ICH Q9
‘Quality Risk Management’
- an industry view

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Contents

How did we get here?
  • FDA 21st Century GMP Initiative
  • ICH activity

Introduction to risk management

Links between Q8, Q9 and Q10

Contents of Q9, Draft 4

Implications

Conclusion
FDA Pharmaceutical GMP Initiative

“seeks to integrate quality systems and risk management approaches into the existing programs and encourages adoption of modern and innovative manufacturing technology.”

“intended to enhance the integration of pre-approval review and cGMP programs and achieve more consistent application across agency organization components.”

“use existing and emerging science and analysis to ensure that limited resources are best targeted to address important quality issues, especially those associated with predictable or identifiable health risks.”

_Lester M. Crawford, FDA Deputy Commissioner, 21-August-2002_
Flexible regulatory approach

Regulators evaluate category of risk, based on:
- Product, process and facility
- Controls to assess & mitigate risk
- Quality system implementation

Regulators determine ‘risk category’ and modify level of oversight accordingly for:
- Post-approval change review
- GMP inspections

Result:
- Removal of barriers to continuous improvement
- Efficient use of resources by industry & regulators
A Challenge to Industry:

At the end of the cGMP Initiative the pharmaceutical community has arrived at a cross-road; one path goes towards the desired state and the other maintains the current state. The path towards the desired state is unfamiliar to many while the current state provides the comfort of predictability. The Agency hopes the pharmaceutical community will choose to move towards the desired state.
What Is Risk?

RISK = combination of probability of harm and severity of that harm

Source: ISO Guide 51
Advantages of risk based GMP

Systematic, scientific & data-driven (reduces subjectivity)

Ranks risk - allows prioritization

Improves decision making
  • Identifies what gives most benefit to the patient

Means of building in quality

Documented – improves communication
Pharmaceutical industry and risk management

Pharmaceuticals have lagged behind related industries in adopting formal risk management; e.g.

- Medical devices, ISO 14971
- Food, HACCP

We are using risk management but

- Implementation is patchy
- It is often not fully integrated with rest of the Quality System
Risk Management: Introduction

Risk Management is **NOT** about:
- making do with insufficient time, money, or people,
- providing an excuse not to do the right things,
- deciding what to do based on what might be observed during an inspection.

Risk Management does **NOT** provide an excuse to be out of compliance with applicable regulations.
Risk Management: Introduction

Risk Management IS about:

• knowing our processes (manufacturing and business),
• understanding what’s truly important,
• not spending time on a low risk activity, process, event, or system BECAUSE IT JUST DOESN’T MATTER!
• focusing our money, time, energy, and people on the things that are really important; i.e.,
• focusing our efforts and resources on the things that provide quality assurance to our customers.
Risk Management: Introduction

If we do Risk Management properly, we should be able to:

• demonstrate that we understand what is important about our business;
• have a documented, approved rationale for our decisions;
• be proud to share these with regulatory agencies because they demonstrate our knowledge and logical thought processes.
Risk Management: Introduction

We have to do our Risk management properly.

Poor Risk Management will not impress regulators.

At best, they will think we do not know what’s really important.
  • If we don’t know what’s trivial, how can we know what’s important?
  • If everything is critical, nothing is critical.

Ultimately, it is about credibility.

A rational approach has to begin with the question “What is the impact on the patient?”
It was agreed that the FDA’s 21st Century GMP initiative should form basis for discussions at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
International Conference on Harmonisation (ICH)

Merging of regulatory authorities & industry

Not legal binding, unless incorporated in local law

Expert Working Groups (EWGs)

Quality
- chemical and pharmaceutical QA

Safety
- in vitro and in-vivo pre-clinical studies

Efficacy
- clinical studies in human subject

Multidisciplinary
- general topics

Ministry of Health, Labour and Welfare

World Health Organization

FDA

PhRMA

Japan Pharmaceutical Manufacturers Association

MRCG

EMEA

Europa

Elpis

World Health Organization
## Timeline of Key Events 2002 - 2004

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<tr>
<th>Month</th>
<th>Event</th>
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<tr>
<td>Aug. 2002</td>
<td>FDA launch 21st century GMP initiative</td>
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<tr>
<td>Jul. 2003</td>
<td>ICH GMP Workshop</td>
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<td>Sep. 2003</td>
<td>ICH Q8 ‘Pharmaceutical Development’ EWG established</td>
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<tr>
<td>Nov. 2003</td>
<td>ICH Q9 ‘Risk Management’ EWG established</td>
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<tr>
<td>Jun. 2004</td>
<td>ICH Q10 ‘Quality Management’ agreed “in principle”</td>
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<tr>
<td>Sep. 2004</td>
<td>FDA announcements on implementation</td>
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<td>Nov. 2004</td>
<td>ICH EWG meetings</td>
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ICH GMP related activities
- current status

**Q8** – Pharmaceutical Development
- Part 1 reached step 2 in Nov. ‘04

**Q9** – Quality Risk Management
- At Step 1, draft 4 produced Nov. ‘04
- Likely to reach step 2 in March 2005

**Q10** – Quality Management
- Agreed ‘in principle’
- Waiting for Q9 to reach Step 2 before starting
Links between ICH Q8, 9 & 10

Quality System Risk at Manufacturing Site

High

Low

“Q10” Quality Management

Continuous improvement

Q8 Pharmaceutical Development

Using Q9

High

Low

Product/Process Risk

Base: J. Ramsbotham, Solvay Pharm. NL / EFPIA
品質にかかわるリスクマネージメント

横浜
1. Introduction
2. Scope
3. Principles of Quality Risk Management (QRM)
4. General Quality Risk Management Process
5. Risk Management Tools
6. Integration of QRM process into industry & regulatory operations
7. Glossary
8. References
Annex I: Potential opportunities for conducting QRM
1. Introduction

Risk Management
Quality Risk Management
Harm
Severity
Stakeholders
Product life cycle
Quality
2. Scope

This guideline provides a framework that may be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, inspection and submission/review processes throughout the lifecycle of drug substances and drug products, biological and biotechnological products, and the use of raw materials, solvents, excipients, packaging and labeling materials.
3. Principles of Quality Risk Management

Two primary principles:

1. The evaluation of the quality risk should ultimately link back to the potential harm to the patient.

2. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.
4. Quality Risk Management Process

- **Initiate Risk Management Process**
  - Risk Assessment
    - Risk Identification
    - Risk Analysis
    - Risk Evaluation
  - Risk Control
    - Risk Reduction
    - Risk Acceptance
  - Risk Communication
    - Output/Results of the Risk Management Process
  - Risk Review
    - Risk Acceptance
    - Review Events

- Risk Management tools

- Risk Interpretation
  - unacceptable

- Risk Review
  - Risk Acceptance

- Risk Communication
  - acceptable
5. Risk Management Tools

- Failure Mode Effects Analysis (FMEA)
- Failure Mode Effects & Criticality Analysis (FMCEA)
- Fault tree analysis (FTA)
- Hazard Analysis of Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Risk Ranking and Filtering
- Preliminary Hazard Analysis (PHA)

Supporting statistical tools

For each tool:
Short description
Potential areas of use
Q9 – Implications

Companies can choose whether to use formal quality risk management
  • If used it should enable regulators to adopt a more flexible approach to their oversight of a site

It will be acceptable to continue to use informal approaches to managing risk

Quality risk management is likely to become ‘best practice’ over time
Q9 – Implications

Significant risk management knowledge gap

- Both in industry and regulatory authorities
- ICH EWG plan to produce training guidance

Industry and regulatory authorities will need to initiate programs to

- Educate broadly on quality risk management
- Train a cadre of experts who can facilitate implementation of the risk management process
Conclusion

Quality Risk Management provides a useful process that enables both industry and regulators to focus on what is important for patients.

Integration of Quality Risk Management into existing systems and regulatory process will take time.

ICH Q8, Q9 & Q10 together will enable the pharmaceutical community to move towards the desired state for 21st century quality management.