Workshop for Combination Products Risk Management: Integration Of ICH Q9(R1) And ISO 14971:2019

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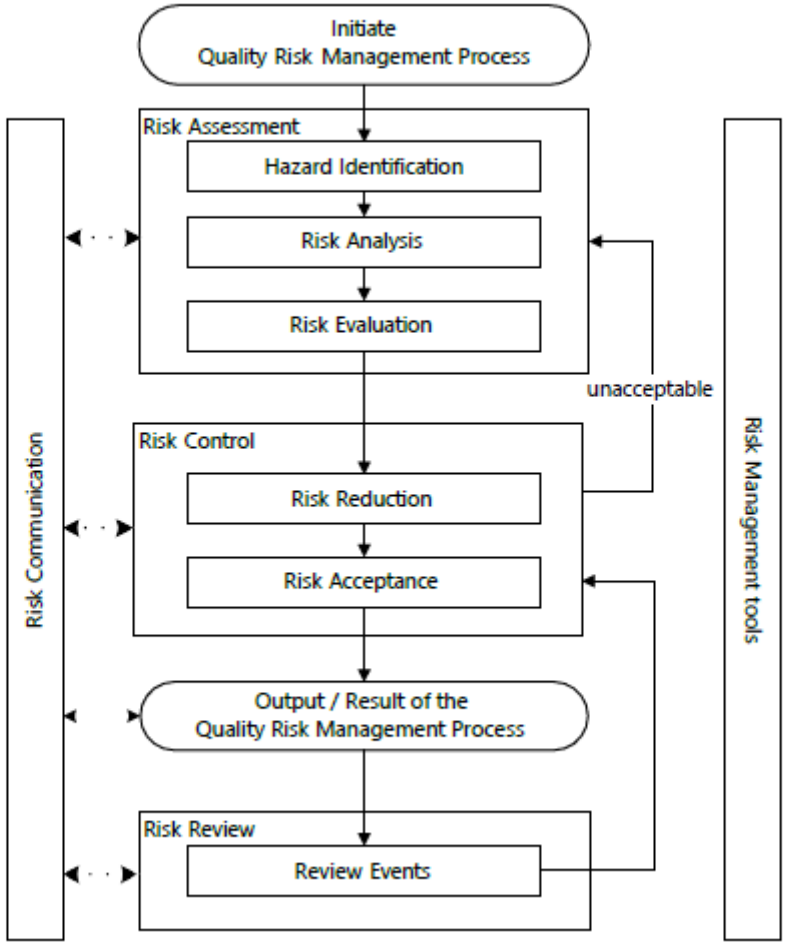
ICH Q9: General Quality Risk Management Process

Figure 1: Overview of a typical quality risk management process.



Case Study

Combination Product (Rescue Inhaler)

This case study illustrates how timely and comprehensive Quality Risk Management (QRM) by both the Contract Manufacturing Organization (CMO) and the Sponsor is essential for combination product manufacturers to avoid serious quality problems and related product supply issues.

Case Study
Combination Product – Rescue Inhaler

Background

- Metered Dose Inhaler product indicated for asthma (rescue inhaler).
  - Medically necessary product and associated concerns for product availability
- Sponsor contracts a CMO site to manufacture the product.
- CMO company has never manufactured inhalers at this site. Equipment installed and new employees hired.
- CMO launches and contributes major volume of commercial batches (100+) to the market. Approximately 5% of batches rejected for manufacturing issues and defects.
- **The Sponsor receives more than 10,000 complaints in short time. Major quality/safety signal** shortly after launch. More than 90% are product quality complaints for critical device failure (failure to dispense).
  - Numerous Adverse Events
- Markedly disproportionate high share of these critical complaints in the marketplace vs. the same product made by other CMOs.

Case Study
Combination Product – Rescue Inhaler

Background (cont'd)

- CMO performs **an investigation** and initially states that they are confident that the manufacturing process is not the cause, and product is of acceptable quality.
  - The CMO initially blamed it on user error, but their investigation revealed that the combination product was malfunctioning due to significant device and component variances. They also found flaws in canister processing, causing leaks and resulting in the loss of propellant, leaving only the drug behind
- CMO updated the regulatory agency on this.
- Inadequate process development led to poor capability process and serious quality problems when commercial product was launched.
  - Signals appeared during the development stage and in commercial lots produced before approval, revealing insufficient process understanding and a failure to address manufacturing issues. This was worsened by inadequate control of device components and a lack of oversight over excessive batch variability

Case Study
Combination Product – Rescue Inhaler

For-cause Inspection conducted within first year of product launch found several GMP issues, including:

- Major trend of machinery faults and in-process failures.
- Significant increase in critical device malfunction complaints.
- Deficient device design control, validation, and verification.
  - Insufficient records to show defined user needs were met.
  - Inadequate design and development plan.
- Critical manufacturing equipment was low capability and performed outside required tolerances.
- Quality/safety complaints and batch failures still not investigated adequately, including ineffective CAPA, insufficient determination of root cause(s), and lack of timely QRM (e.g., failed to promptly perform risk review).

Case Study
Combination Product – Rescue Inhaler

Post-Inspection Actions:

- Shortly after, the firm conducted a **voluntarily recall of the product** from the market.
- CMO determines (in coordination with the sponsor) that they need to **voluntarily cease manufacture** of product due to severe manufacturing quality problems.
  - CMO also committed to investigate potential root causes of the critical device failure complaints and not to recommence production until root cause identified and full CAPA implemented
- **Ultimately, the sponsor contracted a <u>new</u> CMO to manufacture the product.**

Case Study
Combination Product – Rescue Inhaler

Capability and Supplier Oversight

- **Low capability operations can lead to high risks**
  - Serious **quality defects**
  - The **lack of availability** of medically needed products for patients
- **Supplier oversight** of CMO requires ongoing engagement and active oversight.
  - Initial risk assessments were inadequate, as they failed to identify, analyze and apply adequate risk controls to reduce risks from the multiple variables that were critical to quality
- **Special Quality Risk Management attention** especially needed due to multiple critical factors related to the product, including:
  - Initial launch of new product
  - CMO had no prior experience producing this dosage form
  - Complex drug-device product
  - Product is a critical medicine for patients

Case Study
Combination Product – Rescue Inhaler

- Successful **quality risk management** for combination products depends on understanding each constituent part, including how they work, interact, and interrelate. **Design** problems for device constituent part(s) and process should be identified during development and analyzed in timely manner.
- **At each stage,** from development through to commercial manufacture and distribution, personnel with relevant expertise need to be engaged to ensure appropriate CMO manufacturing capability, constituent parts, batch performance, sound testing, and process monitoring,
- **Timely, comprehensive Quality Risk Management** (including timely risk review) by both CMO and Sponsor is essential for combination product manufacturers to avoid such serious quality/safety problems.
- Lack of understanding, management, and **oversight of activities** and risks, by both the CMO and Sponsor, may lead to product failures, recalls, and possible discontinuation of product.

- Risk Management incorporates a holistic approach
- No one component of risk management stands alone
- Continual basis
- Applies to drugs (application or non-application) and combination products

Q9(R1) Quality Risk Management

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
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Email: ocod@fda.hhs.gov
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Guidance for Industry and FDA Staff:

Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

The draft of this document was issued in January 2015.

Additional copies are available from:
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For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

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