

RISK ANALYSIS EVALUATION OF PIROXICAM 20MG CAPSULES MANUFACTURE PROCESS BY FMEA TECHNIQUE

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CASE STUDY

Cardoso Priscila*, Marotta Flávia, Siqueira Kelen.

Pharmascience Indústria Farmacêutica, Minas Gerais, Brazil.

*Corresponding Author's E-mail: cardosopriscila18@gmail.com

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ABSTRACT

This paper presents an application of FMEA (Failure Mode and Effects Analysis) on the manufacturing process of Piroxicam 20mg capsules, with the objective of identifying possible failures and creates subsidies for improvement of the production stages. Brainstorming or Collaborative critical analysis was used as a tool to collect information and support FMEA's application. After the risk analysis, evaluation of the production process using FMEA, manipulation and secondary packaging were found to be the critical stages in the production process necessary for implementation of actions in order to mitigate the risks.

Keywords: Risk analysis, FMEA, Piroxicam, manufacture process.

INTRODUCTION

The risk, according to the Q9 guide "Quality risk management" of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), is the combination of the probability of occurrence of an undesired event and the severity of this damage in a context of uncertainty. In the pharmaceutical industry, risk analysis is carried out in order to estimate the risk associated with identified hazards. This is an instrument that assists in decision making about processes and allows the prioritization of the factors with greater influence on the quality of the product. (1-3)

In Brazil, pharmaceutical industries have been facing continually increasing regulatory requirements, which, in turn, continues to drive demand for a greater understanding of manufacturing processes. (3)

The risk approach has been present in Brazilian health legislation since the publication of the Organic Health Law (Law n° 8080/1990, article 6, § 1), however only with the publication of the Resolution of the Collegiate Board of ANVISA, (RDC) n° 17/2010, which establishes good manufacturing practices (GMP) for

pharmaceutical drugs, has risk management become a real demand for companies. In accordance with the regulation: quality, safety and efficacy must be designed and defined for a product. This indicates that the aspects relating to the product such as Excipients and manufacturing processes must be studied and known. (4,5)

Recently, RDC n° 60/2014 (revoked by RDC n°200/2017) and RDC n° 73/2016, incorporated the demand for risk assessment in the registration and post-registration for new pharmaceutical drugs, generics and similars. Through these resolutions, ANVISA established differentiated procedures and demands according to the complexity of the manufacturing processes and sanitary risk. This started the requirement for manufacturers of the pharmaceutical drugs to demonstrate the critical stages of the manufacturing process in order to classify post-registration changes as greater or less impact. (6-8)

The ICH Q9 defines the concepts and principles of risk management, describes the procedures for risk assessment and proposes examples of applications. This document is widely used by the pharmaceutical industries as a complement to the Brazilian legislation. (1,3,9).

Several methods and tools are available to evaluate and manage risks; all of these tools are based on a process of searching, recognizing and describing hazards. One of the most used quality tools in the pharmaceutical industry is the Failure Mode and Effects Analysis (FMEA). (1,10)

FMEA is a methodology that aims to assess the risk of failure in processes and to identify the most important areas for improvements. FMEA is an essential element for quality planning in a company. It allows accurate detection of the potential failures of a company's processes and their respective occurrences and detection rates. (11-13)

The present study focused on applying FMEA to the manufacturing process of Piroxicam 20 mg capsules. The aim of this work was to recognize potential failures in the productive process, the critical points at which they may occur and identify the actions necessary to eliminate or reduce the possibility or occurrence of these failures.

MATERIAL AND METHODS

Piroxicam is a non-steroidal anti-inflammatory drug, indicated for a variety of conditions that require anti-inflammatory and/or analgesic activity. (14) The product under study is Piroxicam 20 mg capsule. According to the Brazilian Pharmacopoeia 5th edition, the monograph of this product requires disintegration, determination of weight, identification, uniformity of unit doses, dissolution, purity tests (related substances), assay, total count microorganisms and research on pathogenic microorganisms as quality control tests. (15, 16)

Risk analysis – FMEA

The Risk Analysis was performed using the FMEA, to ensure that all possible failures of the process were considered and analyzed. The aim of this approach is to eliminate identified failures before the start of production using recommended corrective actions.

For the evaluation of the risk analysis through FMEA, the risk priority number (RPN) was calculated by multiplying the occurrence, severity and detection for each point. The

occurrence, being an estimate of the probability of process failure due to one or several causes; severity, a reflection of the failure's gravity effect on the process; and the detection, an evaluation of the probability of the failure to be detected at the predicted control point. (13,16,17)

The index of occurrence, severity and detection were assigned as established in table 1. The RPN was then calculated and classified as high, medium and low risk according to the score obtained, being the risk classification (1,11,18):

- Low (score 1 to 6): Tolerable. It does not need to implement corrective actions to reduce risk.
- Medium (scores 8 and 9): Actions should be implemented to reduce the level of risk.
- High (scores 10 to 27): Immediate actions must be implemented to reduce the level of risk.

To analyze the possible failures that may occur during the process, a discussion was conducted in a multidisciplinary group (Brainstorming) and the FMEA form was completed. For this purpose, the following steps were described: process stages and equipment (column 1 and 2 of the form); types of potential failures (column 3); effects of the failure (column 4); possible causes of the failure (column 5); current controls (column 6).

A process point was classified according to its degree of risk. They were considered critical points if they were evaluated with a medium or high risk and noncritical if the point were deemed with low risk. The process stage was considered critical if it contained at least one critical point.

Manufacturing process

The capsule production process may be carried out by wet or dry handling for further encapsulation. For the Piroxicam product, the manufacturing process chosen was the dry process. This process consists of mixing different particles, in which the particles are arranged according to an interaction, forming a repetitive pattern taking into account the size of the particles and their distribution. (19)

The manufacturing process of Piroxicam 20 mg

capsule consists of several steps as described in figure 1.

Table 1: Occurrence, severity and detection index

Index	Occurrence	Severity	Detection
Low	The probability of occurrence is very low, remote.	The failure has low impact. They are minor failures and do not affect the product. They cause reduced process performance and gradual emergence of inefficiency. No impact on public health.	Easily detectable. Existing controls detect the failure.
Medium	The probability of occurrence is moderated, occasional.	The impact of failure is serious. It can affect the quality of the product or the process by leaving them out of their specifications, but it is possible to correct the error during the process. No momentary impact on public health.	Moderately detectable. The controls can identify the failure.
High	The probability of occurrence is very high.	The failure has a high impact. It directly affects the quality of the product or the process by leaving it out of its specifications. Has impact on public health.	Hardly detectable. It is very difficult to identify during the process and/or there are no controls.

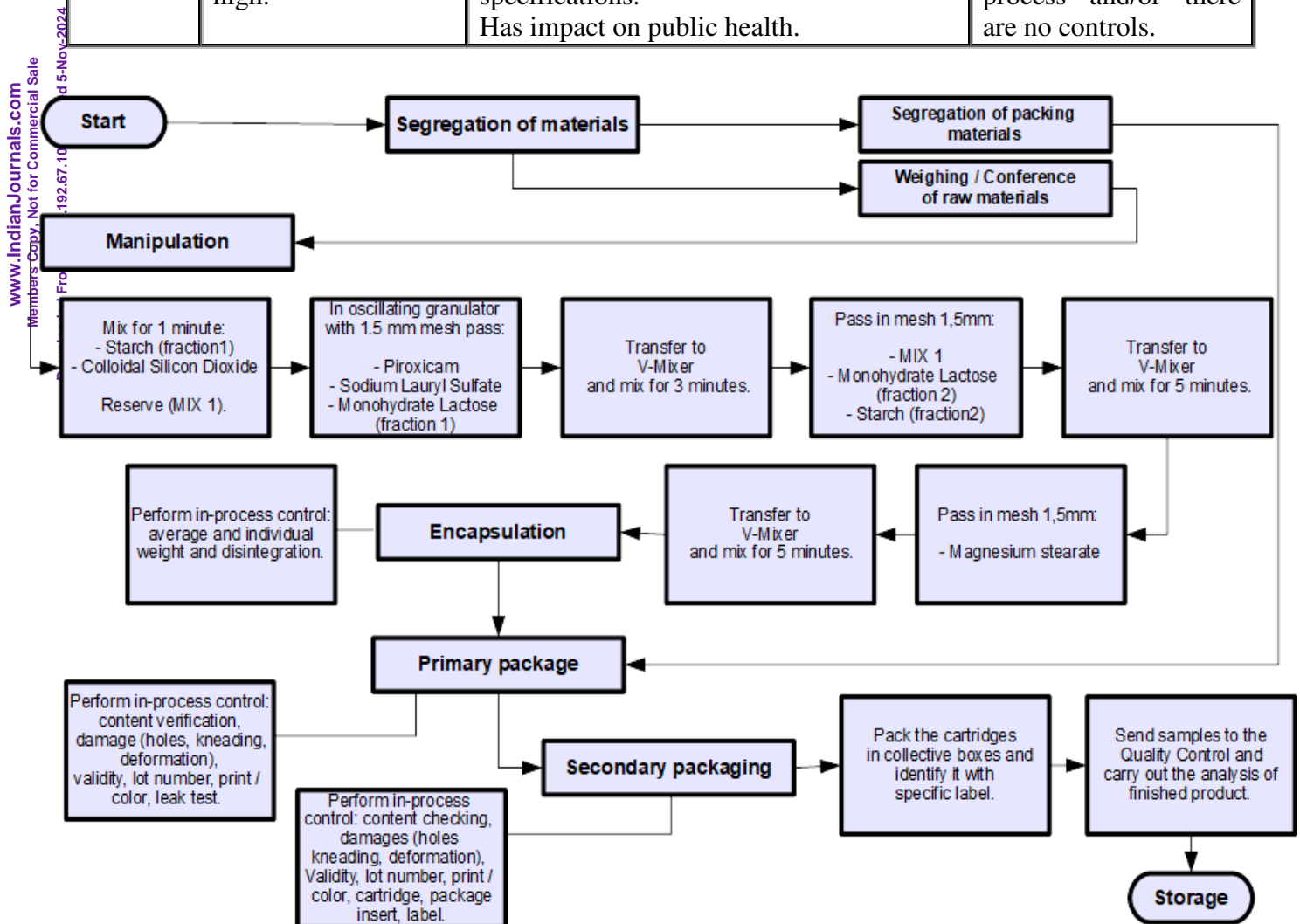


Figure 1: Flowchart of the manufacturing process of Piroxicam 20 mg capsule.

RESULTS AND DISCUSSION

In consonance with the process flow and the unit operations inherent to each stage,

the risk sources of the process were listed. Table 2 shows the study performed using FMEA.

Table 2: FMEA of Piroxicam 20 mg capsules production process

Process stages	Equipment	Failure	Effect	Causes	Controls	occurrence	severity	detection	RPN	risk	
Weighing	Weight balance	Weigh different raw material and / or incorrect quantity of the requested in the production order.	<ul style="list-style-type: none"> * Incorrect manipulation of the product * Process change * Physico-chemical alteration of the product 	<ul style="list-style-type: none"> * Wrong check of Excipients * Decalibrated balance * Non-compliance with production order parameters 	<ul style="list-style-type: none"> * Double check in the weighing step * Checking the raw materials before the manipulation stage * Training * Conference by the Quality Inspector * Daily weight balance's check 	1	3	1	3	Low	
Manipulation	Granulator	Use the mesh with incorrect granulometry.	<ul style="list-style-type: none"> * Final mixing without uniformity * Inadequate drainage * Weight variation * Density variation 	<ul style="list-style-type: none"> * Non-compliance with production order parameters * Inefficiency of employee training 	<ul style="list-style-type: none"> * Training * Mesh mount double check 	1	2	2	4	Low	
	V-Mixer	Divergent mixing time from the production order	<ul style="list-style-type: none"> * Uniformity outside the specified * Inadequate lubrication, with difficulty in draining the powder * Weight variation 	<ul style="list-style-type: none"> * Non-compliance with production order parameters * Inefficiency of employee training * Insufficient mixing time 	<ul style="list-style-type: none"> * Training 	2	2	3	12	High	
Encapsulation	Encapsulator	Unsatisfactory powder flow.	* Weight variation	* Improper manipulation	<ul style="list-style-type: none"> * Non-compliance with production order parameters 	<ul style="list-style-type: none"> * Control in process of weight * Training 	2	3	1	6	Low
		Inadequate filling of capsules.			<ul style="list-style-type: none"> * Non-compliance with production order parameters 	<ul style="list-style-type: none"> * Control in process of weight * Training 	2	3	1	6	Low

		Inadequate fitting, opening and closing of capsules.		* Improper manipulation * Non-compliance with production order parameters * Inadequate lubrication	* Control in process of weight and disintegration * Training	2	3	1	6	Low
Primary Packaging	Blister packaging machine	Incorrect encoding setting.	* Incorrect expiration date and batch * Incorrect or missing information	* Non-compliance with production order parameters * Inefficiency of employee training	* Process control of blister encoding * Conference by another operator, quality inspector or controller * Training * Describe the regulation of the equipment in the production order	1	3	1	3	Low
		Incorrect setting of the blister packaging machine.	* Appearance of the blister in disagreement (presence of holes, kneading or deformation and leakage)	* Non-compliance with production order parameters * Inefficiency of employee training	* In-process control of content verification, leak test and print/colour of the blister * Training	1	3	1	3	Low
		Inefficiency in manual spreading of capsules.	* Blister missing capsule	* Non-compliance with production order parameters * Inefficiency of employee training	* In-process control of blister's content * Training	2	3	1	6	Low
Secondary Packaging	Packing machine	Incorrect encoding setting.	* Incorrect expiration date and batch * Incorrect or missing information	* Non-compliance with production order parameters * Inefficiency of employee training	* Double check conference of the coding * In-process control of cartridge's coding * Training	1	3	1	3	low
		Incomplete and damaged cartridges.	* Cartridge missing blister and package inserts * Cartridge crushed and deformed.	* Non-compliance with production order parameters * Inefficiency of employee training	* In-process control to verify the content and presence of damage in the cartridge * Training	2	3	2	12	high

For scoring purposes, during the evaluation of the risk analysis, it was defined that whenever the current control is performed only with employee training, the process detection will receive the maximum number of the score – 3, since this control can't be quantified during the process.

Regarding the parameter severity, the score was considered high in almost all stages of the process, that is, the failure has a high impact which directly affects the quality of the product or leaves it out of its specifications.

To score the occurrence, it was noted that there is a correlation inversely proportional to the number of existing controls. The greater the number of controls for a given process step, the lower the likelihood of process failure, causing the reduction of the score.

After multiplying the points of the factors of occurrence, severity and detection of the manufacturing process of Piroxicam capsules, a low degree of risk was obtained for weighing, encapsulation and blister stages, considering that the RPN was equal to or lower than 6. However, for manipulation and blistering stages, RPN results were equal to 12 (high degree of risk), resulting in these stages being critical.

In order to reduce the criticality of the manipulation stage, it is suggested to include the conference of the mixing time scheduling of the equipment by another operator. This way, the occurrence will be reduced to 1 and the RPN will result in 6, changing the degree of risk to low.

In order to reduce the criticality of the blister stage, it is suggested to install an analytical balance at the end of the packaging line to verify the weight of the cartridge. If the cartridge is missing blister or has an incorrect blister quantity, it will be easier to detect the failure. This way, the occurrence will be reduced to 1, and the RPN will result in 6, changing the degree of risk to low.

From the obtained data, it can be affirmed that the Piroxicam capsule production process has two critical stages requiring the implementation of actions to reduce their degree of criticality.

After the implementation of the suggested actions in these critical stages, the possible risks will be mitigated, demonstrating safety and control of the evaluated production process.

CONCLUSION

With the increase of regulatory rigor in the pharmaceutical industry the ability recognize failures of the manufacturing process and to propose actions which can eliminate or reduce the occurrence of failures, is fundamental for continuous improvement of the pharmaceutical manufacturing process.

The application of FMEA to evaluate the production process of medicines can predict nonconformities and promote constant improvements in the performed controls. Thus, it is necessary that the FMEA be carried out by a multidisciplinary team, with a broad knowledge of the process, in order to identify the greatest number of possible failures.

Through the risk analysis performed for the production process of Piroxicam 20mg capsules using FMEA, it was possible to detect failures that could occur during the process. With the obtained data, several actions were able to be proposed to reduce the criticality of the process and avoid rework.

DISCLAIMER

The views and opinions expressed in this article are those of the authors and do not reflect or represent the views of the company the authors work for in any manner.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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