ICH Q9 Quality Risk Management - Regulatory Perspective

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Objectives

- Background
- Review of Guideline
- Applications
- Conclusions

**Quality Risk Management**

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
What is Q9?

- A new paradigm of risk-based concepts and principles
- A guideline, not a mandate
- A systemic, process-oriented approach to decision making that is intended to be
  - practical,
  - applicable,
  - predictive,
  - flexible,
  - consistent and integrated

“risk-based” concepts and principles
What is Q9?

The ICH Q9 document:
- Main body explains the “What?”
- Annex (I) give ideas on the “How?”
- Annex (II) give ideas on the “Where?”

It is designed to be implemented by industry and regulators
- Pharmaceutical development (ICH Q8) and Quality Systems (ICH Q10) will facilitate the “What?”, “How?” and “Where?”
Goal is to reduce patient risk

Opportunities to impact risk using quality risk management
What does Q9 offer?

- Quality risk management serves as a foundation to:
  - support other ICH Quality documents and
  - complement best quality practices, requirements, standards, and guidelines within industry and regulators.

- It specifically provides guidance on the principles and some of the tools of quality risk management to enable consistent risk based decisions across the product lifecycle.
The Desired State

- Manage risk to patient, based on science:
  - Product, process and facility
  - Robustness of Quality System
  - Relevant controls to assess & mitigate risk

- Level of oversight required commensurate with the level of risk to patient for:
  - Marketing authorisation applications
  - Post-approval change review
  - GMP inspections

- Barriers to continuous improvement reduced or removed
  - Improved manufacturing efficiency
  - Sustained or improved product quality

- Specifications based on parameters that truly impact product quality

- Common understanding and language on risk

- Both, industry and competent authorities focus on areas of greatest risk and understanding of residual risks
Q9 Contents

1. Introduction
2. Scope
3. Principles of Quality Risk Management (QRM)
4. General Quality Risk Management Process
5. Risk Management Methodology
   *Annex I: Risk Management Methods and Tools*
6. Integration of QRM process
   into Industry and Regulatory operations
   *Annex II: Potential Applications for QRM*
7. Definitions
8. References
1. Introduction

Terms
- Risk Management
- Quality Risk Management
- Quality Systems
- Harm
- Severity
- Stakeholder
- Product Life Cycle
- GMP Compliance

Purpose
- Systematic approach
- Complementary resource
- Provides principles and tools
GUIDELINE

2. Scope - Product Lifecycle

- Research
- Preclinical Phase
- Clinical Phases
- Launch
- Manufacturing & Distribution

- GLP (Safety)
- GCP (Efficacy)
- GMP (Quality)
- GDP (ICH Q9)
The evaluation of the risk to quality should be based on scientific knowledge and ultimately link back to the protection of the patient.

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

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Risk Review
- Review Events

Risk Communication

Output / Result of the Quality Risk Management Process

Risk Management Tools

unacceptable
5. Methodology

- **System Risk (facility & people)**
  - e.g., interfaces, operators risk, environment, components such as equipment, IT, design elements

- **System Risk (organisation)**
  - e.g., Quality systems, controls, measurements, documentation, regulatory compliance

- **Process Risk**
  - e.g., process operations and quality parameters

- **Product Risk (safety & efficacy)**
  - e.g., quality attributes: measured data according to specifications
5. Annex I: Risk Assessment Tools

- Failure Mode & Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis of Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering

Refer to: ICH Q9 Briefing Pack II, July 2006
6. Integration into Operations

- Quality risk management is intended to enable and enhance compliance with regulatory requirements and science-based decisions when integrated into quality systems.

- It is also meant to be applied where it is feasible and valuable.
GUIDELINE

6. Integration into Lifecycle

- Say, what you do
- Gain experience
- Improve it
- Analyse root cause: Continual improvement
- (Risk of) Failure?
- Manufacture
- Do, what you say
- Update information
- Approval

Quality Risk Management (QRM)
6. Annex II: Potential Applications

- Integrated quality management
- Regulatory operations
- Development
- Facilities, equipment, utilities
- Materials management
- Production
- Laboratory control and stability studies
- Packaging and labeling

Refer to: ICH Q9 Briefing Pack II, July 2006
APPLIcATIONS

Applies to Regulators & Industry

- Regulatory operations
  - Inspection and assessment activities
  - Internal systems

- Industry operations
  (with regulatory oversight)
  - Internal systems
  - Development
  - Facilities, equipment, utilities
  - Materials management
  - Production
  - Laboratory control, stability testing
  - Packaging and labelling
Q8 Pharmaceutical Development

- Development studies lead to information for risk management of the product.

- Risk management principles help prioritize development studies.

- Information relating to process in development supports risk management in manufacturing.
Q8(R1) “Quality by Design”

- Link material attributes and process parameters to critical quality attributes
  - Identify and rank parameters, e.g., process, equipment, materials

- Selection of variable within the design space
  - Identify variables and ranges Scale-up risks

- Control strategy
  - Compensate for variability, e.g., raw materials
Q8(R1) Variables & quality attribute

APPLICATIONS

Drying
- Temp
- RH
- Air Flow
- Shock Cycle

Analytical
- Sampling
- Method

Plant Factors
- Temp/RH
- Operator
- Training

Compressing
- Precompressing
- Main Compressing
- Feeder Speed
- Press Speed
- Punch Penetration
- Depth
- Tooling
- Feed Frame

Granulation
- Chopper Speed
- Mixer Speed
- Endpoint
- Power

Raw Materials
- Water
- Binder
- Disintegrant
- Lubricant

Drug Substance
- Age
- P.S.
- Process Conditions
- LOD
- Diluents
- P.S.
- LOD
- Other

Tablet

Method

Analytical

Sampling

Plant Factors

Compressing

Granulation

Raw Materials

Drying

Tablet
ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development ➔ Technology Transfer ➔ Commercial Manufacturing ➔ Product Discontinuation

Investigational products ➔ GMP

Management Responsibilities

Process Performance & Product Quality Monitoring System
Corrective Action & Preventive Action (CAPA) System
Change Management System
Management Review

PQS elements

Knowledge Management

Quality Risk Management

Enablers
Q10 Pharmaceutical Quality System

- Documentation
- Training and education
- Outsourced activities / purchased materials
- Control Strategy
  - Use quality risk management to establish using parameters and attributes and related facility and equipment operating conditions
- Monitoring / Handling Quality Defects (CAPA)
  - The level of effort of the investigation should be commensurate with the level of risk.
  - Result should be product and process improvements
Q10 Pharmaceutical Quality System

- Auditing / Inspection
  - For regulators
  - For companies

- Periodic review

- Change management / change control
  - Level and formality commensurate with risk
    - Effect of the change on the overall process and product
    - Effect on validation
    - Evaluation of the change upon implementation

- Continual improvement
### Risk Assessment

**Drug Product Risk Assessment – ‘Cause & Effect Matrix’**

**Dry Granulate + Blend Example**

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Risk Assessment, Non-quantitative

Demonstrated Multivariate Cause and Effect Relationships

- process parameters
  - Water quantity
  - Comil screen size
  - Comil impeller speed
  - MgSt addition method
  - Pre-compression
  - Press speed

- granule attributes
  - GSA
  - % fines fraction
  - 850 um sieve fraction

- tablet attributes
  - Hardness
  - Capping
  - Picking

Industry Example
Industry Example

- Propose to utilize a CQV approach to process validation
- This will be based on:
  - Process Understanding:
    - Established Design Space from process development
    - Documented risk assessment identifying Critical Process Parameters (CPP’s) and Critical Quality Attributes (CQA’s)
    - Information from full scale development batches in commercial facility which will support Design Space.
  - Process Control strategy
  - Process Analysis
  - Continuous Process Improvement: Utilize gained additional process information based on full scale production experience to make process improvements, as applicable.
Regulatory Operations: FDA

- Site selection process for human drug GMP inspections
- Veterinary drug pre-approval decision support system (PAIDSS)
- Adverse Drug Event (ADE) reporting inspections
- Human drug surveillance sampling programs
FDA Site Selection Risk Model (2008-09)

- Facility Size
- Recalls
- Last 3 District Decisions
- Establishment Type
- Time since Last CGMP Inspection
- Unapproved Drugs
- Therapeutic Class
- Control
- Contamination

Facility

Outdated Information

Product

Process

Score (SRP)
Goals and Conclusions

- Use of Risk Management Tools Provide Basis for:
  - Development and Design
  - Degree of Regulatory Scrutiny
  - Control of Manufacturing Process and change control justified by science - and - in the hands of the manufacturer
Management Responsibilities

- Ensure organisation is aware of ICH Q9 and the opportunity it affords
  - Appropriate education and training

- Encourage open, risk aware culture
  - Establish & support “QRM leaders” across organisations

- Encourage integration of Quality Risk Management with existing Quality systems
  - Do NOT set up as a separate department
  - Coordinate implementation and resource allocation
  - Prioritise; start small, learn as you go
ICH Q9, together with “Pharmaceutical development” [ICH Q8, Q8(R1)] and “Quality systems” [ICH Q10], provides opportunity for a revised, optimised and, less restrictive regulatory paradigm

- Based on scientific knowledge
- Enables continual improvement
- Greater transparency and efficiency
- Focusing on things that add value for patients
- Improved relationship between industry and competent authorities based on trust