



## Pharmaceutical Quality and Risk Assessment: A Case study

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### ABSTRACT

The Quality Risk management is a systematic process for the assessment, control and review of the risks which occur in a process. When either source or problem is known, the series of events that a source may trigger or the events that can lead to a problem can be investigated. In order to identify the risks the ICH and FDA regulators has introduced Risk Management Plan (RMP) which helps to find out the risks and identify the risks. This work mainly deals with the identification and evaluation of risks associated with the pharmaceutical industry. In the present study was done on the risks assessment in the manufacturing of Drug A, Drug B and the equipment High Pressure High Vacuum sterilizer (HPHV). The risk assessment was done using the tools Fault Tree Analysis (FTA), Failure Modes, Effects and Criticality Analysis (FMECA). The basic ideology of this work is following the risk management plan to minimize the risks by predicting them through a proposed model which would ensure high quality zero defective drugs to the consumers. By following the risk management programs most of the risks can be predicted, corrected and prevented, without any discrepancies.

**Keywords:** Risk Management Plan, ICH, FDA regulators, HPHV, FTA, FMECA.

### INTRODUCTION

Risk management is process where it helps to find out the harm and severity of a risk in a process. The principle of quality risk management is defined in ICH Q9. According to that quality risk management includes elements such as risk identification, assessment mitigation, elimination and communication. Today quality risk management in pharmaceutical industry is considered as a valuable component of an effective quality system. Risk Management Plan (RMP) is a process that supports science based and practical decision when integrated into quality system. Quality management system (QMS) can facilitate both industry and regulatory personnel for better use of resources provide with proper training results in greater understanding of decision making process and building confidence in QMS outcome.<sup>1</sup>

### MATERIALS AND METHODS

#### Drugs

Drug A is an aromatase -inhibiting drug approved for treatment of breast cancer after surgery, as well as for metastasis in both pre and post-menopausal women.<sup>11, 12</sup> Drug B is a serotonin 5-HT<sub>3</sub> receptor antagonist it is used as an antiemetic often used during the chemotherapy.<sup>9, 13, 5</sup>

#### Equipments/Instruments<sup>14, 15</sup>

#### High Pressure High Vacuum sterilizer

The technique uses mechanical air removal using vacuum pump, thus eliminating chances of creating

air pockets with better temperature Uniformity. The drying of product which has been sterilized can be ensured by vacuum drying at the end of sterilized hold time.

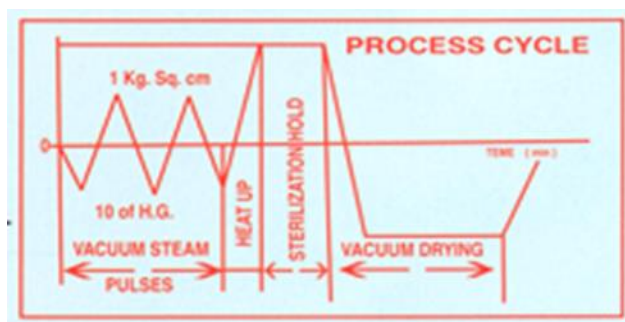


Figure 1: HPHV Sterilizer Process Cycle

### METHODS

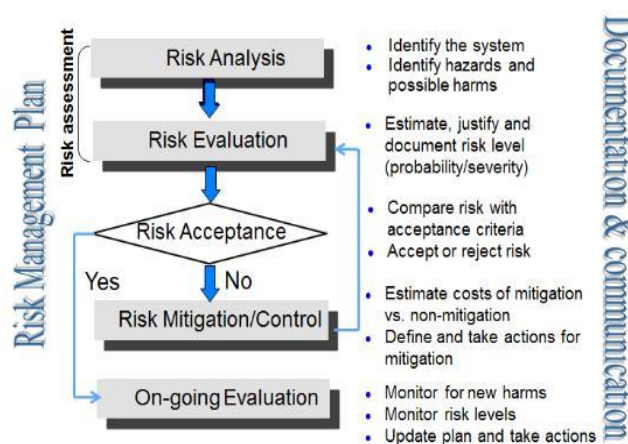


Figure 2: Risk Management plan



**Fault Tree Analysis (FTA)**<sup>1,3,7</sup>

Fault tree analysis is a deductive tool that assumes a failure of the functionality of a product or process. It can be used as a qualitative and quantitative structured tool. It is used to define a particular event and identify its root causes. Results are graphically visualized in a tree of fault modes and this is where the name comes from.

**Advantages and Limitations**

FTA has advantages and limitations.

Advantages are

- Highly systematic but also flexible
- The 'top-down' approach focuses attention on the failure effects which are directly related to the top event
- Useful for analyzing systems with many interfaces
- Pictorial representation helps to easily understand the system behavior

Limitations are

- Uncertainties in the probability of the base events are included in the calculations of the probability of the top event
- The static model does not address time interdependencies
- Fault trees can only deal with binary states (failed/not failed)

**Steps for FTA Analysis****Form a team and determine a team leader**

Team members should have a good knowledge; they should be experienced and well trained in FAT methodology.

**Definition of a problem and justification of the project**

Define the event or describe what it is that should be prevented. The primary reason for the project should be well justified. The definition should also clearly describe the scope and boundaries of the project. Most important is to clearly define the top event and to keep it in line with the project scope.

**Construction of the fault tree**

After acquired all the information about the process, list all possible root causes that could lead to the unwanted event. These "basic" events are linked through "intermediate" events to the top event in a flow chart. For the connection between top and basic events defined logical pathways should be used. A basic event can cause the top event on its own or in combination with others.

**Evaluate the fault tree**

The events are based on probability data. That is only possible if such data are available.

**Prepare a report**

The report should include a description and scope of the project, a system description, all relevant process flow diagrams, fault tree analysis listings and the FTA flow chart. It should also include a conclusion of the analysis related to the original question.

**Failure Modes, Effects and Criticality Analysis (FMECA)**<sup>1,2,10</sup>

Failure Modes and Effects Analysis (FMEA) evaluates a product process for strengths and weaknesses, for potential problem areas, risks or failure modes and prevents failures before they occur. FMEA has the highest impact and should be performed during design or development of a product or process when failures are less expensive to address. FMEA is a bottom up approach to failure mode analysis. It is a time-consuming methodology.

FMECA adds evaluation of the criticality including severity, occurrence and detectability and tries to answer the questions:

- How can a product or process fail?
- What is the likelihood that it fails and if so, what is the likelihood that the failure will be detected? and,
- What will be the effect on the rest of the process or system if a failure occurs and is not detected such that it can be corrected?

**Advantages and Limitations**

FMEA and FMECA have many advantages. They include:

- Wide applicability from design to manufacturing, servicing and maintenance of mechanical and electronic equipment.
- Identifies failure modes, their causes and effects on the system.
- Ideal for simple to medium complex systems.

Limitations include:

- Optimized for single individual failure modes, but they don't work well for combinations of failure modes.
- Can be time-consuming for complex systems.

**Assessment Process**

FMEA and FMECA require a very good knowledge of the product or process. The assessment process is the same as described.

1. Select a team and team leader. All team members must be subject matter experts.
2. Select the FMECA form from the company's Risk Management Master Plan or if not available, create one.



3. Train team members on the process and on criteria for ranking likelihood of occurrence and impact of failure when it occurs.
4. Distribute the documents to all the group members to make them familiar and to get the same understanding among all the group members.
5. Set up one or more brainstorming meetings. Multiple sessions are recommended for complex product/process designs. Individual sessions can focus on subsets of the entire product/process.
6. Brainstorm the product or process design for possible failures. Document the outcome on a flipchart. In the brainstorming meeting the risk management team identifies all possible failures.
7. Sort all suggested failures by categories.
8. Combine or remove similar or duplicate entries.
9. Document potential effects on the system, subsequent operation and end user (e.g., patient).
10. Assign rating factors for each identified severity, occurrence and detectability. Definition and scale of rating factors should be taken from the company's Risk Management Master Plan not only to ensure objectivity and consistency with the project team but also with other risk

management projects. Justify the rating with reference to the plan. For occurrence, historical data from the same or similar projects can be used.

11. For each identified effect list all possible causes of failures with justifications and with all uncertainties.
12. Calculate the risk priority number using the formula from the Risk Management Master Plan. The RPN is a measure for the overall risk associated with the project.
13. Take actions to reduce potential critical risks.
14. Assign owners, a schedule and deliverables for the actions.
15. After the action has been implemented make a new rating for severity, occurrence and detection and calculate the RPN.

The overall risk number is calculated from the probability and severity and the decision is made on which potential failures require risk reduction. Possible follow-up actions could be redesign of products or processes such that either the probability of occurrence or severity factors is reduced such that the overall risk priority number is also reduced.

**Table 1:** Risk ranking method (RPN)

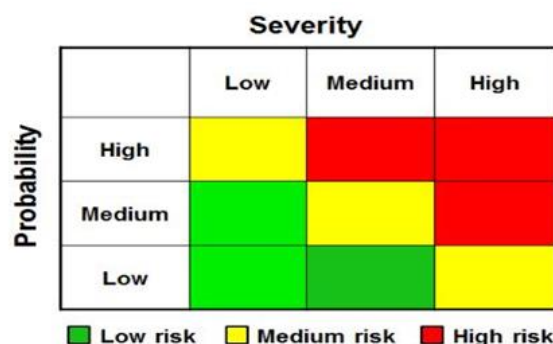
Numerical Ranking	Severity	Frequency of occurrences	Detectability	Max Risk Score
1	Potential minor patient injury, but not permanent. Minor regulatory Compliance issue that can be Corrected.	Isolated occurrences	High ability to identify the risk, and take action to avoid	1
2	Potential serious injury, but not Permanent. Significant regulatory compliance issue	Moderate Likelihood of occurrence	Moderate	8
3	Potential death or permanent injury; Major regulatory compliance issue	Inevitable at some point.	Low ability to detect the risk, and take action to avoid	27

Severity means: How big is the problem if it occurs?

Probability means: What is the likelihood that a problem occurs?

Detectability: what is the ability to monitor the performance of process?

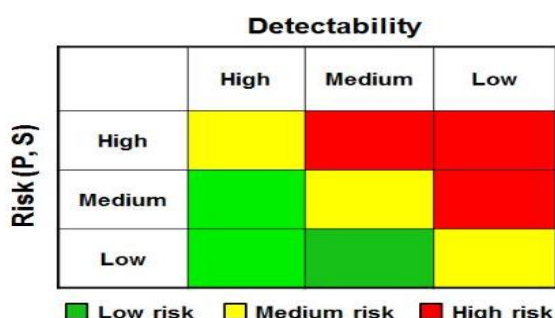
The score of categories is usually 3, 5 or 10 but can be any number up to or more than 10. ICH does not give any preference. The number can be fixed in the master plan for all projects or you can allow two or three options. For example, the final number for a specific project could be dependent on the confidence of the estimates.



**Figure 3:** Graphical determination of risk

### Graphical Determination of the Overall Risk

After values for severity and probability have been assigned, the overall risk is determined. This can be done graphically as shown in Figure 3. Severity levels low, medium and high are drawn as columns and probability as rows. All cells in green are low risk, in yellow medium risk and cells in red are defined as high risk.



**Figure 4:** Graphical determination of risk including detectability

The equivalent graph including detectability is shown in Figure 4. Risk as identified in Figure 6 is drawn using detectability as columns starting with high on the left.

### Determination of the Overall Risk with Risk Priority Numbers

Levels for severity as described before can be converted to numbers, for example 'low' becomes a 1, 'medium' a 2 and 'high' a 3. This is especially convenient for assigning the risk for routine applications for the determination of the overall risk.

Risk priority numbers (RPNs) are calculated from severity and probability levels using the formula:

$$RPN = \text{Severity (S)} \times \text{Probability (P)}$$

Risk (RPN) is expressed as the multiplication of severity with occurrence and detection

$$RPN = S \times O \times D$$

In the example in Figure 6 the RPN can go from 1 in the left lower cell to 9 in the right upper cell. RPNs from 1 to 2 are equivalent to low, 3 to 5 are medium and 6 to 9 are high risk.

### RESULTS AND SUMMARY

In packing area all machines works by air pressure, so if there is any problem in the supply of air may leads to breakdown of the machine. Weighing balances are to be calibrated daily and even when there is change of batch. Air, vacuum pressures are to be maintained continuously to overcome the problem.

**Table 2:** Risk assessment of warehouse

Instrument name /facilities	Causes of Risk	Severity (S)	Occurrence (O)	Detection (D)	Risk Priority Number (SxOxD)	Steps to overcome risks
Warehouse	1. Slips and trips, manual handling, working at heights, forklifts and other vehicles and moving or falling objects.	3	2	1	7	<ul style="list-style-type: none"> <li>Proper training should be given for the workers working in the warehouse.</li> <li>Mock drills are to be conducted.</li> <li>Safety equipments like helmets, radium jackets, fire extinguishers are to be used.</li> </ul>
	2. Improper material handling leads to mix up and cross contamination of the raw materials (API), and tracking of materials, handling of materials, and segregation of materials are difficult.	3	3	3	27	Bar coding systems, Online tracking system of materials. Manual inspection of labels in each and every step. Rejected materials are stored separately, API should be stored as per specifications in order to prevent the contamination and degradation. API should be handled only by authorized persons by wearing gloves, masks etc.,
	3. Misplacing of packaging materials leads to misuse.	3	2	3	18	Log book should be used and continuous monitoring should be done by authorized persons.
	4) Improper dispensing of raw materials leads to batch failure.	3	3	3	27	Dispensing persons should be well trained, instruments like weighing balance, laminar air flow and temperature regulatory systems should be properly maintained and calibrated,
	4) Improper dispensing of raw materials leads to batch failure.	3	3	3	27	Dispensing persons should be well trained, instruments like weighing balance, laminar air flow and temperature regulatory systems should be properly maintained and calibrated,

**Table 3:** Risk assessment of manufacturing of tablet (Drug A, Drug B)

Instrument name	Causes of Risk	Severity (S)	Occurrence (O)	Detection (D)	Risk Priority Number (SxOxD)	Steps to overcome risks
1) Planetary mixer	Steam flow problem. Temperature Inlets. Mixture speed timing and Impeller Problem	2	2	3	12	Continuous monitoring is to be done in case of steam temperature and Mixture speed. Impeller should be regularly observed. Steam and temperature systems are properly calibrated.
2) RMG (Rapid Mixer Granulator)	Chopping speed and impeller problem Air supply problem, Torque, Voltage Fluctuations	2	2	3	12	Speed of chopper and impeller are properly adjusted. Torque is continuously monitored. Supply of air and electricity is monitored.
3) Fluidized Bed Dryer:	Pressure problems Filter bag problem Ex: Leakage, in proper setting of filter bags	3	2	3	18	Filter bag are properly cleaned after each and every batch. Person should be well trained. Pressure gauges are properly monitored.
4) Shifter and Multimill:	Screen integrity should be proper Hot materials should not be used which may leads to color change or melting of materials	3	2	3	18	Screen should be properly fitted without any gaps. Proper training should be given to the operator and screen integrity should be proper
5) Contabin blender:	RPM problem, Vent filter problem and Leakage wall problem	2	3	3	18	RPM problem, Vent filter problem, Leakage wall problem and Time cycle
6) Compression machine:	Hydraulic system problem, Air supply problems, Manual errors And Punching problems.	3	3	3	27	Hydraulic system should be properly monitored before each and every batch. Person should be well trained. Punches should be properly cleaned for each and every batch.
7) Coating Machine:	Color variation of tablets in the same batch. Sticky problems. Embossing filled with coating material. Fan speed and temperature problem. RPM problems.	3	3	3	27	Person should be properly trained. Fan speed should be properly adjusted in each and every batch. Every batch should be loaded at a time interval of 2 minutes. Inlet and bed temperature should be maintained. And RPM should be set based on shape of the tablets.

**Table 4:** Risk assessment of Drug a Drug B

Stages of Risk	Drug A	Drug B	Comments
Nature of Drug	Used to treat breast cancer in post-menopausal women.	Anti-emetic for most chemotherapy patients.	Both are anti-cancer drugs, so risk should be reduced and improve the drug safety.
Warehouse	High RPN	Medium RPN	Drug A is temperature sensitive than Drug B.
Manufacturing	Medium RPN Wet granulation	Medium RPN Wet granulation.	Drug A: Povidone and Water is used as a binder. Drug B: Water is used as a binder.
Compression	Low RPN	Low RPN	Small problems like chipping, tapping, cracking.
Packing	High RPN	High RPN	Packing plays a vital role in both the drugs.
Market Complaints	Medium RPN	Low RPN	Drug A: Black particles in container. Drug B: Less tablets in the container.

**Table 5:** Risk assessment of high pressure and high vacuum sterilizer

Instrument name	Causes of Risk	Severity (S)	Occurrence (O)	Detection (D)	Risk Priority Number(SxOxD)	Steps to overcome risks
HPHV	Vacuum problem	2	3	2	12	Vacuum gauges should be properly checked
	Steam problem	3	2	3	18	Steam inlets and outlets should be properly cleaned
	Breaking of sterilization hold cycle	3	3	3	27	Sterilized hold cycle should not be broken
	Chamber leak	1	2	1	2	Chamber jacket should be properly locked
	Heat up problems	2	3	3	18	Heat should be uniformly distributed in all directions of chamber by the aid of fan.

## Summary

The present study was done on the risk assessment of the Drug A, Drug B and HPHV using the tools FAT and FACE. During the process of study on Drug A, Drug B the various parameters such as nature of drug, warehouse, manufacturing, compression, packing and market complaints were taken into consideration, and it is found that the Drug A was giving high RPN than Drug B. Therefore, during the manufacturing of the Drug A the suggested steps to overcome the risks should be implemented.

In the study of HPHV sterilizer during its process various parameters such as vacuum problem, steam problem, breaking of sterilization hold cycle, chamber leak, heat up problem parameters were considered, based on severity, occurrence and detection risk priority number was given. Breaking of sterilization hold cycle was given high RPN. So steps were suggested to overcome the risk i.e., sterilization hold cycle should not be broken on any circumstances.

**Table 6:** Risk assessment of packaging area

Instrument name	Causes of Risk	Severity (S)	Occurrence (O)	Detection (D)	Risk Priority Number (SxOxD)	Steps to overcome risks
1) Air jet cleaner:	Voltage fluctuations, Pressure problems air and vacuum	3	2	1	6	Visual inspection of bottles. Continuous monitoring air and vacuum pumps. Maintain a log book to note the readings of change.
2) Counting and Filling machine:	Due to vibration problem, Power fluctuation, Shelter closing problem and in proper setting of parameter	3	3	2	18	Visual inspection and Weight checking by using automated weighing balance
3) Rayon plug insertion machine:	Improper quantity of cotton plug insertion in to the bottles, Air pressure and fluctuations in power supply	2	1	1	2	Visual inspection Continuous monitoring and maintaining log book
4) Cap fitting machines:	Torque, problem and Threading problem.	3	1	3	9	Staff should be well trained. regular calibration should be done
5) Electronic balance:	Air difference leads to the proper working.	3	3	3	27	Proper air should be maintained.
6) Induction sealing:	Overheating leads to leak in sealing and even temperature sensitive drugs may get spoiled.	3	2	3	18	Proper temperature is to be maintained throughout the process
7) Label sticking:	Improper spreading of air, Air gaps, Improper batch number, coding problem. Cross labeling and Over printing	3	3	3	27	Checking (inspection), Manual inspection. Automatic camera bar code scanning.
3) Rayon plug insertion machine:	Improper quantity of cotton plug insertion in to the bottles, Air pressure and fluctuations in power supply	2	1	1	2	Visual inspection Continuous monitoring and maintaining log book

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