Lecture 3: Investigation Principles

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Investigation Principles: Quality Culture - Evaluation

Leadership Commitment

1. Leadership Commitment to Quality
   - Accountability and Quality Planning
2. Enabling Capable Resources
   - Feedback and Coaching
   - Training
   - Mentoring
   - Knowledge Management
   - Industry Forum Participation
   - Rewards and Recognition

Communication & Collaboration

3. Quality Communications
   - Quality Communications
4. Collaboration with Auditors
   - Collaboration
   - Operations Readiness & Knowledge
   - Behavior

Employee Ownership

5. Understanding Quality Goals
   - Impact on Product Quality
   - Patient Impact
6. Safety Culture
   - EH&S Program
   - Targets

Continuous Improvement

7. CAPA robustness
   - Root Cause
   - Human Error
8. Management Review and metrics
   - Management Reviews
   - Metrics
9. Clear Quality Objectives
   - Continuous Improvement
10. Internal Stakeholder Feedback
    - Internal Stakeholder Feedback
    - Quality Culture Survey

Technical Excellence

11. Utilization of new proven technologies
    - Manufacturing Technologies
    - New Technology
12. Maturity of Systems
    - QMS Processes
    - Maturity Model
    - Responsibilities

Evaluation

Now you might count the ratings and calculate and compare some figures. However, these figures have only limited value, because

- they represent your individual opinion only
- much more information for improvement can be found in the reason for the individual ratings

Therefore, High Performance Quality Culture Assessments include both, the ratings and the opinions of each employee and manager.

The next step is to learn some tools for root cause investigation and to take effective CAPAs for improvement of your company's Quality Culture.

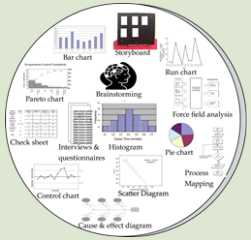
Investigation Principles

What are helpful tools?

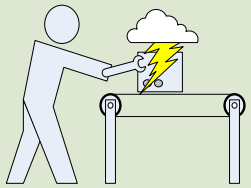
What supports a successful investigation?

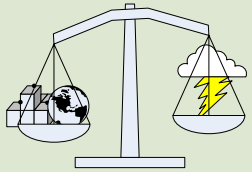
Five Elements of Investigations

WHAT HAPPENED?	WHY IT HAPPENED?	HOW ARE WE ENSURING IT DOESN'T HAPPEN AGAIN?	HOW ARE WE ENSURING IT DOESN'T HAPPEN ANYWHERE ELSE?	WHAT ARE THE RISKS AND THE IMPACT?
Include immediate actions taken (Correction)	Root Cause Analysis (RCA)	Corrective Actions prevent recurrence	Preventive Actions prevent occurence	Materials? Safety? Equipment? Process? Validation? Regulatory?



RCA TOOLS





DOCUMENTATION

Criteria of an effective and successful investigation

- **Timely**
- **Comprehensive**
  - Systems oriented
  - Go beyond the instant case
  - Include all necessary disciplines
  - Other batches
  - Other products
  - Other equipment
  - Link, if any, to previous similar events
- **Identify root cause(s)**
- **Conclusions are supported by facts**
- **Lead to corrective and preventive actions**

Principles of Excellent Root Cause Investigation

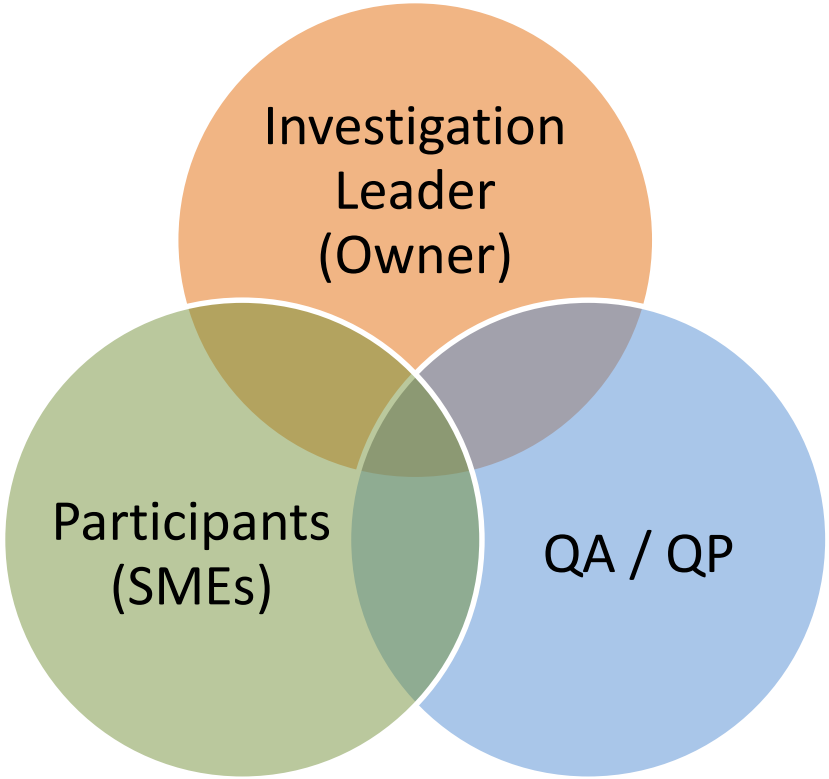
Investigation

- The level of effort and formality of the investigation should be commensurate with the level of risk
  (ICH Q10 PHARMACEUTICAL QUALITY SYSTEM)
- Potentially relevant issues must be identified and assessed
- Relevant personnel must be identified and thoroughly interviewed
- Results must be secured and reviewed

Evaluation

- The evaluation of all the material and information gathered during the investigation must be objective and based solely on the facts

Who should complete your Investigation Team?



Team members must be
- experienced
- trained
- certified (certification process)
- open minded

Team lead should **not** be the causer of the deviation

Teams must be sufficiently resourced

Root cause analysis (RCA)

is a method using systematic tools for identifying the root causes of faults or problems

Root cause

A factor is considered a root cause if removal thereof from the problem-fault-sequence prevents the final undesirable event from recurring

Causal factor (contributing factor)

A causal factor is one that affects an event's outcome, but is not a root cause. Though removing a causal factor can benefit an outcome, it does not prevent its recurrence with certainty.

An example to learn to distinguish …

Introduction / Background

A car accident happened: the driver phoned on his mobile phone while driving. He did not realize the truck that he should haven given way at the crossing. The car driver had not fastened his seat belt and thus, he was severely injured.

➔ What is the root cause for the driver's injuries?

Root cause

The driver phoned while driving his car.

Causal factor (contributing factor)

The driver had not fastened his seat belt.
He would have been less or not injured with his seat belt fastened,
but the accident would have happened even with the seat belt fastened.

Tools for Root Cause Analysis (RCA)

- Fault tree
- Is / Is not-Analysis
- Timeline
- 5 Why
- Fishbone- / Ishikawa-Diagram
- Human Error Questionnaire
- Mind map
- Process flow / Landscape
- …

Supportive Tools for Investigation

- Checklists (One-Size-Fits-All approach may limit creative thinking in unique situations)
- Questionnaires / Memos
- Report templates

Investigation Principles

"There is water on the floor"

Fault Tree

Tree

Root

- Rain
- Flood of the creek
- Piped water
  - Fresh water
    - Cold water
    - Hot water
  - Waste water

Investigation Principles

"There is water on the floor"

Is / Is not

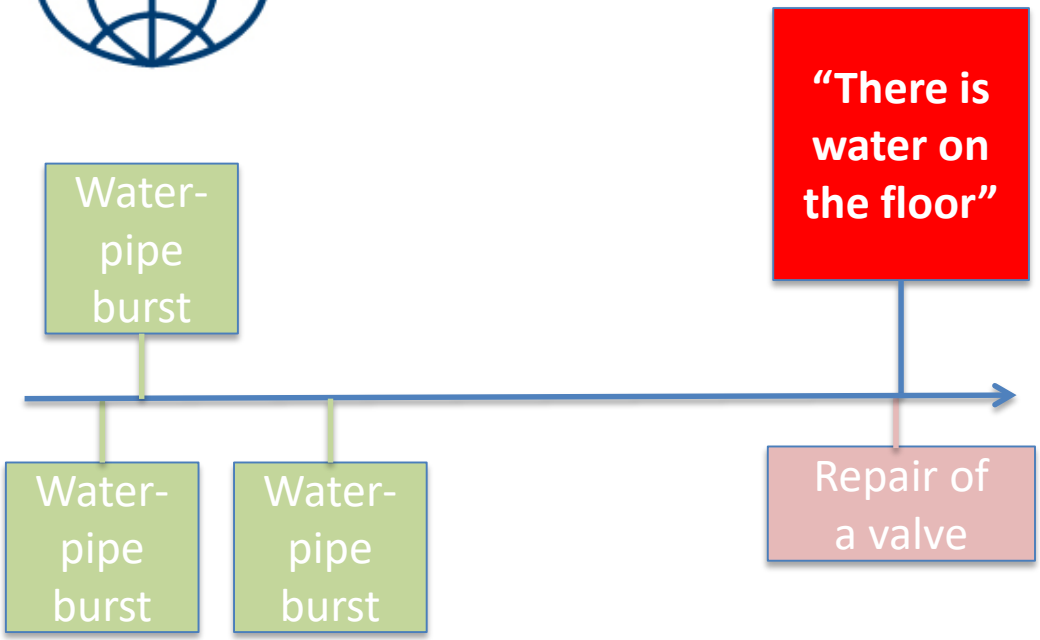
Tree

Root

- Rain
- Flood of the creek
- Piped water
  - Fresh water
    - Cold water
    - Hot water
  - Waste water

Is / Is not table

	IS	IS NOT	Answer
Where	Where is the water?	Where is no water?	Water is in the kitchen only
What	What kind of water is it?	What kind of water is it not?	It is cold and fresh water
When	…	…	…

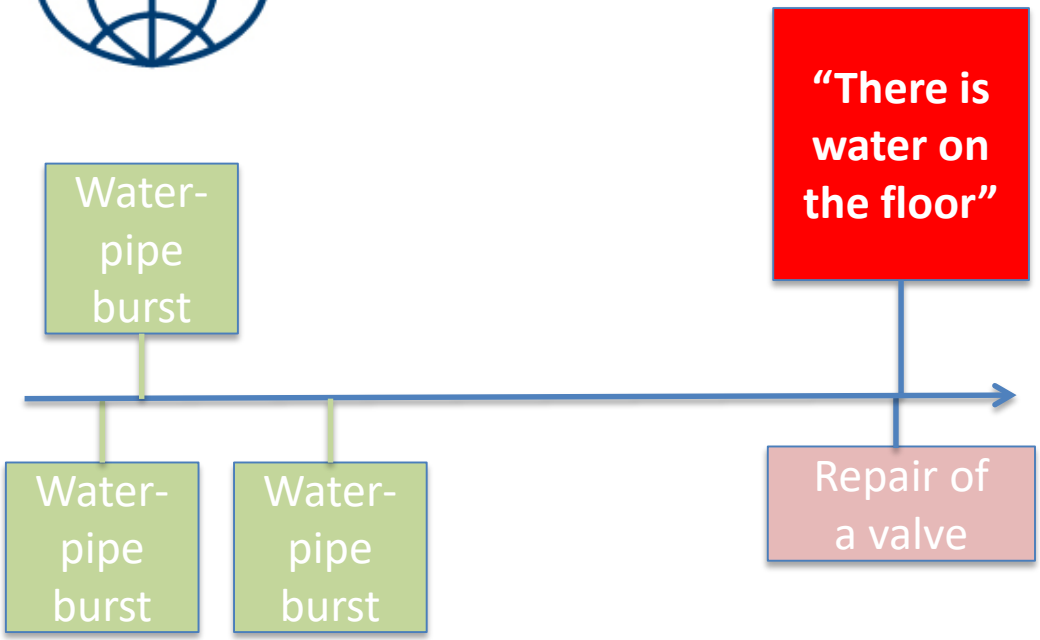


Timeline

The timeline reveals a correlation of incident and impact and supports

➔ Identification of the Root Cause

➔ Assessment of the Impact



5 WHYs

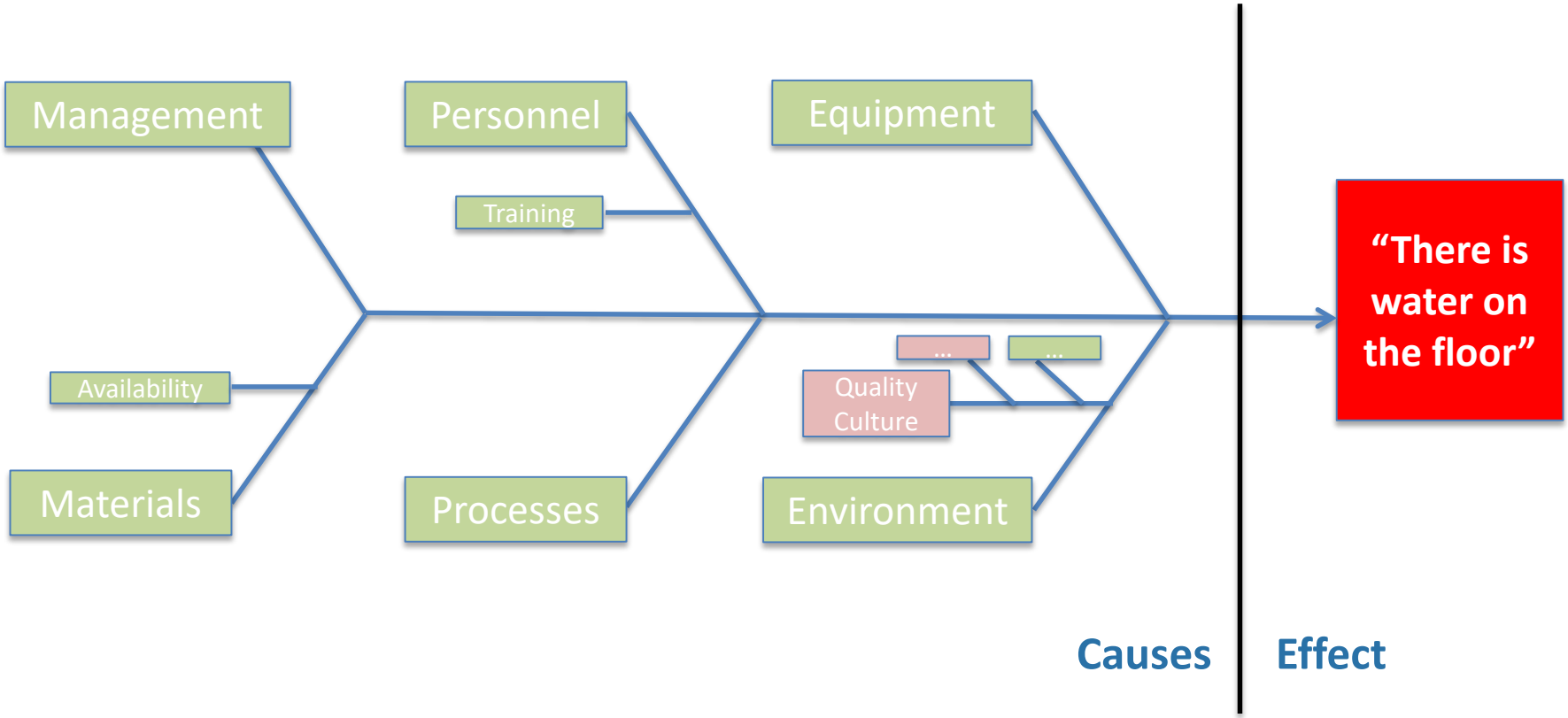
1. WHY is water dripping onto the floor?
   A: The T-connector has not been fastened tight to the valve.

2. WHY is it not fastened tight?
   A: A Teflon tape has been used to tighten the connection.

3. WHY has a Teflon tape been used instead of a sealing ring?
   A1: No sealing ring was available
   A2: The technician has not been trained to use a sealing ring
   A3: The technician used the Teflon tape in bad intention

4. (1) WHY was no sealing ring available?
   (2) WHY ….

Fishbone- or Ishikawa-Diagram

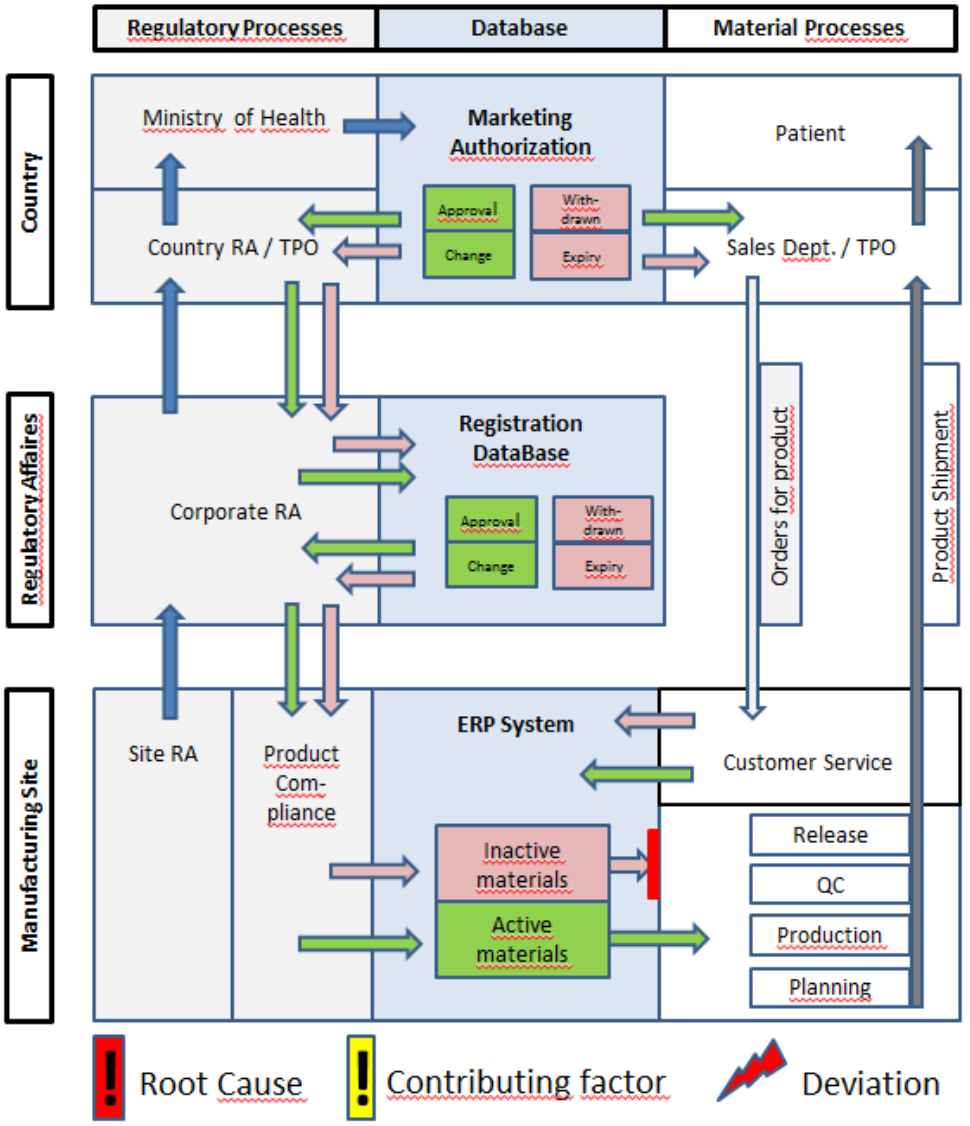


Guidance for choosing the proper Root Cause Tool

- **At least one tool** should be applied (Investigators nearly always use root cause tools even if they are not aware of having used one)
- Usually, **several tools** should be applied and combined
- Each tool has its **individual strengths and weaknesses**
- A **timeline** does not only support the root cause investigation but is also a **main tool to assess the (product quality) impact** of an incident
- Usually, you will find **more than one root cause** and more than one causal factor
- Create your **own tool** (e.g. mind map, process landscape) to support the evaluation of the investigation results, if necessary

Process Landscape

Author: Thomas Krieger



Abbreviations

RA	Regulatory Affaires
TPO	Third Party Organisation
Dept.	Department
ERP	Enterprise Resource Planning
QC	Quality Control

Five Most Common Mistakes when writing an Investigation…

1. Inadequate Quality Impact Assessment
2. Beginning thinking you already know the cause
3. Failing to identify and or execute the appropriate Corrective Action and Preventative Action (CAPA)
4. Poorly Written Investigations
5. Incomplete Investigations

According to the FDA, the third highest cause of 483s, warning letters, or consent decrees was due to discrepancies and or failures in investigations.

Root Cause Classes

Standardized classification of root causes enables

- Identification of root cause clusters
- take comprehensive measures
- Trend effectiveness of improvement of CAPAs

Root Cause Class

- Management
- Material
- People
- Process
- Equipment
- Environment
- …

Root Cause Sub-Class

e.g. People (Human Error)

- Error in decision
- Compromised performance
- Memory gap
- Inadequate communication
- …

Non-Conformity Classes

Non-Conformity Classes categorize the type of faults or mistakes as an impact of the incident.

Non-Conformity Class

- Organization
- Management
- Documentation
- Facilities
- Equipment
- Production Systems
- Quality Systems
- Product Design
- Product Quality
- …

Non-Conformity Sub-Class

e.g. Equipment

- Equipment failure
- Calibration failure
- Qualification failure
- Software failure
- …

ICH Q9 Quality Risk Management

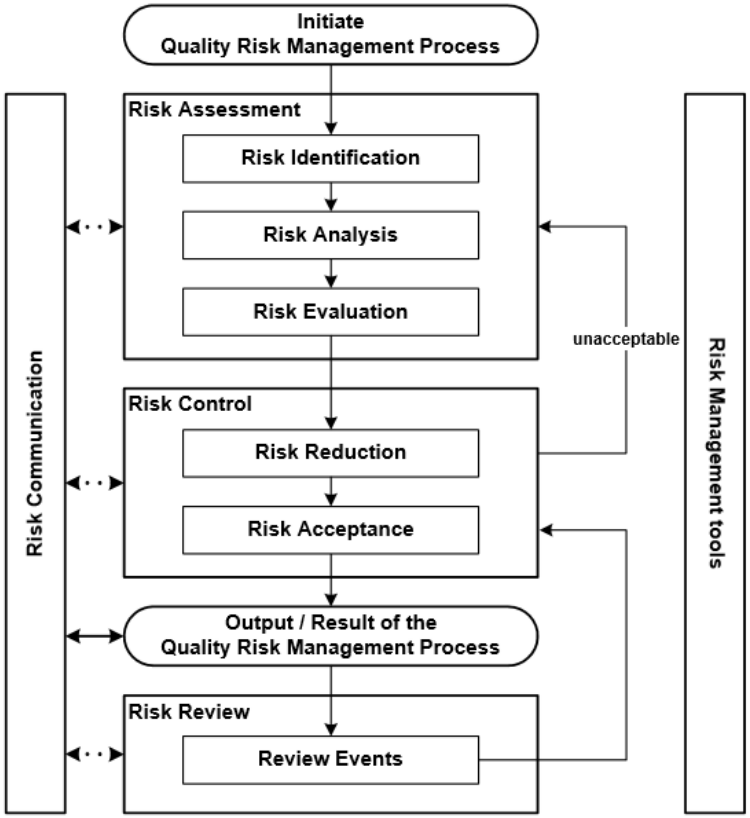
Quality risk management is an important part of an effective pharmaceutical quality system

- It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.
- It facilitates continual improvement of process performance and product quality throughout the product lifecycle.
- ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link 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.

Quality Risk Management Process



Risk management tools

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- **Failure Mode Effects Analysis (FMEA)**
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- **Hazard Analysis and Critical Control Points (HACCP)** → *Food Industry, Hygiene*
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

Quality Risk Management Process

Definition of Risk:

"The combination of the **probability of occurrence (O)** of harm and the **severity of that harm (S)** (ICH Q), ISO/IEC Guide 51)."

FMEA includes a third parameter: **probability of detection (D).**

Each of these parameters is individually ranked:
high critical (10) or no critical (0).

Then a Risk Priority Number (RPN) is calculated: **RPN = O x S x D**

➔ Immediate actions have to be taken for risks with high RPNs

➔ Actions have to be taken for all risks (or justification) and with an extent commensurate to their RPN

Assessment on Product Quality Impact

The assessment of the impact on product quality follows the results of

- the investigation on impacted product, materials, equipment, etc.
- the results of the Risk Assessment

Tools

Timeline: Logbook review, Production lists, etc.

Top-Down-Analysis , Bottom-Up-Analysis: use of starting materials, bulk, etc.

Any Product Quality Impact may lead to severe consequences:

- Rejects or partly rejects of a batch or batches
- Recall of a batch or batches
- Registration suspension or registration withdrawal

➔ Inform the competent Health Authorities (e.g. Field Alert) if indicated!