Risk Analysis of Controlled Release Tablet Formulation by Six Sigma technique.

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Abstract:
Failure Mode and Effects Analysis (FMEA) is a procedure which is performed after a failure mode effects analysis to classify each potential failure effect according to its severity and probability of occurrence. FMEA is a systematic proactive method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the part of the process that are most in need of change.
Subjected a controlled release tablet formulation to a Failure Mode and Effects Analysis, including technical risks as well as risks related to human failure which broke down the formulation into the process steps and identified possible failure modes for each step. Each failure mode was ranked on estimated frequency of occurrence (0), probability that the failure would remain undetected later in the process (D) and severity (S). Human errors turned out to be the most common cause of failure modes. Failure risks were calculated by Risk Priority Number (RPNs) O*D*S. Failure modes with the highest RPN scores were subjected to corrective action and FMEA was repeated.
FMEA is particularly useful in evaluating a new process prior to implementation and in assessing the impact of a proposed change to an existing process which depends on product and process understanding. FMEA is most effective when it occurs before a design is released rather than "after the fact". The aim of this paper is to demonstrate an application of process failure mode and effect analysis (process FMEA) as a performance improvement tool, based on a case analysis of process improvement conducted in an early drug discovery project.
Keywords:
Risk Priority Number (RPN), Severity, Occurrence, Failure Mode and Effects Analysis

INTRODUCTION:

Six Sigma (6 σ) is a statistical term used to measure the performance of products and processes against customer requirements. The Six Sigma approach aims to drive defects and "things gone wrong" to extraordinarily low levels, to increase first pass yield and to consistently exceed customer expectations. First pass yield is a measure of the percentage of jobs that exit the process right, on time, at a single time. For the six sigma analysis, number of techniques can be used such as Capability Analysis, Cause and Effect Diagram, Chi Square-Test, Data Collection Plan, Design Analysis Spreadsheet, Design of Experiment (DOE), Discrete Data Analysis Method, Discrete Event Simulation (Process Model TM), Failure Mode and Effects Analysis (FMEA), Worst case analysis, Gage R & R-Short Method techniques etc. Here FMEA technique has been selected for the application on controlled release tablet formulation.

Failure Mode and Effects Analysis (FMEA) was developed outside of health care and is now being used in health care to assess risk of failure and harm in processes and to identify the most important areas for process improvements. The main objective is the prevention of problems and errors by reducing the RPN (Risk priority number). FMEA is a systematic, proactive method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change.

FMEA includes review of the following:

- Steps in the process.
- Failure modes (What could go wrong?).
- Failure cause (Why would the failure happen?)
- Failure effects (What would be the consequences of each failure?).

It can be applied in the design of a new product and process in order to prevent errors, accidents and adverse reaction. FMEA depends on the product and process understanding. It methodically breaks down the analysis of complex processes into the manageable steps. It provides evaluation of potential failure modes for processes and their likely effect on product performance. The Risk Priority Number (RPN) identifies the greatest area of concern. It comprises the assessment of the: (1) Severity rating, (2) Occurrence rating, and (3) Detection rating. It can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effects on product or process. FMEA is classified into three categories (1) Design FMEA, risk analysis for the design of a system, subsystem or component to assess risk, reduce it, and assure the product is launched successfully; (2) Process FMEA, risk analysis for identifying potential product related failure modes, caused by a manufacturing or assembly process. (3) Machinery FMEA, risk analysis for evaluating equipment and tooling during its design phase in order to improve operator safety, reliability and machinery robustness.

FMEA Variables:

Severity is a rating corresponding to the seriousness of an effect of a potential failure mode (scale: 1: no effect on output, 2: moderate effect, , 5: hazardous effect).

Occurrence is rating corresponding to the rate at which a first level cause and its resultant failure mode will occur over the design life of the system, over the design life of the product ,or before any additional process controls are applied. (Scale: 1: failure unlikely, 2: occasional failure, 5: failures certain).

Detection is a rating corresponding to the likelihood that the detection methods or current controls will detect the potential failure mode before the product is released for production for design or for process before it leaves the production facility. (Scale: 1: will detect failure, 2: might detect failure, 5: almost certain not to be detect failure).

MATERIAL AND METHODS:

Controlled release tablet are designed to achieve the prolonged therapeutic effects by continuous releasing the medication over an extended period of time after administration of a single dose.

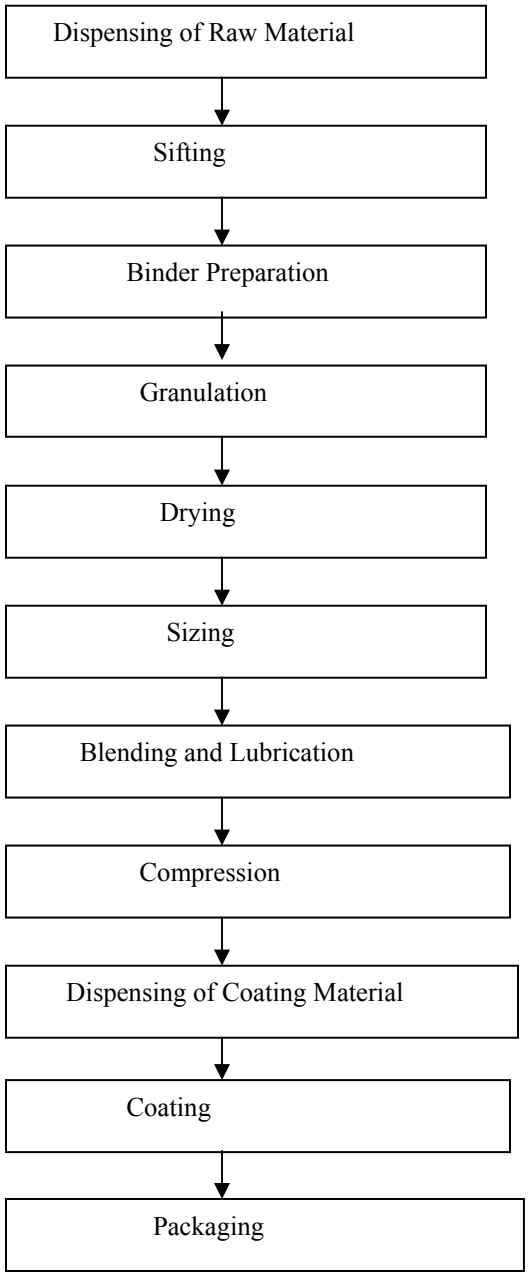
Material:

Table 1: Equipment used in various unit operations.

S.No.	Name of Equipment
Sifting Process	
1.	Vibrator Sifter
Binder Preparation	
2.	Jacketed paste kettle
Granulation	
3.	RMG
Drying Process	
4.	Fluid bed dryer
Sizing	
5.	Multimill
Blending & Lubrication	
6.	Octagonal Blender
Compression	
7.	Compression Machine
Coating	
8.	Auto coater
9.	Moisture Analyzer
10.	Friabilator (USP)

11	Disintegration Apparatus (USP)
Packaging	
12.	Aluminum strip Packaging machine

Figure1: Flow diagram for the production of the controlled release tablet formulation. (It is merely a general procedure and it can't be used as an outcome)



Methods:

The steps someone has to go through to design an FMEA form are described below:
1. Selection of the process. The importance of the process in terms of the impact of potential failures was taken into account as selection criteria. Evaluation using FMEA works best on processes that do not have too many sub processes.
2. Review of the process: The process was analyzed and described in a flowchart and the process design was studied thoroughly for the efficient output.
3. Brainstorm potential failure modes: Each stage of the process was studied and identifies the ways it could potentially fail or the things that might go of wrong.
4. List of potential effects of each failure mode: List of the potential effects and their probable failure were prepared. Cause and Effects analysis (fishbone diagram) was used for this step.
5. Assign a severity rating for each effect: Each effect was given its own severity rating (from 1 to 10, with 10 being the most severe). To quantify or prioritize the effects, Pareto analysis was used.
6. Assign an occurrence rating for each failure mode: After collecting data on the factors responsible for the failure of the product, the failure frequency was determined and it were rated appropriately (from 1 to 10, with 10 being the most likely).
7. Assign a detection rating for each failure mode and effect: List of all controls currently in place to prevent each effect of a failure from occurring was prepared and a detection rating was assigned for each item (from 1 to 10, with 10 being a low likelihood of detection).
8. Calculation of the risk priority number (RPN) for each effect: RPN was calculated by multiplying the severity rating with that of occurrence rating by the detection rating.
9. Prioritize the failure modes for action: Depending upon calculation and analysis carried out, the priority order was decided.
10. Taken action to eliminate or reduce the high risk failure modes: The action to be taken for each high risk failure was determined and a person was assigned to implement the action /change.

RESULTS:

The various critical steps that were expected to occur at each stage of the product process were assessed and findings are tabulated as below.

Sr. No.	Failure Mode	Failure Effects	Failure Cause	Control Measure	S	O	D	RPN	Action
1	Receiving of incorrect material	Contaminati on , Cross contaminatio n in raw material	Incorrect check during receiving of raw material	Raw material received as per approved vendor list	5	2	1	10	System was in control
2	Temperatu re & Relative	Material fails to meet the	Material is not stored as per specified tem.	Area maintained by HVAC System	5	2	1	10	System was in control

	Humidity	specification	& RH						
3	Mixing time	Non uniform mixing of batch	Equipment problem, mixing time not followed as per BMR	Followed SOP and BMR for mixing	5	1	1	5	System was in control
4	Granulation time	Non uniform granulation of batch	Equipment problem, granulation time not followed as per BMR	Followed SOP and BMR for granulation	5	1	1	5	System was in control
5	Drying time	Granules was not proper dried	Equipment problem, drying time not followed as per BMR	Followed SOP and BMR for drying	5	1	1	5	System was in control
6	Compression force	Increase & Decrease hardness and Disintegration time of tablet	Equipment error, untrained staff	Set compression force as per BMR, trained operator	5	1	1	5	System was in control
7	Die fill	Weight variation of tablets	Equipment error, untrained staff	Equipment setting, trained staff	5	1	1	5	System was in control
8	Spray rate	Non uniform weight build up	Equipment error, untrained staff	Spray rate as per BMR	5	1	1	5	System was in control
9	Distance of spray gun to tablet bed	Small droplets,	Untrained staff	Distance of spray gun to tablet bed as per BMR	5	1	1	5	System was in control
10	Finished product mix up	Market complaint	Transfer of goods not follow SOP	As per SOP transfer the goods	5	1	1	5	System was in control
11	Improper carton packing	Market complaint	Untrained packer	In process check of carton	5	1	1	5	System was in control

CONCLUSION

From the above evaluation of risk assessment based on FMEA it was concluded that the various critical step that were expected to occur at each stage of the product process, were adequate to reduce the associated risk. This method helped to us focusing the various critical steps that were critical to the product quality and process. Performing FMEA

analysis includes higher reliability, better quality, increased safety and its contribution towards cost saving includes decreased development time and reduced waste and no value added operation. Results can be used to identify high vulnerability elements and to guide resource development for best benefits.

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