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Improving Quality Risk Management activities to better support GMP Activities

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GMP & Market Compliance Info Day

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Topics for today…

- **Part I:** Reflecting on where the industry and regulators are currently with respect to QRM
  - Key developments since 2000
  - ICH Q9 - 2005
  - Post-2005 Industry and Regulatory initiatives
  - Where are we right now?

- **Part II:** Problems with current approaches to QRM
  - 5 Key problem issues for consideration

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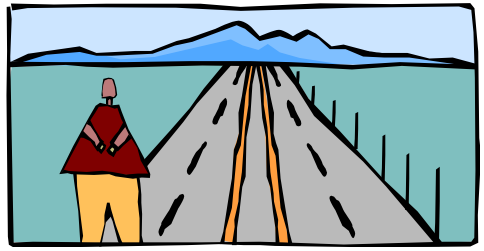
Topics for today…

- **Part III:** Subjectivity and Uncertainty in QRM work
  - Understanding the factors that give rise to such problems
  - Understanding the adverse impacts of human heuristics and risk perception
    - And how they may affect Risk Assessments in the GMP Environment

- **Part IV:** A possible QRM Road-map for the future
  - Key things for the industry to consider



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Part I

Reflecting on where the Industry and Regulators currently are with respect to QRM

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Some Key QRM developments since 2000

- **Since 2000, various initiatives have been undertaken to try to address the risks presented by medicines from a manufacturing perspective**

  - **2001: Annex 15** of the EU GMP Guide (Qualification and Validation) - explicitly required Risk Assessment in validation activities

  - **2001: ISPE Baseline Guide on Commissioning and Qualification** – Impact Assessment methodology

  - **2001**: **ISPE GAMP 4** – Risk assessment approach for Computerised Systems

  - **2002 & Onwards** – many important **FDA initiatives** directly and indirectly related to QRM

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  - **2001**: **ISPE GAMP 4** – Risk assessment approach for Computerised Systems

  - **2002 & Onwards** – many important **FDA initiatives** directly and indirectly related to QRM

During this time, many manufacturers were applying Risk Assessment tools to some degree

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November 2005: ICH Q9

Milestone:

ICH Q9 gave industry and regulators an internationally accepted framework in which to apply QRM principles and concepts in their work

- It offers guidance on the principles and concepts behind QRM, on the various tools that are available (Annex I), and it suggests areas in which QRM 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

  - ICH Q9 indicated the formal acceptance by GMP regulators of risk-based approaches

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Where a deterministic (or fixed rule) approach to GMP is not the only way to do things

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Some Key Developments since 2005:

Various industry working groups were set up to develop and facilitate the application of QRM and ICH Q9

- Useful guidance documents have resulted
  - **ASTM E2500, 2007:** A Standard Guide for the Specification….
  - **GAMP 5, 2008**: A Risk-Based Approach to Compliant GxP Computerized Systems
  - **ISPE Risk MaPP, 2010:** Risk-Based Manufacture of Pharmaceutical Products

- Regulators have supported and contributed to other industry QRM initiatives also, resulting in additional non-official guidance
  - **PDA's (PCMO) Technical Report No. 54, 2012:** Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations
  - **ISPE Project Management Guideline, 2011 –** See Ch 3

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Some Key Developments since 2005:

Regulators have been working to reflect the principles and concepts of ICH Q9 within the GMPs

- In the EU, several GMP Guide revisions have been made
  - ***Chapter 1***, *Quality Management, July 2008*
  - ***Annex 11***, *Computerised Systems, June 2011*
  - ***Part II*** *– GMPs for APIs, July 2010*

- Many other significant GMP revisions are underway in the EU to reflect QRM
  - ***Chapter 3***, Premises and Equipment
  - ***Chapter 5***, Production
  - ***Chapter 8***, Complaints and Product Recall
  - ***Annex 16,*** Certification by a Qualified Person and Batch Release

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Some Key Developments since 2005:

Regulators have also been working to reflect the principles and concepts of ICH Q9 within their own work activities also

- Risk-based inspection planning tools have been developed:
  - **FDA's** Risk Ranking and Filtering tool (2004)
  - **EU** Inspector's Working Party initiative (2008)
  - **MHRA's** Risk-based Inspection Programme (2009)
  - **Japan's** PMDA Desk-top Inspection initiative (2010)
  - **PIC/S** Risk-based Inspection Planning tool (2011)

- **Regulators have also worked on other initiatives:**
  - EMA's QP Discretion Reflection Paper, 2009 (current version)
  - FDA's Revised Process Validation Guidance for Industry , 2011
  - EU Guideline on Process Validation (draft), 2012

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So a lot of work has been done to date!

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Where are we now – Points for Consideration

While much work has been done to incorporate QRM into the regulatory framework and into the manufacture of medicines…

- Many of the problem issues we had before 2005 are still with us:
  - e.g. Various types of manufacturing issues continue to occur
    - leading to very significant and costly investigations and can impact batch release
  - e.g. Serious Quality Defects and Product Recalls
    - including MA Non-compliance issues – sometimes resulting in cessation of Batch Release

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IMB Quality Defect Stats, 2004-2011

Year	2004	2005	2006	2007	2008	2009	2010	2011
Critical	50	66	84	173	127	105	173	231
Major	167	199	238	216	300	345	332	364
Others	93	62	49	84	128	164	246	322
Total	310	327	371	473	555	614	751	917
Recalls	82	74	58	97	141	98	168	253

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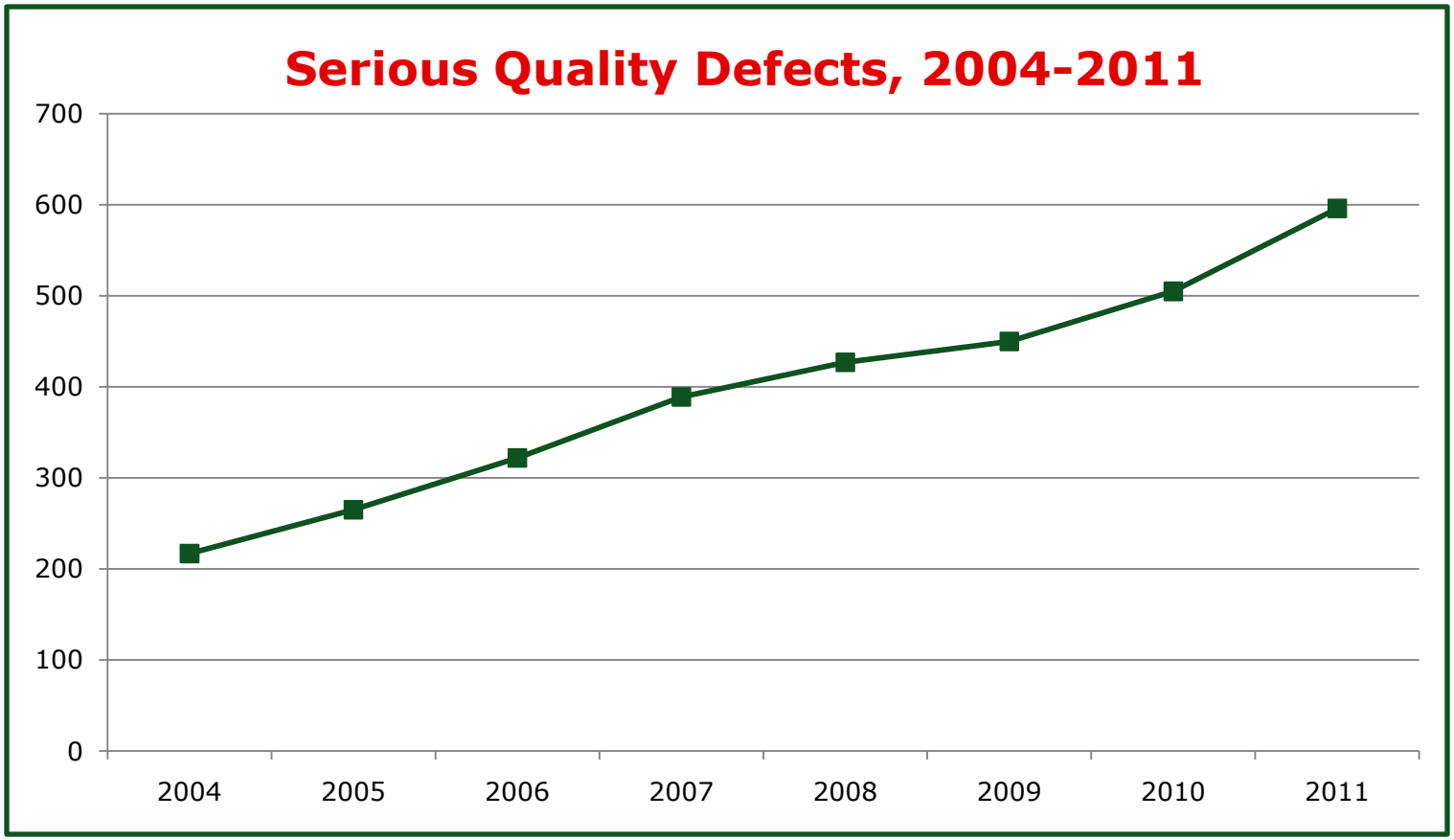

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Other Points for Consideration

- **For Industry: Are the potential benefits of ICH Q9 in terms of achieving some level of reduced regulatory oversight being realised?**
  - What are the factors that come into play here?
    - *Communication issues with Inspectors?*
    - *Lack of clarity as to what constitutes reduced regulatory oversight?*

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Other Points for Consideration

- **For Industry: Are the potential benefits of ICH Q9 in terms of achieving some level of reduced regulatory oversight being realised?**
  - What are the factors that come into play here?
    - *Communication issues with Inspectors?*
    - *Lack of clarity as to what constitutes reduced regulatory oversight?*
- **For Regulators: How much inspection work is currently truly risk-based?**
  - Are the frequencies of inspections currently determined on a risk basis?
    - Is it always appropriate to only schedule inspections on the basis of risk?
  - Is it correct to say that all sterile product manufacturers are high risk?
  - Are we willing to apply reduced regulatory oversight when it is well deserved?
    - What about *increased* regulatory oversight?

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Part II

Problems with current approaches to QRM

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Qualification & Validation and Risk - EU GMP Requirements

Many references to Q&V in the EU GMPs. For example:

- *Annex 15 sets out the main requirements which EU GMP Inspectors use to judge compliance with respect to Qualification & Validation*
  - .... manufacturers must "identify what validation work is needed to prove control of the critical aspects of their particular operations."
  - "Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated."
  - "A risk assessment approach should be used to determine the scope and extent of validation."

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Q&V and Risk References, cont'd

Part II of the EU GMPs (for APIs) - also known as ICH Q7

- "The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered".
- "Critical process parameters should be controlled and monitored during process validation studies."

Useful section on Change Control also…

- "A classification procedure may help in determining the level of testing validation…" to justify the change.

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5 Key Problem Issues…

1: Runaway Subjectivity & Uncertainty – the lack of good science

- Most of the currently used QRM tools & approaches contain **no design features or strategies** to address significant problems of Subjectivity and Uncertainty
- **Over-reliance upon subjective scoring systems** with little if any understanding of the factors that can affect such scores
  - Ratings of Severity, Probability of Occurrence and Detection are **not assigned in an evidence-based, scientific manner**
    - e.g. A low probability of occurrence rating is assigned on the basis of a control that detects something but prevents nothing
    - Very easily challenged by inspectors!

See Journal of Validn Technology, Vol. 16, No. 3, 2010, for discussions in this regard

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Key problem issues, cont'd

2: Widespread use of QRM tools that were never designed for GMP use

- These require **too little critical assessment** of the degree to which GMP controls serve (or fail) to mitigate and manage the risk issue in question
  - *False sense of security in Current Controls*
  - *New controls not demonstrated as being effective*
  - *Poor translation of risk assessment outputs into validation protocols*

- They are sometimes **not capable of achieving the objectives** of the exercise
  - Especially wrt achieving true risk-based Q, V & CC

See 'Quality Risk Management – Putting GMP Controls First', PDA Journal of Pharm. Sci. Technol., May/June 2012

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Key problem issues, cont'd

3: Poorly proceduralised elements of QRM activities

- e.g. **Brainstorming** activities, that are used to identify:
  - *Failure Modes and effects*
  - *Potential root causes*
  - *Risk-mitigating actions*
- e.g. How **Risk Communication** will occur and by whom
- e.g. How, why and when **Risk Review** will be performed

- The lack of robust procedures can adversely affects many activities:
  - *e.g. How failure modes are identified and written*
  - This can translate into ineffective root cause analyses for the real risk issues and in ineffective risk control actions later on

See Journal of Validn Technology, Vol. 12, No. 2, February 2007, for a Case Study in this regard

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Key problem issues, cont'd

4: Over-reliance upon expert opinion without the required controls for this

- Understanding the ***factors which introduce error and bias*** into the opinions of experts (and others) is important
  - But how well are these factors understood in the GMP environment?
    - How much is ***memory*** a factor??
    - Is experience mainly memory-based? How much **intuition** is used?
    - Are experts susceptible to the same **human heuristics** as lay people?
    - What are **human heuristics** anyway?

See Morgan, & Henrion, *"Uncertainty – A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis"*, Cambridge University Press, 1990

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Key problem issues, cont'd

5: Not being able to adequately measure the effectiveness of QRM work

- Current approaches to QRM in the GMP environment often lack any methods to measure how effective that QRM work has been
  - The widespread use of ***qualitative*** approaches to Risk Assessment compounds this problem
  - **Question:** How much has the QRM work done to date in your company added to the quality and safety of the products you produce?
    - *By how much has it improved qualification and validation work?*
    - *How much risk reduction have you achieved?*
    - *By how much has your QRM work protected patients?*

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Discussion on the above

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Part III

Subjectivity and Uncertainty in QRM work

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Subjectivity and Uncertainty in QRM

Question 1

- Does your company have procedures that deal with potential Subjectivity & Uncertainty (S&U) in the outputs of QRM exercises?
  - A – Yes
  - B = No
  - C = Don't Know

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Subjectivity and Uncertainty in QRM

Question 2

- Has your company devoted resources for training users of QRM tools on the human factors that can introduce bias and errors of judgement when assessing risks?
  - A – Yes
  - B = No
  - C = Don't Know

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Subjectivity and Uncertainty in QRM

Question 3

- Has your company put strategies in place to minimise problems of mis-perception when risks are assessed and communicated?
  - A – Yes
  - B = No
  - C = Don't Know

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Discussion on the above

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Uncertainty

Generally unavoidable in QRM work, given the accepted definitions of risk

- Unless the source of the hazard or harm is entirely eliminated, uncertainty cannot be avoided when one tries to estimate and manage resulting risks.

- **ICH Q9**: Uncertainty is due to the combination of:
  - *Incomplete knowledge about a process*
  - *Its expected or unexpected variability*

- Typical sources of uncertainty include:
  - Gaps in knowledge about various things, e.g. sources of harm
  - Gaps in pharmaceutical science, process understanding, etc.

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Subjectivity

Problems of subjectivity also arise during risk assessments

- **ICH Q9:** achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because:
  - *each stakeholder might perceive different potential harms*
  - *place a different probability on each harm occurring*
  - *attribute different severities to each harm*

- But subjectivity can **also** be a consequence of:
  - *the nature of the scoring method used to estimate the risk*
  - *other important human factors (e.g. human heuristics)*

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Risk Perception

Problems of S&U in QRM work can be compounded by Risk Perception issues

- Stakeholders form judgements about risks based on their own perceptions of those risks (ISO 31000)

  …. differences in values, needs, assumptions, concerns

- This can make it difficult to reach agreement on the acceptability of a risk, or on the suitability of a course of action proposed to address the risk

- This is important when it is a Regulatory Inspector who is reviewing that risk
  - She may disagree that the risk controls proposed to reduce an RPN rating actually do reduce that risk!!
  - ***How she <u>perceives</u> that risk may be influencing her opinion!***

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Understanding the factors that influence Risk Perception

How risks are perceived is complicated by the influence of psychological and cognitive processes

- Luckily, this has meant that risk perception has long been an important area of research for psychologists in various disciplines ☺

  - Litai's work at MIT in the late 1970s produced a listing of nine so-called ***quantifiable 'risk factors'*** that relate to risk perception

    - *These indicate how different risks are perceived by the general public*
    - *Latai produced a dichotomous scale which accompanied each risk factor*

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Latai's Risk Factors, 1980

Risk Factor	Dichotomous Scale	Risk Conversation Factor
Volition	Voluntary : Involuntary	100
Severity	Ordinary : Catastrophic	30
Origin	Natural : Man-made	20
Manifestation of Effects	Delayed : Immediate	30
Exposure Pattern	Continuous : Occasional	1
Controllability	Controllable : Uncontrollable	5-10
Familiarity	Common/Old Hazard : Dread/New Hazard	10
Benefit	Clear : Unclear	10
Necessity	Necessary : Luxury	1

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What this research found:

Litai's research found that:

- The public was willing to accept risks that could be considered voluntary that were up to 100 times the magnitude of risks that were considered to be involuntary.

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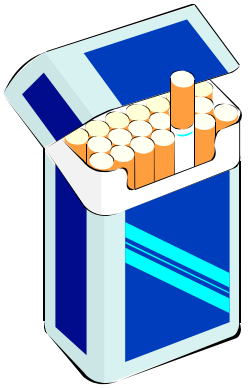
Example of Voluntary Risk:

The risk from smoking cigarettes



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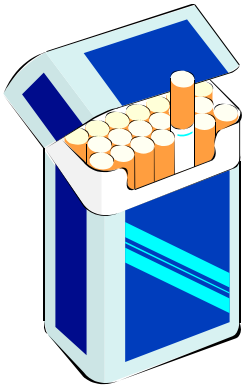

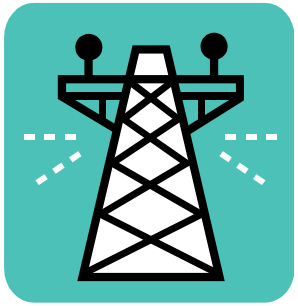

Example of Involuntary Risk:

The risks posed by high voltage electricity lines near one's home

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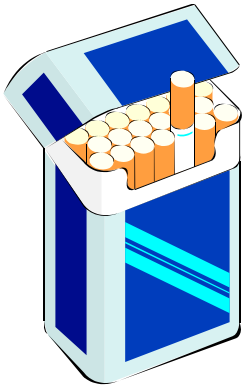

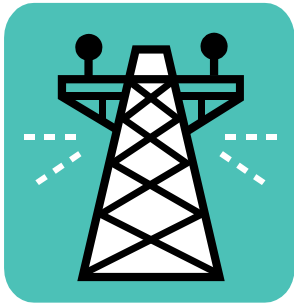

Example of Involuntary Risk:

The risks posed by high voltage electricity lines near one's home

This was the case even when the risk associated with some voluntary activities was estimated to have been ***a lot larger*** than some involuntarily assumed risks.

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'Dreadfulness' and other factors

Research by Slovic and Fischhoff indicated that risk factors can be grouped into three main categories

1. the degree of 'dreadfulness' associated with the issue
2. the degree to which the risk was understood
3. the number of people exposed to the risk in question

- Slovic et al. used these categories to define what was called a ***'Risk Space'***
  - When a hazard came within that space, a person's perception of the risk tended to be significantly affected than when the hazard was outside this space.

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Might such research findings be useful in the GMP environment, when assessing and communicating various types of risks?

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Risk Perception in the GMP Environment

The literature shows that there has been little formal work done in the GMP-environment on how risk perception may affect risk assessments

- But problems of risk perception are as likely to affect GMP risk assessments as assessments in other industries!
  - ***Consider the following example….***

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GMP Example

Consider the risks presented by glass particulates in injectable products:

- These risks might fall into Slovic & Fischhoff 's *dreadfulness* category
- In accordance with Litai's risk factors, they may also be characterised as *involuntary risks*, with perceived *catastrophic consequences*

- While the known occurrence rates of glass particles are usually very low, this type of risk is likely going to be subject to problems of mis-perception among some stakeholders

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How might such problems of risk perception be counteracted???

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GMP Example cont'd

Well, when **documenting** such risks and when **communicating** them, it will be important to clearly describe:

- The known **incidence rates** of such issues
  - *And the data that support those incidence rates*
- How such risks are **controlled** at a practical, detailed level, within the company
  - *Regardless of the known incidence rates*
- Any **design features** in the product or process that can reduce the consequences of such risks
  - *And the known effectiveness of such controls and design features*
- Any **important assumptions** and **sources of uncertainty** in the assessment

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GMP Example cont'd

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See Journal of Validn Technology, Vol. 16, No. 4, Autumn 2010, for a discussion in this regard

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Let's look at a different GMP Example

Consider a Change Control to introduce a new Rapid Microbiological Test Method to replace TVC by membrane filtration on water samples:

- The company risk-assesses this change, using a multi-disciplinary team
  - There are 1 SME and 4 non-SMEs on the QRM team
  - Senior Management, who are not expert in this technology, will ultimately be asked to approve or reject the change control proposal

- **Question:** *Are there any risk perception issues to consider here, given what is known about how non-experts perceive risks presented by new technologies?*
  - Will the risk assessment potentially be biased?
  - How will regulators perceive the risks?

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How many of your companies have introduced Rapid Micro methods??

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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 Practices for Risk Estimation in the GMP Environment

Most of the currently used tools (FMEA, HACCP) 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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Current Practices for Risk Estimation in the GMP Environment

Research has shown that different people view word-based probability scales in very different ways!

- The same is true with Severity and Detection scales

Consider the following:

- Deirdre works in Pharmaceutical Company A
- She's very happy, as she does a lot of interesting risk assessment work
- Her company uses the following probability scale

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Company A - Probability Table

Likelihood of Occurrence	*Guidance*
High	One per 100, very possible
Medium	One per 1000, unlikely
Low	One per 10,000, very unlikely

Note: The company SOP on QRM allows the table to be customised for the risk assessment at hand

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Current Practices for Risk Estimation in the GMP Environment

Deirdre gets head-hunted by Pharmaceutical Company B

- She gets a good relocation package
- A nice team of people to work with
- Her new role will still involve a lot of risk assessment work
- She is happy!

- Her new employer uses the following probability scale

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Company B - Probability Table

Probability (Likelihood failure will happen)		
7	Frequent	Once in a week or more
6	Moderate	Once in 1 month
5	Occasional	Once in 1 year
3	Rare	Once in 10 years (i.e. once in lifecycle of the system)
2	Unlikely	Once in 100 years (i.e. once in lifecycle a site)
1	Improbable	Once in 1000 years or less (i.e. once in lifecycle of the corporate company)

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Confused???

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Problems with such scoring systems:

There is often a high level of subjectivity in how these kinds of scoring systems are used, and there are often no controls in place to overcome this.

Consider the ***Intergovernmental Panel on Climate Change (IPCC), 2007***

- The IPCC uses this scale to rate the probabilities of various climatic events:

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Probability Phrase	IPCC Meaning
Very Likely	>90%
Likely	>66%
Unlikely	<33%
Very Unlikely	<10%

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Very Likely	>90%
Likely	>66%
Unlikely	<33%
Very Unlikely	<10%

Budescu et al. (2009) performed an experiment:
Subjects were asked **to read sentences** from the IPCC 2007 report where these terms were used **and assign a probability** to those events.

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Consider these IPCC sentences…

There is a "very likely increase in frequency of hot extremes, heat waves and heavy precipitation."

Human influences have "likely contributed to changes in wind patterns, affecting extra-tropical storm tracks and temperature patterns."

Changes in many systems consistent with warming are "very unlikely to be due solely to natural variability."

- *Ref: IPCC Climate Change Report 2007, Summary for Policymakers*

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Variances in Understanding the Probability Terms used in IPCC Report

Probability Phrase	IPCC Meaning	Minimum of all responses	Maximum of all responses	% Responses that violated the IPCC Guidelines
Very Likely	>90%	**43%**	**99%**	**58%**
Likely	>66%	**45%**	**84%**	**46%**
Unlikely	<33%	**8%**	**66%**	**43%**
Very Unlikely	<10%	**3%**	**76%**	**67%**

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The use of Ordinal Scales during Risk Estimation

Risk Estimation methods of this nature use what are known as <u>Ordinal Scales</u>

- These scales just indicate a **relative order** of what is being assessed
  - They are not actual units of measurement (Hubbard, 2009)

    ***Example*:** Star Movie Ratings 

- The magnitude of the individual values is not meaningful in a numerical sense (Conrow, 2003)

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As explained by Kmenta and Ishii (2004), it is not mathematically permissible to multiply ordinal numbers!

Numerical operations such as (Risk = 3 x 4) or (RPN = 3 x 4 x 2) have questionable validity!!

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To compound this problem…

Such scales, by definition, produce highly subjective P, S & D ratings

- But what makes matters worse can be the failure to support such ratings with objective evidence or scientific reasoning!

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GMP Example: A deviation related to metallic particles in a batch of API:

- A **Low Severity Rating** was assigned to the risk on the basis that the particles were inert (no basis documented).
- A H**igh Detectability Rating** was assigned (no basis documented).
- The issue was rated as **Low Risk**.
- The batch was not reprocessed or reworked.
- A 100g sample was taken for a solution test and it passed.
- (Note: The contamination was assumed to be homogeneous. Again, not supported by evidence.)
- The batch was released.

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Was this an appropriate application of QRM?

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What are Human heuristics?

Heuristics are Cognitive Behaviours:

- They come into play when we make judgments in the presence of uncertainty
  - They are like ***unconscious rules of thumb*** that affect our cognitive processes
  - They are related to the concept of ***bias*** – *a tendency to think and behave in a way that interferes with rationality and impartiality (Hubbard, 2009)*

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- Much evidence in the literature that heuristics are ***a source of significant bias and errors in judgment***
  - In QRM, heuristics become important because there is usually some level of uncertainty associated with the judgments and decisions that have to be made

Some of the main heuristics are as follows:

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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.

- This first approximation becomes a natural starting point for that person's thought process.
- It is termed an **'anchor'** in the person's thought process
- Its value is known to influence any subsequently **adjusted** values

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Kahneman and Tversky (1972-73) demonstrated that the value of this anchor is <u>critical</u>

- *Even when it is has no scientific basis and is randomly selected!*
- *When adjustments of the initial value are made to arrive at a more accurate answer, the adjusted values are usually **biased** towards the value of the anchor*

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

- Consider how many risk assessments you have been on where someone verbally suggests a probability, severity or detection rating for a failure mode during a brainstorming session!

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GMP Example

A new filling line has been installed for a sterile biological product

- A risk assessment is done in relation to filling line interventions
  - Many such interventions are anticipated and proceduralised
    - *e.g. Manually reaching for a tool when near the filling area*

- **A Failure Mode is written for this during a brainstorming session:**
  - The probability of an operator inappropriately carrying out this task when exposed vials are nearby is estimated….

    - One person in the team suggests a **probability of 2 (Low)** and states why

    - The team discusses this and, after some debate, they eventually arrive at a **final probability estimate of 1 (Remote)**

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GMP Example cont'd

Failure Mode	***Minor Severity***	***Moderate Severity***	***Critical Severity***
4. High	Unacceptable	Intolerable	Intolerable
3. Medium	Acceptable	Unacceptable	Intolerable
2. Low	Acceptable	Acceptable	Unacceptable
1. Remote	Acceptable	Acceptable	Acceptable

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GMP Example – with first suggested probability

Failure Mode	***Minor Severity***	***Moderate Severity***	***Critical Severity***
4. High	Unacceptable	Intolerable	Intolerable
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GMP Example – with agreed probability

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GMP Example – with agreed probability

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Could the Heuristic of Anchoring & Adjustment come into play here?

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The Heuristic of Availability

This Heuristic also adversely affects how people estimate the probability of an event occurring.

- A person's probability judgement is often determined by the ease with which they can **recall** previous occurrences of the event
  - … or the ease with which they can **imagine** the event occurring

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The Heuristic of Availability

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- A person's probability judgement is often determined by the ease with which they can **recall** previous occurrences of the event
  - … or the ease with which they can **imagine** the event occurring

- 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).
  - People often over-estimate the frequency of an event where recall or imagination are enhanced (dramatic, unusual events)
    - leading to **higher estimated probabilities** over what real-life data show
  - The opposite occurs for more mundane events.

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

- Consider how many risk assessments you have been on where one's memory of past events was important (e.g. where real life data were limited)?

- Consider also risk assessments on new processes or on new items of equipment – where there is little or no past experience of failure modes, deviations or complaints, etc.

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GMP Example

A company installs a new packaging line for a new tablet product

- It develops a line clearance procedure that specifically reflects the design of the room and the line itself
- Before production operations begin, the company risk assesses the line clearance controls
  - A multidisciplinary team is assembled, involving some people in the company **a long time** and others who joined more recently

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GMP Example

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- It develops a line clearance procedure that specifically reflects the design of the room and the line itself
- Before production operations begin, the company risk assesses the line clearance controls
  - A multidisciplinary team is assembled, involving some people in the company **a long time** and others who joined more recently
  - A probability of occurrence is estimated for a line clearance failure
    - taking the procedure into account, the room and equipment design, and historical data from other lines.

A heated debate arises as to what probability rating to assign to the failure mode

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GMP Example cont'd

QRM Team Member 1: A QP in the company 12 years

- In the last 10 years, she has dealt with three different marketplace complaints of rogue tablets in packs of three of the company's products
  - Significant investigations into these issues occurred
  - 2 of the 3 cases were inconclusive as to where the mix-up occurred
  - But one of the cases definitely occurred when packaging a batch at the site which she certified for release
- A recall occurred for the latter case
- Highly emotive and stressful time for the QP and other staff

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GMP Example cont'd

QRM Team Member 2: Packaging Line Supervisor

- Also in the company a long time (10 years)
- But until recently he always worked on packaging lines for parenteral products and had no involvement in the above rogue tablet complaint issues
    - He has, however, been involved in many line clearances in which challenge-type tests were periodically performed to challenge the line clearance process
    - *If the test initially failed, the procedure allowed the operator performing the line clearance to repeat the exercise*
        - *If the second attempt passed, the incident was informally referred to as a **near miss** but the test was deemed a success*
        - *If it failed, a **deviation** was raised and retraining on the line clearance procedure occurred.*
- **There had been many near miss incidents, but few deviations**

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GMP Example cont'd

QRM Team Member 3: QA Executive

- Recently joined the company straight from University
- Was involved in the QA review and approval of the new line clearance procedure
- No direct knowledge of any past line clearance issues
  - But any packaging line clearance deviations for the last 5 years site-wide are reviewed during the QRM exercise anyway

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GMP Example cont'd

Is there any potential for the Heuristic of Availability to come into play here?

Remember: With this heuristic, people often over-estimate the frequency of dramatic, unusual events over more mundane events….

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The Heuristic of Representativeness

Let's Toss a Coin 6 Times

Which combination would most people rate as the more likely?

H T H T T H

H T H T H T

H H H T T T

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The Heuristic of Representativeness

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Which combination would most people rate as the more likely?

H T H T T H

H T H T H T

H H H T T T

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The Heuristic of Representativeness

- **Reason: From one's larger experience, people know that the process of coin tossing is random**
  - The sequence HTHTTH **looks more random** than the other two!
  - It looks **more representative** of real life experience!
    - *When two events are equally likely, people tend to assign a **higher probability** to the one that **looks more representative of their wider experience***

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

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Could this Heuristic adversely affect Risk Assessments in the GMP Environment???

Consider risk assessing a deviation in a granulation process for Product A (e.g. too much granulation fluid was added)

The same deviation occurred several times in the past during the granulation of Product B and never led to any problems!

The deviation with Product A may look **representative** of those with Product B, but will the impact of this deviation be the same?

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Given all of the above, what can be done???

Are there things companies can do to counteract the adverse effects of heuristics, risk perception and other problems of subjectivity and uncertainty?

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Definitely!

Design features can be built into QRM tools to counteract all of these problems, and various other strategies can be adopted too!

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Definitely!

Design features can be built into QRM tools to counteract all of these problems, and various other strategies can be adopted too!

See Refs …. but additional research within the GMP environment is needed!

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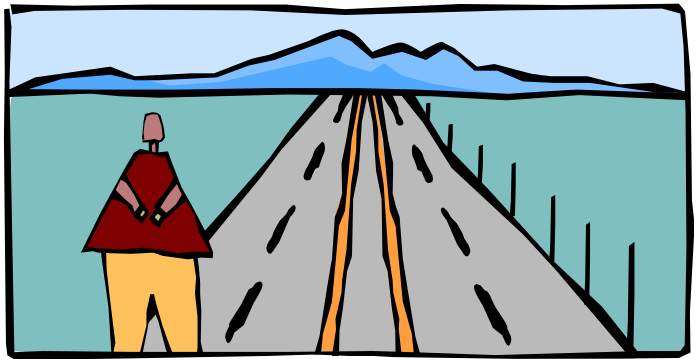
A potential QRM Roadmap for the future



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High Level Considerations…

- **The real benefits of applying QRM principles in medicines manufacturing have probably not yet been realised, in terms of:**
  - Safer medicines for patients and animals
  - More cost effective and efficient approaches to qualification, validation and change control
  - Opportunities for companies to achieve some degree of regulatory flexibility and reduced oversight, when warranted
  - Better approaches to regulation that allow regulators to spend their resources in a way that better reflects risk to patients and animals

- **This presentation set out 5 main problem areas for consideration**
  - *Work should be done in the industry to look at these areas and try to address them*

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A QRM Roadmap for the future

Short term initiatives

- ***Develop QRM tools*** that are specifically designed for the GMP environment!
  - Inspectorates have already started doing this for their own work
  - *See PIC/S Tool for Risk-based GMP Inspection Planning, 2011*

- ***Develop certification programmes*** for individuals to become SMEs in QRM

- ***Upskill ourselves*** to move towards more science-based QRM work:
  - e.g. *Develop strategies to offset the factors that introduce Subjectivity and Uncertainty into QRM*
    - *Human Heuristic, Risk Perception issues*
    - *Explore whether the tools* shown to be highly effective in other fields for calibrating SMEs for probability estimation may work in the GMP environment

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Roadmap cont'd

Medium term initiatives

- ***Extend the application of QRM beyond current activities to other key areas***
  - e.g. Packaging and Labelling Management - many recalls every year
    - How often are these processes risk assessed and validated?

- ***Develop expertise in assessing where 'complexity' is most significant***
  - And focus QRM resources at those areas!
  - **Example:**
    - Ensuring products are always MA-compliant in a global pharma company is a major challenge
    - The systems supporting this are usually very ***complex***
    - ***Potentially a very high risk area.***

See PDA Journal of Pharm. Science & Technology, May/June 2012, for a discussion in this regard

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Roadmap cont'd

Medium term initiatives, cont'd

- Develop methods to formally ***measure the*** **effectiveness** of QRM tools & approaches
  - Learn from research work in other fields how this can be done

    - If possible also, develop ways to assess the ***cost per unit of risk reduction*** achieved via QRM work.
    - NASA has done some work in this area, via its *Risk Balancing Profile Tool*
    - Develop ways to assess the ***benefit per unit of risk reduction*** achieved via QRM work, in terms of benefits to patients and industry

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Roadmap cont'd

Longer term initiatives

- Identify which applications of QRM in the GMP environment lend themselves towards **more quantitative approaches** and work to further develop that area
  - e.g. See Tidswell 2006, *Quantitative Risk Modelling in Aseptic Manufacture*

- Develop formal ***black-belt type training programmes*** for QRM SMEs on:
  - *Probabilistic Risk Assessment techniques*
  - *Quantitative Fault Tree Analysis, Quantitative Event Tree Analysis*
  - *Monte Carlo Simulations, Decision Analysis, Uncertainty Analysis*
  - *Risk Modelling Tools*

- Put in place ***Validation Programmes for QRM tools and procedures***
  - To provide a high level of assurance that the outputs of QRM exercises are scientifically valid!

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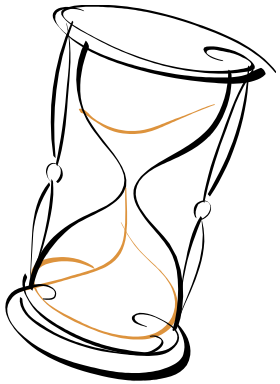
Final Thoughts…

- ***The evolution of QRM in the GMP Environment will take time!***
  - ICH Q9 is now 7 years old
  - Other industries such as Nuclear Power and Aeronautics are much more advanced in their use of Risk Management
    - but they took 40 years to get there!!
    - and they still have not always gotten it right!



We're clearly not there yet, and while we're on the right road, there is still a lot to do!

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