ICH Q9
Quality risk management (QRM)
Challenges and opportunities
A regulatory perspective

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Risk management is not a new concept in EU GMP or EU approach to assessment of quality dossiers

“Risk” concept mentioned 90 times and in 20 documents in EU GMP legislation and guidance

Also used frequently in EU (8) [including ICH (12) Quality guidelines]

In addition “unless otherwise justified” concept frequently used in both GMP and Quality guidelines
Current European requirements for risk assessment/ control

Examples in quality field (guidelines):

- Currently working on a paper
- Development Pharmaceutics: annex on sterilisation
- ICH Q6A: polymorphism (decision tree for identification and qualification aimed at managing risks)
- EU Note for guidance on parametric release (requires “a risk analysis of the sterility assurance system”)
- EU variations regulations: tries to identify variations/changes according to degree on risk
Current European requirements for risk assessment/ control

Examples in quality field

**Sterilization : decision tree (aqueous solution)**

- **Can the product be sterilized by moist heat at 121 °C for 15 minutes**
  - No
  - Can the product be sterilized by moist heat with Fo ≥ 8 minutes achieving SAL of ≤ 10⁻⁶
  - No
  - Can the formulation be filtered through a microbial retentive filter
    - No
    - Use pre-sterilized individual components and aseptic compounding and filling
  - Yes
  - Use autoclaving at 121°C for 15 minutes
    - Yes
    - Use moist heat with Fo ≥ 8 minutes
    - Yes
    - Use a combination of aseptic filtration and aseptic processing
Current European requirements for risk assessment/ control

Examples in quality field

Evaluation of:

- Impact of proposed changes
- Impact of deviations
- Impact of “out of specification” results

EMEA Process Analytical Technology (PAT) team involving assessors and GMP inspectors
Current European requirements for risk assessment/ control

Examples in GMP field

Annex 15: Qualification and Validation

Scope:

- Principles of validation to be applied in manufacture
- Manufacturers to identify what validation work is necessary to control the critical aspects of their operations

“A risk assessment approach should be conducted to determine the scope and extent of validation”
Current European requirements for risk assessment/ control

Examples in GMP field

- Routinely used in evaluating quality product defects
- EU “Rapid Alert System” classifies regulatory actions based on relative risks
- Grading/evaluation of inspection findings – critical, major, minor – also based on relative risks
- Regulatory decision making on acceptability of manufacturing sites
- Decision by GMP inspectorate as to appropriate resources needed to be devoted to an inspection
Current European requirements for risk assessment/ control

Examples in GMP field

- Inspections in the context of Plasma Master File certificates: risk based approach outlines
- Inspections of sites in Non-EU countries - elements of a risk based approach
- Qualified Person (QP) discretion document in the case of minor unplanned deviations
Current European requirements for risk assessment/ control

Examples for GMP inspectors

“Inspection staff are expected to have appropriate qualifications, training, experience and knowledge of the pharmaceutical inspection process. They also need to be able to apply an appropriate degree of risk assessment.”

Extract from EU Quality System framework for GMP inspectorates
Status and implications of the ICH Q9 guideline

Status of Q9

- Adopted in November 2005
- Publication by Commission as Annex 20 foreseen
- QRM implementation groups established at the EMEA level in GMP and quality guideline area
Status and implications of the ICH Q9 guideline

Implications of Q9

- Impact on some existing GMP guidance documents is under consideration introducing the concept of QRM (i.e. in chapter 1 (part one) and section 2 (part two) of the EU GMP guide, ....)
- Similarly for EU Compilation of Procedures (Guidance for GMP inspectorates as for training, inspection planning, quality system…)
- Training of regulators necessary
- Impact on quality guidelines being considered by QWP
Implications of the QRM

In the submission and assessment process

QRM (may be Q9) supports presentation of scientific arguments:

- For proposals in the submission
- For answering subsequent questions and proposals the reviewers may raise
- When linked with “Pharmaceutical development” (ICH Q8) it might avoid the need for such questions by assessors
Implications of the QRM

In the GMP field

ICH Q9 is not mandatory but QRM will be via a modification of the EU GMP guide. ICH Q9 will be presented as a possible model (annex 20).
Implications of the QRM

How can QRM activity be inspected?

- If the company explains that ICH Q9 has been used as reference for establishing the QRM, it will be used by inspectors.
- If not, inspectors might review:
  - Whether the quality risk management performed is integrated in the Quality System of the organization
  - Traceability, transparency
  - How was the decision made?
  - Was a (risk) problem / question defined?
  - Did the process performed answer this question?
  - Were the appropriate functions allocated to all teams?
  - Were the right documents recognized?
  - Was the decision based on scientific knowledge?
Implications of the QRM

How should QRM outcomes be reviewed and inspected?

☞ Competent authorities should check if the science used for the quality risk management process is acceptable
☞ Competent authorities check if the risk questions has been appropriately defined
☞ Competent authorities may not accept the outcome of the risk management process if it is not satisfactory in terms of science (i.e. in assessing a quality defect => withdrawal of a product)

Debate and seek agreement on science
Implications of the QRM

SOP on planning of GMP inspections (reflection)
Inspection frequency and depth should be adapted subject to (and for example):

- Examination of a site master file (if available)
- Review of the products manufactured by the company
- Review of the reports from previous inspections
- Review of the follow-up actions (if any) arising from previous inspections
- Review of product recalls initiated since the previous inspection
  an examination of relevant product defects notified since the previous inspection
- Review of the analysis of any samples analyzed by the Competent Authority since the previous inspection
- Etc …
## Implications of the QRM

### SOP on planning of GMP inspections (reflection)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Description</th>
<th>Inspection intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor compliance level</td>
<td>The last inspection revealed major or critical deficiencies $\geq 6$</td>
<td>$X - 1$</td>
</tr>
<tr>
<td>Acceptable compliance level</td>
<td>The two last inspections have revealed no critical deficiency and less than 6 major deficiencies $2$</td>
<td>$X$ (= regulatory interval)</td>
</tr>
<tr>
<td>Good compliance level</td>
<td>The two last inspections have revealed no critical and no major deficiency</td>
<td>$X + 1$</td>
</tr>
</tbody>
</table>
Implications of the QRM

SOP on planning of GMP inspections (reflection)

- The objectives of Competent Authorities is to optimize the inspection resources.
- Review Frequency and depth of inspection based on QRM are still on discussion in a dedicated EWG (France, Germany, Denmark, Sweden, the UK, the EU Commission and the EMEA).
- Using both QRM and PQS (Pharmaceutical Quality System which could be ICH Q10), confidence between industry and GMP inspectors should be increased with an impact on inspection frequency and depth.
Vision of an ideal world

An enhanced drug substance and drug product development together with an implemented Quality Risk management within the framework of a Pharmaceutical Quality System:

- Risk reduction and better control
- Lower risk operations
- Innovation
- Facilitation of continual improvement
- Optimized change management processes

May challenge many traditional pharmaceutical approaches
Ultimate aim is to improve the quality of pharmaceuticals delivered to patients
Conclusion

Q9 should:

- allow an international harmonization of QRM
- facilitate a better comprehension between stakeholders as QP, regulatory affairs, producers belonging to companies and assessors, GMP inspectors, the EMEA, the EU Commission, Heads of Agencies
- be used both by industry (with big challenges for small and medium companies) and Competent Authorities (CA)
- allow a better use of resources
- increase confidence between industry and CA
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