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PRACTICAL APPLICATION OF QUALITY RISK MANAGEMENT TO CEFTRIAXONE SODIUM DRY POWDER INJECTION MANUFACTURING

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ABSTRACT
This article presents risk analysis performed on the Ceftriaxone sodium dry powder injections manufacturing process and the conclusion obtained from the analysis. The objective of this study was to assess and mitigate the risk at all stages before the manufacturing process initiated and to evaluate the current controls and decide the future actions to be taken for improvement of product/process reliability and quality of the product for commercial use. In addition, the aim of the present work is to illustrate the application of different risk management tools and the permeability of the local pharmaceutical industry to these ideas. Failure Mode and Effects Analysis (FMEA) method was used for evaluating a process to identify where and how it might fail and they were decided on the basis of the rankings given to the severity (S), occurrence (O) and detectability (D) based on the prior experience, regulatory requirements, customer complaints, analytical results of the product testing and knowledge. Failure risks were calculated by Risk Priority Number (RPNs). Failure modes with the highest RPN scores were subjected to corrective action. Results are predicted by RPN that the risk is acceptable, unacceptable or intolerable. According to RPN, the risk is categorized in low, medium and high. The RPN between 1-120 are low risk, RPN between 121-499 is medium and RPN above 500 is high risk. After corrective actions taken, the whole procedure was repeated and RPNs for this was calculated. The reduction in RPN was seen and so the reduction in risk was seen.

KEYWORDS: RPN, Severity, Occurrence, Detectability, FMEA.

INTRODUCTION
Risk management of the manufacturing process is a key activity in product development, especially as a supportive tool in Quality by Design (QbD). To ensure that quality is built in the pharmaceutical products, the most up to date technologies and concepts of risk management should be incorporated into the manufacturing process. As a part of this new approach, work was performed to evaluate the manufacturing process of Ceftriaxone sodium dry powder injections in order to reduce its associated risks, where `risk` is understood as combination of the probability of occurrence of harm and severity of thet harm.[1]

Ceftriaxone sodium is semi synthetic 3rd generation cephalosporin drug of antibiotic/anti bacterial class. During manufacturing, specially in filling of the powder, the powder may exposed to environment which may cause allergic reactions and potential helath effects. It is carcinologic also. Conditions like humidity, warming and light are avoided due to instability.[2]

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

The risk assessment of the manufacturing process was divided into Risk Identification, Risk Analysis and Risk Evaluation. All four components are essential.

Risk Identification: Focused on the identification of hazards and its possible causes and consequences, the risk identification step did not consider probability of occurrence nor severity. The critical points which potentially affect during manufacturing process were identified. This provides the basis for further steps in the quality risk management process.

Risk Analysis: In this present work, risk analysis was considered as defined in ICH Q9, i.e., the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence (O) and severity (S) of the

harms. In the some risk managements tools, the ability to the harm (detectability D) also factors in the estimation of risk.

Risk Evaluation: It is the last step in the risk assessment. Different causes can lead to undesirable critical quality attributes. This work only considered the CQA potentially affected bt deviations in the manufacturing process. These cause their consequences on product quality, and their potential risks on the patient's health.

Risk Reduction: Different mitigation strategies have been proposed to reduce the RPN, mainly focused on the detectabilty improovement.

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 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 operations.

FMEA's provide us with a tool that can assist in providing reliable, safe, and customer pleasing products and processes. Since FMEA help us to identify potential product or process failures, they can use it to.

- 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.
- 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.
- Track and manage potential risks in the design. Tracking the risks contributes to the development of corporate memory and the success of future products as well.
- Ensure that any failures that could occur will not injure or seriously impact the customer of the product/process.

Benefits of FMEA[3]

FMEA is designed to assist the engineer improve the quality and reliability of design. Properly used the FMEA provides several benefits. Among others, these benefits include:

- 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
- 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

MATERIALS AND METHODS

Material (Ceftriaxone sodium) and equipments used for this study were obtained from Pharmanza (Ind.) Pvt.Ltd., Khambhat, Gujarat, India.

Table 1: Equipments used in various unit operations

Process	Equipment Name	Capacity
Vial washing	Automatic high speed linear Vial washing machine	120 vials /min for 10 ml to 50 ml vials
Depyrogination	Sterilizing & depyrogenating tunnel	-
Filling, stoppering and sealing	Automatic injectable powder filling with rubber stoppering machine	120 vials /min
Metal detection	Metal detector	-
Sterilization (Dry)	Dry Heat Sterilizer	-
Sterilization (Moist)	Rectangular double door horizontal HPHV steam sterilizer(Autoclave)	-
Dehumidification	Dehumidifier	1200 CFM

FMEA Procedure[4]

The process for conducting an FMEA is straightforward. The basic steps are outlined below.

Step One: Select a process to evaluate with FMEA

Evaluation using FMEA works best on processes that do not have too many sub processes Instead of doing an FMEA on a large and complex process, such as medication management in a hospital, try doing an FMEA on sub processes or variants. Conducting an FMEA of the entire management process would be an overwhelming task. Instead, consider individual FMEA analyses of the medication ordering, dispensing, and administration processes.

Step Two: Recruit a multidisciplinary team

Be sure to include everyone who is involved at any point in the process. Some people may not need to be part of

the team throughout the entire analysis, but they should certainly be included in discussions of those steps in the process in which they are involved.

Step Three: Have the team meet together to list all of the steps in the process

Number every step of the process, and be as specific as possible. It may take several meetings for the team to complete this part of the FMEA, depending on the number of steps and the complexity of the process. Flowcharting can be a helpful tool for outlining the steps. When you are finished, be sure to obtain consensus from the group. The team should agree that the steps enumerated in the FMEA accurately describe the process.

Step Four: Have the team list failure modes and causes

For each step in the process, list all possible "failure modes"—that is, anything that could go wrong, including minor and rare problems. Then, for each failure mode listed, identify all possible causes.

Step Five: For each failure mode, have the team assign a numeric value (known as the Risk Priority Number, or RPN) for likelihood of occurrence, likelihood of detection, and severity

Assigning RPNs helps the team prioritize areas to focus on and can also help in assessing opportunities for improvement. For every failure mode identified, the team should answer the following questions and assign the appropriate score (the team should do this as a group and have consensus on all values assigned):

- Likelihood of occurrence (O): How likely is it that this failure mode will occur?
  Assign a score between 1 and 10, with 1 meaning "very unlikely to occur" and 10 meaning "very likely to occur."
- Likelihood of detection (D): If this failure mode occurs, how likely is it that the failure will be detected?
  Assign a score between 1 and 10, with 1 meaning "very likely to be detected" and 10 meaning "very unlikely to be detected."
- Severity(S): If this failure mode occurs, how likely is it that harm will occur?
  Assign a score between 1 and 10, with 1 meaning "very unlikely that harm will occur" and 10 meaning "very likely that severe harm will occur." In patient care examples, a score of 10 for harm often denotes death.

Step Six: Evaluate the results

To calculate the Risk Priority Number (RPN) for each failure mode, multiply the three scores obtained (the 1to 10 score for each of likelihood of occurrence, detection, and severity). For example, the failure mode "Wrong medication selected" has a 3 for likelihood of occurrence, a 5 for likelihood of detection, and a 5 for severity, for an overall RPN of 75. The lowest possible score will be 1 and the highest 1,000. Identify the failure modes with the top 10 highest RPNs. These are the ones the team should consider first as improvement opportunities. To calculate the RPN for the entire process, simply add up all of the individual RPNs for each failure mode.

Step Seven: Use RPNs to plan improvement efforts

Failure modes with high RPNs are probably the most important parts of the process on which to focus improvement efforts. Failure modes with very low RPNs are not likely to affect the overall process very much, even if eliminated completely, and they should therefore be at the bottom of the list of priorities.

To calculate revised RPNs, assign a second caluculation of Severity, Occurrence and Detection ratings for failure modes (using the same rating scales) and multiplies the revised ratings to calculate the revised RPNs. When both initial (before corrective actions taken) and revised (after corrective actions taken) RPNs have been assigned, the percent reduction in RPN can also be calculated as follows.[5]

$$\%\text{RPN Reduction} = \frac{\text{Initial RPN} - \text{Revised RPN}}{\text{Initial RPN}}$$

Table 2: FMEA of ceftriaxone dry powder injection

Identification of Hazard	Cause of hazard	Effect of hazard	RPN (S x Ox D)	Corrective actions	Revised RPN	% reduction in RPN
Failure in sterility of raw material	During transportation or human error	Failure in sterility of product	10x5x5=250	Vendor approval, training	10x1x5=50	80
Improper washing of vials	Due to improper force or temp. of air	Particle remain in vial causing sterility failure	8x3x6=144	Check and maintain proper pressure of air	8x2x5=80	44
	Unqualified & quantified distilled or purified water	Failure in sterility	9x3x8=216	Check and control required water specifications	9x2x7=126	42
Insufficient time & temperature of air in depyrogeniation	Insufficient heat distribution and heat penetration	Improper sterilization of vials	10x3x5=150	Check and control air temp and heat distribution	10x1x4=40	73

				periodically		
Unoptimum Speed of conveyer belt	machine speed fault	Improper washing, depyrogenation and filling of vials	8x2x5=80	Measure and control speed of belt	8x1x5=40	50
Improper filling of vials	Due to reduced nitrogen air pressure	Weight variation	7x3x5=105	Control the nitrogen air pressure	7x1x5=35	66
Filling area conditions	Failure in maintenance of area classification -human error	Loss of sterility	10x3x5=150	Check HEPA filter and air pressure periodically -training of personnel	10x1x3=30	80
Missing or dispatched stoppers	Improper force of stoppering	Contamination, leakage and moisture absorption	10x3x7=210	Check and control force of stoppering	10x1x5=50	76
Missing or dispatched seals	Improper Seal strength uniformity	May lead to leakage from vial	7x3x5=105	Check and control force of sealing	7x1x5=35	66
Labeling defects	Improper checking of labels	Misleading labels & market complain	9x4x5=180	Check labels properly and verify all details	9x1x4=36	80
Storage defects	Unoptimum temperature and humidity conditions of storage room	Market complains	7x3x5=105	Assess the adequacy of maintenance of appropriate storage and transport conditions	7x1x4=28	73

RESULTS AND DISSCUSSION

The RPN value for each potential failure can be used to compare the issues identified within the analysis. Typically, if the RPN falls within a pre-determined range, corrective action may be recommended or required to reduce the risk (i.e., to reduce the likelihood of occurrence, increase the likelihood of prior detection or, if possible, reduce the severity of the failure effect). When using this risk assessment technique, it is important to remember that RPN ratings are relative to a particular analysis (performed with a common set of rating scales and an analysis team that strives to make consistent rating assignments for all issues identified within the analysis). Therefore, an RPN before manufacturing is compared to RPNs after manufacturing.

The output of the risk management supports to the organization to meets the defined goals towards protection of public health. In this risk assessment of ceftriaxone sodium dry powder injection, reduction in RPN within all steps of the manufacturing process was seen. The RPN reduction in this process before and after controls taken is shown in figure 1 and 2 respectively. In figure 1 green color shows low RPN which is acceptable risk, blue color indicates medium risk which is unacceptable and red color shows high RPN which is intolerable risk. In figure 2 almost part is showing acceptable risk. So the risk was handled superbly.

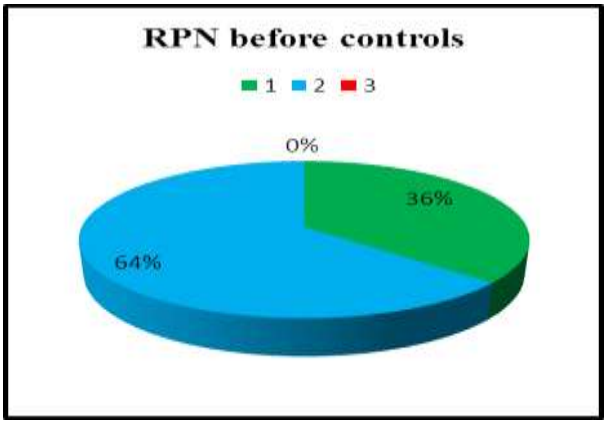

Fig: 1 RPN before the controls measures taken

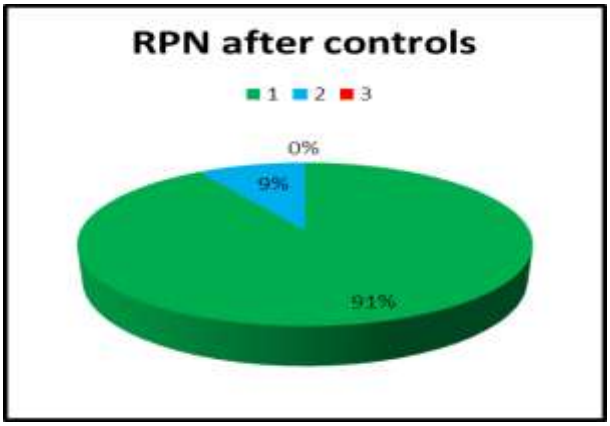

Fig: 2 RPN after the controls measures taken

CONCLUSION

From the above evaluation of risk assessment based on FMEA tool for Ceftriaxone sodium dry powder injection it was concluded that the various critical step that were expected to occur were adequate to reduce the associated risks. Among the mitigation strategies considered, the in-line continuous monitoring would substantially reduce the probability of releasing out-of-specification units in comparison to quality control assays. RPN reduction was seen in this. This method helped to us focusing the various critical steps that were critical to the product quality and process. So, by this implementation of risk assessment approach at early stage of manufacturing, the product or process quality can be improved. It will be beneficial in the terms of cost, time and human resource.

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