the appropriate options:**

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - [ ] Accept the default Probability, Severity & Detection definitions shown on the Card.
   - [ ] Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - [ ] Tick here if any new definitions are attached
   - [✓] Tick here if N/A
### Step 4: What Might Go Wrong ... Identify Potential Negative Events Here:

This involves compiling & reviewing data & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: 1  Session Date: Nov 29 '05

- Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)

- If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No. 123</td>
<td>e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are Released without a PIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Filling Process for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure Occurs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mixer malfunctions during mixing of Suspension Formulation 123 prior to or during filling, resulting in possibly a variable mixing speed, or in a stoppage of the mixer.</td>
<td>Formulation 123 is a high-viscosity suspension. It is mixed at 80 RPM / 30 mins prior to filling. Mixing continues during filling.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
Step 5: Risk Evaluation
Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C,... etc.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mixer malfunctions during mixing of Suspension Formulation 123 prior to or during filling, resulting in possibly a variable mixing speed, or in a stoppage of the mixer.</td>
</tr>
</tbody>
</table>

List the Potential Negative Consequences of this Negative Event, should it occur:

The required mixing is not achieved, leading to a possible non-homogeneous suspension being filled into bottles. This could result in Low & High conc. bottles, leading to possible patient under- or overdosing. This is a paediatric paracetamol suspension, and this could be very harmful.

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C,... etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None.</td>
<td>(However, there are detection controls in place though which can help ensure that such batches are not released to market. See Step 6.)</td>
</tr>
</tbody>
</table>

S: Severity: Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- Critical
- Moderate
- Minor

<table>
<thead>
<tr>
<th>List the Possible Causes or Mechanisms for this Negative Event to Occur:</th>
<th>Current Preventative Controls in place: (List the controls for each individual Negative Event Cause or Mechanism)</th>
<th>P: Prob. of Occurrence of each cause or mechanism</th>
<th>Risk assoc. w/ each cause or mechanism Risk=P x S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Maintenance Dept. has determined the most likely cause of the malfunction to be related to the tension of the belt connecting the motor and the mixer shaft in Vessel VS-04. (This is an old-technology mixer. With an incorrect belt tension, the belt can slip during mixing high viscosity suspensions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: This suspension has a viscosity range near the upper PQ limit for this mixer.</td>
<td>Two such controls are in place: Preventative Maintenance: Mixer is on a PM schedule and this should serve to prevent a mechanical problem with the mixer. (Note however that the PM protocol is not that detailed, and it does not address a belt tension check.)</td>
<td>Medium Note: our deviations data show that the problem occurs in about 1 batch in 5.</td>
<td>Intolerable</td>
</tr>
</tbody>
</table>

Instruction: For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
<table>
<thead>
<tr>
<th>Risk #</th>
<th>Ctrl #</th>
<th>Detection Controls</th>
<th>D Detection Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>List any controls currently in place which detect the Negative Event or its consequences after the Negative Event has occurred.</td>
<td>Hi/Med/ Low/Zero</td>
<td>Is this Risk adequately controlled? – Yes / No i.e. Do these controls give assurance that the risk is adequately controlled &amp; that no further controls are required? Explain Below:</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Note: This is an old-technology mixer. No recording of Mixer Shaft Speed (RPM) is currently possible, and so there is no detection of a change in shaft rotation speed. There are however other detection controls in place:</td>
<td>Low</td>
<td>If No, Go to Step 7. If Yes, Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>In-Process Testing:</strong> After 30mins of mixing the bulk suspension, one in-process sample is taken for appearance, active &amp; preservative content testing. If sample passes, then batch is filled into bottles.</td>
<td></td>
<td><strong>No. This risk is not adequately controlled.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>QC Finished Product Testing:</strong> Three filled bottles (start, middle, end) are analysed as part of QC testing. Samples are also taken after any stoppage or significant intervention.</td>
<td>Medium (Note: we debated between High &amp; Medium ... &amp; we could not decide... the tool thus requires us to select Medium)</td>
<td><strong>Reason:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>This is end product testing – the batch will have been filled by now and this testing is after the fact. Batch could be OOS for paracetamol content.</td>
</tr>
</tbody>
</table>
Step 7: Risk Control

Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk

<table>
<thead>
<tr>
<th>Negative Event No.:</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No.:</td>
<td>1</td>
</tr>
<tr>
<td>□ Unacceptable Risk</td>
<td></td>
</tr>
<tr>
<td>□ Intolerable Risk</td>
<td></td>
</tr>
</tbody>
</table>

State the Cause or Mechanism for the Negative Event to Occur (from Step 5):
Incorrect tension of the belt connecting the motor and the mixer shaft in Vessel VS-04, especially when mixing a suspension with a viscosity at or near the upper PQ limit for this mixer.

<table>
<thead>
<tr>
<th>Risk Reduction Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl # A</td>
</tr>
<tr>
<td>What New or Improved Preventative Controls could prevent this Negative Event?</td>
</tr>
<tr>
<td>Improve the PM work done on this mixer:</td>
</tr>
<tr>
<td>• Define a belt tension spec for the mixer belt, and check tension when doing PM work on this mixer. Also, increase the frequency of the PM checks, say to every 3 months. (Currently this is done only annually.)</td>
</tr>
<tr>
<td>Comment: These actions should help ensure that the belt is within its correct tension at all times, and while the upper viscosity limit for this suspension is still near the upper PQ limit for this mixer, better PM should help reduce the incidence of mixer malfunctions due to belt tension problems. The Probability is now considered Low.</td>
</tr>
</tbody>
</table>

Crtl # A                | What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur? | New S Severity Rating for this Negative Event | New P Prob. Rating for this Negative Event |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None have been identified. So Still Critical.</td>
<td><img src="image" alt="Critical" /></td>
<td><img src="image" alt="Low" /></td>
<td></td>
</tr>
</tbody>
</table>

New Risk Level = □ Acceptable - go to Step 8   ✓ Unacceptable / Intolerable - continue below

If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
</table>
| Ctrl # B                                                      | High           | Is risk now adequately controlled? Yes / No i.e.
| Start Recording Mixer Shaft Speed (80 +/- 5 RPM) and check it routinely during batch processing. |                | Do these controls now give assurance that the risk is adequately controlled & no further controls are required?   |
| Note: Recording Shaft Speed will enable us to detect the effects of this negative event (i.e. variable mixing speed, or a stoppage of the mixer) and this is an important control given that this high viscosity suspension is near the upper PQ limit for this Mixer. |                | ✓ Yes: Go to Step 8
| ✗ No: Repeat this Step                                         |                | Comment/Explanation: Yes, the risk is now adequately controlled. |

Note: if any of the above new controls may introduce a new risk, complete a new Step 4
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (A, B, C,...)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current ☑</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Mixer Preventative Maintenance: We will improve the PM work on this mixer:
- Define a belt tension spec for the mixer belt, and check this during PM work on this mixer;
- Increase the frequency of the PM work to every 3 months.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Revised PM Protocol & Revised PM Schedule for this mixer.

These Items are Already In Place ☐
These Items are Not Already In Place ☑

Complete Either Part A or B Below…

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
If yes, specify these here:

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? ☑ Yes ☐ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Belt Tension is a CPP; limits need to be defined.

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Mixer should be OQ & PQ qualified when a belt tension spec has been developed, so that we demonstrate that at the viscosities expected with Formulation 123, the mixer can operate correctly.

☐ & ☑

What is the Status of this Qualification or Validation exercise?
☐ Completed
☑ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
☑ New Qualification/Validation work needed ☐ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>A</td>
<td>✓Current</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brief Description of the Control:

In-Process Testing:
At the end of mixing the bulk suspension, one in-process sample is taken for appearance, active & preservative content testing. If sample passes, then batch is filled into bottles.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

All documentation & other required items already in place.

These Items are Already In Place ✓
These Items are Not Already In Place □

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control?  Yes  No
If yes, specify these here:

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored?  Yes  No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Suspension appearance, active content & preservative content are all In-Process CPPs here.

Limits are already defined for these in-process tests. The analytical methods have all been validated.

Qualification & Validation Requirements
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

While this in-process sampling is supported by the 2003 process validation study, the PQ work which is required for the mixer (see previous Step 8 worksheet) will be used to re-validate this in-process sampling step via a new batch homogeneity study at that time.

What is the Status of this Qualification or Validation exercise?
Completed ✓
Not Yet Completed □
N/A □

Current Qualification or Validation Status of this Control: (Tick one below)
✓ New Qualification/Validation work needed  □ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>6</th>
<th>Control No. (A, B, C,...)</th>
<th>B</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ Current</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

QC Finished Product Testing:
Three filled bottles (start, middle, end) are analysed as part of QC testing. Samples are also taken after any stoppage or significant intervention.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

All documentation & other required items already in place.

These Items are Already In Place ✓
These Items are Not Already In Place □

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control?  □ Yes  ✓ No
If yes, specify these here:

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored?  ✓ Yes  □ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

The various test parameters measured during the finished product testing are the CPPs here.
The specifications for each test parameter are already defined, and the methods have all been validated.

Qualification & Validation Requirements
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:
All required methods are validated & no new analytical method validation is required.

Q & V
What is the Status of this Qualification or Validation exercise?
✓ Completed
□ Not Yet Completed
□ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
□ New Qualification/Validation work needed  ✓ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (A, B, C,...)</th>
<th>B</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Current</td>
<td></td>
<td>□ Improved</td>
<td></td>
<td>□ New</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Start Recording Mixer Shaft Speed (80 +/- 5 RPM) and check it routinely during batch processing:

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Equipment (calibrated tachometer & calibrated chart recorder) are required to measure & record mixer shaft speed.
- Batch record to be amended to require Operators to check the shaft speed during processing, and to attach the chart from the chart recorder at the end of batch processing for QA review.

These Items are Already In Place □
These Items are Not Already In Place ■

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes ■ No.

If yes, specify these here:

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes ■ No.

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

Mixing Shaft Speed is the CPP here.

The validated range is 80 +/- 5 RPM (as derived from initial process optimisation work & last validated in the 2003 process validation exercise.)

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

This parameter was validated in 2003. However, continuous recording of shaft speed during routine batch processing requires the installation and qualification of a tachometer & chart recorder. (IQ/OQ/PQ required.)

**Q & V**

What is the Status of this Qualification or Validation exercise?

■ Completed
■ Not Yet Completed
□ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

■ New Qualification/Validation work needed
□ No New Qualification/Validation work needed
### Step 9: Action Items

Identify any action items from the completed Qualification & Validation Worksheets

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Revise PM Protocol for Mixer No. VS-04 to define a belt tension spec and a test for same</td>
<td>Maintenance D Dept.</td>
<td>15/12/05</td>
</tr>
<tr>
<td>1</td>
<td>Revise the PM Schedule for this mixer to increase the frequency to every 3 months</td>
<td>Maintenance D Dept. &amp; QA</td>
<td>15/12/05</td>
</tr>
<tr>
<td>1</td>
<td>Re-qualify (OQ &amp; PQ) the mixer to demonstrate that it can mix the viscosity range for Formulation 123</td>
<td>Validation</td>
<td>15/2/06</td>
</tr>
<tr>
<td>1</td>
<td>Do a limited revalidation (PV) exercise on the mixing process to re-validate the in-process sampling step... this can be done during the PQ of the mixer... see above.</td>
<td>Validation</td>
<td>15/2/06</td>
</tr>
<tr>
<td>1</td>
<td>Identify, purchase &amp; install a suitable tachometer and chart recorder for this mixing vessel.</td>
<td>Engineering &amp; Validation</td>
<td>31/1/06</td>
</tr>
<tr>
<td>1</td>
<td>Qualify the tachometer and chart recorder (IQ/OQ/PQ). Note: we will combine these qualification studies with the PQ &amp; PV studies defined above.</td>
<td>Engineering &amp; Validation</td>
<td>15/2/06</td>
</tr>
<tr>
<td>1</td>
<td>Amend the Master Batch Record for Formulation 123 as required for checking shaft speed and for attaching chart to batch record at end of processing.</td>
<td>QA</td>
<td>31/1/06</td>
</tr>
</tbody>
</table>

### Comments or Notes:

None
### Risk Communication Activities

List any communication activities required in order to communicate risks to key groups or stakeholders.

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method</th>
<th>Responsible Group</th>
<th>Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Communicate to Process Operators the risk associated with poor mixer performance and the actions being undertaken as a result of this Risk Management exercise</td>
<td>Validation</td>
<td>20/12/05</td>
</tr>
<tr>
<td>2</td>
<td>Communicate the results of this Risk Management exercise to Snr. Management, including Finance, so that the necessary capital and resources can be expended to address the issues identified.</td>
<td>RM Team Leader</td>
<td>15/12/05</td>
</tr>
<tr>
<td>3</td>
<td>Formally communicate to Engineering the need to take this Mixer out of service until the necessary changes have been implemented and qualified as defined in this Risk Management exercise.</td>
<td>RM Team Leader</td>
<td>Immed. (1/12/05)</td>
</tr>
<tr>
<td>4</td>
<td>Communicate with the Regulatory Group at the MAH office in the UK the actions being undertaken as a result of this Risk Management exercise, so that any regulatory (e.g. variation) obligations can be addressed. (Note: a formal Change Control will be processed anyway and will be circulated to Reg Affairs when the batch record is being amended, but it is considered useful to communicate these issues with Regulatory before then.)</td>
<td>QP</td>
<td>20/12/05</td>
</tr>
</tbody>
</table>

### Periodic Review Activities:

Propose here a Date on which this Risk Assessment will be Reviewed:

- **Proposed Review Date:** End April 2006

If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:

Note: by the end of April 2006, all corrective actions and the necessary Qualification & Validation work should have been completed. Also, several routine batches of Formulation 123 will have been processed in the modified mixer. Therefore, that will be a good time to review this Risk Management exercise, to see have we adequately addressed the risk associated with the problem issue, which prompted this Risk Management exercise.

### Other Comments or Notes:

None
Section 9.2

Case Study:

The application of this Quality Risk Management methodology to a proposed Change Control to introduce a new Critical Product-Contact Material at an Investigational Medicinal Product (i.e. clinical trial product) Manufacturer
### Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>☑ Option 1*</th>
<th>□ Option 2</th>
<th>☑ Option 3**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective RM Exercise</strong></td>
<td><strong>Retrospective RM Exercise</strong></td>
<td><strong>Change Control RM Exercise</strong></td>
</tr>
<tr>
<td>The RM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed...</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
</tbody>
</table>

- Manufacturing Process ***
- Cleaning & Hygiene Process ***
- Labelling & Packaging Process ***
- Training Programme
- Material Sampling Programme
- Pest Control Programme
- Stability Programme
- Preventative Maintenance Programme
- Self-Inspection Programme
- Complaints & Recall Programme
- Reduced Testing Programme
- Item of Laboratory Equipment
- Supplier / Material

*** incorporating the equipment used

- Documentation Management System
- HVAC System
- Building Management System
- Distribution System
- Supplier Approval System
- Regulatory Compliance System
- Materials Management System
- Other - specify below in this box:

- If the RM exercise is to help determine Qualification & Validation status or requirements in response to a **specific issue or problem** (e.g. a series of batch rejects), state the problem here:

  Describe the specific issue or problem here:

### Notes:

* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
Step 1 Cont’d - Preliminary Information on the RM Exercise

<table>
<thead>
<tr>
<th>The Item Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the Item Under Study?</td>
</tr>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A planned new manufacturing process for this (Investigational Medicinal Product) manufacturing site, which involves nano-milling technology, also new to the site. Product X (investigational medicinal product). The approval of a new critical product contact material for the nano-milling process is the item under Study here.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boundary Details:</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the item under study has a boundary, state the boundary here. For example:</td>
</tr>
<tr>
<td>• a boundary could be a P&amp;ID for a piece of equipment or a system</td>
</tr>
<tr>
<td>• it could be 2 points within a manufacturing process, within which the RM exercise applies</td>
</tr>
<tr>
<td>• it could be part of a process, such as the drying &amp; discharge stages in an API manufacturing process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process Map or Schematic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>State the ref. no. of any map or other document which describes / maps the item under study:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Document (if any) associated with Item Under Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Cleaning SOP No. 1234</td>
</tr>
<tr>
<td>e.g. Change Control No. 2005/11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason &amp; Relevant Background Info for this RM Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant.</td>
</tr>
</tbody>
</table>

Change Control No. 2005/61 was raised to manage the approval of a new yttrium zirconium ceramic milling bead material from Manufacturer X (China). This material is to be used in a stirred media (attrition) mill operating in wet-batch mode for the nano-milling of an intermediate investigational medicinal product process. The result is a stabilized sub-micron aqueous colloid. The required particle size profile for the intermediate product is documented in R&D Process Development Report No. 2004/23, and also in product specification document QA-QC-803-32-1. The nano-milling process is described in detail in the aforementioned R&D Process Development Report, and full qualification of milling suite, (a series of five mills in sequence), as well as full validation of the milling process, are planned for 2007. See draft Project Validation Master Plan for 2006, (VMP-2006-803-draft 3) for information on the qualification and validation protocols already developed.

From a risk-perspective, Change Control No. 2005/61 has already investigated and considered the work performed by R&D on some of the known problems with wet stirred media milling. Some such problems relate to energy consumption issues, media wear issues and product contamination (due to the high energy milling process, and wear of the bead milling media), problems achieving the required slurry rheology requirements, and non-homogeneity in particle size reduction issues due to dead zones in the grinding chamber of the mill suite. Other risk areas such as final power handling (after spray drying), the washing and re-use of the beads, micro issues, among others, have also been investigated in Change Control No. 2005/61, and several risk mitigating actions have been identified.

This QRM exercise focuses only on that part of the Change Control concerned with the approval work planned for the Chinese manufacturer of the yttrium zirconium ceramic milling bead material. The Change Control has already identified that an audit of that manufacturer is required; the manufacturer has completed the pre-audit questionnaire, and the audit is planned for Q1, 2006. Two lots of the bead material have to date been used in pilot scale milling work at R&D, and the material performed satisfactorily. See by R&D Process Development Report No. 2004/23.
Step 2: Who’s Who ... Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader</th>
<th>Team Leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position / Area of Expertise</td>
<td>QA Supplier Approval</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name *</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. N. Other</td>
<td>Purchasing Manager</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Validation Engineer</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Process Chemist R&amp;D</td>
</tr>
</tbody>
</table>

*Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

---------------------------

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

* Carry out the following tasks, and complete this table by ticking the appropriate options:*

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.
   - ☑ Accept the default Probability, Severity & Detection definitions shown on the Card.
   - ☐ Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.
   - ☐ Tick here if any new definitions are attached
   - ☐ Tick here if N/A
Step 4: What Might Go Wrong ... Identify Potential Negative Events Here:

*This involves compiling & reviewing data & brainstorming to identify potential negative events for the Item Under Study.*

Data Review & Brainstorming Session No: 1  Session Date: 3/5/2005

**Tick One:**
- [x] Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- [ ] If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference or Notes</th>
</tr>
</thead>
</table>
| 1   | e.g. Cross Contamination Event occurs in Dryer Room No. 123  
    e.g. Glass in Vials of Product X  
    e.g. Packs of Product X are Released without a PIL  
    e.g. Hard, yellow particles observed in batches of API X  
    e.g. Loss of Sterility Assurance for Filling Process for Product X  
    e.g. Low Yield Batches of API X  
    e.g. BMS System Failure Occurs | e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6) |

**Description of Potential Negative Event**

1. A shipment of zirconium ceramic milling head material is received from the supplier which has an incorrect particle size profile.

**Reference or Notes**

Note: Each shipment of this bead material is required to contain five different sub-lots, each with a different range of particle size. One drum per particle size range is required, for use in the five individual nano-mills in the nano-milling process.

2. A shipment of zirconium ceramic milling head material is received from the supplier which contains one or more rogue materials — i.e. not the required zirconium ceramic milling head material.

*Note: To facilitate training on this Quality Risk Management methodology, and for the purposes of the Training & User's Manual on this methodology, the team undergoing the training should take this Case Study and assess (and manage) the risk associated with this Potential Negative Event. For this reason, the remaining Steps of this Quality Risk Management exercise for this Potential Negative Event (No. 2) have been left blank. They should be executed by the trainees, in conjunction with their trainer.*

**Reference or Notes**

It is critical to the milling operation that the correct grinding material is used in the milling process.

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Step 5: Risk Evaluation

*Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C, etc.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A shipment of zirconium ceramic milling bead material is received from the supplier which has an incorrect particle size profile.</td>
</tr>
</tbody>
</table>

List the **Potential Negative Consequences** of this Negative Event, should it occur:

The use of incorrect (or out of sequence) particle size beads in the nano-milling train has been found in R&D to affect milling performance; (see R&D Process Development Report No. 2004-23), Nano-milled IMP batches may not have the required particle size profile. A reprocessing or re-work operation may be required, if problem detected during processing or QC testing. Batches could be rejected. If problem not detected, incorrect particle size IMP batches could be released and used in clinical trials, yielding suspect results. Potential for patient impact in the long term if CT batches do not reflect marketed product. Particle size critical to drug bioavailability for this highly insoluble drug substance.

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List any <strong>Current Back-up Systems / Redundancy Controls</strong> which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C... etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None. No particle size testing is planned for batches of zirconium ceramic milling bead material. Only identify testing is planned. See product specifications, Document No. QA-QC-803-32-1.</td>
</tr>
</tbody>
</table>

### Severity: Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- [ ] Critical  
- [ ] Moderate  
- [ ] Minor

Significant potential negative consequences identified above. These effects are not minor, but probably not critical for patients either. Drug bioavailability is an important issue, but not usually life threatening. Patients may be impacted, but not likely to be injured. The use of this material represents a significant non-compliance with GMP. Moderate Severity rating is appropriate. No controls in place with counteract or eliminate these negative consequences should the Negative Event occur. Moderate Severity.

<table>
<thead>
<tr>
<th>List the Possible Causes or Mechanisms for this Negative Event to Occur: No.</th>
<th>Current <strong>Preventative Controls in place:</strong> (List the controls for each individual Negative Event Cause or Mechanism)</th>
<th><strong>P:</strong> Prob. of Occurrence of each cause / mechanism</th>
<th><strong>Risk assoc. w/ each cause or mechanism</strong></th>
<th><strong>Risk = P x S</strong></th>
<th><strong>Unaccept. Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Labelling mix-up at site of manufacture of the beads, or at any companies in the supply chain performing drum relabelling activities. <strong>Note:</strong> Upon investigation, we have learned that the material goes through a broker in China, who exports it to the EU, and an EU import agent in the UK, another broker. We also learned that the UK broker performs drum over-labelling, with material id and grade (particle size profile) information on these labels, as well as a material bar code.) It is unknown if the Chinese broker performs any over-labelling activity.</td>
<td>Labelling controls (including QA inspection of labelled bags and drums) and Bead manufacturer. <strong>Note:</strong> Bead manufacturer has an ISO 9000 QMS in place; the control of labels and labelling activities is under QMS, and all labelled bags and drums are QA-checked for correct labelled information prior to shipment. (Ref: pre-audit questionnaire received from manufacturer.) These areas need to be inspected thoroughly during the planned QA audit in 2006. However, we have not yet audited the bead manufacturer, and we know nothing about the controls or the level of QMS in place at the two brokers (China &amp; UK). So, controls are not in place to give assurance that a labelling mix-up shall not occur.</td>
<td>The prob. of the error occurring at the manufacturer should be Low, but as no info to go on wrt the 2 brokers, the prob. rating should be Medium - i.e. the Pot. Neg. Event may occur.</td>
<td># 1</td>
<td>Unaccept. Risk</td>
</tr>
</tbody>
</table>

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
### Step 6: Risk Evaluation Cont'd

*This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C.*

<table>
<thead>
<tr>
<th>Risk</th>
<th>Ctrl</th>
<th>Detection Controls</th>
<th>D Detection Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>In-process testing (for particle size) of the milled Investigational Medicinal Product (IMP) suspension during milling:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Notes:*

This control will likely be useful as it may indicate a problem during milling, and it may indicate that an incorrect particle size bead material was used in any one (or more) of the mills.

R&D has demonstrated that each grade of bead material gives a distinctive particle size reduction profile during processing, and that this can be confirmed in-process. See R&D Process Development Report No. 2004/23.

Extensive in-process particle size testing is planned. See draft Batch manufacturing Record for the nano-milling process, No. PRD-345-32.

Having consulted with R&D, based on pilot scale milling studies, R&D is confident that a mix-up in particle size materials in the milling train would be detected in-process. (Ref: report from C. Wilson, R&D, 11/5/05).

| High | No. |

**Explanation:**

This control does not give assurance that the risk in question is adequately controlled & that no further controls are required. This IPC control is 'after the fact'; the IMP batch would likely need to be either re-processed or re-worked as a result of this Potential Negative Event.

Also, the high detectability of the Pot. Negative Event has not been demonstrated at production scale at this time, only in pilot scale. So, one should not have overconfidence in the level of detection which may exist via this IPC for such a Potential Negative Event.
### Step 7: Risk Control

Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>State the Cause or Mechanism for the Negative Event to Occur (from Step 5):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No:</td>
<td>1</td>
<td>Labelling mix-up at site of manufacture of the beads or at any companies in the supply chain performing drum re-labelling activities (EU Import broker, and possibly Chinese Export broker).</td>
</tr>
</tbody>
</table>

#### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Crtl #</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Eliminate the use of the EU Brokerage company involved in the supply of this material to our site; this company is involved in over-labelling of the drums, and our information is that there is no effective QMS in place at that company.</td>
</tr>
<tr>
<td>B</td>
<td>Ensure that no over-labelling (using labels carrying material source, lot, identity or material grade information) is carried out on these drums by the broker in China. (Note: A better solution would be to eliminate the use of this broker. But due to Chinese export licensing requirements, it is not feasible to insist that the Chinese broker is not used in the export of this material out of China.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crtl #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Change the plan to perform only identity testing (and no particle size testing) on incoming batches of this zirconium ceramic bead milling material. Instead, add particle size testing (as well as extra label inspection activities) to the required list of tests for all incoming lots of this material. This will give assurance that if a labelling error occurs at either the manufacturer or the broker in China, the consequences of this PCT Negative event will be counteracted. (Note: This control is both a detection-type control and a Severity-affecting control. This control reduces the Severity rating to Minor.)</td>
</tr>
</tbody>
</table>

**New Risk Level:**

- Acceptable - go to Step 8
- Unacceptable / Intolerable - continue below

#### If the Risk is Still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>Crtl #</th>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes / No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: Repeat this Step</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comment/Explanation</td>
</tr>
</tbody>
</table>

**Note:** If any of the above new controls may introduce a new risk, complete a new Step 4.
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

### Brief Description of the Control:

General labelling controls (including QA Inspection of labelled bags and drums) at the zirconium bead manufacturer.

### Items Required for this Control:

List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Relevant procedure for bag and drum labelling activities.
- Procedure for the approval and control of labels.
- Procedure for the QA inspection of labels and labelled bags & drums.
- QA personnel for the inspection of labels and labelled components.

*Note: During the audit planned for Q1 2006, these items should all be inspected.*

These items are Already In Place ✔
These items are Not Already In Place ☐

### Complete Either Part A or B Below...

#### Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ✔ Yes ☐ No
If yes, specify these here:

The Quality Management System must ensure that labelling controls are being complied with, and that any labelling-related deviation/complaint/reported quality defect is investigated and adequately resolved. Labelling controls should be audited via the site internal audit programme.

Staff involved in labelling and inspection of labelling must be trained on the relevant procedures. Given that the labels in question are in English, the company staff involved in labelling and the inspection of labelling should have sufficient English to allow them to perform their duties effectively.

#### Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? ☐ Yes ✔ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

### Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- The above controls and requirements should be assessed during the planned qualification audit that is planned to take place in Q1 2007 at the manufacturer in China of this yttrium zirconium ceramic bead milling material. See Change Control No. 2005/61 for details.

#### Q & V

What is the Status of this Qualification or Validation exercise?

- ✔ Completed
- ☐ Not Yet Completed
- ☐ N/A

### Current Qualification or Validation Status of this Control:

- ✔ New Qualification/Validation work needed
- ☐ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No.</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
<td>□ Current □ Improved □ New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

In-process testing (for particle size) of the milled Investigational Medicinal Product (IMP) suspension during milling. (Note: this is a new control, simply because it is not yet in place, but it was planned via Change Control No. 2005/61 before this QRM exercise was initiated.)

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Relevant procedure for taking the in-process suspension samples and performing the testing.
- Particle size specifications in place for samples from each mill in the equipment train.
- Relevant particle size analyzer for QC Lab.
- Trained sampling and laboratory personnel.

□ These items are Already In Place
□ These items are Not Already In Place

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No
If yes, specify these here:

Staff involved in the required sampling and analysis activities must be trained and demonstrate competency in these tasks.
This will be managed via our normal training assessment procedures.

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? □ Yes □ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

- Particle size is the CPP for the in-process particle size control. See R&D Process Development Report No. 2004/23 for specification details. (To be incorporated into QC specs as per normal procedures.)

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- Qualification of the particle size analyzer – this has already been planned. See Project Change Control No. 2005/56 and draft Project Validation Master Plan for 2006, (VMP-2006-803-draft 3) for details.

- Validation of the particle size test on the milled suspension. This has also been planned. See Project Change Control No. 2005/56 and draft Project Validation Master Plan for 2006, (VMP-2006-803-draft 3) for details.

□ O & Y
What is the Status of this Qualification or Validation exercise?
□ Completed
□ Not Yet Completed
□ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
□ New Qualification/Validation work needed
□ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>Current ☐</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>Improved ☐</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>New ☑</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Eliminate the use of the EU Brokerage company involved in the supply of this material to our site; this company is involved in over-labelling of the drums, and our information is that there is no effective QMS in place at that company.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Agreement with the material manufacturer and the export broker in China not to use this EU Broker as an intermediary in their supply of the material to our site. (Material to be shipped directly from the Chinese broker to our site.) This arrangement must be made in writing before routine supply of this material begins in 2007, via Tech. Agreements with both parties.
- The Goods-in Approved Supplier List must be updated to reflect this arrangement.

These Items are Already In Place ☐
These Items are Not Already In Place ☑

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑Yes ☐No
If yes, specify these here:

- An acceptable and signed Technical Agreement specifying the above arrangement with both the head manufacturer in China and the Chinese export broker for the material
- An approved Goods-in Approved Supplier List is required that reflects the above arrangement.

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? ☑Yes ☐No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

What is the Status of this Qualification or Validation exercise?

- Completed ☐
- Not Yet Completed ☑
- N/A ☐

Current Qualification or Validation Status of this Control: (Tick one below)

- New Qualification/Validation work needed ☐
- No New Qualification/Validation work needed ☑
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Event No:</th>
<th>Worksheet</th>
<th>Control No.</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1</td>
<td>(A, B, C,...)</td>
<td>Current Improved New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Ensure that no over-labelling (using labels carrying material identity or material grade information) is carried out on these drums by the export broker in China.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Agreement with the export broker in China not to perform any over-labelling of material source, lot, identity or grade information on drums of this yttrium zirconium ceramic bead milling material destined for our company. This agreement must be made in writing before routine supply of this material begins in 2007, via Tech. Agreement.
- Our local (Ireland) Goods-in procedure must be updated to require an inspection of drums of this particular material for any signs of over-labelling.
- A new drum inspection record form is required to allow Goods-in staff to record the results of their drum labelling inspection, as the current form (F0872.3) does not make provision for this.

These Items are Already In Place
These Items are Not Already In Place

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? Yes No
If yes, specify these here:

- An acceptable and signed Technical Agreement specifying the above arrangement with both the Chinese export broker for the material.
- An approved Goods-in Approved Supplier List and associated approved drum inspection record form are required that reflects the above drum inspection arrangement.

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? Yes No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Qualification & Validation Requirements:
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- This export broker in China must be audited and qualified before routine supply of this yttrium zirconium ceramic bead milling material commences.
- The qualification exercise should establish that the contents of the Technical Agreement reflecting the above arrangement are capable of being complied with within the Quality System procedures in place at that broker, if any.

What is the Status of this Qualification or Validation exercise?
- Completed
- Not Yet Completed
- N/A

Current Qualification or Validation Status of this Control: (Tick one below)
- New Qualification/Validation work needed
- No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No</th>
<th>Worksheet Step No</th>
<th>Control No. (A, B, C…)</th>
<th>C</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
<td>☐ Current ☐ Improved ☑ New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Introduce particle size testing (as well as extra label inspection activities) for all drums of all incoming lots of this yttrium zirconium ceramic bead milling material.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- A procedure for performing particle size testing on this yttrium zirconium ceramic bead milling material is available from R&D in the US and should be obtained to prepare for method transfer activities.
- Relevant particle size analyser for the QC Lab.
- Analyst training on running this procedure will be required.
- (See previous Sheet 8 for requirements in relation to the above extra label inspection activities.)

These items are Already In Place ☐
These Items are Not Already In Place ☑

**Complete Either Part A or B Below…**

### Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No

If yes, specify these here:

- The new particle size test method for the bead material must undergo a satisfactory transfer validation exercise in our laboratory.
- Lab analysts running this method must pass the training assessment criteria.

### Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? ☐ Yes ☑ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- Transfer validation of the R&D particle size test method for the bead material.
- Qualification of the particle size analyser for the QC Lab. (Note: R&D has advised that the particle size analyser used for analyzing the in-process suspension samples can be used for analysing the solid bead material also.)

**Q & V**

What is the Status of this Qualification or Validation exercise?

☐ Completed
☒ Not Yet Completed
☐ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

☑ New Qualification/Validation work needed
☐ No New Qualification/Validation work needed
**Step 9: Action Items**

*Identify any action items from the completed Qualification & Validation Worksheets*

---

**Action Items**

*These could be actions to implement a control, or they could be a Qualification or Validation Exercise.*

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
</table>
| 1                       | Perform the planned qualification audit at the Chinese manufacturer of the yttrium zirconium ceramic bead milling material, taking into account the specific requirements documented in this Quality Risk Management exercise for that audit. Some of these requirements have not been documented in Change Control No. 2005/56, so the audit plan will need modification to reflect the findings of this QRM exercise. (See the various Step 8 sheets in this Worksheet for these requirements.) As per Change Control No. 2005/56, put in place the following items:  
  - The procedure for taking the in-process suspension samples from the mills;  
  - The test procedure for the in-process suspension samples, and the related specs;  
  - The particle size analyser for the QC Lab.  
  
Perform the necessary analyst training and training assessment activities as documented in this QRM exercise.  
Perform the qualification of the particle size analyser, but ensure that the requirements for using the analyser in the analysis of solid samples (i.e. the solid beads) are taken into account in the qualification protocol. This has not yet been provided for in either Change Control No. 2005/56 or the draft Project Validation Master Plan for 2006, (VMP-2006-803-draft 3).  
Perform the validation of the particle size test on the milled suspension. This has already been planned. See Project Change Control No. 2005/56 and draft Project Validation Master Plan for 2006, (VMP-2006-803-draft 3) for details.  
Agree in Tech. Agreements with the material manufacturer and the export broker in China not to use this EU Broker as an intermediary in their supply of the material to our site. This has not been provided for in Change control 2005/56.  
Revise the Goods-in Approved Supplier List to reflect the above arrangement. This has not been provided for in Change control 2005/56.  
Agree in the Tech. Agreement with the export broker in China not to perform any over-labelling of material source, lot, identity or grade information on drums of this material that are destined for our company. This has not been provided for in Change control 2005/56.  
Ensure the procedure for Goods-in requires an inspection of the labelling on the drums of this material for any signs of over-labelling. This has not been provided for in Change control 2005/56. | Corporate Auditing Team, US | End Q1 2006 |
<p>| QC                      | End Q1 2006 |
| QC                      | End Q1 2006 |
| QC                      | End Q1 2006 |
| QC                      | End Q2 2006 |
| QC                      | Mid Q2 2006 |
| QC                      | End Q2 2006 |
| QA                      | Mid Q2 2006 |
| QA                      | End Q2 2007 |
| QA                      | Mid Q2 2006 |
| QA                      | End Q2 2006 |</p>
<table>
<thead>
<tr>
<th>Task</th>
<th>Responsible Party</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create a new ‘drum inspection record’ form to allow Goods-in staff to record the results of their drum-labelling inspection. This has not been provided for in Change control 2005/56.</td>
<td>QA</td>
<td>Mid Q2 2006</td>
</tr>
<tr>
<td>Arrange and perform a qualification audit at the Chinese broker for this yttrium zirconium ceramic bead milling material, and establish that the contents of the Technical Agreement reflecting the above arrangement are capable of being complied with within the Quality System procedures in place at that broker, if any. This has not been provided for in Change control 2005/56.</td>
<td>QA &amp; Corporate Auditing Team, US</td>
<td>End Q1 2006</td>
</tr>
<tr>
<td>Obtain the test procedure for performing particle size testing on the bead milling material from R&amp;D in the US. This has not been provided for in Change control 2005/56.</td>
<td>QC</td>
<td>End Q3 2005</td>
</tr>
<tr>
<td>Produce a method transfer validation protocol. This has not been planned in Change Control No. 2005/56.</td>
<td>QC</td>
<td>End Q4 2005</td>
</tr>
<tr>
<td>Perform the method transfer validation exercise on the particle size test method for the bead material. This has not been planned in Change Control No. 2005/56.</td>
<td>QC</td>
<td>End Q1 2006</td>
</tr>
</tbody>
</table>
## Risk Communication Activities

List any communication activities required in order to communicate risks to key groups or stakeholders.

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method:</th>
<th>Responsible Group:</th>
<th>Target Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Communicate with Corporate auditing the need to modify the audit plan for the Chinese manufacturer of the yttrium zirconium ceramic bead milling material, to take into account the specific risk-related requirements documented in this Quality Risk Management exercise for that audit, that were not documented in CC2005/56.</td>
<td>QA</td>
<td>End Q2 2005</td>
</tr>
<tr>
<td></td>
<td>Communicate with Corporate Auditing the need to audit the Chinese broker for this material, to address the specific risk-related issues documented in this Quality Risk Management exercise.</td>
<td>QA</td>
<td>End Q2 2005</td>
</tr>
<tr>
<td></td>
<td>Communicate with R&amp;D the need to obtain and transfer-validate their test procedure for performing particle size testing on the bead material. Advise R&amp;D that they will need to assist with developing the transfer validation protocol in Q4 2005.</td>
<td>QC</td>
<td>End Q2 2005</td>
</tr>
<tr>
<td></td>
<td>Communicate with our Internal Goods in staff the risk-related issues that arose in this Quality Risk Management exercise, and explain what measures are being taken that involve their area to address the issues identified.</td>
<td>QA</td>
<td>End Q4 2005</td>
</tr>
<tr>
<td></td>
<td>Communicate with our Financial controller the outcomes of this Quality Risk Management exercise, to secure the necessary funding for the risk mitigating actions identified.</td>
<td>QA</td>
<td>End Q2 2005</td>
</tr>
</tbody>
</table>

### Periodic Review Activities:

Propose a Date on which this Risk Assessment will be Reviewed:

**Proposed Review Date:**

End Q2 2006

If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:

The Team should focus on reviewing the outcomes of the two audits to be performed by Corporate Auditing in China. These are the audits at the Chinese manufacturer of the yttrium zirconium ceramic bead milling material, to take into account the specific risk-related requirements documented in this Quality Risk Management exercise for that audit, and at the Chinese broker for this material, to address the specific risk-related issues documented in this exercise. The team should determine whether those audits provide adequate assurance that the risk issues identified in this Quality Risk Management exercise have been addressed.

The team should also closely review whether the internal actions documented in this Quality Risk Management exercise have been completed.

**Other Comments or Notes:**
Section 9.3

Case Study:

The application of this Quality Risk Management methodology to a proposed Change Control (for the introduction of ICP-MS analysis) at an API manufacturer.
Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>Option 1*</th>
<th>Option 2</th>
<th>Option 3 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective RM Exercise</td>
<td>Retrospective RM Exercise</td>
<td>Change Control RM Exercise</td>
</tr>
<tr>
<td>The RM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed…</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a…</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a…</td>
</tr>
</tbody>
</table>

- Manufacturing Process ***
- Cleaning & Hygiene Process ***
- Labelling & Packaging Process ***
- Training Programme
- Material Sampling Programme
- Pest Control Programme
- Stability Programme
- Preventative Maintenance Programme
- Self-Inspection Programme
- Complaints & Recall Programme
- Reduced Testing Programme
- Reit of Laboratory Equipment
- Supplier / Material

*** incorporating the equipment used

- Documentation Management System
- HVAC System
- Building Management System
- Distribution System
- Supplier Approval System
- Regulatory Compliance System
- Materials Management System
- Other - specify below in this box:

- If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

  Describe the specific issue or problem here:

Notes:

* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
### Step 1 Cont'd - Preliminary Information

**Item Under Study**

<table>
<thead>
<tr>
<th>What is the Item Under Study?</th>
<th>Change Control proposal No. 2005/25</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Manufacturing Process No. 123/4</td>
<td>This CC proposes to purchase and install an ICP-MS instrument for Nickel determination in API X. (The Change Control also proposes to switch over from AAS to ICP-MS for Zn analysis in API Y, and for metal analysis in water samples.)</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
<td></td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
<td></td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
<td></td>
</tr>
</tbody>
</table>

**Boundary/Scope Details:**

If this RM exercise applies only to a part of the **Item Under Study** (e.g. the drying & discharge stages in an API manufacturing process), then:
- Clearly state the relevant stage or part of the **Item Under Study** here:
- Record N/A if Not Applicable

**If applicable, Start & End Points**

State the Start and End points for this RM Exercise, or the items which come within the scope of this exercise:

**Process Map or Schematic:**

State the ref. no. of any map or other document which describes/maps the **Item Under Study**:

**Other Document (if any) associated with Item Under Study:**

e.g. Cleaning SOP No. 123/4

e.g. Change Control No. 123/4

## Reason & Relevant Background Info for this RM Exercise

*State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant:*

A new synthetic route has been developed for API X. Based on Nickel catalysis in the hydrogenation step, a 8% increase in the API yield. Release spec for the API will be varied in the US and EU MAAs in early 2006 to add a 100ppb limit for Nickel in the API.

An analytical method for Nickel in API X must be implemented at our site. Since AA spectroscopy is unsuitable for Nickel at this concentration, it is proposed via Change Control No. 123/4 that an ICP-MS method for Nickel determination be used. (R&D in the US has experience with this test & equipment). This will require the site to purchase an ICP-MS instrument, (cost approx 120K, capital is approved). There is an added benefit in that all current metal analysis at the site (Zn in API Y, and some metals in water) which is currently done with AA spectroscopy can be done with an ICP-MS, and so it is proposed that AA at the site be phased out once the ICP-MS is qualified and is up and running.

**Assumptions:** All of the ICP-MS methods will be validated in USA, and will be transferred to this site during Q2 2006, after we receive and qualify the new ICP-MS instrument Q1 2006. The supplier of Liquid Argon will be qualified also.

**This Risk Management exercise is to evaluate any risks associated with the above Change Control to introduce ICP-MS to the site as described here.**
Step 2: Who's Who ... Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader:</th>
<th>Team Leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position / Area of Expertise:</td>
<td>Change Control Co-ordinator</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name *</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. N. Other</td>
<td>QC Manager</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Lab Validation Engineer</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>IT Support</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>QA Documentation</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Purchasing Manager</td>
</tr>
</tbody>
</table>

* Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

Carry out the following tasks, and complete this table by ticking the appropriate options:

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - ✔ Accept the default Probability, Severity & Detection definitions shown on the Card.
   - ☐ Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - ☐ Tick here if any new definitions are attached
   - ✔ Tick here if N/A
Step 4: What might go wrong ... Identify Potential Negative Events Here:

This involves compiling & reviewing data, & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: 1  
Session Date: 2/11/2005

**Tick One:**
- Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Sample Descriptions of Potential Negative Events</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No, 123</td>
<td>e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are released without PIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure occurs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The ICP/MS instrument fails or becomes unavailable for use.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 None Identified</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 None Identified</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Step 5: Risk Evaluation

*Use a separate Step 5 for each Negative Event. Number the controls in the format A, B, C... etc.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The ICP/MS instrument fails or becomes unavailable for use.</td>
</tr>
</tbody>
</table>

List the **Potential Negative Consequences** of this Negative Event, should it occur:
- API X cannot be tested for Ni content, API Y cannot be tested for Zn content, and water analysis for metal content cannot be carried out. Supply of the above APIs ceases until the ICP/MS Instrument is back up and running. This can affect the supply of the finished medicinal products which use these APIs, and this can have a patient impact. ICP/MS Instrument would therefore be deemed a critical instrument.

**Ctrl #**

List any **Current Back-up Systems / Redundancy Controls** which counteract or eliminate these negative consequences should the Negative Event occur. *(Note: Number each Control starting with A, B, C... etc.)*

Note: There would be no back-up instrument if the ICP-MS fails and if the AA instrument is decommissioned or taken out of service as planned in this Change Control proposal. However, currently there is no back-up instrument for the AA spectrophotometer either, which is used for API Y, and for water analysis.

**A**

**On-call Instrument Servicing:** This ensures that any problems with the instrument are resolved ASAP by the Service Vendor for the instrument. Thus, this reduces the effects of this negative event. However, it is known that repairs to ICP-MS instruments can sometimes take time, especially if spare parts are required.

**B**

**Supply Chain:** If there are supplies of already released API batches available when the instrument goes down or when it becomes unavailable for use, the impact of the negative event from a supply perspective is reduced. *(This is not a great control – as there is high demand for API X and a “Just in Time” manufacturing and supply policy is in place at our site.)*

### S: Severity

**Rate the Severity of this Negative Event, taking into account the controls listed above:**

- [ ] Critical  
- [ ] Moderate  
- [x] Minor

**Record any necessary explanation or comments below for the Severity Rating chosen:**

Might not be deemed Critical, as we will have a Service Contract in place with the instrument vendor for call-out repairs. However, we do know from experience of colleagues that ICP-MS repairs can take weeks or months in some cases. So, the Severity should probably be classified as Critical just to be safe.

### List the Possible Causes or Mechanisms for this Negative Event to Occur

<table>
<thead>
<tr>
<th>No.</th>
<th>Cause or Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One or all of the three vacuum pumps in the mass detector breaks down and needs repair or replacement (Note: MS operates at very low pressures. The 3rd vacuum pump is the most critical. Pumps operate 24/7. Expensive to replace. 3 month delay in receiving/Installing new pump.)</td>
</tr>
<tr>
<td>2</td>
<td>Liquid Argon of the required quality becomes unavailable due to either quality or supply problems at our Liquid Argon supplier.</td>
</tr>
</tbody>
</table>

**Current Preventative Controls in place:** *(List the controls for each individual Negative Event Cause or Mechanism)*

**Ctrl #**

**C**

The ICP-MS instrument, including the MS detector vacuum pumps will be on a **PM programme** as part of our service agreement with the instrument Vendor.

**P: Prob. of Occurrence of each cause or mechanism**

<table>
<thead>
<tr>
<th>Risk assoc. w/ each cause or mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (Vendor stated known to have a low incidence of failure. 3 year life.)</td>
</tr>
</tbody>
</table>

**Risk:** Unaccept.

**D**

The Liquid Argon supplier will be **qualified** as normal, & will not be approved unless satisfactory outcome from supplier approval process. However, this is a new supplier, and we have no history with this company.

**Medium** *(We don't know the likelihood... decision between Medium & Low)*

**Risk:** Intolerable

### Instruction:

*For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.*
**Step 6: Risk Evaluation Cont'd**

*This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in the format A, B, C...*

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Ctrl</th>
<th>Detection Controls</th>
<th>Detection Rating</th>
<th>Risk Decision Point:</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Visual detection control: The Analyst easily detects the ICP-MS failure because the vacuum pressure in the MS chamber is monitored, checked &amp; recorded each time the instrument is used. The instrument will not operate if the required vacuum is not achieved.</td>
<td>High</td>
<td>No</td>
<td>A high level of detectability is useful because it alerts the user to a problem with the ICP-MS, but it does nothing to control the risk in the event of such an ICP-MS failure. Therefore, this detection control does not give assurance that the risk is adequately controlled &amp; that no further controls are required.</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Visual detection control: The unavailability of the Liquid Argon required for the ICP-MS is of course easily detected</td>
<td>High</td>
<td>No</td>
<td>A high level of detectability is useful because it alerts the user to a problem with the supply of Liquid Argon, but it does nothing to control the risk in the event of such a supply problem. Therefore, this detection control does not give assurance that the risk is adequately controlled &amp; that no further controls are required.</td>
</tr>
</tbody>
</table>
## Step 7: Risk Control

### Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

<table>
<thead>
<tr>
<th>Negative Event No: 1</th>
<th>State the Cause or Mechanism for the Negative Event to Occur (from Step 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No: 1</td>
<td>One or all of the three vacuum pumps in the mass detector component of the ICP-MS instrument breaks down and needs repair/replacement.</td>
</tr>
</tbody>
</table>

### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
<th>New P Prob. Rating for this Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ensure the ICP-MS instrument is operated correctly at all times.</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• This should help reduce the probability of vacuum pump damage caused by instrument mis-use.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Note that it is known that MS pumps can easily be damaged if turned on and off in an inappropriate manner.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Question: Is the probability now Low or Remote? Difficult to decide. To be cautious, we will go with Low, as per the Guidance slide for Step 7.)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
<th>New S Severity Rating for this Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Keep the AA spectrophotometer operational (and not decommissioned as planned) in the event of the ICP-MS negative event (due to the pump failure). This would allow us to test and release batches of API Y for Zn. Also, it will allow us to test the water samples for various metals. (It won’t allow us to test batches of API X for Ni, because the AA cannot analyse for Ni content at 100ppb concentrations.) Thus, some of the effects of the negative event would be reduced with this new control, but not all.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Taken together, these two controls would reduce the effects of the negative event significantly. Severity now considered Minor.</td>
<td></td>
</tr>
</tbody>
</table>

**New Risk Level:**
- [ ] Acceptable - go to Step 8
- [ ] Unacceptable / Intolerable - continue below

### If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes/No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I.e. Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ ] Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ ] No: Repeat this Step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment/Explanation:</td>
</tr>
</tbody>
</table>

**Note:** If any of the above new controls may introduce a new risk, complete a new Step 4
**Step 7: Risk Control**

*Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Statement of Cause or Mechanism for the Negative Event to Occur (from Step 3):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Liquid Argon of the required quality becomes unavailable due to either quality or supply problems at our Liquid Argon supplier.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk No.</th>
<th>2</th>
</tr>
</thead>
</table>

**Risk Reduction Measures**

**Criterion #**

**What New or Improved Preventative Controls could prevent this Negative Event?**

There is really no preventative control we can put in place here, other than qualifying the supplier, which is already covered in step 5. So Probability is still Medium.

<table>
<thead>
<tr>
<th>New P Prob. Rating for this Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Medium</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Remote</td>
</tr>
</tbody>
</table>

**Criterion #**

**What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?**

A. Qualify a second, back-up supplier of Liquid Argon, so that we are not totally dependent on the first supplier. This will significantly reduce the effects of the negative event.

- Severity would now be considered Minor.

<table>
<thead>
<tr>
<th>New S Severity Rating for this Negative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
</tr>
<tr>
<td>Mod.</td>
</tr>
<tr>
<td>Minor</td>
</tr>
</tbody>
</table>

**New Risk Level = ☑ Acceptable - go to Step 8 ☐ Unacceptable / Intolerable - continue below**

---

**If the Risk is still Unacceptable or Intolerable:**

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating:</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes/No i.e. Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☑ Yes: Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ No: Repeat this Step</td>
</tr>
</tbody>
</table>

**Note:** If any of the above new controls may introduce a new risk, complete a new Step 4.
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Worksheet Step No:</th>
<th>Control No. (A, B, C, …)</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>□ Current</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

On-call instrument servicing in the event of a problem with the instrument

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Contract with vendor servicing company

These items are Already In Place
These items are Not Already In Place

**Complete Either Part A or B Below…**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No
If yes, specify these here:

Vendor must be in a position to respond to the call-out request within 24 hours

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes □ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

What is the Status of this Qualification or Validation exercise?
□ Completed
□ Not Yet Completed
☑ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)
□ New Qualification/Validation work needed ☑ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No.</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>B</td>
<td>☑Current ☐Improved ☐New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

A supply of already-released batches of API X & API Y to meet market demand in the event of a cessation of release while the ICP-MS instrument is being repaired.

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

An inventory management system or related procedures must be in place

These items are Already In Place
These items are Not Already In Place

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑Yes ☐No
If yes, specify these here:

The inventory management system or procedures must ensure that there is a supply of released API batches available at all times, if possible

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? ☑Yes ☐No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

What is the Status of this Qualification or Validation exercise?

☑ Completed
☐ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)

☑ New Qualification/Validation work needed
☐ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>5</th>
<th>Control No. (A, B, C,...)</th>
<th>C</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Current □</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved □</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New □</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Preventative Maintenance programme for the ICP-MS instrument

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Contract with vendor servicing company for PM work

Pre-defined and agreed list of the work activities which will make up the PM work, and this list should include the MS detector vacuum pumps

These items are Already In Place □

These items are Not Already In Place ✓

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes ✓ No

If yes, specify these here:

Vendor must be in a position to carry out the scheduled PM work on time and to the required standard

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes ✓ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

**Q & V**

What is the Status of this Qualification or Validation exercise?

□ Completed

□ Not Yet Completed

✓ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

□ New Qualification/Validation work needed

✓ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>1</th>
<th>Worksheet Step No.</th>
<th>5</th>
<th>Control No. (A, B, C, ...)</th>
<th>D</th>
<th>Type of Control: Current</th>
<th>Improved</th>
<th>New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

**Qualified Liquid Argon Supplier**

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Qualification protocol for how this particular supplier will be qualified. (Note that there is a standard supplier approval procedure in place, but this allows for specific supplier approval activities to be specified when approving the supplier of interest. This will likely include in this case a scheduled inspection of the proposed supplier.)

These Items are Already In Place  
These Items are Not Already In Place

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this control?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, specify these here:

The proposed supplier must meet the supplier approval criteria defined in the above protocol.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Qualification of the proposed Liquid Argon supplier

<table>
<thead>
<tr>
<th>Q &amp; V</th>
<th>What is the Status of this Qualification or Validation exercise?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completed</td>
</tr>
</tbody>
</table>

**Current Qualification or Validation Status of this Control:** (Tick one below)

| New Qualification/Validation work needed | No New Qualification/Validation work needed | --- | --- |

| Yes | No | --- | --- |
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>6</th>
<th>Control No.</th>
<th>(A, B, C, ...)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current</td>
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<td></td>
<td></td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Visual detection of MS detector chamber vacuum pressure

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

An SOP and Form are needed for checking, monitoring and recording the MS detector chamber vacuum pressure

These Items are Already In Place ☐
These Items are Not Already In Place ☑

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
If yes, specify these here:

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? ☑ Yes ☐ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

MS detector chamber vacuum pressure is the CPP
The CPP limits are the defined pressure ranges specified by the ICP-MS manufacturer

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

The MS detector vacuum pumps must be OQ/PQ Qualified during the Qualification of the ICP-MS instrument

**Q & V**

What is the Status of this Qualification or Validation exercise?

☑ Completed
☒ Not Yet Completed
☐ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

☑ New Qualification/Validation work needed ☐ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.:</th>
<th>1</th>
<th>Worksheet Step No.:</th>
<th>6</th>
<th>Control No. (A, B, C,...)</th>
<th>B</th>
<th>Type of Control:</th>
<th>☑ Current</th>
<th>☐ Improved</th>
<th>☐ New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

Visual detection control for the quantity of Liquid Argon available in-house

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

An SOP and Form are required for checking and recording the quantity of Liquid Argon available in-house

These Items are Already In Place ☐
These Items are Not Already In Place ☑

---

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
If yes, specify these here:

The Quantity of Liquid Argon available in-house should be 5 litres or more; if less than 5 litres are available, a new supply should be ordered. (This serves as a control that gives us an early warning of any problem at the Argon supplier.)

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? ☑ Yes ☐ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

---

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

<table>
<thead>
<tr>
<th>Q &amp; V</th>
<th>What is the Status of this Qualification or Validation exercise?</th>
<th>☑ Completed</th>
<th>☐ Not Yet Completed</th>
<th>☑ N/A</th>
</tr>
</thead>
</table>

**Current Qualification or Validation Status of this Control:** (Tick one below)

☐ New Qualification/Validation work needed ☑ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (A, B, C,...)</th>
<th>A</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☐ Current</td>
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<tr>
<td></td>
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<td></td>
<td>☐ Improved</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>☑ New</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Correct operation of the ICP-MS instrument at all times

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Detailed SOP on the set-up, operation, and shutting down of the instrument
- Trained analysts for the instrument, as well as one staff member who is considered the in-house instrument expert in terms of the instrument engineering and electronics, and who performs light troubleshooting & light maintenance work

These Items are Already In Place ☐
These Items are Not Already In Place ☑

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
If yes, specify these here:

- The exper. analyst must demonstrate a satisfactory level of competence on the instrument
- All analysts qualified to use the instrument must have passed the assessment of training on operating the instrument

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? ☑ Yes ☐ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Staff member must be qualified as the in-house instrument expert... he or she should attend an external training course on the operation, engineering, electronics, troubleshooting & maintenance of the instrument

Q & V
What is the Status of this Qualification or Validation exercise?
☐ Completed
☑ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
☑ New Qualification/Validation work needed ☐ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

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<tr>
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<th>Control No. (A, B, C, …)</th>
<th>B</th>
<th>Type of Control: □ Current □ Improved □ New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

An operational and in-qualification Atomic Absorption (AA) Spectrophotometer

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

AA Instrument, SOP on its operation & maintenance, validated test procedures

Note: the registered release specs for API Y must continue show AA as an approved method for Zn determination in this API.

Also, the 2006 Lab VMP must be revised to require that the AA instrument be qualified and calibrated in 2006, as per its 2005 schedule – this instrument was removed from the VMP when it was decided that it would be decommissioned.

These Items are Already In Place □
These Items are Not Already In Place ✓

**Complete Either Part A or B Below…**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes  ✓ No
If yes, specify these here:

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes  ✓ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

The AA instrument has several CPPs with associated limits – see annual qualification protocol for the instrument for details

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

AA Instrument must be qualified in 2006, and maintained within its calibrated and qualified state, and any analysts using the instrument must be qualified to use the instrument

**Q & V**

What is the Status of this Qualification or Validation exercise?

□ Completed
✓ Not Yet Completed
□ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

✓ New Qualification/Validation work needed  □ No New Qualification/Validation work needed
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

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<thead>
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<th>Worksheet Step No.</th>
<th>Control No. (A, B, C,...)</th>
<th>C</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>7</td>
<td>C</td>
<td>□ Current</td>
</tr>
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<td></td>
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<td></td>
<td>□ Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✔ New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Arrangement with R&D Lab in the USA to perform ICP-MS analysis of Ni for us in API X, if required

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Technical agreement with the R&D Lab (Not yet in place)
- Qualified ICP-MS instrument at the R&D Lab, and trained personnel on its use (Currently in place)

These items are Already In Place ✔
These items are Not Already In Place

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control?  

- Yes [☐]  
- No [☐]  

If yes, specify these here:

R&D Lab must be able to analyse our samples of API X within the timeframes specified in the Tech Agreement for this analysis.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored?  

- Yes [☐]  
- No [☐]  

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

R&D ICP-MS instrument must be qualified to GMP standards... Note: this level of qualification has not been done within R&D to date.

**Q & V**

What is the Status of this Qualification or Validation exercise?

- Completed [☐]  
- Not Yet Completed [☐]  
- N/A [☐]

**Current Qualification or Validation Status of this Control:** (Tick one below)

- New Qualification/Validation work needed [☐]  
- No New Qualification/Validation work needed [☐]
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

| Negative Event No. | Worksheet Step No. | Control No. (A, B, C,...) | Type of Control |  
|--------------------|--------------------|---------------------------|-----------------|----------
| 1                  | 7                  | A                         | □ Current □ Improved □ New |

**Brief Description of the Control:**

A second qualified supplier of Liquid Argon

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Qualification protocol for how this particular supplier will be qualified. (Note that there is a standard supplier approval procedure in place, and this will be used as a basis for writing the above Qualification protocol. This SOP allows for specific supplier approval activities to be specified when approving the supplier of interest. For example, our checking of this proposed supplier will most likely include a scheduled inspection of the proposed supplier.)

These Items are Already In Place □
These Items are Not Already In Place ☑

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑Yes □ No

*If yes, specify these here:*

The proposed supplier must meet the supplier approval criteria defined in the above protocol.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? ☑Yes □ No

*If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP*

---

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Qualification of the proposed Liquid Argon supplier.

**O & V**

What is the Status of this Qualification or Validation exercise?

□ Completed
☑ Not Yet Completed
□ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

☑ New Qualification/Validation work needed □ No New Qualification/Validation work needed
### Step 9: Action Items

*Identify any action items from the completed Qualification & Validation Worksheets*

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Set up a service contract with the ICP-MS Instrument vendor for call-out repairs as well as for routine Preventative Maintenance work</td>
<td>Purchasing &amp; QC</td>
<td>End 12/05</td>
</tr>
<tr>
<td></td>
<td>Qualify the Liquid Argon supplier which we have identified as our main supplier</td>
<td>Supplier Approval Group QC</td>
<td>End 1/06</td>
</tr>
<tr>
<td></td>
<td>Write a new SOP &amp; Form for checking, monitoring and recording the MS detector chamber vacuum pressure</td>
<td>QC</td>
<td>End 3/06</td>
</tr>
<tr>
<td></td>
<td>Qualify the ICP-MS Instrument, including the MS detector vacuum pumps for IQ/OQ.</td>
<td>QC &amp; Validation QC &amp; QA</td>
<td>End 3/06</td>
</tr>
<tr>
<td></td>
<td>Write a new SOP and Form for checking and recording the quantity of Liquid Argon available in-house</td>
<td>QC &amp; QA</td>
<td>End 3/06</td>
</tr>
<tr>
<td></td>
<td>Write a new SOP on the set-up, operation, and shutting down of the ICP-MS Instrument</td>
<td>QC &amp; Training</td>
<td>End 7/4/06</td>
</tr>
<tr>
<td></td>
<td>Perform analyst training on the instrument</td>
<td>QA to coordinate this</td>
<td>End 3/06</td>
</tr>
<tr>
<td></td>
<td>Qualify one analyst as the in-house instrument expert in terms of the instrument engineering and electronics, and who performs light troubleshooting &amp; light maintenance work</td>
<td>Validation</td>
<td>End 11/05</td>
</tr>
<tr>
<td></td>
<td>Revise the Lab VMP for 2006 to include an annual qualification &amp; routine calibration schedule for the current Atomic Absorption instrument</td>
<td>QA</td>
<td>End 12/05</td>
</tr>
<tr>
<td></td>
<td>Put in place an arrangement with the R&amp;D Lab in the USA to perform ICP-MS analysis of Ni for us in API X, if required</td>
<td>QA</td>
<td>End 12/05</td>
</tr>
<tr>
<td></td>
<td>Get confirmation from R&amp;D that the ICP-MS instrument at R&amp;D in the US will be qualified as per EU GMP requirements by end 3/06</td>
<td>Purchasing</td>
<td>End 3/06</td>
</tr>
<tr>
<td></td>
<td>Identify and Qualify an alternative Liquid Argon supplier</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments or Notes:**

None
### Risk Communication Activities

*List any communication activities required in order to communicate risks to key groups or stakeholders*

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method:</th>
<th>Responsible Group:</th>
<th>Target Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Communicate with analysts the criticality of this new instrument from a risk perspective, and the need to operate it in accordance with defined procedures</td>
<td>Risk Team Leader</td>
<td>End 1/06</td>
</tr>
<tr>
<td>2</td>
<td>Communicate with R&amp;D the risks identified here so that they can understand the reasons for our requiring that they be available to analyse API X for Nickel content, and that their ICP-MS instrument be qualified as per EU GMP Standards... communicate this also to the corporate quality auditing team at HQ</td>
<td>Risk Team Leader</td>
<td>End 12/05</td>
</tr>
<tr>
<td>3</td>
<td>Communicate with our main Liquid Argon supplier the criticality of their material and the need to keep us informed of any situations which might cause them to cease supplying Liquid Argon to us, even on a temporary basis</td>
<td>Purchasing</td>
<td>End 1/06</td>
</tr>
</tbody>
</table>

### Periodic Review Activities:

<table>
<thead>
<tr>
<th>Proposed Review Date:</th>
<th>If there are useful Comments or Recommendations relating to the review of this Risk Management exercise, state those here:</th>
</tr>
</thead>
<tbody>
<tr>
<td>End 3/2006</td>
<td>Note: this Risk management Exercise should be reviewed at the end of March 2006, because it is then that the instrument should be qualified by, and ready for use. It will be a useful exercise to review the Risk management Exercise at that time, before we go live with the instrument for release testing.</td>
</tr>
</tbody>
</table>

### Other Comments or Notes:

None
Volume 2, Part II - The Training & User’s Manual

Section 9.4

Case Study:

The application of this Quality Risk Management methodology to a Product Recall Procedure at a Finished Product Manufacturer
GMP Risk Management (RM) Exercise No: 7/2005

Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>Option 1*</th>
<th>Option 2</th>
<th>Option 3**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective RM Exercise</td>
<td>Retrospective RM Exercise</td>
<td>Change Control RM Exercise</td>
</tr>
<tr>
<td>The RM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed...</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
</tbody>
</table>

- Manufacturing Process ***
- Cleaning & Hygiene Process ***
- Labelling & Packaging Process ***
- Training Programme
- Material Sampling Programme
- Pest Control Programme
- Stability Programme
- Preventative Maintenance Programme
- Self-Inspection Programme
- Complaints & Recall Programme
- Reduced Testing Programme
- Item of Laboratory Equipment
- Supplier

*** incorporating the equipment used

- Documentation Management System
- HVAC System
- Building Management System
- Distribution System
- Supplier Approval System
- Regulatory Compliance System
- Materials Management System
- Other System or Programme (specify below)

State the System or Programme in question here:

- If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

Notes:
* With respect to Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.

** Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.
### Step 1 Cont’d - Preliminary Information

<table>
<thead>
<tr>
<th>Item Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the Item Under Study?</strong></td>
</tr>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
</tr>
<tr>
<td>e.g. Dispensing Room No. 3</td>
</tr>
<tr>
<td>e.g. Upgrade to Room No. ABC</td>
</tr>
<tr>
<td>e.g. New Purified Water System P2</td>
</tr>
<tr>
<td>Recall System in place at company. (Note: company is a manufacturer which distributes its own products to retail pharmacies &amp; hospitals in Ireland. Company is also the MA Holder.</td>
</tr>
<tr>
<td>Boundary/Scope Details:</td>
</tr>
<tr>
<td>If this RM exercise applies only to a part of the Item Under Study (e.g. the drying &amp; discharge stages in an API manufacturing process), then:</td>
</tr>
<tr>
<td>- Clearly state the relevant stage or part of the Item Under Study here:</td>
</tr>
<tr>
<td>- Record N/A if Not Applicable</td>
</tr>
<tr>
<td>If applicable, Start &amp; End Points</td>
</tr>
<tr>
<td>State the Start and End points for this RM Exercise, or the items which come within the scope of this exercise:</td>
</tr>
<tr>
<td>Process Map or Schematic:</td>
</tr>
<tr>
<td>State the ref. no. of any map or other document which describes / maps the item under study:</td>
</tr>
<tr>
<td>Other Document (if any) associated with Item Under Study:</td>
</tr>
<tr>
<td>e.g. Cleaning SOP No. 123/4</td>
</tr>
<tr>
<td>e.g. Change Control No. 2005/11</td>
</tr>
<tr>
<td>Product and Batch Recall SOP, No. 123/4</td>
</tr>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

### Reason & Relevant Background Info for this RM Exercise

*State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant:*

- A recent recall was executed by the company to retail, hospital & patient level in Ireland and UK (Ref: all batches of product X recalled on August 3rd, 2005, due to an impurity issue).

- QA decided to review the recall procedure from a risk management perspective at this time... this was the first recall the company has had, and perhaps useful data were obtained during execution of the recall which we can benefit from, so that any necessary improvements to our recall SOP and related recall systems can be identified and implemented, and any necessary qualification or validation work can be identified.

- The above all batch recall required notifying all customers who received any batch of Product X in the last 5 years, as the product has a five year shelf life. Company Unix system provided the product distribution data, but company recognised a possible vulnerability with relying so heavily on this old (1980s) Unix system. The system has given problems in the area of financial record keeping in the past, and the system has gone down and required Unix servicing several times of the last three years. (Ref: Unix Review Report, June 2005.) As a result of the June review, the Unix system is being replaced with a customised SAP system. New system planned for delivery Q1 2007. (Capital request almost approved 9/2005)
Step 2: Who’s Who! ..... Define our Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader</th>
<th>Team Leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position / Area of Expertise</td>
<td>Recall Co-ordinator</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name *</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. N. Other</td>
<td>QA Batch Review</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Validation Engineer &amp; IT Support</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>QA Documentation</td>
</tr>
<tr>
<td>A. N. Other</td>
<td>Distribution Manager</td>
</tr>
</tbody>
</table>

* Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

Carry out the following tasks, and complete this table by ticking the appropriate options:

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   ✓ Accept the default Probability, Severity & Detection definitions shown on the Card.
   ☐ Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   ☐ Tick here if any new definitions are attached
   ✓ Tick here if N/A
Step 4: What might go wrong?? Identify Potential Negative Events Here:

This involves compiling & reviewing data, & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: 1  Session Date: 1/10/2005

**Tick One:**

- Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Sample Descriptions of Potential Negative Events</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No. 123</td>
<td>e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in: Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are released without PIL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure occurs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Unix System freezes and cannot be used in the event of a recall to generate batch distribution and traceability data.</td>
<td>Note: There have been several problems with the Unix system over last 3 years. It is an 1980's system, &amp; Co. plans to replace the system with a new SAP system, (target Q1 2007). This will provide batch distribution and traceability data, &amp; customer contact data.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Key personnel (both at company and at Competent Authority) cannot be contacted out of hours in a timely manner in relation to an urgent quality defect issue being reported or identified, and recall decisions could therefore be delayed.</td>
<td>Note: Out of hours contact details for company and IMB are held at site security office and in other locations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 None Identified</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Reference or Notes

Note: There have been several problems with the Unix system over last 3 years. It is an 1980’s system, & Co. plans to replace the system with a new SAP system, (target Q1 2007). This will provide batch distribution and traceability data, & customer contact data.

Note: Out of hours contact details for company and IMB are held at site security office and in other locations.
## Step 5: Risk Evaluation

*Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C... etc.*

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unix System freezes and cannot be used in the event of a recall to generate batch distribution and traceability data.</td>
</tr>
</tbody>
</table>

**List the Potential Negative Consequences of this Negative Event, should it occur:**

- Customers who received the batch being recalled cannot be identified in a timely manner
- Recall action gets delayed
- Possible patient impact or injury depending on the quality defect or safety issue at hand
- Possible regulatory consequences for company

**Ctrl #** List any *Current Back-up Systems / Redundancy Controls* which counteract or eliminate these negative consequences should the Negative Event occur. *(Note: Number each Control starting with A, B, C... etc.)*

**A** Sales Invoices: Paper copies of invoices are kept (some on-site and some in archives), which can be used to identify customers who received a batch of a specific product. However, these invoices are not well filed or organised, as they are not subject to a controlled filing system, and they can be difficult to sort through. Unsure if all older invoices contained batch numbers, and some product names not written in full.

**B** Unix back-up files: Unix data are backed up, so the back-up files should provide batch tracking data. However, currently, back-up is only performed once per month, by Unix personnel working remotely. (Technical difficulties in backing up the Unix system has resulted in this situation. So, the back-up data could be up to one month out of date when retrieved.

**S: Severity**: Rate the Severity of this Negative Event, taking into account the controls listed above: *Record any necessary explanation or comments below for the Severity Rating chosen.*

- **Critical**
- **Moderate**
- **Minor**

The Unix back-up files are of limited value given the low frequency of back-up... monthly. Also, batch distribution data are available via the paper invoices, but these are difficult to work with, and it is felt that it would be a very laborious task to generate a customer listing of a particular batch from the invoices in a timely manner, by the way they are stored and filed. Overall, the Severity was judged to be Moderate.

**List the Possible Causes or Mechanisms for this Negative Event to Occur:**

No preventative controls in place. (See above for technical Unix expertise in-house to deal with problems as they arise.)

**Current Preventative Controls in place:**

Comment: The Unix system is under a service contract to our Unix vendor company, who provide a call-out service in the event of a system problem or failure, but this does not include formal preventative maintenance work. This call-out service contract work is not a true preventative measure... It is more reactive.

For Info: As a result of the Unix problems over approx the last three years, and as part of a company wide IT upgrade, a new customised SAP system is being developed. This will reside at Corporate in USA, and we will access remotely.

**P: Prob. of Occurrence of each cause / mechanism**

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>Current Preventative Controls in place</th>
<th>P: Prob. of Occurrence of each cause / mechanism</th>
<th>Risk assoc. w/ each cause or mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No preventative controls in place</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Risk = P x S**

<table>
<thead>
<tr>
<th>Medium</th>
<th>#</th>
<th>Unaccept.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Unaccept.</td>
</tr>
</tbody>
</table>

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6
### Step 6: Risk Evaluation Cont'd

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in the format A, B, C...

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Ctrl #</th>
<th>Detection Controls</th>
<th>D</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Terminal User Detects the Unix System Failure:</td>
<td>High</td>
<td>Is this Risk adequately controlled? – Yes / No i.e. Do these controls give assurance that the risk is adequately controlled &amp; that no further controls are required? Explain below.</td>
</tr>
</tbody>
</table>

**Explanation:** A person using the Unix system to retrieve batch distribution data will easily detect the system failure, as the system freezes. Also, sometimes, error messages appear on screen, and will not allow the generation or reports, and so the failure is detected in this way also. Users are required to report the issue to the distribution manager, who then calls in the Unix vendor.

Therefore, this detection control does not give assurance that the risk is adequately controlled & that no further controls are required.
Step 7: Risk Control
Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No.</td>
<td>1</td>
</tr>
<tr>
<td>☑ Unacceptable Risk</td>
<td></td>
</tr>
</tbody>
</table>

State the Cause or Mechanism for the Negative Event to Occur (from Step 5):
Unix system freezes & won't allow data reports to be generated. The system has not been upgraded in recent years, and there is a lack of technical expertise in-house to deal with problems as they arise.

<table>
<thead>
<tr>
<th>Risk Reduction Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl #</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| Ctrl \# | What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur? |
|        | New S Severity Rating for this Negative Event |
|        | ☑ Minor |
| A      | - Improve the Unix back-up procedures by backing up on a daily basis |
| B      | - Improve our management of paper invoices for product sales & distribution by: |
|        | • ensuring invoices contain batch numbers and full product names, |
|        | • ensuring all invoices going back 5 years (this is the max shelf life of any of our products) are filed correctly, by date of invoice, in a readily retrievable manner |
|        | • updating procedure for retrieving off-site archived invoices to ensure archived invoices are retrievable within half a working day |
| C      | - Initiate recording of first and last date of distribution of a batch of a medicinal product. These records will allow us to determine the time period for which invoices should be checked. |
|        | Severity now considered Minor. |

New Risk Level = ☑ Acceptable - go to Step 8  ☑ Unacceptable / Intolerable - continue below

If the Risk is still Unacceptable or Intolerable:

| Ctrl \# | New or Improved Detection Controls to Detect this Neg. Event? |
|        | New D Rating: |
|        | Risk Decision Point: |
|        | Is the risk now adequately controlled? Yes/No i.e. |
|        | Do these controls now give assurance that the risk is adequately controlled & no further controls are required? |
|        | ☑ Yes: Go to Step 8 |
|        | ☑ No: Repeat this Step |

Note: if any of the above new controls may introduce a new risk, complete a new Step 4
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>6</th>
<th>Control No. (a, b, c,...)</th>
<th>A</th>
<th>Type of Control:</th>
<th>✓ Current</th>
<th>☐ Improved</th>
<th>☐ New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

Terminal User Detects the Unix System Failure

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

This is a visual control. The items required for this control are a terminal, a user, but a controlled form is needed but is not yet in place to record a system failure, when it occurs.

These Items are Already In Place
These Items are Not Already In Place

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control?  ☐ Yes  ✓ No

If yes, specify these here:

N/A

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored?  ☐ Yes  ✓ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

N/A

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

**Q & V**

What is the Status of this Qualification or Validation exercise?

☐ Completed  ☑ Not Yet Completed  ☐ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

☐ New Qualification/Validation work needed  ☑ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (a, b, c,...)</th>
<th></th>
<th>Type of Control:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved [✓]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New [ ]</td>
<td></td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Improve the Unix back-up procedures by backing up on a daily basis

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

A new local Unix back-up SOP for company personnel is req'd. (Currently, all back-up work is done remotely by our contracted Unix Vendor).

Training on new procedure as per normal QMS document training and training assessment.

A new controlled form for recording completion and review of Unix back-up also req'd.

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? [✓] Yes [ ] No

If yes, specify these here:

Training on the new back-up procedure must be completed and trainees must satisfactorily pass training assessment

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? [ ] Yes [✓] No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Comment... see below

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

The new local Unix back-up procedure must be qualified to show that all data are successfully backed up when this procedure is used. (Note: the “amount of data backed up” could be seen to be a CPP, with an acceptance level of 100%. Time taken to complete the back-up could also be viewed as a CPP.)

What is the Status of this Qualification or Validation exercise?

[ ] Completed
[ ] Not Yet Completed
[ ] Not Applicable

New Qualification/Validation Status of this Control: (Tick one below).

[ ] New Qualification/Validation work needed
[ ] No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>1</th>
<th>Worksheet Step No:</th>
<th>7</th>
<th>Control No. (a, b, c,...)</th>
<th>B</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Improve our management of paper invoices for product sales & distribution

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Revised SOP on invoice generation, checking and filing to ensure that all invoices contain product name and batch number data, and are filed by date and are stored in an easily retrievable manner
- New SOP on sending invoices to archives and on retrieving off-site archived invoices... to ensure archived invoices are filed appropriately and are retrievable within half a working day
- Audit of Archiving Company

*These Items are Already In Place* □

*These Items are Not Already In Place* □

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No

If yes, specify these here:

Relevant personnel must be trained on the revised and new SOPs, and archiving company must undergo a successful audit process

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes □ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Qualify the supplier of the archiving service (i.e. the Archive Company) via an audit.

**O & Y**

What is the Status of this Qualification or Validation exercise?

- Completed □
- Not Yet Completed □
- N/A □

**Current Qualification or Validation Status of this Control:** (Tick one below)

- □ New Qualification/Validation work needed
- □ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Event No.</th>
<th>Worksheet No.</th>
<th>Control No. (a, b, c...)</th>
<th>C</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>C</td>
<td>☐</td>
<td>Current</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☐</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>☒</td>
<td>New</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Initiate recording of first and last date of distribution of a batch of a medicinal product... these records will allow us to determine the time period for which invoices should be checked.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- New controlled QMS Form for recording the first and last date of distribution of a batch of a medicinal product
- SOP on maintaining/replenishing stock at the picking locations at wholesaler level of the company needs to be revised to instruct on the completing and filing of these Forms, by product name and batch number.

These items are Already In Place ☒
These items are Not Already In Place ☐

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control?  ☑ Yes  ☐ No
If yes, specify these here:

Relevant personnel must be trained on the new form and on the revised SOP, and, as per normal QMS training procedures, trainees must pass training assessment.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? ☑ Yes  ☐ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

N/A

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

**Q & V**

What is the Status of this Qualification or Validation exercise?

☐ Completed  ☐ Not Yet Completed  ☑ N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)

☐ New Qualification/Validation work needed  ☑ No New Qualification/Validation work needed
**Step 5: Risk Evaluation**
Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C... 

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Key personnel (both at company and at Competent Authority) cannot be contacted out of hours in a timely manner in relation to an urgent quality defect issue being reported or identified, and recall decisions could therefore be delayed.</td>
</tr>
</tbody>
</table>

List the Potential Negative Consequences of this Negative Event, should it occur:
- Urgent decisions within the company such as to consider a recall or call Competent Authority do not get made in a timely manner.
- Competent Authority does not get notified of a potential recall issue.
- A required market action such as a recall or caution in use notification gets delayed.
- Patient impact or injury could occur which was preventable.

List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C... etc.)

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List any Current Back-up Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>In the unlikely event that none of the key contact persons either at the company and at Competent Authority can be contacted out of hours to report and discuss a serious potential recall issue with Corporate QA and Regulatory in the US can be contacted as a back-up, and key decision-making can take place there. (Online Corporate address book has the details and also lists emergency out of hours numbers.)</td>
</tr>
</tbody>
</table>

**S: Severity:** Rate the Severity of this Negative Event, taking into account the controls listed above:
- [ ] Critical
- [ ] Moderate
- [ ] Minor

Minor. Contacting the US can take time, and could still result in some delay, but this control provides some assurance.

<table>
<thead>
<tr>
<th>List the Possible Causes or Mechanisms for this Negative Event to Occur: No.</th>
<th>Current Preventative Controls in place: (List the controls for each individual Negative Event Cause or Mechanism)</th>
<th>P: Prob. of Occurrence of each cause / mechanism</th>
<th>Risk assoc. w/ each cause or mechanism Risk=P x S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Out of hours contact details for key personnel are inaccurate B</td>
<td>Recall SOP contains as an Annex the list of out of hours contact details, and both the SOP and the Annex are controlled documents via the QMS. This formal control helps assure that the details are checked and are correct, and are not changed without formal CC. Also, the SOP is reviewed for content and accuracy yearly, and is audited as part of self-inspections, and QA inspections. The SOP is revised any time IMB or company staff change their out of hours details. Also, it is unlikely that all out of hours contact details for all persons would be incorrect.</td>
<td>Remote</td>
<td>1</td>
</tr>
<tr>
<td>2 Out of hours contact details for key personnel are unavailable B</td>
<td>This is extremely unlikely to occur, because as noted above, the Recall procedure is a controlled QMS document, available in several placers, including at the security hut.</td>
<td>Remote</td>
<td>2</td>
</tr>
</tbody>
</table>

**Instruction:** For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6.
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (a, b, c,...)</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5</td>
<td>A</td>
<td>Current ☑️ Improved ☐ New ☐</td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**
Corporate & Regulatory in US can be contacted via company address book which is on-line via company intranet, and this includes Corporate & Regulatory out of hours and emergency contact numbers.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

Intranet access. (The address book and the intranet site are managed by Corporate in the US.)
Local IT support ensures that the intranet is accessible.

These Items are Already In Place ☑️
These Items are Not Already In Place ☐

**Complete Either Part A or B Below…**

**Part A: Acceptance Criteria or Required Outcomes for this Control**
Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☐ Yes ☑️ No
If yes, specify these here:

**Part B: Critical Process Parameter**
Does this control have any associated CPP to be measured or monitored? ☐ Yes ☑️ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

<table>
<thead>
<tr>
<th>Q &amp; V</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the Status of this Qualification or Validation exercise?</td>
</tr>
<tr>
<td>☐ Completed</td>
</tr>
<tr>
<td>☑️ Not Yet Completed</td>
</tr>
<tr>
<td>☐ N/A</td>
</tr>
</tbody>
</table>

Current Qualification or Validation Status of this Control: (Tick one below)
☐ New Qualification/Validation work needed ☑️ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (a, b, c,...)</th>
<th>B</th>
<th>Type of Control: ☑ Current □ Improved □ New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**

Current Recall SOP includes contact details in an Annex and this is a controlled document; it is checked for accuracy via the document approval stage, and it is updated via CC. It is available in several places on-site, including the security hut.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

The SOP itself and the Change Control procedure. These are in place.

These items are **Already In Place** ☑
These Items are **Not Already In Place** □

**Complete Either Part A or B Below…**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes □ No

If yes, specify these here:

Training on the SOP as per normal QMS training procedures and training assessment. These have been carried out.

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes ☑ No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- The recall procedure needs to be qualified via challenge/evaluation testing as per sections 8.9, 8.10 and 8.15 of the EU GMP Guide, and as per the Principle in the EU GDP Guidelines.

- Given the findings of this exercise, this Qualification exercise should include a simulation of the Unix system failing

**Current Qualification or Validation Status of this Control:** (Tick one below)

☑ New Qualification/Validation work needed □ No New Qualification/Validation work needed
### Step 9: Action Items

Identify any action items from the completed Qualification & Validation Worksheets

These could be actions to implement a control, or they could be a Qualification or Validation Exercise.

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item:</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Write and approve the following QMS documents:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Form for recording Unix system failures</td>
<td>QA + Unix Service provider</td>
<td>Oct 21 2005</td>
</tr>
<tr>
<td></td>
<td>Unix Back-up SOP for Local Back-up activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New form for recording and reviewing Unix Back-up activities</td>
<td>QA</td>
<td>Oct 21 2005</td>
</tr>
<tr>
<td></td>
<td>Revised SOP on Invoice generation, checking and filing</td>
<td>QA</td>
<td>Oct 21 2005</td>
</tr>
<tr>
<td></td>
<td>New SOP on document archiving</td>
<td>QA</td>
<td>Oct 21 2005</td>
</tr>
<tr>
<td></td>
<td>New Form for recording first and last dates of batch distribution</td>
<td>Distribution Mgr</td>
<td>Oct 14 2005</td>
</tr>
<tr>
<td></td>
<td>Revised SOP on maintaining/replenishing stock at picking locations</td>
<td>Distribution Mgr</td>
<td>Oct 14 2005</td>
</tr>
<tr>
<td>1</td>
<td>Perform training on the above documents when they are approved and before issuance</td>
<td>QA Training Unit</td>
<td>Oct 24 2005</td>
</tr>
<tr>
<td>1</td>
<td>Carry out the Unix back-up SOP Qualification</td>
<td>Validation</td>
<td>Oct 31 2005</td>
</tr>
<tr>
<td>2</td>
<td>Carry out a challenge (qualification) of the recall SOP including a simulation of a Unix system failure</td>
<td>Validation</td>
<td>Oct 31 2005</td>
</tr>
</tbody>
</table>

**Comments or Notes:**

None
### Risk Communication Activities

List any communication activities required in order to communicate risks to key groups of stakeholders.

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method:</th>
<th>Responsible Group:</th>
<th>Target Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Communicate Results of this RM Exercise to the following:</td>
<td>RM Team Leader (KO'D)</td>
<td>Oct 21 2005</td>
</tr>
<tr>
<td></td>
<td>• Distribution &amp; Warehouse Staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sales and Office staff involved in invoicing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Contracted Unix Service Provider</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Contracted Archive Company</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Periodic Review Activities:

- Propose here a Date on which this Risk Assessment will be Reviewed:
  - Proposed Review Date: Sept 1, 2006

- If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:
  - In addition to the annual review in Sept 2006, (one year from now) we should monitor compliance to the new invoicing requirements at three months and at regular intervals via self-inspection. Team leader to notify QA to incorporate this into self-inspection programme for 2006.

### Other Comments or Notes:

- None

Section 9.5

Case Study:

The application of this Quality Risk Management methodology to an area not regulated by GMP, but one which is directly related to GMP - A Quality Defect Investigation Programme at an EU Competent Authority
**GMP Risk Management (RM) Exercise No:** 06

**Step 1: Preliminary Information on the RM Exercise**

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

<table>
<thead>
<tr>
<th>☐ Option 1*</th>
<th>☑ Option 2</th>
<th>☐ Option 3**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective RM Exercise</strong></td>
<td><strong>Retrospective RM Exercise</strong></td>
<td><strong>Change Control RM Exercise</strong></td>
</tr>
<tr>
<td>The RM tool is being used to help determine, prospectively, the scope and extent of Qualification &amp; Validation required for a new, or to be changed...</td>
<td>The tool is being used to help determine, retrospectively, the Qualification &amp; Validation status of, and Qualification &amp; Validation requirements for, a...</td>
<td>The tool is being used to evaluate any risks associated with a Change Control proposal relating to a...</td>
</tr>
</tbody>
</table>

- Manufacturing Process
- Cleaning & Hygiene Process
- Labelling & Packaging Process
- Training Programmes
- Material Sampling Programmes
- Pest Control Programmes
- Stability Programmes
- Preventative Maintenance Programmes
- Self-Inspection Programmes
- Complaints & Recall Programmes
- Reduced Testing Programme
- Turn of Laboratory Equipment
- Storage / Material

* incorporating the equipment used

☐ If the RM exercise is to help determine Qualification & Validation status or requirements in response to a specific issue or problem (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here:

---

**Notes:**

* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.
Step 1 Cont'd - Preliminary Information on the RM Exercise

<table>
<thead>
<tr>
<th>The Item Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the Item Under Study?</td>
</tr>
<tr>
<td>e.g. Manufacturing Process No. 1234</td>
</tr>
<tr>
<td>e.g. Drying Room No. 3</td>
</tr>
<tr>
<td>e.g. Ventilation System ABC</td>
</tr>
<tr>
<td>e.g. New Purified Water System (P2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ODR Programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall &amp; Consent</td>
</tr>
<tr>
<td>Communication procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boundary Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the item under study has a boundary, state the boundary here. For example:</td>
</tr>
<tr>
<td>• a boundary could be a P&amp;ID for a piece of equipment or a system</td>
</tr>
<tr>
<td>• it could be points within a manufacturing process within which the RM exercise applies</td>
</tr>
<tr>
<td>• it could be part of a process, such as the drying &amp; discharge stages in an API manufacturing process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process Map or Schematic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>State the ref. no. of any map or other document which describes / maps the item under study:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Document (if any) associated with Item Under Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Cleaning SOP No. 123/4</td>
</tr>
<tr>
<td>e.g. Change Control No. 2005/11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason &amp; Relevant Background Info for this RM Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant:</td>
</tr>
</tbody>
</table>

RM exercise needed to critically evaluate |
Manage exists issue with Recall & CID |
notification contents & 116 HCPs Section |

This exercise includes the handing of |
Road maps for other CAS, as well as |
The receipt of QBD issues from other |
Groups (e.g. 1234 HCPs, Companies, DAT) |
Step 2: Who's Who ... Define the Risk Management Team*

<table>
<thead>
<tr>
<th>Name of RM Team Leader</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Connell</td>
<td>Marine Logistics Manager</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Team Member Name*</th>
<th>Position / Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat Walsh</td>
<td>Supplier Analyst, HCS, 1.76</td>
</tr>
<tr>
<td>Thea Gleason</td>
<td>Technical Officer, HCS, 1.73</td>
</tr>
</tbody>
</table>

*Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

Carry out the following tasks, and complete this table by ticking the appropriate options:

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default Probability, Severity & Detection definitions for this RM Exercise.

2. The team should then either agree to accept the default Probability, Severity & Detection definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - Accept the default Probability, Severity & Detection definitions shown on the Card.
   - Do not Accept these default definitions, and draw up new definitions.

3. If applicable, Document any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - Tick here if any new definitions are attached
   - Tick here if N/A
**Laminated Card**

This Card shows the default Probability, Severity & Detection definitions for the Risk Management tool. It also shows the Risk Table, with the risk acceptability criteria.

Risk = \( P \times S \)

**Important:** The definitions shown for each P, S & D level are default definitions; they can be modified as required. See Step 3 of the Tool Worksheet for details.

<table>
<thead>
<tr>
<th>( P )</th>
<th>Probability of Occurrence</th>
<th>( S )</th>
<th>Severity Levels for the Effects of the Negative Event</th>
</tr>
</thead>
</table>
| High   | The Negative Event is Likely to Occur | Critical | The Effects are Severe  
- Very Significant GMP/MA Non-Compliance  
- Potential Patient Injury |
| Medium | The Negative Event May Occur | Moderate | The Effects are Moderately Severe  
- Significant GMP/MA Non-Compliance  
- Potential Patient Impact |
| Low    | The Negative Event is Unlikely to Occur | Minor | The Effects are Not Severe  
- Minor GMP/MA Non-Compliance  
- No Patient Impact |
| Remote | The Negative Event is Very Unlikely to Occur |        |                                                      |
Step 4: What Might Go Wrong ... Identify Potential Negative Events Here:

This involves compiling & reviewing data & brainstorming to identify potential negative events for the item under study.

Data Review & Brainstorming Session No: 171.06  Session Date: 171.06

**Tick One:**
- Select and list below the most critical and/or complex Potential Negative Events which could be associated with the item under study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- If a Specific Negative Event or Problem has been identified in Step 1 for assessment, delete that below.

<table>
<thead>
<tr>
<th>No.</th>
<th>Examples of Potential Negative Events &amp; Problems</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. Cross Contamination Event occurs in Dryer Room No. 123.</td>
<td>e.g. Glass has been reported in vials of product X several times in the past 5 years. (Ref: Complaint No. 2004/5, 6)</td>
</tr>
<tr>
<td></td>
<td>e.g. Glass in Vials of Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Packs of Product X are Released without a PFL.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hard, yellow particles observed in batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Loss of Sterility Assurance for Filling Process for Product X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Low Yield Batches of API X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. BMS System Failure Occurs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of Potential Negative Event</th>
<th>Reference or Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(1)</strong> Urgent Recall / C/IU communication do not reach intended recipients in a timely manner</td>
<td>Ref: See completion of company procedures (Recall Section)</td>
</tr>
<tr>
<td>- e.g. within 24 hours</td>
<td></td>
</tr>
<tr>
<td>- Wholesalers &amp; pharmacies &amp; others</td>
<td></td>
</tr>
<tr>
<td><strong>(2)</strong> Recall / C/IU letter (Speed)</td>
<td>N/A</td>
</tr>
<tr>
<td>- Contain incorrect product name or batch number data.</td>
<td></td>
</tr>
</tbody>
</table>

**Description of Potential Negative Event**

**All recipients of the defective batch are not identified for communicating to.** (e.g. all defective batches, or product not identified or some recipients not identified.)

Reference or Notes

Wholesalers do not receive the recall record for most transactions.
## Step 5: Risk Evaluation

Use a separate Step 5 for each Negative Event. Number the controls in the format A, B, C, ... etc.

### Brief Description of this Negative Event:
Communication (urgent) do not reach intended recipient in timely manner, etc.

### List the Potential Negative Consequences of this Negative Event, should it occur:
- Recall notice or recall level delayed
- Defective/harmful product may be used/administered
- Possible patient injury

### List any Current Back-up Systems/Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control, starting with A, B, C, ... etc.)

1. **A recall/CTU letter will be received by_recipients of defective/bad/ product in the course (3 days) to be sure can be if recall/TV contain an option, if needed.**

### Severity: Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:
- Critical
- Moderate
- Minor

**For very serious recall/CTU issues, a delay of 2 days could be very serious, eg: Robins Vaccine Recall 2004**

### List the Possible Causes or Mechanisms for this Negative Event to Occur:

<table>
<thead>
<tr>
<th>Cause/Mechanism</th>
<th>Preventative Controls in place:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl #</td>
<td></td>
</tr>
</tbody>
</table>

### Risk Assessment

- **Risk assessment of each cause/mchanism**
- **Occurrence of each cause/mechanism**
- **Prob. of occurrence of each cause/mechanism**
- **Risk = P x S**

**Instruction:** For acceptable risks, go to Step 8. For all other risks, go to Step 6.
**Step 6: Risk Evaluation Cont'd**

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C.

<table>
<thead>
<tr>
<th>Event No: 1</th>
<th>Detection Controls</th>
<th>Detection Rating</th>
<th>Risk Decision Point: Is the Risk adequately controlled?</th>
<th>No</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A</td>
<td>Spot checks (preparation to check hardware)</td>
<td>Low</td>
<td>Do these controls give assurance that the risk is adequately controlled &amp; that no further controls are required? Explained Below.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2 B</td>
<td>As above</td>
<td>Low</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Step 7: Risk Control

Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>1</th>
<th>State the Cause or Mechanism for the Negative Event to Occur (if from Step 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk No.</td>
<td>2</td>
<td>Exercise Control Procedures in 3 days, SLM 0.3% per day ≤ 3 days</td>
</tr>
</tbody>
</table>

#### Risk Reduction Measures

<table>
<thead>
<tr>
<th>Crit #</th>
<th>What New or Improved Preventative Controls could prevent this Negative Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Risk 1 for Neg Event.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crit #</th>
<th>What New or Improved Back-up Systems or Redundancy Controls could counteract the consequences of this Negative Event, should it occur?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New Risk Level</th>
<th>Acceptable - go to Step 8</th>
<th>Unacceptable / Intolerable - continue below</th>
</tr>
</thead>
</table>

#### If the Risk is still Unacceptable or Intolerable:

<table>
<thead>
<tr>
<th>New or Improved Detection Controls to Detect this Neg. Event?</th>
<th>New D Rating</th>
<th>Risk Decision Point:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Is risk now adequately controlled? Yes / No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do these controls now give assurance that the risk is adequately controlled &amp; no further controls are required?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes Go to Step 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No: Repeat this Step</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment/Explanation:</td>
</tr>
</tbody>
</table>

Note: if any of the above new controls may introduce a new risk, complete a new Step 4
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No. (A, B, C...)</th>
<th>Type of Control:</th>
<th>Current</th>
<th>Improved</th>
<th>New</th>
</tr>
</thead>
</table>

Brief Description of the Control:
Recall Letter / CIU Letter is always mailed to recipient if defective product

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

1. 18 in. Sup. or co-molded/fixed issued salt in CIU letters - Sup. S111 & S604 & S5
2. Dedicated Area QDR Team
3. Mailing list of PDI

These items are Already In Place □
These items are Not Already In Place □

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No
If yes, specify these here:
- Financial Recall / CIU Letter must be mailed by QDR Staff in advance of issue
- Timeline for issue is agreed & spot checked done
- Feedback Letter must confirm that issue resolved

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? □ Yes □ No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

None for 1873. Must ensure recall obligation are dealt with in a satisfactory manner.

What is the Status of this Qualification or Validation exercise?
□ Completed
□ Not Yet Completed
□ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
□ New Qualification/Validation work needed
□ No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Event No.</th>
<th>Worksheet No.</th>
<th>Control No. (A, B, C,...)</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**
Radio or TV remain as an option if 3rd party decides such a communication is needed.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:
- dedicated signal with 3rd to draft press release
- Contacter details for TV/press (Leber-Shanwich)

These Items are Already In Place: ☐
These Items are Not Already In Place: ☑

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for the Control**
Are there any Acceptance Criteria or Required Outcomes associated with this Control? ☑ Yes ☐ No
*If yes, specify these here:
- Leber-Shanwich must have up to date TV/radio contracts
- 1st must have a contract in place if W&S would specify their role in this area.

**Part B: Critical Process Parameter**
Does this control have any associated CPP to be measured or monitored? ☑ Yes ☐ No
*If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

**Qualification & Validation Requirements**
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

N/A

What is the Status of this Qualification or Validation exercise?
☐ Completed
☐ Not Yet Completed
☐ N/A

Current Qualification or Validation Status of this Control: (Tick one below)
☐ New Qualification/Validation work needed
☐ No New Qualification/Validation work needed
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No:</th>
<th>Worksheet Step No:</th>
<th>Control No: (A, B, C...)</th>
<th>Type of Control:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

**Brief Description of the Control:**

Spot checks built into existing QDR procedures for procurement & chemicals

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

QDR. Sep S111
Admin resource for this work

These Items are Already In Place [ ]
These Items are Not Already In Place [ ]

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? [ ] Yes [ ] No

If yes, specify these here:

Reg'd outcome: result of spot check must be documented by action & communicated to supplier / site reg

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? [ ] Yes [ ] No

If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

None

<table>
<thead>
<tr>
<th>Q &amp; V</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the Status of this Qualification or Validation exercise?</td>
</tr>
<tr>
<td>[ ] Completed</td>
</tr>
<tr>
<td>[ ] Not Yet Completed</td>
</tr>
<tr>
<td>[ ] N/A</td>
</tr>
</tbody>
</table>

**Current Qualification or Validation Status of this Control**: (Tick one below)

[ ] New Qualification/Validation work needed [ ] No New Qualification/Validation work needed
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No.</th>
<th>Control (A, B, C)</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>A</td>
<td>Current (X)</td>
</tr>
</tbody>
</table>

Brief Description of the Control:

Required: Communication from Retail pharmacies, via PDF Underliner: "Resolution Letter in 1088 Initiative"

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- 1088 PDF procedure (Steps)
- Dedicated staff @ both 1088 & PDF
- Wholesalers & Funds (likely to date)

These Items are Already In Place [X]
These Items are Not Already In Place [ ]

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? [X] Yes [ ] No
If yes, specify these here:

- All PDF Underliner will be required to get the Control to all Retail/Pharmacies within 24 hours

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? [X] Yes [ ] No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:

- Time to Communicate the Message
  - 1088 to PDF
  - To Communicate 1088 to PDF Wholesalers

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

[ ] Yes - Dedicated Validation exercise was to be designed & co-ordinated by 1088

Q & V

What is the Status of this Qualification or Validation exercise?
[ ] Completed
[ ] Not Yet Completed
[ ] N/A

Current Qualification or Validation Status of this Control: [Pick one below]

[ ] New Qualification/Validation work needed
[ ] No New Qualification/Validation work needed

[ ] Time: To receive the message by retail pharmacies
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet Step No.</th>
<th>Control No.</th>
<th>Type of Control</th>
<th>Brief Description of the Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Rapid Communication Mechanism for Hospital Pharmacies</strong></td>
</tr>
</tbody>
</table>

Items Required for this Control: List any items (documentation, equipment, facilities, systems, or personnel resources) which are required for this control to be in place:

- [ ] MB (or) HMI procedure
- [ ] Dedicated staff @ MB (or) HMI responsible for this mechanism
- [ ] Funds (likely reg.)

These Items are Already In Place: [ ]
These Items are Not Already In Place: [ ]

Complete Either Part A or B Below...

Part A: Acceptance Criteria or Required Outcomes for this Control
Are there any Acceptance Criteria or Required Outcomes associated with this Control? [ ] Yes [ ] No
If yes, specify those here:
- All HMI members must receive the notification within 24 hrs.
- At least 1 phone/person per each hospital must not be the awhile within 24 hrs.

Part B: Critical Process Parameter
Does this control have any associated CPP to be measured or monitored? [ ] Yes [ ] No
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP:
- [ ] [ ] [ ] [ ] [ ] [ ] [ ]
- [ ] 1876 → HMI server

Qualification & Validation Requirements
If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

[ ] [ ] [ ] [ ] [ ]

Q & V
What is the Status of the Qualification or Validation exercise?
[ ] Completed
[ ] Not Yet Completed
[ ] N/A

Current Qualification or Validation Status of this Control: (Tick one below)
[ ] New Qualification/Validation work needed
[ ] No New Qualification/Validation work needed
### Step 5: Risk Evaluation

Use a separate Step 5 for each Negative Event. Number the controls in the format A, B, C... etc.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Recall, age, and gender incorrect, product name, batch no.</td>
</tr>
</tbody>
</table>

List the Potential Negative Consequences of the Negative Event, should it occur:

Wrong product/batch gets recalled or is the subject of the CICU message. Pot patient injury as a result.

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>List any Current Backup Systems/Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C... etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

**S: Severity:** Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen.

- [ ] Critical
- [ ] Moderate
- [ ] Minor

<table>
<thead>
<tr>
<th>List the Possible Causes or Mechanisms for this Negative Event to Occur:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

P: Prob. of Occurrence of each cause / mechanism

Risk assoc. w/ each cause or mechanism Risk=P x S

Instruction: For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6
Step 6: Risk Evaluation Cont’d
This sheet is for Unacceptable or In tolerable Risks Only. Number the controls in format A, B, C.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Control</th>
<th>Detection Controls</th>
<th>D</th>
<th>Risk Decision Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A</td>
<td>Accuracy checks for recall (C/IU letters are in place in 1993 and CPR – see CPR from FOIS, version 7, 2003)</td>
<td>High</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

If No, Go to Step 7; If Yes, Go to Step 3.
**Step 8: Qualification & Validation**

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Week No.</th>
<th>Control No. (A, B, C, D)</th>
<th>Type of Control:</th>
<th>A</th>
<th>Improved</th>
<th>New</th>
</tr>
</thead>
</table>

**Brief Description of the Control:**
Accuracy check on Recall & C/IU, letter, and by O/DR staff during fluid supply process.

**Items Required for this Control:** List any items (documentation, equipment, facilities, systems or personal resources) which are required for this control to be in place:
- Accuracy Check on Recall & C/IU, letter
- By O/DR staff during fluid supply process

*See Recall Guidance Note 10/2009

These Items are Already In Place: [ ]
These Items are Not Already In Place: [ ]

**Complete Either Part A or B Below...**

**Part A: Acceptance Criteria or Required Outcomes for this Control**
Are there any Acceptance Criteria or Required Outcomes associated with this Control? [ ] Yes  [ ] No

If Yes, specify these here:

Required Outcomes are:
1. Letter to confirm the accuracy of the recall
2. Confirmation by independent O/DR staff member

**Part B: Critical Process Parameter**
Does this control have any associated CPP to be measured or monitored? [ ] Yes  [ ] No

If Yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

**Qualification & Validation Requirements**
If the control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

Yes - A validation exercise is needed to demonstrate the adequacy of this control.

**Q & V**
What is the Status of this Qualification or Validation exercise?
[ ] Completed
[ ] Not Yet Completed
[ ] N/A

**Current Qualification or Validation Status of this Control:** (Tick one below)
[ ] New Qualification/Validation work needed
[ ] No New Qualification/Validation work needed
### Step 5: Risk Evaluation

Use a separate Step 5 for each Negative Event. Number the controls in the format A, B, C, ... etc.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Brief Description of this Negative Event:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>All recipients of defective hand sanitiser are not identified for communication to...</td>
</tr>
</tbody>
</table>

List the Potential Consequences of this Negative Event, should it occur:

- Some defective hand sanitiser do not get recalled, or some recipients do not receive the CIDE info.

### Ctrl #

List any Current Backup Systems / Redundancy Controls which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C, ... etc.)

None

### S: Severity

Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

- Critical
- Moderate
- Minor

### List the Possible Causes or Mechanisms for this Negative Event to Occur:

<table>
<thead>
<tr>
<th>No.</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiple manufacturers</td>
</tr>
<tr>
<td></td>
<td>One or more manufacturers in the company via discount distributor records</td>
</tr>
<tr>
<td>2</td>
<td>Related products (e.g. spray) not identified in initial log-in</td>
</tr>
</tbody>
</table>

### Current Preventative Controls in Place:

(List the controls for each individual Negative Event Cause or Mechanism)

<table>
<thead>
<tr>
<th>Ctrl #</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1. BS order procedure completed by hospital staff. 2. Ensure detailed investigation by hospital staff. 3. To determine completeness of records of affected product.</td>
</tr>
<tr>
<td>A</td>
<td>Coids present, one or all plasters, cannot be identified. The eider mister is not on all pharmacies.</td>
</tr>
</tbody>
</table>

### P: Prob. of Occurrence of each cause / mechanism

Remote

### Risk assoc. w/ each cause or mechanism

Risk= F x S

Instruction: For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6

* Sup S111, S109, evidence for acid spill & decontamination of wholesaler's premises & distribution of affected products.
Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 3, 6 & 7. However, if a current control is being improved, just complete Step 8 for the improved control only.

<table>
<thead>
<tr>
<th>Negative Event No.</th>
<th>Worksheet No.</th>
<th>Control No. (A, B, C...)</th>
<th>Type of Control Improved</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
<td>A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brief Description of the Control:

1. **C&DR** Supplies Form (S111/S109/S004 & F015)

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

- Trained C&DR Staff

These items are Already in Place □

These Items are Not Already In Place □

Complete Either Part A or B Below:

**Part A: Acceptance Criteria or Required Outcomes for this Control**

Are there any Acceptance Criteria or Required Outcomes associated with this Control? □ Yes □ No

If yes, specify these here:

- C&DR staff must be satisfied (a documented
  visit) then:
  - all related potency failures batches/products
  identified & all lots removed identified by Category

**Part B: Critical Process Parameter**

Does this control have any associated CPP to be measured or monitored? □ Yes □ No

If yes, list the CPP below, and state the Limits/Acceptance Criteria for the CPP

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise:

- The C&DR log procedure must be validated. To determine then related products can be identified when a C&DR report received.

Current Qualification or Validation Status of this Control: (Tick one below)

- [ ] New Qualification/Validation work needed
- [ ] No New Qualification/Validation work needed

Q & V

What is the Status of this Qualification or Validation exercise?

- [ ] Completed
- [ ] No, Yet Completed
- [ ] N/A
### Step 9: Action Items

Identify any action items from the completed Qualification & Validation Worksheets

<table>
<thead>
<tr>
<th>Negative Event Ref. No.</th>
<th>Description of the Action Item</th>
<th>Responsible Person / Group</th>
<th>Completion Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Develop 1183 Sup for 1183 - PDF Rapid Comm. Mech.</td>
<td>HCS</td>
<td>5/06</td>
</tr>
<tr>
<td>1</td>
<td>Validate 1183 - PDF Rapid Comm. Mechanism following development of PDF procedures</td>
<td>HCS/ pdf</td>
<td>03/06</td>
</tr>
<tr>
<td>1</td>
<td>Develop 1183-HPI mechanism for rapid recall/CRI costs - 1183 Sup rec'd</td>
<td>HCS</td>
<td>2/06</td>
</tr>
<tr>
<td>1</td>
<td>Validate above custom rec'd</td>
<td>HCS/HPI</td>
<td>02/06</td>
</tr>
<tr>
<td>2</td>
<td>Publish 1183 guidance on accuracy check on recall letters</td>
<td>HCS</td>
<td>04/04</td>
</tr>
<tr>
<td>2</td>
<td>Amend CDR 5111 Sup to include precision for accuracy check on recall &amp; CRI letter</td>
<td>HCS</td>
<td>2/06</td>
</tr>
<tr>
<td>2</td>
<td>Validate accuracy check procedure</td>
<td>HCS</td>
<td>03/06</td>
</tr>
<tr>
<td>3</td>
<td>Validate CDR Eng-in procedure for identifying problems related to a CDR report.</td>
<td>HCS</td>
<td>03/06</td>
</tr>
</tbody>
</table>

**Comments or Notes:**

*Already completed. See Appendix U-VIII for details on product recall for further details.*
### Risk Communication Activities

<table>
<thead>
<tr>
<th>No.</th>
<th>Communication Activity &amp; Method</th>
<th>Responsible Group</th>
<th>Target Date</th>
</tr>
</thead>
</table>
| 1   | Communicate the results of this exercise with:  
- MCS staff  
- Compliance Dept staff  
- HPSI & PDF | LSM 01/06  
LSM 02/06  
LSM 02/06 | |
| 2   | Communicate the validation requirements to planning reg | LSM 02/06 | |

### Periodic Review Activities

- **Proposed Review Date:** 6 months from now

If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:

- *or sooner, if a significant recall issue arises which requires urgent communication to wholesalers & pharmacists.*

### Other Comments or Notes:
Volume 2, Part II - The Training & User’s Manual

Section 10

Research Papers

Copies of three peer-reviewed research papers describing this Quality Risk Management methodology
A Risk Management Solution
Designed To Facilitate Risk-Based
Qualification, Validation,
And Change Control Activities
Within GMP And Pharmaceutical
Regulatory Compliance
Environments In The EU

PART I
Fundamental Principles,
Design Criteria,
Outline Of Process

By
Kevin O'Donnell (Corresponding Author) Compliance Department, Irish Medicines Board
and
Anne Greene, School of Chemistry and Pharmaceutical Sciences, Dublin Institute of Technology

Note: The views expressed in this paper are those of the authors, and should not be taken to represent the views of the Irish Medicines Board.
PART I

Risk-based Qualification, Validation, and Change Control - Opportunities for Improvement

In the European Union (EU), the Good Manufacturing Practice (GMP) requirements place specific obligations on manufacturers of medicinal products to implement risk-based qualification, validation, and change control programmes. Annex 15 to the EU Guide to GMP titled, “Qualification and Validation,” requires:

a) That a risk assessment approach be used to determine the scope and extent of validation.
   (Note: Within the EU GMP and others, the term, “validation,” is generally understood to encompass qualification as well as validation activities.)

b) That risk analysis be employed when assessing the likely impact of changes.

How these GMP requirements are met has been the subject of much discussion between Regulators and Industry in recent years, and as a Regulatory Agency, the Irish Medicines Board has received numerous requests from Industry for guidance in this area.

From the authors’ experience as a GMP Inspector, it is evident that risk factors are often taken into account when designing qualification and validation programmes, and when processing change control proposals. However, as mentioned in the International Conference on Harmonization (ICH) Guideline on Quality Risk Management, ICH Q9, the use of risk management in the Pharmaceutical Industry has, to date, been limited, and the full benefits of risk management, as a valuable component within a quality system, have yet to be realised.

Despite ever-increasing qualification and validation costs, as described in publications of the International Society of Pharmaceutical Engineering (ISPE) and others, there is evidence that defective and non-compliant medicinal products continue to be manufactured and released. These often result in product recalls being required to protect patients and users of medicinal products. As discussed in ISPE’s White Paper on Risk-Based Qualification for the 21st Century, current qualification practices, for example, are often document-intensive, expensive, and time-consuming, but do not necessarily add value, or lead to clear patient risk-mitigation strategies or process understanding. Likewise, validation activities sometimes do not adequately address the critical aspects of processes. In the area of change control, proposed changes often involve substantial capital expenditure and large project teams, but sometimes important risks introduced by the change are not identified. Therefore, it is likely that the use of more formalised and scientific approaches to risk management may prove beneficial within GMP environments.

A Risk Management Solution for GMP and Regulatory Compliance Environments

There are many formal risk management tools available, such as Fault Tree Analysis, Failure Modes and Effects Analysis (FMEA), and Hazard Analysis and Critical Control Points (HACCP). However, most were not specifically designed for GMP applications, much less as solutions for facilitating risk-based qualification, validation, and change control activities within GMP environments. As a result, a degree of design modification is often required before an existing tool may be used for these activities. Of the tools which are GMP-specific, such as the approaches developed by ISPE and GAMP, their focus tends to be somewhat narrow, being tailored for equipment and systems qualification and computerised systems validation, respectively. As a result, the day-to-day practicalities of how to apply GMP risk management more broadly remain somewhat under-developed.
PART I

In addition, few if any, of the available tools were designed as complete, documented, and ready-to-use risk management methodologies that address all of the components of risk management and have been accepted via ICH Q9 as important. These are as follows: risk assessment, risk control, risk communication and risk review. As a result, a further degree of modification is often required before any of the existing risk management tools may be used as a complete risk management solution.

In response to the requests received by the Irish Medicines Board from Industry for guidance in the interpretation of the risk-related requirements of Annex 15 to the EU GMP Guide, and as part of our efforts to better understand how risk management may be used in practice, the Irish Medicines Board has developed a practical risk management methodology, or tool, designed specifically as a means of addressing those Annex 15 requirements. As part of this work, a series of practical case studies have been developed on the use of this tool, in order to show how the tool works in practice. This risk management solution is designed so that it provides a complete and documented means of addressing all of the aforementioned components of risk management.

In this series of papers, in two parts, this risk management methodology is described. In Part I, the principles underlying this approach are given, and the design criteria used for development of the risk management tool are outlined. The tool uses a documented ten-step process, also described in Part I. In Part II, the scope and structure of the risk management tool are described, and some of the limitations of this tool are given. An outline of some of the principle findings made to date with this tool is also given in Part II. (It is emphasised that this work is not intended to place any specific regulatory obligations on manufacturers, nor is the risk management solution presented here being promoted in any way as a tool that should be used by Industry. This work simply demonstrates how GMP risk management may be applied in practice.)

Is this Risk Management Solution Intended to Replace other Available Tools?

It is not the intent of this work to replace other available tools; existing tools are valuable in their own right. The risk management methodology described here was designed for a specific purpose - to facilitate risk-based and patient-focused qualification, validation, and change control activities. This tool focuses on evaluating how GMP controls, both current and proposed, lead to mitigation and control of the risks identified, and on the qualification and validation status of such controls.

Importantly, this work does not seek to "reinvent the wheel," and during the technical development of this risk management solution, some of the useful features and concepts behind other risk management tools and approaches were adopted or taken into account. For example:

- **FMEA and FMECA**
  
  This risk management solution draws upon some features of FMEA and FMECA in that it recognises the value in assigning Probability, Severity, and Detection ratings during risk assessment work, and in re-assessing these ratings following risk control strategies. It also recognises the value in breaking down the item under study into manageable components for individual assessment.

However, the approach developed here handles risk detection in a markedly different way. Here, detection controls are considered and evaluated after the risk has been estimated, not before,
and significantly, this tool requires a formal and critical evaluation of any detection controls that are in place, in order to determine whether these controls actually give assurance that the risk is adequately controlled and that no further controls are required.

This approach also classifies GMP controls differently, and this impacts upon how risks are generally estimated and controlled. This tool requires one to address qualification and validation issues for current controls as well as for new controls, even when the related risk is deemed acceptable with current controls. Also, this approach does not make use of FMEA’s ‘Risk Priority Number’ concept, and ‘Failure Mode’ terminology is not used.

**HACCP**

This risk management solution draws upon some concepts of HACCP, in that it recognises the value in prevention rather than detection, and the value in determining critical control points, their related limits, and target levels. HACCP also provides a comprehensive and documented approach for practical risk management exercises.

However, HACCP-based applications do not normally offer a clear, formal process for characterising or differentiating (by either qualitative or quantitative means) the risks posed by a potential hazard, and the HACCP requirement to pre-define corrective actions for situations when Critical Control Points (CCP) limits have been exceeded is not used here. Rather, this solution provides a formal means of assessing individual risks, and it focuses on identifying and implementing GMP controls which give assurance, via qualification and validation, that such risks are either reduced to an acceptable level or controlled to an acceptable level.

**The GAMP 4 Risk Assessment Process**

This risk management solution draws upon some features of the GAMP 4 Risk Assessment process, in that it recognises the value in estimating risks on the basis of likelihood and severity considerations only, not on detection factors, and the value in using the risk assessment process to help focus validation activities and to assess change control proposals. Also, the GAMP process considers the complexity and degree of customisation of the item under study when determining how much rigor to apply during the risk management process.

However, the approach described here deals with risk detection in a different way, as it does not allow users to automatically assign risk priorities simply on the basis of detection ratings.

**The ISPE Impact Assessment Process**

This risk management solution draws upon some features of the ISPE Impact Assessment process, as described in ISPE’s Baseline Guide on Commissioning and Validation, in that it recognises the value in using structured and systematic techniques to determine critical components of systems on an “impact” basis, with respect to product quality. It also recognises the value in focusing qualification activities on those critical components.

However, the approach described here addresses additional items, such as the risks presented when equipment and system faults occur, as well as risk control, communication, and review activities.
The Fundamental Principles Underlying this Risk Management Solution

A number of key principles underlie the design of this risk management solution. These were considered fundamental to this application of risk management in GMP and Regulatory Compliance environments, and are shown in Figure 1.

Figure 1

Principles Underlying this Risk Management Solution

<table>
<thead>
<tr>
<th>NO.</th>
<th>PRINCIPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>That the scope and extent of qualification and validation, and the likely impact of changes, should be determined and managed on a risk basis.</td>
</tr>
<tr>
<td>2.</td>
<td>That risk is the combination of the probability of occurrence of harm and the severity of that harm, and that harm is considered to be damage to health, including the damage that can occur from loss of product quality or availability.</td>
</tr>
<tr>
<td>3.</td>
<td>That as a minimum, risk management contains the following four components: risk assessment, risk control, risk communication, and risk review, as defined and described in ICH Q9.</td>
</tr>
<tr>
<td>4.</td>
<td>That a consideration of &quot;what might go wrong&quot; is fundamental to the risk management exercise.</td>
</tr>
<tr>
<td>5.</td>
<td>That there may be some risks that cannot be eliminated or reduced to an acceptable level with current or realistic controls or resources, but that may be controlled to an acceptable level with improved detection or other measures, as determined on a case-by-case basis.</td>
</tr>
<tr>
<td>6.</td>
<td>That risk management is not an exact science and, while a scientific approach should form the basis of the risk management process, there may be uncertainties associated with the outcome of the risk management exercise.</td>
</tr>
<tr>
<td>7.</td>
<td>That risk may be assessed qualitatively as well as quantitatively, and that a good qualitative assessment of risk may be more valid than a poor quantitative assessment.</td>
</tr>
<tr>
<td>8.</td>
<td>That the main stakeholders associated with the application of risk management within GMP and Regulatory Compliance environments are patients and users of medicines, including healthcare professionals, as well as industry and Regulators, and that, while the concerns of all involved stakeholders should be taken into account in any risk management exercise, protection of the patient is of prime importance, and therefore, risk management should ultimately link to the protection of the patient.</td>
</tr>
<tr>
<td>9.</td>
<td>That, in GMP environments, a high detectability of risk does not necessarily mean that the risk is eliminated or adequately controlled.</td>
</tr>
<tr>
<td>10.</td>
<td>That the implementation of risk control measures could, in itself, inadvertently introduce new risks, which will need to be managed.</td>
</tr>
<tr>
<td>11.</td>
<td>That performing risk management exercises can be improved through the use of multi-disciplinary teams.</td>
</tr>
<tr>
<td>12.</td>
<td>That a formal risk management process may not always be necessary or appropriate in all situations, and that the level of effort, rigor, formality, and documentation associated with the risk management process should be commensurate with the complexity and/or criticality of the issue being addressed.</td>
</tr>
</tbody>
</table>
These principles were based primarily upon the guidance of ICH Q9, on the current EU GMP requirements, and on the ISO 14971:2000 Standard, on the application of risk management for medical devices. The authors' own experiences in using other risk management tools, and a broad review of risk management-related publications also provided insight on key issues.

As is evident, the Principles noted in Figure 1 are largely self-explanatory. The following notes provide some background and explanatory information relating to each:

- **Principle 1** is based on Annex F5 (Qualification and Validation) to the EU GMP Guide. It implies that, before validation master plans and qualification and validation protocols are finalised, risks associated with the items under study should be considered, resulting in the identification of risk-based critical parameters requiring qualification or validation. This Principle also implies that, before change control proposals are approved, the potential risks presented by the change should be identified and a strategy determined for managing such risks.

- **Principles 2, 3, and 4** reflect the guidance presented in ICH Q9 and other publications, such as ISO/IEC Guide No. 73, titled, "Risk Management - Vocabulary - Guidelines for Use in Standards." The inclusion of loss of product availability in the definition of harm is considered important in GMP risk management activities, because the loss of product availability may adversely impact not only business, but also patients and users of medicinal products.

- **Principle 5** reflects the author's experience in applying risk management principles and tools to GMP situations - that sometimes, the probability of occurrence of harm, or the severity of that harm, just cannot be reduced to levels that render the risk acceptable with current or realistic resources, but that such risks can be controlled to an acceptable level by means of detection or other risk-control measures.

- **Principles 6 and 7** recognise that risk can be difficult to quantify, and that there may be uncertainties in the outcome of any risk management exercise. As discussed in ICH Q9, for example, different stakeholders may perceive different potential harms, or place a different probability on the occurrence of each harm, or assign different severities to each harm, and this can lead to uncertainty. This principle implies that the risk management solution should be able to address such difficulties and uncertainties. (The papers 19-22, detailed in the References section, provide useful information in this regard.)

- **Principle 8** requires that the risk management solution should help to formally identify who the stakeholders are for the item under study. This enables the concerns of those stakeholders to be taken into account and for appropriate definitions of severity to then be determined.

- **Principle 9** is far reaching, and it renders this solution somewhat different to other risk management tools with respect to dealing with risk detectability. Here, users may not automatically conclude that a high detectability for a negative event or its effects means that a risk is acceptable or adequately controlled. For example, the ability to detect
glass in filled and stoppered vials may sometimes be high, but this detection control
does not mean that the vial filling and sealing process is under adequate GMP control
if the incidence of glass in vials is relatively high.

- Principle 10, also based on ICH Q9, means that the risk management solution must
  formally be able to identify and manage any new risks that may be introduced as part
  of Risk Control activities. New risks can be introduced, for example, when a new
  Process Analytical Technology (PAT)-based sensor is installed in a drying vessel to
  monitor a parameter such as water content. The material housing the sensor may be
  incompatible with the contents of the dryer, or it may not be adequately robust, giving
  rise to a risk of product contamination.

- Principle 11 recognises the benefit of using multi-disciplinary teamwork when perform-
  ing risk management, and is certainly not a new concept. Well established tools such
  as HACCP, as outlined by the Codex Alimentarius Commission, require the use of
  multi-disciplinary teams.

- Finally, Principle 12, again reflecting ICH Q9, recognises that much of what we do
  within GMP environments is risk-based, even if we do not call it that. This is important,
  because often, there may be no need to use a formal risk management tool, when
  existing procedures may be adequate. This principle, in a subtle way, also recognises
  the fact that risk events can have multiple causes, with multiple associated risks, some
  less important than others. This can result in formal risk management activities becom-
  ing costly and quite labour-intensive exercises, and should, therefore, be targeted at
  the most complex or critical issues.

Design Criteria for this Risk Management Solution

During the design stage for this risk management solution, it was determined that the tool
had to meet certain pre-defined criteria if it was going to serve its intended purpose: to facili-
tate risk-based qualification, validation, and change control activities.

These pre-defined criteria were as follows:

- That the tool should offer GMP and Regulatory Compliance environments a documented,
  scientific, practical, systematic, transparent and flexible solution for determining and man-
  aging, on a risk basis, the scope and extent of qualification and validation, and the likely
  impact of changes.

- That the tool should allow for the highest risks to be identified and prioritised for action.

- That the tool should be a readily usable and complete risk management solution, with-
  out requiring extensive modification before it may be used to address all of the required
  elements of risk management.
• That the tool should have wide applicability across GMP and Regulatory Compliance environments.

• That the tool should directly conform to each of the twelve aforementioned principles which were defined as being important for facilitating risk-based qualification, validation, and change control activities within GMP and Regulatory Compliance environments.

With the above design criteria in mind, a structured and systematic risk management process was developed. This comprises of ten discrete process steps, as outlined in Figure 2. A detailed, instructional worksheet has been developed, which facilitates each of the ten steps. This worksheet is used to document the risk management exercise, and to guide users through the actual risk management process. Detailed guidance on carrying out each of these ten steps is available in the Tool's User Manual.

**Figure 2**

A Ten-Step Risk Management Process

**Step 1: Document Specific information on the Risk Management Exercise Being Undertaken:**
- Identify whether the exercise is a Prospective, Retrospective, or a Change Control risk management exercise.
- Define the item under study and the scope of the exercise. If possible, define boundaries for the item under study.
- Provide relevant background information so that the reason for the risk management exercise is made clear.
- State any pertinent assumptions being made, especially those relating to qualification and validation, and document any significant uncertainties associated with the data being used in the exercise.

**Step 2: Who's Who? - Define the Risk Management Team:**
- Identify the risk management team leader and other team members.
- The team should be multi-disciplinary and include persons knowledgeable in the item under study.
- At least one person should have a firm understanding of the risk management process, principles, and methodology.
- If possible, there should be personnel on the team who have the necessary authority (or the means) to make key decisions regarding the implementation and funding of risk mitigation controls.

**Step 3: Review the Default Definitions Provided for Negative Event-Probability, Severity, and Detection:**
- Review the default Probability, Severity, and Detection definitions provided in this Risk Management Tool. These are presented on a laminate card, which accompanies the tool worksheet.
- The team then decides whether the default definitions as provided are appropriate for the specific risk management exercise at hand.
PART I

- This is where new or modified Probability, Severity, and Detection definitions can be drawn up, if required. For example, the definitions for Probability of Occurrence can be made quantitative, or the Severity definitions can be altered to better reflect the concerns of any specific stakeholders.
- A Risk Table (or matrix) is used by this Risk Management Tool, and this is also shown on the laminated card. (See page 25.)

Step 4: What Might Go Wrong? - Identify Potential Negative Events:
- Review relevant documentation, records and data, and use brainstorming techniques to identify potential negative events for the item under study. (Note: Guidance on brainstorming is provided in a Questions and Answers document provided with the tool.)
- Of the potential negative events identified, review each, discussing their potential severities, and select and list those considered to be the most critical and/or complex negative events, for formal evaluation in this exercise.
- As this is a formal and rigorous risk management methodology, only the highest priority or most important potential negative events should normally be selected for formal evaluation. However, any number can be selected.

Step 5: Risk Evaluation - Is the Risk Acceptable, Unacceptable, or Intolerable?
- For each potential negative event, identify and document the potential negative consequences.
- Document and critically evaluate any currently in place back-up or redundancy controls for the potential negative event, and assign a Severity rating.
- Identify and document the cause(s) of each potential negative event.
- Document and critically evaluate any currently in place preventive controls for each cause, and assign a Probability of Occurrence rating to each cause.
- Using the Risk Table provided on the laminated card which accompanies the tool worksheet, estimate each risk associated with the potential negative event.
- This results in the classification of each risk as either Acceptable, Unacceptable, or Intolerable.
- Risks deemed to be Acceptable progress directly to Step 8 of the worksheet; all other risks progress to Step 6.

Step 6: Risk Evaluation - Is the Risk Adequately Controlled?
- Document and critically evaluate any detection controls currently in place for each Unacceptable and intolerable risk.
- Assign a Detection rating to these controls, and determine whether these controls give assurance that the risk is adequately controlled and that no further controls are required.
- Risks that are considered adequately controlled progress directly to Step 8. All other risks progress to Step 7.

Step 7: Risk Control:
- Identify and critically evaluate any new or improved back-up or redundancy controls, which may be put in place for Unacceptable and Intolerable risks.
- With these controls in mind, assign a new Severity rating to the potential negative event.
- Identify and critically evaluate any new or improved preventive controls, which may be put in place for the cause(s) of each Unacceptable and Intolerable risk.
- With these controls in mind, assign a new Probability of Occurrence rating to each cause.
PART I

- Using the Risk Table provided on the laminated card, which accompanies the tool worksheet, re-
  estimate each risk.
- This results in the re-classification of each risk as either Acceptable, Unacceptable, or Intolerable.
- Risks deemed to be Acceptable progress to Step 8 of the worksheet; all other risks continue
  through Step 7.
- Identify and critically evaluate any new or improved detection controls for each Unacceptable and
  Intolerable risk.
- Assign a Detection rating to these controls, and determine whether these controls give assurance
  that the risk is now adequately controlled and that no further controls are required.
- Risks that are considered adequately controlled progress to Step 8.
- For risks that are still not considered adequately controlled, Step 7 (Risk Control), should be
  repeated. (A redesign of the item under study may be necessary in order to eliminate the potential
  negative event.)

Step 8: Qualification and Validation:

- For each control listed on Worksheets No. 5, 6, and 7, identify the items (such as documentation,
  equipment, facilities, personnel resources, etc.), which are required for the control to be in place.
- Determine Critical Process Parameters, their limits, and any other acceptance criteria or required outcomes for each control.
- Determine any training and assessment of training requirements for each control.
- Determine any Qualification or Validation activities required for each control, and assign a Qualification and Validation status to each.

Step 9: Action Items:

- Document any action items arising out of the risk management exercise, and assign responsibilities for each.
- These could be actions required to implement a control, or they could be Qualification or Validation exercises.

Step 10: Risk Communication and Continuous Improvement (Periodic Review) Activities:

- Identify and document any communication activities required for the risks identified during the
  exercise.
- Assign responsibilities and timelines for each communication.
- Define when the risk management exercise should be reviewed as part of continuous improvement, and document any key areas or issues to be reviewed at that time.
- Close out the risk management exercise.

This ten-step process, as outlined above, complements some of the points made in ISPE's
White Paper of 2005, which, while focused only on equipment and facility qualification, made
a number of very useful recommendations on ways to achieve true risk-based qualification.
One was that risk assessments, process development, and experimental design should be
used to identify critical features, functions, and critical process parameters, and that qualification efforts should be process-based, and focused on the concept of risk-mitigation for
patients. The risk management solution developed here offers a practical means for how this
might be achieved.
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While this risk management methodology provides a means by which risk management might be of use within GMP environments, at the same time, it was designed to serve as a potential risk management solution for GMP regulators, for use within their own work activities. This is considered important, recognising the significant contribution made by ICH Q9 in promoting the use of risk management principles and tools by both parties. This aspect of the tool is explained in more detail in Part II of this paper.

CONCLUSION

In Part I of this paper, a risk management solution is described that is designed to facilitate risk-based qualification, validation, and change control activities within GMP and regulatory compliance environments in the EU. This solution is based upon a set of pre-defined, fundamental principles and design criteria, which were considered important. It offers a documented and ready-to-use ten-step process for determining and managing, on a risk basis, the scope and extent of qualification and validation, and the likely impact of changes.

This is a formal and rigorous approach to risk management. As such, it is designed so that its use should be commensurate with the complexity and/or criticality of the issue to be addressed. It is not intended for use in all situations, or to address all risk areas or concerns, and in many instances, in line with ICH Q9 principles, a more informal approach to risk management may be more appropriate, and indeed proportionate.

In Part II of this paper, the scope of this risk management solution is presented, and the structure of the tool and some of its key features are described. Some novel aspects relating to this risk management solution are also presented, and a number of limitations associated with this solution are discussed. Finally, an outline of the main findings made to date with using this tool is given.

Overall, this work seeks to demonstrate how risk management principles may be used in practical terms across a broad range of EU GMP and Regulatory Compliance environments. It is hoped that these efforts will serve to build upon the milestone that was ICH Q9, and the work done to date by FDA, ISPE, GAMP and many others in promoting true risk-based qualification, validation and change control activities.

ABOUT THE AUTHORS

Kevin O’Donnell is currently Market Compliance Manager at the Irish Medicines Board (IMB), Dublin, Ireland. He joined the Inspectorate Department of the IMB in 2001; he was appointed a GMP Inspector in 2002, and took up his current position in 2005. His current responsibilities involve managing a number of compliance programmes within the IMB, including IMB’s Quality Defect and Recall programme and its Sampling and Analysis Market Surveillance activities.

Kevin has a chemistry background; he obtained his Chemistry Degree from University College Galway, Ireland, in 1991, and his Masters Degree in Pharmaceutical Quality Assurance from the Dublin Institute of Technology, Dublin, in 2002. He spent a number of years working in the Pharmaceutical
PART I

Industry, both in Ireland and in the United States before joining the IMB, Kevin has an active interest in education, having spent three years as a Mathematics teacher in his native County Donegal, Ireland. He lectures occasionally, in pharmaceutical-related degree courses in Dublin. Kevin can be reached at kod1@eircm.net.

Anne Greene, PhD, is currently a lecturer in Pharmaceutical Technology at the School of Chemical and Pharmaceutical Sciences at the Dublin Institute of Technology in Dublin, Ireland. She is also Course Director for Masters of Sciences studies in Pharmaceutical Quality Assurance and Validation Technology at DIT.

Professor Greene came to academia after serving as Technical Services Chemist at Sterling Winthrop from 1990 through 1992 and as Validation Manager at Wyeth Medica Ireland from 1992 through 1996. She can be reached via email at anne.greene@dit.ie.

REFERENCES

9. For information on recalls which have occurred in the UK over recent years, see the Drug Alerts section of the website of the UK Medicines and Healthcare Products Regulatory Agency, at http://www.mhra.gov.uk.
10. For information in this regard, see the presentations from the Irish Medicines Board Inspectorate Information Days of 27 September 2002 and 15 October 2004, available from the IMB upon request.
11. IEC 61925 - Fault Tree Analysis.
23. Recommended International Code of Practice: General Principles of Food Hygiene cadrap 1-1969, res. 3-1997, and (1999). [Note: This document is from the Codex Alimentarius Commission and the FAO/WHO Food Standards Programme.]

### Article Acronym Listing

- **CCP**: Critical Control Point
- **CPP**: Critical Process Parameter
- **EU**: European Union
- **FDA**: Food and Drug Administration
- **FMEA**: Failure Mode and Effects Analysis
- **FMECA**: Failure Mode, Effects and Criticality Analysis
- **GAMP**: Good Automated Manufacturing Practice
- **GMP**: Good Manufacturing Practice
- **HACCP**: Hazard Analysis and Critical Control Points
- **ICH**: International Conference on Harmonization
- **ISO**: International Organization for Standardization
- **ISPE**: International Society of Pharmaceutical Engineering
- **MA**: Marketing Authorization
- **PAT**: Process Analytical Technology
Addendum
Laminated Card for the Risk Management Tool

This Card shows the default Probability, Severity, and Detection definitions for the Risk Management Tool. It also shows the Risk Table, with the Risk Acceptability criteria. Important: The definitions shown for each P, S, & D Level are default definitions; they can be modified as required. See Step 3 of the Tool Worksheet for details.

### Probability of Occurrence Levels for the Negative Event

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>The Negative Event is Likely to Occur</td>
</tr>
<tr>
<td>Medium</td>
<td>The Negative Event May Occur</td>
</tr>
<tr>
<td>Low</td>
<td>The Negative Event is Unlikely to Occur</td>
</tr>
<tr>
<td>Remote</td>
<td>The Negative Event is Very Unlikely to Occur, or is Extremely Unlikely to occur</td>
</tr>
</tbody>
</table>

### Severity Levels for the Effects of the Negative Event

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>The Effects are Severe</td>
</tr>
<tr>
<td></td>
<td>• Very Significant GMP/MA Non-Compliance</td>
</tr>
<tr>
<td></td>
<td>• Potential Patient Injury</td>
</tr>
<tr>
<td>Moderate</td>
<td>The Effects are Moderately Severe</td>
</tr>
<tr>
<td></td>
<td>• Significant GMP/MA Non-Compliance</td>
</tr>
<tr>
<td></td>
<td>• Potential Patient Impact</td>
</tr>
<tr>
<td>Minor</td>
<td>The Effects are Not Severe</td>
</tr>
<tr>
<td></td>
<td>• Minor GMP/MA Non-Compliance</td>
</tr>
<tr>
<td></td>
<td>• No Patient Impact</td>
</tr>
</tbody>
</table>

### Risk = P x S

<table>
<thead>
<tr>
<th>Negative Event Prob:</th>
<th>Minor Severity</th>
<th>Moderate Severity</th>
<th>Critical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Unacceptable Risk</td>
<td>Insoluble Risk</td>
<td>Insoluble Risk</td>
</tr>
<tr>
<td>Medium</td>
<td>Acceptable Risk</td>
<td>Unacceptable Risk</td>
<td>Insoluble Risk</td>
</tr>
<tr>
<td>Low</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
<td>Unacceptable Risk</td>
</tr>
<tr>
<td>Remote</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
<td>Acceptable Risk</td>
</tr>
</tbody>
</table>

**RISK DEFINITIONS:**

- **Intolerable:** Work to eliminate the Negative Event, or build in systems or controls to ensure the effects of the Negative Event are not realised (e.g. via back-up or redundant controls).
- **Unacceptable:** Reduce the risk, or control the risk to an acceptable level.
- **Acceptable:** The risk is acceptable as is. No risk reduction or new controls are required.

### Detection Control Ratings:

- **High**: the control will likely detect the negative event or its effects
- **Medium**: the control may detect the negative event or its effects
- **Low**: it is not likely that the control will detect the negative event or its effects
- **Zero**: no detection control in place
A Risk Management Solution Designed To Facilitate Risk-Based Qualification, Validation, And Change Control Activities Within GMP And Pharmaceutical Regulatory Compliance Environments In The EU

PART II
Tool Scope, Structure, Limitations, Principle Findings, And Novel Elements

By
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and
Anne Greene, School of Chemistry and Pharmaceutical Sciences, Dublin Institute of Technology

Note: The views expressed in this paper are those of the authors, and should not be taken to represent the views of the Irish Medicines Board.
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INTRODUCTION

In Part I of this paper, a risk management methodology was described that was designed to facilitate the European Union (EU) Good Manufacturing Practice (GMP) requirements for risk-based qualification, validation, and change control activities. Based on the guidance and principles presented by the International Conference on Harmonization (ICH) in its Q9 Guideline on Quality Risk Management,¹ and utilising a documented ten-step process, this methodology, or tool, offers a documented and systematic solution for determining and managing, on a risk basis, the scope and extent of qualification and validation, and the likely impact of changes. This tool is based upon a set of fundamental principles and pre-defined design criteria, which were also discussed in Part I.

In this Part, the scope of this risk management tool is outlined, and the structure of the tool is explained. Some of the key features of this tool are outlined, and a number of its limitations are highlighted. Some novel elements behind this approach are discussed, and several of the main findings made to date using this tool are presented.

Scope of this Risk Management Solution

This risk management solution allows for a structured risk management approach to be applied to qualification, validation, and change control activities across a wide range of areas. These areas include:

- **GMP Processes**, such as Manufacturing, Cleaning, and Packaging processes, together with their related items of equipment
- **GMP Systems**, such as Heating, Ventilation, and Air Conditioning (HVAC), Building Management, Distribution, and company Regulatory Compliance systems
- **GMP Programmes**, such as Stability, Complaints and Recalls, Pest Control, Supplier Approval, and Self-inspection programmes
- **GMP Regulatory Compliance activities**, such as Market Surveillance programmes carried out by regulators

This risk management solution is flexible in how it may be used. It is designed so that it may be applied retrospectively or prospectively to the item under study and can also be applied to change control requests, which are, by definition, prospective in nature. The tool can also be used to address specific known problems with the item under study that have already been identified. Alternatively, it can be used to address potential risks, which have yet to be realised in practice.

With respect to regulators, one of the objectives laid down during the development of this risk management solution was that the scope of the tool should extend to Regulatory Compliance environments, such as Inspectorate and Official Medicines Control Laboratory (OMCL)² related activities, and not be limited to manufacturing. To this end, the Market Compliance Section within the Compliance (Inspectorate) Department at the Irish Medicines Board, Ireland, took the opportunity to investigate whether a risk management approach might help identify areas within its own core business activities that might benefit from risk-based qualification, validation, and change control.

The timing for this was opportune, given the finalisation of ICH Q9 in November 2005, which presented detailed risk management guidance for Regulators as well as for Industry. The publication of an Irish Government Risk Management paper in March 2004³ meant that agencies such as IMB were now required to apply Risk Management principles to their work in a formal manner. It was found, however, that there was no one risk management tool available that could be readily applied to this task without
some modification, and this, in part, drove the development of this risk management solution.

One might ask, however, what do risk-based qualification, validation, and change control have to do with the work of regulatory authorities? Are these activities not specific to GMP-regulated environments, that is, to industry? At a fundamental level, the authors believe that qualification, validation, and change control are broad, useful concepts, and that there is no reason why these concepts cannot benefit regulators as well as industry. This is particularly so within Regulatory Compliance environments such as inspectorates and official medicines control laboratories which are concerned (directly and sometimes indirectly) with GMP. Indeed, the Compilation of Community Procedures on Inspections and Exchange of Information, which is published by the European Medicines Evaluation Agency (EMEA) on behalf of the European Commission, outlines certain change control and validation requirements for EU GMP inspectorates. Thus, the concepts of change control and validation are already applicable to the work of GMP inspectorates and the Risk Management methodology outlined here is designed to demonstrate how such activities can be made risk-based.

**Tool Structure**

This risk management tool is comprised of three discrete components: a tool worksheet, a laminated card, and a user manual.

- **The Tool Worksheet**

  This is a structured, instructional worksheet, addressing each of the ten steps making up the risk management process outlined in Part I of this paper. It is used to direct and document the risk management exercise, from defining the purpose and nature of the specific exercise at hand (Step 1), through to planning for a formal review of the risk management exercise at a later time (Step 10). The worksheet was developed and optimised using a series of case studies and practical examples, and it has been subjected to extensive user testing with industry and with academic validation and quality assurance groups.

- **The Laminated Card (See Addendum page 25):**

  This is used in conjunction with the tool worksheet, particularly during Step 3 of this risk management process. Its main purpose is to facilitate a review of the various default definitions for Probability, Severity, and Detection given by this tool, so that these definitions may either be agreed upon by the risk management team, or modified as required. This is where the tool may be customised to suit the particular exercise at hand. For example, there are default definitions given on the laminated card for the three seventy levels used in the tool - Critical, Moderate, and Minor. These can be modified in order to reflect any specific stakeholders associated with the particular item under study. The laminated card also serves as an aide-memoir for the team performing the risk management exercise, because the reverse side of the card contains an outline of the complete ten-step process.

- **The User Manual**

  This contains information and guidance on:

  - The key concepts behind this risk management solution
  - The principles upon which this risk management solution is based
  - A general overview of the structure of this risk management tool, its uses, and scope
  - A series of completed real-life case studies that show, in practical terms, how this risk management tool is used, and the expected outputs of the tool
  - A Questions and Answers guidance document pertaining to each of the ten steps of the risk management solution
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Key Features of this Risk Management Solution

This risk management solution provides a documented means for identifying GMP controls and critical process parameters, which are directly related to product quality and patient risk. It should be noted that in the authors' experience, no one tool can identify all of the critical controls and critical process parameters that relate to the item under study. However, many of these will already be known through routine product and process development work and existing scientific knowledge.

The following are some of the key features of this solution:

- **Complexity and Criticality Considerations**
  As a formal and rigorous approach to risk management, this tool is designed so that its use should be commensurate with the complexity and/or criticality of the issue to be addressed. To this end, only the highest priority or most important potential negative events should be selected for formal evaluation. This tool is not designed for use in all situations, or to address all risk areas or concerns, and in many instances, in line with ICH Q9 principles, a more informal approach to risk management may be more appropriate, and indeed proportionate.

- **Negative Events**
  This process uses the concept of negative events, which are defined simply as "what can go wrong." A negative event can be a single event, or a number of individual occurrences leading to a negative outcome. Risks arising from negative events are estimated, assessed, and controlled in Steps 5-7 of the process. The term, negative event, is advantageous in that it is easy to understand, it is applicable to a wide range of activities and areas, and is perhaps simpler than the more commonly used terms: failure modes and hazards. Recognising the fact that individual negative events can have multiple causes with different probabilities of occurrence, the tool is designed to address the multiple risks, which may be associated with a single negative event, as documented in Step 4 of the tool worksheet.

- **GMP Controls**
  The tool focuses specifically on GMP controls and it requires a critical evaluation of current and proposed controls with respect to how they mitigate risk. The tool also offers a large degree of flexibility in how it deals with such controls. This is important because, from the authors' experience, too restrictive an approach can mean that a particular risk management tool cannot be used in many situations.

  - For example, different types of controls may be encountered in GMP environments that provide risk control. However, while some controls have associated critical process parameters that can be measured or verified, such as an in-process acidity test, which has pH as its critical process parameter, others, such as personnel training, or supplier qualification, are not so easily described in terms of critical process parameters. This can cause problems when one applies a risk management approach focused only on critical process parameters.

  - The tool addresses this difficulty through the design of Step 8 of the tool worksheet. Step 8 allows one to define acceptance criteria or required outcomes for a control, such as satisfactory performance in a training assessment test, without having to determine formal critical
process parameters that can be measured or verified. Regardless of the terminology one uses in Step 8 of the worksheet, the end result is the same in that key measurables and expected outcomes for the control in question are defined and their qualification and validation requirements identified.

• **Qualification and Validation**

These considerations are integral to the tool. In Step 8, the qualification and validation status of, and the related requirements for, the various controls documented in Steps 5-7 are critically determined. Given that some GMP controls required to address an identified risk will be personnel or training-based, the requirements for personnel competency and training-related controls are likewise evaluated and determined in Step 8 of the tool.

• **Multiple Tool Outputs**

The tool has a large number of outputs and these are shown in Figure 1.

**Note:** This risk management solution need not be used in a stand-alone way, in isolation, and it may in fact be used in a synergistic manner with other risk management tools. These include formal Process Mapping, which can be of use during Step 4 of this Risk Management process when identifying potential negative events, and simple Cause and Effect diagrams, which can help provide causal information for Step 5 of the Risk Management exercise.

**Limitations of this Risk Management Methodology**

This is not a universal risk management solution that may be applied in all situations across all areas. For example, while this approach provides a means of prioritising risks and their required risk control activities, it does not provide a methodology for formal risk filtering activities. Therefore, when prioritising sites for GMP inspection, or suppliers for auditing, this solution does not offer a means of doing this. There are specific and better tools available for these purposes, and ICH Q9 gives information in this regard.

Also, and as noted earlier, this is a formal and rigorous methodology, involving a detailed risk management process with ten discrete steps, and a tool worksheet that requires completion as the risk management exercise progresses. This means that documentation, effort, and training are required in order for this tool to be used effectively. As a result, this tool has been specifically designed to evaluate only a small number of potential negative events - those considered to be the most critical and/or most complex. While this is a key strength behind this approach, it also limits the application of this tool to a degree, and if a large number of negative events are to be studied, a less-detailed cause and effect approach, or a **Hazard Analysis and Critical Control Points (HACCP)** or **Failure Mode and Effects Analysis (FMEA)**-based approach may be more appropriate.
Figure 1

Tool Outputs

The Main Outputs from this Tool:
- Risks associated with the item under study
- A critical evaluation of current GMP controls from a risk perspective
- A critical evaluation of proposed, new GMP controls from a risk perspective
- Risk-based critical process parameters, together with their limits or other acceptance criteria
- The required outcomes for controls that may not have formal critical process parameters associated with them
- The Qualification and Validation status of each control
- Qualification and Validation requirements for the item under study
- Personnel training and training assessment requirements
- Risks associated with implementing a Change Control and a strategy for dealing with such risks
- A means of evaluating and justifying Process Analytical Technology (PAT) initiatives
- A strategy for communicating risks to stakeholders
- A plan for the continuous improvement of the risk management exercise
- A documented and systematic means of meeting the EU GMP requirements to implement risk-based validation and change control programmes

Principle Findings to Date

Several detailed case studies have been developed on the application of this risk management solution across a number of very different areas relating to GMP and Regulatory Compliance activities. These included a manufacturing process, a laboratory-related change control, a company product recall procedure, and a regulatory quality defect and recall programme, as outlined below.

- The manufacturing process was in place at a finished products manufacturing site. Here, the final mixing and filling steps for a paracetamol oral suspension product were assessed from a risk perspective. This was in response to concerns relating to the occurrence of repeated process deviations during mixing and filling. (This was a retrospective application of the risk management tool.)
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- The **change control** related to quality control testing at an Active Pharmaceutical Ingredient (API) manufacturing site involved a proposal to introduce Inductively-Coupled Plasma (ICP) technology to the site for the analysis of nickel in a new API material. The change control also proposed switching over from Atomic Absorption Spectroscopy to ICP for the analysis of zinc in another API, and for the analysis of various metals in site water samples. (This was a prospective application of the risk management tool.)

- The **product recall procedure** was in place at a finished product manufacturer that supplies compounded finished product directly to pharmacies and hospitals. The company had recently executed a product recall using this procedure, and it was an opportunity to determine any risk-based qualification and validation work required. (This was a retrospective application of the risk management tool.)

- The **regulatory quality defect and recall programme** was in place within the Compliance Department of the Irish Medicines Board, in Dublin, Ireland. This programme is used to investigate notifications of suspected quality defects that are received (via Rapid Alerts) from other Competent Authorities, and to the mechanisms in place for communicating serious recall issues within Ireland. (This was, again, a retrospective application of this risk management tool.)

The above case-studies were based on real-life situations and experiences, but they have been written in a general manner, and some details have been changed so as not to indicate the companies or products concerned. In each case, the risk management solution identified and assessed risks of various magnitudes, some being significant which were associated with the items under study. Also, it identified several new qualification, validation, and training activities which were considered to be required in order to address the risks identified. These were over-and-above the qualification, validation, and training work that had already been performed, or for which planning had already been completed.

These exercises provide detailed and documented examples that demonstrate how risk management may be used in practice within GMP and Regulatory Compliance environments to facilitate risk-based qualification, validation, and change control activities.

**Some Novel Aspects to this Risk Management Solution**

In Part I of this paper, we discussed how this risk management solution builds upon some of the useful concepts and features of other risk management tools and approaches, such as FMEA, Failure Mode, Effects, and Criticality Analysis (FMECA), and the Food and Drug Administration’s (FDA) GMP 4 Risk Assessment process, and the International Society of Pharmaceutical Engineers Impact Assessment process. However, there are several features associated with this risk management solution that differentiate it from other approaches. For example:

- This risk management solution provides a documented and simple strategy for dealing with uncertainties, conflicts, and doubts that may arise during certain stages of a risk management exercise, such as when estimating probability of occurrence and severity ratings for a particular negative event.

- This solution is designed to serve as a direct aid when addressing the new Product Quality Review requirements of revised Chapter 1 of the EU GMP Guide, which include an assessment...
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of any revalidation work required. This is because one output of the tool, via Step 8 of this risk management process, is an assessment of the Qualification and Validation status of the item under study.

- Steps 5, 6, and 7 of this risk management process require a critical evaluation of the merit of each current and proposed new or improved GMP control from the perspective of risk control and protection of the patient. (This is required even when the risk is considered to be acceptable without any new or improved controls being put in place.)

- As a result, this tool can help identify any required qualification or validation work for current controls that may have been overlooked to date.

- This feature may serve as a means to justify the removal of some controls, which might not add value in terms of product quality, or which might not serve to benefit the patient. Examples here could include some in-process and finished product tests. Importantly, such controls should not be removed without first addressing any Marketing Authorization validation requirements that might be relevant.

- This feature may also serve to justify the reduction of some ongoing qualification and validation activities for some older processes, where Critical Process Parameters (CPP) may have been registered in Marketing Authorisations without adequate scientific foundation.

- This risk management solution can be used to formally identify and justify Process Analytical Technology (PAT)-based initiatives. This is because this approach can show in a scientific manner how PAT-based monitoring of a process may reduce or control an important risk.

- This solution is designed so that it can be easily customised in a pre-defined way to suit the particular application at hand. For example, Step 3 of the risk management process allows the default definitions for Probability and Severity to be changed, perhaps by making them quantitative, and Severity ratings can be further modified to better reflect who the specific stakeholders are for the particular item under study.

CONCLUSION

In Parts I and II of this paper we highlight the need for patient-focused and value-adding qualification, validation, and change control programmes for manufacturing and regulating medicinal products in the EU, which are cost-effective and in-line with current regulatory requirements and guidance. To this end, a formal risk management solution was presented that seeks to demonstrate, in a practical way, how Regulators and Industry in the EU may achieve these goals.

This solution represents a formal and rigorous approach to risk management, offering a scientific and practical means for determining and managing, on a risk basis, the scope and extent of qualification and validation, and the likely impact of changes. Based on a ten-step, systematic process, this approach offers a ready-to-use and documented risk management methodology for these activities.

This tool is not intended for use in all situations, or to address all risk areas or concerns encountered in GMP and Regulatory Compliance environments. Rather, its use should be commensurate with the complexity and/or criticality of the issue to be addressed, and in many instances, and in-line with ICH Q9
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principles, a more informal approach to risk management may be more useful, and indeed proportionate. It is hoped that this work will serve to build upon the milestone that was ICH Q9, and the work done to date by Food and Drug Administration (FDA), ISPE. GAMP and many others in promoting true risk-based qualification, validation, and change control activities. □

ACKNOWLEDGEMENTS

Kevin O’Donnell thanks the Irish Medicines Board for its support and for funding this work. Acknowledgements and gratitude are also extended to his IMB colleagues Pat Walsh, Mauro O’Connell, Paul Sexton, Deirdre Morgan, Anne Hayes, Chris Cullen, Mike Morris, Ann O’Connor, and John Lynch for their valuable suggestions during the course of this work. Special thanks also to Mitsuko Osato.

All views expressed in these papers are those of the authors.

ABOUT THE AUTHORS

Kevin O’Donnell is currently Market Compliance Manager at the Irish Medicines Board (IMB), Dublin, Ireland. He joined the Inspectorate Department of the IMB in 2001; he was appointed a GMP Inspector in 2002, and took up his current position in 2005. His current responsibilities involve managing a number of compliance programmes within the IMB, including IMB’s Quality Defect and Recall programme and its Sampling and Analysis Market Surveillance activities.

Kevin has a chemistry background; he obtained his Chemistry Degree from University College Galway, Ireland, in 1981, and his Masters Degree in Pharmaceutical Quality Assurance from the Dublin Institute of Technology, Dublin, in 2002. He spent a number of years working in the Pharmaceutical Industry, both in Ireland and in the United States before joining the IMB. Kevin has an active interest in education, having spent three years as a Mathematics teacher in his native County Donegal, Ireland. He lectures occasionally, in pharmaceutical-related degree courses in Dublin. Kevin can be reached at kod1@eicomm.net.

Anne Greene, PhD, is currently a lecturer in Pharmaceutical Technology at the School of Chemical and Pharmaceutical Sciences at the Dublin Institute of Technology in Dublin, Ireland. She is also Course Director for Masters of Sciences studies in Pharmaceutical Quality Assurance and Validation Technology at DIT.

Professor Greene came to academia after serving as Technical Services Chemist at Sterling Winthrop from 1990 through 1992 and as Validation Manager at Wyeth Medica Ireland from 1992 through 1996. She can be reached via email at anne.greene@dit.ie.
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REFERENCES

2. An Official Medicines Control Laboratory is an independent laboratory used by regulatory authorities to independently analyse medicinal products and active pharmaceutical ingredients. Further information relating to OMCL activities may be obtained from www.pheur.org
5. A series of presentations and technical workshops were given to, and run with, academic and industry partners during 2004 and 2005, in order to test the underlying principles behind this Risk Management solution, and the resulting Risk Management process. These presentations and workshops, which used detailed case studies on use of the tool, allowed the structure and design of the tool worksheet to be evaluated and optimised.

Article Acronym Listing

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Evaluation Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (U.S.)</td>
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<tr>
<td>FMEA</td>
<td>Failure Mode and Effects Analysis</td>
</tr>
<tr>
<td>FMECA</td>
<td>Failure Mode, Effects, and Criticality Analysis</td>
</tr>
<tr>
<td>GAMP</td>
<td>Good Automated Manufacturing Practice</td>
</tr>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
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<td>HACCP</td>
<td>Hazard Analysis and Critical Control Points</td>
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<tr>
<td>HVAC</td>
<td>Heating, Ventilation, and Air Conditioning</td>
</tr>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
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<td>ICP</td>
<td>Inductively-Coupled Plasma</td>
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<td>OMCL</td>
<td>Official Medicines Control Laboratory</td>
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<tr>
<td>PAT</td>
<td>Process Analytical Technology</td>
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</table>
Failure Modes: Simple Strategies for Improving Qualitative Quality Risk Management Exercises during Qualification, Validation, and Change Control Activities

BY KEVIN O'DONNELL AND ANNE GREENE

Note: The views expressed in this paper are those of the authors, and should not be taken to represent the views of the Irish Medicines Board.

INTRODUCTION

The September 18, 2006 European edition of Time Magazine carried three interesting letters from readers on the subject of airline security and the related governmental risk control measures. Under the heading “How Much Risk Can We Take?” the letters showed, in very simple terms, how the perception of risk and risk control measures can be widely subjective, and how there can be much perceived uncertainty in the approaches used for managing risks.

In the above Time letters, one reader indicated a strong support for tightened security measures at airports, and promoted “giving up some freedoms” in place of accepting “a high risk of more attacks.” Another reader took a widely differing view of the whole airline security issue, arguing that current risk control measures were merely attempts by governments “to seize the opportunity to pass draconian measures to control the population.” In the third letter, it was argued that the current airline risk control strategies have actually “lost sight” of the real problem, which, in that reader’s mind, lies in the cargo hold of the airplane being infiltrated with a small bomb, and not through what passengers carry onto airplanes.

As different as each reader’s opinion is, there was an element common to each letter. This was the level of uncertainty voiced by each reader, despite their stated convictions, on the management of the risks concerned. The three readers’ letters contained phrases indicative of uncertainty, such as “It seems that not much has changed since then...,” “...we seem to have lost sight of the problem...,” and “what they seem to have lost sight of is...”

Such problems of subjectivity and uncertainty are not confined to airline Risk Management activities. In the Pharmaceutical Industry, the incorporation of Quality Risk Management concepts and tools within Good Manufacturing Practice (GMP) environments is an area that has been under considerable development in recent years, and there are many references in the literature to the subjective and uncer-
tainty of Risk Management for pharmaceutical applications and in other areas also.2,4

Uncertainty and Subjectivity in Formal Quality Risk Management

In the author's experience as a GMP Inspector in the EU, informal approaches to Quality Risk Management have been utilised for a considerable time by medicinal product manufacturers during qualification, validation, and change control activities. However, it is evident that there is currently a move towards the use of more formalised Risk Management approaches for these and other activities within GMP environments.6,13 Often the use of such formalised approaches is coupled with efforts to promote better and more meaningful User Requirement Specifications for items being qualified or validated,4,13 and this is considered a positive development.

The increase in the use of formalised Risk Management tools and approaches has probably been accelerated by a number of developments, including the guidance presented in International Conference on Harmonization (ICH) Q9 on formal Quality Risk Management tools, and the higher focus which GMP inspectors are nowadays giving to Quality Risk Management activities within pharmaceutical companies.6,13,14,17 The promotion of more systematic and rigorous approaches to Quality Risk Management by regulatory agencies, such as FDA,18 has been a significant driving factor also.

Uncertainty

Problems of subjectivity and uncertainty during formal Quality Risk Management activities are to be expected. Uncertainty is unavoidable, given the generally accepted definition of risk, which includes a probability factor for the occurrence of a hazard or harm. ICH Q9 lists some typical sources of uncertainty during Quality Risk Management, and these include gaps in knowledge, gaps in pharmaceutical science and process understanding, and importantly for the discussion below, uncertainty in sources of harm (e.g. failure modes of a process). In many cases, unless the source of the hazard or harm is entirely eliminated, uncertainty cannot be avoided when one tries to estimate and manage resulting risks.

Subjectivity

With respect to problems of subjectivity, this is acknowledged as an issue in many publications, including ICH Q9, which explains how "each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm."

Despite these inherent problems, it should not be taken that the levels of uncertainty and subjectivity cannot be reduced during Quality Risk Management activities. With the use of formal, science-based and rigorous approaches, it is reasonable to believe that uncertainty and subjectivity can be reduced and that an increased level of confidence in the results and outputs of Quality Risk Management exercises may be obtained. Within GMP environments, when such Quality Risk Management methodologies are used as an aid to qualification, validation, and change control activities, this should have two important outcomes:

- Increased assurance in the manufacturing processes and controls which have been validated based on the outcomes of Quality Risk Management exercises
- Increased assurance that potential quality-related risks associated with such manufacturing processes have been addressed

Over the course of the past three years, the authors have been researching how Quality Risk Management concepts and methodologies may be used within EU-regulated GMP environments in the manufacture of medicinal products and active pharmaceutical ingredients (APIs). The GMP areas of concern in this research were those relating to qualification, validation, and change control activities and a formal and rigorous qualitative Quality Risk Management methodology was developed to demonstrate a means by which compliance with the risk-related requirements of Annex 15 (Qualification and Validation) to the EU Guide to GMP may be achieved.19,22

b Risk is defined in the ISO/IEC Guide 51:1999 as "the combination of the probability of occurrence of harm and the severity of that harm."

c These areas were chosen because, in the EU, there are specific and explicit obligations placed on manufacturers of medicinal products to employ risk-based qualification, validation and change control programmes;24,25 but to date, there has been a lack of detailed guidance on how these requirements may be implemented in practice.
A major focus of this research has been on identifying strategies that might address some of the uncertainty and subjectivity issues that arise during Quality Risk Management activities.

**Opportunities for Improvement**

During the above work, it was observed that there are many areas within formal Quality Risk Management activities that present opportunities for reducing such uncertainty and subjectivity. Some of these areas include:

- Identifying Failure Modes, Hazards, Faults, and their causes. (This is sometimes referred to as Risk Identification.)

- Estimating probability of occurrence values for Failure Modes, Hazards and Faults, the severity of their effects, and the Risks associated with such Failure Modes, Hazards, or Faults. (This is sometimes referred to as Risk Analysis.)

- Selecting Risk Priority Number (RPN) cut-off values. This is a feature of some applications of Failure Modes and Effects Analysis (FMEA) and Failure Modes, Effects, and Criticality Analysis (FMECA) based methodologies.\(^7,10,19,26\)

- Evaluating the contribution of detection-type controls to the mitigation of risks.

- Using quantitative approaches for determining or estimating risks, as sometimes the data are simply not available to have confidence in the results.

- Estimating the impact of Risk Control measures on Risks.

During the testing of the formal Quality Risk Management methodology under development here,\(^9\) a number of practical workshops were run to investigate the application of this methodology as an aid to qualification, validation, and change control activities. The workshops involved a large number of real-life, GMP-related case studies, which spanned a wide range of areas relevant to GMP environments. These included:

- A Change Control proposal to introduce a new starting material for an API manufacturing process.

- A recall procedure at a medicinal product manufacturer which supplied products directly to end-users and hospitals.

- A tablet film coating process at a medicinal product manufacturer.

- A Change Control proposal which proposed to install a filter dryer in an API manufacturing process.

- The final mixing and filling steps in a paracetamol suspension manufacturing process.

- The early stages of a fermentation process used in the manufacture of an antibiotic medicinal product.

- A Change Control proposal to introduce Inductively-Coupled Plasma Mass Spectroscopy analytical methodology to an API manufacturing site for the analysis of a new API, and to switch over from Atomic Absorption spectroscopy to ICP-MS for the analysis of metals in an existing API.

- A Quality Defect and Recall programme in place within a European regulatory authority.

During the above workshops and case studies, some simple and easy-to-implement strategies were developed which helped to reduce the level of guesswork, subjectivity, and uncertainty associated with the Quality Risk Management exercises, and which helped to increase confidence in the results obtained. Such strategies served to facilitate more meaningful and value-adding Quality Risk Management exercises for qualification, validation, and change control activities.

These strategies are science-based and qualitative in nature, and many are common sense approaches. Often, however, they have been overlooked, or have not been developed appropriately, by the current Quality Risk Management methodologies that are available to date. For example:

1. During Risk Assessment activities, when risks are being estimated using probability and severity ratings, or when Risk Priority Numbers (RPNs) are...
being determined using probability, severity, and detection ratings as in many PMEA and PMECA-type approaches, it makes sense, and it is scientific, to first consider, document, and evaluate the GMP controls that may already be in place which influence or limit the probability, severity, or detectability of the risk event or its cause occurring. This helps to ensure that the resulting risks or RPNs that are arrived at reflect the current state of control and represent the current situation.

We have found that when this simple approach is not used:

- There can be an over-reliance on guesswork when selecting or assigning probability, severity, and detection ratings.
- The resulting risks, which are estimated using these ratings, or the resulting RPNs which are calculated, are likely to be prone to levels of uncertainty and subjectivity which cannot easily be dismissed or dealt with.
- The next time a risk assessment exercise is performed on the same process or item under study, there is little assurance that a consistent approach will be taken when estimating risks and when calculating RPNs. Thus, during such periodic review activities, one can be unsure how meaningful the results are.

2. When Quality Risk Management methodologies are being used which require Failure Modes to be identified, it is important that scientific and documented methods be in place for the identification, evaluation, and documentation of such Failure Modes. This may sound like an obvious thing to do, but it is surprising how often this is not a clear requirement of many existing Quality Risk Management methodologies.

- In our experience, poorly defined brainstorming techniques, the use of subjective guesswork, and an over-reliance on expert opinion without evaluating or documenting the strength of evidence supporting such opinions, can often make up significant parts of the Failure Mode identification process.
- Such practices contribute to problems of subjectivity and uncertainty during Quality Risk Management activities, and thus inevitably introduce a lack of confidence in the results and recommendations of Quality Risk Management exercises.

In relation to potential failure modes, a common problem that we have observed in practical Quality Risk Management exercises (and also in GMP inspections) is that, during brainstorming sessions, there can be a lack of clear procedure and rigor applied to the process of identifying and documenting potential failure modes. This can result in potential failure modes being documented at too high an incidence level in the system under study, and there can be considerable confusion between failure modes and their effects. As a result, potential failure modes can sometimes be ill-defined and documented in a way that renders them the same as their potential effects. This can have a significant and unexpected negative impact on the outcome of the exercises. To demonstrate the above, consider the following practical case study:

**PRACTICAL CASE STUDY – A Change Control Proposal to Install a Filter Dryer in an API Manufacturing Process**

During this case study, two workshops were run in which early versions of the Quality Risk Management methodology under development were applied to the above filter dryer change control proposal. In the first workshop, “low yield” of API material following drying was identified and documented in a brainstorming session as a potential...
failure mode. A number of potential causes were identified for this failure mode, including, breakage of, or damage to, the stainless steel mesh screen in the filter dryer. It was documented that this could result in a physical loss of filtered, solid API material through the screen.

When it came to recording the potential consequences, or effects, of this failure mode, the effects were recorded as “Yield loss, cGMP deviation, economic business effect - unable to meet customer demand.” Thus, the failure mode and one of the main effects of the failure mode were essentially the same – “low yield and yield loss.”

As this workshop progressed, it was evident that selecting such a high level potential Failure Mode significantly limited the extent to which causative factors and their mitigating controls were identified, and documenting the failure mode in this manner impacted the outcome of the risk management exercise in quite a significant way. For example:

- The potential cause(s) of the actual breakage of, or damage to, the mesh screen was not identified or discussed in any way. It is not unreasonable to expect causative factors at this indenture level to have been identified, and there was, for example, no discussion during the workshop on whether an incorrectly rated screen (from a pressure perspective) could have been a potential cause for the screen breakage.

- With respect to risk-mitigating controls, the following five risk-mitigating controls were documented in the Quality Risk Management exercise as being important for addressing the risk associated with this failure mode:

1. Monitor the pressure in the dryer during operation, as a significant pressure drop may indicate a screen failure.

2. Do a screen integrity check before first batch and after fifth batch.

3. Do a heavy metals test on the finished API in order to detect screen particles.

4. Visually inspect the mother liquor for presence of particulates.

5. Ensure the screen is on a regular preventive maintenance schedule.

An analysis of the above five controls shows that 80% of the controls are detection-related. The fifth control serves as a preventive measure that may reduce the probability of screen damage or breakage, but to what extent this was unknown. Thus, it is clear that the above controls were heavily skewed towards detection as the primary means of addressing the risk posed by the failure mode in question. This is likely a result of documenting the Failure Mode at such a high indenture level and in a manner that rendered it effectively equivalent to its main end effects. When this occurred, it meant that the causative factors identified were, by definition, quite high level also, and it was found that preventive controls were not as readily determined as with lower level causative events.

A second workshop was then run to investigate the impact on the results of the above Quality Risk Management exercise when more care and vigor were applied to the failure mode identification and documentation process. The strategies outlined below were adopted during this repeat case study, and a simple Fault Tree Analysis (FTA) approach was used during a brainstorming session to determine causative factors for the selected high level fault.

The intent here was that causative events could be identified via more vigorous, but simple, procedures, and these could then be used to select potential failure modes and the causes of such failure modes. This approach ensured that the potential failure modes that were identified and documented were adequately differentiated from the high level faults that they related to, in this case the high level fault

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1 FTA is useful when Failure Modes need to be identified during FMEA and FMECA-based Quality Risk Management exercises. When using FTA methodology, there can be many causative events identified at the same or at different indenture levels in the fault tree and these may contribute to the high level fault. All of these causative events could potentially be considered to be failure modes, and this presents a practical difficulty when FTA approaches are used to identify failure modes, as it can sometimes be difficult to determine where in the fault tree the failure mode(s) should be selected. We have found it useful to first select the causes of the failure mode, before identifying the corresponding failure mode from the fault tree. (The latter will normally be one level above on the fault tree.) The causes of the failure mode can then be chosen from the fault tree by examining which causative factors in the tree are most readily suitable for assigning meaningful and practical preventive, detection or other controls to. This is a simple approach, but it has been found by the authors to be useable and effective.
being “Low Yield API Batches.” The approach also ensured that the causative events were at a sufficiently low indenture level to facilitate meaningful and preventive risk mitigation. Importantly, as a control between the two workshops, the high level fault selected in Workshop Number Two was the same as the failure mode selected in the first workshop on this Change Control case study.

In this second workshop, the first causative event identified under the high level fault was “the stainless steel mesh screen in the filter breaks or is damaged.” The three subsequent causative events were then identified at the next indenture level below this one. These three subsequent causative events, each separated by “or” gates in the Fault Tree, included:

1. The mesh screen in the dryer is not chemically resistant to the slurry material (including the solvent) being filter-dried.

2. The drying process uses an incorrectly rated screen from a pressure perspective, and the screen is unable to withstand the pressure exerted upon it when the filter dryer is at maximum agitation speed and contains a maximum load.

3. A wrong screen is installed in the filter dryer during set-up for this API manufacturing campaign.

The first causative event documented in the Fault Tree under the high level fault was selected as the potential failure mode, and in the indenture level below this in the Fault Tree, the three causative factors mentioned above were taken to be the potential causes of this particular failure mode. When the above failure mode, together with the associated three potential causes, was input to the risk management methodology under study here, substantially different and more useful results were obtained compared to those from the first workshop, even though the issue of concern was essentially the same – low yield API batches.

In the second workshop on the same case study, nine risk mitigating controls were identified this time, for the same low yield problem described in the first workshop. These were as follows:

1. Identify the correct pressure rating for the screen by determining (either via developmental batches or engineering calculations) the pressures expected to be exerted upon the screen when the dryer is in operation at maximum agitation speed and at maximum load. Then, ensure that this screen is used in the drying process.

2. Monitor the pressure across the screen in the dryer during operation. A significant pressure drop may indicate a screen failure.

3. Have a second person verify that the correct screen was chosen during set up of the dryer for this campaign.

4. Determine whether the screen material is inert with respect to the material being screened, and ensure that an inert screen material is chosen for this process.

5. Do a screen integrity check before drying the first batch in the campaign and after every fifth batch in the campaign.

6. Do a heavy metals test on the finished API batches.

7. Visually inspect the mother liquor for the presence of gross particulates.

8. Ensure the screen is on a regular preventive maintenance schedule.

9. Measure the yield of dried API for each batch. This may detect any gross screen failure, as there will be physical loss of API to the mother liquor.

An analysis of these controls presents a number of important findings. Firstly, an extra four risk mitigating controls were identified for the same low yield problem when more rigorous and defined procedures were used for identifying and documenting failure modes, in accordance with the strategies listed below. This was an increase of 80% over the controls identified during the first workshop on this same case study for the same problem.

Secondly, in the repeat workshop, the risk mitigating controls that were identified were based much more on prevention rather than on detection. Four of the nine controls, numbered 1, 3, 4 and 8 above were preventives in nature, as opposed to only one such control identified during the first workshop. Similar findings have been observed with other case studies when this approach was used.

When these preventive controls are considered, the subjectivity and uncertainty associated with assigning probability of occurrence values to the causes of the failure mode are reduced, even with this qualitative methodology, because we are not now merely guessing probability of occurrence values for the causes of failure modes. Rather, there is now a more scientific rationale behind any probability of occurrence values that are assigned.
Five Simple Strategies when Identifying and Documenting Failure Modes

Manufacturers of pharmaceutical products often use failure mode-based Quality Risk Management methodologies such as those based on FMEA and FMECA. Indeed, these approaches appear to be the methods of choice in GMP environments when formal Quality Risk Management methodologies are employed.

In order to reduce the problems of subjectivity and uncertainty that were discussed earlier in this paper, it is of prime importance that failure modes be identified and documented in a scientific manner, using meaningful, consistent, and systematic processes. This is because, with failure mode-based methodologies, the risks or RPNs that are generated, and the overall results obtained from the Quality Risk Management exercises, directly relate to, and are usually wholly dependent upon, the failure modes that are identified and input to the methodology being used.

In the International Standard on Analysis Techniques for System Reliability, International Electrotechnical Commission (IEC) 60812:2006, a failure is defined as “termination of the ability of an item to perform a required function,” and a failure mode is defined as the “manner in which an item fails.” There are many other definitions used for the term Failure Mode in the literature, such as “the manner in which a component, subsystem, or system could potentially fail to meet the design intent” and “a situation resulting in an undesirable effect that may ultimately pose a hazard or inconvenience to an end user.” While IEC 60812:2006 provides useful and detailed information on both the FMEA and FMECA methodologies, it provides only limited and relatively high level conceptual guidance on procedures for identifying and documenting failure modes, and this is seen with other publications on FMEA and FMECA-based approaches also.

From a review of relevant Quality Risk Management methodologies and their applications in the literature and in the author’s experience from inspecting manufacturers’ Quality Risk Management procedures and activities during GMP inspections, it is evident that the practical procedures for the identification and documentation of failure modes, faults, or hazards are often not adequately described.ICH Q9 does not provide much guidance in this specific area, and there is often scant instruction provided in other publications and in company Quality Risk Management procedures on how to actually identify and document failure modes, beyond main conceptual steps.

From the practical case studies carried out as part of this research, it is evident that there is a need for more rigorous and clear instruction or guidance in Quality Risk Management methodologies in relation to the practicalities of identifying and documenting failure modes, particularly during brainstorming sessions. In the following sections of this paper, a number of simple and easy-to-implement strategies are presented for use when identifying and documenting failure modes, which the authors have found useful when developing and testing Quality Risk Management concepts and approaches for GMP applications.

STRATEGY 1: Prepare for Better Brainstorming

Brainstorming is a widely used component of Quality Risk Management processes, and it is an effective method to determine “what might go wrong” with the item under study, because it encourages lateral thinking. But brainstorming is often not formally or adequately proceduralised, and formal training is often not provided in this area to users of Quality Risk Management methodologies. There is generally little guidance provided in the literature or elsewhere on how to actually perform or to manage brainstorming sessions for GMP environments. As a result, brainstorming sessions can often be poorly structured, not science-based, and inconsistent in approach.

- When brainstorming is used in order to identify potential failure modes, the following approaches have been found to be helpful in reducing problems of subjectivity and uncertainty:
• Ensure that documented and formal procedures are in place for carrying out brainstorming. Define in advance the training requirements for those participating in brainstorming activities.

• Ensure that any potential failure modes documented during brainstorming sessions for the system under consideration are at an indenture level in the system that can provide causative events that lead to appropriate risk mitigation and control. (The case study presented above provides a detailed example in relation to this point.)

• Formally review the potential effects of each proposed failure mode at the time the failure mode is proposed, to ensure that failure modes are not documented that are essentially the same as their effects. (The case study presented above provides a detailed example in relation to this point.) In this regard, it can be useful if the following questions are put to the Risk Management team during brainstorming or other activities when Failure Modes are being identified: What can go wrong? What are the effects or consequences of this going wrong? Is the failure mode, as proposed, the same as its effects? If the latter is the case, work to determine the true failure mode relating to these effects.

 ✓ These simple questions force the Quality Risk Management team to differentiate between proposed Failure Modes and the effects of such. As the Case Study in this paper demonstrates, it is important to ensure that each proposed Failure Mode represents a true failure mode in relation to the effects envisaged, and is not merely the equivalent of those effects written another way.

 ✓ Confusion between failure modes, their causes and effects can occur in FMEA-based applications, because potential effects identified in one indenture level of the system under study may become failure modes at a higher level. Also, failure modes identified in one indenture level may become failure mode causes at a higher indenture level.21

“"In all cases, brainstorming could be used as a means of identifying failure modes, faults, or hazards, and in all cases, there were no documented instructions in place for how such brainstorming was to be carried out.”

• Ensure that any pertinent assumptions that are made relating to qualification and validation issues, and which may be significant for specific failure modes, are discussed and clearly documented during brainstorming sessions. For example, assumptions relating to the qualification status of items of equipment, or of maintenance activities for items of equipment to maintain qualification or calibration status, can be important when equipment-related failure modes are being identified, and these assumptions should be stated up-front.

• Ensure that any significant sources of uncertainty in relation to specific failure modes are documented during brainstorming sessions, and that they are dealt with in a scientific manner. For example, there can be significant uncertainty associated with the likelihood of a failure mode cause occurring.

 ✓ In such instances, as a cautionary measure some quantitative Quality Risk Management applications assign the highest possible probability of occurrence value to such events.
However, this is not a scientific approach, as the resulting risks or RPNs can be greatly overestimated, and this can distort the outcome of Quality Risk Management exercises, leading towards risk mitigation and validation activities that have little scientific basis.

- In such instances, adopting more qualitative approaches and formally documenting the uncertainty in any risk that may be estimated, or even accepting that the risk cannot be estimated at that time without additional studies, may be useful.

**STRATEGY 2:**
**Evaluate the Number of Causes Associated with each Proposed Failure Mode before Accepting the Proposed Failure Mode**

When failure modes are being identified, it is useful to briefly review the potential causes of each proposed Failure Mode in order to determine whether the proposed Failure Mode is documented at a level that is workable when the Risk Assessment activity begins.

- In several practical case studies, we observed that when a proposed Failure Mode has a very large number of potential causes, it can be so broad in scope that it can be practically unmanageable during the Quality Risk Management exercise.
- For example, proposed Failure Modes such as “Out-of-Specification Batches” or “Loss of Sterility Assurance” can have so many causes that the Quality Risk Management exercise becomes very large and difficult to work through in practice.
- Potential Failure Modes should be specific and narrow enough in scope so as to facilitate a workable Risk Assessment exercise. As a guide, we have found that if more than five potential causes are identified for a proposed failure mode, the proposed failure mode is probably at too high an incidence level and, if possible, should probably be broken down into more specific potential failure modes.

**STRATEGY 3:**
**Encourage and Capture the Reporting of Near Miss Incidents**

It is well established that, when identifying potential failure modes, it is useful to review obvious sources of information, such as data on process deviations, batch rejects, product complaints and defects, production problems, qualification and validation incidents, reasons for change controls, etc. However, one area that is often overlooked in formal Quality Risk Management methodologies is the occurrence of near miss events, or problem incidents that almost occurred.

- Near miss incidents can provide valuable and real information on potential failure modes and their frequencies, but they are often not formally documented.
- To facilitate the use of near miss data, it is necessary to formally encourage a culture of reporting of near misses within the organisation, and to integrate such reporting as a formal element of the Quality System, similar perhaps to how deviations are reported.

**STRATEGY 4:**
**Do not Merely Map the Process; Assemble Comprehensive Data on the Item under Study**

Some methodologies recommend that a map of the process under study be generated, which can then be used to determine where potential failures may occur in the process or item under study. This is very useful, but in our experience and from workshops we have carried out, process maps sometimes provide only very limited and basic information, and can be of little value during Quality Risk Management exercises.

It is more useful, therefore, to ensure that the procedures in place for Quality Risk Management exercises define in detail the data and documentation that should be assembled on the item under study. If a process map or flowchart of the item under study is to be used, it should be sufficiently detailed and descriptive if it is to be of value. We have found it helpful to extend the scope of what is normally considered a “Process Map,” so that more comprehensive information is assembled on the item under study. This information can include:
STRATEGY 5: Look for Strength of Evidence when Expert Judgment and Informed Opinions Are Used

It is, of course, good practice to obtain informed opinion and expert judgement when identifying potential failure modes, but it is important to always seek and assess the strength of evidence for each opinion or suggestion proposed. This adds rigor to the exercise, and it helps reduce the level of subjectivity and guesswork that can arise during the failure mode identification process. In this regard, it is helpful to:

- Seek the opinions of actual users and operators of the item under study. A process operator may know very well what can go wrong with a process or activity, and he or she may be in a position to advise as to its potential frequency.

- Seek the opinions of those employees or others who are knowledgeable in the item under study. For example, during equipment-related Quality Risk Management exercises, the vendor may have valuable knowledge about likely problems and potential rates of failure of components, etc.

- Where possible, take into account the concerns of stakeholder groups when considering “what might go wrong” with an item under study. For example, if a change control is proposed to roll out a new labelling and livery design for a range of medicinal products, practicing pharmacists may usefully advise about risks of dispensing or usage errors which may be introduced by the change, even if the new labelling is fully compliant with Marketing Authorisation labelling requirements.

CONCLUSIONS

In this paper, the problems of subjectivity and uncertainty that are associated with formal Quality Risk Management methodologies are discussed. When such methodologies are used as an aid to qualification, validation, and change control activities within GMP environments, this research has found that an area that can greatly influence the validity of the outcome of the exercise is the identification and documentation of potential Failure Modes.
Following a review of the relevant literature, and based on the author's experiences as a GMP inspector, it is evident that the identification and documentation of potential Failure Modes is an activity that is often not adequately proceduralized within failure mode-based Quality Risk Management methodologies and their applications.

During the course of this research, using a wide range of real-life GMP-related case studies and workshops, it was observed that, in the absence of clear and rigorous procedures, failure modes are sometimes poorly identified and documented. This can have a significant impact on the results of the Quality Risk Management exercise in question. The outputs and conclusions of such exercises may be questionable, lacking in scientific evidence, and there may be a lack of confidence in the results generated. This problem especially arises when failure modes are selected for assessment which are identified at too high an indenture level in the system under consideration, or when the failure mode is documented in a way that renders it essentially the same as, or very similar to, the potential effects of that failure mode.

A detailed case study presented demonstrates the above, and a number of simple strategies are proposed which can be adopted to improve how failure modes are identified and documented. This work has found that when such strategies are used, a greater level of confidence can be placed in the output from such Quality Risk Management exercises, and subjectivity and uncertainty issues can be reduced.

REFERENCES


35. For example, see the EMEA Public Statement of 18 October 2006 on the risk of inhibitor development for Factor VIII recombinant products, available at http://www.emea.eu.int.


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