Risk Management in R&D Pharmaceutical Projects

The Hovione Case Study

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Abstract

To catch up with the increasing pressure to adhere to new technologies, and to achieve differentiation from competitors, pharmaceutical companies are exposed to a vast number of uncertainties within their Research & Development projects. Pharmaceutical clients are meticulous and demanding, and every process in the pharmaceutical industry is highly legislated. R&D projects in this industry are complex and arise in an environment full of uncertainty. Under such circumstances, it is crucial that companies do efficient management of project's risks.

Hovione Farmaciência is a pharmaceutical company that develops and produces Active Pharmaceutical Ingredients (APIs) and Drug Products (DPs) for branded pharmaceutical customers. Hovione is in pursuit of an efficient risk management methodology that can be applied in their projects. Past attempts to do so were not successful due to the inability to develop a strategy to manage risks that would not represent a complex or extensive process in short term projects.

After defining the problem and conducting a literature review, it was verified that the risk management methodology had to be simple, as it must be understood by new team members and it cannot be too time consuming. Still, the methodology must allow effective, early and iterative identification of risks, as well as periodic risk reviews. This dissertation proposes a risk management methodology with such characteristics, defining the tools and techniques to be used at each phase of the risk management process, and tests it in two Hovione projects. After being tested, adjustments to the methodology were done, in order to accommodate Hovione's employees' behaviors and fast pace, observed in the case study projects.

Key-words: *Risk, Risk Management, Projects, R&D projects, Pharmaceutical Projects*

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Le – Expected loss

Lt – Total Loss

Pe – Probability of risk event

Pi – Probability of impact

List of Abbreviations and Acronyms

AAR – *After Action Review*

API – *Active Product Ingredient*

APM - *Association for Project Management*

BLA – *Biological Licensing Application*

CGMP – *Current Good Manufacturing Practices*

DOE - *Design of Experiments*

DPI – *Drug Product Intermediate*

DPD – *Drug Product Development*

ETA – Event Tree Analysis

FDA – *Food and Drug Administration*

FMEA – *Failure Mode and Effects Analysis*

FMECA – *Failure Mode, Effects and Criticality Analysis*

FTA – *Fault Tree Analysis*

HACCP - *Hazard Analysis and Critical Control Point*

HAZOP - *Hazard and Operability Study*

HSE – *Health, Safety, and Environment*

ICH - *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use*

IND – *Investigational New Drug*

NDA – *New Drug Application*

NPD – *New Product Development*

OTIF – *On Time In Full*

PCD – *Process Chemistry Development*

PMBOK – *Project Management Body of Knowledge*

PMI – P*roject Management Institute*

QA – *Quality Assurance*

R&D – R*esearch and Development*

RFMEA – *Reverse Evaluation of Failure Mode and Effects Analysis*

RMP – *Risk Management Processes*

WBS – *Work Breakdown Structure*

Chapter 1: Introduction

This first chapter has as main objective to present the dissertation's context, motivation, and objectives. To do so, it is divided in three sections: section 1.1 contextualizes the problem to approach in this project, section 1.2 describes the objectives to achieve with its development, and section 1.3 describes the structure in which the dissertation is organized.

By the end of this chapter, the reader should have an overall view about the work done during the dissertation and its chain of activities.

1.1 Problem Context

We live in an ever-changing world where companies are forced to deal with uncertainty every day. New technologies, competition, globalization, innovation in products and processes influence the dynamic process of decision making. How organizations deal with uncertainty and the incredibly diverse number of risks they face, can be a key success factor. In an increasingly competitive and globalized marketplace, technological innovation has been referred to, as one of the most important key strategies for high technology enterprises to survive and achieve corporate growth (Teece, 1986; Freeman and Soete, 1997). However, various forms of innovation involve different degrees of uncertainty. In technology-related industries, this may result in failures in R&D projects. And so, risks should be managed and controlled for innovative R&D projects through all their progress.

Due to its importance, risk management has become a top-of-mind issue for senior executives and boards around the world, and nowhere more than in pharmaceutical companies. The pharmaceutical industry works in a politically and economically turbulent environment. The risks pharmaceutical companies face, especially in clinical-trial design and execution, drug approval, product quality, and global commercial practices, are increasing both in frequency and magnitude of impacts (Dhankhar et al., 2018).

The pharmaceutical industry is unique in several ways, one of them being the challenges it faces in R&D processes and the complex requirements and legislations for market access. Typically, companies in this sector, have high capital expenditure and long pay-off periods for assets. Pharmaceutical companies work in a highly regulated environment in which compliance risks are substantial and many other risks are present across markets globally, such as cyber threat, data breaches, supply chain risks, quality risks, geopolitical exposure and risks from third and fourth parties (Dhankhar et al., 2018).

To achieve the objectives of a project, managers must be ready to face risk and uncertainty and they need to be able to identify, analyze and manage risks for effective decision-making. Risk and uncertainty can have a real impact on project returns, stakeholder's cash flows and shareholder value, therefore, it is essential that project managers are able to see both positive opportunities and negative

consequences associated with risk. This allows a more informed, and thus more effective decision making (Koleczko, 2012).

Risk is not a recent concept at all, however, as a tool for business, risk, and uncertainty analysis has historically lacked in sound, which is surprising, considering that many business decisions are based on values that are calculated through analysis of some kind. It is not uncommon in project assessment, for companies to spend considerable effort into forecasting future values and very little time is spent in understanding the uncertainty surrounding such values (Koleczko, 2012).

1.2 Objectives

This dissertation has as main goal the development of a risk management methodology to be applied in Hovione's DPD projects. The development or such tools and techniques should allow the company to improve its OTIF (On Time In Full) performance and customers satisfaction. This way, it can be defined that the dissertation's objectives are:

- Developing the risk management tools and techniques that better allows solving the company's problem, taking into consideration the projects' and company's characteristics.
- Implementing the developed methodology into two case study projects (applying in the second case study, the lessons learned of the first one).
- Evaluating the methodology's effectiveness based on the results of the implementations in the case studies.
- Propose to the company a final version of the methodology.

1.3 Dissertation's Structure

The present dissertation is divided into seven chapters:

Chapter 1 – Introduction: This chapter, the present one, includes the problem context and reveals the main issue to be addressed, providing the main objectives of this study and the structure of the work.

Chapter 2 – Problem Definition: The purpose of this chapter is to give the reader a presentation on the company, its background, and its environment, focusing on project management and risk management of the company's projects.

Chapter 3 – Literature Review: After the main challenges have been identified, chapter 3 is where the literature on risk management in pharmaceutical projects and on R&D projects is presented, as well as the main concepts related to risk, necessary to understand the problem at hand.

Chapter 4 –Research Methodology: Chapter 4 explains the methodology that was followed to do the research involved in this dissertation.

Chapter 5 – Risk Management Methodology: Chapter 5 is where the description of the methodology developed to approach the problem is made, including the tools and techniques to be applied in each phase of the risk management process.

Chapter 6 – Implementation: This chapter follows the results of the implementation of the risk management methodology in both case studies, presenting the conclusions taken and improvement suggestions.

Chapter 7 – Conclusions and Future Work: By last, chapter 7 synthesizes the several conclusions taken in the previous chapters and presents suggestions for future work on this subject.

Chapter 2: Problem Definition

The purpose of this chapter is to characterize the activities of Hovione and its historical background. It starts with section 2.1 in which the company's history, evolution, and activity is described, as well as its markets. Section 2.2, focuses on R&D projects, explaining what they are and how the R&D area is organized. Section 2.3, describes the processes and tools used in Hovione's project management. And finally, section 2.4 describes current practices applied in the company's R&D projects concerning risk management.

2.1 About Hovione

Hovione FarmaCiência is a Portuguese pharmaceutical company that dedicates its activities to helping pharmaceutical customers to bring new drugs to market. It has 60 years of experience in the development and compliant manufacture of Active Pharmaceutical Ingredients (APIs) and 15 years in Drug Product Intermediates (DPIs) using advanced technologies. With four FDA (Food and Drug Administration) inspected sites in the USA, China, Ireland and Portugal, Hovione offers to branded pharmaceutical customers services for the development and manufacture of innovative new drugs, including highly potent compounds. For generic pharmaceutical customers, the company provides niche generic API products. Its activities are based on innovation, quality, and delivery.

An API is any component that is intended to furnish pharmacological activity or other direct effects in the diagnoses, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of human or animal body (Applications for FDA Approval to Market a New Drug, 2018). DPI is the mixture of the API with a non-active pharmaceutical ingredient, it is intermediate because it is not yet in the final dosage form.

Hovione was established in Portugal in 1959 by Ivan Villax and his wife Diane Villax and two other Hungarian WWII refugees: Nicholas de Horty and Andrew Onod. The first two letters of the founders' surnames, HO, VI, and ON were used to create the name Hovione. The major milestones of the history of the company are depicted in Figure 1.

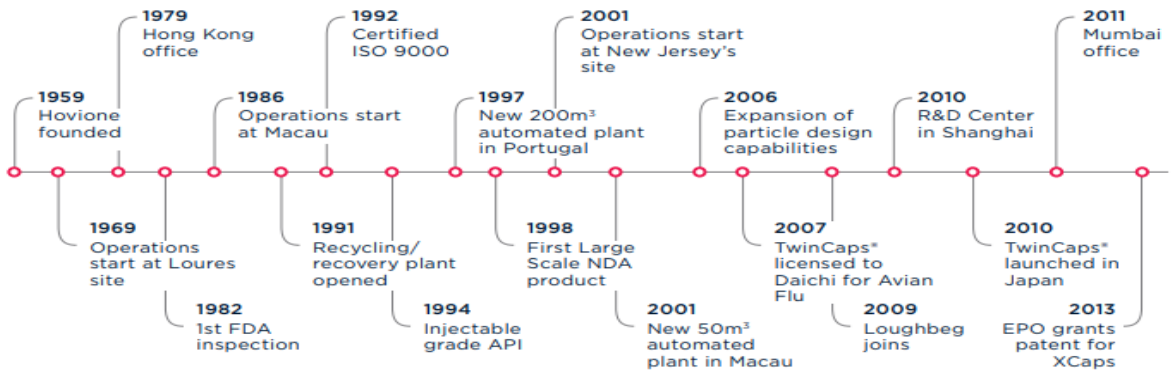

Figure 1 - Hovione's milestones (Source: Hovione, 2014)

Working initially on a basement in the Villax family home in Lisbon, Ivan started to research semi-synthetic tetracycline (antibiotics) and anti-inflammatory corticosteroids. Success soon followed in form of royalties that surged from licensing patents to multinational drug companies. This led to small-scale production and the export of products.

As the business grew, Hovione built its first industrial manufacturing plant in 1969, located in Loures, on the outskirts of Lisbon. This new factory enabled Hovione to establish and reinforce its position as a key player in the worldwide market of APIs. From the very beginning, what distinguished Hovione's products from others were the technological content and quality of their manufacture. Being research-oriented, the company focused on products that were difficult to manufacture, providing it an assured market.

Major commercial success came in the 60s and 70s with the sales of betamethasone and derivative products, mainly to Japan. Wanting to expand to Asia, Villax opened an office in Hong Kong in 1979. In 1982, the Loures plant was inspected by the US Food and Drug Administration (FDA) for the first time, allowing Hovione to start exporting the semi-synthetic antibiotic, doxycycline to the USA as it came off patent. In 1986, a second manufacturing site was opened in Macau. During the 90s, the company developed and started supplying contrast media agents and, in 1997, the factory in Portugal expanded, with a brand new 200 m^3 automated plant. In 2001, a third manufacturing site was opened in New Jersey, USA, which allowed the company to offer an extensive range of capabilities to innovative drug companies. A growing reputation for outstanding quality led to Hovione becoming a leading provider of drug development services and clinical trial materials.

Extending the range of services offered, Hovione established and expanded its particle engineering service. Particle engineering is the application of the science behind modifying particles, to obtain optimal particle sizes and size distributions as well as other aspects of particle’s morphology and surface characteristics. Spray drying is a technology that allows transforming crystalline substances into amorphous, and its commercial use was pioneered by Hovione.

Hovione soon became an industry leader in this spray drying processes. The company's ability to address drug delivery problems allowed its unique expertise in inhalation products. Expanding further in Asia, Hovione acquired a Chinese partner Hisyn, in 2008 and then established an R&D center in Shanghai. In 2009, a fourth facility in Cork, Ireland was added. In addition, in 2016, Hovione opened its office in Japan, reinforcing the company’s global position (see Figure 2).

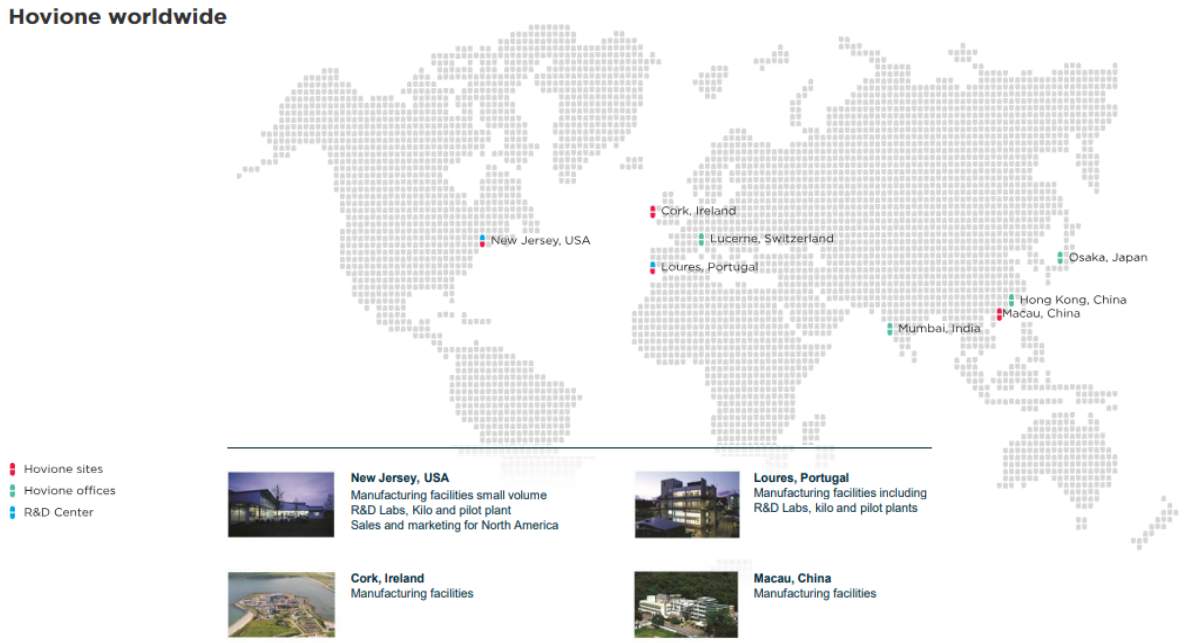

Figure 2 - Hovione worldwide (Source: Hovione, 2018)

Today, Hovione employs more than 1600 people worldwide and offers around 1300 m^3 of manufacturing capacity around the world. The foundation of Hovione and a big part of its success are due to the inventions of its founder, Ivan Villax, author and proprietor of a large number of patents. In 2016 a total 175 projects from different departments were executed. Hovione today, owns more than 400 patents registered worldwide. In Portugal, it is recognized year after year as one of the companies with more patents in the country and by being the biggest employer of Ph.D. workers. Hovione's key numbers are shown in Figure 3.

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Figure 3 - Hovione's 2016 key numbers (Source: Hovione, 2016)

Hovione's main markets today are North America, Europe and Japan. The company procduces and provides technical services for both large pharmaceutical companies and small/medium biotech or drug recovery companies.

Figure 4 shows an organizational chart of how Hovione is structured nowadays. The R&D department is highlighted because it is the focus of this work.

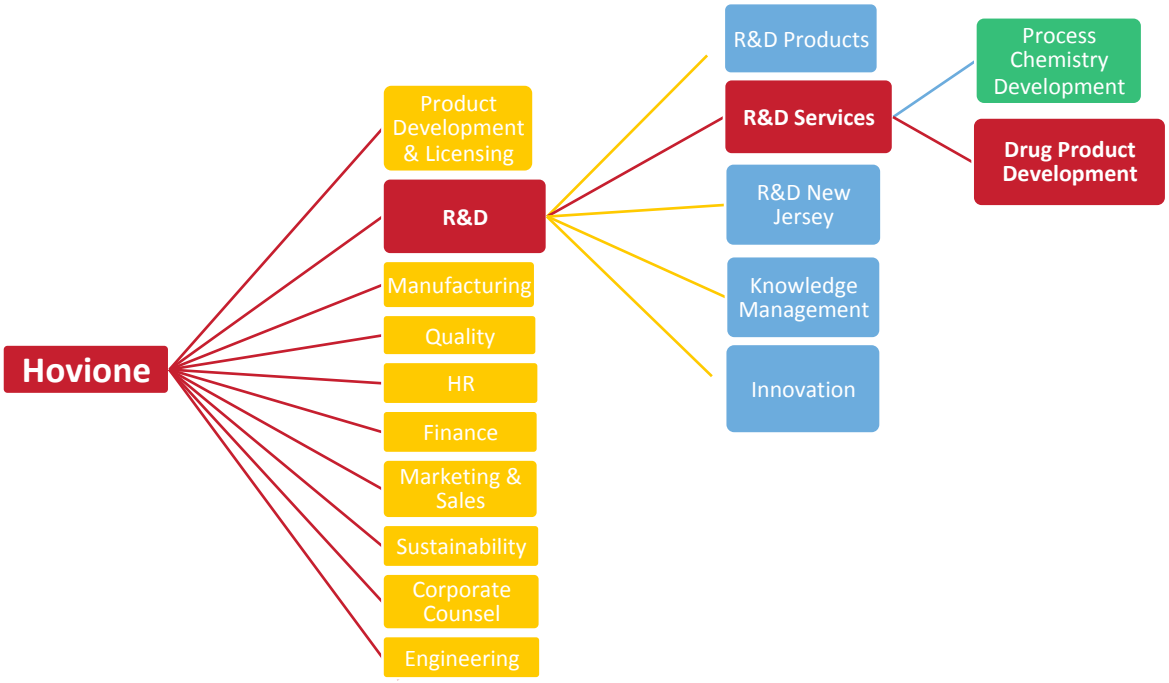


Figure 4 - Hovione's Organizational Chart (Source: Author)

2.2 Research & Development (R&D) projects at Hovione

At Hovione, the Research and Development department is divided into five different areas. Three of them are:

- **R&D New Jersey:** Responsible for the research and development activities performed at the New Jersey site.
- **Knowledge Management:** Deals with capturing and documenting information and knowledge from experts, making it available to the entire company.
- **Innovation:** Promotes, manages and rewards innovation within Hovione, in order to transform the company's know-how into value.

The remaining two are **R&D Services** and **R&D Products**, which are the two divisions of the R&D department that involve drug research and development projects.

In order to comprehend better what R&D projects from these two divisions are, it is important to understand the drug development process itself, explained in Figure 5.

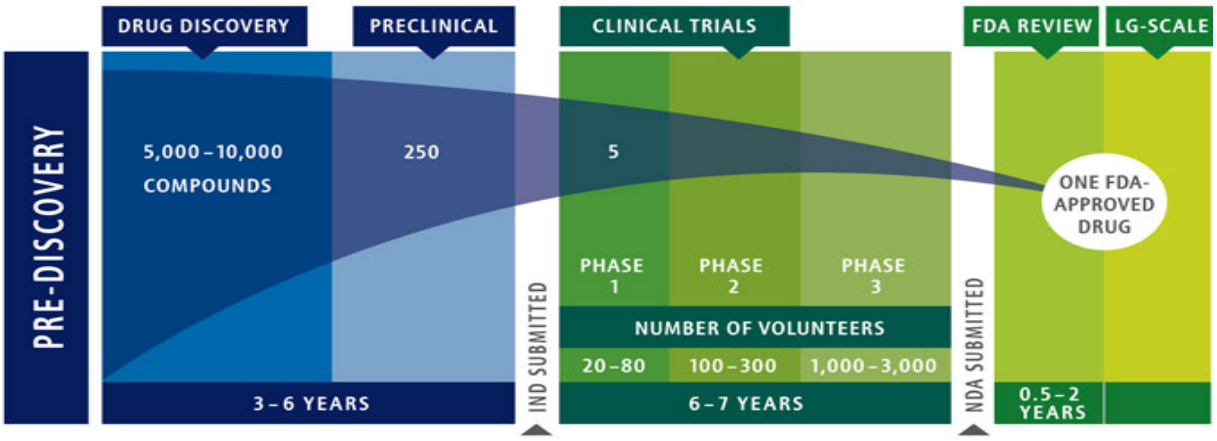


Figure 5 - Drug development process (Source: Pharmaceutical Research and Manufacturers of America, 2015)

The drug development process is described as it follows:

1. **Drug Discovery -** Researchers discover a compound promising for development and conduct experiments to gather information on it. Typically, it takes between 3 to 5 years until the drug is ready for the next phase, preclinical trials.

2. **Preclinical Trials** - Researchers perform studies in animals to provide detailed information on dosing and on toxicity levels. After reviewing the results, they decide whether the drug should be tested on people or not. This process takes 1 to 2 years to be completed. In order to get the authority's approval to administer an investigational drug to humans, the company needs to file an Investigational New Drug (IND) request.

3. **Clinical Research** - Refers to studies or trials that are done in people. It goes on for around 6/7 years and it is divided into 3 phases:
   - **Phase 1 –** Study of safety and dosage in 20 to 100 healthy volunteers or people with the disease/condition. Approximately 70% of drugs move to the next phase.
   - **Phase 2 –** Study of efficacy and side effects in up to a few hundred people with the disease/condition. Approximately 33% of drugs move to the next phase.

     Phase 3 – Study of efficacy and monitoring of adverse effects in 1 000 to 3 000 volunteers who have the disease/condition. Approximately 25-30% of drugs move to the next phase.

4. **Validation -** After the three phases of clinical trials, a validation campaign is conducted. It implies producing three equal batches of the drug, in order to test its robustness, homogeneity, and specifications.

5. **Regulatory review** - If evidence is found from tests, preclinical and clinical research, that the drug is safe and effective for its intended use, the company can file an application to the regulatory authority to market the drug called New Drug Administration (NDA) request or Biologic Licensing Application (BLA) request. It takes 1 to 2 years to get regulatory approval.

6. **Post-approval research** -- After being launched in the market, the regulatory authority keeps reviewing the drug's efficacy and safety for an indefinite period of time.

R&D Products is the division dedicated to responding to the needs of the internal clients like the departments of Marketing & Sales and Manufacturing.

On the other hand, R&D Services handles external clients. These external clients are usually branded pharmaceutical companies who hire Hovione to develop or produce API, DPI or formulated product for them, to support their drug development processes. Both these divisions work in the following:

- **APIs:** improving of the manufacturing process, improvement of physical/chemical properties and pilot scale manufacturing.
- **Particle Engineering:** improving physical-chemical characteristics of the API particles, facilitation of the API processing during formulation.
- **Formulation:** mixing the active ingredient with excipients in order to facilitate its manipulation, administration and to improve the performance of the final product.

The focus of this dissertation is the R&D Services division. This is the area where Hovione wishes to improve risk management.

As shown in Figure 5 of the previous chapter, the two areas of R&D Services are: Process Chemistry Development (PCD) and Drug Product Development (DPD).

Process Chemistry Development projects have as objective, the chemical development and optimization of API production processes. This group develops and manages scientifically sound and scalable projects to meet the needs of customers. Typically, these projects' duration goes from three to twelve months.

As for Drug Product Development projects, the focus is on developing processes in order to improve the physical and chemical characteristics and performance (e.g. stability, solubility, and absorption) of APIs through Particle Engineering techniques. In addition, these projects include the development of formulations that allow the administration of an API to patients with the desired performance (e.g. dissolution, aerodynamic performance or absorption), according to the client's requirements. In sum, DPD projects are the research on how to produce a drug, which includes deciding on what technologies to use and which excipients mix the API with, in order to meet the customer's requirements.

Projects are managed by the R&D department from clinical trials to validation. After validation the Projects are handed over to the Manufacturing department.

The duration of the execution phase of DPD projects duration can go from one week to one month. The average duration is three weeks. In the past year of 2017, Hovione developed 71 R&D projects.

2.3 Project Management at Hovione

Hovione's approach to Project Management relies on strong project management skills. Its certified project managers work to ensure proactive identification of the customer's needs within the PMI (Project Management Institute) framework and try to provide solutions without exceeding the timelines of clients.

Supporting compounds during their clinical development involves improving processes, developing analytical methods and building supply chains. These processes are complex and require experienced multi-disciplinary teams and, good decision-making and taking into account to assure the future commercial success. This means that both sophisticated and efficient project management and effective communication skills are necessary.

Hovione's projects' teams try to be an extension of their clients' teams and their organization, by actively listening to their needs and understanding their challenges. With this, Hovione hopes to consolidate customer relationships and share risks and rewards with its partners. Hovione communicates regularly with its clients, through team meetings with agreed-upon agendas and takes lead on one-on-one communications whenever needed. A Project Management IT supporting toolbox allows remote real-time project monitoring at different dimensions (documentation, operations, analytical testing, etc.). The company provides up-to-date systems for document sharing and online process monitoring.

The process used to manage R&D Services projects follows a standard approach created internally and available in the company's intranet. This approach is based on the Project Management Body Of Knowledge (PMBOK), an industry standard methodology from the Project Management Institute. Its purpose is to provide tools to generate customer satisfaction by taking advantage of the range of technical skills and strengths within Hovione, in an effective and efficient way. These methodologies repeatedly used in projects, assure the high standards of Hovione project management.

This approach follows a systematized methodology that includes the following phases within a project life cycle (see Figure 6):

1. **Initiation** – Determines the project "WHAT"
2. **Planning** – Determines the project "HOW"
3. **Execution** – Includes Execution and Monitor and Control of project activities

4. **Closeout** – Lessons Learned – “More than just Goodbye and Move on!”

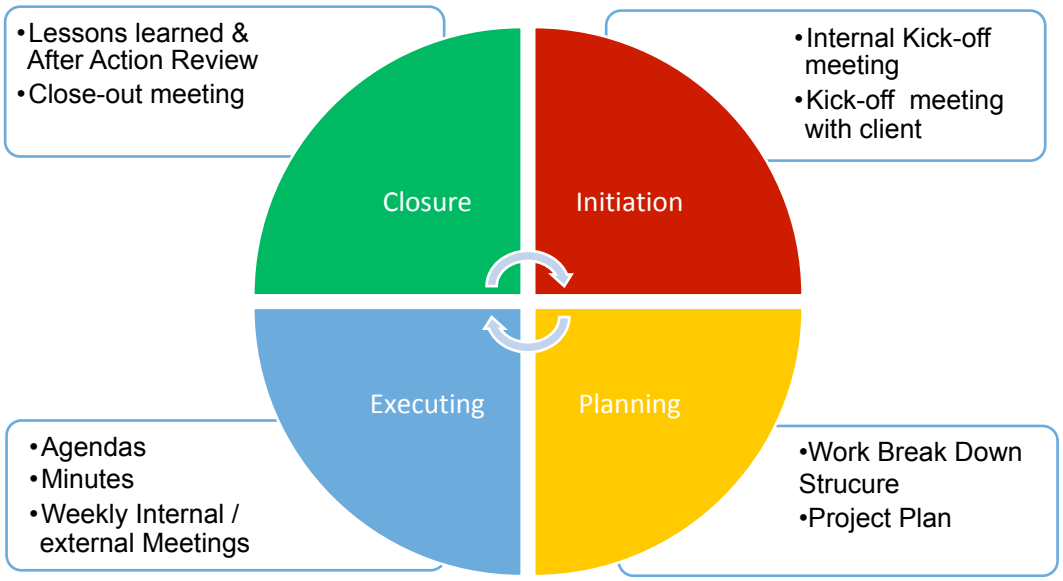


Figure 6 - Project Lifecycle and tools at Hovione (Source: Author)

For each phase, there is a set of objectives and tools well defined. Communication with the client is transversal to all phases of the project and it takes place proactively and in whatever way the client decides. Typically, it occurs weekly through conference calls in which Hovione updates the client on the progress of the project. Before each conference call, Hovione’s project manager sends an email to the client’s team with the meeting’s agenda. Besides these meetings, the client has access to a SharePoint folder where they can see the current status of their project and emails are exchanged between the two teams to complement the online available information.

The project starts with the initiation phase, which begins after the client’s signature of the contract. It starts with the definition of the project’s core team, always including the project manager and a representative from each area involved. Afterwards, the internal kick-off meeting takes place. In this meeting the team:

- agrees with the proposed communication plan,
- identifies the key stakeholders and their contributions to the project,
- assesses the clients’ needs and expectations,
- details the scope of the work,
- defines functional technical requirements,
- agrees on project milestones,

After this, a kick-off meeting with the client takes place and the objectives and timelines agreed by Hovione’s team in the internal kick-off meeting are discussed and agreed between both teams.

In the project planning phase, the involvement and commitment of the project team are required. It includes the confirmation of the scope of work, the creation of the Work Breakdown Structure (WBS) and the definition of the Project Plan. Planning is an interactive and ongoing activity.

The Executing phase ensures that the project's activities are properly executed and controlled, and that periodic evaluation and management of changes and conflicts are rightly addressed. The phase's tools include agendas, minutes, regular internal meetings and conference calls to manage communications. This phase implies monitoring and controlling how the project is doing against the scope and time baseline. To communicate the project status to the stakeholders and to senior management the company uses a project status dashboard to report the situation of each project.

In the project's closeout, an After Action Review (AAR) is made. It is an assessment conducted during the closeout of a project or major activity, which allows the team members to recall and learn from what happened during the project. Lessons learned are gathered by the project manager, documented and communicated. The project team proactively participates in the close-out. In the end, all the documentation regarding the project is given to the client, as well as a customer satisfaction questionnaire for them to fill.

Throughout the entire duration of projects, from initiation to closure, the team meets weekly to review action items. Team members update each other on the project's status and eventual issues are discussed.

As an example of a project handled by the project managers from R&D Services, project A, it was a Drug Product Development project. The client was a global biopharmaceutical company, who was entering phase III of clinical trials of a drug for treating immunological diseases. The project's goal was to produce 42 kg of the drug while complying with the client's requirements about the product's characteristics. The agreement was that such characteristics would be reached within seven trials. In each trial, the process included a key unit process step and three secondary dryings. A portion of each trial was sent to a tray dryer equipment. The main fractions of were post dried in two different pieces of equipment, according on the trial. After equipment is used, it needs to be cleaned before being used for other projects. -

Hovione's core team for Project A is composed of the Project Manager, an Analytical Chemist Lead, a Lead Scientist, a QA (Quality Assurance) Lead, a Manufacturing Engineer Lead, and an Account Manager. The support team is composed of a Process Safety Lead and a representative from the Logistics and Purchasing areas. The execution phase of the project was planned to last 35 workdays.

The equipment used in Project A (key unit equipment and secondary dryers) are common to other projects and to the production of commercial batches.

The fact that resources (equipment and people) are not exclusive for Project A represents source of risk. Over allocated team members may not have time to fulfill their tasks within deadlines, and delays in the activities of other scheduled projects, that use the same equipment as Project A, can delay the release of the equipment, and therefore, force the late start of Project A's subsequent activities.

The production of the drug was done in the factory of Loures, Portugal. Hovione already possessed all the raw materials necessary within their facilities, but part had to ship some from the New Jersey site to Loures. No external resources were utilized.

The project manager of Project A had many roles in several aspects of the project: First, to promote proactive and transparent communication by ensuring clarity of communication, and that project

scope, milestones, deliverables, and clients' expectations were clear to all stakeholders. This means that before meetings, the project manager prepared the agenda, gathered topics for discussion and made sure to bring together people from different areas who made decisions and contributed with specific knowledge from their areas. The project manager's main mission was to ensure the fulfillment of the plans agreed between the company and its client in terms of quality and deadlines of delivery. This involved planning, monitoring and controlling deliverables and invoices and continuously analyzing and measuring the project's performance against the plan and coaching the team to enhance effectiveness and efficiency, to make sure they accomplished the timelines/deliverables defined for the project.

2.4 Risk Management in projects at Hovione

In 2010, new methodologies and tools were implemented. Amongst the tools and processes developed, a risk management methodology was created. However, it was too complex to be used in a timely manner on DPD projects, whose duration is typically between one to three months (from initiation to closure) and therefore were simplified. The tools and techniques utilized in this methodology are shown in Table 1.

Table 1 - Hovione's former risk management methodology (Source: Author)

Phase	***Tools and Techniques***
Identification	Brainstorming for threats and opportunities
Analysis	Identifying causes Identifying risk category Qualify probability using a qualitative scale (*Very High, High, Medium, Low, Very Low*) Qualify impact in each project objective (scope, schedule, cost and quality) using a qualitative scale (*Very High, High, Medium, Low, Very Low*) Assign risk owners
Response Planning	Decide to which risks to develop an action plan Assign performer Establish deadline Identify residual risks
Monitoring and Control	Monitor risk status and register alterations

TThis new methodology consists in identifying and discussing, through brainstorming, the biggest risk to the project and what could be its impact on the timelines.

The brainstorming process happens during the kick-off meeting. Among the PowerPoint slides that the project manager presents during the meeting, one of them is directed to risk management (See Figure 7).

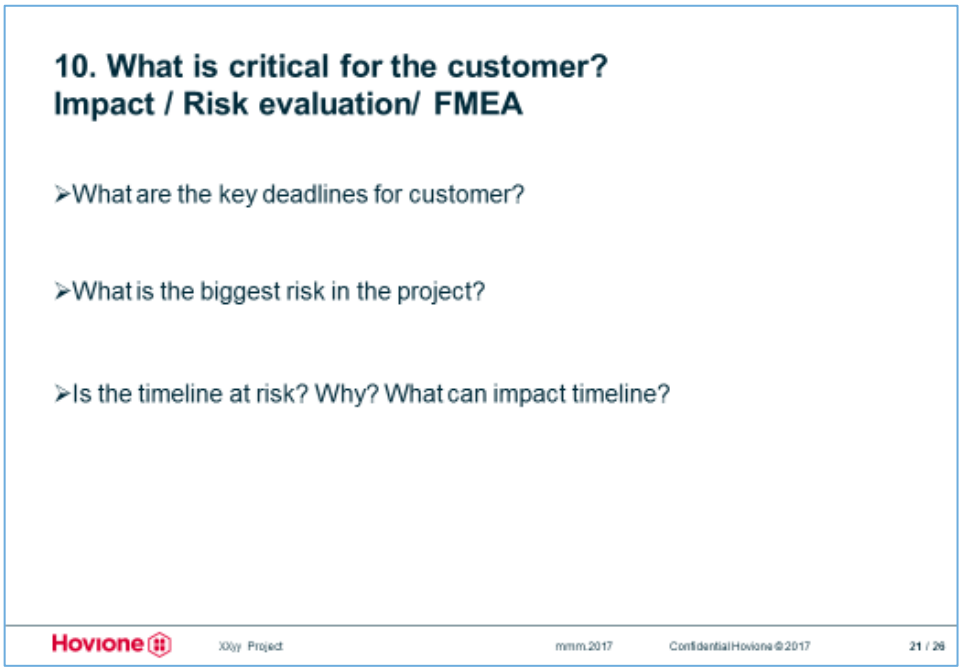


Figure 7 - Risk Management Slide from Kick-off Meeting Template (Source: Hovione, 2019)

After all other meeting topics have been covered, the project manager asks the team the questions seen in Figure 7: “What are the key deadlines for the customer?”, “What is the biggest risk in the project?” and “Is the timeline at risk? Why? What can impact the timeline?” These questions generate a brainstorming discussion between team members and the identified risks are registered by the project manager. After identifying the existing risks, the team proceeds into developing actions to prevent them or to decrease their impacts. As actions are being developed, it is also discussed if they are worth implementing or not, considering the perceived severity of risks and the resources needed for action plans. The identified risks are shared with the client. The established actions are assigned to specific team members and registered in an actions document. This document includes the description of the action, the person responsible for assuring its completion and a deadline. When actions are completed, the project manager changes their status of it in this document.

This risk management strategy in use at Hovione has many limitations. Although brainstorming is usually an effective way of channeling natural creativity into identifying what can go wrong on the project, the risks that are being identified in Hovione’s projects are usually always the same ones, and for most of them, no response plan is developed because the team cannot find one, so opts for accepting the risks. This means that both the identification and response planning phases of the risk management process are not being done correctly. Plus, this risk management exercise is not a formal one and there is no follow up or revision of the risks that are in fact identified nor of their response plans.

The purpose of this dissertation is to develop a methodology to substitute the current one, described above.

During the Project A, two events occurred that could have been foreseen and addressed if better risk management was applied. First, the project team could not be sure if the stock inventories of raw

materials on the inventory management software were correct, and so, they did not know how much they needed to order. This, apparently, happens quite often and if the risk had been identified in advance, the team could have checked the inventories before placing the orders, avoiding having to order in excess to assure the necessary amount on time. Second, the client scheduled a visit to the factory and they expected to watch some of the operations Project A, however, due to schedule delays, no operation was being conducted during the time of the visit. This impacted on customer relationship. The situation could have been handled differently if the team had foreseen the risks that impacted on the schedule. Even if the team could not avoid their occurrence, at least they would not have been caught by surprise and could have warned the client in time for them to change the dates of their visit, which was already impossible to do by the time Hovione's team found out about the issue.

Both Hovione's project managers, and clients, are aware of the limitations of Hovione's risk management practices. In the customer surveys of 2016 and 2017, customers indicates that the risk management is one of the the items that needs to be improved.

Putting all of this, Hovione is interested in implementing a new strategy for risk management that protects their costly projects from uncertainties. The risk management methodology to be implemented should aim to address project risks and not process risks. Hovione already addresses efficiently process and safety risks with techniques like Failure Mode Effects Analysis (FMEA), Process Hazard Analysis (PHA) and Hazard and Operability studies (HAZOP), performed by the FMEA team, which belongs to the Manufacturing department.

The methodology has to be effective and allow better and proactive identification of risks and response plans. At the same time, it has to be simple, and it cannot take too much of the project managers valuable time, so that it does not enter in conflict with the rest of their activities.

2.5 Chapter's Conclusions

In the present chapter, the company Hovione was described and characterized. It was possible to conclude that the cutting edge technology that Hovione owns and uses in the research and production of compounds represent a competitive advantage for the company. Hovione's success resides in its knowledge, technology, and patents.

Using innovative processes in projects creates uncertainty, and the demanding pharmaceutical clients who render high valued R&D projects such as Drug Product Development increase the pressure to successfully complete the projects within their specifications, timelines, and cost. This combination of characteristics of DPD projects justifies the need to readjust the current project risk management strategy, which apparently, is not effective. With the implementation of a new methodology, Hovione intends to achieve higher rates of project success, while complying with the predefined budgets, timelines and quality requirements of projects and to improve customer satisfaction and relationship. It has been noted in customer surveys that the lack of proper risk management has been jeopardizing customer satisfaction. Clients pointed it out as an aspect to improve.

The number of projects handled by Hovione is high and it represents a big part of their revenues. One could think that handling Hovione's projects as a portfolio would be more efficient. However, Hovione's R&D project managers believe that, before delving deep into risk management at portfolio level, the company needs to look at risks in individual projects first. Plus, the actions that will be taken to solve the company's risk management issues will be performed and conducted by the project managers, so the methodology to implement has to be within their capacities at Hovione. Thus, the risk management methodology developed in this work is to be applied in projects individually and not as a portfolio.DPD projects are of short duration (execution phase of three weeks on average-), which is an uncommon characteristic considering they are R&D projects.

The challenge will be to search for methodologies that have been considered effective in R&D and pharmaceutical projects in past studies and to find which can be adapted to R&D pharmaceutical short-term projects as DPD projects are. It is expected that the future dissertation originates results on which risk management methodology, tools and techniques to implement and how to implement them. At last, the final challenge will be to implement the new methodology and evaluate if it is effective or not.

Chapter 3: Literature Review

The intent of this chapter is to describe and explain the concepts and definitions found during the literature review that are pertinent to the understanding the better methodology o implement on the R&D projects. The chapter begins with section 3.1, which provides the explanation and definition of the most important concepts related to project risk management. On sections 3.2 and 3.3, the objective is to characterize the environment and specifications of R&D and pharmaceutical projects, respectively, their characteristics and also, to investigate which risk management approaches have already been studied and developed for them and what the outcomes did they produce. As for section 3.4, it describes the criteria found in literature, for deciding on risk management methods and techniques and when to apply them during project lifecycles.

3.1 Fundamental Concepts

A project can be defined as an endeavor in which human, material and financial resources are organized in a novel way, to undertake a unique scope of work, of a given specification, within constraints of cost and time, so as to achieve beneficial change defined by quantitative and qualitative objectives (Turner, 2009). This definition highlights the ever-changing nature of projects, the need to organize a variety of resources under constraints, and, the major role of objectives in project definition. It also suggests intrinsic uncertainty linked to novel organization and unique scope of work, which raises attention to risks. A risk is an uncertain event or condition that, if it occurs, has a positive or negative effect on a project objective (PMI, 2017). Risk management contributes to the correct realization of the project objectives and it helps to prevent unnecessary wastes in resources and time. Thus, it is necessary for successful project management. In sum, risk management leads to project success and allows the project managers to identify the risks that may impact on the project's objectives.

When taking risk into consideration, the consequences or damage associated with the event occurring must also be taken into account. To evaluate risk is not simple. The probability of occurrence and the consequence of occurrence are usually not directly measurable parameters and must be estimated by judgment, statistical, or other procedures. In broad terms, as either the probability or consequence increases, so does the risk (Kerzner, 1998). Both the probability and consequence must be considered in risk management.

Project management is the practice of planning, organizing, securing, and managing resources to achieve specific predetermined expectations (Kerzner, 1998). Project management faces various challenges. Primarily, the challenge is to achieve all project goals and objectives while respecting the predefined parameters such as scope, time, specification, quality and budget matters within the control and authority of the project manager.

To accomplish this, it's necessary a practical risk management procedure that promotes the timely identification and prioritization of the project's risks (and opportunities). This procedure enables a more knowledgeable decision making and strengthens management skills when in the face of uncertainty and change. The importance of risk to project management can be shown in the difference between bringing in cost and budget, achieving a revenue or profit objective, succeeding or failing as an enterprise, and maintaining credibility in the eyes of stakeholders (Rodger & Petch, 1999). When it comes to project management, all commercial and professional activities are bets on the future. All types of organizations face internal and external factors that make the achievement of project objectives uncertain. Risk management requires both science and judgment to identify the probability and impact of each risk.

Risk management is the systematic process of identifying, analyzing, and responding to project risk. It includes maximizing the probability and consequences of positive events and minimizing the probability and consequences of adverse events to project objectives (PMI, 2017).

The problem faced by project managers is how to recognize which risk management approach is appropriate for the particular project in hand. There are a few guides to conduct project managers in decision making under risk and uncertainty, but still, intuition and experience is needed to guide decision-making.

One of the most recognized of these guides is the Project Management Institute's (PMI®) *A Guide to the Project Management Body of Knowledge (PMBOK® Guide),* which is an inclusive guide that describes the sum of knowledge within the profession of project management. According to PMI (2017), the risk management process comprises the six following stages:

1. **Risk Management Planning—**deciding how to approach and plan the risk management activities for a project. Tools and techniques include analytical techniques, expert judgment, and planning meetings.

2. **Risk Identification—**determining which risks might affect the project and documenting their characteristics. Tools and techniques include documentation reviews, information-gathering techniques (brainstorming, Delphi technique, and interviewing and root cause analysis), checklist analysis, assumptions analysis, diagramming techniques (Cause-and-effect diagrams, System or process flow charts and Influence diagrams) and Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis.

3. **Qualitative Risk Analysis—**performing a qualitative analysis of risks and conditions to prioritize their effects on project objectives. Tools and techniques include risk probability and impact assessments, probability and impact matrixes, risk data quality assessment, risk categorization, risk urgency assessment, and expert judgment.

4. **Quantitative Risk Analysis**—measuring the probability and consequences of risks and estimating their implications for project objectives. Tools and Techniques include interviewing, probability distributions, sensitivity analysis, expected monetary value analysis, modeling and simulation, and expert judgment.

5. **Risk Response Planning**—developing procedures and techniques to enhance opportunities and reduce threats to the project's objectives. Tools and techniques include strategies for negative risks or threats, strategies for positive risks or opportunities, contingent response strategies and expert judgment. There are four main response strategies to deal with negative risks:

   - **Avoidance –** Acting to eliminate threat or impact on the project.
   - **Transference –** Shifting the impact of a threat to a third party, together with ownership of the response.
   - **Mitigation –** Acting to reduce the probability of occurrence or impact of risk.
   - **Acceptance -** Acknowledging the risk and not taking any action unless the risk occurs.

Risk Monitoring and Control—monitoring residual risks, identifying new risks, executing risk reduction plans, and evaluating their effectiveness throughout the project life cycle. Tools and techniques include risk reassessment, risk audits, variance and trends analysis, technical performance measurement, reserves analysis, and meetings.

(See Appendix A1 for the explanation of the tools and techniques)

The Association of Project Management (APM) (2013) *Body of Knowledge* also suggested a risk management process, which can be compared to the one from PMI (2017). The phases on both methodologies are similar. Figure 8 demonstrates the process defined by APM (2013).

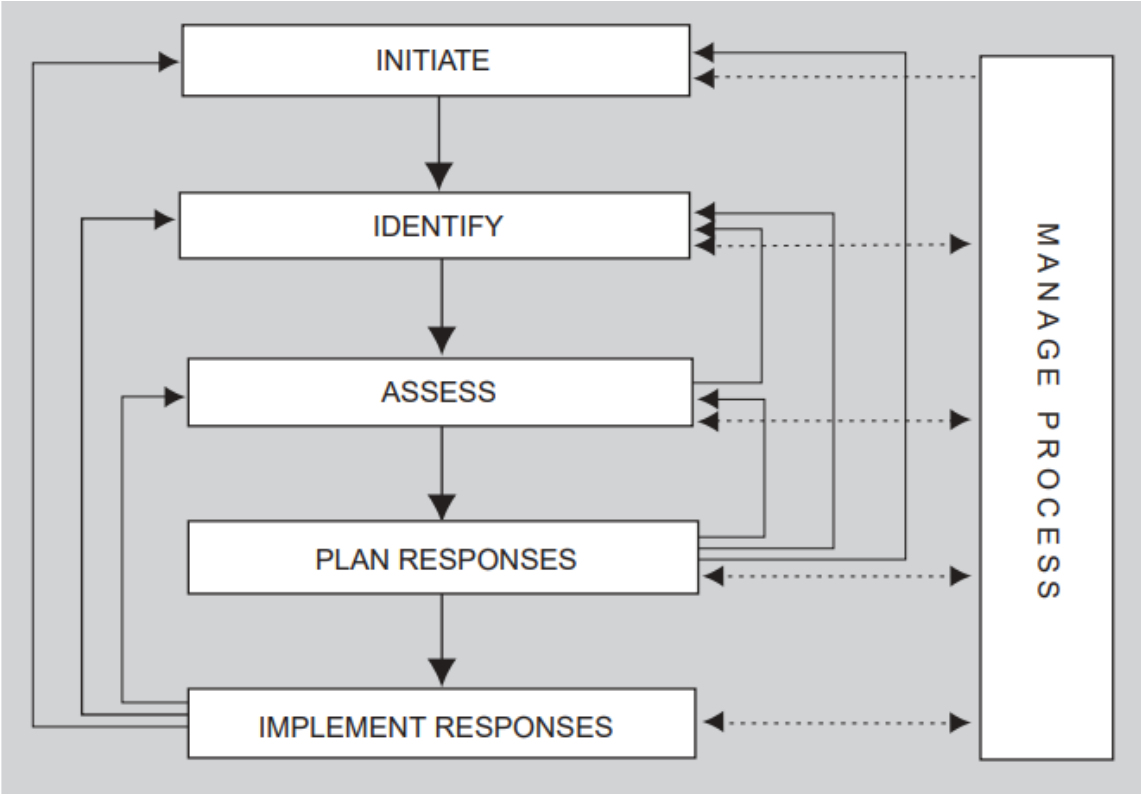


Figure 8 - The Risk Management Process (Source: APM, 2013)

The risk management process illustrated above requires an initiation step to define scope and objectives, after which risks can be identified. The relative significance of identified risks is assessed

using qualitative techniques to enable them to be prioritized for further attention. Quantitative risk analysis may also be used to determine the combined effect of risks on overall project outcome. A range of techniques are suggested by APM (2013), such as Monte Carlo simulation, decision trees and influence diagrams.

The process continues with risk response planning, aiming to avoid, reduce, transfer or accept threats as well as to exploit, enhance, share or accept opportunities, with contingency for risks which cannot be handled proactively. The next step is implementation of agreed responses, followed by iterative identification, review and update throughout the project life cycle to maintain awareness of current risk exposure.

In both guides, the processes and phases suggested interact with each other and with the processes in the other knowledge areas. Each process generally occurs at least once in every project. To be successful, the organization must be committed to addressing risk management throughout every stage of the project.

3.2 Risk Management in R&D Projects

In recent years, many industrial organizations have been changing the way they manage their R&D activities (Kasap & Asyali, 2007). The differences between an R&D project and other common projects can be found when comparing them with classic projects in terms of scope (quality), cost and schedule.

- **Scope and Quality:** R&D projects typically present a scope that is significantly less well defined.
- **Cost:** Every industrial R&D project plan envisions a payoff. In financial terms, this payoff can be represented by:
    - time value of money;
    - risk of technical failure;
    - cost of the R&D program itself.
- **Schedule:** an R&D project may have very poorly defined product quality and performance requirements, leading to vague task descriptions, deliverables, milestones, and schedule estimates.

In addition to this, the operating environment can also provide clues to the unique risks that may befall an R&D project (Rodage, et al., 2004).

In the literature about R&D project management, uncertainty is defined as the unpredictability of the environment (Milliken, 1987), inability to predict the impacts of environmental change (Raz & Michael, 2001), and inability to predict the consequences of a response choice (Sicotte & Bourgault, 2008). Several studies have found that applying risk management techniques to innovative projects can increase their success rates (Salomo et al., 2007;Mu et al., 2009; Raz et al., 2002).

By its very nature, R&D is a process that is covered with uncertainty, and with uncertainty comes risk. R&D projects are influenced by numerous external factors. The impact of the uncertainties associated

with these factors can be seen as the reason behind the low success rates of such projects. In practice, it is ineffective management of uncertainties and risks that results in poor project performance (Mastroianni, 2011) Seemingly, these could be overcome by applying more effective risk management techniques (Keizer & Halman, 2009).

R&D projects suffer from the adverse influence of a vast number of risks (Pinto & Covin, 1989). This problem is aggravated by the absence of knowledge about the factors that create additional uncertainty in projects and support innovations in organizations (Jalonen, 2011). Once the risks have been identified, contingency plans and strategies must be developed and applied.

Most of the studies found about risk management frameworks apply only to manufacturing or services projects and industry needs, and as such, they have been found insufficient in managing risks associated with R&D projects efficiently. Due to the inadequacies of the existing risk management approaches for managing uncertainties in R&D, some investigators have developed entirely new risk management frameworks to increase success rates in R&D projects, in an attempt to find specific risk management practices for this kind of projects.

R&D projects need experience, understanding, information, and skills to be successful, and they need people to do the work involved, so Cooper (2003) proposed using knowledge management systems and collaboration tools to capture the expert's experience for reducing R&D risks. Keizer et al. (2005) projected a risk reference framework for diagnosing risks in technological innovative projects and concluded that the success of breakthrough projects could be improved through formal risk assessment. Gidel et al. (2005) developed a decision-making framework for risk management from the cognitive science viewpoint.

Leung & Isaacs (2008) identified practices like the employment of risk experts and the use of analytical tools for risk-based decisions as effective in managing R&D projects. The study conducted by Wageman (2004) examined risk management in R&D projects using a process similar to those described above. However, he identified a set of specific tools and techniques that can be applied to better manage risks in R&D projects, including checklists, templates, expert interviews, plan evaluations, decision analysis, network analysis, and cost and schedule risk simulation. He also suggested the employment of risk experts to facilitate the risk management process but warned about the potential inconsistencies in doing so, as a result of the widely differing opinions that may come from various experts in a given field. This framework presents specific tools and techniques that may be used to aid in risk analysis and prioritization.

Vargas-Hernandez (2011) developed a methodology that utilizes a four-phase risk management methodology:

1. **Identifying parameters -** The author defines seven parameters: Environment, Technical, Resources, Integration, Management Marketing, and Strategy. The first stage of the methodology is to select which ones create risk, based on the kind of industry, size of the company, countries in which the company is located and the company's situation.

2. **Analyzing -** Risk events are the parameters which are recognized as risks. Analyzing the company should estimate probabilities of risks and the impact of their consequence and also

prioritize these different risk factors in order to solve them, because the company cannot solve all risks (limited resources, time, etc) and also the innovation is inherently risky, and if the company manages all risks, it may suppress innovation. The methodology suggests that risks could be prioritized through the calculation of their expected loss, using equation (1), in which: Pe is the probability of risk event, Pi the probability of impact and Lt the total loss.

$$Expected\ Loss\ (Le) = Lt * Pe * Pi \quad (1)$$

The probability of success can be calculated as:

$$Pe = 1 - Psucess = 1 - (P1 * P2 * \dots) \quad (2)$$

And the probability of impact (Pi) equals one minus the probability of success.

3. **Solving/Acting -** In phase three, the company should find different methods for solving these risks in different stages of innovation, through deferring action for more information, accepting the risk, buying out risk (transfer to a third party) or through parallel contingency development.

4. **Monitoring & Learning -** The company should monitor the process and also learn for a future risk management system. It should determine successful action plans, create action plans for risk now above the threshold or new risk identification and document the process to use it in the next projects.

This methodology can be compared with others from risk management guides such as the ones from PMI (2017) and APM (2013). Although it does not include a planning/initiating phase, the phases of Vargas-Hernandez (2011) are similar to some from these guides. The main differences is on the prioritization method by calculation of expected lost, which is not referred in none of these project management guides.

Wang et al. (2010) aligned R&D project risk management with corporate strategy and a performance measurement system to increase success rates and achieve corporate objectives and Wang and Yang (2012) conducted a study, incorporating managerial flexibility into R&D project planning to decrease technical and market risks. The methodology presented is divided into three steps:

1. **Identifying critical risks -** The first step includes risk identification by a survey, interview, brainstorming, etc. It also includes risk qualitative analysis and risk prioritization in terms of likelihood of occurrence and severity of impact, describing them as High, Medium or Low and displaying the risks in a 3 x 3 risk matrix. It suggests that high and medium risks should be controlled and monitored.

2. **Recognizing appropriate options structure -** According to the critical steps identified in step 1, this step maps the risks required to manage appropriate R&D options to increase upside potentials while decreasing downside losses. According to the authors, some R&D options have been used to enhance managerial flexibility in the pharmaceutical industry: Continue/abandon option, Expand/contraction options, Co-development option, Licensing option, Contract option and Defer option.

3. **Selecting Optimal R&D options -** The optimal options are selected through the real options model developed by Huchzermeier and Loch (2001) that connects the operational sources of uncertainty like product performance, budget, market requirement, which are usually observed in the practical R&D environment to the real option value of managerial flexibility. The authors believe that this allows decision makers to determine the option value of managerial flexibility in making operational decisions.

The risk identification and analysis tools suggested by Wang & Yang (2012) can be found in many risk management guides and are transversal to all kinds of projects. The options can be compared to the ones on the response strategies described on the Project Management Institute's (PMI®) *A Guide to the Project Management Body of Knowledge (PMBOK® Guide)*, although the ones suggested are strategies specific for the pharmaceutical industry. The selection method used was constructed based on the belief that managerial flexibility has value in the context of uncertain R&D projects, as management can repeatedly gather information about uncertain project and market characteristics and, based on this information, change its course of action. (Huchzermeier and Loch, 2001)

What distinguishes the foregoing methods from other risk management methodologies is that they consider the specific characteristics of R&D projects, such as the fact that they are innovative. Cooper (2003) by recognizing that knowledge is a major part of R&D and that the better it is spread and managed within a company, the more efficiently risks are reduced. Gidel et al. (2005), by considering the non-repetitive and complex nature of innovative projects when developing a decision-making framework complementary to risk identification to satisfy both the project objectives and the team. Both Leung & Isacs (2008) and Wageman (2004) identified tools that their findings shown that can be used efficiently specifically in R&D projects. These tools are also mentioned in other methodologies and guides not specific for R&D projects such as the *PMBOK® Guide.*

Some studies have been conducted, investigating methodologies for managing risk in R&D projects, specifically from the pharmaceutical sector. Kwak & Dixon (2008) developed a research that focused on risk management frameworks used by a number of R&D organizations around the world in an effort to identify best practices that could be implemented in pharmaceutical R&D projects. Their study found that some of these methodologies were more applicable to specific types of industries than to others. These results were later confirmed in the research by Vargas-Hernández et al. (2010). The 13 best practices identified are:

- develop a risk decision-making model
- approach risk management analytically
- involve team members
- use flexible tools
- draw upon academic research
- use analytical tools
- assess risks continuously
- benchmark

- incorporate risk management into project timelines
- outsource
- manage regulatory risk efficiently
- use scenario planning
- employ risk experts

Also, Lavallee (2010) developed a four-step project risk management qualitative model for biomedical and pharmaceutical projects, based on the basic premise that teams have more risks than they have time and resources to address them effectively. The model is based on the *PMBOK® Guide* strategy, although it combines the identification and analysis stages:

1. **Pre-Work** - Includes preparing the team to identify risks in Stage 2. Stage 1 begins with a plan and should end with a team that is ready and willing to engage in the process. Includes establishing the scope of the PRM. At the end of the stage, initial risks should be consolidated in the initial risks into a preliminary risk register.
2. **Identification and Analysis** - The purpose of Stage 2 is to identify project risks, record them in the risk register, assign probabilities and impact ratings to them, prioritize them, and assign risk owners. Each of the initial risks is to be reviewed to ensure that they are clearly understood by all participants and modified as necessary.
3. **Preparation of risk management plan** - Each risk owner should create an effective action plan for their risks. The range of approaches should be aimed at achieving one or more of the following: Reducing probability of occurrence, mitigate the impact if it occurs and developing a contingency plan to execute if the risk occurs
4. **Management of risks and opportunities** - Stage 4 addresses the establishment of the PRM Plan as a constant process and to maintain the plan as a living document.

The pharmaceutical setting is in constant change as markets are growing and merging with big companies. Authors of the biopharmaceutical industry know that drug development is a riskier project than most. To be in the lead and to gain competitive advantage, pharmaceutical companies need to be more specialized and flexible. Thus, the importance of project management. To bring a successful product to the market, risk management in the pharmaceutical environment cannot be ignored.

These methods seem to be accepted as effective strategies within the literature.

3.3 Risk Management in Pharmaceutical Projects

In the pharmaceutical industry, the risk management problem usually includes deciding on which new products to develop, continue to research, terminate or invest in. The complexity and uncertainty of the new drug development process can make optimal solutions hard to obtain and may result in the employment of less complicated, and therefore, less precise methods of new product identification (Gino & Pisano, 2006). Although risk management has been known to drive industrial success in other industries, in the pharmaceutical industry it has only been introduced in the last decade and it has been continuously growing (Pattanaik, 2014).

It is well established that research-based pharmaceutical industries are the main source of all modern pharmaceutical products. Innovative medicines control healthcare costs. For every 24 US dollars spent on new medicines for cardiovascular diseases, 89 US dollars are saved in hospitalization and other healthcare costs. (Lichtenberg, 2008)

This problem of risk forecasting is aggravated especially in complex projects with long life cycles and multiple dependencies, as is characteristic of drug development programs. (Zameer, 2017)

The Food and Drug Administration, as a federal agency of the US Department of Health and Human Health, it is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal food & feed and veterinary products. In 2002, the FDA announced the “Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century: A Risk-Based Approach”. They defined Risk management as “a strategic safety program designed to decrease product risk by using one or more intervention tools” and proposed that “the sponsor of every product submitted for approval considered how to minimize risks from the product's use. Risk management planning generally encompasses all efforts by a sponsor to minimize the risk from its product's use and may include product labeling, risk assessment, pharmacovigilance, and special studies or interventions.” FDA (2002) expects the risk management to follow a basic process:

1. Learning about interpreting a product’s benefits and risks
2. Designing and implementing interventions
3. Evaluating interventions in light of new knowledge that is acquired over time
4. Revising interventions when appropriate

Also, according to FDA (2002), an overall approach to risk evaluation ideally would:

Select a well-defined validated metrics. Use at least two different evaluation methods for key Risk Management Processes (RMP) goals or objectives. Preferably, the different evaluation methods would both be qualitative and representative to offset the biases that are intrinsic to any evaluation process.

- Use qualitative data collected from a large and diverse group of patients when quantitative date is either not available or not applicable to the evaluation measurement. Qualitative data such

as focus group testing may be useful in assessing the effectiveness of education and comprehension about safety and risk information.

- Consider using evaluation methods to check if RMP tools are performing as intended.
- There should be a methodology established that ensures that the RMP is regularly reviewed and updated as necessary, depending upon the status against the stated risk reduction goals.

The ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) is a project that brings together the regulatory authorities of Europe, Japan, and the US and experts from the pharmaceutical industry in three regions to discuss scientific and technical aspects of pharmaceutical product registration.

ICH (2005) proposed a set of methods and tools for risk management in the *ICJ Q9 Guideline - Quality risk management* and they are widely used in the industry. (Bhattacharya, 2015)

- **Basic risk management methods: Flow Charts/Process mapping, checklists, cause-effect diagrams**

Used to structure risk management by organizing data and facilitating decision-making in the areas of failure investigation and root-cause analysis.

- **Failure Mode Analysis (FMEA)**

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities, can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on a product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

- **Failure Mode, Effects and Criticality Analysis (FMECA)**

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

- **Fault Tree Analysis (FTA)**

FTA can be used to establish the pathway to the root cause of the failure and to investigate complaints of deviations in order to fully understand their root cause and ensure that intended improvements will fully resolve the issue and not lead to other issues. Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. It is useful both for risk assessment and in developing monitoring programs.

- **Hazard Analysis and Critical Control Points (HACCP)**

HACCP might be used to identify risks associated with physical, chemical and biological hazards. It is most useful when product and process understanding is sufficiently comprehensive to support the identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

- **Hazard Operability Analysis (HAZOP)**

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of HAZOP is a list of critical points in the manufacturing process.

Table 2 is a HAZOP example table.

No	Guide Word	Element	Deviation	Possible Causes	Consequence	Safeguard	Comment	Actions Required	Actions Assigned To
1	No	Cleaning Agent	No detergent added during cleaning cycle	Detergent supply reservoir empty	Residues not effectively removed, leaving system in an unclean state	Technicians check detergent reservoir before every cycle	Assumes technicians can reliably estimate volume visually	Consider alarm for low detergent reservoir lever	Engineer
2	Other than	Cleaning Agent	Wrong detergent used	Technician retrieves wrong detergent from warehouse	Incorrect detergent may be ineffective at removing residues, leaving system in an unclean state	Cleaning log requires verification of proper detergent use. Detergent is labeled	Many different detergent container look alike	Ensure technician training addresses detergent selection	Trainer

Table 2 - HAZOP example table (Source: Product Quality Research Institute, 2015)

- **Preliminary Hazard Analysis (PHA)**

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process, and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

- **Risk Ranking and Filtering.**

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the number of risks and the underlying consequences to be managed are diverse difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate quantitatively-assessed and qualitatively-assessed risks within the same organizational framework. Table 3 is a risk matrix, used for qualifying the priority of each risk according to impact and likelihood of occurrence.

Impact \ Probability	Low	Medium	High
High	Medium Risk	High Risk	High Risk
Medium	Low Risk	Medium Risk	High Risk
Low	Low Risk	Low Risk	Medium Risk

Table 3 - Risk Impact/Probability Matrix (Source: Author)

- **Supporting Statistical Tools**

  Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

  - Control Charts
  - Design of Experiments (DOE)
  - Histograms
  - Pareto Charts
  - Process Capability Analysis

  It seems that it might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality. The degree of rigor and formality should reflect the available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed.

Some tools suggested by ICH (2005) are also mentioned in the *PMI Project Management Body Of Knowledge (PMBOK),* such as checklist analysis, risk probability vs. impact matrixes and some statistical tools as well.

Besides the two guides presented, not many other studies on risk management in pharmaceutical projects were conducted yet. It is important to notice that the foregoing guides were created to deal with pharmaceutical quality, process and safety risks. Some of these risks may also be considered project risks, as their occurrence is likely to impact on the projects' objectives. However, at Hovione, these risks are managed by a different team, outside of project management. Process risks are not the focus of this study

3.4 Criteria for deciding on risk management tools and techniques

Multiple aspects regarding the type of project may be taken into account when choosing between tools and techniques for risk management in a project.

According to the literature, aspects like simplicity of use (Marle & Gidel, 2012), interactions considerations (Heal & Kunreuther 2007; Marle & Vidal 2010), completeness (Cooper, 2003), number of risk characteristics (Marle & Gidel, 2012), type of data (Cox et al., 2005), graphical display (Fan & Yu 2004; Lee et al. 2008) specificity and notoriety of the method (Marle & Gidel 2012), can all influence the suitability of risk management tools and techniques in projects.

Two of the challenges faced by new product development projects is how to acquire knowledge and manage sources of uncertainty in order to reduce the risk of failure of either the project or the resulting product. Under ideal conditions, the project would be able to identify all unknowns and to implement a risk management program to address them systematically (Cooper 2003). This highlights the question of the *completeness* of the identification. Some project risk management methods are applicable to a particular type of project (innovation or construction projects for instance) or to a particular type of risk (investment decision, planning uncertainty, cost risk, schedule risk, quality risk). These parameters are summarized in a criterion called *specificity*. That means that the method can only be applied in particular contexts. Due to the complexity of the project, related to several factors, such as size, diversity, context, and presence of interdependencies between its components, many potential interactions exist between risks. These interactions can have an influence on the behavior and so the performance of the project, including its outcomes, and should then be considered when making decisions. Even if some works have been done in order to model interdependencies between risks (Heal & Kunreuther 2007; Marle & Vidal 2015). This justifies the introduction of a criterion related to the *consideration of interactions* between risks. Some information cannot be managed in all projects (for instance detection ability, influence capacity), so the *number of risk characteristics* used in each method is also a criterion. In the same project, it is often a mix of different types of information. So, if a method does not permit the management of some *types of data*, then it has an influence on the final decisions. Depending on the skills and experience of people in risk management, the decision-maker may want to implement a very simple method. On the contrary, he may also prefer a more sophisticated method, even if it has some theoretical prerequisites. We introduce thus the *simplicity* criterion. When two methods have similar characteristics, the method which is best known can be better accepted and implemented. This criterion of *notoriety* is mainly subjective, however, it has to be taken into account for real-life implementation. Finally, some methods do have a *graphical display* which enables easier reporting and decision-making, like all cause-effect trees, Bayesian Networks (Fan & Yu 2004; Lee et al. 2008) or vulnerability graphs (Holmgren 2006). It may also be a preference for the decision- maker to choose a method which includes easy-to-do and easy-to-understand graphs.

Based on a careful analysis of the characteristics of the techniques supporting risk management proposed in the literature and applied in business practice, there are three project features that seem to be the most accepted by authors as criteria for deciding on risk management tools and techniques:

- Phase of risk management process and phase of project life cycle
- Corporate Maturity Level
- Product Innovation Degree

For deciding on what risk management tools to apply in Hovione's projects, the criterion of corporate maturity level will not be considered, as it does not make sense to evaluate the corporate maturity level of project risk management without evaluating the maturity of the project management area of R&D at the company.

3.4.1 Risk Management Process phase and Phase of Project Life Cycle

Any risky event unfolds through an escalation process composed of causes, an occurrence, and consequences (Hillson, 2003). Risk events are addressed by the phases of the risk management process, namely planning, identification, analysis, response, and monitoring and control (see figure 9).

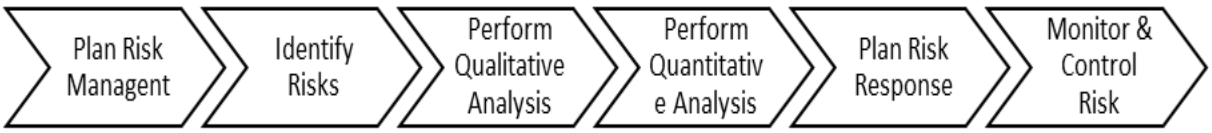


Figure 9 - Risk Management Process (Source: Based on PMBOK, 2017)

Risk management planning identifies the objectives, the approach and the resources to carry out risk treatment activities. Risk identification defines the causes of the risks to which the project is exposed. Risk analysis determines the probabilities of occurrence and the associated impacts on project outcomes in terms of cost, schedule, scope and quality variance. Risk response develops actions to increase opportunities and decrease threats. Finally, the risk monitoring and control phase is the ongoing identification and management of new risks that become known during a project, the tracking of already identified risks, the implementation of planned responses and the review of their effectiveness, the development of additional actions, if needed, and the formalization of lessons learned about risk.

There are different goals and levels of detail during the project life cycle in each stage of the risk management process, and they require the application of appropriate techniques according to the level and nature of the information that will increase as the risk management process progresses. The nature and the quantity of available information determine which techniques should be applied.

The studies of Chapman & Ward (2003) reveal that moving from one project life cycle stage to another implies more detailed and quantitative information available, leading to a different degree of uncertainty. Thus, the focus of any risk analysis and the adopted risk management techniques need to vary with the phases of the project life cycle.

In the initiation phase, decision-makers have a high degree of freedom in defining project goals, however, the necessary information for a complete investigation of risk is not always available, because not all specifications on how to meet the project goals are defined yet. Extractors of information like interviews or group techniques, such as brainstorming, Delphi and expert judgment, can be applied for this purpose. At the same time, experts should be trained so that they can make good judgments. However, in the case of repetitive projects, the greater availability of information

allows the use of detailed tables like Failure Mode and Effects Analysis (FMEA) (Grusbisic et al., 2011) and makes it possible to define occurrence probabilities and economic and/or time impacts for every alternative event. In this situation, decision-makers could move on to a quantitative analysis of risks through the use of Failure Mode and Effects Criticality Analysis (FMECA) tables, Decision Trees and Event Tree Analysis (ETA). Therefore, the quantity and kind of information in the initiation phase usually allows risk identification and occasionally also risk analysis. (Cagliano, et al., 2015)

The ways and means to achieve the project objectives become clearer in the planning phase thanks to a considerable increase in the available information, which allows a complete investigation of risks. All the techniques for risk management can be used in this project stage based on the phases of identification, analysis, and response to risk and on the type of information available.

In general, the degree of knowledge and the ability to influence the course of a project are inversely proportional as the project develops. Thus, in the execution phase, there will be a high level of knowledge about project constraints but a low ability to influence events because all the most important project and risk management decisions have been already made in the previous phases. In this stage, the time and economic performance resulting from the project choices and the actions undertaken to either mitigate or exploit risk can be controlled and monitored. Therefore, in the execution phase, the results of the techniques applied in risk identification, analysis or response will be revised and the outcomes of the implementation of designed actions will be monitored by means of careful and sensible human action. In addition, the risk management techniques used in the planning phase can be applied again to identify and analyze new risks that did not emerge before

The termination phase involves commissioning and handover, reviewing the lessons learned during the project, and assuring the necessary support to the product of the project until it is discarded or disposed, however, it is not considered because the risk management effort is more relevant in the previous stages of the project life cycle. Also, the risk management planning phase is not included, being less operational in nature than the subsequent phases and more focused on the strategy to deal with risk and project goals.

Different risk management activities can be associated with each phase of the life cycle of a project. (Chapman & Ward, 2003). In sum, the identification of sources of uncertainty takes place in the initiation phase, while managing foreseen risks and monitoring changes are typical tasks of the execution phase. Moreover, the degree of information accuracy is heterogeneous along the project life cycle. In the final phases of a project, when risks are mainly related to the consequences of decisions made in the previous steps of the project or are the effects of risks already manifested, their sources, occurrence, and impacts can be characterized in a more accurate way due to the more information available. (Tah & Carr, 2001).

These considerations support the need for project managers to focus on each stage of a project by means of suitable techniques to identify, assess and treat risks in order to meet cost, schedule and performance requirements.

3.4.2 Product Innovation Degree

Projects with innovative profiles involve risks and so are in greater need of risk management. Therefore, it is known that the presence of risks is a characteristic inherent to innovation. Thus, the product innovation criterion assumes a fundamental role in the choice of the risk identification method to be used in project management. According to the literature, the criterion of product innovation degree allows deciding between risk identification tools. Pahl et al. (2007) proposed a product innovation classification model with three levels of product types:

- **Innovative:** New tasks or problems are assisted by a new principle solution or a new combination of a family of principle solutions. It is worth pointing out the difference between invention that is truly treated of a discovery that is often based on the application of new scientific knowledge, with innovation, new functions and new characteristics of a product are materialized. This can occur perfectly through recombination of a family of solutions.
- **Adaptable:** The principle solution is preserved and only the configuration is adapted to the new peripheral conditions.
- **Alternative:** The size and/or the arrangement of components or subgroups is varied, which is typical of series constructive and/or modular systems

According to the literature, there are three ways to classify risk identification methods according to their innovation degree and the team's experience and knowledge needed:

1. **Analogical approach:** The analogical approach complemented of the cumulative experience of the project team it is a great aid to inexperienced project team leaders. The use of the team's experience in combination with the checklist items to remind its members of the types of issues that may arise is recommended (Riek, 2001). The analogous comparison consists of investigating what happened in similar previous projects in order to identify possible risks in the current project. For this, information regarding registered changes and problems which occurred in past projects, along with customer satisfaction information, can be useful.

2. **Heuristics approach:** As the heuristic approach is based on the exploitation of the participants' creativity for the identification of the maximum possible risks, the level of maturity advisable for the successful application of these methods is level is 2, since it is thus assured that all the project team members have understood the product design problem and are familiarized with the project context. This approach is best used when a problem is well defined, the major issues involved in the problem have already been identified and there is no need to explore the problem further. It is also important to consider basic rules for the successful application of this approach. In the case of the brainstorming method, an essential condition is that in the risk identification meetings, it is not recommended that the risks be quantified and measures defined to minimize them simultaneously. Not only would this lead to more time being spent, but significant risks could be discarded precipitately (Riek, 2001). The heuristic approach is more suitable for innovative and adaptable projects. These project types require the stimulation of the project team to identify new risks, mainly in the case of the innovative projects due to their high degree of

originality in terms of product, project management etc. For instance, brainstorming sessions are an effective way of channeling natural creativity into identifying what can go wrong on the project. One person's idea can trigger someone else's (Coppendale, 1995). As the base of the heuristic approach is concentrated on the identification of a great number of risks, without initially being concerned whether they are pertinent to the project, the presence of specialists who are sufficiently creative is fundamental to obtaining good results. With regard to the risk identification approach adopted, the company must constantly evaluate it and verify whether it is consistent with the needs of the product design and project management processes, as well as the project team expectations. The methods based on heuristics mainly use expert creativity, sometimes with a mix of experience and expertise. Experts may have experience with a part of the project, and they have to mix in not only their risk identification and risk analysis data which come from previous experience but also data that are completely new.

3. **Analytic approach:** Analytic approach is the most known and currently used in the industry for the study of technical risks (Gidel & Zonghero, 2006). This approach is based on the Failure Mode and Effects Analysis (FMEA) method that gives procedures applicable to project management. In this method, the analysis is focused on the project processes, having identified the failure possibilities, the internal or external causes of failures and imperfection, and their effect on the output elements (that frequent constitute the input elements of the next process). The analytic methods are mainly based on systematic analysis of the project activities. By analyzing potential failures on project tasks or project resources or project results, it is possible to identify a great number of risks.

Considering the literature review on the risk identification methods, some of these methods are grouped according to the classification of risk identification above. It is worth pointing out that, although each method is classified into a specific approach, it can, and frequently does, present characteristics of another approach.

(See Appendix A2 for the classification of some risk tools in terms of risk process phase and product innovation degree)

3.5 Conclusion

In this chapter, a framework for the problem at hand has been described, with the purpose of supporting the case study with notions, concepts, and approaches about project risk management. This chapter is divided into four major sections: Risk and Uncertainty, Risk Management in R&D projects, Risk Management in Pharmaceutical Projects and Criteria for deciding on risk management tools and techniques.

In chapter 3.1 the concepts of risk, project, project management and project risk management have been thoroughly reviewed and described and it has been concluded that no project is free of risk and that risk management should be a systematic part of project management in order to achieve success and performance goals, especially in industries with high uncertainty environments, as is the pharmaceutical.

Researchers have suggested different techniques to manage risk, according to the characteristics of the projects. Some of the tools investigated seem to be suitable to manage the risks of Hovione's DPD projects. In sections 3.2 and 3.3 show that several studies have been written regarding R&D projects and some on pharmaceutical projects. Authors have found limitations in each other's methodologies so that, after the analysis of their researches, it is possible to conclude that the suitable framework to implement needs to be flexible and adaptable to accommodate the uncertainty associated with the research component of R&D projects. A methodology comprising a baseline set of processes, procedures, and templates that could be tailored to suit each individual project seems to be a good starting point. The methodology to implement must not be intrusive. Which means that it must involve relatively simple processes and procedures such that it does not impose a significant overhead to the execution of projects, as they are of short duration.

In addition, this study included, in chapter 3.4, a research on the criteria for deciding on project risk management tools and techniques. Several researchers have written papers on this subject, highlighting several aspects of projects that they believe to be relevant when choosing risk management techniques. The ones to which more authors agreed as being decisive factors and easier to evaluate are the company's maturity level, the project life cycle phase and the phase of the process risk management, and the innovation degree of the product and process. Only the las two were considered. Simplicity of use has also been mentioned in the literature on this subject, and as the projects to be analyzed are of short duration, this aspect is considered critical. Meaning, the risk management framework to implement cannot be to complex and/or time-consuming.

Chapter 4: Research Methodology

The characterization of the company and its practices, done in chapter 2, alongside with the literature review on risk management methodologies in R&D and pharmaceutical projects, done in chapter 3, served as basis for the development of a risk management methodology, whose effectiveness will be tested in two different projects. To do this, it was necessary to conduct a research following methodological steps, in order to, in the end, propose to Hovione a final and official set of risk management tools and techniques to be implemented in DPD projects.

This chapter is divided in two sections: section 4.1 describes the case study research method which was used in this dissertation, and section 4.2 describes the methodology followed to propose a risk management methodology that fits Hovione's projects.

4.1 Research Approach

Research is the process of collecting, analyzing, and interpreting data in order to understand a phenomenon (Leedy & Ormrod, 2001). There are two types of research methods: quantitative and qualitative.

Quantitative research can be used in response to relational questions of variables within a research. Creswell (2003) states that quantitative research employ strategies of inquiry, such as experimental and surveys, and collect data on predetermined instruments that yield statistical data. The findings from quantitative research can be predictive, explanatory, and confirming. Quantitative research involves the collection of data so that information can be quantified and subjected o statistical treatment in order to support or refute "alternate knowledge claims" (Creswell, 2003).
On the other hand, qualitative research is a holistic approach that involves discovery. Qualitative research is also described as an unfolding model that occurs in a natural setting that enables the researcher to develop a level of detail from high involvement in the actual experiences (Creswell, 2003). One identifier of a qualitative research is that the social phenomenon is being investigated from the participant's viewpoint. Qualitative research involves purposeful use for describing, explaining, and interpreting collected data.

Under this framework, the research methodology used to develop this dissertation is qualitative, and the method used was case study research. The essence of a case study is that it tries to illuminate a decision or set of decisions: why they were taken, how they were implemented, and with what result. In this case, it was used to describe an intervention (risk management implementation) in the real-life context in which it occurred.

As stated by Seuring (2005), the principal criticism from reviewers and associate editors to case study research process is the papers' lack of rigor. In order to combine relevancy with a more rigorous case research approach, the research and dissemination process of this dissertation follows the five critical stages illustrated in Figure 10.

Figure 10 - The five stage research process model (Stuart et al., 2002)

Defining the research question: The research question was what risk management methodology is more efficient to manage risks of short-term R&D pharmaceutical projects. Hovione has had troubles in implementing a successful methodology in the past and the lack of risk management has been recognized as an issue by clients and project managers. The case presents a critical case (Yin, 2003), in which a methodology believed to be efficient under the case study circumstances is tested in order to be confirmed, challenged or extended. Hovione provided the project case studies.

Instrument development and site selection: The case study was researched by having access to staff, project meetings and documentation at Hovione. As the first mode of access, interviews were chosen, as they provide a flexible instrument to get into the field and become familiar with the object studied, while also providing a flexible mode of data gathering. Assisting to meetings allowed a detailed understanding of similar project examples. Documents were available on the company's websites and were analyzed with the help of the project managers of Hovione.

Data gathering: For data collection, semi-structured face-to-face interviews were conducted with project managers of Hovione. They provided initial insights into the history of the company and on the project management and risk management practices under use. A DPD project (Project A) was selected to be followed, to gather data on team's behaviors and project lifecycles. Again, data was only accessible through Hovione's staff and websites. All projects (both project A and the case study projects) analyzed are representative of the related projects managed by Hovione.

Analyzing data: Data analysis was carried out by transcribing the interview's and document's data. The findings were discussed with Hovione's staff to validate the findings. A second mode of analysis was seen in comparing the research to those of other researches addressing similar questions, which served as additional mode of triangulation.

Dissemination: This dissertation presents evidentiary base with summaries, tables, charts and selected examples. It indicates the links between these and the evidentiary base. It includes demonstrations of chains of evidence (from raw data to summary) for portions of the overall data, which were handled similarly as the rest of the data. Plus, the case study research follows Yin's (1989) guidelines for enhancing reliability and validity. It takes into consideration the author's logical tests for judging research design.

(1) It describes how data was collected, via which sources and establishes chains of evidence. It describes how someone with the same raw data could derive the same summary values for the various constructs for the study. Plus, the draft case study report was reviewed by key informants.
(2) Causal relationships are established. Certain conditions are shown to lead to other conditions. It can be shown that actual data patterns match proposed patterns.
(3) Study's findings or presumed causal relationships may be generalized. The selection of the cases was based in theoretical sampling and fill theoretical niches.
(4) Study's operations can be repeated, with the same results. Maintaining the case study database and notes, another researcher could repeat the analytical procedures beginning with the raw data.

Conclusions and further explanation and dissemination of the case studies is done in the following chapters.

4.2 Methodology

To propose a risk management methodology that fit the Hovione's DPD projects, the methodology shown in Figure 11 was followed.

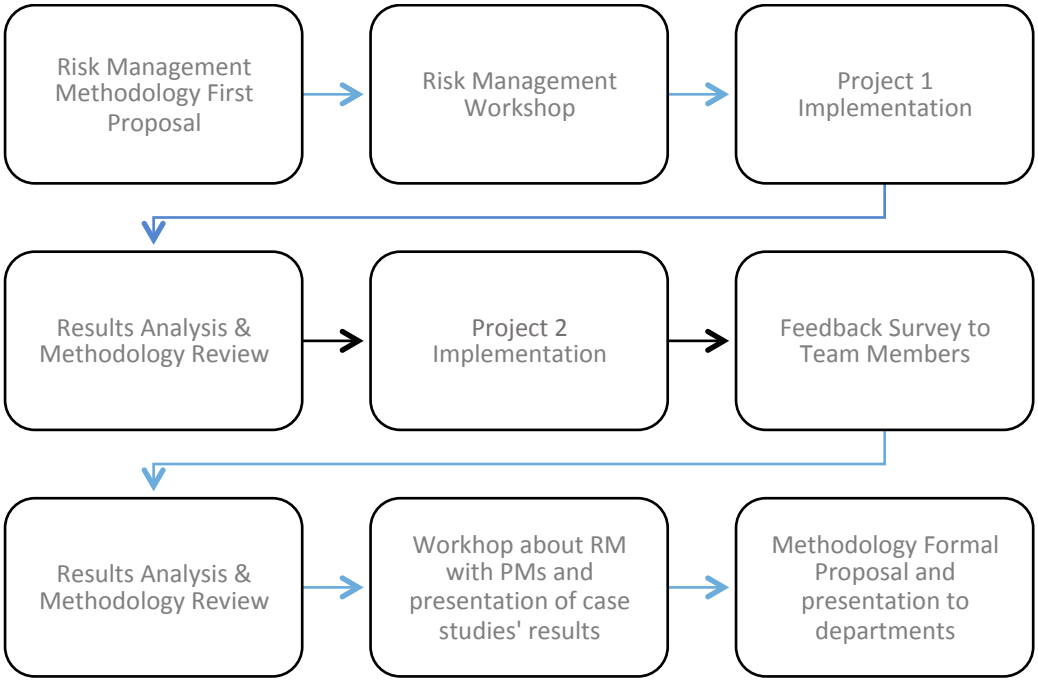


Figure 11 - Dissertation's Methodology (Source: Author)

The process of developing a risk management methodology started when a first draft methodology was presented to two project managers, who helped in its development, and the R&D Project Management Director. The director gave his approval to proceed with the implementation in the pilot projects. After this, a risk workshop for the project managers was scheduled. It was presented by the director who explained all concepts related to risk, the benefits of risk management and then the draft risk methodology was presented.

The next step was the implementation of risk management methodology in the first case project, Project 1. The approved approach to risk was announced to Project 1's team by the project manager in such a way that everyone understood it and recognized its advantages and value.

It was successfully implemented along the project's lifecycle. The team member's reactions and behaviors were observed and documented. In the end of the project, a presentation of the methodology's results was done to the team and they were given an evaluation questionnaire, with the purpose of evaluating the efficacy of the methodology in managing risks. A comparison's analysis was made in order to evaluate the results of the methodology.

Through the evolution of the project, lessons learned were gathered and alterations to the methodology were done and implemented on the second pilot project, which began about one month after the beginning of Project 1. The second pilot project was Project 2. The methodology was implemented in this second project and result's analyses and evaluation was done through the same means as in Project 1.

These two projects were chosen due to their timelines. No other projects would allow proposing a final risk management methodology to Hovione ready within their deadline. For this reason, the second pilot project chosen was one that started before the end of Project 1.

After both projects had finished, it was possible to gather a set of conclusions about the methodology's effectiveness and necessary improvements, and to collect the teams' feedback from the surveys. The results were analyzed, lessons learned were withdrawn and adapting the risk methodology. These changes were then presented and discussed with the director who approved them.

Afterwards, a risk management meeting was conducted with all the project managers, in which the risk methodology was formally presented and explained to all, along with the results of the two case studies.

The timeline of the methodology is depicted in Figure 12.

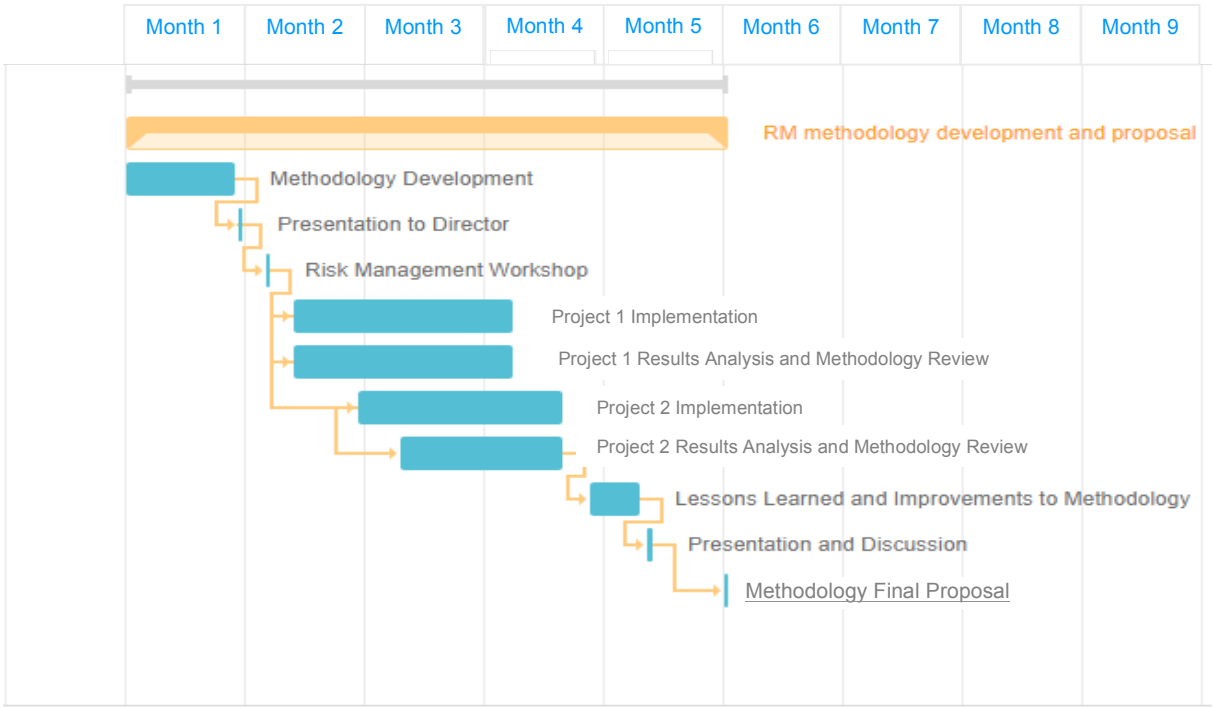


Figure 12 - Methodology Timeline (Source: Author)

This way, the rest of this dissertation is composed of three chapters. Firstly, chapter 5 aims to thoroughly describe the methodology that was developed taking into consideration the findings of the literature review, and the tools and techniques to apply in each stage of the risk management process. Chapter 6 consists in the description of the implementation of the risk management methodology in the two pilot projects and of the conclusions taken from it. Chapter 7 describes the conclusions taken from the case studies and the limitations of the research conducted along the dissertation.

Chapter 5: Risk Management Methodology

The purpose of this chapter is to describe the risk management methodology that was developed and tested in the first pilot project, and adapted for the second one. It is divided into six sections: section 6.1 explains the purpose of the methodology and why it was chosen and developed this way. Sections 6.2, 6.3, 6.4, 6.5 and 6.6 describe the tools and techniques to be applied in each phase of the risk management process: risk management planning, risk identification, risk analysis, risk response planning, and risk monitoring and control.

5.1 Groundwork

After conducting the literature review, and analyzing the characteristics of DPD projects, it was possible to identify which characteristics are the most important in the risk management methodologies for Hovione's type of projects. It allowed understanding how risk management framework needs to be constructed, what methodologies have failed or succeeded on similar projects in the past, the sequential phases of the risk management process and also in which phase of the project life cycle each technique is more effective and appropriate.

The most relevant studies used to develop the risk management methodology can be seen on Table 4.

Table 4 - Most relevant studies for developing the risk management methodology (Source: Author)

Reference	*Description*
Kwak & Dixon (2008)	Best practices used in R&D that should have good results when applied to pharmaceutical projects. Some of the identified practices seem to be necessarily addressed at Hovione's projects, such as assessing risk continuously and using flexible tools.
Wageman (2004)	Suggests a set of tools and techniques to be applied in R&D projects, and some of them, per example the checklist method, seem to be simple enough to be applied at Hovione's short-term projects.
Lavallee (2010)	Proposed a methodology based on the *PMBOK® Guide* that, combined with the right set of simple tools and techniques, and adapted to Hovione's fast pace, seems to be appropriate to manage DPD's risks.
Marle & Gidel (2012)	Defined simplicity as a criterion to take into account in risk management strategies. For Hovione, the methodology has to be simple, due to the high workloads of employees, short duration of projects and lack of historical data on risks to manage them more complexly.

From all the methodologies found during the research, many had some characteristics in common, and these seem to be considered important to authors, to successfully manage risks. These were taken into account in the development of the risk management methodology. They are: 1) early and iterative identification of risks, 2) periodic monitoring and control of risks and response plans. Early and iterative risk identification is indispensable in risk management methodologies for projects such as DPD, in which, the time between a risk appearance and its occurrence can be very short. The methodology has to allow identifying risks in time to address them. Periodic monitoring is necessary to avoid the waste of resources on out-of-date response plans and to timely address risk that have aggravated.

The suitable framework to implement needs to be flexible and adaptable to accommodate the uncertainty associated with the research component of R&D projects. Ideally, the methodology should comprise a baseline set of processes, procedures, and templates that could be tailored to suit each individual project. From the literature review, it was also found that the risk management tools and techniques have to be adapted to the characteristics of the projects. DPD projects are short duration. This means that the methodology must involve only relatively simple processes and procedures such that it does not impose a significant overhead to the execution of the project. Plus, it should not be intrusive. The fact that the risks repeat themselves from project to project, should be taken into consideration when choosing risk identification tools.

As a result of the information collected, the present chapter intends to explain the risk management methodology that is to be tested in the first pilot project. The methodology is based on the approach

proposed by Lavallee (2010), including tools from Wageman (2004) and considering the findings of Kwak & Dixon (2008) and Marle & Gidel (2012).

The basic premise behind this risk management methodology developed is that project's teams have more risks than they have time and resources to address them effectively. To develop this framework, it was assumed that if a team knew about project risks and that they could be prevented (or its potential impact reduced) by expending resources, they would, in fact, prevent it. Even if the capability or desire to address risks did not exist, there may still be value in engaging in the process. The methodology described in the next sections provides a framework for identifying and documenting project risks, and assessing each of them in a way that allows their prioritization relative to other project risks. Most important risks can be highlighted for in-depth consideration. The team can then allocate resources to address the most important risks, maximizing the effectiveness of their mitigation efforts

This risk management methodology should be, by no means, definite or final. Rather, it is intended to provide to the project managers, a new, simple, and straightforward approach for implementing the fundamentals of qualitative risk management. This methodology is supposed to be a starting point to a more complete one, to which the company is not yet ready to implement, but it should be soon.

After the complete implementation of this methodology in all Hovione's DPD projects, benefits from it should start arising, some more obvious, other subtler. The following outcomes are expected:

- Better understanding of what each team member is accountable for, including risks. Engaging the team in formal project risk management involves subjecting them to a thorough discussion of the overall project objectives, processes, and activities that are required to achieve those objectives. The wide-ranging nature of the methodology ensures that the participants from different fictional disciplines gain a broader view of the project scope.
- Improvement of the ability to forecast outcomes. An in-depth understanding of the source of project risks inevitably leads to an improved understanding of the uncertainty that underlies those risks. When those uncertainties can be addressed directly, the likelihood increases that the team will complete its activities on schedule, and to the level of quality originally planned.
- Clearer communication regarding risks. Until a team has taken the time to characterize and document the risk drivers within their project, they are limited to general and often trivial statements regarding programmatic risks. If they don't detail the legitimate risks within their project, the team will often avoid statements that imply anything could go wrong and miss opportunities to obtain the resources to significantly improve their chances for success.
- Clearer expectations from senior management. Understanding and communicating the major risks facing a project to senior managers allows the team to manage senior management's expectations more efficiently. When a team can clearly articulate the major project risk drivers and their plans for addressing those risks, they have proven to senior management that they take their responsibilities seriously and have a thorough grasp of the intricacies of the assigned task.
- Consensus on team members' opinion on issues. Project risk management focuses teams on the uncertainties of projects and it also leads to discussions on the issues that the team is

currently facing. The broad scope of the process leads to establishing a better understanding across the entire team.

- Greater visibility of issues by senior management. Formally documenting risks and risk sources will allow keeping an accurate historical record of risks that, when communicated to senior management, will allow a visibility of issues that need to be addressed outside the responsibilities of project management.

5.2 The methodology

This methodology is a simplified version of the risk management methodology espoused by the Project Management Institute in the *PMBOK® Guide*, although it combines the identification and analysis in one single stage, and it defines the timings of each phase. In project management, Hovione follows the *PMBOK® Guide*, so it made only sense to follow it as well in project risk management.

The methodology is composed by six stages, as shown in Figure 13.

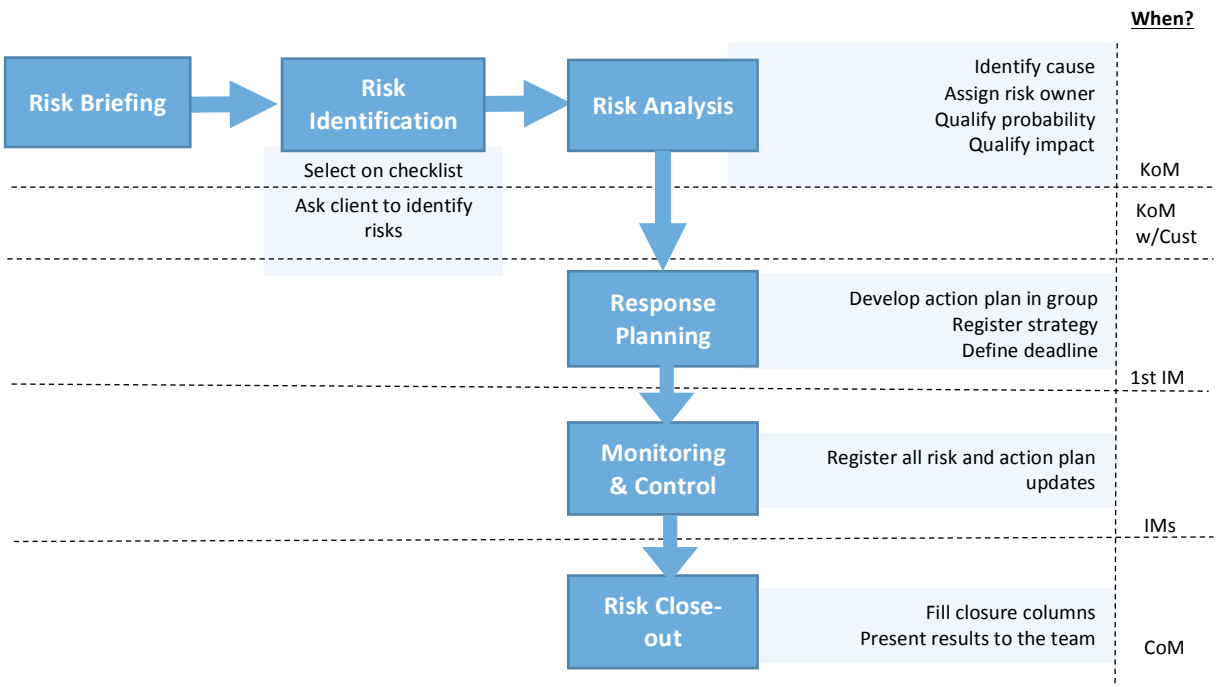


Figure 13 - Draft Methodology (Source: Author)

The methodology's six stages are described in the following sections.

To aid the risk management process and registering of risks and action plans, an Excel tool was developed. These excel files are supposed to, in the future, be adapted to fit the project management software that is under implementation at Hovione.

5.2.1 Risk Briefing

One of the characteristics that was considered important for the risk methodology was adaptability. As so, the methodology developed can be applied without alterations to any DPD project and for this reason, there is no need for much risk management planning, as all risk management activities are already defined. Nevertheless, a pre-work/briefing phase is essential to the successful implementation of the process. It is critical that the team understands and identifies the need for risk management. The goals in risk management planning are to prepare the team to manage risks, and explain to them how the process will elapse. Ideally, this stage would end with a team ready and willing to engage in the process. To achieve this, the project manager must assure that the team is sold on the benefits or risk management and what their investment is going to be in terms of time and effort, and how this investment will pay off.

After an initial briefing, it should be clear to the team that risk management improves the capacity to forecast outcomes and that when uncertainties are addressed directly, the likelihood of the team completing its activities on schedule increases. The briefing should happen before risk identification, which should take place during the internal kick-off meeting. So, the briefing must happen either in a prior, separate meeting, or on the internal kick-off meeting as well. During it, it is important that the team is educated on risks and how they should be expressed. Each team member will have a different level of understanding, but almost all will be unclear on the concepts. The process of risk management tools and techniques that will be applied and its timings should be presented to the team during the risk briefing. After the methodology is fully implemented and all teams have already been through risk briefing in previous projects, this step can be suppressed, since everyone will already know the briefing's information.

5.3 Risk Identification

Before the kick-off internal meeting, the project manager should send an email to all team members with the risk checklist as attachment, so that they can take a look at it and fill it before the meeting. This risk checklist comprises 54 risks separated by categories and it was developed with the help of Hovione's project managers. It leaves space for team members to add new risks. The checklist is supposed to be a live document. (See Appendix 3 for the checklist's initial version). The initial purpose of sending the checklist before the meeting is to get the team members to start thinking about risks. This checklist is the first tab of the Excel tools developed. All checked risks are automatically transferred to the next ones.

After the briefing is done, the team can proceed to risk identification. This should be done during the kick-off meeting. Performing risk management during the team's usual meetings should be perceived as less work than if done in separate meetings. The checklist should be displayed on the screen of the meeting room, and all identified risks should be consolidated into it, in real time during the meeting.

Projecting the list will allow all the team members to see the risks that are being checked and this will enhance the meeting's effectiveness. Capturing someone's idea immediately makes it clear that it was taken seriously, and it provides subtle validation that every idea is important. As each risk is checked,

it is confirmed and can be immediately edited to ensure that it has been captured correctly. Seeing the risks that have already been recorded will reduce the number of duplicates and trigger new ideas as people read back through the list. This checklist should promote a clear description of each risk and facilitate further refinement of the risk in terms of assigning a probability and impact rating, and other key information. As the risks are consolidated, some clean-up, including deleting duplicates, can be done. It should be assured that each risk is understood by all participants.

Although the identification process is to be done using the checklist method, it should also work as a brainstorming exercise. Every idea should be accepted uncritically. The team is welcome to add new risks to the list as they identify them.

The checklist approach has a risk associated with it. Teams may focus on the checklist and forget to explore other risks that are not present on it. But for the case study projects, it should be the most suitable method. Checklists are a fast and simple way of identifying risks, and in these projects, risks are repetitive from project to project, so if the checklist is updated every time new risks arise, eventually, all risks will be listed.

The second stage of the identification phase is to involve the client. and it takes place during the Kickoff meeting with the client. The project manager should ask what are the project risks and add them to the checklist to be analyzed by the team in the analysis phase.

5.4 Risk Analysis

After completing the identification and cleanup of risks, it will be necessary to analyze each one with regard to cause, probability that it will occur and the impact that it will have on the overall project if it does occur. The list of risks should include by now, the risks identified by the client as well.

The assessment of probability and impact is central to determining the highest priority risks for which action plans will be generated. Identifying the cause of each risk makes developing action plans easier, as they can be constructed to directly address risk causes.

Risk analysis will be done qualitatively because, at Hovione there is no sufficient available data to support numerical probabilities and impact estimates. It is expected that, when project risk management has been fully implemented, teams will eventually, have collected enough risk data and records, so that, in the future, it should be possible to assess these records and analyze risk quantitatively, instead of qualitatively.

For each risk, the team should find its cause and register it. Then, they should assess the probability of the event occurring and the relative impact of its occurrence on the project. These will be recorded in the risk analysis excel template, which will be used to drive the prioritization of the risks. Both probabilities and impacts should be analyzed qualitatively, using the terms: *Very Low, Low, Medium, High,* and *Very High.* These terms are not absolute, and classifications given should be done relatively to other risks. These processes will become easier as the team gains experience. If the team ever has difficulty agreeing on a probability or impact rating, the project manager should have them compare the risk to one which has already been evaluated and ask them which would have a higher probability or be more impactful. When there is a debate over a probability or impact that seems irreconcilable,

there are two principles to invoke: first, if one of the positions would result in deletion of a risk from the list, it should be left on the list. Second, the opinion of the team member who is most informed on the nature of the risk should carry more credibility over other opinions.

The objectives of DPD projects at Hovione are scope, costs, timelines, and quality. Ideally, the methodology would allow analyzing impacts in each objective, but Hovione is not yet ready to apply methods that complex, as it would imply disposing a lot more time, which team members do not have. At such an initial stage of risk management, the team should consider timelines the most when analyzing risk impacts. Timelines are the project objective that is more often affected and it is the most important one to Hovione's clients. In the future, this methodology should be adapted to consider other project objectives as well.

The approach developed considers each risk and assigns it a priority of *high*, *medium* or *low*. These categories reflect the relative importance of implementing an action plan for each risk. To help sorting similarly rated risks through a large list, a risk matrix will be used to help (See Figure 14). The Excel tab destined to risk analysis, fills the priority column automatically, according to the priorities and probabilities chosen.

Hovione's project managers consider that the company's risk profile is risk-averse, which means, it opts for safer options or with lower uncertainty. The risk matrix was developed according to the company's risk profile, however, it is subject to future alterations after the pilot projects, if considered necessary.

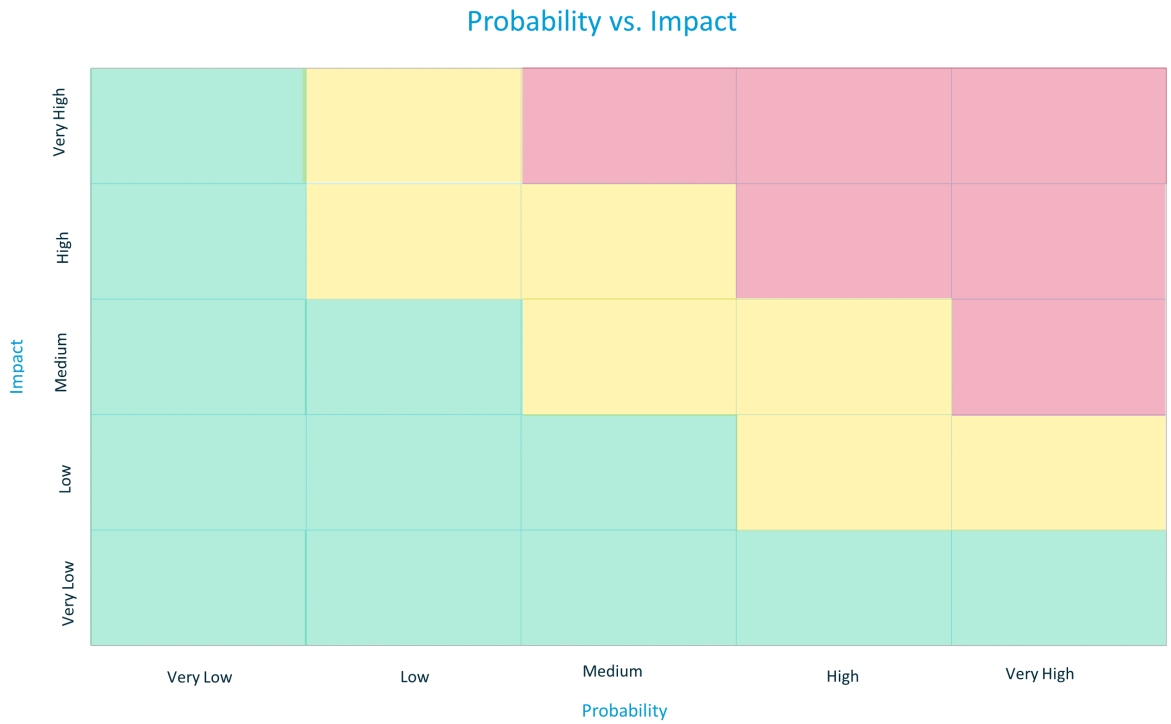


Figure 14 - Risk Matrix (Source: Author)

This risk matrix was constructed taking into consideration the mathematical properties and limitations of risk matrix defined by Cox (2008). According to it, in order to be most useful, risk matrixes should satisfy four axioms.

The Axiom of *weak consistency* means that points in the top risk category (red) represent higher quantitative risks than quantitative risks than points in its bottom category. This allows the risk matrix to discriminate reliably between at least some risks, even though it does not require quantifying probability and impact attributes. This way, the risk matrix can serve as a useful screening tool, as red cells do represent unambiguously higher risks than green cells. Red cells denote the highest priority level and green denotes the lowest priority level.

The risk matrix assumes that the rows and columns are interpreted as equal partitions of two numerical scales. If a scale from 0 to 1 is used, any point in the red are has at least a risk factor of 0.32 and no point in the green area has a value greater than 0.24.

The existence of a yellow area allows satisfying the *betweenness* axiom, making every positively sloped line segment between the green area at its lower end, and the red area at its upper end, passes through at least one intermediate cell between them. This means that small increases in probability or impact will not create discontinuous jumps in risk categorization from lowest priority to top priority. Plus, this matrix also satisfies the axiom of *consisting coloring.* All red cells contain points with quantitative risks at least as high those in other red cells, all green cells contain some points with risk as small as those in other green cells and all yellow cells lie between a red and green cell or contain points with quantitative risks higher than those in some red cells and also some points with quantitative risks lower than those in some green cells.

This analysis should be done in group by the team and the opinion of all members should be taken into consideration. There is no objective way to classify the relative impacts and probabilities of each risk, but doing this analysis in group will take into consideration the different risk profiles of team members, and it should be possible to reach accurate enough results. A table of severity levels could help team members to qualify the impacts of each risk, but this table had to be divided by project objectives, and it would not be possible to use the same one in all DPD projects, as the critical objectives can change from one to another. Some of Hovione's clients consider staying on schedule the most important objective, others consider staying on budget instead. The idea of this risk analysis is to help decide on which risks to take an action plan.

It was decided that action plans would be developed for both high and medium priority risks. Action plans for high priority risks (red) should be implemented immediately. Yellow risks on the other hand, should be monitored, and unless they aggravate into high priority risks, no action plan should be implemented. It is important to develop action plans for medium priority risks as well, because if they aggravate during the project, there might be no time to consider action plans and apply them in time. Short term projects evolve very fast and the time between a risk aggravating and its occurrence can be very short. Low priority risks should also be monitored.

When determining the subset of risks for which risk response planning will be conducted, an evaluation of the potential effectiveness of mitigation activities should also be considered. There may be a high priority risk for which there is no effective mitigation and few contingencies. For this kind of risks, developing efficient action plans can be impossible. At the same time, a low or medium priority risk could have a very evident action plan that consumes very few resources. Effective risk management decisions should not in general be based solely on mapping ordered categorical ratings

of probability and impact into recommended risk management decisions or priorities, as optimal resource allocation may depend on many other factors.

Qualitative risk analysis through risk matrix was chosen because of its simplicity, as it provides a clear framework for systematic review of individual risks, convenient documentation for the rationale of risk rankings and priority setting and relatively simple inputs and outputs. But it must not be forgotten that the input information going into risk matrixes is not sufficient to guide effective risk management resource allocation. The idea is that, once the company is ready for more complex analysis methods and when it owns enough historical records on risks, it switches to quantitative risk analysis, as it is more precise and accurate.

The last step of this stage is to assign risk owners to risks, who will develop action plans for each high priority and medium priority risk. Risk owner assignments should be based on the level of knowledge and expertise needed for addressing the risk. The person should understand the underlying concerns and the types of activities that could reduce the impact or probability of occurrence. The second criterion is the person's level of engagement; whether they have a vested interest in the outcome of abating the risk. Given the cross-functional nature of drug development, it is understandable that some team members will have a higher interest in their particular part of the process. The interest level can be used to find the best match of risks and risk owners. By the end of this stage, the output should be a highly evolved list of risks that have been prioritized to highlight the most significant threats to the project for which action should be taken and that identifies the person that will develop the appropriate action based on the identified cause of the risk.

5.5 Risk Response Planning

In risk response planning, the team converts concerns into action. Starting with a fully developed risk analysis, this ends with a risk response plan that details the effort and resources necessary to ensure the achievement of the project's goals.

Each risk owner will create an effective action plan for their risk. The range of approaches that can be taken is fairly broad, but in general, will be aimed at achieving one or more of the following three basic objectives:

- Actions that reduce the probability of a risk occurrence are identified.
- Actions that mitigate the impact if risk should occur are identified.
- Contingency plans are developed to execute if the risk occurs.

There are a number of options for responding to risk, as shown in Table 5, which will be provided to the team. The effectiveness, and generally the investment in time and resources, increases from the bottom of the list to the top. Response 11 represents passive acceptance that sometimes is unavoidable.

Table 5 - Risk Response Strategies (Source: Lavallee, 2010)

Risk strategies	*Comments/examples*
1. Convert risk into opportunity	Per example by converting a side effect into a selling point
2. Avoid risk	Avoid sources of risk, for example by reformulating a drug or using lower doses of a drug
3. Modify project objectives to yield a better benefit/risk profile	This can be accomplished by for instance developing a drug indication where the risk-benefit tradeoffs are more appealing
4. Transfer risk to others	A straight forward example of this out-licensing to avoid financial risks (ex.: subcontracting, insurance)
5. Share risks with others	Co-development and co-promotion are two of the most commonly used risk-sharing strategies
6. Prevent risk	The most obvious way of preventing a risk is to take actions that minimize the probability of a risk materializing
7. Mitigate risks	This is done by taking actions that minimize the impact of risk before it occurs.
8. Develop contingency plans	Set aside resources to provide a reactive ability to cope with risks when they occur, clearly state the trigger
9. Keep options open	Delay choices and commitment based on predefined strategic options
10. Monitor risks	Collect and update about probabilities of occurrence, anticipated risk impacts.
11. Accept risk and do nothing about them	Accept risk exposure and do nothing about them. Some risks just cannot be managed.

In general, the action plans should be practical, executable within the allotted budget, personnel, time-constrained, and have a reasonable likelihood to achieve the expected risk mitigation. The team needs to understand that every action plan is made to be implemented. Developing an action plan is not an intellectual exercise. The risk owners need to understand that their plans must be practical and achievable. Each risk can be approached in several ways, if necessary, the plan can include both mitigation actions and contingency plans.

With the help of table 5, risk owners prepare their draft plans and present them on the first weekly meeting. The team reviews the action plans to ensure they are acceptable. Risk owners may default to an approach that is barely beyond risk acceptance by suggesting that the team monitor the risk and respond, if necessary. This might indicate that this risk owner either did not have the time to adequately consider an appropriate action plan or did not have the knowledge and experience necessary to develop a suitable set of mitigations and contingencies. Another short-coming that can be found in action plans is a tendency to provide tentative or uncertain responses. A tentative risk response would be to consider increasing funding for site advertising if there is a slow enrollment. The plan should be specific, and implementing the plan should yield results that will impact the risk. It may be necessary for the team, during the meeting, to revise and strengthen the action plans before implementing them. The project manager should be the final authority in approving the plan.

After action plans have been developed for all high and medium priority risks, a deadline for implementation in high priority risks should be established and the risk owner is the responsible person for assuring that the plan is in fact executed. All of this is registered in the Excel tool, on the response planning tab.

All risks should be monitored. High and medium priority risks are monitored by its risk owners and low priority risks are monitored by the project manager.

5.6 Risk Monitoring and Control

The larger goal of this methodology is to establish a long-term risk management process, and ultimately, a risk culture. A risk culture performs risk assessments and mitigation as part of the team's daily business, always considering the drivers of uncertainty. This stage addresses the establishment of the project risk management plan as a constant process and how to maintain the plan as a living document

The team members should review each assigned risk and check if the risk has changed regularly and let the rest of the team know of updates on the weekly meetings. The risk may have occurred and became a certainty or the trigger for the risk or opportunity may have passed and the risk is no longer worth consideration. A low probability risk that might not have warranted an action plan may now have risen to a high enough probability to justify action planning. In addition, risk owners should also review their action plans to determine if they are still relevant and sufficient and they should adjust them as necessary to ensure the response is optimized.

All changes, both in risks and action plans, should be documented on the Excel tool. Keeping track of changes and of efficient action plans will allow better and more oriented management of risks in future projects. The Excel file created is prepared to receive updates weekly.

After a certain period of time elapsed after the complete implementation of the methodology in all projects, the checklist will be complete, including all repetitive project risks, and it will be possible to qualify probabilities of occurrence and impacts more accurately by checking historical records. Risk owners will have less work to do, because the efficient action plans for each risk and their results will already be known. Risk owners will only have to assure that the plans are implemented and to monitor risks and changes. The goal is that, in the future, risk management will not take as much time and effort as in the beginning.

Once the project reaches its close-out phase, a full review of the risk templates should be done. In the end, all data should be gathered in a risk record sheet.

Chapter 6: Case Study Implementation

The purpose of chapter 6 is to describe the process of implementation of the risk management methodology developed, in two of Hovione's DPD projects, Project 1 and Project 2 (sections 6.1 and 6.2). These projects were followed up close and each of the risk management stages are described step by step, in four stages: Risk Identification and Analysis (6.1.1 and 6.2.1), Risk Response Planning (6.1.2 and 6.2.2), Monitoring and Control (6.1.3 and 6.2.3) and Results Analysis (6.1.4 and 6.2.4). In the end of the chapter, on section 6.3 the overall results and conclusions of both the implementations are explained.

6.1 Project 1

The first project in which the methodology was tested, was called Project 1. The client was a pharmaceutical corporation that develops and produces medicines for a wide range of medical disciplines. The drug being developed is currently undergoing Phase III clinical trials. This drug is obtained by isolation from a solution with solids load through a key unit process. The remaining feed solution is composed of water. The project's objective was to dilute the feed solution, if necessary, in a lower concentration of API in order to expand the process flexibility to obtain a high process yield and material within specifications and later sent to the client to be formulated.

The overall scope of work includes three stages:

- **Stage 1 –Trials at a lower concentration of API**

  Stage 1 was the performing of three key unit processes trials with different concentrations of API in solution to gather more experimental data at these feed solution conditions. Each trial run for 3 hours to ensure the powder properties are stable. These were short trials.

- **Stage 2 – Long run to evaluate process variability**

  Trial 4 was a long-run targeting a concentrated feed solution that was further diluted and dried.

  Stage 3 – Production of a Good Manufacturing Practices (GMP) batch

  The success criteria proposed by the client were achieved and Hovione moved to the final stage which was to produce the drug and send it to the client to be used in clinical trials.

Hovione's core team for this project was composed of the project manager, a DPD lead scientist, two lead analytical chemists, a lead QA development, two lead manufacturing engineers, a representative from order processing and shipment, a logistics representative and an account manager (a total of 10 team members, all from Hovione). The project execution phase was planned to last 26 days.

To produce this drug, Hovione needed to buy the methanol solution, the containers to ship the product back to the client, the WFI and also a pipe to use in the process. These were all bought to external suppliers.

6.1.1 Risk Identification and Analysis

As explained in the previous chapter, a lot of the risk management activities (risk briefing, risk identification, identification of causes, analysis and assignment of risk owners) were planned to happen during the internal kick-off meeting. The project manager convoked all the team members to an 1 hour 35-minute kick-off meeting, and sent the agenda of the meeting, including in it, that the last 45 minutes of the meeting were to be dedicated to risk management. Five of the ten team members attended this meeting.

As part of the risk management planning phase, a risk briefing was to be performed. However, due to the fast pace and over-allocation of team members, it was not possible to conduct this briefing. It would occupy too much time of the kick-off meeting, and there would be no time to discuss all topics planned for the meeting. Instead, it was decided that the risk activities would be explained, one at a time, as they were to be conducted. In the kick-off meeting, the project manager explained briefly why this exercise was being conducted and what the expected benefits were. The team seemed to agree that risk management was, in fact, a need at Hovione and that it should be performed.

Before the meeting, the project manager emailed the risk checklist to the team members so that they could bring it filled. Only one member did it. Fortunately, the project manager already expected this to happen and printed checklists to be distributed to the team members so that they could take a look at it during the meeting and identify the risks individually before starting the collective exercise. Five minutes were given to do this.

Next, the team proceeded to consolidating the identified risks in one checklist only, projected by the project manager on the screen and filled *in loco,* and visible to everyone. Through observing the meeting and of the team behavior, some conclusions could be obtained. At first, the team was participating voluntarily and sharing opinions between them. They even gave ideas of new risks to add to the checklist, per example, risk 9.3 initially was *Losses of material or having to repeat process due to inexperience* was split in two separate risks: 9.9 *Losses of material* and 9.3 *Having to repeat process due to inexperience*. But after a while, the enthusiasm began to fade. The meeting's duration extended out of the schedule and most of the team members could not stay until the end of it, because they had other work to do. The team was impatient to leave the meeting, either because they were tired of the long duration of the meeting, or because they had other work to do and were in a hurry. It was not possible to finish risk analyzes, as planned. All risks were identified, however, only half were analyzed and no risk causes were identified in this stage. Still, it is worth remarking that, in the beginning, most of the team was participative and the team members agreed with each other in which risks existed and which not. In total, the team identified seventeen risks, and added two to the checklist. The identified risks are displayed on table 6. All identified risks were inserted on the Excel checklist and automatically sent to the risk analysis and response plan tabs.

Table 6 – Project 1 Risks identified on KoM (Source: Author)

ID	*Risk*	*Cause*
1.4	Client's expectations change during project	Objectives of client's team are misaligned between R&D and commercial areas
1.5	Client demands additional scope (not initially planned	Client does not trust Hovione and may order additional trials
2.2	Client's team communication points misaligned	Client's team miscommunication between members. Big team size
2.4	Client demands excessive communication	Client worries about API (which is expensive). Big pharma companies expect priority over other projects.
2.5	Client delays project	Client does not trust trial results
3.1	Client's expectations not met during visit	In previous visit client has seen more than what protocols allow and may expect the same treatment
6.1	Delays in previous operations cause domino effect and impact project	Not enough buffer in operations preceding project
6.2	Process issues	Powder properties out of expected range Utilities or automation issues
7.1	Delayed arrival of raw materials	Supplier delays. Need for approvals before ordering
7.10	Missing documentation on export materials	Miscommunication with client
9.1	Equipment not fit for purpose	Pipe for WFI wrongly designed Room not adequate for endotoxins control
9.3	Having to repeat process due to inexperience	Pipe for WFI not working – never used before
9.5	Equipment utilities failing	Mechanical fails can cause valve malfunctions
9.7	Wrong assemble of new installation/ revamp	Operators may assemble equipment wrongly or lose parts
10.1	Project attracts senior management's attention	Big pharma client
11.1	Misalignment of client's expectations/needs	Client changes strategy during project
13.3	Human Resources over allocated	Team involved in several simultaneous projects

The project manager decided that the risks not analyzed during kick-off would be analyzed in the first internal meeting, before the development of action plans.

After the internal kick-off meeting, a kick-off conference call with the client was conducted two days later. In order to also consider the client's opinion on existing risks, the project manager asked the client to identify project risks as well. From the client's answer, it was possible to conclude that the definition of project risk was not clear to the client's team, as the risks identified were all process risks and not project risks. This issue raised a question: should process risks that impact on the project's objectives be addresses in project risk management as well? Or be left to be dealt by FMEA Team? This issue will be discussed further in this chapter's conclusions.

The first internal meeting was scheduled and the first 30 minutes were dedicated to risk management. This time, risk management activities were done at the beginning of the meeting instead of in the end,

to assure that the team stayed focused and willing to participate. Six members of the core team attended, and they finished analyzing the risks, identifying its causes and defining risk owners.

It was clear from the one meeting to the other, that the team was much more willing and enthusiastic to proactively participate in risk management. The team members were not complaining about the duration of the meeting nor the risk management process, as they were before. Again, the team seemed to be very in agreement when defining probabilities, impacts, causes and action plans.

Table 7 shows the analysis made during the first internal meeting and the risk owners assigned for Project B's risks.

Table 7 – Project 1 Risk Analysis and risk owner assignment (Source: Author)

ID	*Probability*	*Impact*	*Priority*	*Risk Owner*
1.4	H	H		Project Manager
1.5	H	H		Project Manager
2.2	H	L		Project Manager
2.4	H	L		Project Manager
2.5	M	L		DPD Lead Scientist
3.1	M	M		Lead Manufacturing Engineer 1
6.1	VH	VH		Project Manager
6.2	L	H		Lead Manufacturing Engineer 2
7.1	H	H		Assistant Buyer
7.10	L	L		Project Manager
9.1	L	VH		DPD Lead Scientist
9.3	M	H		DPD Lead Scientist
9.5	M	H		DPD Lead Scientist
9.7	M	M		DPD Lead Scientist
10.1	L	L		Project Manager
11.1	L	L		Project Manager
13.3	VH	L		Project Manager

On the column "Priority", the color red is for high priority risks, yellow for medium priority and green for low priority. These colors represent the three regions of the probability vs impact matrix presented in the previous chapter. During the meeting, the information of table 7 was registered on the excel sheet for risk analysis. The priority column of this excel table fills itself automatically according to the probability and impact combination that is chosen.

6.1.2 Risk Response Planning

After completing the risk analysis and assigning the risk owners, the team proceeded to develop the action plans for each risk. As risk owners were only assigned in the first internal meeting, the same meeting where action were to be presented, no team member prepared anything to present. Instead,

the project manager planned to develop these action plans in group, with the entire team during the meeting, taking into consideration everyone's attention.

Before preparing the action plans, the team was given the response plan table (table 5, chapter 5) to read, however, it did not seem very helpful. The project manager gave some suggestions for action plans, which helped guide the meeting, and after that, ideas and opinions started flowing. The team members gave their input on risks from their areas and were in agreement with each other.

After defining action plans for all the identified risks, the team identified a secondary risk that could accrue from the implementation of one of the action plans. This secondary risk was *14.1 Hovione's team unable to follow the communication plan,* accrued from the action plan of risk *2.4 Client demands excessive communication,* and the team established that its probability was very high, and its impact medium.

Table 8 shows the action plans defined during the first weekly internal meeting of Project 1:

Table 8 – Project 1 Risk Response Plan (Source: Author)

ID	*Priority*	*Strategy*	*Action Plan*
1.4		Mitigate	Validate success criteria with both client's teams
1.5		Mitigate	Agree with client on maximum number of trials
2.2		Mitigate	Define communication point
2.4		Mitigate	Define communication plan and agree it with client
2.5		Monitor	Monitor
3.1		Mitigate	Define visit's plan and agree it with client
6.1		Monitor	Monitor and warn client if trigger occurs
6.2		Monitor	Monitor
7.1		Mitigate	Ask client if they want to pay for urgent shipment
7.10		Monitor	Monitor
9.1		Mitigate	Test pipe
9.3		Accept	Accept (and try to install sensor on equipment for future projects)
9.5		Accept	Accept
9.7		Accept	Accept
10.1		Monitor	Monitor
11.1		Monitor	Monitor
13.3		Accept	Accept

Readers familiar with risk management may notice that none of the action plans developed includes creating reserves. Creating reserves is not a common practice at Hovione for two reasons: first, because most clients do not accept schedule reserves and second because people are so over-allocated that, if time reserves existed, they would, with no doubt, be used every time.

As explained in chapter 5, for red risks action plans was to be immediately implemented, but not for yellow risks. However, during these two meetings, the team realized that some of the action plans

developed for yellow risks were easy to implement, and did not require many resources. It was decided, that these action plans were to be implemented as well. Deadlines for these action plans were established and the team seemed committed into complying with them.

In the end of the risk management activities of the first weekly internal meeting, the team agreed on the deadlines form implementing the action plans.

6.1.3 Monitoring and Control

During the following weekly internal meetings, the team reserved a small amount of time per meeting to monitor and control the identified risks. In each meeting, the team was asked about the current status of each risk in terms of probability and impact. The status evolution was registered, and this allowed evaluating if the action plans implemented were effective or not. Four more risks emerged during the project lifecycle and the team was able to detect them. The total number of risks raised from seventeen to twenty-one. The alterations were registered in an excel follow-up table that allows registering changes week by week.

New risks were identified during this phase and some impacts occurred. The new risks that were identified during monitoring and control can be seen in table 9.

Table 9 - New risks identified in Project 1 (Source: Author)

ID	*Risk*	*Cause*
14.1	Team not able to keep up with communication plan	Secondary risk of 2.4
14.2	Not being able to agree on concentration range with the client	Process has not been tested out of a certain range. GC can be higher than expected
14.3	Concentration results below agreed range	Charging errors. Wrong concentration value
14.4	Concentration results above agreed range	Evaporation of solver. Wrong PLC value. Not enough water

Its analysis can be seen on table 10:

Table 10 – Project 1 New risks' analysis (Source: Author)

ID	*Probability*	*Impact*	*Priority*	*Risk Owner*
14.1	VH	M		Project Manager
14.2	H	H		Lead Manufacturing Engineer 2
14.3	M	VH		Lead Manufacturing Engineer 2
14.4	M	L		Lead Manufacturing Engineer 2

And the action plans on table 11:

Table 11 – Project 1 New risks' action plans (Source: Author)

ID	*Priority*	*Strategy*	*Action Plan*
14.1		Mitigate	Send results even if not complete
14.2		Mitigate	Reason with client
14.3		Accept	Accept
14.4		Contingency	Add water if it occurs

During the monitoring and control phase, an unexpected event occurred that impacted majorly on the project's timeline and it was not identified as a risk. The process used to clean the key unit equipment after the preparation of the long run had to be finished before a specific date in order to proceed to the production of the GMP batch in the equipment. This sanitization process was never done at Hovione before. It was expected to last 4 days and the team believed that this time estimate was accurate, thus not identifying delays in cleaning as a risk. The sanitization took longer than expected and the production of the GMP batch had to be rescheduled to start later. The project delayed 16 days due to this occurrence; however, this did not have much on the client, who was not upset by this delay. The risk 6.4 *Delays in cleaning processes* was added to the checklist, and a plan B schedule was given to the client.

One other risk impacted on the timelines. Risk *6.2 Process issues.* Although it had been identified as a risk for this project, the causes that truly triggered its occurrence were not, as they were very unlikely to occur. Again, this rises awareness to the subject of dealing with process issues within project management.

Besides these two, two other risks occurred but with no impact to the project. *Risk 13.3 Human Resources over allocated.* The fact that process issues occurred, forced some team members to work over hours to solve them. Plus, the risk *9.1 Equipment not fit for purpose*, which had also been identified, occurred with no impact. The pipe used in this project was never used before and the team was not sure if it would work, so as action plan, they tested it before the project and it worked, lowering the probability of occurrence of this risk. However, when the execution phase started, the containers under use were deeper than the ones tested, so the pipe could not reach its bottom. This issue was rapidly solved by substituting the containers for ones, that, by coincidence, Hovione already possessed. These new containers were not predicted in the contingency plan for risk 9.1.

In the end of this phase, a report table was constructed, comparing the initial and final states of each project. This report allowed developing several graphs that were useful for evaluating the effectiveness of the methodology and of the action plans. The conclusions and results taken from this report's analysis are explain in the next section.

6.1.4 Results' Analysis

Figure 19 shows the number of risks identified along the project, by priority level.

It can be seen that on Project 1, a total of twenty-one risks were identified along the entire duration of the project. 15 in the KOM and 2. Seven of them were considered high priority, ten were medium priority and four were of low priority.

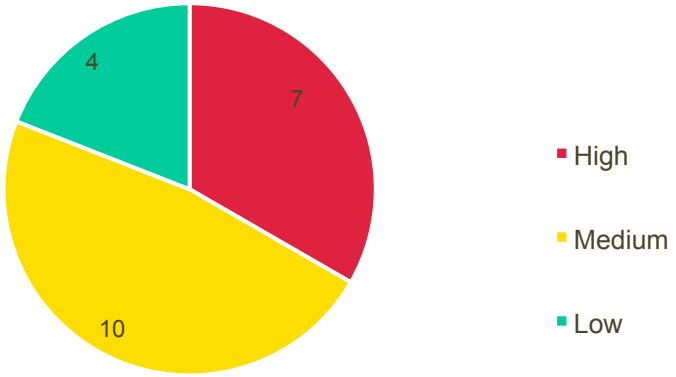


Figure 15 - Project 1's Risks by priority (Source: Author)

In chapter 5, it was established that action plans would only be immediately implemented in high priority risks, but soon the team realized that some of the action plans for yellow risks were quite simple to implement and did not require many resources, so they were implemented. The response plan types that were developed for high and medium priority risks are demonstrated in Figure 16 bellow:

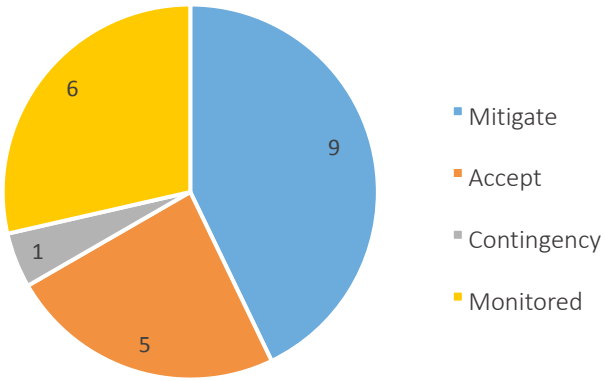


Figure 16- Project 1 Response Strategies (Source: Author)

During the implementation of risk management on Project 1 and the development of action plans it was possible to note that Lavallee's terminology is not always easy to comprehend and apply, especially when dealing with a group of people not experienced in risk terms. Per example, in Lavalle's terminology, shown in chapter 5, response strategies such as *Avoid, Mitigate* and *Prevent* are not always easy to distinguish or explain.

For this reason, a different terminology was used, mixing Lavalle (2010) and the *PMBOK Guide* (2017) was used:

- **Transference –** Shifting the impact of a threat to a third party, together with ownership of the response.
- **Avoidance –** Acting to eliminate threat or impact on the project.
- **Mitigation –** Acting to reduce the probability of occurrence or impact of risk.
- **Contingency –** Set aside resources to provide a reactive ability to cope with risks when they occur, clearly state the trigger.
- **Monitoring -** Collect and update about probabilities of occurrence, anticipated risk impacts.
- **Acceptance -** Accept risk exposure and do nothing about them. Some risks just cannot be managed.

Figure 17 shows the results of applying the action plans on risks.

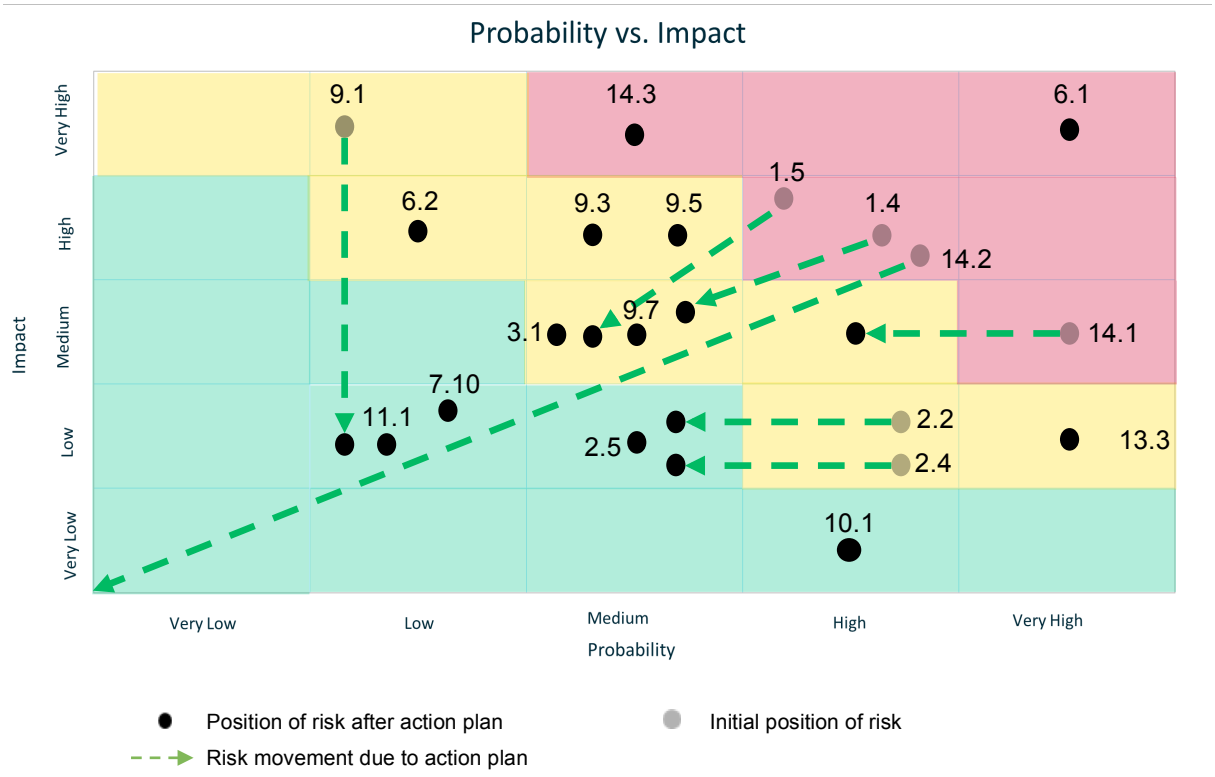
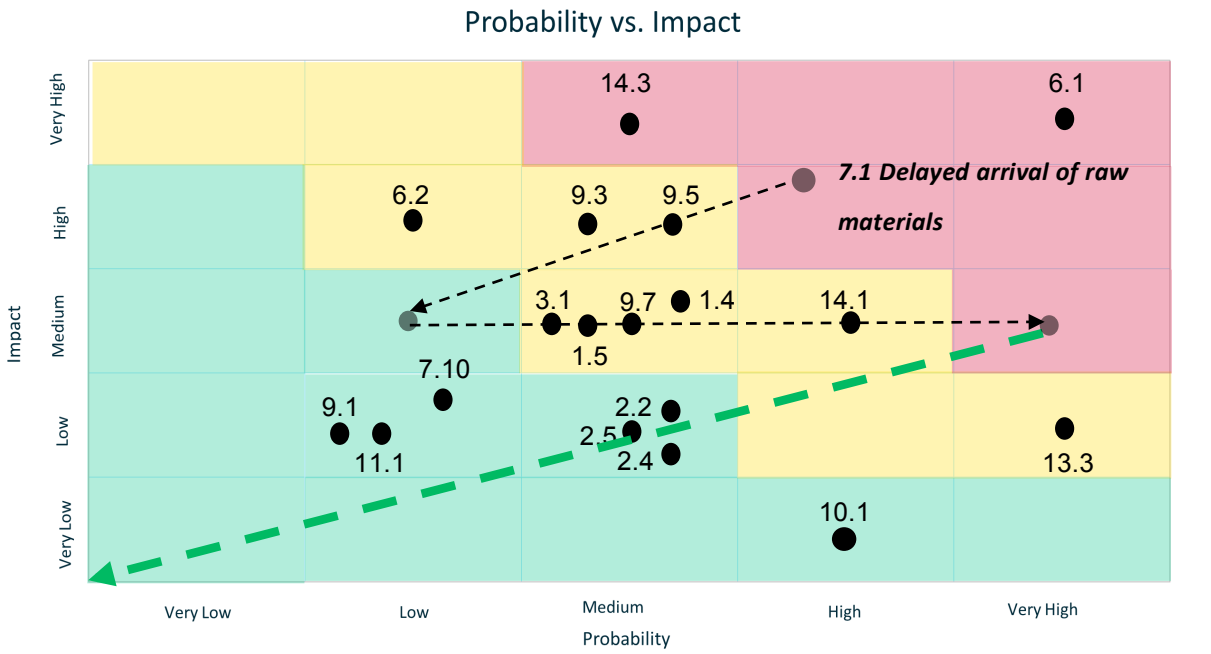


Figure 17 - Project 1 Results of Action Plans (Source: Author)

Figure 18 only shows twenty risks instead of twenty one risks. Risk 7.1 changed more than one time and is shown in separate further ahead, so that the matrix remains perceptible.



Note that, even though inside some cells of the matrix there are several scattered risks, they all have

Figure 18 - Risk 7.1 evolution (Source: Author)

the probability and impact. They were separated for purposes of clear interpretation of the graph, by avoiding overlapping points.

The green arrows in Figures 17 and 18, demonstrate the changes of risks' probabilities and impacts due to the effect of the action plans applied. In Figure 17, seven risks have green arrows. This means that from the nine mitigation plans implemented, seven were able to reduce either the risk probability or potential impact and one solved it. Besides these changes in the status of risks, the status of the risk *7.1 Delayed arrival of raw materials* also changed, but not due to an action plan. Its probability decreased just due to the natural development of the project. As more raw materials arrived, lower was the probability of any of them arriving late and once the supplier informed of a likely delay the probability increased. That was when a contingency plan was defined that would completely eliminate the impact of the risk, so the team considered the risk solved. In Figure 18 it is possible to see the movement of the risks 7.1 within the matrix.

During the execution phase, three risks impacted. These can be seen in Figure 19.

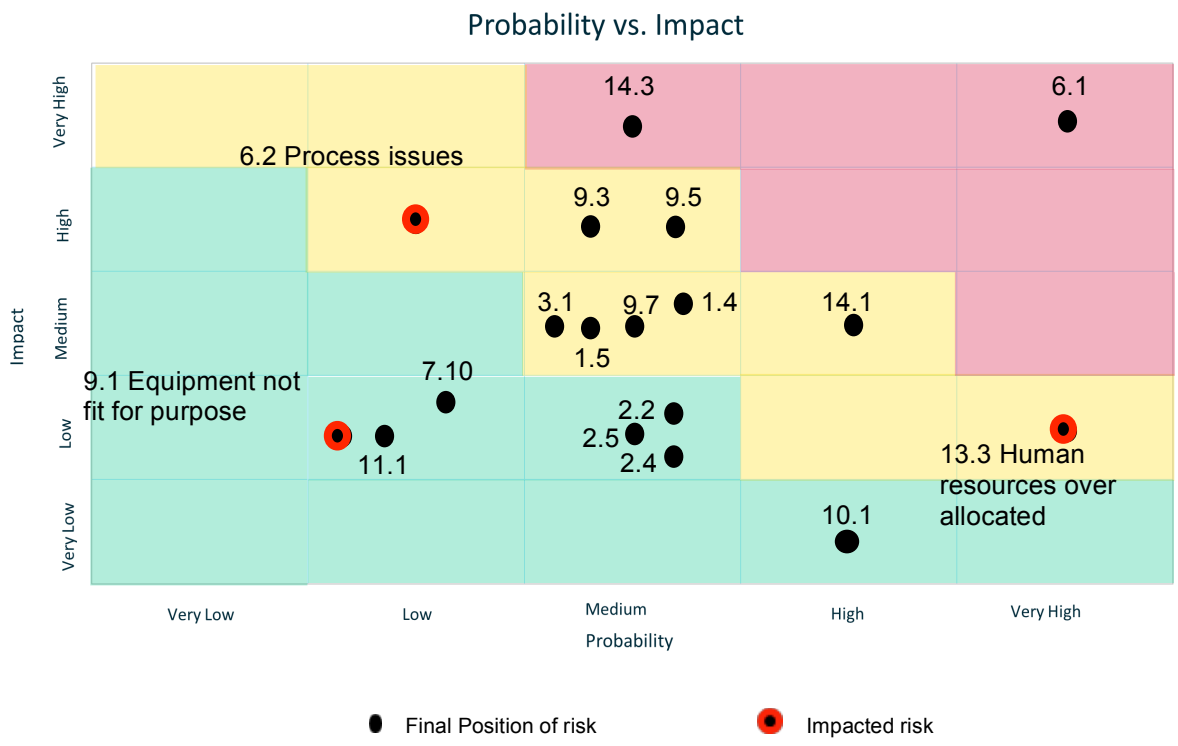


Figure 19 - Project 1 Impacted Risks (Source: Author)

Risk 6.2 was identified as a potential risk and it was being monitored, but the cause that made the risk impact was not the one that had been identified, so it was not detected, so it delayed the project. The real cause for this risk was very unlikely to occur. Risk 9.1 impacted because, the pipe that was used in the process did not work as expected, although it had been tested. This risk had no impact on the project's objectives because the container, which was incompatible with the pipe, was switched for a different one. The impact of risk 6.2 made the team have to work extra hours on Project 1, cause the impact of risk 13.3, which also did not have impact on the project's objectives.

Figure 20 shows the different types of risk closures that occurred in Project 1.

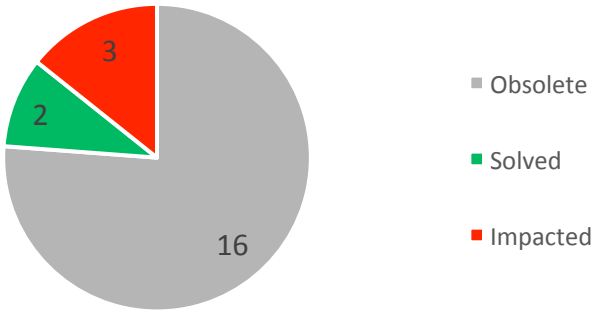


Figure 20 - Project 1 Risk Closures (Source: Author)

Two risks were solved by action plans, three impacted, and the remaining 16 closed by obsoleteness.

From the observation of the team member's behaviors and the meetings in which risks were addressed, it was possible to conclude that some changes in the methodology could improve its effectiveness.

From the beginning of Project 1, it was possible to observe that the project team was over-allocated. This was in fact, expected and it was identified as a potential risk in this project (and it impacted). The fact that this happens more often than it does not can also impact on the efficiency of the risk management methodology. Since there is not much it can be done to solve this issue, at least at a project management level, some adaptations to the methodology should be made in order to accommodate these inconveniences.

First, risk identification and analysis need to be done in a separate risk meeting. It was possible to conclude that the time added to the kick-off meeting was not sufficient to perform all the planned risk activities. By the time the risk management started (after 1h of meeting), the team was already impatient and in a hurry to leave the meeting, because they had other work to do. It seems that scheduling a risk meeting for this purpose only would be more efficient. The fact that, in the first internal meeting, risk analysis was performed at the beginning, and at the team was much more engaged and participative supports the motives for this alteration to the methodology.

Second, during the first conference call, the client was not able to identify any project risks, only process risks. Process risks are the ones that impact on the process or the quality of the product. At Hovione, there is already a specialized team that deals with these risks in validation projects. They perform FMEAS to cover process risks. This raised a question within the team: should process risks with possible impacts on the projects' objectives, be handled by project teams as well as by FMEA Team? After consideration and discussion with some of the project managers, it was decided that, as some process risks also fit the definition of project risk, they should be considered by both FMEA and project teams, and the client should see the risks (filtered) the team identified before being asked to identify new ones. Showing the identified risks should give the client an idea of what project risks are.

As for action plans, the project team should decide on a new action plans to act on the risks in a different way that what was defined within the FMEA exercise, focusing on the project objectives.

Because the analysis method of the methodology is very democratic, there was a risk that the team would enter in conflict when qualifying probabilities and impacts. This was not observed. The team member's opinions were very much in line and almost all decisions were consensual, both in the analysis and in the response planning phases. This is probably due to the fact that the teams are experienced, and the risks are repetitive from project to project, and team members are already used to dealing with them, even if not in a formal way. Since no issue was encountered, the risk analysis method will be maintained for further observation in the second pilot project.

As mentioned before, the risk matrix was subject to alterations. Nevertheless, there seems to be no need for that. The project manager and the teams agree with the color code of the risks.

Third alteration is related to action plans: It was initially defined that for red risks they would be immediately implemented and for yellow risks they would be developed but not implemented unless the risk aggravated. During that project response planning phase, it was possible to see that some of

the action plans developed for yellow risks were quite easy to implement and would decrease the risk's severity. For the next pilot project, the suggestion is that action plans for yellow risks are implemented whenever possible if they are easy and do not consume many resources.

Also considering the response planning phase, for Project 1, the team members only developed the action plans on the risk meeting and it worked out well. For the next project, the same approach will be tested. Instead of risk owners developing an action plan individually and presenting it to the team, as it was originally though, all team members will contribute with ideas for action plans of each risk. Of course, the opinion of the team members that work on areas more related to a risk, will be valued more. It is very likely that project team members would not develop the action plans individually prior the meeting, and this alteration will solve this issue.

In sum, the alterations made in the methodology from one project to the other are described in Table 12:

Table 12 - Alterations to the methodology after Project 1 (Source: Author)

Initial Version	*Observations of Project 1*	*Alterations*
Risk Identification done in the Kickoff meeting	The time destined to risk management during the Kickoff meeting was not enough for risk identification	1. Risk Identification done in a separate risk meeting
Ask client to identify project risks	Client could only identify process risks	2. Show client the risks identified and manage process risks that are a threat to the projects objectives
Monitor medium priority risks	Some medium priority risks could be easily be solved/prevented by applying minimal resources	3.Apply action plans to medium priority risks, if they don't require too many resources
Risk owners develop action plans individually	Develop action plans in group was efficient	4. Develop action plans in group, on the first weekly meeting

6.2 Project 2

The second project in which the methodology was tested, was Project 2. The API being developed is a candidate API is currently undergoing Phase III clinical trials. The project objective is to a mixture of API and a polymer dissolved in a solvent. This implies a key unit process and post-drying. The objective of the project is to produce a cGMP batch of the mixture.

Hovione's core team for this project is composed of the project manager, an account manager, a DPD scientist, an Analytical Chemistry Development (ACD) chemist, Pharmaceutical Operations

(PharmOps) Process Engineer and a QA responsible. The project execution phase is expected to last 13 days.

To produce this product, Hovione needed three different raw materials: the API, which was already on site, but needed testing before being approved; a polymer and a solvent, which were both bought to external suppliers.

As it can be seen, Project 2 involves a lot less activities in its execution phase when compared to Project 1. A lower number of risks was expected.

Due to the need to obey Hovione's deadlines for the risk management implementation, this project was assigned last minute as the second pilot project and while it was already under initiation phase. No other project would allow respecting the defined timelines.

6.2.1 Risk Identification and Analysis

As described in Project 1's conclusion, in this second project, risk identification and analysis were performed in a separate meeting that took place after the kick-off. Before the meeting, the project manager emailed the check-list to the team members and scheduled a 50-minute risk meeting. The project manager of Project 2 also opted for printing the checklist and bring it to the meeting to be distributed. This was done for the same reasons that it was done in Project 1. The project manager did not believe the team would look at it before the meeting.

To this risk meeting, four of the seven core team members attended. As before, none of the team members had seen the checklist, so the project manager gave them time to do so. After this, the risks were consolidated in one checklist only, as planned. The risks that team members identified individually were different from each other, however, as each person read their risks out loud, others agreed, even if they had not marked them on their own checklists at first.

Then, the team proceeded to qualifying probabilities and impacts. Although they were not always in agreement, team members in disagreement often settled with the majority's opinion. The team identified the causes of risks, which for some, was not an easy task. Per example, the causes of risks related to the client's behaviors are not always clear. The meeting duration was enough to conduct all planned activities and the team participated proactively.

Six risks were identified. This may seem too few compared with the previous project. The difference may come from the fact that Project 1's client was a big pharma company, and the production process was much more complex. Projects from big pharma clients have many risks associated that projects from smaller companies do not.

During the entire project, eight risks were identified. As expected, the number of risks identified on Project 2 was much lower than on Project 1. Table 13 shows the risks identified on the risk meeting and their causes.

Table 13 – Project 2 Risks and Causes (Source: Author)

ID	*Risk*	*Cause*
1.5	Client demands additional scope (not initially planned	Client might be worried about new requirements from regulatory authorities concerning benzene
3.1	Client's expectations not met during visit	Production delays may mean that during visit there will be no production for the client to see
6.1	Delays in previous operations cause domino effect and impact project	Not enough buffer in operations preceding project
6.4	Lack of documentation delays schedule	Documents needed to start production need to be approved by both Hovione and client staff. On holiday season there may be no one to do this on time
7.1	Delayed arrival of raw materials	Supplier informed that polymer may not arrive on time
7.11	Issues with raw material approval	API has not been approved because it is Out Of Specification (OOS) and might not be approved in time. Testing will be repeated but may fail again. OOS results are more likely to be due to the testing process than due to API quality
9.1	Equipment not fit for purpose	The pump has never been used before for this drug, it might not work
13.3	Human Resources over allocated	Team involved in several simultaneous projects

Risks 6.4 and 7.1 were not in the checklist and were added to it by the team during this meeting.

Table 14 shows the results of the risk analyses performed on this risk meeting.

Table 14 - Project 2 Risk Analysis (Source: Author)

ID	*Probability*	*Impact*	*Priority*	*Risk Owner*
1.5	H	VL		Account Manager
3.1	M	M		Project Manager
6.1	L	H		Project Manager
6.4	L	H		Quality Assurance Responsible
7.1	VH	M		Purchasing (Non-core team)
9.1	L	L		PharmOps Process Engineer
13.3	VH	L		Project Manager
14.1	VH	H		Quality Assurance Responsible

The team members participated proactively in risk identification and analysis, and did not complain about the process duration as the team of Project 1. However, this may also be related to the fact that the process was shorter, as a lot less risks were identified and analyzed.

Unfortunately, it was not possible to test if sending the analysis table to the client would conduct them into identified project risks because, when the risk management started in Project 2, the kick-off meeting with the client had already taken place.

6.2.2 Risk Response Planning

Risk response plans were scheduled to be developed during the second weekly internal meeting (the first weekly meeting had already taken place before the project was assigned as pilot). From one meeting to another, the project manager sent the risk response strategy table to the team members so that they could prepare themselves for the development of action plans. Besides sending the table, the project manager also printed it to be used during the meeting if necessary.

Risk response planning was conducted in the last 20 minutes of the meeting. It was not conducted on the beginning because the other topics to be discussed were very few and the project manager was confident that the discussion of them would be very fast and that the team would still be willing to develop the risk action plans after.

The team was asked to develop risk response plans for each risk. In the beginning, they seemed to have some difficulties in doing so. It seemed that the team needed some guidance from the project manager. In order to help the brainstorming procedure to flow, some questions were made to the team: "What can we do to stop this risk from occurring?", "What can we do to lower the impact delay on schedule/client relationship, in case this risk occurs?" or "How can we detect if this risk is about to occur", etc. Through these questions, the team was able to initiate the discussion and for the last risks, there was no need to ask any more questions. This showed that the team members were not, in fact, used to risk language and were not familiar with the existing risk response strategies. Each team member had the risk response table with them, as it was distributed during the meeting, however, it was of no use. Table 15 shows the action plans developed by the team for each risk.

Table 15 - Action Plans of Project 2 (Source: Author)

ID	*Priority*	*Strategy*	*Action Plan*
1.5		Monitor	Monitor
3.1		Mitigate + Monitor	Define visit's plan and monitor delays
6.1		Monitor + Contingency	Monitor and warn client if trigger occurs
6.4		Contingency	Find another QA to review documentation if necessary
7.1		Mitigate	Order urgent shipment and inform client of possible delay
9.1		Monitor	Monitor
13.3		Accept	Accept
14.1		Contingency	If API is OOS again, ship under quarantine to buy time to solve the issue

Deadlines were established and risk owners assumed the responsibility of guaranteeing the implementation of their action plans and of monitoring their risks.

Again, the team participated proactively and enthusiastically.

6.2.3 Monitoring and Control

During the following weeks, several events happened. The first one was the impacting of risk *14.1 Issues with raw material approval* due OOS results. As it can be seen on Table 13, the team suspected that the problem was analytical and not from the API. The action plan that they developed was based on this assumption, but, when the OOS results came out, there was no proof that the problem was in fact from the testing method. Shipping the API under quarantine was only a possible action plan if the team was sure about the origin of the issue being analytical. For this reason, it was not possible to implement the action plan developed. This led to a delay of the project of 15 days because the requirements to start production had not been yet met. Another project went through on the equipment, as Project 2 was not ready to start.

The fact that the project delayed, reduced the probability of other risks that were related to schedule. Table 16 shows the risk status at this point of the project cycle.

Table 16 - Project 2 First Monitoring and Control (Source: Author)

ID	*Probability*	*Impact*	*Priority*
1.5	H	VL	
3.1	VH	M	
6.1	L	H	
6.4			Obsolete
7.1	L	M	
9.1	L	L	
13.3	H	M	
14.1	VH	H	

Risk *6.4 Lack of documentation delays schedule* became obsolete because it was related to holiday season. The 15-day delay meant that the approval of the documentation to start production would not be done during holiday anymore. Risk *14.1 Issues with raw material approval* remained active, as the API quality requirements had not been proven yet. Its probability of delaying the project (again) decreased because, at this point, the team had 15 more days to find the issue and solve it. The probability of occurrence of risk *3.1 Clients expectations not met during visit* increased to *Very High* because, on the dates the client informed they would be visiting, there would be no production because of the delay. The team warned the client and they cancel their flights

The week after the occurrence of the risk that delayed the project, other two risks impacted. *6.1. Delays in previous operations cause domino effect and impact project*, and *7.4 No response to Request for Proposal (RFP),* which had not been identified. Due to holiday season, the supplier of the polymer only saw the request for urgent shipment too late, which meant that this raw material got to the factory later than it was supposed to. This had no impact on the project because of the previously mentioned domino effect delay, delayed Project 2 10 days, which meat the polymer would get to Hovione in time of the new production start date. The probability of occurrence of risk *7.1 Delayed arrival of raw materials* remained the same because of these simultaneous occurrences. The client was warned about this delay and scheduled new flights considering the new schedule. Besides this, the team decided to increase the probability of risk *9.1 Equipment not fit for purpose,* as the pump did not work in another project. In the meantime, the team considered that risk *1.5 Client demands additional scope* became obsolete. Also, the probability of occurrence of risk *14.1 Issues with raw material approval decreased,* because the 10-day delay meant more time to get the approval of the API.

Table 17 shows the status of each risk at this point.

Table 17 - Project 2 Second Monitoring and Control (Source: Author)

ID	*Probability*	*Impact*	*Priority*
1.5	H	VL	Obsolete
3.1	L	M	
6.1	L	H	Impacted
6.4			Obsolete
7.1	L	M	
9.1	M	M	
13.3	H	M	
14.1	L	H	

The team developed a new response plan for risk *9.1 Equipment not fit for purpose* which was: Choose alternative equipment to use if pump fails. This was done and the impact of occurrence of the risk decreased to *Very Low.*

As the API got approved, the raw materials had arrived and the key unit equipment was free to be used, production started the team and other two issues occurred. First, the pump did not work, and it was evaluated that the other pump would not work either. This meant repeating the process without any pump which meant a one day and a half delay. Also, due to a failure, the pressure conditions of one of the rooms that was needed for the process were not within the required range. This could have been identified as risk *9.5 Equipment utilities failing*. It was not identified because none of the team members had ever seen it happen, so they did not consider its probability.

6.2.4 Results' Analysis

During the entire project life cycle, eight risks were identified, six in the identification stage and 2 in the following meetings. Their initial priorities are demonstrated in Figure 21.

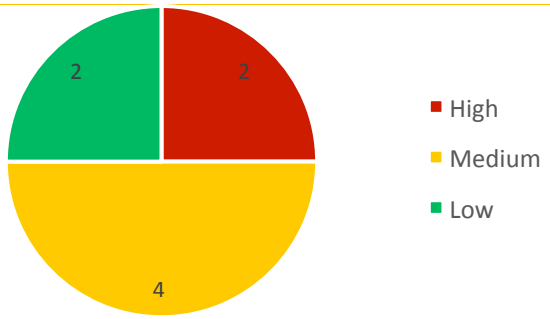


Figure 21- Project 2 Risks by priority (Source: Author)

The types of risk response strategies applied to yellow and red risks can be seen on Figure 22. Low priority risks were only monitored.

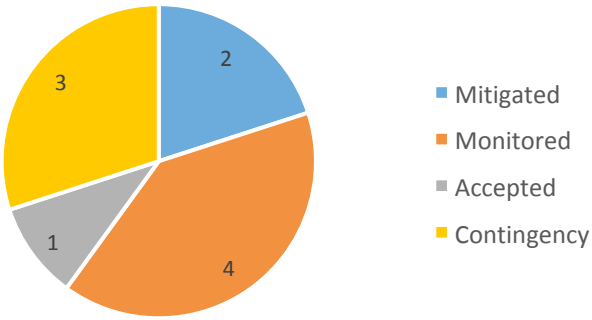


Figure 22 - Project 2 Response Strategies (Source: Author)

The graph shows ten response strategies instead of 8 (which is the number of risks) because for two of the identified risks, two response plans were defined, as it can be seen in Table 15.

From these response strategies, one of the mitigation plans did not work as the risk occurred with the same impact as without it, and the other was developed but not implemented because the risk became obsolete before the implementation deadline and the other was efficient. For the risk *3.1 Client's expectation not met during visit,* the plan was to agree on the visits plan and it decreased the probability of the risk occurring. After the action plan was implemented, the risk was monitored. This monitoring was also efficient, as delays were detected and it was possible to warn the client on time.

Both of the monitored risks impacted and both were detected in advance, meaning, the monitoring plans were efficient. Besides the response strategies represented on Figure 27, one of the low priority risks that was under monitoring aggravated, the team detected its aggravation and developed a different action plan for it. The action plan lowered the probability of the risk occurring but it ended up impacting anyway. The monitoring of this risk was efficient, as changes in its status were detected.

Figure 23 demonstrates the evolution of the risk status of the risks identified for Project 2, due to the action plans implemented.

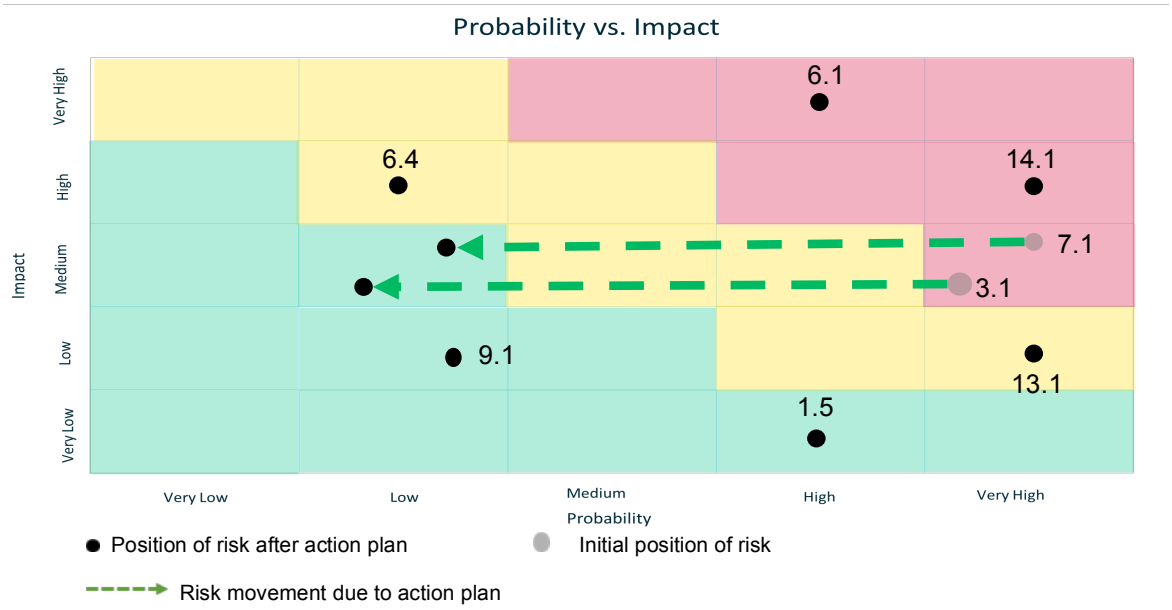


Figure 23 - Project 2 evolution (Source: Author)

Besides the risks seen moving in Figure 23, other risks also moved within the matrix due to the developing of the project, as it can be seen in Figure 24.

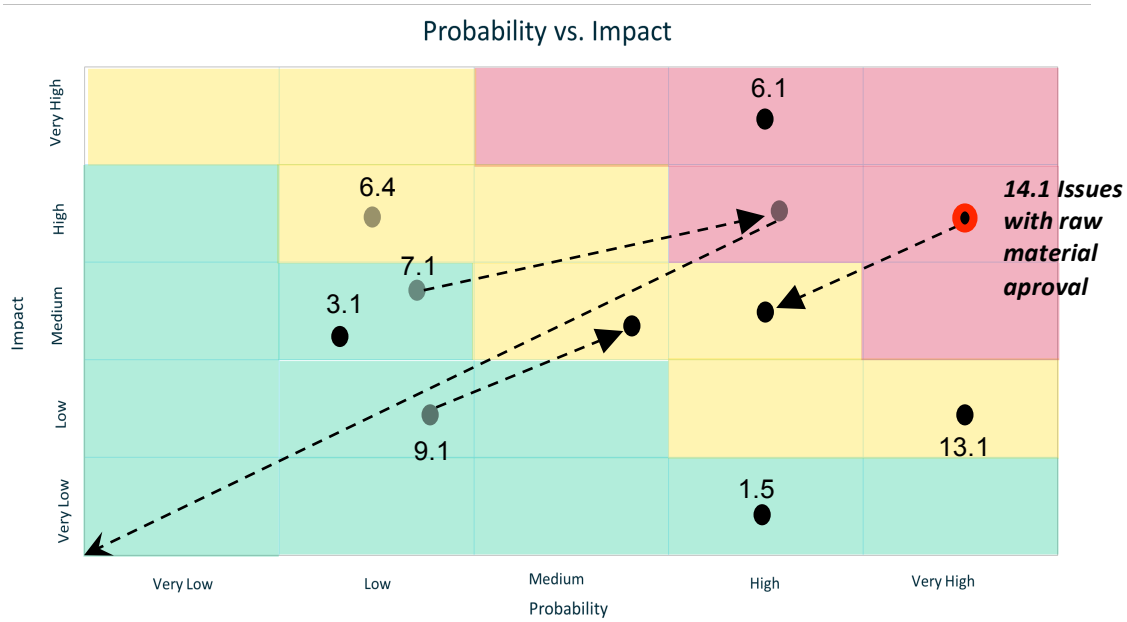


Figure 24 - Project 2 second evolution (Source: Author)

During the entire projects, three risks impacted, as it can be seen in Figure 25:

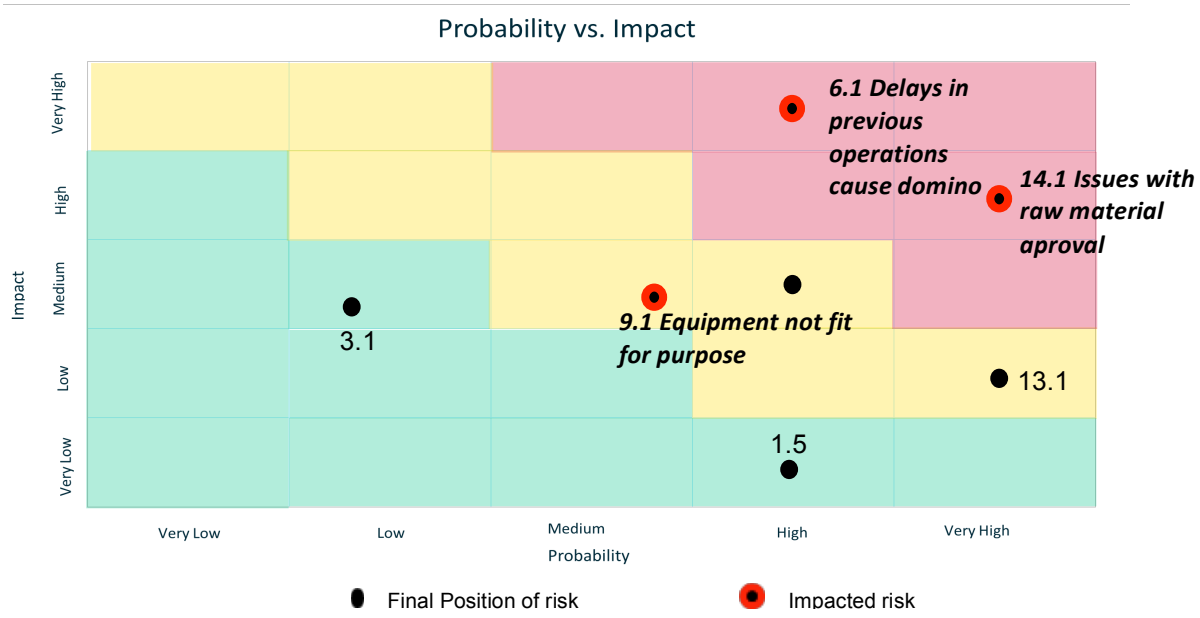


Figure 25 - Project 2 Imacted Risks (Source: Author)

As it can be seen from Figure 26, three risks impacted. *Risk 6.1 Delays in previous operations cause domino effect and impact project, risk 9.1 Equipment no fit for purpose* and *14.1 Issues with raw material approval.* A mitigation plan was developed for risks 9.1 and 14.1. For risk 9.1, the team thought the action plan had been efficient in decreasing the impact of occurrence but it was not and for risk 14.1 the mitigation could not be implemented when it was necessary. Risk 6.1 was being monitored and its occurrence was detected in time, avoiding a bigger impact. Plus, one other risk would occur due to the impact of the other risks on the schedule of the project, but it did not because this risk was being monitored and it was detected in time to avoid its occurrence. Risk *3.1 Client's expectations not met during visit* was at first, mitigated efficiently by the agreement with the client on the visits plan, after this it was monitored. When the trigger for its occurrence was detected, the client was warned in time to change their flights dates.

After the closure of Project 2 it was possible to consolidate all conclusions regarding the risk management methodology from both pilot project. The closures of Project 2's risks can be seen in Figure 26 bellow.

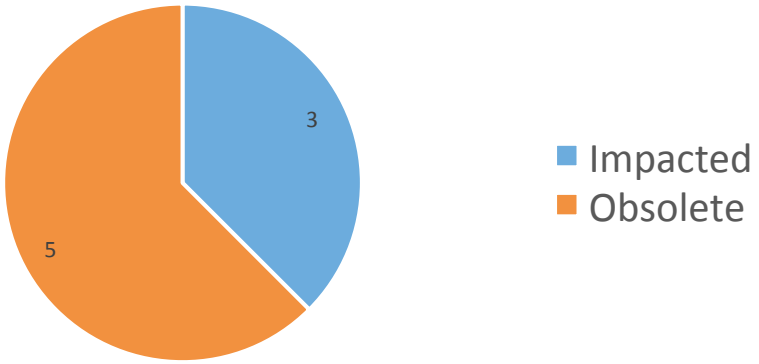


Figure 26 - Project 2 Risk Closures (Source: Author)

In both projects it was not possible to perform the risk briefing to the team, but still, this step is important and should be part of risk management as long as there is still team members who never participated on projects with this risk management methodology. A risk briefing will make other risk activities faster and more efficient.

As for the risk meeting, in Project 1, it was much more effective, as it was possible to conclude all planned activities on time, without the team having to leave. Scheduling a separate risk meeting is more effective, as the team was more engaged and willing to participate. Still, the project manager should have the risk identification and analysis documents ready on kick-off meetings, in case all other topics are discussed earlier than expected. In that case, the project manager should at least start risk identification and analysis making use of the team member's free time. Hovione works at a very fast pace and it would make no sense to waste the kick-off meeting time if team members already expected to have it occupied with the project.

It has been noticed in both projects that team members do not perform individual risk identification prior to the first meeting as they are asked to by the project manager. It seems that project managers can expect this to happen in most of their projects, so it will be more efficient to reserve five minutes of the meeting, for the team to look at the checklists.

Besides this, the risk response table seems to be of no use. Even if the table is given to the team members during the meeting, they do not read it when considering response plans and those who do read it, don't seem to retain the information in it. Instead, it might be more effective if the project manager guides the team members into developing the action plans. During Project 2, it was observed that through asking certain questions, team members switched from being confused on was expected from them, into actually starting a discussion on which action plans would work better for each risk. For this reason, the following questions should be used to guide the team into developing the action plans:

1. Is there a way to transform this risk into an opportunity?
2. Is there a way to avoid the source of this risk?
3. Can we modify the project objectives to yield this risk?
4. Is there a way to share this risk with the client/supplier?

5. Is there anything that can be done to decrease the probability of occurrence of this risk?
6. Is there anything that can be done to decrease the impact of this risk in case it occurs?
7. If the risk occurs, is there anything that can be done after to decrease its impact?
8. Can we detect if this risk is about to happen?

These questions should be asked by the project manager in this order until the team answers “yes” to one of them. The idea is that when there’s a “yes” answer, the plan is developed to achieve the result they considered possible when answering.

In sum, the alterations made in the methodology after Project 2 are explained in Table 18:

Table 18 - Alterations to the methodology after Project 2 (Source: Author)

Initial Version	*Observations of Project 2*	*Alterations*
Risk Identification and analysis done in a Risk Meeting	There is time to conduct risk identification and analysis in some Kick-off Meetings	1. Risk Identification done during Kickoff meeting if there is enough time, if not, it should be done, or continued, in a Risk Meeting
Send checklist to team members by e-mail	No one fills the checklist before the meeting	2. Print the checklist and bring it to the meeting to be filled
Use Risk Response table (Table 5, Chapter 5) to guide response planning	Risk response table is of no use and team members have difficulties developing action plans	3. Ask 9 pre-defined questions to guide response planning

6.3 Survey Results

In the end of both projects, a questionnaire with questions regarding the efficiency of the methodology was sent to the core team members from both Project 1and Project 2. Eight team members answered the survey, and it was possible to construct the graph shown in Figure 27, that demonstrates the average answer to each question and the range of answers. The participants were asked to choose a level of agreement from 1 to 5. 1 being *strongly disagree* and 5 *strongly agree*.

Figure 27 - Survey Results (Source: Author)

The answers given by the teams' members show that, in general, they agree that the methodology accomplishes the objectives it was designed to cover. Being simple, adaptable, not too time consuming and still be effective.

Some participants who gave low scores to some of the questions were asked about why they did it. For the affirmation "The methodology is effective in solving risks", team members from Project 2 seemed to think that the action plans implemented did not solve the risks. Although this might have happened, and it might still happen in the future, this cannot be considered a flaw of the methodology, but of the team members' perception of how to solve the risks. Through documenting the risks and action plans, it will be possible in the future, to check them every time a repetitive risk appears and there will be no need to try new action plans, as the effective ones will already be registered and proven to be successful. As for affirmation "The methodology is effective in solving risks", participants from Project 1 though that some process risks were not identified. This happened because these risks were very unlikely to occur, and again, in the future, they will already be considered as risks, because their probability increased after this occurrence. The methodology is a work in progress and it will become more efficient as records are being saved and more risks are being managed.

The fact that the necessity of risk management is recognized and that the overall experience of the participants was rated positively should indicate that the implementation of the methodology will be well accepted.

Chapter 7: Conclusions and future work

This chapter 7 is divided into two sections. Section 7.1 resumes the conclusions withdrawn from the methodology implementation and the characteristics found to be crucial for the success of a risk management methodology for R&D pharmaceutical projects such as Hovione's. Section 7.2 describes the challenges met during the development of the dissertation, limitations of the conclusions taken and suggestions for future studies.

7.1 Conclusions

Through the characterization of Hovione, its activities, objectives, history, its organizational structure, and current practices, it was possible to take some conclusions. Hovione, as a pharmaceutical company that offers to pharmaceutical customers, contract services to bring new and off-patent drugs to market, is recognized worldwide within the pharmaceutical industry for its avant-garde technologies and leading-edge laboratories. Hovione's mission is to do well what is innovative and difficult, and to be recognized by costumers, regulators, and competitors as number 1 in the segments it targets. Implementing a successful and efficient risk management methodology to identify and respond to projects risks will allow a better fulfillment of this mission. Project risk management decreases schedule delays, improves customer satisfaction, and avoids unexpected costs and quality deviations, which increases project success rates. One of the most important benefits of risk management to Hovione is the fact that it should allow a faster and clearer communication of issues to senior management. When a project team faces a risk that cannot be handled by the team itself, the problem is communicated to senior management. The fact that risk management implies clearer documentation of risks, permits clearer visibility of the severity and frequency of risks. Besides this, project risk management will allow a more realistic definition of project results and adjustment of expectations, resulting in fewer surprises for both the teams and the clients. These benefits of project risk management should represent a step towards the company's mission, increasing customer satisfaction and the company’s OTIF.

Through this dissertation, many project risk management methodologies were analyzed, each with its own specifications. Despite them being significantly different from each other, the analysis of these methodologies allowed comprehending which tools and techniques are more suitable to each kind of projects and what improvements could be done to the existent methodologies to make them suitable to Hovione's projects. In addition, it was noticed that many of the methodologies studied have characteristics in common that can be considered critical for the success of risk management, such as early and iterative identification of risks and continuous monitoring and control of risks and response plans.

This dissertation evaluated the project management and risk management practices in vigor at the company. The procedures used to manage R&D projects follow a standard approach created

internally and available in the company's intranet. This approach is inspired by the *PMI Project Management Body Of Knowledge (PMBOK® Guide)*. As for project risk management, no methodology is applied, which results in a high rate of project schedule delays.

Furthermore, and given the knowledge gathered in this dissertation, it was possible to suggest a risk management methodology to be implemented at Hovione's DPD projects. This methodology took into consideration three main characteristics of DPD projects. First, because of the fact that Hovione's R&D projects are of short duration, the methodology to implement had to be simple and short. This means that, the analysis phase of the risk management methodology should be qualitative and not quantitative, and be done using the risk matrix. The entire methodology was designed to be simple and fast to apply. Second, as the risks are recurrent from project to project, the solution proposed to identify risks was the checklist method, which takes advantage of the fact that risks repeat themselves and, at the same time, contributes to the simplicity of the methodology. Third, the project teams were already overloaded with work, so, performing risk management could not be seen as a too much of extra work or a waste of time, thus the need for a risk management briefing at the beginning of the project. This briefing should diminish the overall time consumed by risk management. Table 19 summarizes the steps, tools and techniques and in which meeting each step of the risk management methodology should happen.

Table 19 - Final Risk Management Methodology (Source: Author)

Risk Management Process Phase	*Steps*	*Tools and Techniques*	*Meeting*
Risk Planning	1. Risk Briefing	PowerPoint presentation	KoM ideally, but if time is not enough, Risk Meeting
Risk Identification	2. Risk Identification 3. Cause Identification´ 4. Assignment of Risk Owners	Checklist Brainstorming Excel "Checklist" sheet	KoM ideally, but if time is not enough, Risk Meeting
Risk Analysis	5. Qualify Probability 6. Qualify Impact	Excel "Analysis" sheet Brainstorming º Risk Matrix Qualitative Scale with 5 levels	KoM ideally, but if time is not enough, Risk Meeting
Risk Response Planning	7. Develop action plans in group 8. Register risk strategy 9. Establish deadlines	Brainstorming Excel "Response Plan" sheet 8 question set	1st Weekly Meeting
Risk Monitoring and Control	10. Register Risk Status 11. Define new probabilities 12. Define new impacts 13. Define new action plan	Brainstorming Excel " Response Plan" sheet	Weekly internal meetings

(See Appendix 4 for Risk Checklist final version, Appendix 5 for Excel "Checklist" sheet, Appendix 6 for Excel "Analysis" sheet and Appendix 7 for Excel "Response Plan" sheet).

This methodology was tested through case study research, and refined based on the conclusions obtained from it. Conducting case study research allowed observing and analyzing the reactions and behaviors of Hovione's employees towards risk management and the methodology. It allowed adapting the steps, tools and timings to Hovione's people and work style, suiting better their fast pace and their current risk knowledge.

In the end of both projects, a presentation of the results and of the methodology was done to all R&D project managers who were all very interested and gave really positive feedback. Next steps into fully implementing the tools in all projects will be to provide training to the project managers and to organize a general briefing with all team members. The excel files should be uploaded in the company's web platform.

The resulting excel files of each project will allow project managers check past project records. This should be very useful, as many projects have the same clients, the same drug to be developed and the same equipment.

7.2 Challenges and Future work

Throughout the development of this dissertation, some obstacles and challenges were encountered. First, the lack of knowledge on the subject of pharmacy and chemistry represented difficulties in researching and selecting relevant and reliant information to conduct the investigation. Large amounts of online information are available and it was not easy to filter what was trustworthy and relevant, and what was not. Eventually, after reading and researching scientific articles, books and conference proceedings, technical terms became more familiar and it was possible to realize that it was conceivable to write this dissertation without much pharmaceutical knowledge.

After fully implemented, this methodology will still have a lot to be improved. As time goes by, more information about risk probabilities and impacts will be gathered, and eventually, quantitative analysis of risks should be possible, without it representing a too complex and timely process, because data will be available. Another objective that should be in sight would be to evaluate the probability and impact of each risk in terms of each project objective: schedule, cost, quality, and customer satisfaction. The suggested methodology allows only an overall classification. However, in a short term, Hovione's next objective regarding risk management should be discovering a tool for registering risks instead of Excel, in order to create a data base of risks in which the project manager can search down the risk and check its records. Excel will only allow saving each project record, and not risk by risk.

Plus, as Hovione is starting to use a new software for managing projects, ideally, one of the next steps, would be to combine the risk methodology to the software. This could be done by changing the software's default definitions in order to accommodate the methodology developed. But in a short term, uploading the excel files into the software is enough to provide insight on past risks from past projects.

Also, as mentioned in chapter 2, it might be advantageous to start to look at projects and their risks as a portfolio instead of individually. Hovione's manages a high number of projects and the risks that impact them are very repetitive from one to another. Looking at a risks and projects in a portfolio perspective should be something to consider in the future. Through the application of this risk methodology, the company will be able to keep record of risks and action plans, and this will make Hovione more prepared to start managing project portfolios.

This dissertation contributes to the study of risk management in pharmaceutical projects, however, the findings and results should be viewed taking into consideration the limitations of the work done. This includes taking into account that only two case study projects were used, and both were from the same company. Also, the fact that the second pilot project started before the end of the first one and that the second implementation only took place mid-project, may have biased the results of the second implementation, and it is not possible to distinguish if such results would still occur if the implementation was done as planned. This happened due to Hovione's requirement of having the dissertations results at a specific date and no other project besides Project 2 would be finished in time. As such, future studies should take into account these considerations. It is also worth considering that the case study projects were short term projects and that the methodology implemented was developed taking that into consideration. Most pharmaceutical projects are long-term, so the work developed in this dissertation may not be the most appropriate to be applied in all types of pharmaceutical projects. These limitations can be seen as an opportunity for further research in this area, including conducting case study research on a larger number of R&D pharmaceutical projects, preferably from different companies. Future work can provide a fertile ground on which to validate the results in various contexts, evaluating different types of pharmaceutical projects, from different pharmaceutical companies.

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APPENDICES

APPENDIX A1 – Description of Risk Management Techniques

Table 20- Description of Risk Management Techniques (Source: Adapted from Grimaldi et al., 2012)

Technique	Description
Brainstorming	An effective way to generate lots of ideas on a specific issue and then determine which ideas are the best possible solution. Ideas about project risk are generated under the leadership of a facilitator.
Cause and Consequence Analysis (CCA) / Cause Effect Analysis (CEA)	It identifies the set of unwanted effects and goes backwards to trace the causal chain.
Checklist	It is a detailed aide-memoire for the identification of potential risks. It can be developed based on historical information and knowledge that have been accumulated from previous similar projects
Decision Tree Analysis	It is usually structured using a decision tree diagram that describes a situation and the implications of each of the available choices and possible scenarios. It incorporates the cost of each available choice, the probabilities of each possible scenario, and the rewards of each logical path
Delphi	The purpose is to elicit information and judgments from participants to facilitate problem- solving, planning, and decision- making. A facilitator uses a questionnaire to solicit ideas about the important project risks and the experts participate anonymously.
Event Tree Analysis (ETA)	It is an analysis technique that models the range of possible outcomes of one or a category of initiating events.
Expert Judgement	Technique based on the experts' opinion. It is useful for the evaluation of the failure rate and the success chances of the overall project.
Fault Tree Analysis (FTA)	An approach that starts from a particular event, known as the top event, in an attempt to identify all the possible event sequences giving rise to it.
Failure Mode and Effects Analysis (FMEA)	An analysis technique used in high-risk organizations to identify failure modes in systems/processes and work out response strategies.
Failure Mode and Effects Criticality Analysis (FMECA)	An analysis technique used in high-risk organizations to identify and assess failure modes in systems/processes and work out response strategies.
Hazard and Operability (HAZOP)	It is a hazard identification technique that uses a structured and systematic team review of a system or process to identify the possible deviations from normal operations and their causes and consequences. It uses a standard list of guidewords combined with process conditions to systematically consider all the possible deviations from the normal conditions. For each deviation, possible causes and consequences are identified as well as whether additional safeguards should be recommended.
Interviews	The list of risks is produced by interviewing project managers or experts on the applications of the project. The risks are identified and defined and a risk management capability score can be determined from a five-point scale.

Monte Carlo	A type of spreadsheet simulation that randomly and continuously generates values for uncertain variables to simulate a model.
Pareto Analysis (PA) or ABC analysis	It is a technique that is used to identify and prioritize the most significant items, like causes and contributing factors or effects of accidents. This technique employs the Pareto which says that about 80 percent of the effects are generated by about 20 percent of the causes.
Preliminary Hazard Analysis (PHA)	It is used to identify hazards, assess the severity of potential accidents that may happen, and identify measures for reducing or eliminating the risks associated with the hazards.
Risk Breakdown Structure (RBS)	It is a source-oriented grouping of project risks that defines the total risk exposure of a project. Each descending level represents an increasingly detailed definition of sources of risk to the project.
Risk Mapping, Risk Matrix, Probability and Impact Matrix	It is a qualitative technique that can be used to evaluate and prioritize a group of risks which could significantly impact on a project
Risk Probability and Impact Assessment, Risk Ranking/Risk Index	It investigates the likelihood that each specific risk will occur and the potential effects on the objectives of a project, such as time, cost, scope, or quality.

APENDIX A2 – Classification of Risk Management Techniques in each criterion

Table 21 - Classification of Risk Management Techniques in each criterion (Source: Adapted from Grimaldi et al., 2012)

No.	Technique	Life Cycle Phase	RM Phase	Typology
1	**Brainstorming**	Initiation, Planning, Execution	I, QIA	Heuristic
2	**Cause and Consequence Analysis (CCA)**	Planning, Execution	I, QIA	Heuristic
3	**Checklist**	Initiation, Planning	I, QIA	Analogical
4	**Decision Tree Analysis**	Initiation, Planning	QtA, R	Analytical
5	**Delphi**	Planning	I, QIA	Heuristic
6	**Event Tree Analysis (ETA)**	Planning, Execution	I, QIA, QtA	Analytical
7	**Expert Judgement**	Initiation, Planning	I, QIA, QtA, R	Heuristic
8	**Fault Tree Analysis (FTA)**	Initiation, Planning	I, QIA, QtA	Analytical
9	**Failure Mode and Effects Analysis (FMEA)**	Initiation, Planning	I,R	Analytical
10	**Failure Mode and Effects Criticality Analysis (FMECA)**	Initiation, Planning, Execution	I, QIA, QtA, R	Analytical
11	**Hazard and Operability (HAZOP)**	Planning	I,R	Analytical
12	**Interviews**	Initiation, Planning, Execution	I, QIA, QtA, R	Heuristic
13	**Monte Carlo**	Planning	QIA	
14	**Pareto Analysis (PA) or ABC analysis**	Planning	QIA	
15	**Preliminary Hazard Analysis (PHA)**	Planning	I, QIA, P	Heuristic
16	**Risk Breakdown Structure (RBS)**	Initiation, Planning	I	Heuristic
17	**Risk Mapping, Risk Matrix, Probability and Impact Matrix**	Planning	I, QIA	Heuristic
18	**Risk Probability and Impact Assessment, Risk Ranking/Risk Index**	Planning	QIA, QtA	

APPENDIX 3 – Initial Risk Checklist

Table 22 - Initial Risk Checklist (Source: Author)

ID	RISKS	
1	**Scope**	
1.1	Scope is incomplete	
1.2	Scope is unclear (Success criteria not clear)	
1.3	Tasks get added during project without approval	
1.4	Client expectations change during project	
1.5	Client demands additional scope (not initially planned)	
2	**Client Relationship**	
2.1	Communication software difficulties: Webex, Navstream	
2.2	Client's team size is too big. Too many communication points misaligned	
2.3	Client has access to senior management and bypasses team when challenges arise	
2.4	Client demands excessive communication (high maintenance)	
2.5	Client delays project	
3	**Client Visit**	
3.1	Client's expectations not met during visit	
3.2	Client wants to stay for too long	
4	**Work Proposal Value**	
4.1	Project cost not recovered	
4.2	Not enough profit	
4.3	Funding is cut	
4.4	Technological change, changes costs	
5	**Technology/Process**	
5.1	Technology not fit for purpose	
5.2	Complex technology	
5.3	Inexperienced technology	
5.4	Technology not scalable	
5.5	Technology not reliable	
6	**Scheduling**	
6.1	Delays in previous operations cause domino effect and impact project	
6.2	Process issues	
6.3	Delays due to worker injury or fatality	
7	**Supply Chain**	
7.1	Delayed arrival of raw materials	
7.2	Inventories in SAP not correct	
7.3	Supplier fails to meet requirements	
7.4	No response to RFP	
7.5	Low quality response to RFP	
7.6	Unacceptable contract terms	
7.7	Failing to negotiate reasonable prices	
7.8	Product retained at customs	
7.9	Missing documentation on import of materials	
7.10	Missing documentation on export of materials	
8	**Development Stage**	
8.1	Technology transfer not done correctly	
8.2	Development/familiarization not successful	
8.3	Development not enough to support validation	
8.4	Development not enough to move to GMP	
9	**Installation/Progress**	
9.1	Equipment not fit for purpose	
9.2	Equipment not scalable	
9.3	Losses of material or having to repeat process due to inexperience	
9.4	Equipment not reliable	
9.5	Equipment utilities failing	
9.6	No available equipment	
9.7	New installation/ revamp	
9.8	Lack of documentation on the equipment	
10	**Internal Visibility**	
10.1	Project relevance attracts other senior stakeholders attention	
11	**Market Demand**	
11.1	Misalignment of client's expectations/needs	
12	**Human Resources Experience**	
12.1	Team is inexperienced in process	
12.2	Training is not available	
13	**Human Resources Occupation**	
13.1	No Human Resources available	
13.2	Worker Injury	
13.3	Human Resources over allocated	
14	**Other**	
14.1		
14.2		
14.3		
14.4		
14.5		
14.6		
14.7		

APPENDIX 4 – Final Risk Checklist

Table 23 - Final Risk Checklist (Source: Author)

ID	RISKS	
1	**Scope**	
1.1	Scope is incomplete	
1.2	Scope is unclear (Success criteria not clear)	
1.3	Tasks get added during project without approval	
1.4	Client expectations change during project	
1.5	Client demands additional scope (not initially planned)	
2	**Client Relationship**	
2.1	Communication software difficulties: Webex, Navstream	
2.2	Client's team size is too big. Too many communication points misaligned	
2.3	Client has access to senior management and bypasses team when challenges arise	
2.4	Client demands excessive communication (high maintenance)	
2.5	Client delays project	
3	**Client Visit**	
3.1	Client's expectations not met during visit	
3.2	Client wants to stay for too long	
4	**Work Proposal Value**	
4.1	Project cost not recovered	
4.2	Not enough profit	
4.3	Funding is cut	
4.4	Technological change, changes costs	
5	**Technology/Process**	
5.1	Technology not fit for purpose	
5.2	Complex technology	
5.3	Inexperienced technology	
5.4	Technology not scalable	
5.5	Technology not reliable	
6	**Scheduling**	
6.1	Delays in previous operations cause domino effect and impact project	
6.2	Process issues	
6.3	Delays due to worker injury or fatality	
6.4	Delays in cleaning process *	
7	**Supply Chain**	
7.1	Delayed arrival of raw materials	
7.2	Inventories in SAP not correct	
7.3	Supplier fails to meet requirements	
7.4	No response to RFP	
7.5	Low quality response to RFP	
7.6	Unacceptable contract terms	
7.7	Failing to negotiate reasonable prices	
7.8	Product retained at customs	
7.9	Missing documentation on import of materials	
7.10	Missing documentation on export of materials	
7.11	Issues with raw material approval *	
8	**Development Stage**	
8.1	Technology transfer not done correctly	
8.2	Development/familiarization not successful	
8.3	Development not enough to support validation	
8.4	Development not enough to move to GMP	
9	**Installation/Progress**	
9.1	Equipment not fit for purpose	
9.2	Equipment not scalable	
9.3	Having to repeat process due to inexperience *	
9.4	Equipment not reliable	
9.5	Equipment utilities failing	
9.6	No available equipment	
9.7	New installation/ revamp	
9.8	Lack of documentation on the equipment	
9.9	Losses of material *	
10	**Internal Visibility**	
10.1	Project relevance attracts other senior stakeholders attention	
11	**Market Demand**	
11.1	Misalignment of client's expectations/needs	
12	**Human Resources Experience**	
12.1	Team is inexperienced in process	
12.2	Training is not available	
13	**Human Resources Occupation**	
13.1	No Human Resources available	
13.2	Worker Injury	
13.3	Human Resources over allocated	
14	**Other**	
14.1		
14.2		
14.3		
14.4		
14.5		
14.6		
14.7		

* New entries

APPENDIX 5 – Excel “Checklist” sheet

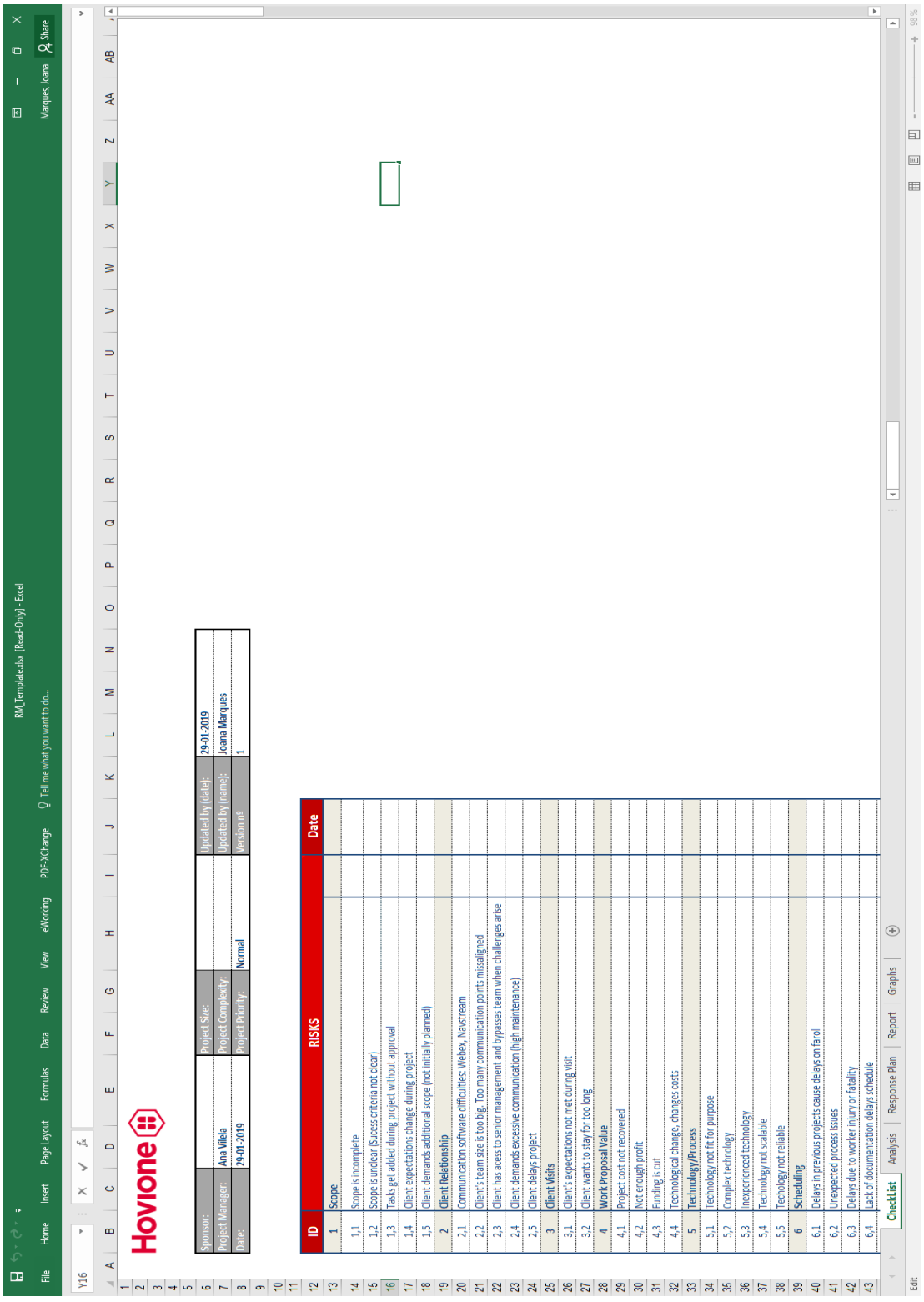

Figure 29 - Excel "Checklist" Sheet (Source: Author)

Appendix 6 – Excel “Analysis” table

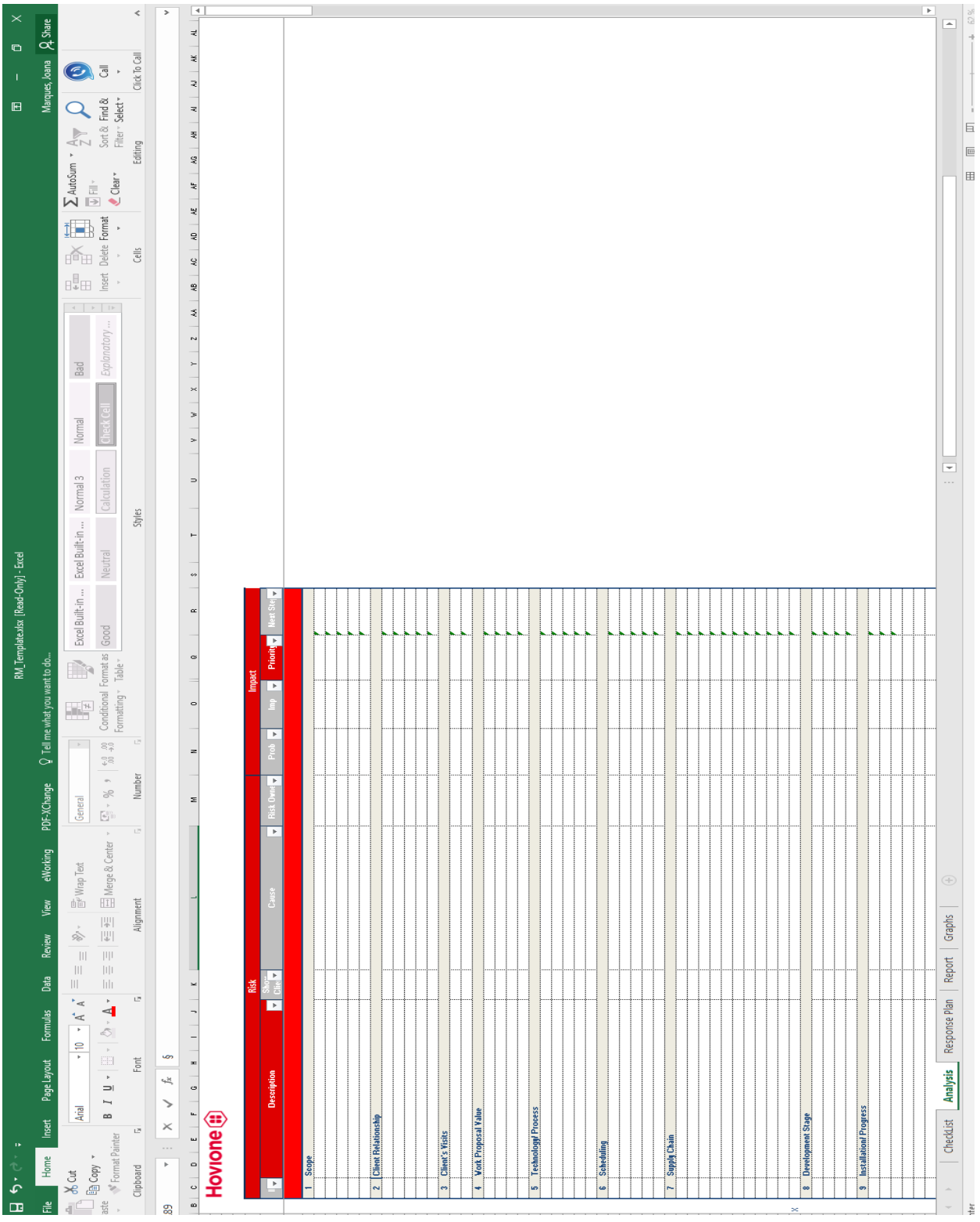

Figure 30 - Excel Analysis sheet (Source: Author)

Appendix 7 – Excel “Risk Response planning” table

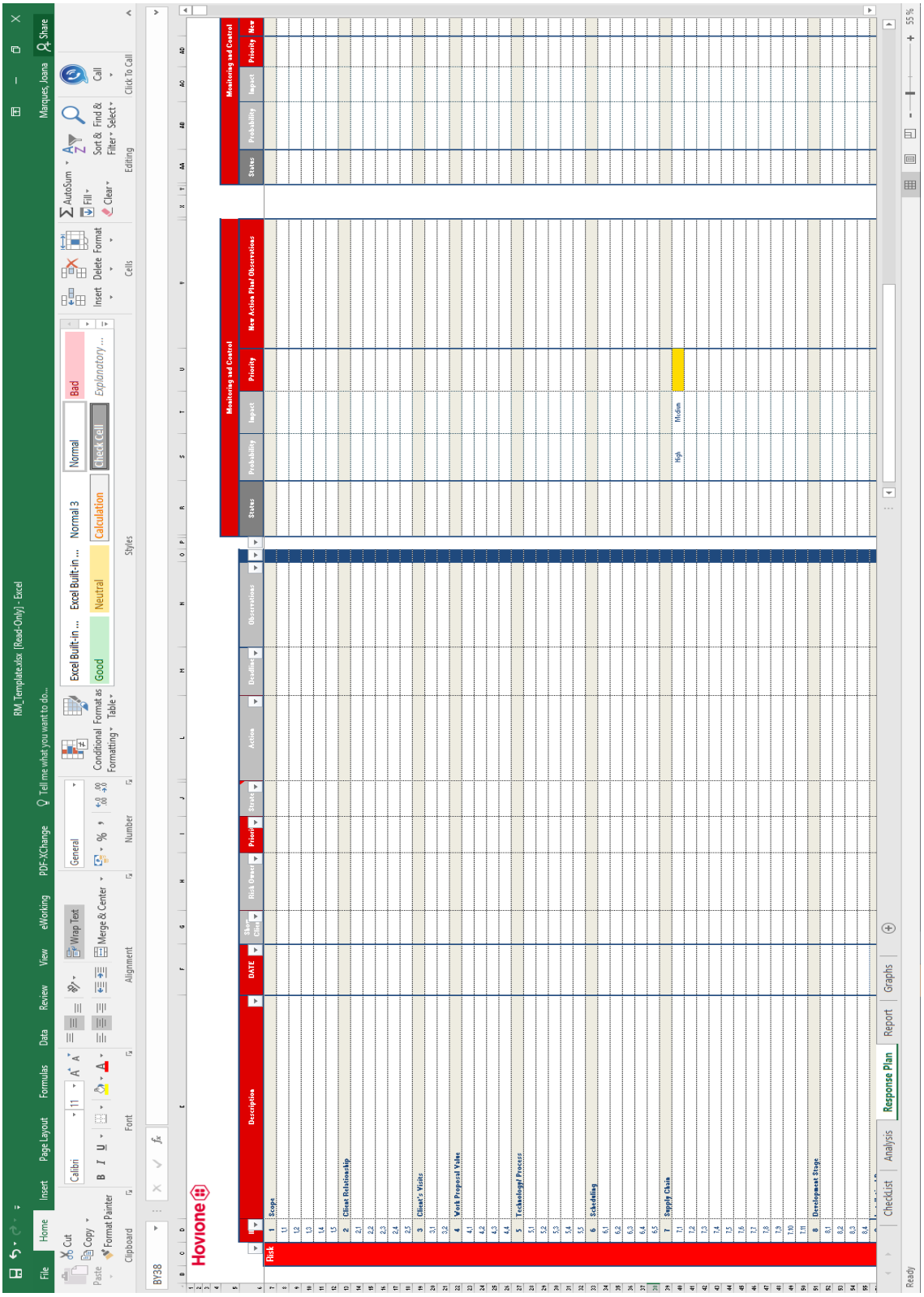

Figure 31 - Excel "Response Plan" sheet (Source: Author)