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) nº 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 nº 60/2014 (revoked by RDC nº200/2017) and RDC nº 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...
A 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. | * Incorrect manipulation of the product | * Wrong check of Excipients | * Double check in the weighing step | 1 | 3 | 1 | 3 | Low |
| Granulator     | Use the mesh with incorrect granulometry. | * Final mixing without uniformity | * Non-compliance with production order parameters | * Training | 1 | 2 | 2 | 4 | Low |
| Manipulation   | Divergent mixing time from the production order | * Uniformity outside the specified range | * Non-compliance with production order parameters | * Training | 2 | 2 | 3 | 12 | High |
| V-Mixer        | Unsatisfactory powder flow. | * Weight variation | * Non-compliance with production order parameters | * Control in process of weight | 2 | 3 | 1 | 6 | Low |
| Encapsulation  | Inadequate filling of capsules. | * Weight variation | * Improper manipulation | * Control in process of weight | 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**    | Incorrect encoding setting.                         | * Incorrect expiration date and batch * Incorrect or missing information                          | * 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 |
| **Blister packaging machine** | 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     | 1 3 1 3 | Low |
|                          |                                                     | * Blister missing capsule                                                                                                                        | * In-process control of blister’s content * Training                                              | 2 3 1 6 | Low |
|                          |                                                     | * Non-compliance with production order parameters * Inefficiency of employee training                                                            |                                                                                                   |        |     |
|                          |                                                     | * Inefficient in manual spreading of capsules.                                                                                                     |                                                                                                   |        |     |
|                          |                                                     | * Cartridge missing blister and package inserts * Cartridge crushed and deformed.                                                                   |                                                                                                   |        |     |
| **Secondary Packaging**  | Incorrect encoding setting.                         | * Incorrect expiration date and batch * Incorrect or missing information                          | * Double check conference of the coding * In-process control of cartridge’s coding * Training    | 1 3 1 3 | low |
| **Packing machine**      |                                                     | * Non-compliance with production order parameters * Inefficiency of employee training                                                            |                                                                                                   |        |     |
|                          |                                                     | * Incomplete and damaged cartridges.                                                                                                               |                                                                                                   |        |     |

© 2018 IJDRA Publishing Group, All rights reserved
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.

**ACKNOWLEDGEMENT**

We take this opportunity to express deep sense of gratitude to IJDRA journal for publishing my article.

**CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest.

**REFERENCES**

1. ICH. Quality Risk Management Q9 [Internet]. ICH, 2005 Nov 09 [Cited 2018 Feb 01]. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guide line.pdf
2. Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical Experimental Design. New York: Marcel Dekker; 1999.

3. Moretto LD, Calixto J. Estrutura do Novo Sistema da Qualidade para a Industria Farmacêutica. São Paulo: Sindus farma; 2011.

4. Brasil. Law nº 8080/1990 [Internet]. Official Diary of the Union, 1990 Sept 19 [Cited 2018 Feb 01]. Available from: http://www2.camara.leg.br/legin/fed/lei/1990/lei-8080-19-setembro-1990-365093-normaatualizada-pl.pdf

5. Brasil. Resolution of the collegiate board of ANVISA nº 17/2010 [Internet]. Official Diary of the Union, 2010 Apr 16 [Cited 2018 Jan 01]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0017_16_04_2010.html

6. Brasil. Resolution of the collegiate board of ANVISA nº 60/2014 [Internet]. Official Diary of the Union, 2014 Oct 10 [Cited 2018 Jan 01]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2014/rdc0060_10_10_2014.pdf

7. Brasil. Resolution of the collegiate board of ANVISA nº 200/2010 [Internet]. Official Diary of the Union, 2017 Dec 26 [Cited 2018 Jan 01]. Available from: http://www.poderesaude.com.br/novosite/images/Publica%C3%A7%C3%A3o_3_-_28.12.2017.pdf

8. Brasil. Resolution of the collegiate board of ANVISA nº 73/2016 [Internet]. Official Diary of the Union. 2016 Apr 7 [Cited 2018 Jan 20] Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2016/rdc0073_07_04_2016.pdf

9. Kayrak-Talay D, Dale S, Wassgren C, Litster J. Quality by design for wet granulation in pharmaceutical processing: Assessing models for a priori design and scaling. Powder Technology. 2013; 240:7-18.

10. Sidor L, Lewus P. Validation & Compliance: Using Risk Analysis in Process Validation. BioPharm International. 2007; 20(2):1-7

11. Medermott R, Mikulak R, Beauregard M. The basics of FMEA. 2nd ed. New York: Productivity Press; 2009.

12. Mascia S, Heider PL, Zhang H, Lakerveld R, Benyiah B, Barton PI. End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation. Angewandte Chemie International Edition. 2013; 52:12359-63.

13. Leeuwen JFV, Nauta MJ, Kaste D, Odekerken-Rombouts YMCF, Oldenhof MT, Vredenbregt MJ, Barends DM. Risk analysis by FMEA as an element of analytical validation. Journal of pharmaceutical and biomedical analysis. 2009; 50(5):1085-87.

14. Brunton LL, Lazo JS, Parker KL. As Bases Farmacológicas da Terapêutica de Goodman & Gilman.12nd ed. Rio de Janeiro: McGraw Hill; 2006.

15. Brasil. Farmacopeia Brasileira. 5th ed. Brasília: Agência Nacional de Vigilância Sanitária; 2010. p. 59-65.

16. Brasil. Farmacopeia Brasileira. 5th ed. Brasília: Agência Nacional de Vigilância Sanitária; 2010. p. 1204-5

17. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK. Understanding pharmaceutical quality by design. AAPS Journal. 2014; 16:771-83.

18. Helman H, Andery PRP. Análise de Falhas. Aplicação de FMEA e FTA. 1st ed. Belo Horizonte: Fundação Cristiano Ottoni; 1995.

19. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987. p. 3-18.