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Lecture 4:
Risk Analysis and Risk Management

Topics

- Adverse events of the past
- Risk Analysis Tools
- Risk Assessment/Management Example

Sulfaniliamide Tragedy - 1937

- The Exlixir Sulfanilamide tragedy occurred in 1937.

- Elixir Sulfaniliamide was an improperly prepared antibiotic treatment. Diethylene glycol (anti-freeze) used to dissolve the drug.
- The product was sold without safety testing or appropriate risk control and an estimated 107 people (mainly children) were killed by poisoning.

- 1938 - Food, Drug and Cosmetics Act was introduced as a result of the Sulfaniliamide tragedy. **The act required manufacturers to prove safety** of a drug before it could be marketed (by submitting a NDA - New Drug Application).

Sulfathiazole Disaster - 1941

- A company called Winthrop Chemicals were manufacturing two different drugs at the same plant.
- Cross contamination between the two drugs led to lethal doses of Phenobarbital (antiepileptic) in Sulfathiazole (antibacterial) tablets.
- Several hundred people were killed before the problem was identified and the contaminated product identified and located.
- The Sulfathiazole disaster led to more stringent enforcement of **Good Manufacturing Practice (GMP) and process control.**

Cutter Laboratories - 1955

- In 1955, the first Polio vaccine was introduced to the market. More than 10 million children were vaccinated across 5 countries in the first year.

- Several companies were recruited to produce the batches of vaccine necessary for this massive vaccination effort, including Cutter Laboratories. In April 1955, during this mass vaccination drive, public health officials in California noticed an increase in reported cases of polio.

- A subsequent investigation showed that over 200,000 people had been inoculated with a vaccine prepared by Cutter Laboratories that inadvertently contained the live polio virus instead of an inactive virus.

Cutter Laboratories - 1955

- Vaccines are often prepared from either attenuated (weakened or modified to render them inactive) or completely inactivated infectious agents. In the case of the polio vaccine, the live virus was prepared and then inactivated by treating it with formaldehyde.

- At the time, viral inactivation was **assumed** to be effective at large-scale manufacture based on small-scale studies. No validation studies of large-scale viral inactivation were carried out.

- Instances such as the Cutter incident have led to the requirement for validation in the pharmaceutical and biopharmaceutical industry; not just validation on small scale processes but on manufacturing processes as well.

Thalidomide Disaster – 1950-1960s

- Thalidomide was a drug prescribed to pregnant women as a sleep-aid or anti-nausea treatment.
- Birth defects in thousands of babies born in western Europe began to occur. However, Thalidomide was not immediately identified as the cause.
- Dr. Frances Kelsey, an FDA Medical Officer, famously halted the drug's introduction to the U.S. market following her analysis of the drug's data in Europe and her own suspicions/concerns. She later received a President's Award for Distinguished Federal Civilian Service.

Cases of Biological & Particulate Contamination

Viral Contamination

- **June 2009, Genzyme, Allston, MA**
- Bioreactors contaminated with Vesivirus 2117.
- The viral contamination came from a contaminated culture medium.
- Resulted in a shortage of the drugs Cerezyme and Fabrazyme. $100-300 million in lost sales.

Fungal Contamination

- **2012, NECC, MA**
- Injections of methylprednisolone (anti-inflammatory steroid) contaminated with a black mould
- 76 deaths and over 800 reported cases in 20 States (2015)
- The root causes of the contamination included poor air quality control, poor sanitisation practices, the use of poor quality, non-sterile and expired raw materials.

Particulate Contamination

- **Hospira, August 2017**
- Voluntary recall of one lot of Vancomycin HCl injection (used to treat MRSA) due to physical glass in one vial.
- **Mylan Pharmaceuticals, 2015**
- Recalled several lots of Gemcitabine (cancer) and Methotrexate (Psoriasis, Arthritis) injectable products due to the presence of visible particulate matter.

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ICH Q9: Quality Risk Management

1. Risk evaluation should be based on scientific knowledge and patient protection.
2. The level of effort, formality, and documentation should be commensurate with ("match") the level of risk.

- Not all elements of a validation program are of equal criticality/risk. Therefore, it is essential to **identify those elements that are likely to pose the greatest risk to the product and process.**

- This helps to **reduce the validation workload** by eliminating or reducing activities that have little or no impact on the product/process, or are unlikely to ever occur.

ICH Q10: Pharmaceutical Quality System (PQS)

Pharmaceutical Quality System (PQS): *"A management system to direct and control a pharmaceutical company with regard to quality"* (ICH Q10).

- Both FDA and EMA guidelines recommend integrating Process Validation activities into the Pharmaceutical Quality System.

1. Initially, this means integrating the process design into the PQS to ensure that the final commercial scale process will be compatible with the manufacturer's quality system.

2. Later, the scope of validation activities should be based on Quality Risk Management strategies dictated by the manufacturer's PQS.

3. During Commercial manufacturer, Continuous Verification should be governed by the PQS.

Lifecycle Risk Analysis Example

Stage 1 – Process Design:

1. Product Attribute Criticality Assessment (i.e. identify Critical Quality Attributes)
   - product knowledge, pre-clinical/clinical studies.
2. Process Risk Assessments (i.e. identify Critical Process Parameters and Control Strategy)
   - process characterisation studies, design of experiments (DoE).

Stage 2 – Process Qualification

1. System Impact Assessment (“Direct Impact” or “Not Direct Impact” on product quality)
   - determine which systems must be Qualified in addition to Commissioned
2. System Risk Assessments (identify “Critical Aspects” of Direct Impact systems and focus validation effort)
   - prioritise qualification activities based on risk of failure

Stage 3 – Continuous Process Verification

1. Commercial Manufacture – RA should continue, particularly if any changes are made to the process.

Risk Analysis Methods - Examples

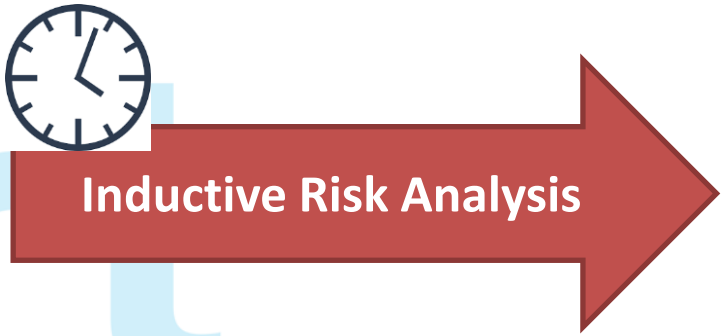
- **PHA (Preliminary Hazard Analysis)**
  - Applies knowledge from previous experience to identify known, potential hazards.
- **FMEA (Failure Mode & Effects Analysis) / FMECA (Failure Mode, Effects & Criticality Analysis)**
  - Rates risk based on severity, occurrence, and detection to give a risk-priority number (RPN).
- **FTA (Fault Tree Analysis)**
  - Asks what caused a failure to happen – Yes / No flow diagrams
  - Can also be used to determine what could go wrong
- **Fishbone (Ishikawa) Diagram**
  - Cause and Effect Analysis

Once the risks have been identified, they must be either eliminated or controlled to an acceptable level. This is the aim of the QRM program.

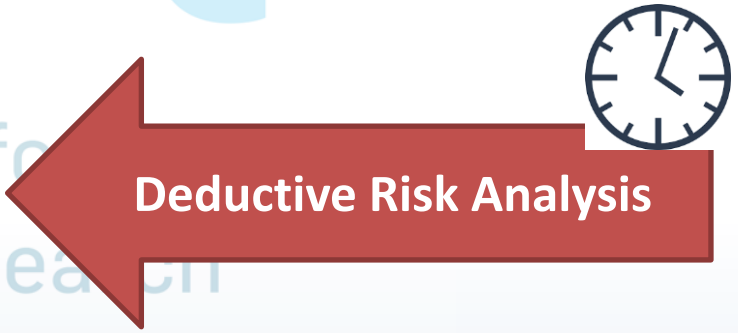
Which Risk Analysis Tool?

Depends on whether you are looking at what *could* happen or what *did* happen.

- *"What could happen if this failure occurred?"*
  - This is **inductive** reasoning,
    - e.g. Preliminary Hazard Analysis, Failure Modes and Effects Analysis.



- *"What caused this issue or failure to happen?"*
  - This is **deductive** reasoning
    - e.g. Fault Tree Analysis, Fishbone Diagram.



- Sometimes deductive RA tools can be used as inductive tools i.e. *imagine* an issue occurred to establish the most likely causes and ensure they are avoided.

1. Preliminary Hazard Analysis (PHA)

- Applies previous experience/knowledge of a specific risk to identify possible future hazards/risk events.

- PHA is *inductive* - used at early-stage process development before design details and operating processes are finalized. PHA is often a precursor to future risk studies.

Example:

1. A company wants to produce a monoclonal antibody product
2. From existing knowledge and previous experience of monoclonal antibodies, the company carries out an initial PHA to identify possible risks associated with the production process
3. Based on these identified risks, broad decisions can be made in terms of process design or focus areas
4. Later, when the company has more specific data and equipment design is more advanced, the PHA results may help to focus further Risk Analyses

2. Failure Mode, Effects & Criticality Analysis (FMECA)

- FMEA – Failure Mode & Effects Analysis
- FMECA – Failure Mode, Effects & Criticality Analysis

- Typically inductive (i.e., performed before any validation takes place) but can also be deductive (i.e. if a problem occurs or risks need to be reevaluated).

- FMECA looks at the following aspects of a product/process:
  1. Potential **Failures**
  2. Potential **Effects** of each failure
  3. Potential **Causes** of each failure
  4. Probability of **Occurrence** of each cause
  5. **Current Controls** to prevent each failure or to detect it if it does occur
  6. The **Risk Priority Number** (Severity x Probability x Detectability) for each failure/risk

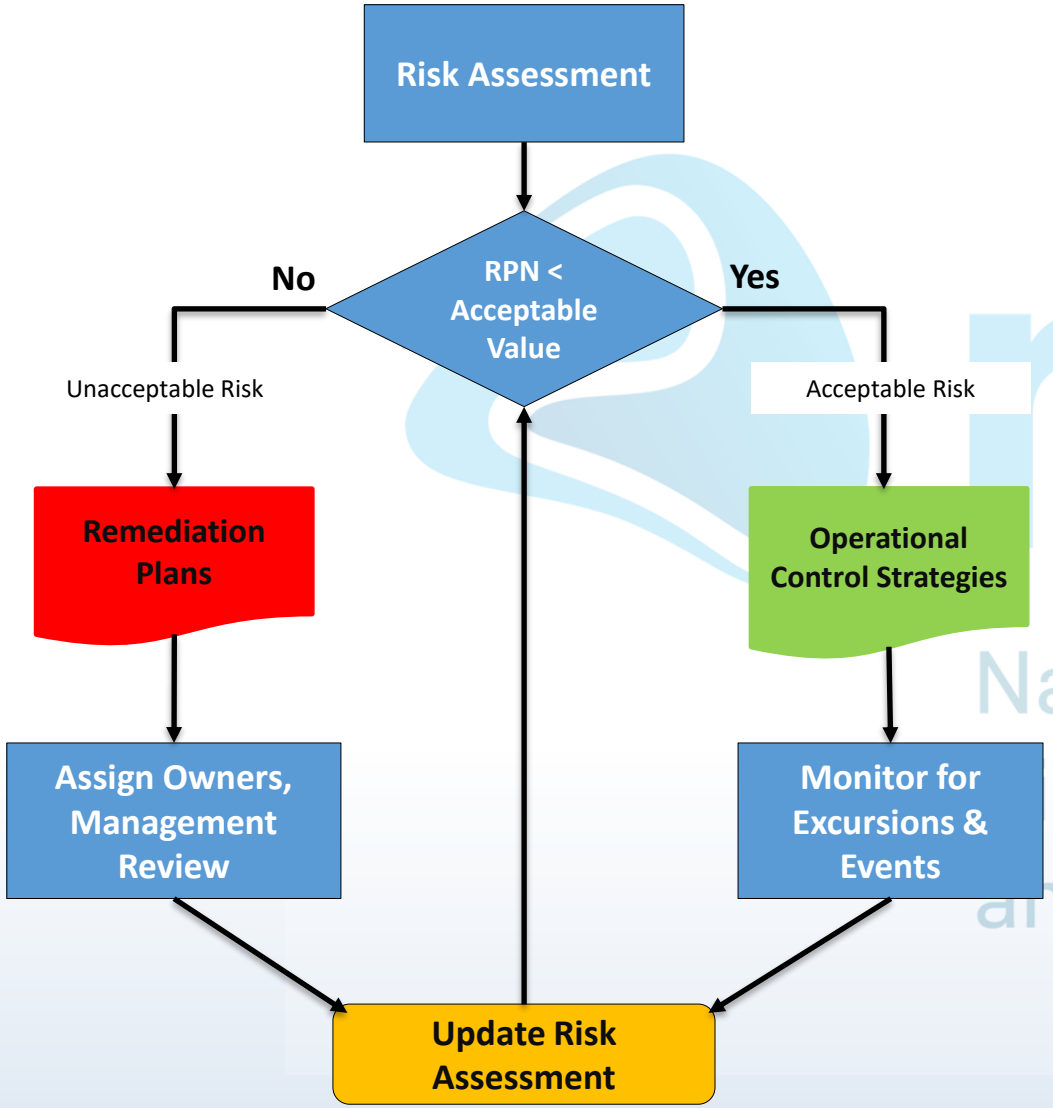
FMECA Matrix & Scoring

- FMECA uses a scoring system, typically based on a scale of 1-10.

- This enables each risk element to be scored and ranked in terms of:
  - **Severity:** impact on product/outcome.
  - **Occurrence:** probability of occurrence.
  - **Detectability (aka Controls):** the ease of detection or current controls

- By focusing on the features with the highest scoring, the most critical elements of the product/process can be adequately addressed as part of the overall validation program.

FMECA - Risk Ranking



- Risk Priority Number **(RPN)** =
  - Severity **(S)** x Occurrence **(O)** x Detectability **(D)**

Example ranking ranges:

- Severity: 1-10 (1 = low severity, 10 = high severity)
- Occurrence: 1-10 (1 = low probability, 10 = high probability)
- Detection: 1-10 (1 = high detectability, 10 = low detectability)
- Select a limit for RPN, beyond which action must be taken e.g. max acceptable RPN = 100

FMECA Matrix Example

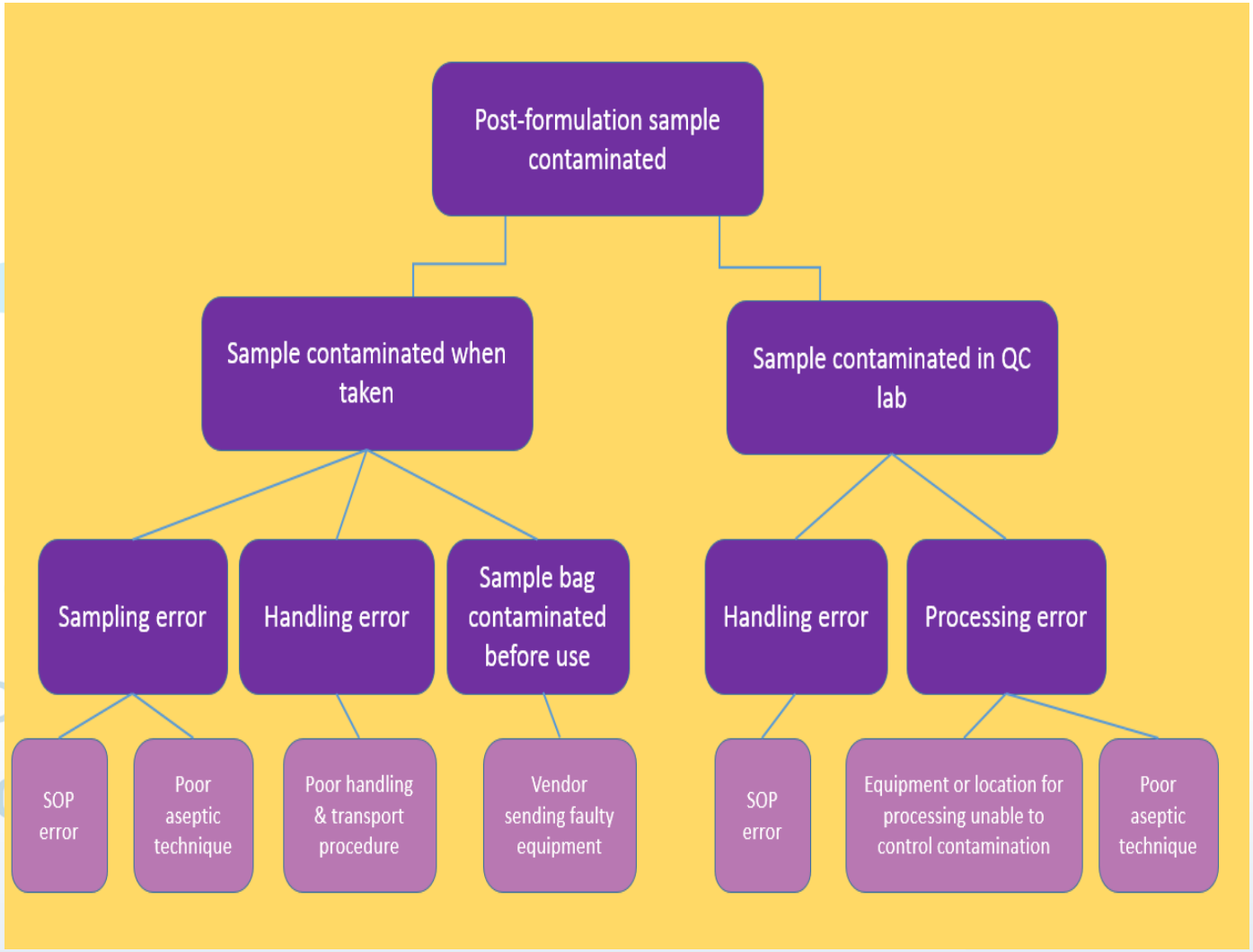
Process Step or Variable	Potential Failure Mode	Potential Failure Effects	SEV	Potential Causes	OCC	Current Process Controls	DET	RPN	Actions Recommended	Resp.& Target Date	Actions Taken	SEV	OCC	DET	RPN
What is the process step?	In what ways can the Process Step or variable go wrong?	What would be the impact?	How Severe is the effect?	What could cause the issue?	How frequently is the cause likely to Occur?	What are the existing controls that prevent/detect the failure	How probable is Detection of the cause?	Risk Priority Number	What actions could reduce Occurrence or improve Detection? N.B. actions required for RPN >100	Who's Responsible? What date?	What were the actions implemented?				
Daily Sampling for Cell Density/ Viability	Incorrect sample volume	Not enough sample for analysis	4	Poor operator sampling technique	3	Compulsory aseptic training	5	60	n/a	n/a	n/a				
				Sample bag leaked	2	None	2	16	n/a	n/a	n/a				
				SOP not appropriate	3	Approved SOP for sampling	2	24	n/a	n/a	n/a				
	Incorrect sampling results	Incorrect data used for cell culture scale up/calculations	8	Poor operator sampling and analysis technique	3	Compulsory aseptic training	2	48	n/a	n/a	n/a				
				SOP not appropriate	3	Approved SOP for sampling and analysis	2	48	n/a	n/a	n/a				
				Faulty cell analyzer machine	3	Calibration (every 6 months) and standardization (daily)	5	120	Calibration of machine every 2 months	Eng, Ops 01AUG2022	Calibration of machine every 2 months and enhanced cals checks	8	2	2	32
				Incorrect transcription of data by operator	2	None	7	112	Introduction of Electronic Batch Records	Eng, Ops, Aut 01DEC2022	EBRs introduced. Automatic transcription of data	8	1	1	8
	Sample missed	Process delays	8	Poor operator observation/training	1	Compulsory training	2	16	n/a	n/a	n/a				
				SOP not appropriate	2	Approved SOP for sampling and analysis	1	16	n/a	n/a	n/a				
				Lack of automated sample prompts	5	Approved SOP for sampling and analysis	5	200	Automated prompts when sampling is due	Eng, Ops, Aut 01AUG2022	Automated prompts when sampling is due introduced to control system	8	2	2	32

3. Fault Tree Analysis Example

- FTA is typically **deductive**
  - what caused a particular failure.

- Starts from an observed/assumed failure and looks at possible causes in the form of a “tree” of fault modes.

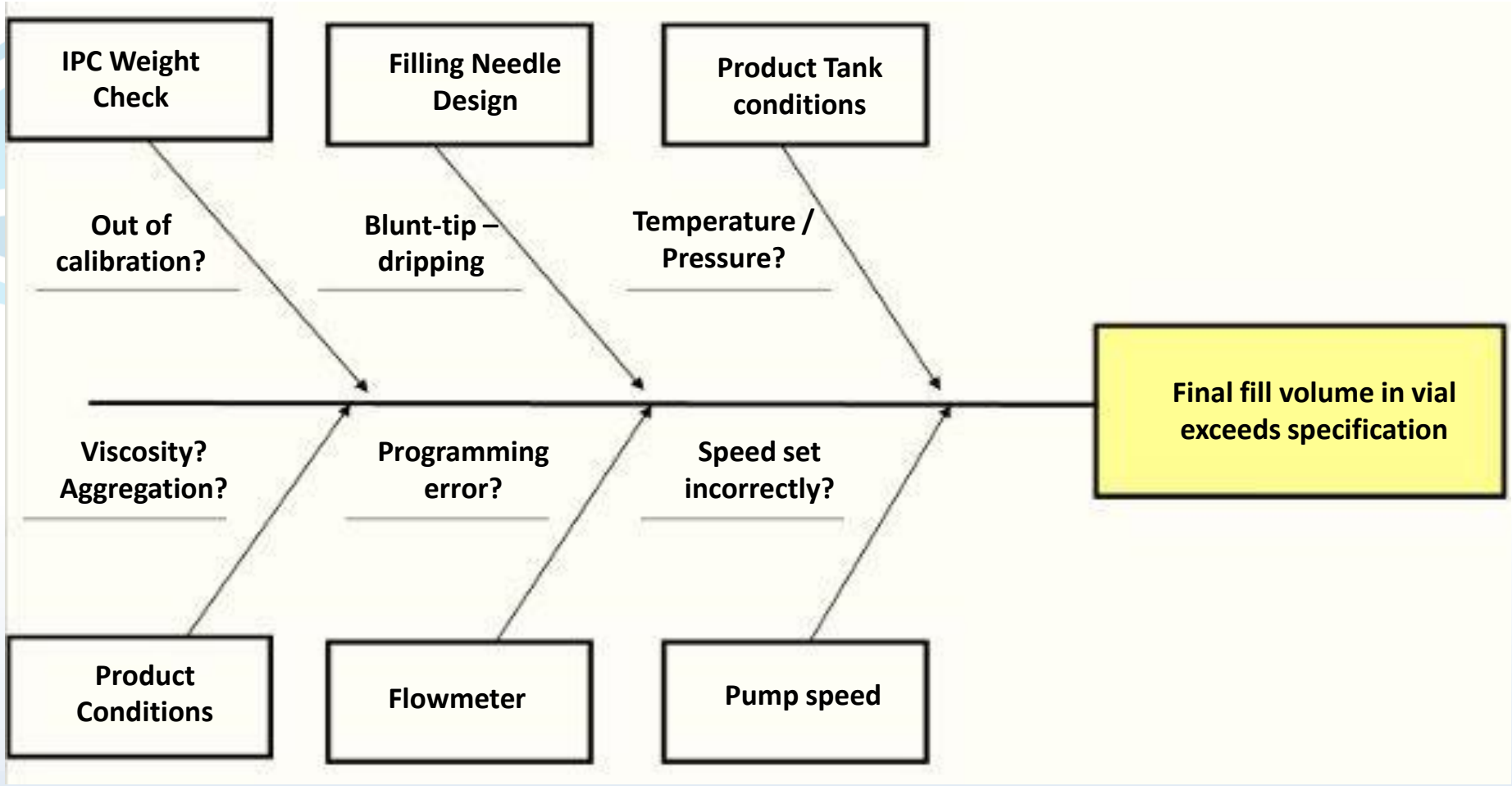
- Typically used for analysing:
  1. Hazards/faults that were previously identified using inductive techniques such as PHA, FMEA.
  2. Hazards/faults which occur during manufacture (in real-time).



4. Cause and Effect Analysis e.g. Fishbone (Ishikawa) Diagram

Cause and Effect Analysis is **a technique that helps you identify all the likely causes of a problem**

The problem shown is the Effect, and the contributing/ potential issues are the Cause.



5. Hazard Analysis & Critical Control Points (HACCP)

- HACCP is traditionally known to be a food safety management system intended to stop known hazards and to reduce the risks that they pose at certain points in the food chain.
- This methodology is now becoming increasingly popular in other industries such as biopharma.
- Good Manufacturing Practices (GMP) is used to control hazards affecting quality through the validation of critical operations and processes in the manufacturing process.
- HACCP can be applied here e.g., identifying sample points for environmental monitoring to ensure that cleanrooms/areas stay within required specifications, thus reducing the impact of environmental hazards to the product.

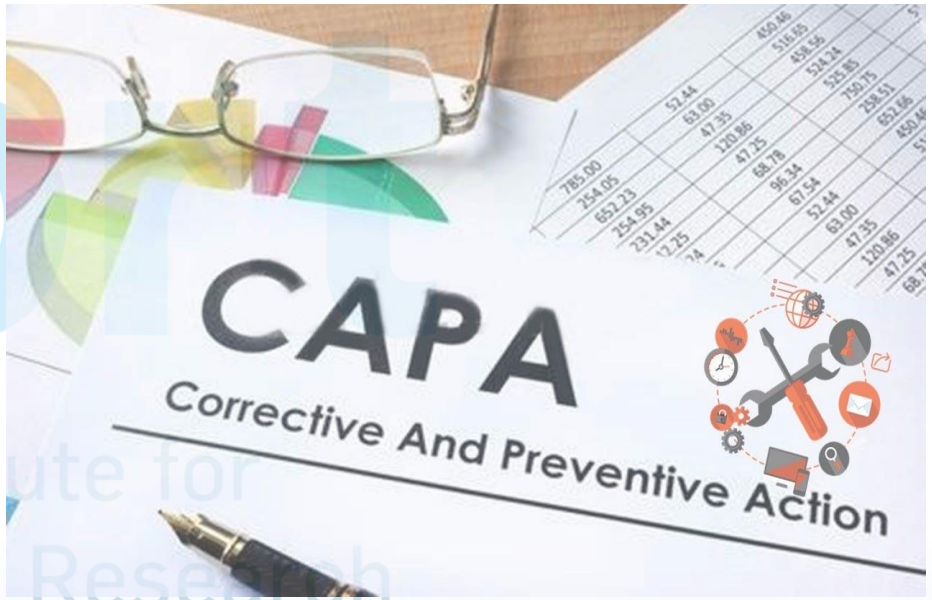
Risk Management - CAPAs

Corrective Action, Preventative Action (CAPA)

- Following an incident, corrective actions must be put in place to resolve the issue, and preventative actions must be put in place to prevent future occurrence.

Risk Assessment & CAPAs

- Early, inductive RA should reduce the number of incidents that occur, and thus the number of CAPAs required.
- Incorporating deductive RA into CAPAs should reduce the likelihood of an incident occurring again.



Process Performance and Product Quality Monitoring

Audits

- An organisation should continuously audit its processes to identify any gaps in its system, streamline operations and develop corrective actions

Complaint handling/Adverse effects tracking

- Feedback should be provided from both internal and external sources
- These can be linked to CAPA

Non conforming products

- Any non conforming products should be tracked and monitored, review and dispositioned and a corrective action should be generated directly

Supplier management

- Visibility into supplier performance is critical

Management Reviews

Reporting System

- Allows management teams to understand the quality challenges they face and provides them with the visibility to make better decisions
- Tracks progress, isolates problems, compares results and trends in data
- Allows company to take actions to mitigate risk

Topics

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QRM Case Study

- Let’s examine a case study in which a risk-based approach was used to evaluate a typical mammalian cell culture and purification process.
- This risk assessment used a Failure Modes and Effects Analysis (FMEA) to evaluate the impact of potential failures and the likelihood of their occurrence for each unit operation.
- Unit operations/process steps included in the process validation required a risk priority number greater than or equal to a specified threshold value.
- The risk assessment covered the entire process, and a portion of the assessment is reviewed here.

Initiation Phase

- Various activities must be carried out before initiating the risk assessment phase of a risk management program.

These activities are common to all types of risk analysis tools and include, but are not limited to:

1. Defining the scope of the assessment;
2. Team selection;
3. Establishing action thresholds for making decisions;
4. Defining the types of decisions to be made when the assessment is complete.

Defining the Scope

- The scope was confined to the primary unit operations of a mammalian cell culture and purification process.
- Defining the scope focuses the team's effort and ensures that all team members have the same level of understanding for the analysis phase.
- For example, failures that could result in an environmental spill were out of scope of this assessment.

Team Selection

- Team selection is also key to the success of a risk assessment.
- The team must be cross functional and represent the appropriate areas as defined by the scope.
- The team used for the process validation case study included individuals from four departments: validation, process development, quality, and manufacturing.
- This provided the necessary subject matter expertise to understand the details of running the manufacturing equipment and the design of the process.

Selecting a Risk Analysis Tool

- The RA tool will dictate the structure used throughout the risk assessment phase. The choice of tool depends on the logic of the tool and the amount of information and data available.
- In this process validation case study, a tool that looks forward in time was the best choice. The goal was to look at the types of failures that could occur and list the product quality consequences of each potential failure's occurrence.
- In this example, a very detailed level of understanding is assumed to exist through extensive process characterization work. Therefore, an inductive risk analysis tool that is designed to handle a well-defined process is needed – FMEA!

Risk Assessment

STEP 1: Review the process	Use a process flowchart to identify each process component. List each process component in the FMEA table. If it starts feeling like the scope is too big, it probably is. This is a good time to break the Process Failure Modes and Effects Analysis into more manageable chunks.
STEP 2: Brainstorm potential failure modes	Review existing documentation and data for clues about all of the ways each component can fail. The list should be exhaustive – it can be paired down and items can be combined after this initial list is generated. There will likely be several potential failures for each component.
STEP 3: List potential effects of each failure	The effect is the impact the failure has on the end-product or on subsequent steps in the process. There will likely be more than one effect for each failure.
STEP 4: Assign Severity rankings	Based on the severity of the consequences of failure.
STEP 5: Assign Occurrence rankings	How likely is it that a certain failure will occur?
STEP 6: Assign Detection rankings	What are the chances the failure will be detected prior to it occurring?
STEP 7: Calculate the RPN	Severity X Occurrence X Detection
STEP 8: Develop the action plan	Decide which failures will be worked on based on the Risk Priority Numbers. Focus on the highest RPNs. Define who will do what by when.
STEP 9: Take action	Implement the improvements identified by your Process Failure Modes and Effects Analysis team.
STEP 10: Re-calculate the resulting RPN	Re-evaluate each of the potential failures once improvements have been made and determine the impact of the improvements.

Risk Management

- At this point, the risk assessment phase ends.
- The risk management process would continue through the steps of risk control, risk review, and risk communication.
- This implies that over the course of the product's lifecycle, the risk assessment is reviewed.
- This review includes adjustments to regulatory requirements or to additional information related to the new process.

ICH Q9 – Quality Risk Management

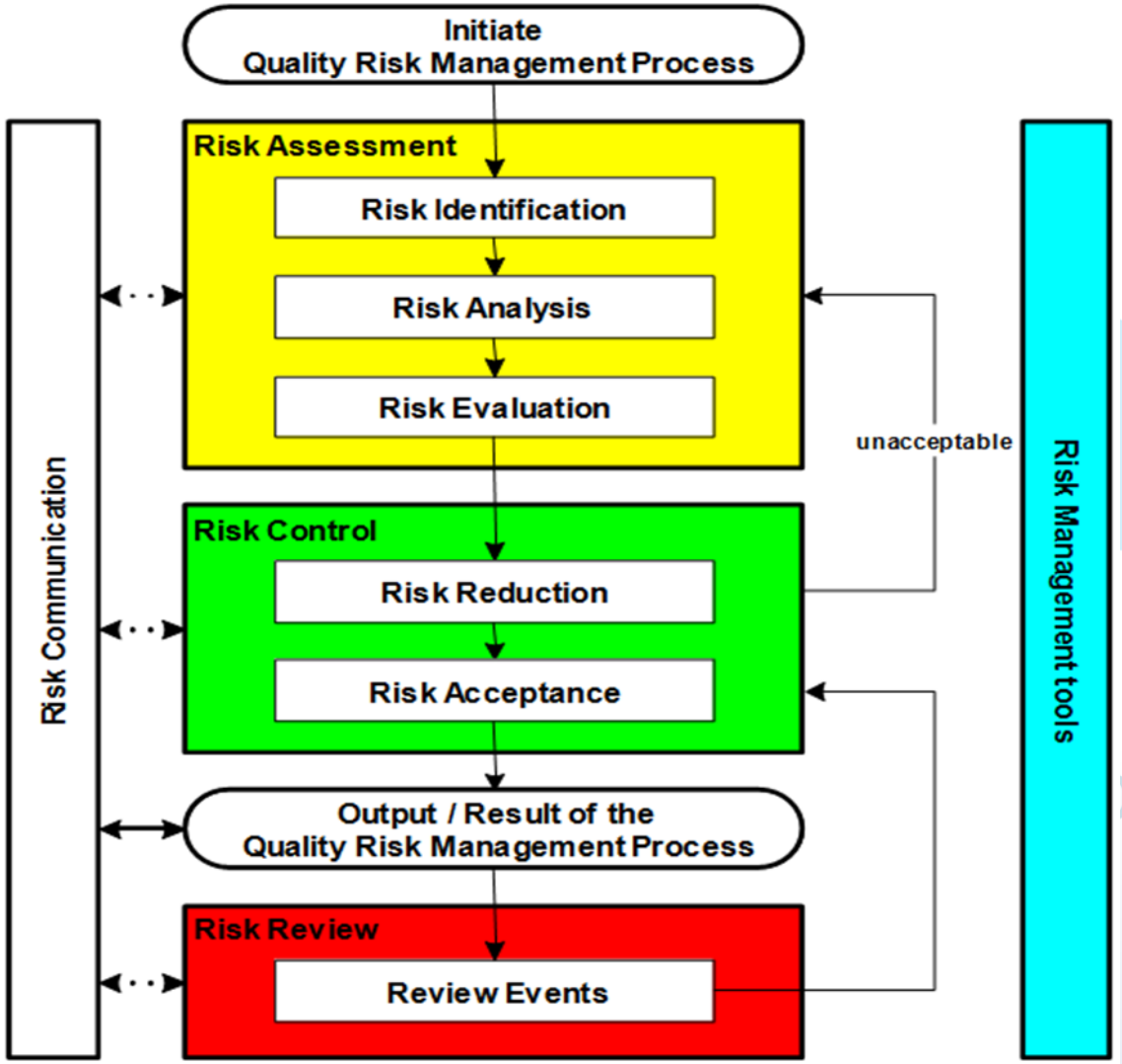


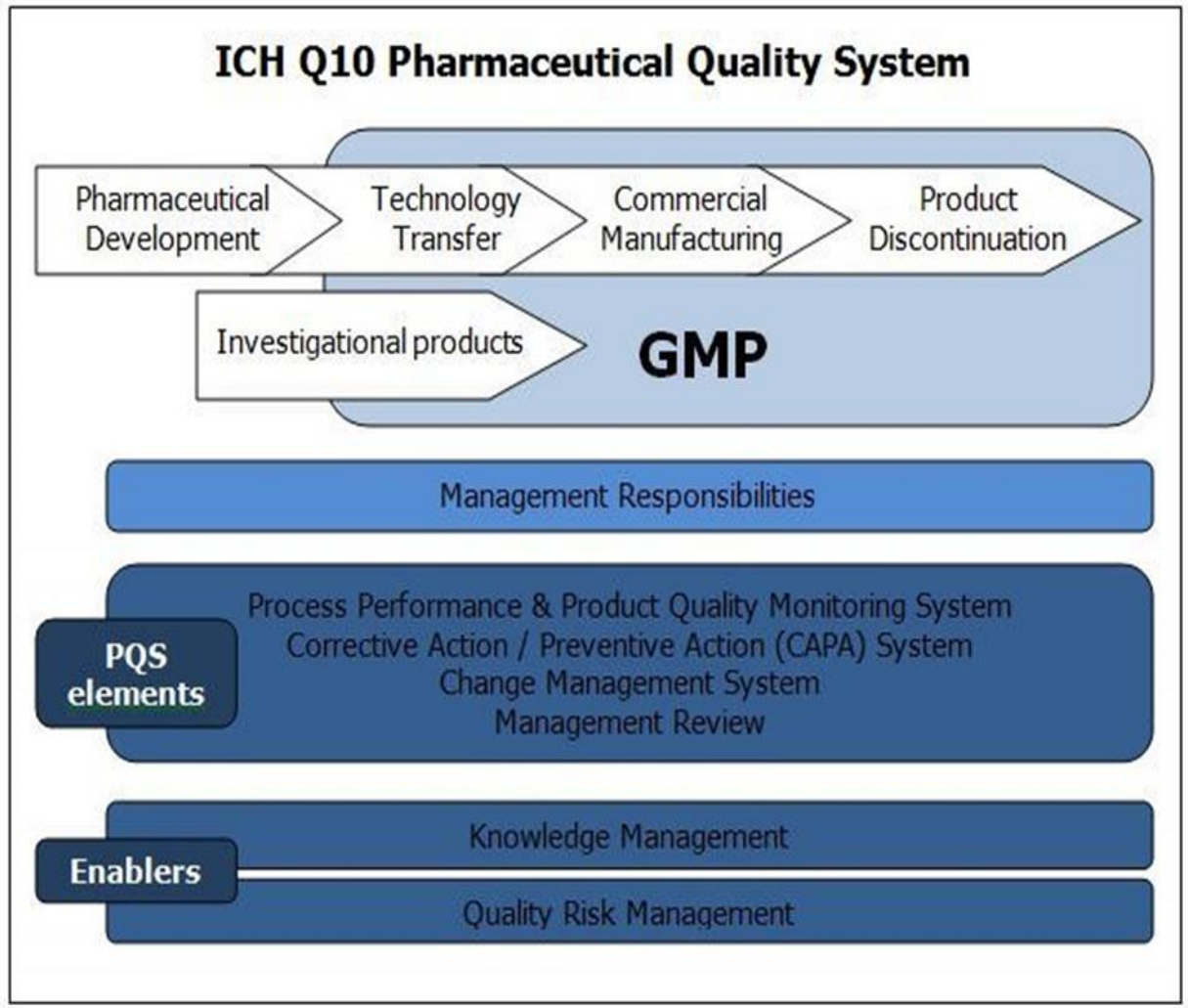
Figure 1: ICH Q9 QRM Process

- The ICH Q9 guideline, *Quality Risk Management*, provides a structure to initiate and follow a risk management process.
- The basic flow (Figure 1) for a risk management program consists of four major components:

1. Risk assessment,
2. Risk control,
3. Risk review,
4. Risk communication.

All four components are essential.

ICH Q10 – Pharmaceutical Quality System



- Risk management as an integral part of any pharmaceutical quality system as it "provides a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality".
- Further, it recommends this risk management should occur across the whole lifecycle of the drug product from development through to use and discontinuance.

Thank You