



THE MANAGEMENT OF PROCESS LEAD TIME IN THE RELEASE OF STERILE PHARMACEUTICAL BATCHES: A CASE STUDY OF OPTIMIZATION IN AN OFFICIAL BRAZILIAN PHARMACEUTICAL LABORATORY

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Abstract

Medicines must comply with quality, safety, and efficacy pillars. Nowadays, organizations seek to incorporate new management models encouraged by quality program following the world trend regarding the technological revolution. The present research aims to improve the sterile pharmaceutical product batches release process, using the Failure Mode Effects Analysis (FMEA) method. This study addresses the gap in literature on quality risk management during batch release. The methodology uses a form adapted to the process in order to systematize the information, improving its comparison and analysis, thus estimating, the identification of potential failure modes and their effects on their performance. Made it possible to assign values for the severity, occurrence, and failure modes detection, to then determine the risk level and the priority of risk level. The results obtained showed the mitigation and elimination of failures in the process, as well as opportunities for improvement and causes of failures identification, improvement in the process performance indicators, greater reliability, and reduction in batch release time.

Keywords: good manufacturing practices pharmaceutical industry, risk management, risk management tools

Introduction

The pharmaceutical sector has great importance for global public health, providing medicines, health products, wellness programs, and also acting in the discovery of new drugs or for the health of society's technologies. The development of new therapies and the growth of investments in pharmaceutical sector, lead to an increase in the global pharmaceutical market value (Haraszkiwicz et al. 2019).

Technological advancement has driven the technological Revolution. Companies increasingly need effective and innovative processes to maintain themselves in a global competitive environment. In this context, the pharmaceutical industries constantly seek technological innovation with investments to achieve continuous improvement in their Quality System, aiming at maintaining the supply of products and services with quality and safety to population's health. In compliance with regulatory orders, it is essential to evaluate processes and manage quality risk as integral parts in the identification of potential failure modes, their probable effects as well as, identifying responses facilitating accurate decision-making for adequate risk treatment, eliminating or mitigating its impacts.

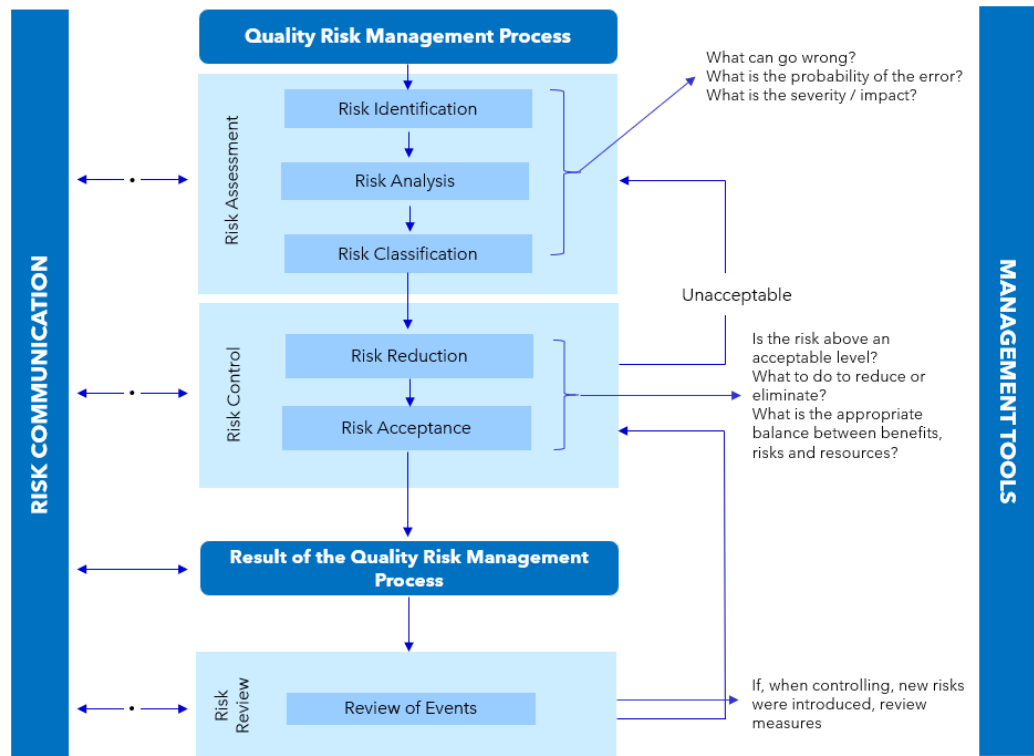
The pharmaceutical industry must reach the quality objective reliably, being necessary to have a comprehensive Pharmaceutical Quality System, correctly implemented, incorporating good manufacturing practices and quality risk management (Brazil, 2019). In this perspective, Paim et al. (2009) stated that the process improvement attitude is a basic action on the part of organizations to answer to constant changes in their operating environment. Therefore, improving processes is a critical factor for the institutional success of any organization, whether public or private, as long as it is carried out in a systematic way and is understood by all company's employees.

The International Conference on Harmonization (ICH) of technical requirements for medicines for human use brings together regulatory authorities from Europe, Japan, United States and ANVISA (most recent member). Its objective is the discussion related to the scientific and technical aspects of drug registrations. For this purpose, related Quality Guides were developed, such as ICH Q8 for Pharmaceutical Development, ICH Q9 for Quality Risk Management and ICH Q10 for Pharmaceutical Quality System (Nunes Pinheiro, 2017).

In 2005, ICH Q9 is the landmark document in the recognition of risk management as a quality system practice for the pharmaceutical industry, whose basic objective is to provide principles and tools to apply to different aspects of quality (in the areas of development, manufacture, release, distribution, inspection and others) throughout the life cycle of drugs, medicines, biological and biotechnological products (ICH, 2005).

The quality and risk management process is a systematic process for assessing, controlling, communicating and reviewing risks to product quality throughout its life cycle. A model for this management is shown in the figure 1.

Figure 1
Overview of a Quality Risk Management Process



Source: Created by the authors from ICH Q9 (2005) and SINDUSFARMA (2018)

The emphasis of each component in this structure may differ from each specific case. However, a solid process will consider all elements at a level of detail commensurate with the specific risk.

To support the application of risk assessment, ICH Q9 has some reproducible tools that can be adapted to carry out the stages of the quality risk management process based on its knowledge. The table 01 highlights these main tools.

Table 01
Key Risk Management Tools

Main Risk Analysis Tools		
Tool	Definition	Objective
FMEA Failure Mode Effects Analysis	Failure Mode and Effects Analysis	Define, identify, and eliminate potential failures
FMECA Failure Mode, Effects and Criticality Analysis	Analysis of Mode Criticality and Failure Effects	Estimate the severity of failure modes; The probability of failure modes occurring; analyze the criticality
FTA Fault Tree Analysis	Fault Tree Analysis	It addresses a failure system, as it combines its multiple causes
HACCP Hazard Analysis and Critical Control Points	Hazard Analysis and Critical Control Points	Conduct a hazard analysis; Identify preventive measures for each stage of the process; Determine critical control points; Establish critical limits; Establish a system to monitor critical control points; Establish corrective actions to be taken; Establish a system to verify that HACCP is efficient and; Establish a record-keeping system
HAZOP Hazard Operability Analysis	Analysis of Operational Hazards	Qualitative, systematic, and structured approach through the appropriate use of guide words applied to critical points related to the process under analysis
PHA Preliminary Hazard Analysis	Preliminary Hazard Analysis	Identify future hazards so that preventive measures can be estimated before a process, system or product enters its operational phase
Risk Ranking and Filtering	Risk Classification and Filtering	Compare and classify risks

Source: Created by the authors from ICH Q9 (2005) and SINDUSFARMA (2018)

The Failure Mode and Effect Analysis (FMEA) tools also known as Effect Analysis and Failure Modes, widely applied in some organizations like pharmaceuticals sector.

The use of FMEA is universally applicable and is based on the following steps:

- 1 - Select the item (example: product / process) to be analyzed;
- 2 - Identify the potential failure modes;
- 3 - Identify the possible effects of failure modes;
- 4 - Identify the respective causes;
- 5 - Estimate the severity of the failure modes;
- 6 - Estimate the probability of failure modes occurring;
- 7 - Estimate the probability of detecting failure modes;
- 8 - Identify the existing controls;
- 9 - Estimate the risk priority number (NPR);

10 - Determine recommendation actions to reduce the number assigned to the risk. These actions may include inspections, preparation or review of procedures, among others;

11 - Review the FMEA according to changes made or the appearance of new information. (Sindusfarma, 2018).

Research Aim

Identify the potential failure modes using FMEA tool. Analyze causes and effects on the performance of the process of releasing batches of sterile products.

Research Methodology

The careful and systematic investigation of the process and the improvement of theoretical knowledge provided elements that made possible the use and choice of the FMEA tool, allowed the identification the potential modes of failures, their causes and effects, as well as the development of actions to manage the faults detected in batch release process.

Giorgetti et al. (2020) stated that its use and choice is justified by its approach in allowing the identification of potential irregularities that represent risk to the process and its effects on the performance of the process. However, it allows the planning of actions capable of avoiding such failures, reducing occurrences chances, increasing the reliability of the activity. (Giorgetti et al., 2020).

Therefore, for this identification, the following questions were listed: What can go wrong/ fail? What can be the failure's consequence? How serious is this failure when it occurs? How many times can it occur? Are there any controls defined in the step? Is it possible to identify the fault before it occurs?

The use of FMEA tool was based on the systematic application of process identifying dangers information, the possibility of occurrence and severity (determination of the level of risk_ by the product of the severity and occurrence); conducting a critical analysis of risks, showing the existing controls in the stages (determination of the level of risk priority_ by the product of severity, frequency of occurrence and detection); and definition of actions to mitigate all identified problems.

The FMEA tool form was adapted to assess the risks inherent batch release process (see frame 1).

Frame 1

FMEA Form Application

RISK ASSESSMENT FORM - BATCH RELEASE PROCESS																
Activity	Fail mode	Potential Effect	Severity	Potential Cause	Occurrence	NR	Existing Controls	Detection	NRP	Risk accepted	Action / Recommendation	Risk Reduction Estimate			Responsible	When?
												Severity	Occurrence	Detection		RR

Source: Created by the authors from SINDUSFARMA (2018)

Evaluation was carried out in three stages, contemplating the sequential phases of the releasing sterile product batches process.

- 1st step) Reconciliation of production processing documentation and filling in the reconciliation activity record, among which all physical and electronic records of production, materials and inputs of the production process and in-process control reports stood out;

- 2nd step) Release of products purchased / distributed, intermediate and bulk purchased, highlighting the records of the technological partner, deviations related to the product, temperature parameter recorders for products subject to temperature control, analysis reports and batch status;
- 3rd step) Compilation of the batch documentation, analysis certificates, release activity and filling in the records of the product release finished activity, including all the batch's final processing records, analysis records, processing deviations and analysis, good documentation practices and activities batch release indicators.

The occurrences were determined based on previous consultations of deviation reports related to the identified flaws. Thus, doing all evaluations.

Research Results

After applying the FMEA tool observed: 64 failure modes 5 high severity risks, however, with low occurrence being kept within the low risk level. For each failure mode, it was possible to identify at least one existing control measure and according to their efficiency, it was possible to determine the detection degree. In addition, for failure modes with NPR even evaluated with a low priority level of risk, improvement actions were recommended in order to reduce the risks.

The analysis successfully enabled the identification of potential failures, their causes, severities, frequency of occurrences at each stage of the activities and gradually identified the existence of controls, such as: specific procedures, resources, equipment, registration protocols, among others, demonstrating a controlled process with low and acceptable levels. Scales were defined considering the levels of Severity, Occurrence, NR (Risk Level - Brazilian term) and Detection to determine the NPR (Risk Priority Level - Brazilian term) set out in the tables 2, 3, 4 and 5.

Table 2
Severity Classification

Index	Severity	Rating criteria
1	Very low	Does not affect batch release
2	Low	Affects batch release with possibility of reversal
3	Moderate	Possibility of affecting the batch release
4	High	Retains the batch with the possibility of batch release
5	Very High	Retains batch without possibility of batch release

Source: Created by the authors (2020)

Table 2 shows the degrees of severity with indexes from 1 to 4, where 1 is assigned the lowest. 5 is the highest value.

Table 3
Occurrence probability rating

Index	Occurrence	Rating criteria
1	Very low	Unlikely to occur
2	Low	There is no record of occurrence
3	Moderate	Likely to occur over time
4	High	Likely to occur within a medium term

Source: Created by the authors (2020)

Table 3 shows the degrees related to the occurrence. The assigned values are from 1 (lowest) to 4 (highest).

Table 4
Range of NR

Range of NR	Risk level
1-8	Low
9-12	Average
13-25	High

Source: Created by the authors (2020)

Concerning table 4, it is possible to notice the NR range obtained. Values between 1 to 8 (low), 9 to 12 (average) and between 13 to 25 (highest)

Table 5
Detection Classification

Index	Detection	Detection Ease Criteria	Time criterion required for detection
1	Very High	Almost certain detection	Immediate detection
2	High	High probability of detection	Short-term detection
3	Moderate	Average chance of detection	Medium-term detection
4	Low	Low probability of detection	Long-term detection
5	Very low	Detection almost impossible	Detection almost impossible

Source: Created by the authors (2020)

The table 5 shows the detection criteria. It is important to note the importance of the time required for detection and the criteria for it. The assignment given ranges from 1 (very high) to 5 (very low).

Based on the risk assessment it was possible to list some proposals as described:

Action 1 - The processing documentation verification must be carried out and validated by a designated person from the production area in their own records;

Action 2 - The identification of non-conformities related to processing, as well as

deviations for a process control must be evidenced by the processing area and then verified by the quality assurance area;

Action 3 - The validity of the printed arts and their control through the ERP system (Enterprise Resource Planning) must be considered, as it is a validated system and suitable for use;

Action 4 - The ranges of process control limits (points mapped in the production area) must be included in the batch release record, thus facilitating the immediate checking;

Action 5 - Weekly alignment must be carried out with the interface areas (deviation management, technician responsible) prior to the batch release;

Action 6 - Check list of temperature recorders must be inserted in all loads of purchased products subject to temperature control;

Action 7 - Immediately after receiving the registrars, they must be read.

These actions were implemented as appropriate additional measures in order to minimize or reduce failures, making the process more effective and optimized.

Discussion

The quality risk management (QRM) is an activity that integrates identification of quality risk, risk analysis, risk assessment, developing strategies to manage them. Some traditional QRM exercises are focused on pharmaceutical manufacturing only, however, the gap observed during batch release poses business challenges finally leading to market complaints, recall, rejections, and regulatory actions. A model way to deal quality risk during release operation provides more insight to continued process verification strategy. The quality risk management during continuous manufacturing process helps effective management of quality risks to ensure release continuity which is a significant challenge and has the following key steps.

Make quality and risk management as key elements during batch release. Ensure that risk management is an on-going activity, not one-time action. Enhance communication about risk elements and controls exercised across the process. Each pharmaceutical organization must establish a mechanism for quality risk management during batch release to accomplish the goals of patient's safety and customer satisfaction without apprehension of drug regulatory actions due to quality risk.

Conclusions

The application of the FMEA risk analysis tool proved to be efficient to assist in the process management process in the product's lead time.

The implementation of improvement actions in the process provided greater speed in the demands for product distribution such as: increased reliability and overcoming the expectations of the services provided, as well as facilitating the prioritization of failures, making it possible to reduce or eliminate them. The role of the Quality system is essential to meet the strategic needs of the organization.

The approach to risks and opportunities for improvement establishes a basis for increasing the effectiveness of the Quality Management System. Likewise, were observed the achievement of better and more appropriate results like, and the mitigation of negative effects.

In addition, it is important to emphasize that the continuity of the monitoring of the process as well as the assessment of the need taking new actions are important to keep the cycle of continuous improvement underway, in order to guarantee competitiveness survival of the institution.

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