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Quality risk management in manufacturing of oral dosage formulations

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Abstract
The risk management program consists of four major components: risk assessment, risk control, risk review, and risk communication. All four components are essential. All the above methods should address the mentioned four basic components. Team selection and method selection are also plays a vital role in the risk management process, so care should be taken while selection of risk management team and method. FMEA/FMECA is the preferable method for risk management in the pharmaceutical industry as FMEA analysis include higher reliability, better quality, increased safety and its contribution towards cost saving includes decreased development time and reduced waste and non-value added operation.

Keywords: risk based approach, risk management program, patient safety, failure modes and effects analysis (FMEA), product quality, pharmaceutical industry

1. Introduction
QRM is a major tool and can be applied to different aspects of pharmaceutical quality system i. emanufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, biological, drug products, and biotechnological products, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products.

1.1 The FDA'S risk-based approach
FDA has concluded that modern quality system can handle many types of changes related to facilities, systems, equipment and process without permission of regulatory submission by using effective risk management practices. Robust quality system and appropriate process knowledge can implement many types of manufacturing improvements.

2. Quality Risk Management
2.1 Quality Risk Management Process
Risk assessment, Risk Identification, Risk analysis, Risk Evaluation, Risk Control, Risk Reduction, Risk Acceptance and Risk Communication

2.2 Quality Risk Management Techniques/Tools
Following risk assessment techniques are widely used depending on appropriateness of the technique.
Failure mode and effect analysis (FMEA), Hazard and Operability study (HAZOP), Hazard Analysis Critical control Point (HACCP), Failure Mode, Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Process Decision Programme Chart (PDPC)

Failure mode and effect analysis (FMEA): Examples of simplified FMEA Table

Table 1

Sr. No.	Potential Failure mode	Potential Effect (Process / End users) or Consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1.	Temperature and RH of processing areas goes out of limit	This may affect product stability. It may increase bio load of area.	3	Malfunctioning of AHU system Power failure	2	It is specified in the procedure that if Temperature and RH goes beyond set limit operation should be suspended till conditions are restored.	1	3 x 2 x 1=6	Current control Measure are adequate
2.	Differential pressure goes out of limit	May lead to cross contamination.	5	Improper air balancing. Malfunctioning of Air Handling units	2	Alarms are provided for differential pressure failure. Differential pressure is recorded daily. It is specified in the procedure that details care to be taken in case of AHU failure. Restrict man movement and opening of doors.	1	5 x 2 x 1=10	Current control measures are adequate.
3.	Cross contamination of one product with other product.	Undesirable therapeutic effect on patient.	4	Common equipments in the process are not cleaned as per	1	Cleaning methods for machine are validated. Standard operating procedures are available for product to	1	4 x 1 x 1=4	Current control measures are adequate

				standard operating procedure. Common AHU. Differential pressures are not maintained. Improper area cleaning		product and batch to batch cleaning. All the persons involved in the cleaning operation of equipments are trained and periodically retrained. Cubicle dedicated AHU's are provided for compression area. Set standard operating procedure area cleaning is available and followed.			

3. Conclusion

Effective Quality Risk Management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight.

4. Results and Discussions

Batch Details for study

As per plan of work the study has been conducted at the design stage of OSD facility and during validation stage / performance qualification–

Following are the product / batch details used during to perform quality risk management:

BMR Number: BMR/PLCE 300 mg/01

1. Product Name: Placebo tablets
2. Product Code: PLCE 300 mg
3. Batch Size: 333,333
4. Pack size: 10 x 10's
5. Composition of batch:

Table 2

Material/Ingredient	Specification/ Spec. no.	Unit formula mg/tab	Function of ingredient
Lactose Monohydrate	Ph. Eur.	210	Filler/Diluent
Maize starch	Ph. Eur.	72	Disintegrant
Polyvinyl pyrrolidone K 30 (Povidone K-30)	Ph. Eur.	12	Binder
Purified Water	---	QS	Solvent
Magnesium Stearate	Ph. Eur.	5.94	Lubricant
Blended Lake (Orange)	---	0.06	Colorant
Total		300.00	

4.1 Common Potential Failure Mode: Process/Product

Based on the objective, the risk assessment for manufacturing of oral solid dosage form facility has been performed. Following are the causes, current controls and proposed plan for each failure which was observed during assessment:

Table 3

Sr. No.	Potential Failure mode	Potential Effect (Process / End users) or Consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1.	Temperature and RH of processing areas goes out of limit	This may affect product stability. It may increase bio load of area.	3	Malfunctioning of AHU system Power failure	2	It is specified in the procedure that if Temperature and RH goes beyond set limit operation should be suspended till conditions are restored.	1	3 x 2 x 1=6	Current control Measure are adequate
2.	Differential pressure goes out of limit	May lead to cross contamination.	5	Improper air balancing. Malfunctioning of Air Handling units	2	Alarms are provided for differential pressure failure. Differential pressure is recorded daily. It is specified in the procedure that details care to be taken in case of AHU failure. Restrict man movement and opening of doors.	1	5 x 2 x 1=10	Current control measures are adequate.
3.	Cross contamination of one product with other product.	Undesirable therapeutic effect on patient.	4	Common equipments in the process are not cleaned as per standard operating procedure. Common AHU. Differential pressures are not maintained. Improper area	1	Cleaning methods for machine are validated. Standard operating procedures are available for product to product and batch to batch cleaning. All the persons involved in the cleaning operation of equipments are trained and periodically retrained. Cubicle dedicated AHU's are	1	4 x 1 x 1=4	Current control measures are adequate

				cleaning		provided for compression area. Set standard operating procedure area cleaning is available and followed.			

4.2 Granulation: Process / Product / Item

Table 4

Sr. No.	Potential Failure mode	Potential Effect (Process / end users) or consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1.	Choking of drain point in the FBE Area.	It may lead to flooding of area with drain water. This may result in increase of bio load of the area and increase in humidity of the area.	4	Choking of drainpipe.	1	Drain points are sanitized and cleaned regularly as per the procedure.	2	4 x 1 x 2 = 8	Current control measures are adequate
2.	Product degradation due to exposure to light.	Product degradation on exposure to light may later its chemical nature and result in change in efficacy.	4	Exposure of light sensitive material to light during processing.	1	Sun control film are applied to the windows	1	4 x 1 x 1= 4	Current control measures are adequate
3.	Fire during sifting.	Can cause major accident. Loss of material Injury to human	5	Due to development of static charge during sifting.	2	Earthing is given from sifter to earthing stud of electric point.	1	5 x 2 x 1= 10	Current control measures are adequate
4.	Loss of integrity of sifter / multimill sieves/ screen	Sifting operation will not be as per process specifications. Improper particle distribution. Problem during compression. Content uniformity may be affected. Flow of granules may not be good enough for compression. Bulk density may be out of specification.	5	Sieve / screen may damage during operation, cleaning or improper handling.	2	Sieve / Screen integrity is checked before and after every sifting / screening operating. Magnetic grills are used to pass sifted materials coming from sifter and multimill. If sieve integrity is found to be lost after sifting, the entire material is resifted using intact sieve. All tablets are passed through metal detectors	1	5 x 1 x 1=10	Current control measures are adequate
5.	Improper particle size distribution	Failure of granules with respect to specification. Poor granules flow leading to problems during compression. Content uniformity may be affected.	5	Milling of granules is not done at the specified speeds and direction of blades. Improper blending.	1	Speed and directions of the blades for milling is mentioned in the BMR. Blending activity is carried out at specified RPM for specified time as mentioned in the BMR. Persons carrying out milling operation are trained and retrained periodically.	2	5 x 1 x 2=10	Current control measures are adequate
6.	FBE finger bag ruptures.	Loss of product	5	The bag can be damaged during granulation, drying, blending / lubrication, handling or washing.	1	Solid flow monitor is installed after finger bag, which trips the FBE whenever it detects flow of powder. The functioning of solid flow monitor is checked every month. The bags are critically checked visually before and after usage.	1	5 x 1 x 1 = 5	Current control measures are adequate
7.	Explosion in FBE	Explosion can cause major accident, which possibly may lead to loss of material or man.	5	Due to friction among particles of power, static charge is developed which leads to generation of spark resulting in to explosion. If flammable solvents are used for granulation explosion	1	Explosion duct is provided in all machines, which opens after pressures increases beyond predefined limit. Earthing is provided between powder bowl and expansion chamber.	1	5 x 1 x 1 = 5	Current control measures are adequate

				may occur.					
8.	Explosion in FBE	Explosion can cause major accident, which possibly may lead to loss of material or man.	5	Due to friction among particles of powder, static charge is developed which leads to generation of spark resulting in to explosion. If flammable solvents are used for granulation explosion may occur.	1	Explosion duct is provided in all machines, which opens after pressures increases beyond predefined limit. Earthing is provided between powder bowl and expansion chamber.	1	5 x 1 x 1 = 5	Current control measures are adequate
9.	Over drying and under drying of Granules in FBE	Flow problems during compression. Hardness less than standard. Thickness more than standard. Friability more than standard. Capping tendency.	5	Incorrect feeding of inlet, outlet and bed temperature in PLC of FBE. Malfunctioning of temperature sensors. Temperature control steam valve has been bypassed. Raking not done appropriately. FBE finger bag choked. Incorrect setting of % flap opening.	1	Recipes are feed in to PLC of machines by production officer. PLC is access controlled. Every time a new lot is taken recipe is counter checked with batch records instruction. Temperature sensors are calibrated periodically. The PLC is validated periodically for its functions. FBE mesh is validated periodically for its function. FBE mesh is cleaned after every batch or whenever required. FBE finger bag is subjected for intermittent shaking or cleaning. Flap opening is regulated through PLC.	1	5 x 1 x 1 = 5	Current control measures are adequate

4.3 Compression: Process / Product / Item

Table 5

Sr. No.	Potential Failure mode	Potential Effect (Process / end users) or consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1.	Integrity of HEPA filter is lost	Unclassified air is supplied to the production cubical.	4	Damage during installation or subsequent use. Damage during cleaning of pre-filters or during preventive maintenance activity.	1	HEPA Filter integrity is checked just after installation and there after every six months. Operators are trained for the cleaning and preventive maintenance procedure.	1	4 x 1 x 1 = 4	Current control Measures are adequate.
2.	Black or foreign particles in compressed tablets	Many lead to undesirable effect. Patient non compliance. Market complaint	4	Black or foreign particles in granules. Black particles generation during compression. Introduction of foreign particles from supplied air of area.	2	All new materials during sifting are checked for presence of any black or foreign particles by visual inspections, inspection under microscopic and by addition to water. Upper punches of compression have provision for using dust cups which prevent introduction of black particles during compression.	1	4 x 2 x 1 = 8	Current control Measures are adequate
3.	Accidental contamination of tablets with lubrication oil.	It may impart undesirable therapeutic effect on patient. Patient non compliance Market complaint.	4	Oil drip tray on compression machine gets leaked. Spillage of oil. Excess lubrication.	2	Oil drip trays are regularly checked for any leakage. Only food grade oil is used for lubrication. Intermittently compressed tablets are checked during compression activity.	1	4 x 2 x 1 = 8	Current control Measures are adequate
4.	Non compliance with safe	Injury to the body part. Permanent damage to the body part.	5	Accidental contact of operator body with moving parts of	1	All the moving parts of the compression machine are properly enclosed by guards.	1	5 x 1 x 1 = 5	Current control measures are

	operating practices			compression machine. By pass of safety interlock guards. Negligence on the part of operator. Lack of knowledge for working on this kind of machines.		The guards around turret are made up of transparent material and are interlocked with the machine. Operators are continuously trained maintenance (preventive and routine) of machine.			adequate
5.	Tablet fails in weight variation test.	Out of specification tablets w.r.t weight variation. Tablets failing in assay. Variation in tablet thickness. Variation in hardness	5	Poor granules flow. Non-uniform particles size distribution of granules. Large variation in machine speed. Variation of granules level in hopper. Improper functioning of forced feeders. Variation in compression force.	1	During validation flow of granules is checked as in process check and standardized. Particle size distribution and bulk density is checked Machine speed is standardized during product validation. Proper functioning of forced feeders is checked during machine set up. Compression force is standardized during validation	1	5 x 1 x 1 = 5	Current control measures are adequate.

4.4 Change Control: Process / Product / Item

Table 6

Sr. No.	Potential Failure Mode	Potential Effect (Process / end users) or consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1	A change is made without going through the change control procedure	May effect other processes.	4	Lack of Knowledge Not followed SOP's	2	Individuals are trained on change control procedures. For all activities SOP's to be followed	1	4 x 2 x 1 = 8	Current control measures are adequate
2	Person raising the change control may not have understand the reason for the change and hence will not address all the issues.	Required changes are not done.	4	Not followed SOP's. Deviation in the system.	2	Individuals are trained on change control procedures. Training is imparted to all at periodic intervals.	1	4 x 2 x 1 = 8	Current control measures are adequate
3	May not be trained to handle and raise change controls on the lines of CGMP.	Required change may not get done or some changes are made which are not supposed to be made.	4	Deviation in the system.	2	Individuals are trained on change control procedure.	1	4 x 2 x 1 = 8	Current control measures are adequate
4	Not evaluated correctly ad completely	Inaccurate filing in regulated market leading to difficulties / inabilities to meet the requirements	5	Lack of knowledge	2	Individuals are trained on change control procedure.	1	5 x 2 x 1 = 10	Current control measures are adequate
5	Details not documented (although) are orally discussed.	Non-conformances during audits.	5	Incomplete information available at a later date of	2	All relevant details to be incorporated in change control	1	5 x 2 x 1 = 10	Current control measures are adequate
6	Change not adequately justified or supported	Inability to meet the changed requirements on a routine basis. Non-conformances during audits.	5	Non complains and product hold/ recall	2	Monitoring of the change controls. Change controls are closed after confirmation of agreed actions.	1	5 x 2 x 1 = 10	Current control measures are adequate

4.5 Deviations: Process / Product / Item

Table 7

Sr. No.	Potential Failure Mode	Potential Effect (Process / end users) or consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1	Person raising the deviation may not have understood the reason for the deviation and hence will not address all the issues.	Surprises during processing, which were not anticipated, leading to further delays. Batch failure to meet the release or shelf life specifications. Observation during audits.	4	Lack of knowledge. Deviation in the system. Improper evaluation leading to non-compliance during audits.	2	Only Provide people who understand the deviation and its concept should raise the deviation. Evaluation of existing facilities and systems and processes which will prevent any deviation from happening.	1	4 x 2 x 1 = 8	Current control measures are adequate
2	May not be trained properly to handle and raise deviation.	Inadequate and incomplete information. Observation during audits.	5	Lack of information. Improper training.	2	Corrective feedback in case to case basis. People are trained properly to handle deviation.	1	5 x 2 x 1 = 10	Current control measures are adequate
3	May not be on the lines of CGMP	Inadequate and incomplete information. Observation during audits.	4	Lack of information. Improper training.	2	Corrective feedback in case to case basis. Each individual should be trained on CGMP.	1	4 x 2 x1 = 8	Current control measures are adequate
4	Not evaluated correctly and completely.	Inadequate and incomplete information. Observation during audits.	4	Lack of information. Improper training.	2	Evaluation shall be done accurately.	1	4 x 2 x 1 = 8	Current control measures are adequate
5	Details not documented (although are orallydiscussed)	Inadequate and incomplete information. Observation during audits	5	Lack of information. Improper training.	2	Training on document writing.	1	5 x 2 x 1 = 10	Current control measures are adequate
6	Repeated deviations	Observation by auditors.	5	Deviation in system. Improper training.	2	Trending is performed on monthly as well as bi annually to address all repeat deviations.	1	5 x 2 x 1 = 10	Current control measures are adequate

4.6 Product Quality Complaints / Recalls: Process / Product / Item

Table 8

Sr. No.	Potential Failure Mode	Potential Effect (process / end users) or consequences	S	Potential causes	O	Current control measures	D	RPN (SxOxD)	Proposed Action Plan
1	A complaint information given to the company may not get logged and investigated.	The defect in the process or system will continue and may lead to more complaints.	5	Investigation has not been done properly. Lack of proper communication.	2	A central point (i.e CQA) ispresent which logs complaints. Repeated training and information to the marketing group and departments to ensure any such information is passed on to CQA for login.	1	5 x 2 x 1 = 10	Current control measures are adequate
2	Complaint may not get addressed timely considering the seriousness of the complaint.	Customer may move to other brands. Could generate a negative opinion of the company.	4	Lack of information about complaints. Communication is not proper.	2	Management shall act within 24 hours of the complaint to assess the situation and investigate the cause. Communication shall be proper.	1	4 x 2 x 1 = 8	Current control measures are adequate
3	Root causes may not be identified.	Complaint may repeat.	4	Investigation has not been carried out properly.	2	Investigation shall be done properly. Action plans shall be made around the most probable causes implemented and monitored.	1	4 x 2 x 1 = 8	Current control measures are adequate
4	Remedial actions may not be taken.	Complaints may repeat.	4	Lack of practical knowledge.	2	Action plans must be practicable and agreed upon. Periodic monitoring of implementation of action plan.	1	4 x 2 x 1 = 8	Current control measures are adequate
5	Complaints can be repetitive.	Loss of company image in the market. Regulatory audits	5	Lack of proper investigation. Wrong conclusion	2	Repetitive complaints have to be identified and focused investigation involving all concerned departments.	1	5 x 2 x 1 = 10	Current control measures are adequate

		observation.		drawn.		Adequacy and effectiveness of action plan implementation of the previous complaint to be reviewed.			
6	Critical complaints may not get reported to FDA	FDA may pull up the company and put products under recall process.	5	Reporting has not done properly.	2	Reporting shall be done properly. One person shall be assign to carryout such activities so as not to lose the focus.	1	5 x 2 x 1 = 10	Current control measures are adequate

5. Discussions

The study focuses on providing a tool for quality risk management that can be applied to different aspects of manufacturing of pharmaceutical products.

The FDA's risk-based approach initiative for the 21st century was considered. Risk based quality management has come out with a clear theme, that the patient need not to worry about quality, instead it is the responsibility of the manufacturer's and regulatory authorities to give quality products which is safe, effective and should be 'fit for use'.

The FMEA was carried out on following processes / systems:

Study has been completed on common potential failure mode in the process / system of (Granulation, Compression, Coating, Capsule Filling, Packing, Change Control, Deviation, Product Quality Complaints / Recalls &Batch Release) followed by evaluation of potential failure modes of individual processes.

The action plan was proposed for individual potential failure modes based on the RPN.

5.1 Overview of the study

Table 9

Sl. No	Details	Observations
01	Total No. of potential failure modes identified	97
02	Total No. of Processes carried out for the study	5
03	Total No. of systems carried out for the study	4
04	Average No. of potential failure	11

5.2 Acceptance Criteria

Table 10

Sr. No.	Acceptable RPN (Risk Priority Number)
1.	Should be less than or equal to 10

5.3 Observed RPN during the study

Table 11

Sr. No.	Description	Observed RPN (Risk Priority Number)
1.	Minimum RPN observed	4
2.	Maximum RPN observed	10
3.	Average RPN observed	7

5.3 Proposed Action Plan

As the maximum RPN observed during the study is well within the acceptable limit of less than or equal to 10 and the current control measures are found to be adequate.

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