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GDP Quality Risk Management Activities – Key points

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IMB GDP Information Day

September 28th, 2012

Before we begin..... Formal vs. Informal QRM

QRM is not a new area of activity for wholesalers

- Informal QRM-related activities taking place for many years
- Warehouse temperature mapping and monitoring – a Quality Risk Management activity
  - It acknowledges the risks to product quality via unsuitable temperatures
  - It recognises the value in assessing those risks (mapping study)
  - In controlling those risks (by identifying and specifying the storage locations that are suitable)
  - In continuously managing those risks
    - Ongoing temperature monitoring
    - Assessing the risks presented by proposed changes in storage areas
- Self-inspection and supplier approval are other Quality Risk Management-related activities

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Formal vs. Informal QRM cont'd

But there is a higher emphasis now on adopting more formalised approaches to Quality Risk Management

The new draft GDPs contain many requirements in relation to risk:

- QRM should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.
- The duties placed on any individual should not be so extensive as to present unacceptable risk to product quality.
- The scope and extent of … validations should be determined by a documented risk assessment approach.

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ICH Q9 Quality Risk Management

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What ICH Q9 offers the GDP Environment

ICH Q9 is a 2005 guidance document on QRM, available at www.ich.org.

- It has given the pharmaceutical and regulatory environments an internationally accepted voluntary framework in which to apply Quality Risk Management principles and concepts in our work environments

- It offers guidance on the principles and concepts behind Quality Risk Management, on the various tools that are available, (Annex I), and it suggests areas in which Quality Risk Management might be applied (Annex II)

- It promotes a move towards risk-based thinking in pharmaceutical environments, in an effort to improve decision-making in the face of uncertainty

    - The management of risk is one area in which uncertainty is usually unavoidable

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ICH Q9 wrt Storage & Distribution

In Storage, logistics and distribution conditions, QRM can be used:

- To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);
- To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;
- To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);
- To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

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But ICH Q9 is not the total QRM solution for wholesalers

- ICH Q9 provides only high level, conceptual guidance on Quality Risk Management
  - Not designed as a solution for carrying out at a practical level Quality Risk Management activities within a pharmaceutical company or Competent Authority
- Much of the guidance on methods and tools is largely conceptual, and was largely available in the literature
  - It does not offer any substantial guidance on how the various tools differ from each other, or how to chose one tool over another
  - Or how to apply any of the formal Quality Risk Management methodologies at a practical level in our day-to-day work activities.
- It does not offer guidance on how to address the problems of subjectivity and uncertainty that are often experienced during Quality Risk Management exercises

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Risk Concepts, Definitions & General Considerations

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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.)

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Consider Risk Estimation Activities

- Risk is regarded as the combination of the probability of occurrence of harm and the severity of that harm
  - 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) = Low

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Current Issues for Risk Estimation in the GMP Environment

Most of the currently used tools (FMEA, HACCP, PHA) are highly qualitative in how risks are estimated

- They usually employ ***non-quantitative approaches***
- They have risk scoring systems which are ***highly subjective***
  - Many different types of scoring models available
- They usually provide ***no strategies*** to overcome the potential problems of Subjectivity and Uncertainty

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Sample Probability & Severity Levels

Probability

5	Very Likely
4	
3	
2	
1	Remote

Severity

5	Catastrophic
4	
3	
2	
1	No impact

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Sample Risk Table - Risk Estimation

Severity

Probability	1	2	3	4	5
1	1	2	3	4	5
2	2	4	6	8	10
3	3	6	9	12	15
4	4	8	12	16	20
5	5	10	15	20	25

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Sample Risk Table – Acceptance Criteria

Severity

Probability	1	2	3	4	5
1	1	2	3	4	5
2	2	4	6	8	10
3	3	6	9	12	15
4	4	8	12	16	20
5	5	10	15	20	25

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What about Detection?

- Are Detection Controls not taken into account?

- Is Risk Not Probability x Severity x Detection?
  - Risk Priority Number (P x S x D) often used, especially in the FMEA Risk Assessment tools
  - Advantage – simple concept, easy to use and understand
  - Disadvantage – including Detection rating in risk assessments can lead to over-relying on detecting problems rather than preventing them!

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FMEA-based tools uses Detection

This uses P, S & D numbers to Rate & Prioritise each Risk… e.g.

- Probability Scale 1 though 5 (Lowest Prob. = 1)
- Severity Scale 1 though 5 (Lowest Severity = 1)
- Detection Scale 1 though 5 (Highest Detection = 1)
  - Risk Priority Number: RPN = P x S x D
  - Minimum RPN = 1
  - Maximum RPN = 125
- A Cut-Off RPN is used to judge risk acceptability and priority
  - Cut-Off RPN = ?????
  - Also, Detection in RPN can pose a difficulty for GDP applications

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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 freezer unit at a wholesaler that is used to freeze ice packs for cold chain transportation fails

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What is Risk Assessment?

Risk Assessment is a method which…

- identifies hazards or failure modes in a process, facility, system or product*
- estimates or calculates the risk associated with these hazards or failure modes*
- assesses that risk by comparing it against predefined risk acceptability criteria**

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

** This is often called Risk Analysis*

*** This is often called Risk Evaluation*

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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

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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 failure mode

- Risk Control work also helps determine:
  - Critical Control Points, (or *Critical Process Parameters)*,
  - how they will be monitored,
  - and what level of Qualification & Validation are required.

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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
- Risk Management should be viewed as an on-going Quality Management process

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General Considerations, Cont'd

Hazard / Failure Mode Identification is perhaps most crucial step!

We see a variety of approaches used here, e.g….

- Brainstorming… within the right team of people
- Informed opinion (Science-based)
- Cause & Effect Diagrams
- Evaluation of Complaints, Deviations, Rejects Data, etc.
- Fault Tree Analysis

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Risk – Should we Quantify or Qualify?

What do you think????

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Risk – Should we Quantify or Qualify?

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

Reasons:

- Probability relates not to the effects of the failure, but to the probability of occurrence of the failure mode itself or to its cause, and this can be difficult to determine accurately
- Some hazards occur because of systematic errors & random errors…. & these can be difficult to quantify

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Quantify vs Qualify?

- Severity & Probability are 'ordinal' scales
  - their magnitude is not meaningful
  - a Probability of Occurrence of 4 is higher but not necessarily twice as likely as a Probability of 2
  - it is not mathematically permissible to multiply 'ordinal' scales.
  - numerical operations such as (Risk = 3 x 4) or (Risk = 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 one will not then be tempted to multiply categories

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Risk Assessment & Quality Risk Management Tools

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Risk Assessment & Risk Management Tools

Many formal tools are available…

- HACCP - Hazard Analysis and Critical Control Points
- HAZOP – Hazard Operability Analysis
- FTA – Fault Tree Analysis (really a root cause analysis tool!)
- FMEA – Failure Mode & Effects Analysis
- FMECA - Failure Mode, Effects & Criticality Analysis
- PHA - Preliminary Hazard Analysis
- ISPE's Impact Assessment Method for GEP, Commissioning & Qualification
- GAMP 4 & 5 & related *GAMP Forum* methods

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General Comments…

Some of these techniques are complementary…

- FTA aids FMEA in Failure Mode Identification –
  - one is almost the reverse of the other.
- HACCP aids FMECA in determining Critical Control Points (or *Critical Process Parameters*).

Most tools were developed for non-pharma industries.

Most do not address Qualification & Validation requirements…

- So a significant degree of modification can be required…
- Disadvantage!

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What is HACCP?
Hazard Analysis and Critical Control Points

A Risk Assessment tool based around *Critical Control Points*

In HACCP…

- Hazards & their Preventative Measures are Identified
- Critical Control Points are Devised
  - *we will use Critical Process Parameters*
- CCP Limits & Monitoring Methods are Established
- Corrective Actions are Pre-determined for Deviations
- CCPs are Verified (… or validated in the pharma industry)
- Record keeping requirements are Defined

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What is FMEA?
Failure Mode and Effects Analysis

A Risk Assessment tool based around *Failure Modes*

- A Failure Mode is a way in which a process can fail to provide the anticipated result

FMEA…

- Identifies potential Failure Modes in a system, facility, process or product
- Prioritises the Failure Modes in accordance with their risk
- Puts controls in place to address the most serious concerns

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FMEA's Risk Priority Numbers (RPNs)

This uses P, S & D numbers to Rate & Prioritise each Risk… e.g.

- Probability Scale 1 though 5 (Lowest Prob = 1)
- Severity Scale 1 though 5 (Lowest Severity = 1)
- Detection Scale 1 though 5 (Highest Detection = 1)
  - RPN = P x S x D
  - Minimum RPN = 1
  - Maximum RPN = 125
- A Cut-Off RPN is used to judge risk acceptability and priority
  - Cut-Off RPN = ?????

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Example of Qualitative Probability Levels

Probability	*This Means The Failure Mode…*
5	… May Occur > 50% of the time
4	… May Occur > 20% of the time
3	… May Occur 5 – 20% of the time
2	… May Occur 0.1 – 5% of the time
1	… May Occur < 0.1% of the time

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Example of Qualitative Probability Levels

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1	… May Occur < 0.1% of the time

How practical are these levels for you?

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Example of Qualitative Probability Levels

Probability	*This means the Negative Event …*
High	… is Likely to Occur
Medium	… May Occur
Low	… is Unlikely to Occur
Remote	… is Very Unlikely to Occur

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Example of Qualitative Probability Levels

Probability	*This means the Negative Event …*
High	… is Likely to Occur
Medium	… May Occur
Low	… is Unlikely to Occur
Remote	… is Very Unlikely to Occur

Which do you think are more useable for you?

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Example of Severity Levels

Severity	*This means the effects of the Negative Event are, or may be,*
Critical	**Severe** - Very Significant Non-Compliance with GDP - Potential Patient Injury
Moderate	**Moderately Severe** - Significant Non-Compliance with GDP - Potential Patient Impact
Minor	**Not Severe** - Minor Infringement of GDP - No expected Patient Impact

Quantitative levels are used less often for Severity Ratings

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Example of a Risk Table – Acceptance Criteria

$$Risk = P \times S$$

Negative Event	*Minor Severity*	*Major Severity*	*Critical Severity*
High Prob.			
Med. Prob.			
Low Prob.			
Remote			

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And a slightly modified version.....

Risk = P x S

Negative Event	*Minor Severity*	*Moderate Severity*	*Critical Severity*
High Prob.			
Medium Prob.			
Low Prob.			
Remote Prob.			

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… And with risk levels shown

Risk = P x S

Negative Event	***Minor Severity***	***Moderate Severity***	***Critical Severity***
High	Unacceptable	Intolerable	Intolerable
Medium	Acceptable	Unacceptable	Intolerable
Low	Acceptable	Acceptable	Unacceptable
Remote	Acceptable	Acceptable	Acceptable???

Any Comments??

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What the Risk Levels mean…

- **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 Reduction or New Controls are Required.

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Example of Detection Levels

Detection	*This means that …*
High	The Control will likely Detect the Negative Event or its Effects
Medium	The Control may Detect the Negative Event or its Effects
Low	The Control will probably not Detect the Negative Event or its Effects
None	There is no detection control in place

Quantitative labels for detection can also be used

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Practical Case Study

The application of Risk Assessment to the Returns Area in a wholesale facility

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