Universidade de Lisboa

Faculdade de Farmácia

Quality Risk Assessment on The Development of a Generic Product

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Monografia orientada pelo Professor Doutor João Pedro Martins de Almeida Lopes, Categoria Professor Auxiliar

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

A gestão da qualidade de risco é um processo que acresce valor e facilita o sistema de qualidade das empresas farmacêuticas. No entanto nem sempre as empresas aplicam este método da melhora forma acabando por ter um grande consumo de recursos.

O objectivo desta dissertação é desenvolver uma avaliação de risco para um processo de engenharia reversa no âmbito do desenvolvimento de um medicamento genérico, identificando os possíveis riscos e formas de mitigá-los. Pretende-se, também, desenhar um esquema de trabalho baseado no risco que possa ser reutilizado como um fluxo de trabalho para o desenvolvimento de medicamentos genéricos.

A avaliação de risco nesta monografia foi referente ao processo de engenharia reversa para o desenvolvimento de um medicamento genérico, cujo produto de referência é um shampoo de cetoconazol a 2%.

Para identificar os riscos associados e possíveis mitigações utilizaram-se métodos como diagrama em espinha de peixe e análise de modo e de falha (FMEA). O diagrama em espinha de peixe permitiu discernir sobre as possíveis causas para o problema identificado, de uma forma organizada e concisa. A análise FMEA baseou-se em, após terem sido identificados os possíveis riscos, responder às perguntas: "Qual o impacto?" (severidade) "Qual a probabilidade de correr mal?" (probabilidade) "Qual a probabilidade de ser detetado" (detetabilidade). Tendo cada um destes pontos sido classificados com base nos níveis definidos de 1 a 5. E posteriormente multiplicou-se o valor atribuído à severidade, ocurrência e detectibilidade obtendo-se o valor de RPN. Esta metodologia demonstrou ser eficiente e permitir um pensamento metódico e organizado sob o problema. A forma como este projeto foi estruturado permite, também, que este esquema de trabalho seja aplicado em outros projectos de desenvolvimento de medicamentos genéricos.

Com este projeto foi também possível perceber que as empresas farmacêuticas, que pretendam desenvolver medicamentos genéricos, podem beneficiar se aliarem o processo de engenharia reversa à gestão de risco permitindo um desenvolvimento do medicamento genérico mais custo efetivo.

Palavras-chave: Gestão do Risco para a Qualidade; Engenharia Reversa; FMEA; Medicamentos genéricos

Abstract

Quality risk management adds value and facilitates the quality system in pharmaceutical companies. However, not all companies apply this method in the best way ending up having a big consumption of resources.

The aim of this dissertation is to develop a quality risk assessment for a process of reverse engineering within the scope of the development of a generic product, identifying possible risks and how to mitigate them. This work is also intended to design a risk-based framework that can be reused as a workflow for the development of generic medicines.

The risk management proposal in this dissertation concerns a reverse engineering process for the development of a generic medicine, whose reference product is a ketoconazole shampoo at 2%.

In order to identify the risks and possible ways of mitigating them, two methods were used: fishbone diagram and failure mode and effects analysis (FMEA). The fishbone diagram permitted to analyse possible causes for the problem identified, in an organized and concise way. The FMEA was based on answering questions such as “what are the consequences?” (effects/severity), “which are the possible causes” and “which is the likelihood it will go wrong?” (probability). Each of these points, severity, probability, and detection were classified from 1 to 5. Afterwards they were multiplied and the RPN value was obtained.

This methodology was efficient and allowed a methodical and organized way of thinking about the problem. The way this process was structured also enables the application of this workflow in other projects for the development of generic medicines.

With this project it was possible to understand that pharmaceutical companies which intend to develop generic medicines can benefit when allying reverse engineering with quality risk management, permitting a more cost-effective development.

Keywords: Quality Risk Management; Reverse Engineering; FMEA; Generic Medicines

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And I thank God for being with me no matter what.

Abbreviations

CQA – Critical Quality Attribute

DoE – Design of Experiments

EMA – European Medicines Agency

FMEA – Failure Mode and Effect Analysis

FMECA – Failure Mode, Effects and Criticality Analysis

FTA – Fault Tree Analysis

FTIR – Fourier-transform infrared spectroscopy

HACCP – Hazard Analysis and Critical Control Points

HAZOP – Hazard Operability Analysis

PAT – Process Analytical Technology

PHA - Preliminary Hazard Analysis

QbD – Quality by Design

QRM – Quality Risk Management

QTPP – Quality Target Product Profile

RE – Reverse Engineering

RPN – Risk Priority Number

Table of Contents

List of Figures

List of Tables

1 Introduction

1.1 Generic Development

Once the period of data exclusivity on the reference medicine has expired, in general 10 years from the date of first authorisation, a company can develop a generic medicine.

According to EMA a generic medicine must contain the same active substance(s) as the reference medicine, and it must be used at the same dose(s) to treat the same disease(s).

As the information regarding safety and efficacy of the substance(s) is already available from the reference medicine, companies producing generic medicines normally only need to grant information on the quality of the medicine and prove that the generic medicine produces the same levels of the active substance in the human body as the reference medicine. (1)

Taking into to account the information provided by the company, regulatory authorities will decide if there is a need for additional tests to grant a marketing authorisation.

The company responsible for the development of the generic product does not have to grant information of preclinical tests and of clinical trials as it can assume the ones associated with the reference product, this is only possible when applying the concept of bioequivalence which is fundamental.

While developing a generic product it is advisable to use the drug product information present in the packaging insert, patents, and published literature for the reference product. The major formulation goal a company aims to achieve is quantitative sameness (Q1, same components as the reference product) and qualitative sameness (Q2, same components in same concentration as the reference product). (2)

Pharmaceutical companies have a vast variety of ways to investigate and study the reference product to develop a generic product which is bioequivalent, one of those ways is through reverse engineering (RE). When using this method companies are able to minimize potential issues related with critical product attributes, stability, and efficacy. (2)

1.2 Brief description on RE

Reverse engineering is a scientifically sound and cost-effective strategy for accelerating the development of a generic products (3), allowing to collect clear and detailed information of the reference product on both a quality and quantitative point of view.

Reverse engineering is also known as backwards engineering or back engineering. It is a process or method used to examine and investigate an existing product to determine how it was developed and its composition in terms of which raw materials were used and their quantities. This method can accelerate the development of generic products. (4)

Using information from literature sources combined with de-formulation studies can enable the development a formula that is qualitatively and quantitatively as similar to the reference product as possible, providing greater confidence about the performance of the generic product. (3)

1.3 Product Characterization

In this dissertation our reference product is a shampoo composed of ketoconazole 2%. It is a medicinal product which does not obligate having a medical prescription to acquire, used for treatment and prophylaxis of infections involving pityrosporum yeast, such as pityriasis versicolor (localized), seborrheic dermatitis and pityriasis capitis (dandruff). (5)

1.3.1 Active Pharmaceutical Ingredient

Ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) is an antifungal agent, it is a white/almost white powder, whose content is of 99.0% to 101.0% (dried substance) and has a fusion point from 148ºC to 152ºC. It is practically insoluble in water, easily soluble in methylene chloride, soluble in methanol and slightly soluble in ethanol at 96%. Loss by drying maximum 0.5% determined

in 1.000g of sample in kiln at 105ºC. (6) Ketoconazole's molecular structure is represented below.

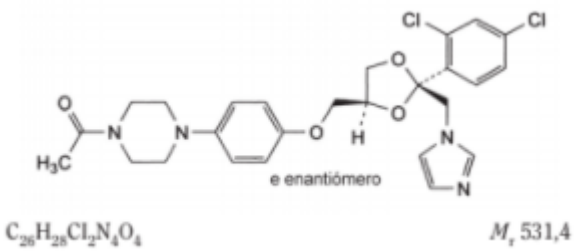

Figure 1 – Ketoconazole's Molecular Structure

1.3.2 Excipients

Table 1 – Characterization of Excipients (7,8)

Excipient	Function	Characteristics
Sodium Lauryl Sulfate	Anionic Surfactant	Freely soluble in water, giving an opalescent solution Hydrolysis at a pH of 2.5. Use as detergent in medicated shampoos ≈ 10%
Disodium monolauryl ether sulfosuccinate	Anionic Surfactant	-
Cocamide DEA	Emulsion Stabilising, Foaming Agent, Viscosity controlling	-
Collagen	Hair Conditioning	-
PEG 120 Methyl Glucose Dioleate	Thickening agent	Hygroscopic, soluble in water, acetone, alcohols, benzene, glycerine, and glycols. All grades can exhibit some oxidizing activity owing to the presence of trace peroxide impurities
Sodium Chloride	Viscosity controlling	Solubility at 20ºC: Slightly soluble in Ethanol. Ethanol (95%) 1 in 250. Glycerine 1 in 10. Water 1 in 2.8 or 1 in 2.6 at 100%
Hydrochloric acid	Acidulant	Miscible with water, soluble in diethyl ether, ethanol (95%), and methanol
Imidurea	Antimicrobial preservative	Effective at pH 3-9 Loss on drying ≤3%

		Soluble in water and in glycerol, but insoluble in almost all organic solvents
Sodium Hydroxide	Alkalizing agent (adjust the PH of solutions)	Solubility at 20ºC: Ethanol 1 in 7.2. Practically insoluble in Ether. Soluble in Glycerine. Methanol 1 in 4.2. Water 1 in 0.9 or 1 in 0.3 at 100ºC.
Parfum	Odour	-
Erythrosine (E127)	Colouring Material	-
Purified water	Vehicle	Clear and colourless liquid

In annex 1 are spectra from some of the excipients.

With the information available in literature, we know the excipient values should vary between these values: (9)

a) 36% to 45% surfactants

(b) 2% to 6% foaming agent

(d) 0.2% to 1 .3% thickener

(e) preservatives sufficient to retard degradation of the final composition in order to give adequate shelf life

(f) acid, base or buffer to yield a pH in the desired range

(g) water QS ad 100% (that is, sufficient water to make 100%)

1.4 Quality by design

According to EMA, one of the goals of quality by design (QbD) is to ensure that all sources of variability affecting a process are identified, explained, and managed by appropriate measures. (10) This can be achieved by using several tools such as risk assessment, design of experiments (DoE), and process analytical technologies (PAT), etc. (11)

The first step of QbD is to define a quality target product profile (QTPP) as well as the critical quality attributes (CQAs). The next step is to identify the risk of the proposed process and the critical parameters that need to be investigated. DoE studies can be a key point in implementing optimized processes within acceptable design space to consistently deliver high quality

products. (11) An appropriate combination of some of QbD tools may very well help improve a process, such as the development of a pharmaceutical product.

1.5 Quality Risk Management

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. (12)

Quality must be maintained throughout the product's lifecycle, so the aspects which are important to control for quality should remain consistent according to those in clinical studies. Quality risk management (QRM) is a process which allows an appropriate managing of the risks, providing a rationale to understand risk and mitigate it through applicable and robust controls. (13)

An effective QRM approach can ensure the high quality of the medicinal drug product to the patient by providing means to identify and control potential quality issues during development and manufacturing. Furthermore, QRM can have an important role in improving decision making if a quality problem arises, by allowing better and more informed decisions. This can beneficially affect the extent and level of direct regulatory oversight since it can provide a greater assurance to regulators of a company's ability to deal with potential risk. (12,13)

QRM relies in two primary principles: (12,13)

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to protection of the patient.
- The level of effort, formality, and documentation of the QRM process should be commensurate with the level of risk.

Besides these two principles, QRM methodology should be dynamic, responsive to change and the capability for continual improvement should remain present.

A QRM process has five major steps:

1. **Definition of the problem and/or risk question**, this step should include pertinent assumptions identifying the potential for risk and assemble background information and/or data on relevant aspects to the risk assessment. (12,13)

2. **Risk Assessment** which consists of the identification of hazards and the evaluation of risks associated with exposure of those hazards. This step includes risk identification, risk analysis and risk evaluation and should answer three fundamental questions “What might go wrong?”. “What is the likelihood (probability) it will go wrong?” and “What are the consequences (severity)?” (12,13)

3. **Risk control** includes risk reduction which focuses on mitigation or avoidance of quality risk when it exceeds an acceptable level and risk acceptance which can be a formal decision or a passive decision in which residual risks are not specified. (12,13)

4. **Risk Communication** consists in sharing information about risk and risk management between the decision makers and others. (12,13)

5. **Risk review**, this step allows to take in account new knowledge and experience, since QRM follows the whole development process. (12,13)

QRM can be implemented using recognized tools for assessment and management of risk. Some of these tools are: (12,13)

- Basic risk management facilitation methods

(Flowcharts, check sheets etc.)

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

The risk management tools used in this dissertation were fishbone diagram together with FMEA.

The fishbone diagram (also known as Ishikawa diagram) is a tool used to identify the multiples possible causes of a certain effect. The structure of the diagram helps to determine the root causes of a problem by thinking in a systematic way. When implementing the fishbone diagram, it is important to define the risk and identify the main and secondary causes. (14)

Failure Mode Effects Analysis (FMEA) allows the assessment of potential failures modes for processes, possible causes of the failure and the impact on outcomes and/or product performance. Once failure modes are known, risk reduction actions can be enforced to eliminate, reduce, or control potential failures. (12,13)

The FMEA process helps to minimize the potential impact of risk through the risk priority number (RPN) which is the product of severity, probability, and detection or: RPN = S x Px D

The higher the RPN number the more concern.

Severity is defined as the impact the failure has. Probability relies on the estimated frequency or cumulative number of failures. Finally, detection is the probability that the failure will be discovered. (13)

There is great advantage in implementing a quality risk assessment when developing a pharmaceutical product. It allows a greater understanding of the drug substance and the manufacturing process enabling a more flexible regulatory approach, which can be foreseen by the level of relevant scientific knowledge provided in the application for authorisation. (15)

2 Aim of the dissertation

The aim of this dissertation is to develop a quality risk assessment for a process of RE within the scope of the development of a generic product.

The intention of this approach is to identify the possible risks and how a pharmaceutical company is able to mitigate such risks. This work is also intended to design a risk-based framework that can be reused as a workflow for the development of generic medicines.

3 Methods

First, we used a fishbone diagram to identify the possible causes for our problem. Afterwards, we applied a Failure Mode Effect Analysis (FMEA). Our analysis was based on the steps listed in Fig. 2.

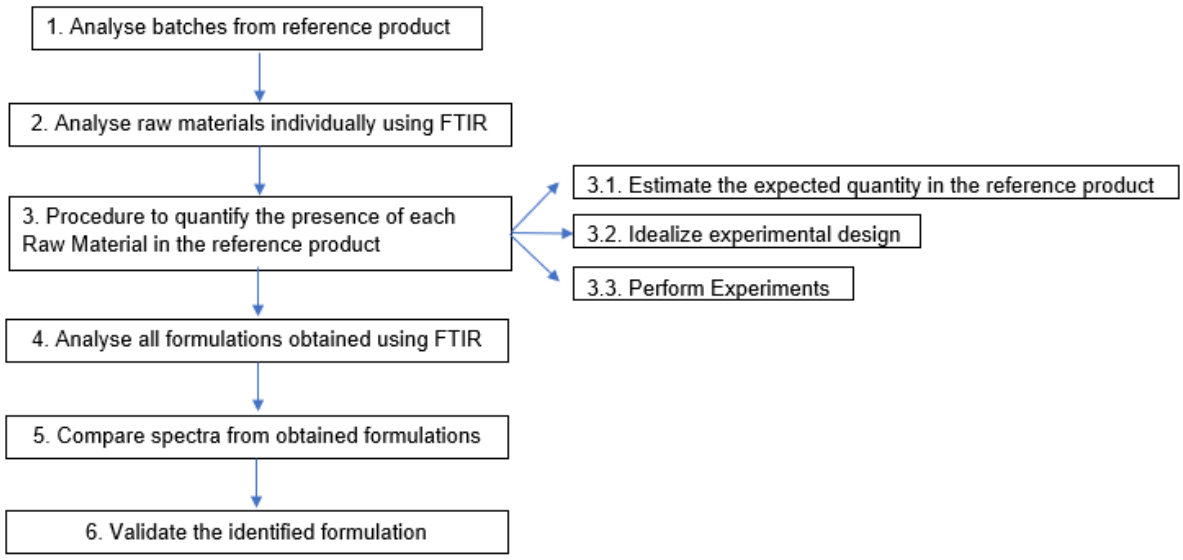

Figure 2 – The steps adopted to conduct a RE approach towards the estimation of the quantitative formula.

4 Results

4.1 Fishbone Diagram

The fishbone was achieved by evaluating every step of the process taking into to account what could go wrong in terms of material, operator, equipment, etc.

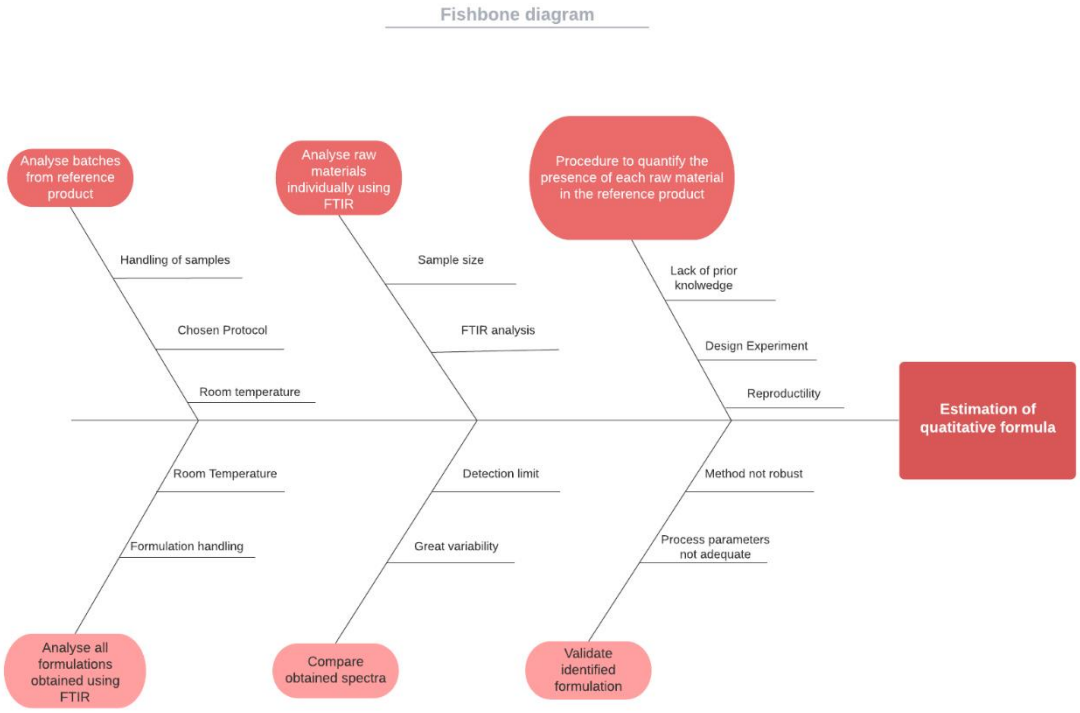

Figure 3 – Fishbone diagram of reverse engineering process

4.2 Failure Mode Effect Analysis (FMEA)

The first step for the FMEA analysis was defining the range levels of probability, severity, and detectability.

Probability (adapted from (16,17)):

1. The failure is unlikely to occur

3. The failure may occur sometimes

5. Great probability of failure occurring

Severity (adapted from (16,17)):

1. Minimal/low impact

3. Moderate impact

5. High impact

Detectability (adapted from (16,17)):

1. The failure will certainly be detected

3. The failure is likely to be detected

5. Low/no detectability

Afterwards each step of the RE process was analysed individually for possible failures.

4.2.1 Analyse batches from the reference product

This step consists on the analysis of the reference product, typically by a fast and sensitive analytical method. For simplicity in this work only Fourier-transform infrared spectroscopy (FTIR) was considered. Whenever performing a FTIR analysis it is important to make sure that the equipment is well calibrated, to reduce the risks. One of the major issues encountered in this step can be the influence of the water bands. It is therefore important to adjust the drying

conditions. To help eliminate this problem the company can also run a background with water and subtract it to the sample of the reference product.

In this step it is also possible to encounter some variability between batches. In this case, companies can look to it from a strategic point of view and state in the marketing authorization that even in the reference product there is minor variability between batches.

4.2.2 Analyse raw material individually using FTIR spectroscopy

When analysing raw materials with FTIR spectroscopy it is essential to know there physical and chemical proprieties. This will allow a better assessment of what can possibly go wrong, and on how the raw material must be manipulated before being analysed.

Depending on the product a company intends to develop the number of raw materials can vary. A higher number of raw materials is associated with a higher probability of errors, so it is advised that the company outline a systematic way of analysing the raw materials, which must include cleaning of the crystal between analysis with enough time for the cleaning solvent to evaporate and not interfere with the spectra.

One of the biggest problems when analysing a raw material is not knowing which grade of material was used in the reference product. This is considered a risk since even though the materials have different grades, in terms of the physical-chemical properties they will be very similar.

4.2.3 Procedure to quantify the presence of raw materials in the reference product

This step of the process is divided in three parts. First, the company must estimate the expected quantity of the excipients in the reference product. For this task one might resource on information available in the literature regarding the percentage of each component in the drug product. There is still a risk that the company makes an estimate that is too far from reality.

Secondly, the company must idealize an experimental design. A design of experiments (DoE) consists in a structured and organized method which determines the relationship between several factors using mathematical models. This approach varies controlled input factors in a systematic way allowing to know what are the effects of these variations and which are the

most important input factors. (18) There is a vast number of mathematical models that can be used to develop a DoE, whenever choosing the mathematical model it is important to take in accounts certain factors such as number of experiments, number of input factors etc. The choice of the DoE is crucial to make correct and robust decisions.

Finally, the last step of the process includes conducting the experiments. A lot can go wrong when experimenting. At this stage it is essential for the company to gain as much knowledge as possible about the production process, which steps does it include, which equipment, if it is possible to scale up. One of the biggest problems of developing a topical product can be to achieve robustness, so the more knowledge a company has regarding the process steps, and the material characteristics the easier it can be to find ways to solve it.

4.2.4 Analyse formulations obtained by DoE using FTIR

Risks that can occur in this step of the process are practically the same as the ones that can occur in the first step of the proposed RE process.

4.2.5 Compare signals

In this step, the company must compare signals (in this case spectra) from the reference product with spectra from the produced formulations. The main goal of this step is to encounter the spectrum of the "best candidate" meaning the spectrum of the formulations developed which is the most similar to the spectrum of the reference product.

If the mathematical model chosen for the DoE is not correct, the company may risk of having spectra's which are very distinct or not identifying the "better candidate".

4.2.6 Validate the selected formulation

The final step of this RE process is the validation of the formulation, which is vital to assure the quality of the estimation.

At this point, the pharmaceutical company must evaluate if the final formulation has the same organoleptic characteristics as the reference product. If it does not, they must find the cause, which can be the sequence of addition of the materials during the production process, or the

amount of colouring for example, and decide if the difference is crucial for the quality, efficacy, and safety of the product. In this step the company must also perform the mandatory quality control tests. Considering this particular product as a single formulation with a single-phase, it waivers to provide permeation kinetic or pharmacodynamic equivalence data. (19) The only test the company is obliged to perform is efficacy of antimicrobial preservation test. (6) And must also provide data regarding to organoleptic characteristics, pH and Viscosity.

Tables 2 to 7 provide a thorough FMEA analysis for each step. Each table contains several possible failure modes, what are the possible effects, possible cause, and possible actions towards the failure. It also contains the classification in terms of severity, occurrence, and detectability for each point, including the value of the risk priority number. Based on the levels established for severity, occurrence, and detectability, the maximum RPN value possible would be 125 and the lowest 1. After calculating each RPN, we obtained a histogram (figure 4), and defined our threshold to be ≥ 15, meaning that the parameters that fall into this range need to have a closer attention.

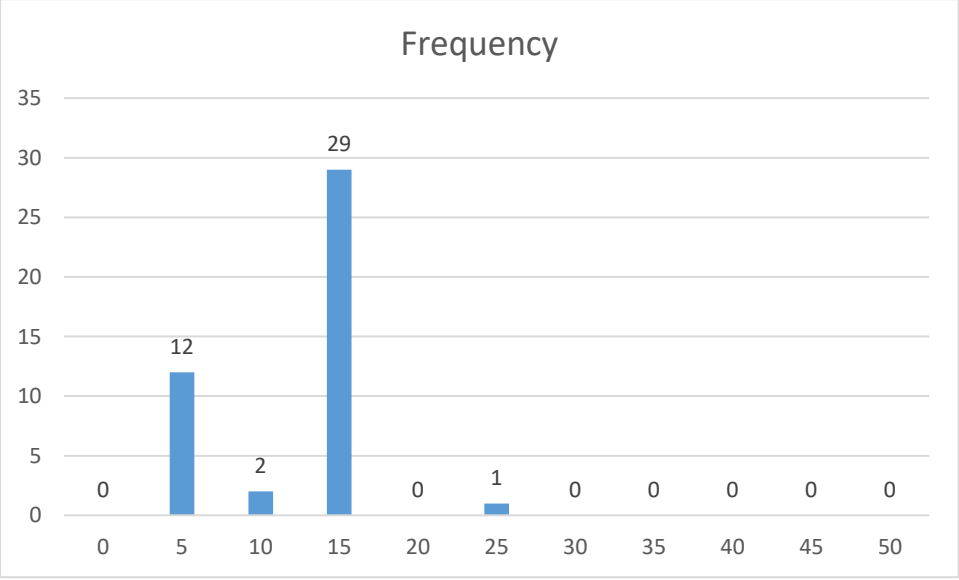

Figure 4 – Histogram based on the estimated RPN values

Table 2 – FMEA for step 1 of the RE process: reference product analysis

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
1.Refere product analysis	Method	Water content in the sample	Impact on the spectrum	5	Drying step not optimized	3	1	15	Prior study of the optimization values of temperature and drying time
	Method	Variability in development protocol	Variability in sample preparation and data acquisition	3	Missing prior knowledge	5	1	15	Be rigorous on the development of the protocol
	Material	Different batches, same producer	Samples variability	5	Acquisition of reference product in client market	1	1	5	Make sure we always buy the same batches
	Material	Achievement of optimal sample drying	Variability on the water content	5	Poor drying	5	1	25	Close control of drying step
	Material	Sample size	Not able to obtain spectra	1	Insufficient sample quantity	1	1	1	Cover the crystal with enough sample
	Material	Presence of many minor compounds (<ppm)	Unable to detect	5	Formulation itself				Select an appropriate analytical method for minor components detection
	Material	Presence of impurities or degradation products	Spectra interference	5	Incorrect manipulation of samples	3	1	15	Guarantee the correct manipulation of samples, guarantee the correct environment conditions
	Equipment	Number of spectra collected not correct	Unable to achieve precise spectra. Spectra with noise	5	Insufficient number of spectra/analysis	3	1	15	Identify the minimum number of spectra needed to achieve an accurate result
	Environment	Laboratory temperature variations	Variability in spectra	3	Air conditioning	5	1	15	Try maintaining the same room temperature and air flow scheme

Table 3 – FMEA for step 2 of RE process: analyse raw materials individually using FTIR spectroscopy

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
2.Analyse raw material individually using FTIR	Method	Water content in the sample	Impact on spectrum	5	Incorrect drying step procedure	3	1	15	Do we have to dry Raw material? If yes, study optimization values of temperature and time of drying phase
	Material	Loss of content in drying step	Weak spectra, not according to reality	5	Physic-chemical characteristics of raw materials	3	1	15	Adjust drying conditions, control drying in real time
	Material	Solid state	Spectra unable or difficult to detect	5	Bad manipulation of raw material, preparation step incorrectly executed	3	1	15	Adequate preparation step according to raw material
	Material	Raw material is not pure	Spectra with interferents	5	Contamination	1	1	15	Make sure we buy certified raw material, and we are careful with the manipulation
	Material	High number of raw materials	Errors associated with exchange of material	1	High number of raw materials	3	1	3	Systematic way of analysing
	Material	ATR Crystral contamination of prior sample	Contaminated spectrum	3	Incorrect cleaning procedure	1	3	3	Correct cleaning of crystal
	Material	Homogeneous sample	Spectra not accurate, peaks not well defined	5	Incorrect homogenization	1	1	5	Homogenise sample
	Material	Cleaning solvent interference	Cleaning solvent peaks appear in spectrum	1	Not enough time given to evaporation	1	1	1	Allow solvent to evaporate

	Material	Not knowing raw material grade	Uncertain on which grade to use on the development of the product	5	Existence of a variety of grades	3	1	15	Test more than one grade
	Operator	No background run	Spectra with noise	5	Operator's error	1	1	5	Make sure to include in protocol, and train collaborator
	Equipment	Weak signal of raw material	Spectrum unable or difficult to interpret	5	Detection limit of the equipment is not adequate	3	1	15	
	Equipment	Poorly defined spectrum	Spectrum unable or difficult to interpret	5	Equipment not robust	3	1	15	Increase the number of spectra. adequate number of spectra

Table 4 – FMEA for step 3 of RE process: procedure to quantify the formulation components in the reference product

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
3.1. Estimate expected quantity in reference product	Method	Estimate too far from real for most components	Unable to achieve the correct formula	5	Bad analysis of results/Lack of prior knowledge	3	1	15	Search in literature
	Method	Estimate too far from real in most important components	Unable to achieve the correct formula	5	Bad analysis of results/Lack of prior knowledge	3	1	15	Search in literature
3.2 DoE	Method	Experimental outline not adequate	Unable to make conclusions	5	Lack of prior knowledge/Studying the product	1	1	5	
	Method	Variation interval not adequate	Not applicable to our product, not able to obtain results	5	Lack of prior knowledge	3	1	15	Search in literature
	Method	Number of outline experiments lower than needed	Outline not robust	3	Availability from the company	3	1	9	With the experiments obtained with DoE choose the best to "try"
3.3. Experiments	Method	Reproducibility	Unable to produce similar batches	5	Process is not robust	3	1	15	Optimize process/use PAT
	Method	Production scale is not the same	Unable to scale up	5	Equipment not available	3	1	15	Optimize usage of equipment to obtain more similar results
	Method	Steps of production of the reference product unknown	Difficulty in having a similar as possible process to the one of the reference product	3	Steps of the production process of reference product unknown	5	1	15	

	Method	Some experiments do not reproduce acceptable formulations	Cannot be used for upcoming experiments	5	Incorrect quantity of raw materials, incorrect conditions of storage, incorrect addition of raw material	1	1	5	Discsard these formulations
	Material	Different physical characteristics	Unable to achieve formulation similar to reference product	5	Number of compounds, differences applying production process	3	1	15	
	Equipment	Different equipment	Differences on final product characteristics	5	Available equipment at the moment	3	1	15	Optimize usage of equipment to obtain more similar results

Table 5 – FMEA for step 4 of RE process: analyse formulations obtained by DoE using FTIR spectroscopy

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
4.Analyse formulations obtained by DoE using FTIR	Method	Water content in the sample	Water band on spectra with high impact	5	Drying step incorrectly executed	3	1	15	Prior study of the optimization values of temperature and time of drying phase
	Method	Variability in the protocol	Differences in sample preparation and data acquisition	3	Missing prior knowledge	5	1	15	Be rigorous on the development of the protocol
	Material	Achievement of optimal sample drying	Variability of water content	5	Poor drying	3	1	15	Adjust drying conditions or control drying in real time
	Material	Sample size	Not able to obtain spectra	1	Insufficient sample quantity	1	1	1	Cover the crystal with enough sample
	Equipment	Number of spectra collected not correct	Noisy spectra	5	Number of spectra bellow the necessary	3	1	15	Identify the minimum number of spectra needed to achieve an accurate result
	Environment	Laboratory temperature variations	Variability in spectra	3	Air conditioning	5	1	15	Control the room temperature

Table 6 – FMEA for step 5 of RE process: compare signals

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
5. Compare signals	Method	Not possible to choose the better candidate	Difficult to achieve the most similar formulation	5	None of the spectra matches the reference product spectrum	3	1	15	New DoE, based on the most similar formulations
	Method	Mathematical model	Not able to distinguish between similar reference product spectrum	5	Mathematical model not adequate	1	1	5	Switch mathematical model
	Equipment	Spectra are very different	Unable to connect the information	5	Concentrations in formulations far from reality	3	1	15	Adjust formulations
	Equipment	Concentration below limit of detection	Unable to detect	5	Low concentration in formulation	3	1	15	Compound dependent

Table 7 – FMEA for step 6 of RE process: validate the selected formulation

Process Step	Category	Failure Mode	Effects	S	Causes	P	D	RPN	Recommended Action
6. Validate the selected formulation	Method	Unable to reproduce formulation	Unable to guarantee quality	5	Method not robust enough	3	1	15	Adjust method's parameters
	Material	Different pH between formulations	Not robust	5	Different amounts of acidulant	3	1	15	Adjust amount
	Material	Different viscosity	Differences in physical characteristics	5	Process parameters not adequate	3	1	15	Adjust process parameters
	Material	Does not meet the efficacy of antimicrobial preservation test (PF 9.0 - 5.1.4 category 2)	Unable to be authorized	5	Inadequate amount of preservative or wrong preservative	3	1	15	Adjust amount or switch preservative

5 Conclusion

The aim of this dissertation was assessing a quality risk management on the process of RE to development of a generic product. This was achieved with the design of a risk-based framework. The design was drawn by defining the steps to conduct a RE approach for estimating the quantitative formula and assessing its risks trough a fishbone diagram and a FMEA.

The FMEA was conducted by elaborating a systematic table for each step of the RE process. To elaborate the tables, for each step of the process, failures modes where identified. And for each failure mode the questions: “What are the consequences?” (Effects/Severity), “Which are the possible causes” and “Wich is the likelihood it will go wrong?” (Probability) were answered. To finalize, an action was recommended for each failure mode.

Throughout this assessment, many risks were identified in each step of the process by using tools such as fishbone diagram and FMEA. These tools proved to be an asset when undergoing a risk management, since they allow a systematic way of thinking enabling an optimized risk mitigated.

In conclusion, pharmaceutical companies can benefit from this risk-based framework and reuse it for other developments of generic medicines. Since this framework enables a methodical way of working, allowing the company to identify which are the possible risks and how they can impact the process.

References

1. European Medicines Agency (EMA). Generic and hybrid medicines [Internet] [Cited 2021 April 24] Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines [Internet]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines

2. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products: Formulation development, process development, and testing of topical dermatologic products. AAPS J. 2013;15(1):41–52.

3. Bansal AK, Koradia V. The Role of Reverse Engineering in the Development of Generic Formulations [Internet]. Vol. 29. 2005 [cited 2021 April 24]. Available from: http://www.pharmtech.com/role-reverse-engineering-development-generic_formulations?id=&pageID.

4. Narang AS, Boddu SH. Excipient applications in formulation design and drug delivery. Excipient Applications in Formulation Design and Drug Delivery. 2015. 1–681 p.

5. HAS 2010. RCM Nizoral. Vol. 53, Journal of Chemical Information and Modeling. 2013. p. 1689–99.

6. Infarmed. Farmacopeia Portuguesa 9 (2009). Ed. INFARMED – Ministério da Saúde, Lisboa. Farmacopeia Portuguesa IX. 1842. 598 p.

7. Sheskey PJ, Cook Walter G, Cable CG. Handbook of Pharmaceutical Excipients. 8th Edition. Pharmaceutical Press; 2017.

8. European Comission. CosIng [Internet] [cited 2021 June 22] Available from: https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple.

9. Em S, Friburgo N. Yusuf M, Liu J, Wang J. IMPROVED ANTI-DANDRUFF SHAMPOO. EP 0 758 879 B1. 1995;2(19):1–16.

10. European Medicines Agency (EMA). Quality by design [Internet] [Cited 2021 june 22].

11. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products, part II: Quality by design for topical semisolid products. AAPS J. 2013;15(3):674–83.

12. International Conference Harmonisation. ICH Guideline Q9 on quality risk management. Regul ICH [Internet]. 2005;44(1):1–20. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf

13. Han ES, goleman, daniel; boyatzis, Richard; Mckee A, Organización Mundial de la Salud (OMS). WHO guidelines on quality risk management. Anexx 2. J Chem Inf Model. 2013;47(9):61–91.

14. Ilie G, Ciocoiu CN. Ilie G. and. Ciocoiu C.N. APPLICATION OF FISHBONE DIAGRAM TO DETERMINE THE RISK OF AN EVENT WITH MULTIPLE CAUSES MANAGEMENT RESEARCH APPLICATION OF FISHBONE DIAGRAM TO DETERMINE THE RISK OF AN EVENT WITH MULTIPLE CAUSES. Manag Res Pract [Internet]. 2010;2(1):1–20. Available from: http://mrp.ase.ro/no21/f1.pdf

15. ICH Q11. ICH Q11 on Development and Manufacture of Drug Substances. Eur Med Agency [Internet]. 2012;224(77):69634–5. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000354.jsp&mid=WC0b01ac0580028bfd

16. Iurian S, Turdean L, Tomuta I. Risk assessment and experimental design in the development of a prolonged release drug delivery system with paliperidone. Drug Des Devel Ther. 2017;11:733–46.

17. Bhattacharya J. Quality Risk Management-Understanding and Control the Risk in Pharmaceutical Manufacturing Industry. Int J Pharm Sci Invent. 2015;4(1):29–41.

18. Fukuda IM, Pinto CFF, Moreira CDS, Saviano AM, Lourenço FR. Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD). Brazilian J Pharm Sci. 2018;54(Special Issue):1–16.

19. European Medicines Agency. Draft Guideline on quality and equivalence of

topical products. Ema/Chmp/Qwp/708282/2018. 2018;44(October):1–36.

Annexes

A1. FTIR spectra from some excipients (adapted from 7)

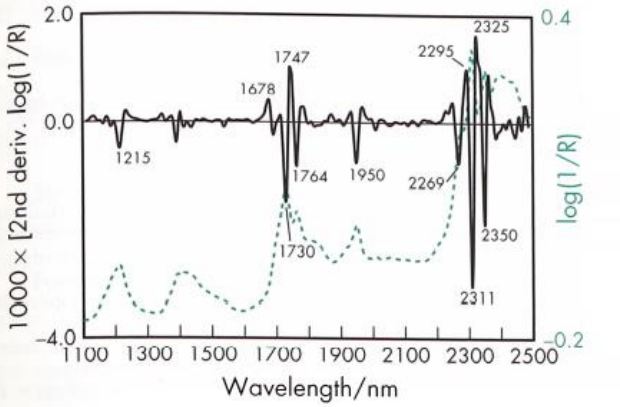

Figure 2: Near-infrared spectrum of sodium lauryl sulfate measured by reflectance.

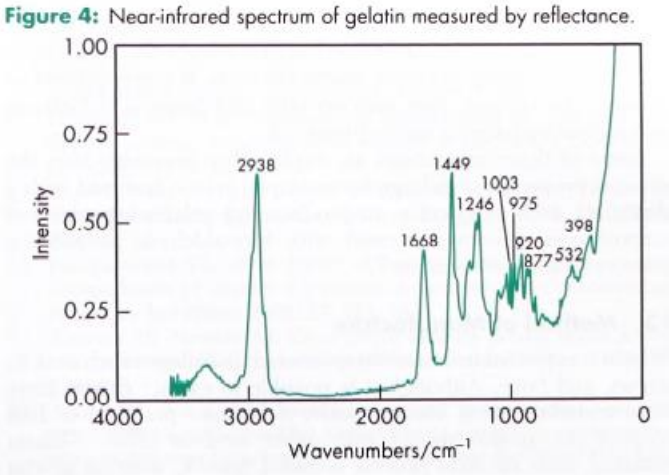

Figure 4: Near-infrared spectrum of gelatin measured by reflectance.

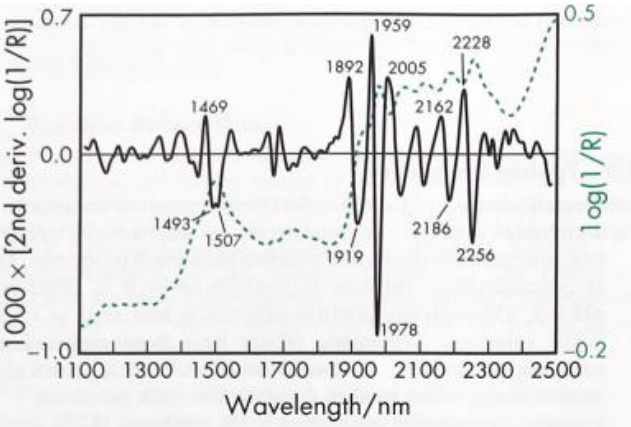

Figure 1: Near-infrared spectrum of imidurea measured by reflectance.

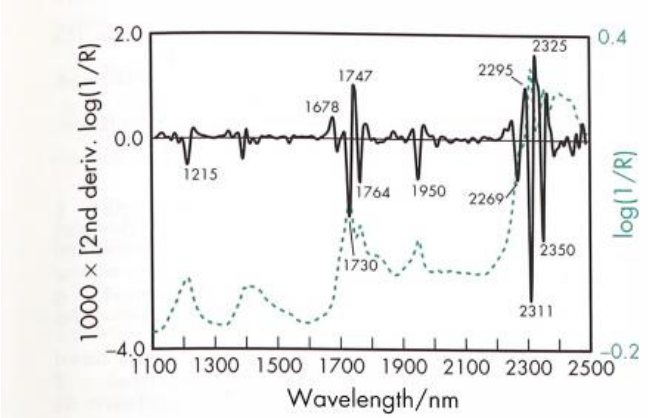

Figure 2: Near-infrared spectrum of sodium lauryl sulfate measured by reflectance.

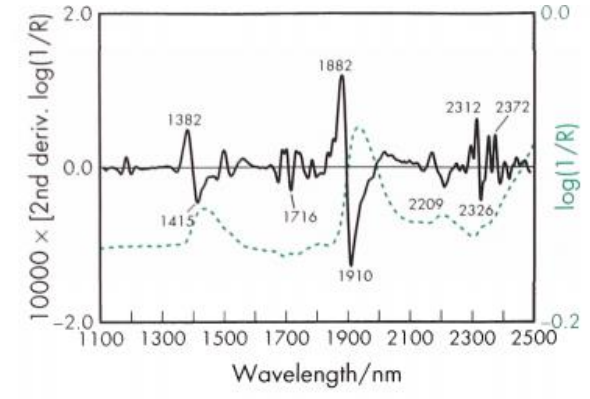

Figure 2: Near-infrared spectrum of sodium chloride measured by reflectance. Sodium chloride does not absorb in the near-infrared region; however, it will generally show some peaks due to traces of moisture (approx. 1450 nm and 1950 nm).