Introduction

26 years in the pharmaceutical industry which includes 4 in API and 2 in Excipient manufacture:

Solid dose, liquids/creams/ointments, p-MDI, SVP, transdermal

23 years as a lead auditor

20 years in supply chain quality management

Degree in Chemistry, 2 years study with DBA to become a QP

MSc in Pharmaceutical Quality and GMP

8 years as a Qualified Person, 2 years releasing IMPs

5 years as a QP Assessor

Fellow of the Royal Society of Chemistry / Chartered Chemist

Member of the Chartered Quality Institute. Chartered Quality Professional
Qualified Person

The QP is essential to the safe control of medicines and needs to have extensive training and in-depth critical understanding of all the aspects associated with manufacturing and distribution.

QPs are responsible for undertaking their duties in accordance with a professional Code of Practice. The aims and objectives of the Code of Practice are to provide operational guidelines for carrying out the functions of the QP in accordance with Article 56 of Council Directive 2001/82/EC and/or Article 52 of Council Directive 2001/83/EC.

Annex 16 of the “Orange Guide” requires that for every batch a QP:

- Confirms compliance to MAA / PSF
- Confirms compliance to GMP and national law
- Certifies in a register
The MHRA and Veterinary Medicines Directorate (VMD) require the Royal Pharmaceutical Society of Great Britain, the Society of Biology, and the Royal Society of Chemistry ('Joint Professional Bodies') to assess the eligibility of their members for QP status.

Each professional body has a Panel of Assessors with a Chairman who review a 20 page application then ask knowledge and scenario based questions against a Study Guide for approximately 90 minutes.

Although it is the opinion of the professional body concerned whether a member meets the statutory requirements to become a QP, it is up to individual companies to satisfy themselves of the suitability of any individual applicant for a particular post. MHRA or VMD are ultimately responsible for determining who can be named as a Qualified Person on a particular Manufacturer's Licence.
Objectives

Provide an overview and summary of Risk-based Management
Explain the benefits of this approach for all
Discuss GMP expectations
How should you aim to implement Risk Management?
What are the key points to consider / stumbling blocks to avoid?
Where does QRM feature in EU Inspection trends?
What have QA to do?

Quality Assurance need to align all of their processes with the risk management guidance of ICHQ9

First of all, understand how Risk Management works

Decide what specific goals you want to achieve

Train the relevant people in the relevant risk assessment tools

Keep it simple - implement

Then repeat the cycle, evolve, integrate the process and repeat in another area
Warning!

There is ‘the potential for quality risk-management to degenerate into a non-value added exercise of identifying non-critical, improbable, low risk scenarios indefinitely’. (J. Orloff, *Pharm. Technol.* **35** (2) 38–40 (2011)).
What is a Risk? .... Definition

This risk can best be expressed by the question:
- “What if the project/activity/function fails to perform as expected?”

Otherwise a risk is simply defined as a situation which would lead to negative consequences.

**Risk = Severity (of event occurring) Vs likelihood (of event occurring)**

The risk is then managed by
- Treat
- Transfer
- Terminate
- Tolerate
Do we recognise Risk?

Is avoidance just luck?
Our knowledge?
Our awareness?

Decision making?
Risk-Based Management

FDA GMPs for the 21st Century – A Risk-Based Approach
ICH Q9
Alignment with other industries / other quality standards
PDA Guide 44 Risk Assessment of Aseptic Processes
PQG Guide to Supplier Risk Management
MHRA / FDA inspections based on this principle
  • MLX345 Risk Based Inspection program in UK
ISPE Good Practice Guide « Applied Risk Management for Commissioning and Qualification »
Recent issues

Contamination e.g. glycerol, heparin
Recalls
Counterfeiting e.g. Lipitor in UK

NEED TO AVOID THESE ISSUES TO BE HEALTHY BOTH IN TERMS OF PATIENTS AND FINANCIALLY
Benefits to companies

Value adding compliance
More effective prioritisation
More efficient use of resources
Proactive not reactive → ongoing risk reduction
Lower risk to business and lower overall cost
Improved customer satisfaction (patient / regulator / purchasing company)
Safer medicines
Quality Risk Management:

- Should either drive, or be consistent with, all decisions and activities
- **Must be proactive** ... not a justification for poor GMP or bad decisions previously

View of the Regulators?
Risk Management Strategy

Use a structured approach
Must cover the life-cycle of products
Must be pro-active
Must be reiterative
Link into the QMS
Use those trained in tools other activities
Simple Risk Management Process

Specific risks identified are agreed and documented.

Data is refreshed and entered every 6 months.

Risk is evaluated by the scorecard’s macros to provide a rank list of risk total scores.

A level is set of what is acceptable and anything above this requires a strategy of how to mitigate the risk.

Proposals are communicated to the Quality Steering Team.

A formal review starts the process again.
Implementation - Getting started is the hardest part
Known issues:
- Critical Control Points
- Deviations
- Complaints
- Audit findings
- Near misses
- Your customer’s products e.g. route of administration, sterile, non-sterile
- Key Performance Indicators
  - *If these don’t measure risks then they should!*
Risk Identification

Potential issues:
- Brainstorming
- Process mapping
- Fishbone / Ishikawa / Cause & Effect diagrams
- FMEA failure mode steps
- Trend analysis e.g. Pareto, Cusum, Cpk, etc
- Reliance on key personnel (expertise, knowledge)
Risk Identification

Knowledge in the public domain:
- News of fires, floods, earthquakes etc.
- Raw material availability e.g. crop failures
- Changes in legislation
- Regulatory findings
- Changes: site of manufacture, closure of site, takeovers,

*Do you have a process to collect this information and react to it?*
Risk Identification – Brainstorming using 5 M’s

- **Material**
  - Raw materials, intermediates, products, inventory
  - Data, numbers, information, contract, 2nd source

- **Machine**
  - Equipments, tools, Computers
  - Complexity, change-over, scrap

- **Manpower**
  - Operators, supervisors, managers
  - Technicians, employees, Skills, Training

- **Method**
  - Procedures, regulatory requirements, costs
  - Instructions, operating guide, control, productivity

- **Environment** (Medium)
  - Workshops, stores
  - Offices, Atmosphere

---

Risk Identified - Environment (Medium)
RISK IDENTIFICATION METHODOLOGY

Risk / ‘hazard’ identification: using the 5Ms methodology:
Simple & systematic, not too heavy

Brainstorming in Multidisciplinary team
Risk Analysis

Which Tool to use?

ICH Q9 gives lots of alternatives but does not specify which to use or in which circumstances to use it.

Sometimes this is the most difficult and confusing part of Risk Management …

- Simple? Fit for purpose?
- Ranks / differentiates risks?
- Accurate? Or based on assumptions?
- Try it then evolve!
Risk Analysis

Different techniques can be used throughout the lifecycle:

Basic attributes / Qualitative

Attribute Scoring

Quantitative Analysis
Qualitative Risk Assessment

Example from clinical development:

<table>
<thead>
<tr>
<th>Category of Risk</th>
<th>Category of Risk</th>
<th>Category of Risk</th>
<th>Category of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific</td>
<td>Molecule Associated</td>
<td>Clinical Nature</td>
<td>Risk</td>
</tr>
<tr>
<td>Validation level</td>
<td>Molecular Properties</td>
<td>Clinical Development</td>
<td>Intellectual Property</td>
</tr>
<tr>
<td>Chemical Tractability</td>
<td>Antibody Entity</td>
<td>Translational Biology</td>
<td>Commercial View</td>
</tr>
<tr>
<td>Biological Tractability</td>
<td>Process Manufacture</td>
<td>Regulatory</td>
<td></td>
</tr>
<tr>
<td>Pharmacological Tractability</td>
<td>Synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism Related Safety</td>
<td>PK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacological Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Risk Rating Scales – Example 2 Corporate

### Impact

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Description</th>
<th>Sales / Reputation</th>
<th>Duration</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Catastrophic</td>
<td>&gt; 500M / or</td>
<td>Irrecoverable</td>
<td>Collapse of market capitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete loss of confidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical</td>
<td>&lt;500m / or</td>
<td>Recoverable in the long term (i.e. 24-36 months)</td>
<td>&gt; 50% reduction in market capitalization, accession liquidity reserve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sustained loss of confidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>&lt;100m / or</td>
<td>Recoverable in the short term (i.e. 12-24 months)</td>
<td>&gt;30% reduction in market capitalization, minimal operating cash flow, maintenance of liquidity reserve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate loss of confidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>&lt;30m / or limited to minor / short term loss of confidence</td>
<td>Temporary (i.e. less than 12 months)</td>
<td>Miss forecast and or budget</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td>&lt;10m</td>
<td>Relatively insignificant impact on the achievement of business objectives</td>
<td></td>
</tr>
</tbody>
</table>
# Simple Quantitative Risk Assessment

## Risk Ranking

<table>
<thead>
<tr>
<th>Potential Risks (Risk Identification)</th>
<th>Risk Analysis</th>
<th>Risk Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability</td>
<td>Severity</td>
</tr>
<tr>
<td>Risk 1</td>
<td>Low (1)</td>
<td>High (3)</td>
</tr>
<tr>
<td>Risk 2</td>
<td>Med (2)</td>
<td>Low (1)</td>
</tr>
<tr>
<td>Risk 3</td>
<td>Med (2)</td>
<td>Med (2)</td>
</tr>
<tr>
<td>Risk 4</td>
<td>Med (2)</td>
<td>High (3)</td>
</tr>
<tr>
<td>Risk 5</td>
<td>Low (1)</td>
<td>Low (1)</td>
</tr>
<tr>
<td>Risk 6</td>
<td>High (3)</td>
<td>High (3)</td>
</tr>
<tr>
<td>Risk 7</td>
<td>Low (1)</td>
<td>Low (1)</td>
</tr>
</tbody>
</table>

### Risk Evaluation Score

- Increasing Probability of an error or system failure:
  - 1 (Low), 2 (Medium), 3 (High)

- Increasing Outcome Severity, as a result of error or system failure:
  - 1 (Low), 2 (Medium), 3 (High)
**Quantitative Risk Assessment: FMEA Example**

Failure Mode and Effects Analysis

**EXAMPLE FMEA table:**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Failure Mode</th>
<th>Effect of failure</th>
<th>Severity</th>
<th>Potential Cause(s)</th>
<th>Occurrence</th>
<th>Current Controls</th>
<th>Detection</th>
<th>Risk Score</th>
<th>Recommended Action</th>
<th>Severity</th>
<th>Occurrence</th>
<th>Detection</th>
<th>After Action Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The FMEA procedure

Define failure modes

Define process
Define steps

Define effects

Define a team

Evaluate risk

Define “corrections”

Acceptable

Define “changes”
FMEA Tree - Onion

- A layered approach is highly recommended as FMEA can get complex.

- FMEA are like ONIONS/LAYERS.
  - Each layer is more detailed
  - Each layer is closer to the root cause

  ➡️ But ... do too many, and you will cry.

Full FMEA is not simple or quick, therefore where you can, use a more qualitative approach
### SUMmARY

**SUPPLIER RISK EVALUATION**

<table>
<thead>
<tr>
<th>Supplier Name</th>
<th>Risk Total</th>
<th>Supplier Interface Contact / Responsible Person</th>
<th>Supplier Number</th>
<th>Supplier Location</th>
<th>Commodity / Supplier Type (Manufacturer, Service, Agent / Distributor)</th>
<th>Scored By (BR, BU, SLH, ROC, etc.)</th>
<th>2008 Total Spend in Euro</th>
<th>Sourcing Strategies / Supply Agreement &amp;/or Quality Agreement</th>
<th>Continuity of Supply</th>
<th>Quality</th>
<th>Delivery</th>
<th>Compliance: Audit Rating</th>
<th>RPN Score</th>
<th>Absolute RPN Risk rating (H,M,L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>142</td>
<td>CMO</td>
<td>BR</td>
<td></td>
<td></td>
<td>6,120,000</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>15</td>
<td>CMO</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Example 2</td>
<td>105</td>
<td>Laboratory</td>
<td>BR</td>
<td></td>
<td></td>
<td>98,000</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Laboratory</td>
<td>105</td>
<td>105</td>
</tr>
</tbody>
</table>

#### Business team together decide on specific risks and weight these to reflect the level of risk

- **The Risk Total score is calculated**
- **How to reduce the Risk Total Score is summarised here**
- **Some of this data might not be easily available and systems need to be developed !!!**

---

**Quantitative Risk Assessment e.g. C&E Matrix**

- **Weighting**
  - Weighted rating of risk:
    - 9 = extremely important
    - 3 = moderately important
    - 0 = low importance

- **Weight**
  - 6, 10, 11, 4, 7

- **Distribution**
  - 1st Quartile
  - Median
  - 3rd Quartile
  - Maximum

- **Distribution**
  - #VALUE! 1st Quartile
  - #VALUE! Median
  - #VALUE! 3rd Quartile
  - #VALUE! Maximum

- **Where is the data?**
- **Needs to come from both Purchasing and Quality**
- **Where is the data?**
- **Where is the data?**
- **Do the Compliance group have a system for scoring audits?**
- **#VALUE! #VALUE!"
Quantitative Risk Assessment (continued)

**IMPACT ASSESSMENT**

<table>
<thead>
<tr>
<th>Relative RPN Risk Rating (H,M,L)</th>
<th>Ability To Detect (H, M, L)</th>
<th>Sourcing Situation (Spend, Leverage)</th>
<th>Strategic Importance</th>
<th>Regulatory Impact of Change</th>
<th>Impact Assessment Total</th>
<th>Significant Changes/Compliance History</th>
<th>Finished Product or Service</th>
<th>Spend (Impact on UCB Business)</th>
<th>Time Since Last Audit</th>
<th>Audit Risk Total</th>
<th>Material Classification</th>
<th>Audit / Vendor Assurance Comments</th>
<th>Date of Last Audit (dd-mm-yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;50K Euro</strong></td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>126</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>192</td>
<td>3</td>
<td>247</td>
<td>#VALUE!</td>
</tr>
<tr>
<td></td>
<td><strong>&lt;50K Euro</strong></td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>126</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>192</td>
<td>3</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td><strong>&lt;250K Euro</strong></td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>126</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>192</td>
<td>3</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td><strong>&gt;1000K Euro</strong></td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>126</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>192</td>
<td>3</td>
<td>247</td>
</tr>
</tbody>
</table>

Weightings used in the calculation of Audit Risk total are specified in the formula.

**AUDIT / VENDOR ASSURANCE**

- **3 = Significant Impact**
  - Finished Product (CMO) or APIs
- **9 = Finished Product (CMO) or APIs**
  - >1000K Euro
- **5 = Major Services (Labs or Engineering) / Software Audits**
- **3 = >250K Euro**
  - Last audit between 2 and 3 years ago
- **1 = Slight Impact**
  - Excipient / Major Component
- **3 = >50K Euro**
  - Last audit between 1 and 2 years ago
- **0 = No Impact**
  - Minor Component or 0 = Minor Services
  - 0 = >50K Euro
  - Audited less than 1 year ago

How to decide whether to perform a planned audit?

What is the potential impact of change?

---

**Note:**

- IMDG: International Maritime Dangerous Goods Code
- CMO: Contract Manufacturer and Oligonucleotide
- CBE: Change of Batch Estimation
- CM: Contract Manufacturer
- QM: Quality Management
- UCB: United BioPharma
- #VALUE!: Indicates a cell that is empty or has an error.
See the “big picture” …

Focus too much on one source of information……

And you might just miss something important!
WARNING

The output prioritises your future actions. If you get this step wrong
  • It means that you may not work on the most important issues
  • You will waste time, resource and may still end up ‘fighting the fire’ you were trying to avoid
  • You will have to go back and address the issue(s) you missed (i.e. prioritised incorrectly/inaccurately)

CHECK your output:
  • Does it feel right?
  • Does it make sense?
Risk Evaluation

A sorting or ranking process How do you decide where to draw the line?

- Over time (as risks are reduced and systems for data collection are introduced/refined) risk scores may reduce
- Often part of the tool e.g. FMEA
- Leads to a clear decision and action

QUESTION:

Is it the risk score that is important OR is it your interpretation of the data and the decision you make that is the key step?
Risk Evaluation using Pareto Analysis

Where you evaluate as the cut off point (acceptable / not acceptable) is up to you to defend to the FDA / EMEA.
Risk Mitigation strategies

Mitigation strategy and actions based on the "4 T’s":

TREAT a risk to prevent it occurring or reduce its potential impact.
  • Have processes in place that improve the control effectiveness.
  • The amount of effort to control risk should be proportional to the significance of the risk

TRANSFER the risk to someone else
  • Risk financing, insurance, contracting out, etc.
  • Some of the impact of the risk is transferred, not the responsibility the business has for managing the risk.

TERMINATE the risk – i.e. stop doing whatever it is that is exposing the business to the risk.

TOLERATE the risk after deciding that the risk has been reduced to an acceptable level.
Risk Reduction

High risks need to be reduced
Risk Mitigation Strategies need to be formally defined and documented
Resource, cost and time estimates are needed to enable approval
Vulnerabilities and contingency plans may be needed to run in parallel

- Keep actions SMART
### Risk Mitigation Plan Template

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Area</th>
<th>Ownership &amp; Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total score</th>
<th>Before mitigation:</th>
<th>After mitigation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitigation Plan Strategy</th>
<th>Timelines and deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barriers:</th>
<th>Needs:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk Acceptance

Determines when inaction is appropriate, justified and agreed

Risk acceptance is not automatic nor implied

It is an output of the risk evaluation proposal that is communicated to stakeholders for their input
Risk Acceptance

A critical step that requires formal Senior Management signature

- *Needs to be auditable*
- *Anyone can propose acceptance of a risk but only the Head of Department makes the decision / is accountable*

This Risk Acceptance is timebound since a periodic review is routinely required

- The risk needs evaluating every X months
Risk Communication

Takes place throughout the process of Risk Management

Needs formalising at end of process every X months

Tell management? Yes
Tell customers? Possibly
Tell suppliers? Sometimes
Tell regulators, patients, media etc.? Rarely / Unlikely

How to communicate?
- Dashboard
- Boston box
- Report
Risk Communication

Development Portfolio - Risk Return Bubble Diameter = Peak Sales

NPV if successful (€M) vs. Probability of Success (%RANPV/NPV)
Risk Review

Periodic assessment that the output of Risk Management process hasn’t changed

Reactive assessment when new and potentially significant information is identified
Risk Management Process ... again

- Initiate Quality Risk Management Process
  - Risk Assessment
    - Risk Identification
    - Risk Analysis
    - Risk Evaluation
  - Risk Control
    - Risk Reduction
    - Risk Acceptance
  - Output / Result of the Quality Risk Management Process
- Risk Review
  - Review Events
- Risk Management tools
Chapter 1 of the EU GMP guide states that ‘...the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk’. Companies can get this wrong e.g. too little of one or all of these:

- Strategy not linked clearly to objectives
- Responsibilities not defined
- Key departments ‘opt-out’ / do not contribute
- System gaps not filled i.e. too reliant on opinion and accurate data not available
- Risk Mitigation actions not completed / no successful
- Considered a ‘one-off’ exercise i.e. no review
- Communication to stakeholders & customers not performed / too late / too little
How to evolve your current RM approach?

Learning opportunities should be captured
Precision of data can be improved
Qualitative tools can be made quantitative in order to provide greater accuracy and discrimination
Quantitative tools can be made slicker
The ‘umbrella’ can cover the whole business and all functions
FDA Globalisation Act will drive suppliers to be integrated into companies’ "Quality Risk Management Plans"."
Supplier Management – a key application

Risk Management

Selection
Evaluation
Monitoring
Improvement
Funnel down …

• Use available tools to understand your processes, improve processes / products and reduce risks e.g.

- **Measure**
  - Process Map, C&E Matrix, MSA, Cpk

- **Analyze**
  - FMEA, Multi-vare

- **Improve**
  - Design of Experiments

- **Control**
  - SPC, Fail-safing, Control Plans
PQG Guidance

“A Guide to Supply Chain Risk Management for Suppliers to the Pharmaceutical Industry”

Bridges the gap between ISO and ICH approaches

Provides additional guidance and examples specific to supply chain for implementing ICH Q9 et al

Published 2010

An electronic version available on PQG website
Risk Management Guide issued to support ICH Q9 (mainly for Development QA)
Provides a roadmap for a migration from traditional qualification practices towards science and risk-based approaches.

Practical methods for applying QRM to equipment, systems and facilities.

Concepts to “cross the bridge”
- Introduce Good Engineering Practice (GEP)
- Use product and process understanding as its basis
- Focus on achieving suitability for intended use
- Refocus the Quality Unit
- Use QRM as the basis for the extent of verification activities
Focus being given to key audience by the Head of the MHRA, referring to QRM:

“QbD … based on sound science and quality risk management”

Product Knowledge and Process Understanding requires acceptance criteria based on patient needs and risk assessment

Quality Attributes become critical when there is a probable or actual impact on safety, quality and efficacy
ICH Q11 – development and manufacture of Drug Substances 1st May 2012, Step 4

Section 8.1:

- Quality risk management can be used at different stages during process development and manufacturing implementation. The assessments used to guide and justify development decisions (e.g., risk analyses and functional relationships linking material attributes and process parameters to drug substance CQAs) can be summarised in section 3.2.S.2.6.

Section 10.2 (case study)

- **Iterative** quality risk assessment

- Risk Ranking Histogram (i.e. a pareto chart)

- Risk should be reassessed throughout the lifecycle as process understanding increases

- Changes in level of risk (from data / experience) may lead to updates of the dossier / filing
Required by 2011/62/EC Falsified Medicines Directive requires that the holder of a manufacturing authorisation shall ensure that excipients are suitable by ascertaining what the appropriate GMP is on the basis of a formal risk assessment.

21CFR 314.94(a) and 331.1(e) require that NDAs show (excipients) are safe and do not affect the safety or efficacy of the drug product.

An appropriate Risk Assessment Model is being worked on by IPEC, PQG and EFPIA
PDA Technical Report No. 54 (TR 54) Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

- provides detailed guidance for the application and implementation of quality risk management (QRM) principles throughout the product lifecycle
- Intended to present information that can be helpful on how to implement QRM
- emphasizes QRM application during commercial manufacturing and integrating QRM into the pharmaceutical quality system.

PDA Technical Report No. 58 (TR 58) Risk Management for Temperature-Controlled Distribution

- assist stakeholders in the supply chain to preserve the quality, safety and efficacy of these products during distribution
- serves to complement ICH Q9 guideline (Quality Risk Management) and previously published PDA Technical Reports No. 39, 46, 52 and 53 by assessing, controlling and reviewing risks in systems and processes during distribution.
To contribute to a harmonised approach for inspection of QRM in industry

This document …reflected the current state of the art

QRM is not intended to be a barrier to technical innovation or the pursuit of excellence

QRM should not be an isolated System of QA, it should be fully embedded into the QA or QM-System.

gather evidence that:

- The use of QRM is planned;
- The key elements of the QRM program are clearly defined and documented;
- Senior Management provides visible support to QRM;
- Key outcomes of QRM are communicated to and acted upon by Senior Management

Review of residual risk and improvement of QRM processes
largely based on ICH Q9 but the WHO draft presents detailed explanations as well as detailed provisions e.g. at least one "Risk Review" should be signed by quality assurance. Verification of the QRM processes and specific QRM applications should be performed by a third party. In addition, a risk matrix in a tabular form describes examples and risk management tools (methods, description of the methods, potential applications). A publication of the "Manufacturing Technology Committee" from the "Pharmaceutical Quality Research Institute" (PQRI-MTC) dated from 2008 is explicitly quoted for the examples presented.

COMMENTS

- a flowchart is recommended to be able to perform the risk-based analysis of a process. In the draft, the use of a flowchart is described as "if needed" and not really binding ("may use").

- inconsistencies exist with regard to responsibilities. E.g. the signature of QA is required for "Risk Review" but the responsibility is not mentioned in the respective chapter 3.2.

- regarding the use of QRM for qualification activities (chapter 3.4), the document concedes that often only IQ, OQ, PQ are being performed. In this context, DQ plays a decisive role in the qualification life cycle and should be therefore integrated in the QRM process - except for the qualification of older facilities.
Inspection Trends

Italian (AIFA) require risk matrix for manufacturing site risks to be catalogued and scored

Danish require raw materials to be held in quarantine until a satisfactory audit of the supplier is performed

MHRA website states “The legislative focus for risk-management systems is on forward planning that is dynamic and proportionate to risk.

There is also a focus on methods to try to monitor the effectiveness of any risk-minimisation measures. 
PSURs are retrospective benefit-risk assessments.”

MHRA Vigilance Risk Management of Medicines Division
Inspection Trends

Deficiency Data Review 2012 – 16 out of 670 Critical or Major findings due to Risk Management failings

http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con149837.pdf

1. Investigation of anomalies
2. Quality management (Change Control)
3. Corrective action/preventive action (CAPA)
4. Complaints and Product Recall
5. Quality management
6. Supplier and Contractor Audit
7. Contamination, Chemical/Physical – Potential For
8. Documentation – PSF/Procedures/Technical Agreements
9. Documentation – Manufacturing
10. Process Validation
Clearer guidance on exactly *what* and *how* is coming out

More examples of applications / best practice

Better knowledge from regulators = tougher & more observations

Not a one-off … needs to be iterative, repeated and a life-cycle approach

Value adding, especially if you move from qualitative to quantitative

Are your people *fully* trained? Do you have experts (or just people who talk a lot)?

Are you doing it because you have to or because it makes real and lasting improvements for your company and its patients?
Key point to remember

QRM is about avoiding large risks through an ongoing process of risk awareness and reduction

- Avoid deaths, recalls, companies going bust
- Supports improvement / investment