European Medicines Agency

Quality Risk Management – an EU regulator's perspective

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Contents

- What is Quality Risk Management?
- European legal basis for risk management
- Current European requirements for risk assessment/control
- Current European initiatives on Process Analytical Technology
- The role of the ICH Q9 Guideline
- Perspectives for the future

What is Quality Risk Management?

- Proposed ICH Q9 definition:

"Quality risk management is a systematic process for the identification, assessment and control of risks to the quality of pharmaceutical products across the product lifecycle."

Why is Quality Risk Management important?

Any decision–making process about risks to product quality involves risk management to a greater or lesser extent.

But no common understanding about what quality risk management means and how it is applied in the pharmaceutical environment.

European legal position

- Directive 2003/94 (legal basis for EU GMP guide)
- EU GMP guide (chapters and annexes) specific reference to risk analysis and risk assessment

European legal position- 2

- 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

European requirements for 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

Examples (EU GMP guide)

- Quality Management- chapter one

"Manufacturers must ensure that medicinal products .. are fit for their intended use and do not place patients at **risk** due to inadequate safety, quality or efficacy"

Fundamental basis for quality risk management – patient safety- confirmed by ICH Q9

Examples (GMP guide)

- Personnel- chapter two

"The responsibilities placed on any one individual should not be so extensive as to present any **risk** to quality"

Principle: Avoid risks to quality by properly assigning staff to tasks

Examples (GMP guide)

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**"

Examples (Quality Guidelines)

- ICH Q3A and Q3B: Impurities
- 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 EU regulatory activities in the risk management area- 1

- Routinely used in evaluating 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 site
- Decision by GMP inspectorate as to appropriate resources needed to be devoted to an inspection

Current EU regulatory activities in the risk management area- 2

Evaluation of :

impact of proposed changes

Impact of deviations

Impact of “out of specification” results

Current EU activities in the risk management area- 3

- Process Analytical Technology
- Contribution to ICH Q9: Quality risk Management
- Other “hot topic” discussions:
- 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
- Discretion of the Qualified Person (EU concept of responsible person for manufacturing) in the case of minor deviations

Process Analytical Technology (PAT)

- Concept of PAT based on identification and control of risks during the manufacturing and control of a medicinal product
- EU working on defining a regulatory approach to use of PAT by companies
- EU PAT team set up in 2003

Process Analytical Technology (EU regulatory background)

- 2003 – Presentations from companies to joint GMP inspectors/Quality Working Party group
- End 2003 – Agreement to establish specific PAT team within EMEA: 4 inspectors, 4 quality assessors, chair of QWP, Chair of ad hoc GMP inspectors, representative from BWP joined for meeting 3
- 5 meetings in 2004
- 1 joint training session assessors/inspectors

Process Analytical Technology
Mandate of EU team

A forum for dialogue and understanding between QWP and ad hoc GMP inspections services to prepare a harmonised approach in Europe on assessment of applications and inspections of systems/facilities including new approaches to manufacturing and control of active substance,medicinal product, packaging material etc. (PAT)

Process Analytical Technology (activities of EU team to-date)

- Open invitation for companies to provide “mock submissions”
- Challenged companies to submit “minimum information”
- Distinguish between information in dossier and information (available on-site)
- Less straightforward than it might seem
- Concepts seem easier than translation into practical applications

Potential Implications of Q9 for EU

- Harmonised approach for risk management activities throughout the lifecycle of a product
- Impact on product and patient safety
- Better use of resources regionally and possibly globally
- No new criteria – mechanism to better guarantee existing criteria
- ICH Q9 provides a horizontal approach
- Can be applied by companies irrespective of size
- Facilitates flexibility of approaches

Potential Implications of Q9 for EU -2

- Will be implemented as a new annex to EU GMP guide
- Possible Impact on some existing GMP guidance documents will need to be evaluated
- Similarly for EU Compilation of Procedures (Guidance for inspectorates)
- Training of regulators likely to be necessary

Perspectives for the future

- Quality Risk Management (Q9), combined with more information on Pharmaceutical Development (Q8) will contribute to better understanding of
  - Critical formulation and process variables
  - Sources of variability in these variable
- Leading to:
  - Risk reduction and better control
  - Facilitation of continuous improvement
- May challenge many traditional pharmaceutical approaches
- Ultimate aim is to improve the quality of pharmaceuticals delivered to patients

Abbreviations

EU – European Union

GMP – Good Manufacturing practice

ICH – International conference on Harmonisation

Q9 – ICH draft guidelines on Quality Risk Management

Q8 – ICH draft guideline on Pharmaceutical development

References

- EU “GMP guide” – Volume 4 of the Rules governing medicinal products in the European Union: Good Manufacturing Practices
- Compilation of Community procedures for Inspection and exchange of information
- www.emea.eu.int/inspections