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. 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. This paper proposes a risk management methodology that allows effective, early and iterative risk management and periodic risk reviews, while defining the tools and techniques to be used at each phase of the risk management process, and tests it in two Hovione projects.

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

1. Introduction

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). This paper has as main goal the development of a risk management methodology to be applied in Hovione's projects. The development of such tools and techniques should allow the company to improve its OTIF (On Time In Full) performance and customer satisfaction.

2. Problem Definition

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. The focus of this paper is the R&D Services division. This is the area where Hovione needs to improve project risk management. 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. Hovione follows a standard approach for project management based on the Project Management Body Of Knowledge (PMBOK), an industry standard methodology from the Project Management Institute. This approach follows a systematized methodology that includes the following phases within a project life cycle:

1. Initiation
2. Planning
3. Execution
4. Closeout

In the past, Hovione has hired a management and technology consulting firm to restructure the process of project management of the company. 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 short-time projects, whose duration is typically between one to three months (from initiation to closeout). So project managers started applying only a very basic methodology, which consists in identifying and discussing, through brainstorming, the biggest risk to the project and what could be its impact on the timelines. The purpose of this paper is to develop a methodology to substitute the current one, described above, which has many

limitations when it comes to accurately identifying risks and treating them.

2. Literature Review

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). A risk is an uncertain event or condition that, if it occurs, has a positive or negative effect on a project objective (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. 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;
2. Risk Identification;
3. Qualitative Risk Analysis;
4. Quantitative Risk Analysis;
5. Risk Response Planning
6. Risk Monitoring and Control.

Researchers have suggested different techniques to manage risks in R&D and pharmaceutical projects, according to their characteristics. Some of the tools investigated seem to be suitable to manage the risks of Hovione's 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. The methodology described in the following chapters, takes into account the researches described in Table 1.

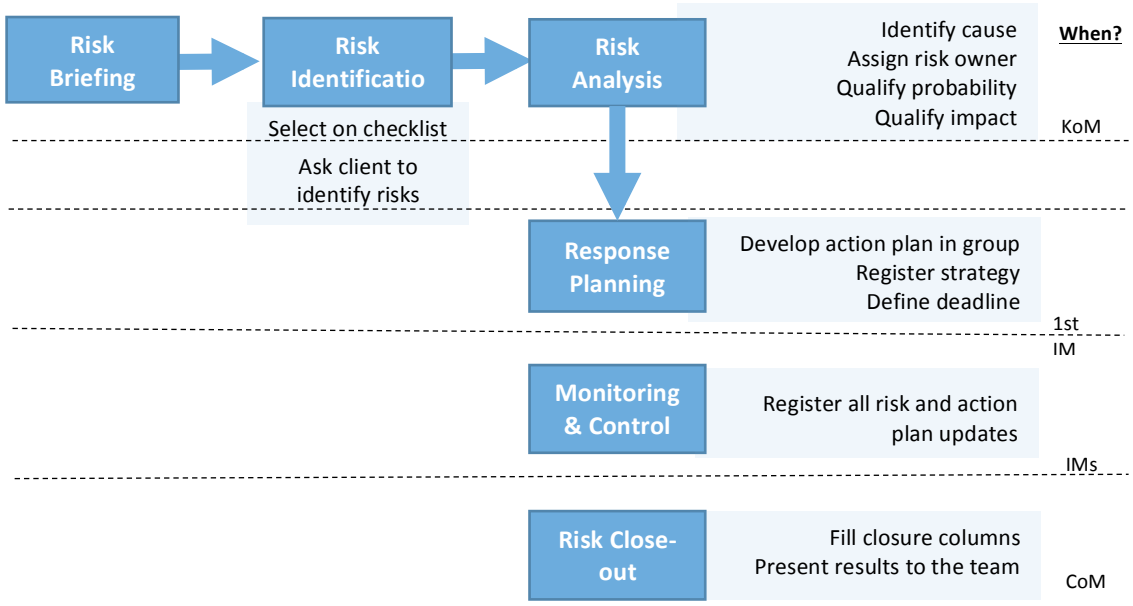
Table 1 - Most relevant studies for the development of the risk management methodology for Hovione (Source: Author)

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.

After studying the existing researches, it was possible to conclude that a methodology comprising a baseline set of processes, procedures, and templates that could be tailored to suit each individual project was a good starting point for Hovione. 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. 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, which the company is not yet ready to implement, but it should be in the future.

3. The methodology

The methodology developed after analyzing the company and reviewing the existing literature on the topic is a simplified version of the risk management methodology espoused by the Project Management Institute in the *PMBOK® Guide*. It combines the identification and analysis in one single stage, and it defines the timings of each phase by project meeting. Hovione follows the *PMBOK® Guide* for managing projects, so it made only sense to follow it as well in project risk management. The preliminary methodology developed is schematized in Figure 1.



KoM: Kickoff meeting; KoM w/ Cust: Kickoff Meeting with Customer; IM: Internal Meeting CoM: Close-out Meeting

Figure 1- Preliminary Methodology Proposed (Source:Author)

3.1 Risk Briefing

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 of this stage is 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.

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.

3.2 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). After the briefing is done, the team can proceed to risk identification. This should be done during the kick-off meeting. 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.

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.

3.3 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 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.

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. Both probabilities and impacts should be analyzed qualitatively, using the terms: *Very Low, Low, Medium, High,* and *Very High.* 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 2).

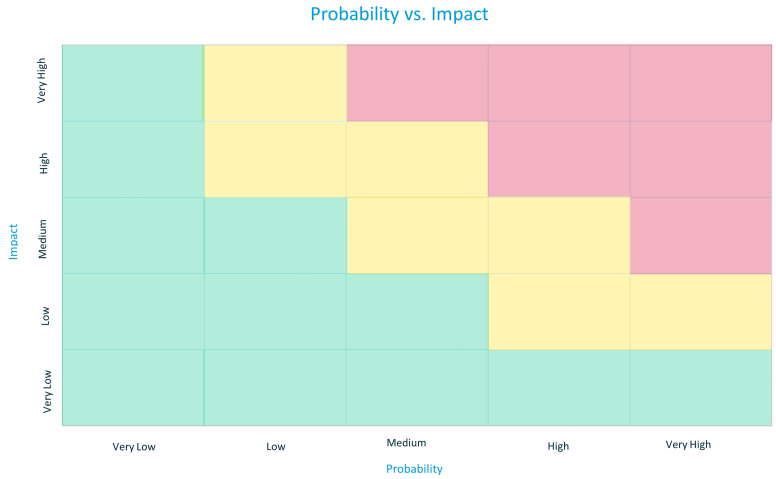


Figure 2- Risk Matrix (Source: Author)

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. 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.

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.

3.5 Risk Response Planning

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, which will be provided to the team.

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. 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.

3.6 Risk Monitoring and Control

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.

Once the project reaches its close-out phase, a full review of the risk templates should be done and all data should be registered

4. Case Study Results

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. The final version of the methodology will be described further ahead.

Project 1: The objective of Project 1 was to dilute a feed solution in a lower concentration of an API in order to expand the process flexibility to obtain a high process yield and material within specifications and later sent it to the client to be formulated. The project execution phase was planned to last 26 days.

The methodology described in the previous section was applied. A total of twenty-one risks were identified along the entire duration of the project. 18 in the KOM and 2. Seven of them were considered high priority, ten were medium priority and four were of low priority. These risks can be seen in the matrix in Figure 3.

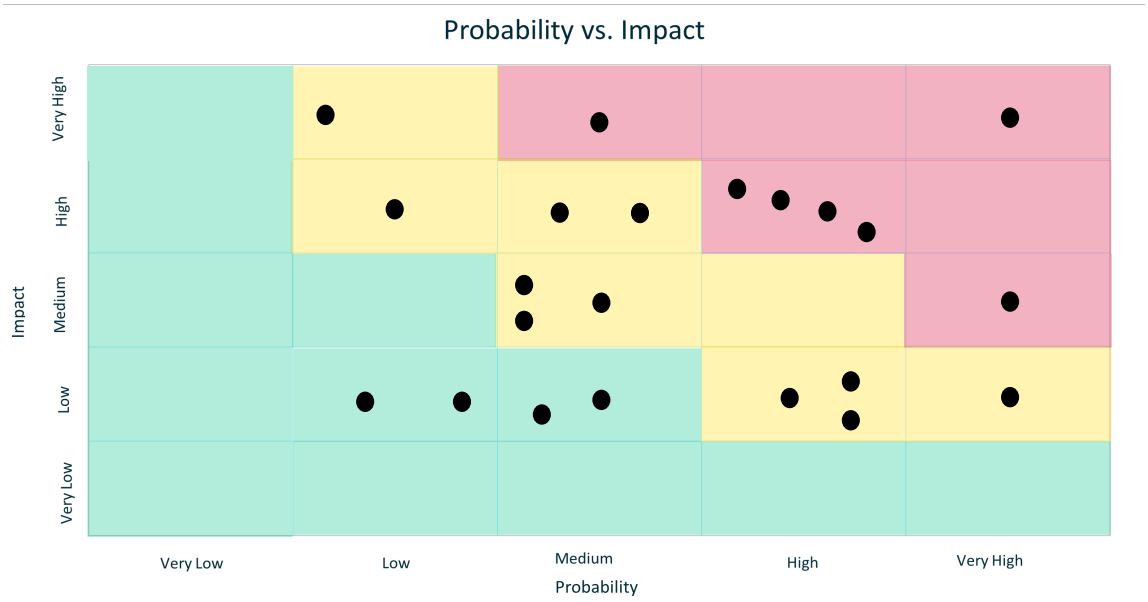


Figure 3 - Risk Matrix of identified risks in Project 1

Figure 4 represents de changes that occurred to each risk priority level. Green arrows represent the changes caused by the response plans and black arrows the changes due to the natural development of the project.

The four red dots represent the risks that impacted. These risks were:

1. Process Risk: This risk was identified because the team thought that it was possible that the final powder properties were out of the expected range and also because necessary utilities could fail. These causes for the risk were not correctly identified, so when the action plan (monitoring), was put to action, the triggers of the real causes, which were very unlikely, were not detected.

in case the ordered ones did not arrived. It was successful and eliminated the impact of the risk.

2. Equipment not fit for purpose: The pipe used in the process had never been used before, so there was a probability of failing. The team decided that the action plan (mitigation) was to test the pipe before using it. Nevertheless, the pipe did not work on the process but this issue was rapidly solved with no impact

3. Human Resources over-allocated: The action plan for this risk was to accept, because it was not possible to apply any other strategy. There was no impact on the project though.

4. Delayed arrival of raw materials: A contingency plan was defined, which was, to use different raw materials

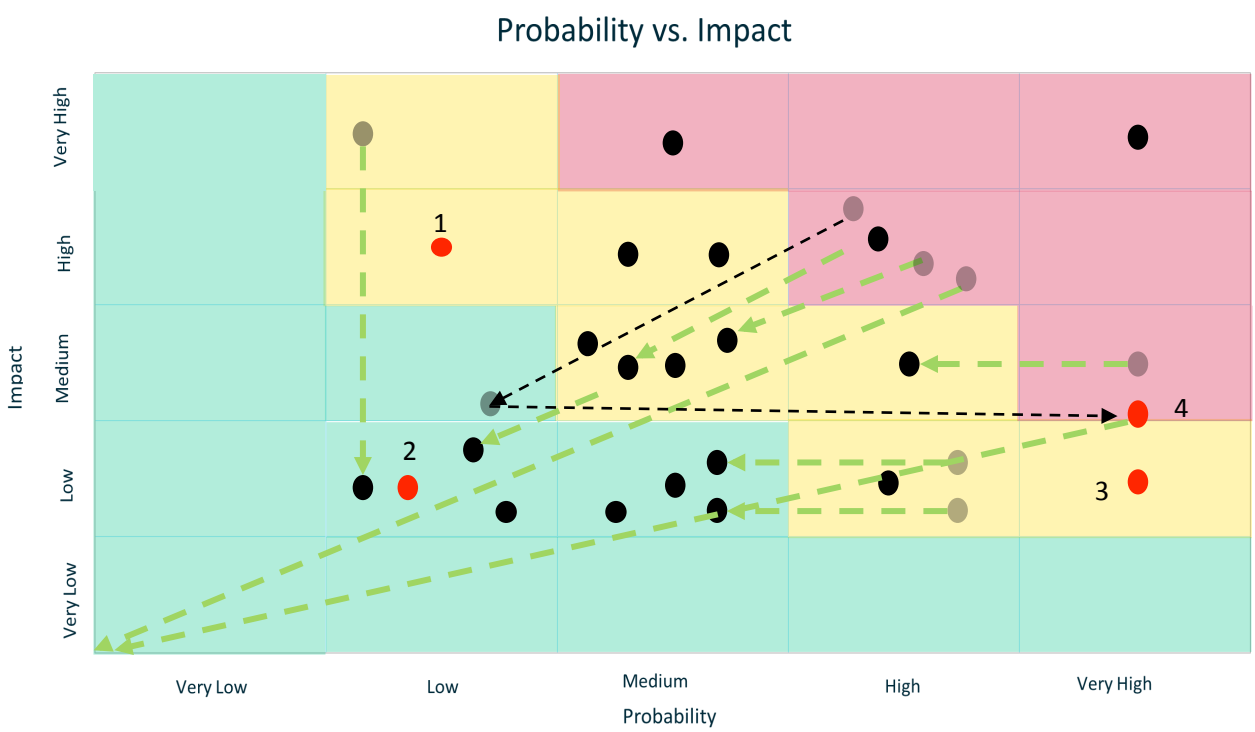


Figure 4 - Project 1 Risk Matrix evolution

After the end of the project, it was possible to make some conclusions regarding the efficiency of the

methodology and what alterations were necessary. These alterations are summarized in table 2.

Initial Version	*Observations of Project 1*	*Alterations to be made*
Risk Identification done in the Kickoff meeting	The time destined to risk management during the Kickoff meeting was not enough for risk identification	Risk Identification done in a separate risk meeting
Ask client to identify project risks	Client could only identify process risks	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	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	Develop action plans in group, on the first weekly meeting

Table 2 - Alterations made to the methodology after Project 1

Project 2: The client was a pharmaceutical company that focuses on investigating oral anti-inflammatory drugs. The project execution phase is expected to last 13 days. During the entire project life cycle, eight risks were identified and action plans were defined. Four of the risks where medium priority, two of high priority and one of low priority. This can be seen in Figure 5.

Figure 6 represents de changes that occurred to each risk priority level and the risks that impacted

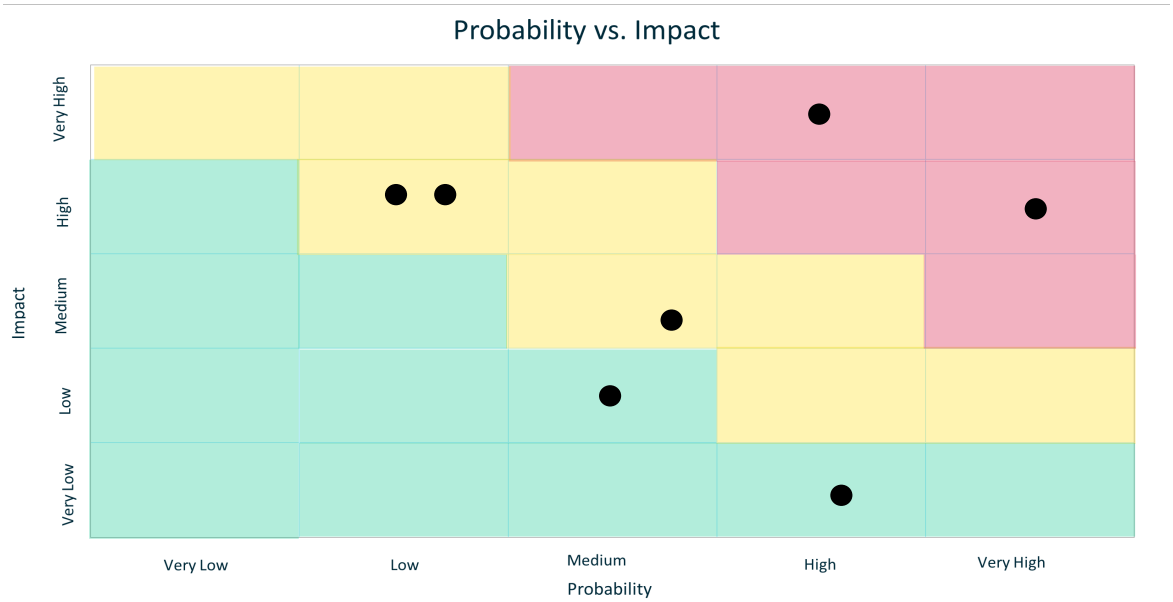


Figure 5- Risk Matrix with identified risks in Project 2

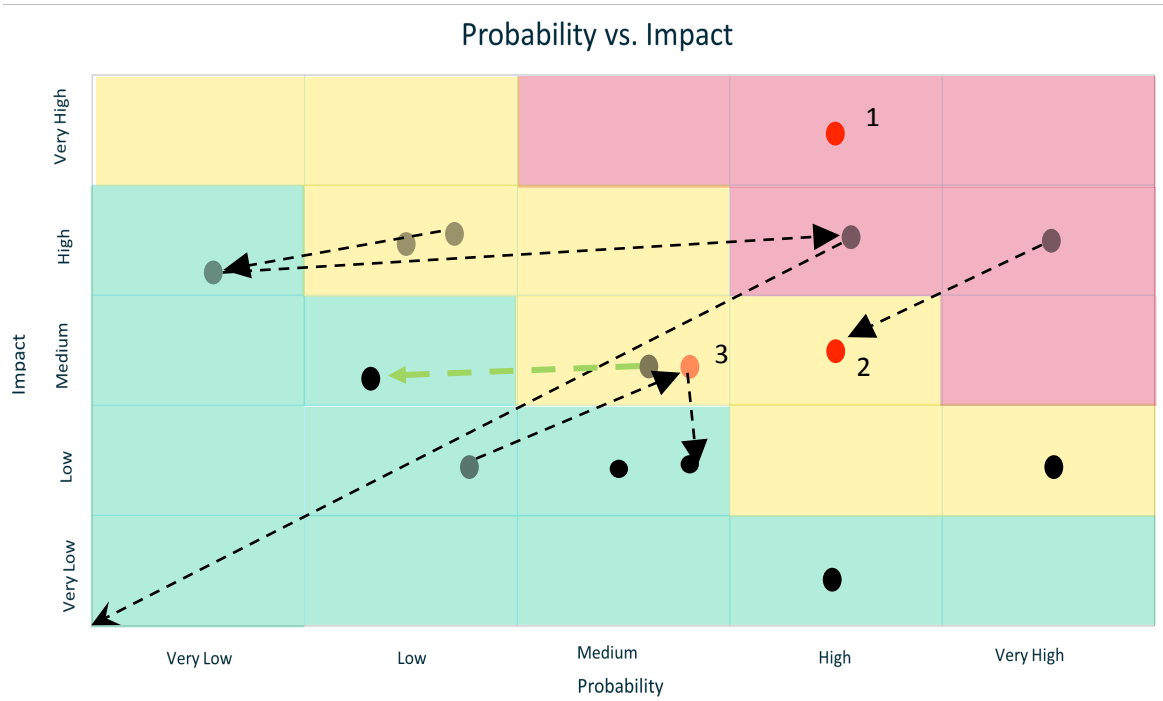


Figure 3 - Project 2 Risk Martrix evolution

The risks that impacted during Project 2 are represented by the red dots and they were the following:

1. Domino effect: In the equipment schedule, the production of Project 2 was scheduled without time buffer between other activities from other projects. Meaning that production delays in the preceding projects could delay project 2. The action plan for this risk was to monitor it. Its trigger was detected, and although it was not possible to prevent the risk from occurring, this could have had a bigger impact if it was not detected in time. The monitoring of this risk prevented others from impacting.

2 Issues with raw material approval: The API for this project was not approved at first, so the team considered that there was a high probability that the testing for the approval failed again, as the problem seem to be in the testing method.The action plan was to use the API under quarantine if the testing failed again. This means that the team opted by producing the product without approval, expecting it to be approved soon. This contingency plan did not work because it was never possible to prove that the problem was in the testing process.

3. Equipment no fit for purpose: The pump required for the project had never been used before, so it could fail. The action plan was to choose an alternative pump in case the first on failed. The problem was that none of the pumps worked.

Again, after the end of the project, it was possible to observe that the methodology needed some alterations. These are summarized in table 3.

Table 3 - Alterations made to the methodology after Project 1

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	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	Print the checklist and bring it to the meeting to be filled
Use Risk Response table to guide response planning	Risk response table is of no use and team members have difficulties developing action plans	Ask 9 pre-defined questions to guide response planning

5. 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 32, 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*. 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.

6. Conclusions and Future work

Through the characterization of Hovione and a research on existing techniques for managing risk in pharmaceutical and R&D projects, it was possible. to suggest a risk management methodology to be implemented in Hovione's projects. This methodology took into consideration three main characteristics of the 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 3 summarizes the steps, tools and techniques and in which meeting each step of the risk management methodology should happen.

Table 3 - Final Risk Management Methodology

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

7. Future Work

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.

References

Kwak, Y. , & Dixon, C. K. (2008). Risk management framework for pharmaceutical research and development projects. *International Journal of Managing Projects in Business*, *1*(4), 552–565.

Lavallee, R. Courtland (2010) Pharmaceutical and Biomedical project management in a changing global environment (1st ed.). Hoboken, NJ: John Wiley & Sons

Marle, F., & Gidel, T. (2012). A Multi-Criteria Decision Making Process for Project Risk Management Method Selection. *International Journal of Project Organization and Management*, *2(2)*, 189-

223.

Project Management Institute (2017). A Guide to the Project Management Body of Knowledge (PMBOK® guide) (6nd ed.). Newtoun Square, PA.

Turner, J. R. (2009). The Handbook of Project Based Management: Leading Strategic Change in Organizations. Manager (3rd ed.). London, UK: McGraw-Hill.

Wageman, S. W. (2004). Risk management on research and development projects. AACE International Transactions pp. RI71–RI76.