RISK ASSESMENT TOOLS

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

FDA announcement 27 Sep. 2004

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.

RISK MANAGEMENT

RISK MANAGEMENT - OVERVIEW

- Why to manage risk?
- Life cycle for risk management
- Design and development
- Elements of risk management
- Tools
- Risk analysis & Evaluation
- Risk Control & Communication

WHY TO MANAGE RISKS ?

- To balance cost against need - What will add value?
- To ensure that all risks are considered
- To establish priorities
- To help in planning validation projects

WHY TO MANAGE RISKS ?

- To ensure system / process performance and maintenance validated status
- To establish early warning system for loss of control - i.e. setting “Alert” and “Action” levels
- To assist decisions on batch disposition
- **To help in troubleshooting**

WHY TO MANAGE RISKS ?

- If done correctly,
  - Identifies critical control points
  - Connects to key characteristics
  - Enables focusing of resources
  - Provides a rational foundation for decisions concerning risk

DEFINITIONS ……

- RISK
  - The possibility of suffering harm or loss; danger

  This can be also defined as ….
  - Combination of the probability of occurrence of harm and severity of the harm

DEFINITIONS ……

- RISK ANALYSIS
  - A structured tool for the **evaluation of potential problems** which could be encountered in connection the use of a drug or device
  - What is the probably that something **will go wrong**, and what is **the benefit** to migrating that
  - Also **determines extent of validation**

DEFINITIONS ……

- HAZARD is any operation that could possibly could result in injury to personnel. THE POTENTIAL SOURCE OF HARM

- HAZARD ANALYSIS
  - What can go WRONG

WHAT IS RISK MANAGEMENT ?

RISK MANAGEMENT

Examine the cause of hazards and decrease the probability of their occurrence and reduce the consequences.

RISK MANAGEMENT

- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

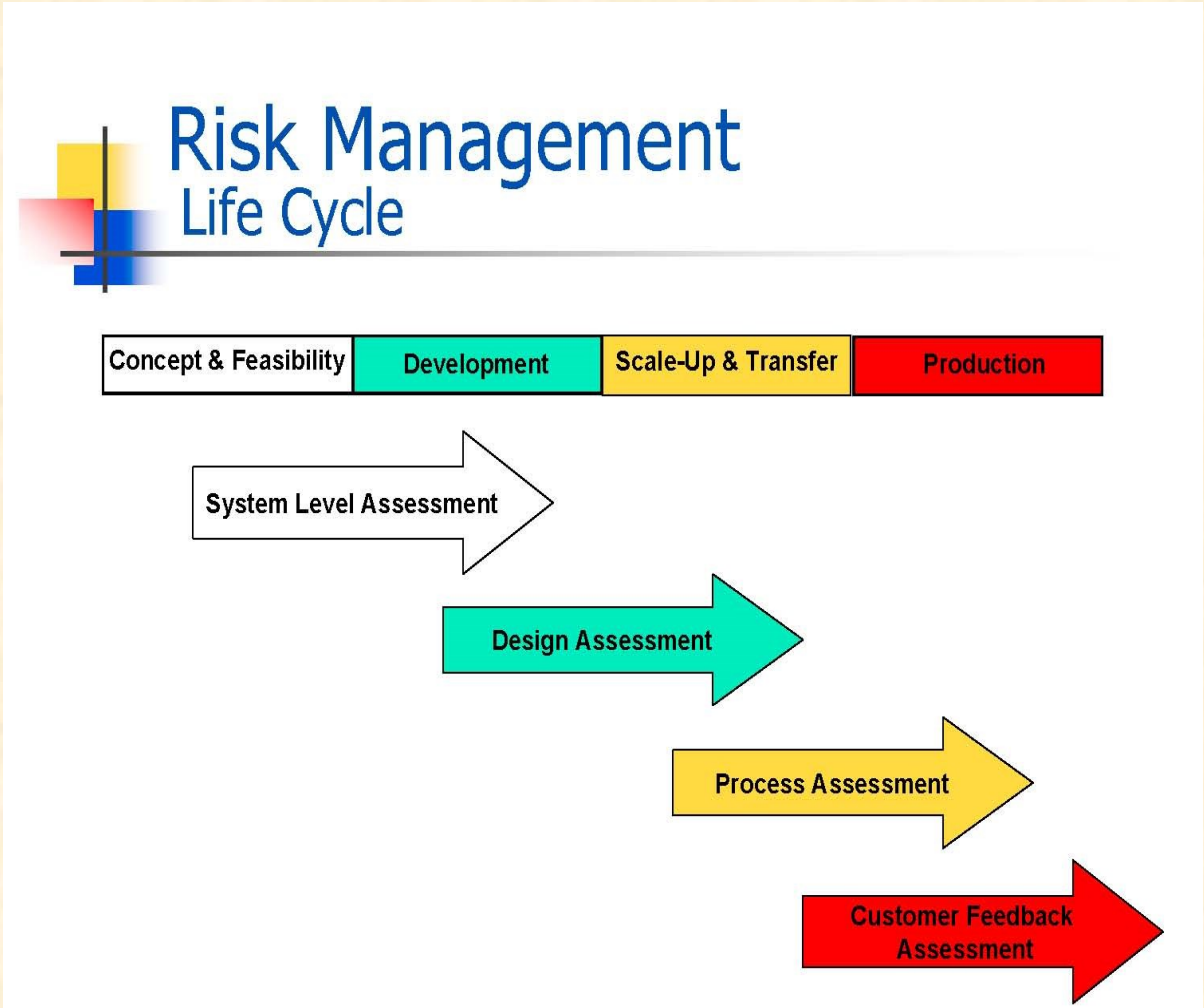
(ICH Q9 QUALITY RISK MANAGEMENT)

PRINCIPLES OF RISK MANAGEMENT

The evaluation of the risk to quality should be based on **scientific knowledge** and ultimately link to the protection of the patient; and

The level of effort, formality and documentation of the quality risk management process should be equal with the level of risk.

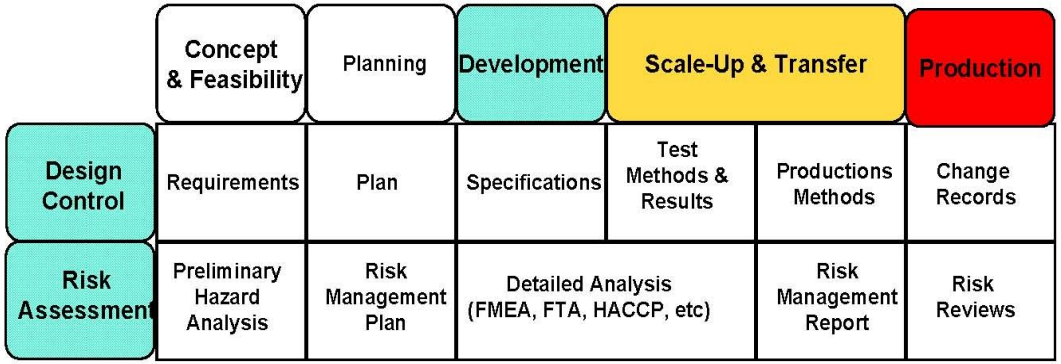
RISK MANAGEMENT



AREAS OF APPLICATION

- Product/facility design
  - Facility and Equipment Qualification
  - Process validation and Process Parameter
- Manufacturing controls
- Product failure risk
- Regulatory assessment
- Complaints
- Change control
- Patient safety

DESIGN & DEVELOPMENT



	Concept & Feasibility	Planning	Development	Scale-Up & Transfer		Production
Design Control	Requirements	Plan	Specifications	Test Methods & Results	Productions Methods	Change Records
Risk Assessment	Preliminary Hazard Analysis	Risk Management Plan	Detailed Analysis (FMEA, FTA, HACCP, etc)		Risk Management Report	Risk Reviews

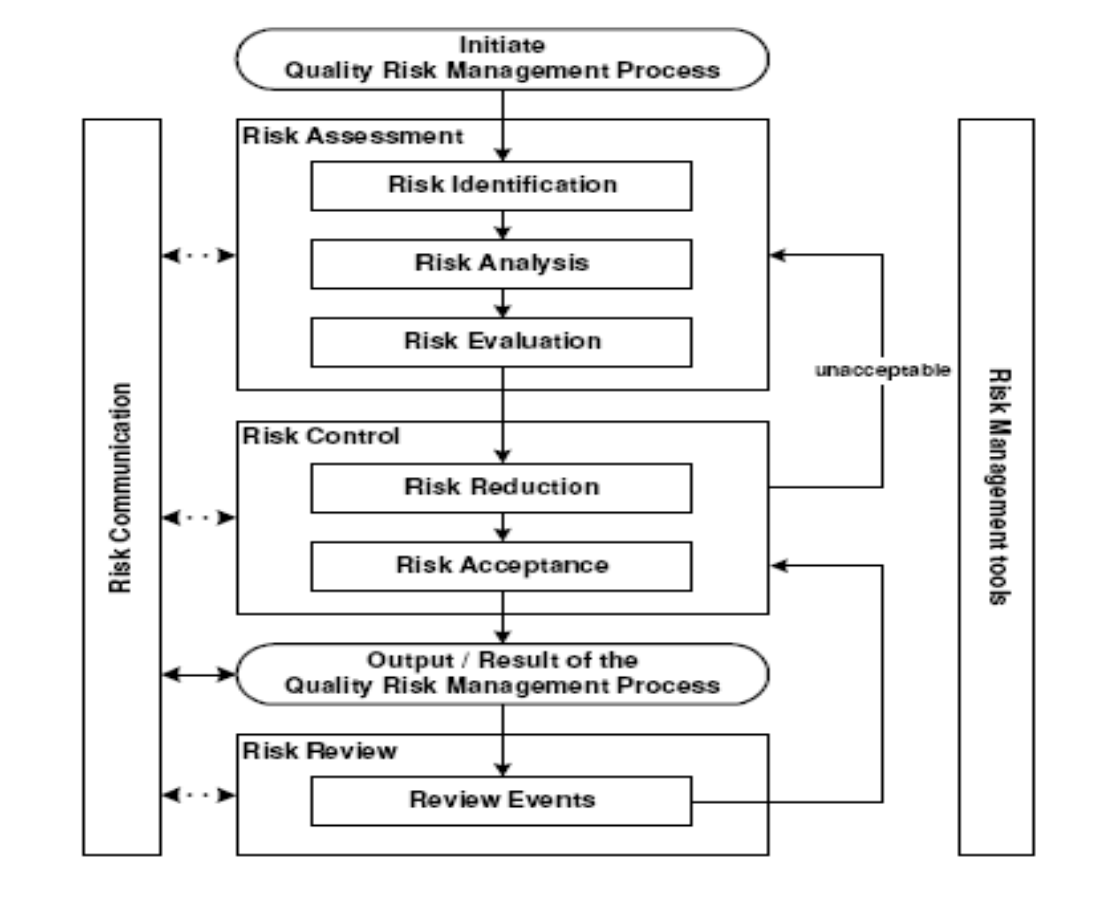
RISK MANAGEMENT

- Concept of risk has two components
  - **Probability** of occurrence
  - **Consequence**
- Both influence acceptability of risk and risk management action plan

RISK MANAGEMENT PROCESS

- Examine all processes
- Identify big risks
- Quantify consequence and probabilities
- Determine risk consequence
- Determine alternatives/option analysis
- Evaluate impact of regulations
- Develop controls to reduce probability
- Overall risk acceptance

RISK MANAGEMENT PROCESS



RISK MANAGEMENT PROCESS

- **INITIATION**

  Quality risk management should include **systematic processes** designed to coordinate, facilitate and improve **science-based decision** making with respect to risk.

RISK MANAGEMENT

- Quality risk management is a **systematic process** for the **assessment, control, communication** and **review of risks** to the quality of the drug (medicinal) product across the product lifecycle.

(ICH Q9 QUALITY RISK MANAGEMENT)

RISK MANAGEMENT PROCESS

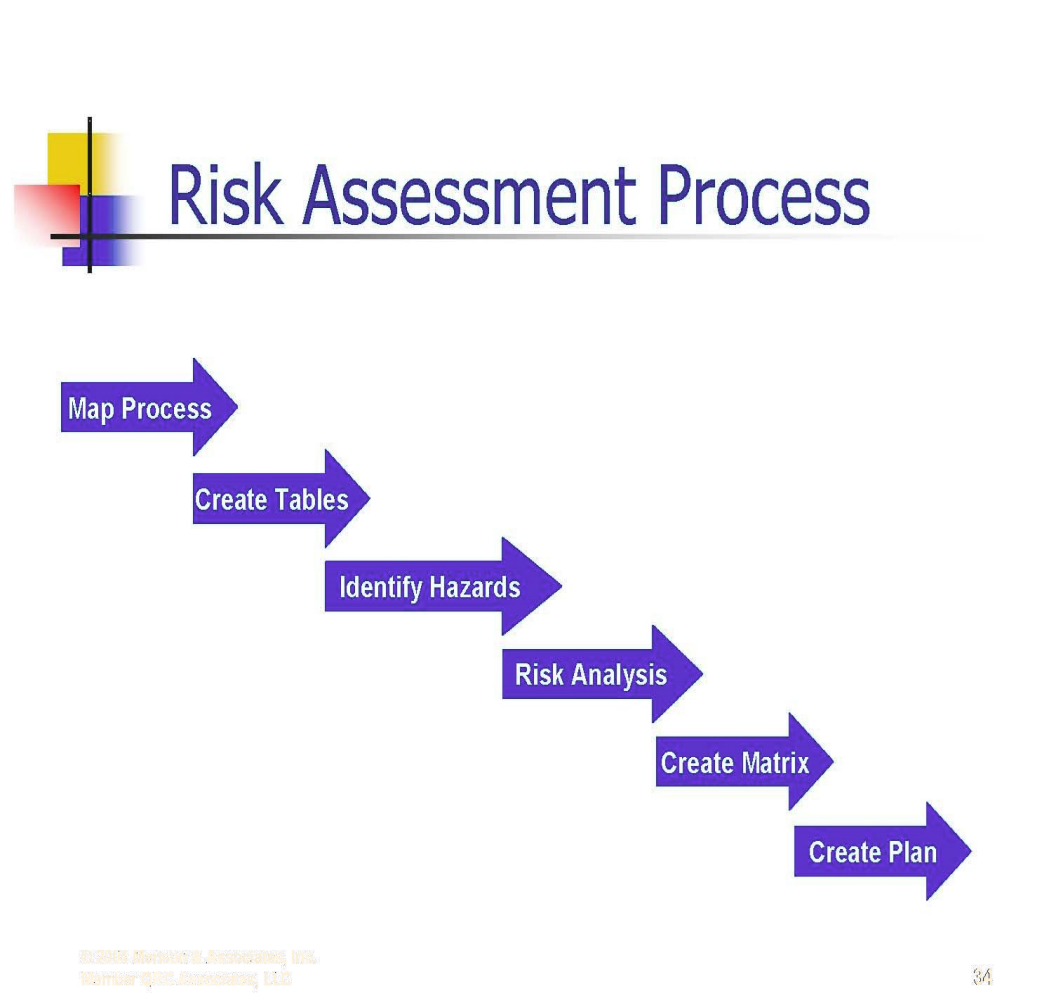
- **Define the problem** including pertinent assumptions identifying the potential for risk
- Assemble background **information and data** on the potential hazard, harm or human health impact relevant to the risk assessment
- **Identify a leader** and **resources**
- **Specify a timeline**, deliverables

RISK ASSESSMENT

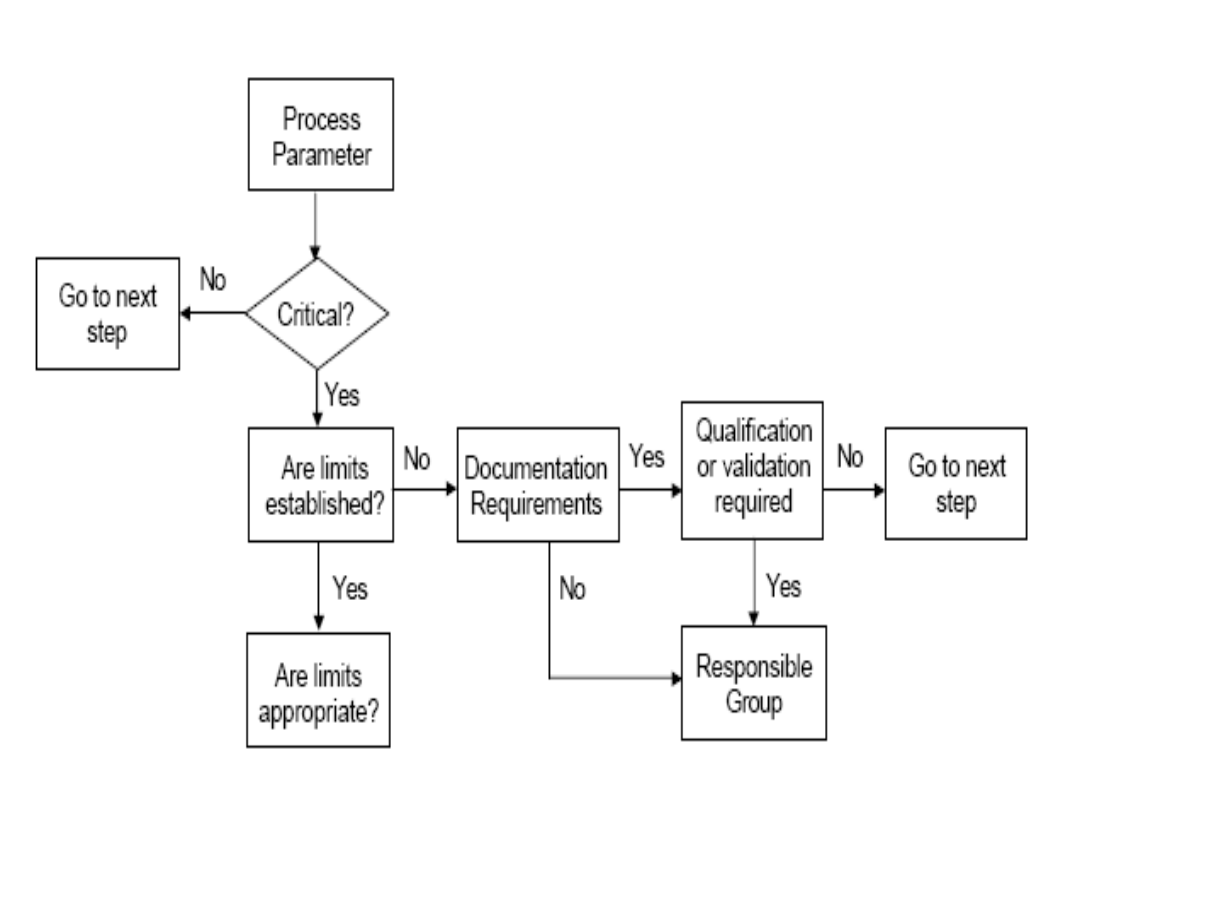
- Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards ….

1. What might go wrong?
2. What is the probability it will go wrong?
3. What are the consequences (severity)?

RISK ASSESSMENT



RISK ASSESSMENT



RISK ASSESSMENT

- **RISK INDENTIFICATION**

  (What could go wrong?)

- **RISK ANALYSIS**

  (What is the probability?)

- **RISK EVALUATION**

  (How much is severity?)

RISK IDENTIFICATION

RISK IDENTIFICATION

- ***Risk identification*** is a systematic use of ***information*** to identify hazards referring to the risk question or problem description.
- Risk identification addresses ***"What might go wrong?"***, including ***identifying*** the possible consequences.

RISK IDENTIFICATION

- Information can include
  - historical data,
  - theoretical analysis,
  - informed opinions, and
  - the concerns of stakeholders.
- This *provides the basis* for further steps in the quality risk management process.

RISK ANALYSIS

- Estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

RISK EVALUATION

- This compares the identified and analyzed risk against given risk criteria.
- Risk evaluations consider the strength of evidence for all three of the fundamental questions.

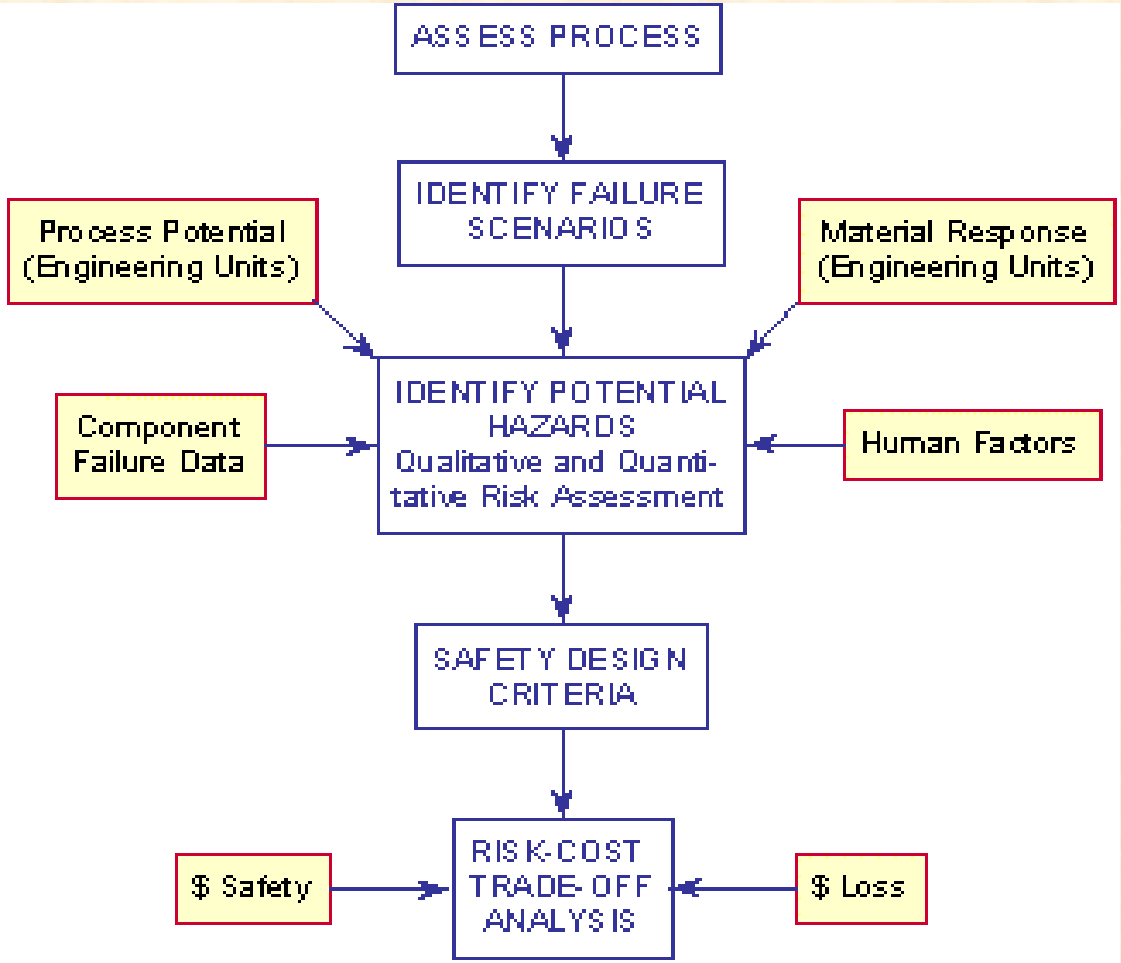
RISK MANAGEMENT TOOLS

- PHA
  (Preliminary Hazard Analysis)
- FTA
  (Fault Tree Analysis)
- HAZOP
  (Hazard Operability Analysis)
- FME(C)A
  (Failure Mode Effects (Criticality) Analysis)
- HACCP
  (Hazard Analysis and Critical Control Point)

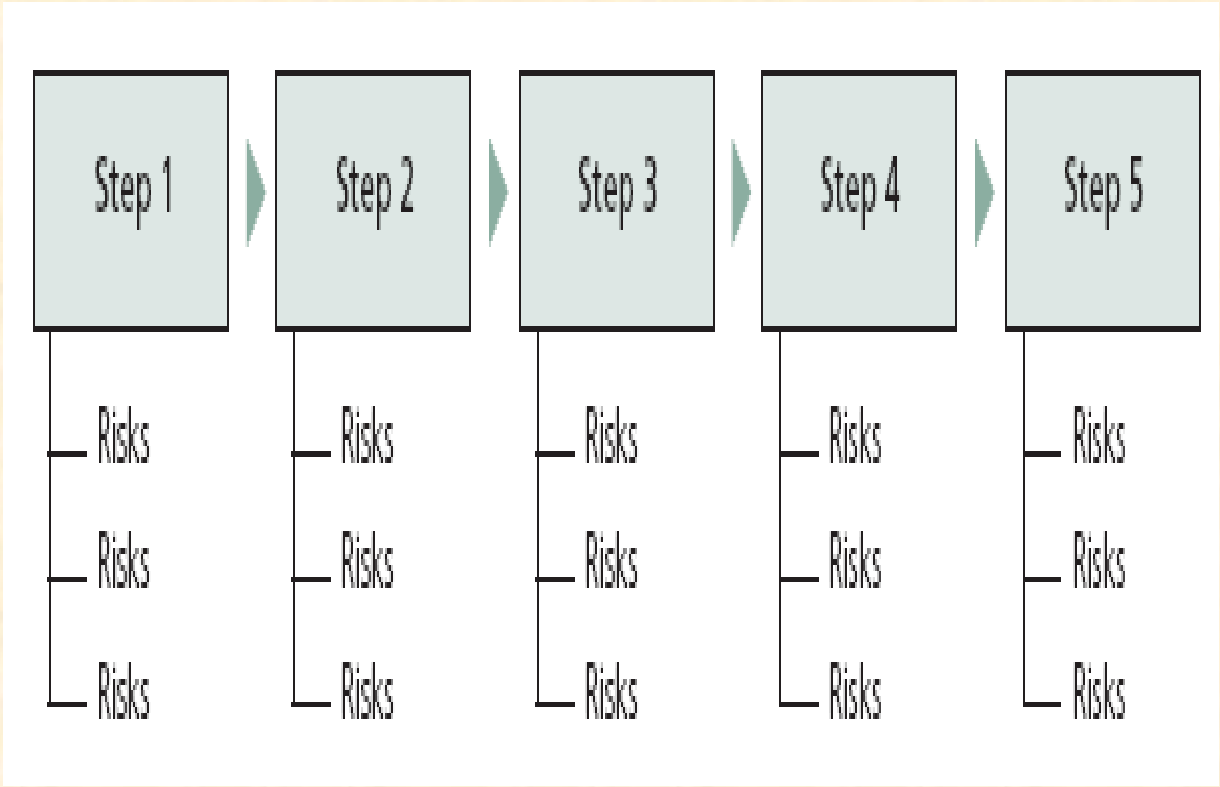
PHA (Preliminary Hazard Analysis)

- Good screening tool
- Used in early phases of design and development
- Less quantitative then FMEA/FMECA
- Does not require detailed product design
- Start with general product type

PHA (Preliminary Hazard Analysis)



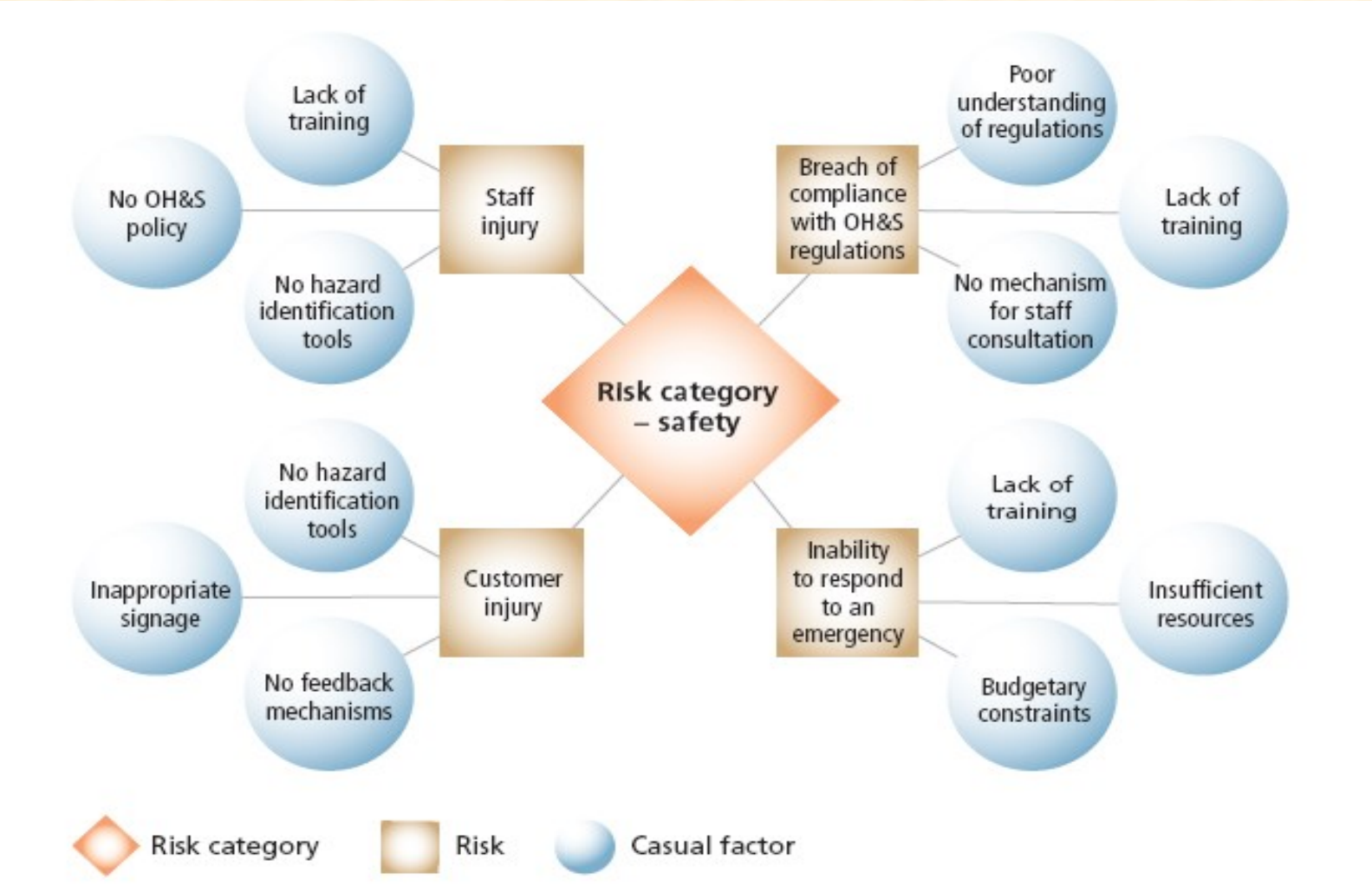
PHA (Preliminary Hazard Analysis)



FTA (FAULT TREE ANALYSIS)

- Assumes fault and analyzes possible causes
- Top down
- Can combine multiple causes
  - Operator error
  - Documentation error
  - Environmental error
- Graphical presentation – visual picture

FTA (FAULT TREE ANALYSIS)



FTA (FAULT TREE ANALYSIS)

- Limitations
  - Only as good as input
  - Needs FMEA as a complement
  - Requires input from many experts
  - Human errors are difficult to predict

HAZOP (Hazard Operability Analysis)

- Hazard and Operability study
  - Bottom up analysis
  - Deviations from design intentions
  - Systematic brainstorming based on guide words

HAZOP (Hazard Operability Analysis)

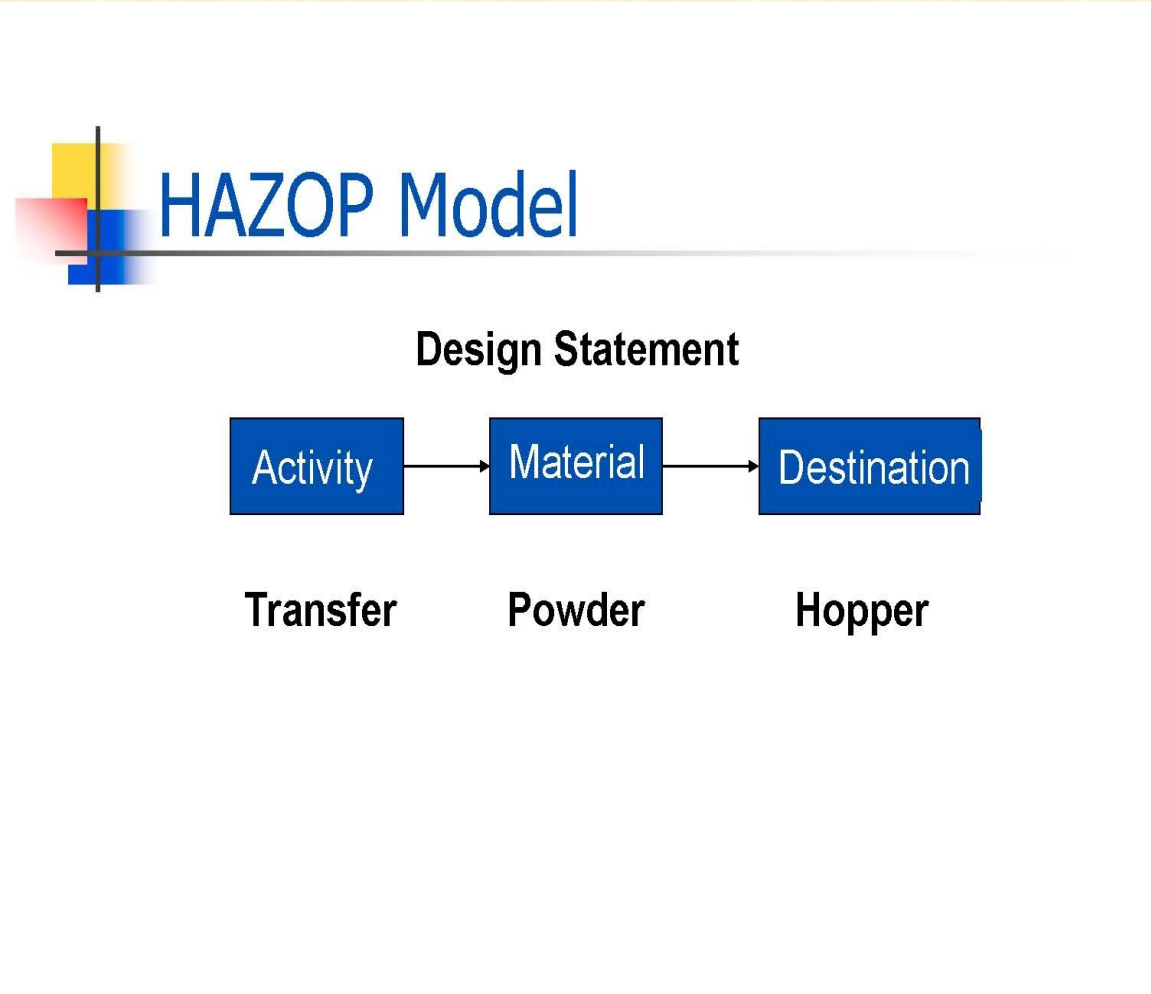
- The HAZOP team focuses on specific portions of the process called "nodes".

- Generally these are identified from the P&ID of the process before the study begins.

HAZOP (Hazard Operability Analysis)

- A process parameter is identified, say flow, and an intention is created for the node under consideration. Then a series of guidewords is combined with the parameter "flow" to create a deviations.
- For example, the guideword "no" is combined with the parameter flow to give the deviation "no flow".

HAZOP (Hazard Operability Analysis)



HAZOP (Hazard Operability Analysis)

HAZOP Plan

Guide	Deviation	Causes	Risk	Action	Who
NO	Powder flow	Valve closed Line blocked Pump broken	Low Med Med	Interlock Operator training PM	

FME(C)A (Failure Mode Effect (Criticality) Analysis)

- Evaluation and documentation of potential failure modes for
  - Product and /or
  - Processes
  - Its effect on product performance
- Problem mitigation through either
  - Elimination or
  - Reduction or
  - Controlling the potential failure

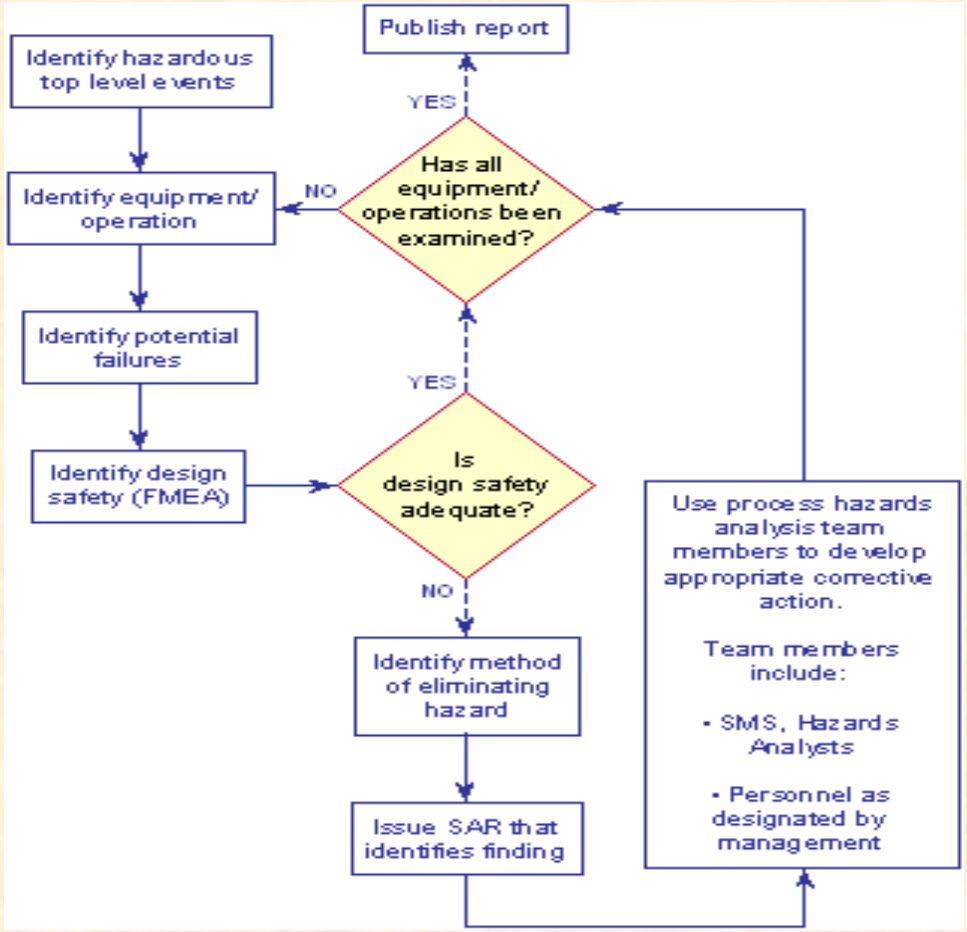
FME(C)A (Failure Mode Effect (Criticality) Analysis)

- Well documented in literature
- Methodical
- Breaks large complex products /processes into manageable steps
- Bottom up approach
- Complements FTA

FME(C)A (Failure Mode Effect (Criticality) Analysis)

- Powerful tool for summarizing:
  - Important modes of failure
  - Causative factors
  - Effects of these failures
  - Risk prioritization
  - Identify plan to control and to monitor

FME(C)A (Failure Mode Effect (Criticality) Analysis)



FME(C)A (Failure Mode Effect (Criticality) Analysis)

- FMEA should always be done whenever failures would mean potential harm or injury to the user of the end item being designed.

- The FMEA is applicable for System, Design, Process, Services & Software

FME(C)A APPLICATIONS

- Develop product or process requirements that minimize the likelihood of those failures.

- Evaluate the requirements obtained from the customer or other participants in the design process to ensure that those requirements do not introduce potential failures.

FME(C)A APPLICATIONS

- Identify design characteristics that contribute to failures and design them out of the system or at least minimize the resulting effects.

- Develop methods and procedures to develop and test the product/process to ensure that the failures have been successfully eliminated.

FME(C)A APPLICATIONS

- Track and manage potential risks in the design.

- Ensure that any failures that could occur will not injure or seriously impact the customer of the product/process.

FME(C)A BENIFITS

- Improve product/process reliability and quality
- Increase customer satisfaction
- Early identification and elimination of potential product/process failure modes
- Prioritize product/process deficiencies
- Capture engineering/organization knowledge

FME(C)A BENIFITS

- Emphasizes problem prevention
- Documents risk and actions taken to reduce risk
- Provide focus for improved testing and development
- Minimizes late changes and associated cost
- Catalyst for teamwork and idea exchange between functions

FME(C)A PROCEDURE

- Describe the product/process and its function. An understanding of the product or process under consideration is very important.
- Create a Block Diagram of the product or process
- List down the items, functions or components, list them in a logical manner under their subsystem based on the block diagram

FME(C)A PROCEDURE

- Identify Failure Modes. A failure mode is defined as the manner in which a component, subsystem, system, process, etc. could potentially fail to meet the design intent.

- Failure modes should be listed for function of each component or process step.

FME(C)A PROCEDURE

- Describe the effects of those failure modes. For each failure mode identified the team should determine what the ultimate effect will be.

- A failure effect is defined as the result of a failure mode on the function of the product/process as perceived by the customer.

FME(C)A PROCEDURE

- Identify the causes for each failure mode.
- A failure cause is defined as a design weakness that may result in a failure.
- The potential causes for each failure mode should be identified and documented.

FME(C)A PROCEDURE

- Enter the Probability factor.
- A numerical weight should be assigned to each cause that indicates how likely that cause is (probability of the cause occurring).
- A common industry standard scale uses 1 to represent not likely and 5 to indicate most probable.

FME(C)A PROCEDURE

- Identify Current Controls (design or process).
- Current Controls are the mechanisms that prevent the cause of the failure mode from occurring or which detect the failure before it reaches the Customer.
- Determine the likelihood of Detection.

FME(C)A PROCEDURE

- Detection is an assessment of the likelihood that the Current Controls (design and process) will detect the Cause of the Failure Mode or the Failure Mode itself, thus preventing it from reaching the Customer.
- Based on the Current Controls, consider the likelihood of Detection

FME(C)A PROCEDURE

- Review Risk Priority Numbers (RPN). The Risk Priority Number is a mathematical product of the numerical Severity, Probability, and Detection ratings:

RPN = (Severity) x (Probability) x (Detection)

- The RPN is used to prioritize items that require additional quality planning or action

FAILURE MODE AND EFFECT ANALYSIS (RISK ASSESSMENT)

Department: Stores **Date:**

Equipment / Process: Storage & dispensing of materials **Team:**

Code No. :

#	Potential Failure Mode	Potential Effect (Process/ End Users) or Consequences	S	Potential Causes	O	Current Control Measures	D	RPN	RPN Rank
1	Improper storage of RM and PM	Mix-up leading to adulteration. Wrong Issues / Accounting of material Physical / chemical effect on material.	4	Improper storage conditions No written / defined procedures Non availability of sufficient space for storage Untrained staff	2	Well defined Storage condition Storage condition of each material received in the unit is available with stores. Clear written down procedures for storage conditions. Temperature and humidity controlled area. Periodic temperature mapping of the area. Clear written down procedure to handle the situation of power failure Incorporation of data loggers wherever required Adequate space for storage of materials. Checking, Re checking & Certification procedure in practice Periodic training of concerned staff.	2	16	Rank V
2	Pest Control	Contamination & Cross contamination	5	Uncontrolled entry on receiving bay Inappropriate man- material movement	3	Controlled entry on receiving by, closed shutters provided. Separate man & material entry provided.	2	30	Rank II

S : Severity **O : Occurrences** **D : Level of Detection** **RPN : Risk Priority Number**

Compiled by : _____ **Approved by :** _____ **Authorized by :** _____

Date : **Date :** **Date :**

HACCP (Hazard Analysis &Critical Control Points)

The HACCP system is a scientific, rational and systematic approach to identification, assessment and control of hazards during production, processing, manufacturing, preparation and use of pharmaceutical preparations to ensure that they are safe when consumed.

Currently well adopted in FOOD INDUSTRY

APPLICATIONS OF HACCP PRINCIPLES

The HACCP system overcomes many of the limitations of the traditional approaches to quality control (generally based on `snap-shot' inspection and end-product testing), including

- ✓ Obtains meaningful representative information, in a timely manner and without the high cost of end-product analysis
- ✓ Reducing the potential for product recall

HACCP PROCESS MAP

- Conduct hazard analysis and identify preventive measures
- Identify critical control points
- Establish target levels and critical limits
- Monitor each control point
- Establish corrective action for each possible deviation
- Establish verification procedures
- Establish record keeping system

HACCP SUMMARY

- Focuses on potential hazards
- Assess hazards
- Establish control
- Focus on prevention
- Not a replacement for GMPs
- Science based
- Preventive
- Allows risk control

RISK ANALYSIS

- Estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

RISK ANALYSIS

Frequency of Occurrence	Severity			
	(1) Catastrophic	(2) Critical	(3) Marginal	(4) Negligible
(A) Frequent	1A	2A	3A	4A
(B) Probable	1B	2B	3B	4B
(C) Occasional	1C	2C	3C	4C
(D) Remote	1D	2D	3D	4D
(E) Improbable	1E	2E	3E	4E

Risk Categories:

High Serious Medium Low

Table 6.1 Qualitative risk analysis

	LEGEND	Extreme	High	Medium	Low					
	Consequence					Likelihood				
						Almost certain	Likely	Possible	Unlikely	Rare
	Commercial	Finance	Security	Safety	Legal and regulatory compliance	Almost certain to occur at some time.	Known to have been present or occurred/ likely to occur.	Not likely to occur in normal situations.	Unlikely to occur.	Has not occurred in the past and requires unusual circumstances to occur.
Significant	Significant loss of market share resulting in 10–30% loss of current clients and no increase in new clients over a three-month period.	Loss > 30% of total income or budget.	Fraud resulting in financial loss. Staff threat resulting in serious injury requiring hospitalisation. Significant reputation damage.	Death or multiple injuries requiring hospitalisation.	Investigation by authority and significant penalty awarded. Very serious litigation, including class actions. Closure of business.	Extreme	Extreme	Extreme	High	High
Major	Major loss of market share resulting in <10% loss of current clients. No new clients for 1–3 months.	Loss of 20–30% of total income or budget.	Fraud resulting in financial loss. Staff threat resulting in serious injury requiring hospitalisation. Some reputation damage.	Major injury requiring hospitalisation.	Major breach with potential major penalty and/or investigation and prosecution by authority. Major litigation. Future of the business threatened.	Extreme	Extreme	High	High	Medium
Moderate	Loss of market share. Current clients are retained but no new clients for 1–3 months.	Loss of 10–20% of total income or budget.	Staff threat resulting in some injury but no hospitalisation required. Minor reputation damage.	Minor injury – first aid required.	Serious breach with investigation by or report to authority. Moderate penalty possible.	High	High	Medium	Medium	Low
Minor	Minor loss of market share. Current clients are retained but new clients have visibly decreased (50% of normal uptake).	Loss < 10% of income or total budget.	Staff threatened, but no injury. No reputation damage.	No injury.	Low-level legal issue. Penalty or prosecution unlikely.	High	Medium	Medium	Low	Low

RISK EVALUATION

- This compares the identified and analyzed risk against given risk criteria.
- Risk evaluations consider the strength of evidence for all three of the fundamental questions.

RISK CONTROL

- Risk control includes decision making to reduce and/or accept risks.
- The purpose of risk control is to reduce the risk to an acceptable level.
- The amount of effort used for risk control should be proportional to the significance of the risk.

RISK COMMUNICATIONS

- Risk communication is the sharing of information about risk and risk management between the decision makers and others.
- The output/result of the quality risk management process should be appropriately communicated and documented

RISK REVIEW

- Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.
- The output/results of the risk management process should be reviewed to take into account new knowledge and experience.
- The frequency of any review should be based upon the level of risk.

SUMMARY

- Quality risk management supports a **scientific and practical approach** to decision-making.

- It provides **documented, transparent and reproducible methods** to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk

SUMMARY

- 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.

SUMMARY

- 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,
  - focusing our efforts and resources on the things that provide quality assurance to our customers.

Thanks