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Developing Systematic Assessment for Manufacturing Materials in a Pharmaceutical Company

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Abstract

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The thesis focuses on establishing a systematic risk assessment procedure for manufacturing materials in a pharmaceutical company's procurement department. The risk assessment procedure helps to rate manufacturing materials' criticality for the drug based on pre-defined risks.

The thesis started by discussing the theoretical framework related to procurement risks, risk assessment methods available, and analyzed pharmaceutical industry regulatory requirements for manufacturing materials. The research development parts relied on utilizing qualitative research methods, interviews and document analysis. The thesis used the 5x5 risk matrix methodology to improve the risk assessment tool. The department's materials criticality was scored for pre-defined supply chain risks and their impact on drug manufacturing. Subsequently, mitigation actions suitable for the company were applied, and the standardized risk assessment procedure was established.

After the development, the evaluation was complimented by incorporating a quantitative research method, a survey, to measure the success of the newly established risk assessment procedure. The results of the survey showed a high satisfaction with the newly established procedure. As the risk assessment procedure was established, the company can be consistent and thus can benefit from performing risk assessments for manufacturing materials on a yearly basis. The risk assessment procedure can be further revised according to the company's needs, adding new materials or suppliers.

Keywords: Risk assessment tool, risk assessment procedure, procurement risks, risk management, manufacturing materials, 5x5 risk matrix

Contents

1 Introduction

1.1 Background to the thesis topic

The pharmaceutical sector is one of the most regulated industries worldwide, driven by the necessity to protect the safety, efficacy, and quality of products that have a direct impact on the health of patients (Sandesh L. et al., 2022). Compliance requirements to the industry standards and regulations, such as those established by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are very strict. These regulations cover all aspects of production – from the raw materials to final product distribution (Towse A. and Danzon P. M., 2010).

Risk assessment is not only important in ensuring product quality but also in the overall efficiency of the operations and compliance with the standards and requirements. The proper implementation of risk assessment procedures is vital in the identification of potential risks, their control measures and, more importantly, in ensuring that the highest standards of manufacturing quality are maintained (Mollah A. H. et al., 2014).

The pivotal role of the manufacturing materials used in drug manufacturing cannot be overstated, as they are considered as the cornerstone of the entire manufacturing process. Of those, the raw materials group can be classified as being the most important when drug manufacturing is concerned, mostly because they form the foundation of the drug. Also, if any safety and/or efficacy problems arise, they are always linked to raw materials (Henderson T., 2024). When it comes to raw materials sourcing and testing, many regulatory authorities, such as the FDA, have implemented quite rigid guidelines for their testing. This is mostly due to the fact that any small deviation in the raw materials quality has a detrimental effect on the final product, and that may potentially lead to safety issues, altered drug efficacy, or, in extreme cases, to regulatory non-compliance (Shadle, P. J., 2004). Therefore, great attention has to be paid to the manufacturing materials purchasing process, as well as their testing and certification. Moreover, it has to be ensured that the end product is reliable and safe for consumption and that all quality requirements are met (GMP Standards for Raw Material Procurement in Pharmaceutical Manufacturing). However, this does not mean that the importance of other materials, such as plastics, processing aids, etc., has to be neglected. They also play a vital role in the manufacturing process.

The topic of this thesis was to develop a systematic risk assessment procedure for manufacturing materials used in a pharmaceutical manufacturing company. The thesis was based on action research, and its focus was on developing a risk assessment for manufacturing materials according to the risk matrix. After the evaluation tool was designed and implemented, a standard operating procedure (SOP) was created for the yearly evaluation of manufacturing materials. This SOP ensures that the evaluation process is consistent.

Establishing a risk assessment procedure for manufacturing materials will bring the following benefits. It helps the company in mitigating supply chain disruptions by noticing potential risks early enough and preparing risk mitigation and contingency plans. This helps to prevent or reduce manufacturing delays or stoppages because risks would be noticed before they happen. Another benefit is that the procedure is beneficial for cost efficiency through inventory optimization. As the procedure helps to identify critical materials, the company can manage inventory levels more efficiently and decide for which items it is a must to have safety stocks. In this way a long-term planning is supported as well. In addition, the identification of critical materials helps the company to better see which suppliers the company should be in a closer relationship with.

1.2 Case company

Company X stands as a rapidly expanding and leading cGMP (current Good Manufacturing Practice) manufacturer in gene therapy products. With over 500 employees and structured into nine distinct departments, the company owns a wide range of competencies that contain the entire product development process. These departments are:

- Finance
- People and Communication
- IT
- Manufacturing, Science and Technology
- Engineering
- Supply and Logistics → The procurement team belongs to this department
- Quality Unit
- Manufacturing
- Project Management

Company X has an extensive range of capabilities that contain the entire product development process, starting with pre-clinical and clinical stages, throughout the product development process, analytical development, GMP manufacturing, and aseptic fill and finish. These capabilities vary from the pre-clinical stage to the supply of commercial products. The involvement of the Procurement team is essential for all the aforementioned activities. By achieving the task of securing all required services and purchasing materials, the procurement team makes sure that the manufacturing process and testing of drug runs smoothly. This includes but is not limited to, the raw materials required for drug formulation, the machines used in manufacturing, the packaging of materials and supplies used in laboratories. The services include outsourced testing, any required transportation, and maintenance requirements. Therefore, the procurement team plays an essential role in guaranteeing the continues flow of materials and services without any disruption in manufacturing.

At Company X, I work in the Manufacturing, Science, and Technology department as part of the analytical team. Our analytical team supports the Quality Control team with the analytical methods development and validation.

Analytical methods are used to test the quality of the drug and to ensure that the drug is sterile, does not have any impurities, and is safe to use. I also participate in monitoring the performance of these methods over time (in other words, overseeing the trends), analyzing data, and addressing any issues that may arise.

1.3 Current state

The general information provided in this chapter is based on my work experience and observations in Company X.

Manufacturing materials can refer to any materials or components used during the process of drug manufacturing. At Company X, these materials are broadly placed into the following groups:

- Raw materials (active pharmaceutical ingredients (API), excipients, solvents, intermediates, reagents (which are also used in quality control activities)).
- Processing aids (e.g., filters, tubing, etc.).
- Plastics (e.g., serological pipettes, pipette tips, single-used systems, sterile plasticware, etc.).
- Packaging and labeling materials (e.g., vials, labels).
- Materials used to maintain facility and/or equipment status (e.g., disinfectants, cleaning solutions, gloves, etc.)

In Company X, manufacturing materials are mainly purchased from only one supplier. These materials have been tested and used, validated for manufacturing use, and are highly tied to the production process and any change of them is very complicated and time consuming, and would require many different tests to be done and validations. Since there is only one supplier of the manufacturing materials, Company X is at risk if, e.g., the shortage of materials or any other type of supply interruption from the supplier side occurs. However, to change or to add substitutes for these materials is a complicated, time-consuming and expensive process, mostly due to:

- Compatibility issues. The introduction of new materials might require compatibility with current equipment, processes, and other materials used in production. Making sure that the new materials fit seamlessly without any disruptions or compromised product quality, can be challenging.
- Testing and validation. The current raw materials were thoroughly tested and validated, and any replacements must also go through the same process to confirm they are of the same quality and comply with regulatory requirements. This whole testing process is time and resource-consuming.
- Production downtime. Changes to manufacturing materials often require stopping or slowing down production, which generates lost income and additional costs. Careful planning and coordination are required to make those transitions.
- Cost considerations. Exploring alternative suppliers and materials may entail more upfront spending in procurement, testing, and validation. Company X must weigh the possible benefits of a material change against the cost and risk of doing so. In addition, a switch to an alternative supplier involves performing supplier assessment, and often an audit to see if a supplier is considerable, developing new relationships, negotiating contracts, and ensuring quality and reliability. A lot of documentation, related to a change, is needed as well during this process.

As a result, seeking replacements for these manufacturing materials is costly and time-consuming, and it could result in manufacturing stoppage. For the aforementioned reasons, Company X has to have mitigation actions in place. For example, in the case of machinery, replacing one item may necessitate replacing another due to compatibility issues.

Before starting to prepare my thesis proposal, I met with the procurement manager to understand their current challenges and determine if any of these could be relevant to my action research. The meeting took place on February 2024. During our discussion, the manager outlined the existing problem – there is no risk assessment procedure in place, and, since Company X sources materials from one supplier, without a risk assessment, it is impossible to see the ranking of materials and which ones have the highest criticality towards the manufacture of the drug in case any unforeseen challenges happen with a supplier. The lack of a risk assessment for materials and their criticality scoring was identified by the Quality Assurance team during an internal audit in May 2019. The audit report, which I found in our document management system, among all the other findings, highlighted the absence of risk assessment for materials. The reason behind the finding was not mentioned in the report. However, after a short meeting with the procurement manager to clear this out, it turned out that the absence of a risk assessment was identified as a gap. A gap that is a discrepancy between the current state (absence of risk assessment to identify critical materials plus the absence of mitigation actions, in relation to critical materials in case of unforeseen supply issues) and the desired state (having a risk assessment procedure). In the presence of production scale-up and having this gap, the company was at a high risk of facing manufacturing delays and/or stoppages, causing financial losses. Although, the efforts to address the absence of a risk assessment procedure began shortly after the audit (the action card in the company's system was created in September 2019), the drafting of the risk assessment faced delays due to resource constraints, and it was not completed until 2022. The second risk assessment was carried out in 2023. However, at that time, it was noticed that the same tool used in 2022 was too complicated – causing input errors and difficulties for updates. Based on this, the tool was simplified. In 2024, the risk assessment tool was identified as requiring improvement again, and it was also noticed that a risk assessment procedure, that would guarantee a continuous performance of risk assessment, has to be established, especially now, when the business is scaling up its manufacturing capacity. The process of identifying the problem related to risk assessment is illustrated in figure 1.

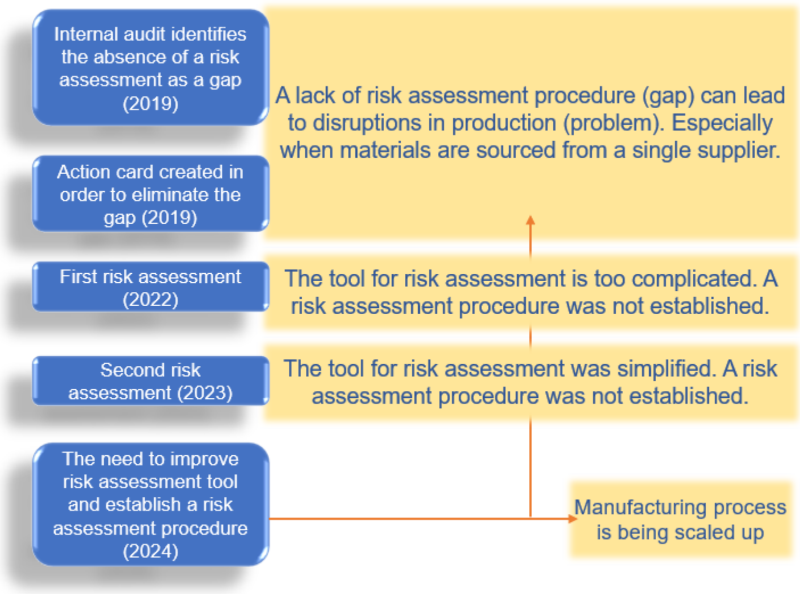

Figure 1. Visual representation of the stages of identifying the problem in risk assessment related to procurement.

A risk assessment is supposed to be performed every year for an upcoming year to evaluate the number of critical items supplied in the storage that could guarantee manufacturing without brakes and/or stoppages, especially at this moment, when drug production has been scaled up. However, since there is no established procedure, a risk assessment for the manufacturing materials can be easily forgotten to implement. Manufacturing materials criticality must be estimated annually, and if there are changes at Company X or on the supplier’s end. Based on the results of a risk assessment and the prioritization of high-risk materials, the appropriate mitigation actions must be implemented, which may include setting or changing safety stock levels, identifying alternative suppliers and/or materials, etc.

2 Research Design

2.1 Research problem and root causes

The problem statement arises from the current state analysis presented in chapter 1.3. It can be expressed as follows:

- Lack of a formal risk assessment procedure prevents identifying critical manufacturing materials and makes the business vulnerable and subject to supply chain disruptions.

A stable and reliable supply chain is needed when production is being scaled up. Without a formal risk assessment procedure to identify critical manufacturing materials, the company faces a significant threat. Without this procedure and a contingency plan, the business is vulnerable to unforeseen supply chain disruptions that might lead to manufacturing delays or stoppages and in turn, to lost revenue. Besides, without identifying which items are the most critical, it is difficult for the company to keep safety stocks balanced and figure out which materials must have safety stocks. This, in turn, complicates long-term planning.

The Fishbone diagram to identify possible causes for the problem is provided in figure 2.

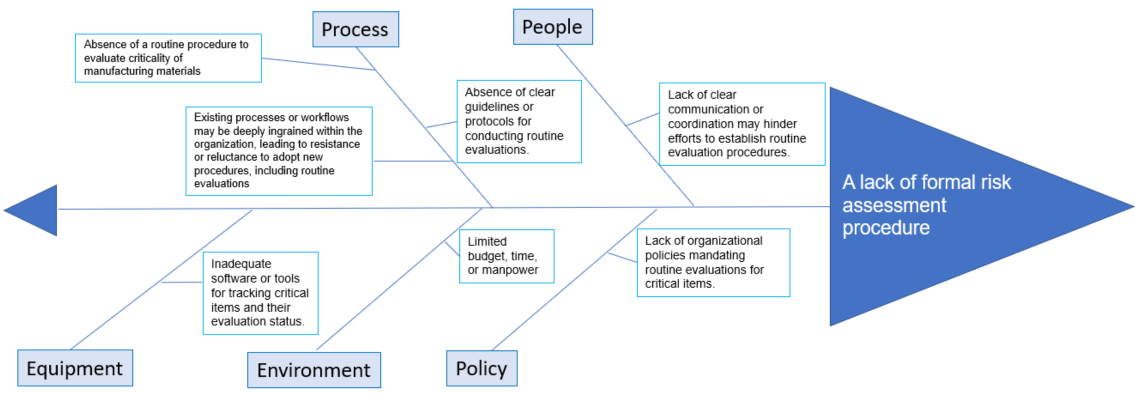

Figure 2. Fishbone analysis of root causes.

The 5 WHYs methodology is a problem-solving technique that uses repeated “why?” questions in order to dig deeper into the root cause of a problem. Typically, the question starting with a word “why” is asked five times what is believed to be sufficient to reach the answer. Each answer is the basis for the next question (Serrat O., 2017). However, as Liker Jeffrey K. (2020) states, asking five times does not necessarily give the ultimate answer. It can be argued that questioning might be continued even further if deemed necessary, but yet, five times appears to be a standard.

5 WHYs analysis is provided below, which was done to delve deeper into the root cause of the problem:

Q1: Why there is no routine evaluation procedure in procurement for manufacturing materials?

- Because there is no established process in place.

Q2: Why there is no established process in place?

- Because it has never been prioritized or recognized as necessary.

Q3: Why has it never been prioritized or recognized as necessary?

- Because there was a lack of resources.

Q4: Why was there a lack of resources?

- Because there was insufficient communication or education about the benefits of routine evaluation and its impact on procurement efficiency and risk management, and manufacturing process.

Q5: Why was there insufficient communication or education?

- Because there was a lack of leadership support or investment in developing or implementing such procedures, possibly due to other priorities or limited resources.

The problem has not been fully resolved and the company is still lacking a risk assessment procedure, because of:

- Resources constraint (limited budget, time, and manpower limited the implementation of risk assessment procedure).
- Different priorities were recognized as more important at that time, especially when the company was about to start scaling up production.
- Complexity of risk assessment procedures (the first risk assessment tool was created with a help of a parent company)

The main possible consequence of not solving the problem is operational disruptions. Unforeseen issues related with critical manufacturing materials can disrupt production schedules, delay project timelines, cause stoppages resulting in lost revenue and customer dissatisfaction.

2.2 Research objectives and questions

The purpose of this chapter is to describe the objectives and research questions that guide the development project.

The objectives of the development plan are:

- To review existing standards and/or guidelines for risk assessment for manufacturing materials.

- To design risk assessment framework/procedure tailored to Company X needs and establish a procedure to evaluate the criticality of manufacturing materials, so the evaluation could be performed continuously and risks, if any, associated with critical materials would be identified and mitigated.

- To pilot risk assessment framework/procedure in order to test its effectiveness and gather feedback from the participants involved in the process so that the procedure would be refined and improved.

The research questions formulated from the objectives are:

1. What are the current industry standards and/or regulatory guidelines for manufacturing materials in the pharmaceutical industry?

The purpose of this research question is to check and overview current standards and/or guidelines (if there are any applicable ones) set for the pharmaceutical industry and analyze how these standards/regulations define manufacturing materials. The purpose is also to check if standards/guidelines provide any information for risk assessment of manufacturing materials. It is important to understand this to ensure that material evaluation meets those standards/guidelines, if any.

2. How to design and customize a risk assessment framework/procedure so that it assesses the criticality of manufacturing materials while also taking into account the needs of Company X?

This question is addressed by creating a risk assessment framework/procedure tailored to Company X needs. This framework/procedure will help in assessing the criticality of manufacturing materials by scoring them based on associated risks. It also addresses all the possible challenges arising during the development process.

3. How effective is the risk evaluation framework/procedure in order to identify and mitigate risks associated with critical manufacturing materials?

This question helps to examine the effectiveness of the risk evaluation framework/procedure, and to determine how well the framework/procedure works in order to pinpoint critical materials as well as strengths and weaknesses. At this stage, it is also important to decide how this framework/procedure will be monitored and improved (if needed) later, once it becomes a routine procedure of assessing the risks and setting criticality for manufacturing materials.

2.3 Research methods

2.3.1 Action research

The approach to this development plan is action research. According to Saunders M., et al. (2012), action research is an interactive and cyclical method to address problems/challenges and find effective solutions. In action research, researchers and organization members collaborate together towards the mutual goal. Stephen Kemmis (2013) writes that action research is a disciplined way of making a change. The author also highlights that this type of research is different than standard research methods because it is conducted in a cyclical manner of planning, acting, observing, reflecting (see figure 3). Also, if needed, after the reflecting comes re-planning, acting and observing, and reflecting again, and the cycle continues as long as needed in order for a change to be implemented. According to Stephen Kemmis (2013), in reality the cycle is not that neat because stages can overlap, plans can become obsolete during the process due to learning from experience.

Figure 3. Action research cycle (adapted from Kemmis Stephan, 2013)

According to Shani Abraham B. and Coghlan David (2021), action research is now recognized as a global family of related approaches that include theory and practice to address important organizational issues in collaboration with those who are affected.

2.3.2 Qualitative research

The research methodology is qualitative. The methods used so far were meetings with unstructured interviews – conversational discussions where only the subject area to discuss was defined. Interviews are among the most commonly used data collection methods in qualitative research that is commonly classified into three groups: unstructured, semi-structured, and structured. The authors draw attention to unstructured and semi-structured interviews, stating their importance in producing quantitative data by researchers who use the method (DiCicco-Bloom, B. and Crabtree, B. F., 2006). According to Chauhan Rahul S. (2022), unstructured interviews still remain the most common and preferred form of an interview. While structured interviews have prepared questions, unstructured interviews are lacking them and tend to be more conversational between the interviewer and interviewee. Unstructured interviews are useful when colleting information for the first time (Chauhan R. S., 2022). During an unstructured interview, the interviewer listens to the interviewee's story and asks spontaneous questions based on their observations (Zhang Y. and Wildemuth B. M., 2017).

Another type of qualitative research methods used was a document review that I performed for audit report that is placed in organizations documents management system. According to Morgan Hani (2022), any document that contains text is a potential source for qualitative analysis. Bowen Glen A. (2009) states “document analysis is a systematic procedure for reviewing or evaluating documents – both printed and electronic (computer-based and Internet-transmitted) material”. Organizational and institutional reports are one kind of form of document that can be used in the research. Document analysis is a research method that is especially suitable for qualitative case studies (Bowen G. A., 2022).

2.3.3 Quantitative research

For the metrics part, an online questionnaire with close-ended questions was used to see the overall user satisfaction with the risk assessment procedure. The close-ended questions questionnaire falls within the quantitative research methods (Larson J., 2024). According to Kurzhals K. (2021), a questionnaire is a commonly used research practice when the aim is to collect data from different respondents. According to the author, online questionnaires are deemed to be a convenient and flexible way to collect the data since recipients use their own suitable time to answer the questions. Close-ended questions are the questions that have a set of prepared answers and all the respondents choose from the same answers pool. However, close-ended questions can further be split into categories such as single and multi-select multiple choice questions, and Likert scale questions where the intensity of agreement or disagreement is measured (Rashid M., 2024). Likert scale questions are widely used to measure opinions. Instead of questions, these questionnaires have statements followed by multiple response options (Talebi P., 2024).

2.4 Metrics

The success of the development project was measured by how well the new assessment procedure meets its intended objectives which were set in the chapter 2.2. Data for the evaluation was collected at the end of the development work using a questionnaire with close-ended questions (Appendix 5). The questionnaire was delivered to the recipients as an online questionnaire. The questionnaire was sent to 4 recipients: the procurement manager, the senior supplier quality specialist – as they were directly involved in the risk assessment procedure development, and the procurement specialist and supplier quality specialist, who were introduced to the procedure after its completion. Collecting answers from a close-ended questionnaire is a suitable method to measure how users and people involved in the creation of the new procedure perceive it in terms of effectivity, usability, easiness of use, and overall satisfaction. Each answer to the question was assigned a numeric value/score (see Appendix 5), and an average of the scores was calculated using the formula below:

$$Average = \frac{\text{Sum of scores from all answers}}{\text{Number of questions x number of respondents}}$$

The average result showing the overall satisfaction towards the newly established procedure was interpreted as follows:

- 1.0 to 1.4 - the new procedure is not recognized as satisfactory

- 1.5 - 2.4 - poor or below-average satisfaction
- 2.5 - 3.4 - above average and good satisfaction
- 3.5 - 4.0 - good to high satisfaction

The development project primarily uses qualitative methods described in section 2.2.2, however, a short questionnaire was used to get numerical indicators in order to measure the overall satisfaction of the established procedure. Other than that quantifiable metrics were not applied because the outcomes and success of the development efforts were not easily quantifiable. Even if quantification were possible, observing meaningful trends in results would require several years since the risk assessment procedure is conducted on an annual basis. Relying on quantitative metrics would, therefore, hinder the timely completion of this thesis.

2.5 Research plan and schedule

The action research was carried out by setting up meetings to better understand what was exactly needed, to design the risk assessment procedure, and to discuss the progress. Once the risk assessment tool was ready, it was piloted. After that the risk assessment procedure was written and established. The feedback from the participating parties was collected in the way of a survey to evaluate the qualities of the procedure (e.g., how easy or time-consuming it is, etc.). Any challenges observed were noted. Once the procedure was approved by the company’s Supplier Quality team specialists, it became a routine activity to be carried out yearly in the procurement team. Action research phases and timeline can be seen in figure 4.

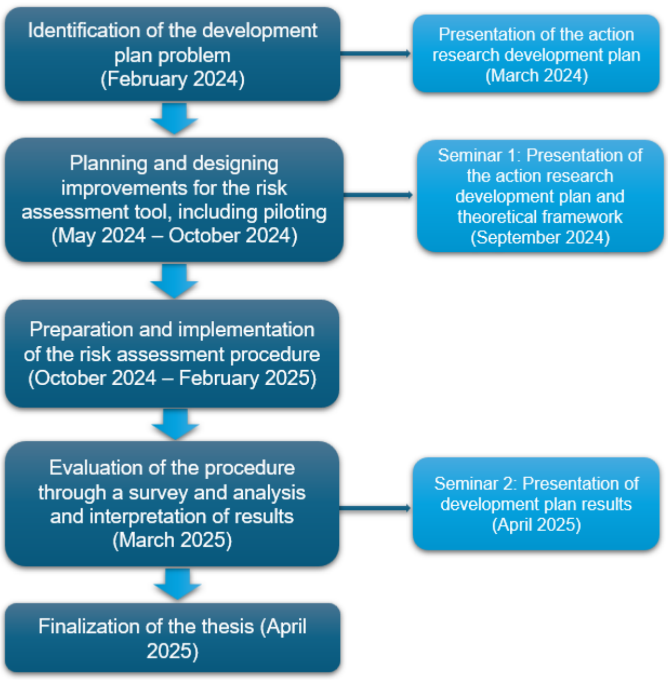

Figure 4. Action research timeline.

The table in Appendix 1 describes the meetings that were held, their dates, participants, and the subjects that were discussed in relation to the risk assessment tool improvement and establishment of the risk assessment procedure.

3 Theoretical framework

3.1 Procurement risks

A risk is a chance of an event or condition happening that could negatively affect an objective or outcome (Hopkin P., 2018). It involves uncertainty and possible negative outcomes, meanwhile Risk Management Guidelines ISO 31000:2018 (which is a set of international risk management standards by the International Organization for Standardization) describes a risk as “effect of uncertainty on objectives”. Blunden T. and Thirlwell J. (2021) state that the current international definition of risk is "the effect of uncertainty on objectives," where risk refers to potential future events. Authors also state that risk management is understanding about the chain of causality which is a simple sequence of cause → event → effect (Blunden T. and Thirlwell J., 2021). Crouhy M., et al. (2023) define risk management as a formal discipline and notes that sometimes identifying a risk might be a problem itself. While there might be some differences between the definitions provided from different authors, the main idea of the risk remains the same, that the risk is considered to be something negative or bringing negative outcomes.

In the procurement setting there can be many risks associated with procurement process and it is hard to foresee what kind of a risk the company will face, however, during the risk assessment the company has to identify possible risk factors and to draft an action plan as if the risk has happened. Risks are divided in external and internal risks. Helmold M., et al. (2022) distinguishes risks as:

- External, factors that are beyond of the company's control. External risks can be demand risks, supply risks, environmental risks, business risks, and physical factory risks.
- Internal, which are within company's control. Internal risks can be manufacturing risks, business risks, planning and control risks, mitigation and contingency risks, cultural risks.

Internal risks emerge from within the company, giving a better opportunity for people to mitigate them (Helmold M., et al., 2022). Further, Blunden T. and Thirlwell J. (2021) note that external risks can be coded as PRESTEL:

- Political - political uncertainty may impact national and international markets.
- Regulatory – e.g., laws related to product approval and development, privacy, and general governance expectations.
- Economic - economic conditions may restrict growth labour market, new competitors and disrupters. Rising cost of labour. Inflation.
- Social – companies experience influence from social media, the press, politicians, and broader society. Changes in ethics and culture, also epidemics and pandemics, shape business environment.
- Technological – new technology or inventions (e.g., AI or robotics), e-business. Unpreparedness for cyber attacks can interrupt operations and cause brand damage.

- Environmental – the effect of climate change, impact of using specific raw materials, carbon footprint, emission reduction, etc.
- Legal – regulations and laws, evolving labor laws.

Katsaliaki K., et al. (2022) group risks according to their frequency of occurrence. The following risks are listed from low to high occurrence frequency:

- Catastrophic events/macro level risks (natural disasters, terror attacks, political instability, wars, diseases and epidemics, pollution, legal, bureaucratic events, political factors, currency exchange rate, business ethics).
- Demand side effects (rush orders and customers not giving enough information about their orders).
- Supply side events (supplier failure, e.g., bankruptcy, supplier products quality problems, sourcing constraints).
- Logistics-transportation events (poor logistic performance that causes delays, scheduling errors, non-optimal route selection, transport disruption due to weather conditions, traffics, customs).
- Production infrastructural events (equipment breakdown, labor related issues such as labor strikes, industrial accidents, cyber-attacks and data breach).

According to Langedal B. (2023), the most common risks are not analysing needs well enough, choosing the wrong provider, supply chain problems, bad contract management, and not keeping track of relationships with suppliers. Rohn S. (2022) separates 13 risks associated with procurement which, besides the previously mentioned ones, not training suppliers and vendors properly, price changes, manual procurement processes and poor e-procurement adoption, not accurate forecasting, compliance management, budget excess, talent shortage. Shuler K. (2021) points out another risks, that are complicated projects, fraud, changing work environments, bad supplier performance, and unethical sourcing.

Chichilnisky G. and Geoffrey H. (1998) point out the possibility of unknown risks. Unknown risks are the risks that organization has not faced yet in the past. Examples of unknown risks are environmental health risks of new epidemics or catastrophic events, unpredictability regarding the climate change (e.g., frequency or new incidents of hurricanes). Since it the linearity of climatic events can not be predicted, organizations face a risk. Unknown risks can also be called force majeure.

Supply chain risks are potential interruptions and uncertainties that may hinder the flow of goods, services, information, and payments within a supply chain. According to Ivanov D. (2021) these risks may arise from various factors, e.g., supply, demand, production and logistic process. In addition, supply chain risks are vulnerable to macro level risks such as climate changes, natural resources, geopolitical situation, etc. Truong Quang H. and Hara Y. (2017) distinguish seven groups of risks:

- External risks (risks come from an external perspective of supply chain that can be cause by sociological, geopolitical reasons, etc.).
- Time risks (delays in supply chain)
- Information risks (miscommunication, distorted information, etc.)
- Financial risks (currency fluctuations, interest rates, etc.)
- Supply risks (unstable quality, price fluctuations, supplier bankruptcy, etc.)
- Operational risks (caused by problems within organization)
- Demand risks (a lot of competition in the market, customer bankruptcy, etc.)

Various frameworks and categories were used to define procurement risks by different authors. However, the basic idea is still the same, procurement risks contain uncertainty, and possible disruptions may occur when purchasing products and services. Even though, several viewpoints were reflected, they all emphasize one crucial requirement, which is managing uncertainty to ensure the stability of the supply chain.

3.2 Risk management process

According to Risk Management Guidelines ISO 31000:2018, risk management refers to coordinated operations aimed to direct and control an organization's risk exposure (Risk Management Guidelines ISO31000:2018). These guidelines show an organized way for business in all fields to find, evaluate and mitigate risks. According to Gurtu A. and Johny J. (2021), risk management involves coordinating actions and processes to reduce risk and achieve business goals. It is important to remember that Risk Management Guidelines ISO31000:2018 represents the term likelihood of a risk as a chance for something to happen, either if it is defined, measured or concluded objectively or subjectively, in a qualitative or numeric way. The goal of risk management is to create value and protect it. Risk Management Guidelines ISO31000:2018 help organizations to manage risks by providing a set of principles and emphasizes that every company would have a risk management that is tailored to its needs.

The effectiveness of supply management heavily depends on procurement risk management (Hong Z. and Lee C., 2013). The main goal of risk management in procurement is to detect, evaluate, and minimize risks that may arise throughout the procurement process in order to provide a seamless and effective procurement process. Figure 5 shows components that belong to the risk management process.

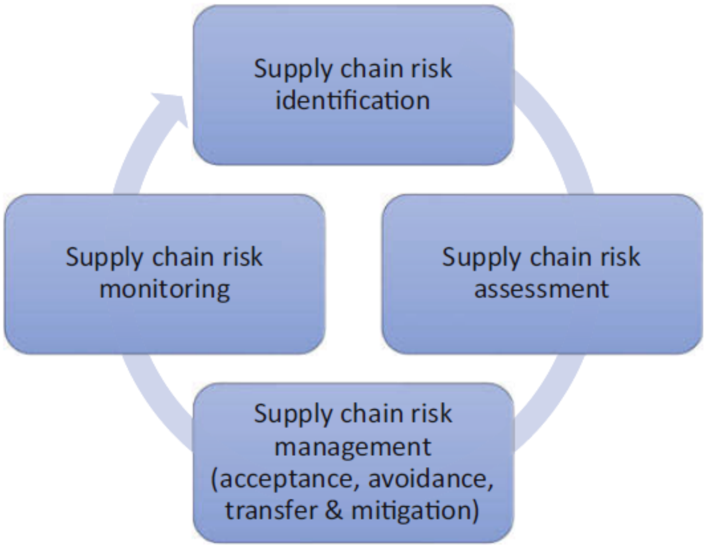

Figure 5. Supply chain risk management process (Khojasteh Y., et al. 2021)

Identifying, evaluating and mitigating risks are all parts of the risk management process. The mode of risk management is cyclical, implying that process is continuous. Risk identification is the first step, during which possible risks are highlighted. This is followed by a risk assessment that analyzes the possibility and consequences of identified risks. Once the assessment is done, mitigation actions are created. This stage might also include steps of doing nothing with a risk, what is called risk acceptance. The cycle is completed with monitoring and review to follow up on mitigation actions if they were effective (Khojasteh Y., et al. 2021).

3.2.1 Risk identification

A key component of risk management is risk identification and organizations should identify all risks, whether or not they are under their control (Hallikas J., et al. 2004, Risk Management Guidelines ISO31000:2018, Rao S. and Goldsby T., 2009). As per Risk Management Guidelines ISO3100:2018, finding, identifying and characterizing risks, is the goal of risk identification. There are plenty of risks that can interrupt materials flow, e.g., natural disasters, transportation accidents, geopolitical events, etc. It is worth noting, that e.g., force majeure disruptions are challenging to foresee and manage (Gurtu A. and

Johny J., 2021). However, there are other kind of risks that might not stop the flow of materials, but could mean that the organization has to change how it works, for example, its environmental policies (Khojasteh Y., et al. 2022).

It is the responsibility of every company to identify its own risks, and typically does so from its own perspective (Hallikas J., et al. 2004). There are many diverse methods to help identifying risks and organizations can use different approaches. Some of the common techniques are summarized below, based on Khojasteh Y., 2022, Tummala R. and Schoenherr T., 2011, Risk Management – Risk Assessment Techniques Guidelines ISO31010:2009, and Hopkin P., 2018:

- Supply chain mapping. This technique is used to visually depict supply chain flows. Potential risks can be better detected if the supply chain details have been mapped.
- Brainstorming sessions. A team of people (with knowledge of systems, processes, etc.) collaboratively create a list of risks. Brainstorming can be formal, structured when participants prepare in advance, and informal – less structured and more *ad-hoc*.
- Checklists. They are used to identify how often the exact failure happened in the past, and if it may be evaluated as a risk for the future.
- Fault tree analysis. This technique starts with an undesired incident and analysis the possibilities for how it could have occurred.
- Failure mode and effect analysis (FMEA). By using this technique, the ways in which the product or process can fail are identified, as well as its implications.
- Ishikawa (Fishbone diagram). By using this approach, the possible causes for a problem are identified. This technique is often used to facilitate brainstorming.
- 5 WHYs technique. Repeatedly asking “why?” to each of the answers until the root cause is found.

Selecting the appropriate risk identification method calls for understanding the specific needs, resource availability, understanding and scheduling limitations. According to Paul Hopkin (2018), risk assessment can be done by involving staff members and departmental management, however, the overall approach will be influenced by selected risk assessment techniques, because certain techniques might require different employees’ involvement. By identifying possible risks, organizations can prepare for the unexpected. The process of risks' identification is the foundation of risk management, which also establishes a basis for practical measures (Hopkin P., 2018).

3.2.2 Risk assessment

According to Paul Hopkin (2018), risk identification and risk rating belong to risk assessment. After the risks have been identified, the following step in risk management cycle is risk rating or evaluation, where the nature of risks is understood and rated accordingly by significance. The level of information and complexity of a risk analysis depends on its intended use. When a risk evaluation is being done, the results of the risk analysis are compared to the set risk guidelines to see what other steps need to be taken. This can help to decide whether to do nothing or look into ways to minimize the risk (Risk Management Guidelines ISO31000:2018). The company needs to do a risk review and set priorities in order to choose the best management actions (Hallikas J., et al., 2004).

In this stage, a popular tool in risk assessment, is a risk ranking/prioritization matrix or also called as a heat map (Khojasteh Y., 2022, Hopkin P., 2018). Risk matrices are well-liked and frequently used because they are straightforward and efficient methods of managing risks. There might be different types of risk matrices, however, the most popular one is 5x5 risk matrix. In risk matrices, the "likelihood" or "probability", or "frequency" of an identified risk has several categories in its rows or columns, and a severity of its "impact" or "consequences" has several categories as well in its columns or rows, and are usually evaluated on a five-class scale (Cox A. L. J., 2008).

Figure 6 shows an example of a standard 5x5 matrix. At this point, the most important thing is to prioritize risks, so the organization can focus on high-probability and/or severity risks. However, organizations are more prone to pay attention to high-severity and high-probability risks because they are likely to happen and, if occurred, would highly impact operations. Materials that are single or sole-sourced present a significant risk as well (Khojasteh Y., 2022). By giving risks a visual representation, the risk matrix facilitates comprehension and communication of risk intensity. The risk matrix allows the rating of the risks so that priority can be identified. The final rate of a risk in the matrix is calculated by multiplying likelihood with the impact (Hopkin P., 2018, Tummala R. and Schoenherr T., 2011)

Risk exposure value = Risk likelihood index x Severity index

Likelihood		Severity: Minimal *1*	Minor *2*	Moderate *3*	Major *4*	Extreme *5*
Extremely likely	*5*	5	10	15	20	25
Somewhat likely	*4*	4	8	12	16	20
Neither likely nor unlikely	*3*	3	6	9	12	15
Somewhat unlikely	*2*	2	4	6	8	10
Extremely unlikely	*1*	1	2	3	4	5

Risk tolerance
Non-tolerance
Low tolerance
Medium tolerance
High tolerance
Acceptance

Figure 6. An example of a supply chain risk prioritization matrix (heat map) (adapted from Khojasteh Y., 2022)

Numbers in the risk matrix show different levels of severity, e.g., numbers 16 – 25 are considered to belong to the most critical class. Besides, color coding can be implemented to better depict the values range. Risks in risk matrix can be segregated into five color-coded zones, based on Qazi A. and Akhtar P., 2020, Khojasteh Y., 2022, and Hopkin P., 2018:

- Negligible or acceptance zone (dark green zone) – risks are rare to occur and there is no need for further concern.
- Acceptable or high tolerance zone (light green zone) – risks are unlikely to occur but might happen and risks have to be monitored. Both green zones mean that organization will be comfortable by taking those risks, because the impact is too low.
- Medium tolerance or controllable zone (yellow zone) – risks are possible and likely to occur. There is a need for adopting emergency plans.
- Low tolerance or critical zone (orange zone) – risks are likely to occur frequently and there is a need to have mitigation plans in place.
- Non-tolerance or unacceptable zone (red zone) – risks are almost certain to occur. The criticality of risk must be brought down by establishing immediate mitigation actions. This zone represents the risks that will be of a concern of an organization.

The matrix is divided into different zones that shows different risks' grading and means different level of risk severity. It is also possible to have a different color coding by using only three colors and their meanings: green (low risk), yellow (medium risk), and red (high risk), however it is up to an organization what style they would choose since there are multiple variations (Cox A. L. J., 2008).

Risk assessment activities can reveal that various workshop attendees will have different perceptions of risks (Hopkin P., 2018). It is always helpful to talk about reasons for varying opinions regarding the risk, and this could possibly lead to a mutual agreement for risk evaluation.

A company probably will not have all the tools it needs to handle every risk. As a result, it has to choose which risks to accept for the short and long term, manage actively, or just monitor. However, there is no absolute rule as to how a risk assessment has to be performed, and it is up to an organization at what depth they want to perform a risk assessment and how (Ostrom L. T. and Wilhelmsen C., 2012).

3.2.3 Risk control

Risk control and mitigation are another important part of the risk management cycle involving methods and strategies how to minimize, eliminate or control the impact of risks. Only the most important and high-risk issues need to be brought to the upper level of department or organization. Once the most important risks are identified, the organization should review the existing measures and decide if any further actions are needed.

Crouhy M. et al., 2023, Khojasteh Y., 2022 and Hopkin P., 2018 separate four ways to respond to risks. There are different words used for the ways to respond to risks:

- Tolerate (accept/keep/retain). The risk is identified and kept, no reaction toward the risk, because the impact of the risk happening would be too low or a risk itself is rated as a rare risk. Quite often the strategy to keep the risk is chosen when applying other risk strategies is too costly. Also, it is impossible for the organization to eliminate all risks, and some of them will remain.

- Treat (mitigate/control/reduce). The risk is not eliminated, however the organization tries to do everything to prevent it or reduce the risk to an acceptable level. Actions to reduce the probability of risk occurrence or its severity are taken.
- Transfer. This approach shifts the responsibility on the third party, and often it is insurance company. Possible risk transfer strategies are supply chain disruption insurance, outsourcing, risk-transfer contracts. However, the risk transfer strategies may not eliminate the risk or its exposure and impact, it just moves the risk to another party. This option is good when organizations face financial risks.
- Terminate (avoid, eliminate). The risk is considered as unacceptable. The organization has to eliminate it before the risk occurs.

A part of a risk control is about making decisions how to mitigate and/or accept risks (ICH guideline Q9 on quality risk management). Risk controls can be detective, corrective, directive, and preventive (Blunden T. and Thirlwell J., 2021, Hopkin P., 2018):

- Preventive (terminate) controls act to prevent the risk from happening again.
- Corrective (treat) controls are put in place after the risk has happened to reduce the impact of the event. Usually, corrective controls are taking action on following risk monitoring.
- Directive (transfer) controls ensure that a particular outcome is achieved. They give directions to people on how to ensure that risk does not occur again, and usually policies, procedures, and manuals are used for that purpose.
- Detective (tolerate) controls are used after the risk has happened and identify and mitigate that risk.

After risks have been mitigated and corrected as effectively as possible, the organization should then focus on implementing directive controls aimed at guiding the actions of those involved in managing that specific risk (Hopkin P., 2018).

Since businesses are unable to react to threats that have not been detected, risk mitigation is a crucial component of risk management (Chapman R. J., 2011). Depending on the sector a company works in, different supply chain risk mitigation techniques and risk tolerance levels will be used (Khojasteh Y., 2022).

3.2.4 Risk monitoring

The final step of the risk management process is risk monitoring which is a continuous process involving observation and evaluation of identified risks and their mitigation strategies, and identifying new risks. This step also includes observations about changing situations and environment, because previously unidentified risks might occur (Kırılmaz O. and Erol S., 2017). According to Khojasteh Y., 2022, an organization has to frequently check its internal operations, supply chain and external environment to spot new sources of risks, and also assess if the established risk mitigation strategies are effective. As Kırılmaz O. and Erol S. (2017) state, effective risk monitoring also depends much on real-time observation and tracking. According to Risk Management Guidelines ISO31000:2018, the risk management method and its results should be reviewed and monitored on a regular basis. This should be planned as part of the process, and everyone should know what their role is. The risk management process and its outcomes have to be documented. The main aims of this are to provide information for decision making, improve risk management activities, inform organization about risk management activities (Risk Management Guidelines ISO31000:2018, ICH guideline Q7).

3.3 Review of industry guidelines

Pharmaceutical manufacturing companies should adhere to industry requirements and guidelines, which define good manufacturing practice (GMP) process and what has to be evaluated throughout it. Only a few guidelines define a general framework for risk management and risk quality management and they do not offer any specific directives for procurement operations. This is because risk management approach is universal and can be adapted across all departments and customized to the company’s needs. The short overview of the guidelines is described next.

ICH guide Q7 guidelines focus more on the quality management, buildings and facilities, equipment, documentation and recording, in-process controls, packaging, storing and also material management. Material management in this case involves guidelines for receipt and quarantine, testing and release, storage and re-evaluation. Those rules apply to raw materials. As the guideline states “Materials should be purchased against of agreed specification from a supplier, or suppliers, approved by the quality unit”. However, in the guideline, there is nothing related to the materials risk assessment. The same guideline is followed by Food and Drug Administration (FDA) (ICH guide Q7).

FDA GMP guidelines 21 CFR (Code of Federal Regulations) part 211 defines minimal GMP requirements for methods, facilities, production, process and laboratory controls to be used for the manufacturing, processing, packaging and hold of a drug, so a drug meets quality characteristics. Subpart E of the document also describes the handling of materials the same way as mentioned in ICH guide Q7, but it does not address the risk assessments for manufacturing materials (CFR title 21 guide 211).

EudraLex Volume 4 (The collection of rules and regulations governing medicinal products in the European Union) guidelines present the GMP requirements that should be applied in the manufacturing of advanced therapy medicinal products (ATMPs). Besides all other criteria drawn on personnel, premises, equipment, documentation, production, qualification and validation, drug batch release, and quality control. Regarding starting and raw materials, the guideline emphasizes the importance of documentation for their control and use, for example, after the receipt, materials have to be documented, all of them have to have specifications, etc. (EudraLex Volume 4, 2014, Good Manufacturing Practice specific to Advanced Therapy Medicinal Products and EudraLex Volume 4, 2017, Basic Requirements for Active Substances used as Starting Materials).

However, as in previous documents, this volume provides quality characteristics that raw materials must comply with, similar to the ones in ICH guide Q7.

Next, I will explain guidelines that apply to risk management and quality risk management. However, none of them mention risk assessments of the manufacturing materials.

Risk Management Guidelines ISO31000:2018 is not specific for pharmaceutical industry, however, it provides a comprehensive approach to risk management that can be used by organization of any size in any field, because the document is not industry-specific. The document provides an approach to manage any kind of risk and it can be used by people in the organization who manage risks and make decisions.

The ICH guideline Q9 offers pharmaceutical companies quality risk management guidelines for evaluating, controlling, communicating, and reviewing medication quality risks throughout its lifecycle. Quality risk management applies the same framework outlined in the Risk Management Guidelines ISO31000:2018, but in the pharmaceutical setting.

To summarize the overview of internationally recognized standards and regulatory guidelines, they describe GMP requirements, and mention raw materials and what procedures they have to undergo in order to comply to quality requirements. However, no guideline provided an insight towards all manufacturing materials and their risk assessments. Given this information and ISO31000 guidelines, it can be concluded that the general principles of risk assessment apply and can be followed for manufacturing materials risk assessment preparation.

4 Developing the Risk Assessment Procedure

4.1 Applying Theory to Risk Assessment Tool Development

This part of the thesis focuses on a practical part of the development plan implementation, where the risk assessment tool was further developed and improved, and a risk assessment procedure, described in the SOP, was established in the company to be followed on a yearly basis. Taking into account the risk management theory, the initial steps, as described by Khojastek Y., et al. (2021), were applied throughout the risk assessment tool and procedure development process: risk identification, risk assessment, mitigation actions, and monitoring. As Hallikas J. et al. (2004) noted, it is the duty of every company to identify its own risks. The same approach was applied to the risk assessment tool preparations where the potential risks for Company's X materials were predefined. The risk assessment tool was further improved based on the literature, specifically, the 5x5 risk matrix theory adaptation, which helped in the preparation of the risk assessment tool and materials scoring and interpretation. By using a risk matrix, the materials were scored for predefined risks, and color-coding was assigned for immediate visibility and priority identification, so Company X could focus on remedial actions. Since the most critical materials have to be highlighted by the procedure, the tool was developed so that it could reflect not only the supply chain risks, but also that each material would be scored for risk factors that come from the factual data as such: delivery times, sole or single sourced, etc. (section 4.1.3).

4.2 Improving the Risk Assessment Tool

The risk assessment tool, as stated in section 1.3, was initially used in 2022, but in 2023 it was noticed to be too complicated – causing input errors and difficulties for updates. Based on this, the tool was simplified. And in 2024, the risk assessment tool was identified as requiring further improvements. The initial step in the development project involved re-designing the risk assessment tool so that every manufacturing material could be evaluated and categorized based on its criticality for the manufactured drug.

An initial meeting, dedicated to start the risk assessment tool improvement work, was held on May 15th, 2024 (see Appendix 1). During the meeting, it was agreed that materials would be rated using the 5x5 risk matrix. Following the meeting, actual work on improving the risk assessment tool began. Periodical meetings were held to follow the progress of the work, to discuss suggestions for the risk assessment tool's improvements, and to address any other issues. The participants in the meetings, besides myself, were the Procurement Manager and Supplier Quality Senior Specialist. The following sections of the thesis provide a more detailed explanation of the risk assessment tool development.

4.2.1 Supplier and Material Data Collection

A part of the risk assessment tool was dedicated to collect essential data about suppliers and materials that would help assess and evaluate risks better (see Appendix 2). This part of the tool was optimized by carefully evaluating existing columns and either excluding some or adding new ones. Excluded columns were seen as non-essential for the improved risk assessment process. These columns were named “easiness to introduce a new supplier due to regulatory constraints” and “mentioned in the biological license application”. The logic behind excluding these columns was that it is not easy to introduce a new supplier due to the heavily regulated pharmaceutical field the company is in, time-consuming processes that have to be compliant with the documentation, and the fact that the majority of the materials are mentioned in the license application. This information was considered unnecessary and would not provide any benefit during the risk assessment, and every material would be assigned the same score. However, additional columns, such as “if there is the second production site” and “if the second production site was approved”, were added to collect important information that was previously missing. The identification of the second manufacturing site, whether it exists or not, provides more insight in case of disruptions in the primary site. In addition, it was important to have the information on whether the second site was approved (complies with regulations and standards) or not. Unapproved sites cannot be backup options in case of disruptions. An example of material and supplier data collection is provided in Appendix 2. In the visual representations of the risk assessment tool, information on materials, vendors, and suppliers was anonymized. Materials were assigned generic names, while vendors and suppliers were represented by numbers.

4.2.2 Risk assessment for supply chain risks

Risk assessment for the supply chain risks section was designed with the same principle as the 5x5 risk matrix – materials were scored based on the likelihood that the pre-defined risk will occur and its potential impact, and the final score was determined by multiplying likelihood and impact scores (see Appendix 3). Likelihood was scored on a scale of 1 – 5, where 1 indicates a rare likelihood and 5 indicates a certain likelihood for an event to occur (see Table 1).

Table 1. Likelihood and impact scores and their meanings.

Score	Likelihood	Impact
1	Rare	Insignificant
2	Unlikely	Minor
3	Moderate	Significant
4	Likely	Major
5	Certain	Severe

Each pre-defined risk represented a factor that could disrupt or negatively influence the supply chain. Pre-defined supply chain risks were the following:

- Supplier historical supply issues or capacity constraints. These risks were based on the previous suppliers' performance. For example, if performance is poor, it is forecasted to be the same the next year and vice versa.
- Geopolitical factors in the continent and country. It assessed the stability of the country, and region where suppliers' manufacturing sites are.

- Logistics and transportation (focusing mainly on delivery times). For example, if delays were experienced involving a specific supplier, it is forecasted to be the same the next year as well.
- Historical quality issues and complaints.

The scoring system, which ranges from 1 to 5, is systematic and follows a defined framework. Each material is assigned likelihood and impact scores according to the guidelines provided in Table 2 and 3. For example, in the risk assessment, if the material had four reclamations raised during the last year, for the likelihood of the "historical quality issues and complaints on products", it received a score of 3.

Table 2. Risk factors scoring criteria for likelihood and their explanations.

	Score 1	Score 2	Score 3	Score 4	Score 5
Supplier historical supply issues and capacity constraints	Excellent performance, no supply issues, consistent, reliable supply, no shortages	Good performance, rare or minor shortages that are quickly resolved	Average performance, occasional supply issues that do not occur often and are resolved with minimal impact	Poor performance, ongoing supply issues that occur frequently, and regular shortages	Very poor performance, persistent supply problems, constant shortages
Geopolitical factors	Europe (EU) countries (Countries with high stability, predictable regulatory environments, and strong economic conditions)	Europe (non-EU) countries, USA, Canada, Australia, New Zealand (Countries with stable conditions but with some variability or different levels of predictability compared to the lowest risk category.)	Asian countries, Mexico, Tunisia, Puerto Rico (Countries with higher levels of political, economic, or regulatory uncertainty, potentially impacting business operations and supply chains more significantly)	N/A	N/A
Logistics and transportation	On-time deliveries, rarely any delays	Rare delays that are usually minor and have minimal impact on operations	Occasional delays that are ypically handled without major disruptions	Regular delays that cause noticeable disruptions but are somewhat manageable	Persistent and severe delays in transportation that disrupt operations regularly
Historical quality issues and complaints on products	0 or 1 reclamation/year	2 - 3 reclamations/year	4 - 6 reclamations/year	7 - 9 reclamations/year	over 10 reclamations/year

The impact, that each pre-defined risk had on materials, was evaluated based on the group each material belonged to. Materials were categorized into groups according to their function during the manufacturing processes: excipients, raw materials, materials used in analytical work, materials used to maintain facility/equipment status, product contact plastic, primary packaging materials, labeling, and others. Also, these materials were sub-grouped inside the category group. For example, excipients and raw materials can be custom or standard materials. Also, other sub-groups were separated. Table 3 shows a detailed explanation of materials grouping and their impact scores assigned.

Table 3. Impact scoring criteria for each material group.

	Materials' groups	Score
1	**Excipient**	
1.1	Custom excipient	5
1.2	Standard excipient	4
2	**Raw material**	
2.1	Custom raw material	5
2.2	Standard raw material	4
3	**Materials used in analytical work**	
3.1	Used only in analytical work (reagents)	4
3.2	Used only in analytical work (everything else, but not reagents) (e.g., plastics, cell scrapers etc.)	3
3.3	Materials used in analytical work and upstream/ downstream/buffer/facility	5
4	**Materials used to maintain facility/equipment status**	2
5	**Product contact plastic**	
5.1	Product contact plastic (Custom)	5
5.2	Product contact plastic (Standard)	4
5.3	Product contact plastic but not in product contact	3
6	**Other**	
6.1	Other (Custom)	4
6.2	Other (Standard)	3
6.3	Other not in product contact material	2
7	Primary packaging material	5
8	Labelling	5

The more critical the material is for manufacturing, the higher the assigned score will be. For example, custom raw materials, excipients, product contact plastics, primary packaging, and labeling materials were assigned the highest score of 5, which means that they had a severe impact on the manufacturing process (see Table 2).

When the material is assigned scores, the assessment of each risk factor is determined by multiplying its likelihood score by its impact score. The final score of the material (column “AVERAGE of Supply Chain risks”) is calculated by averaging the scores across all evaluated risk factors. The final scores are assigned a color code based on the 5x5 risk matrix color coding explained in section 3.2.2. For reference, see Appendix 3, where a part of the improved risk assessment tool is provided for a demonstrative purpose.

4.2.3 Materials criticality for the drug

The final section of the risk assessment tool was dedicated to scoring materials based on their criticality for a manufactured drug by Company X (see Appendix 4). Since the risk assessment for supply chain risks does not show which materials are the most critical for drug manufacturing, a different type of criticality evaluation was decided to be implemented. For this assessment, the criticality of materials to the drug is evaluated using a binary scoring system (either 0 or 5) based on the selected categories (Table 4) from the “Material and Supplier Data” information (described in section 4.2.1). Using this scoring system, a score of 5 shows a higher level of risk, while a score of 0 shows no risk or minimal risk.

Each selected criterion is linked with potential risks that are associated to the manufacturing process. As such, materials that are purchased from a sole supplier hold a significant risk due to the absence of alternative suppliers. A second manufacturing site is also important because it mitigates disruption risks in case any unforeseen events happen on the first site (e.g., natural disasters, labor strikes, etc.). Customized materials also present a higher risk because they have different manufacturing processes than the standard ones. Any disruption in the availability of excipients and/or raw materials can severely impact the drug manufacturing process due to their importance to the manufacturing process. Excipients and raw materials are important because they are the main components in drug manufacturing, and any disruption in their availability can cause a stoppage in the drug manufacturing process. The last criterion is the prolonged lead times which can predispose to delays in manufacturing, complicated production planning as well as inventory management. After prioritizing these criteria, the materials’ criticality assessment emphasizes areas that are most likely to impact the production.

Table 4. Material scoring system for the selected criteria.

Criteria	YES	NO
1. A Sole supplier	5	0
2. There is a Second manufacturing site	0	5
3. A Customized item	5	0
4. An Excipient	5	0
5. A Raw material	5	0
	> 80 days	**≤ 80**
6.Lead times	5	0

Materials sourced from a sole supplier, custom materials, excipients, raw materials, or those with long lead times are associated with a higher risk, therefore, they receive a score of 5. The final score for a material is calculated by summing up all the scores. The same color-coding principle as used in the 5x5 risk matrix was adopted. See the explanation in Figure 7.

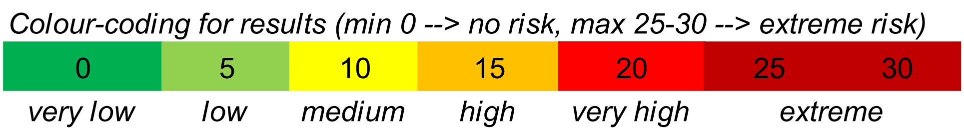

Figure 7. Color coding representation of the materials' criticality to the drug.

Meaning of colors and scores:

- Dark green color – very low risk (score 0).
- Green color – low risk (score 5).
- Yellow color – medium risk (score 10).
- Orange color – high risk (score 15).
- Red color – very high risk (score 20).
- Dark red color – extremely high risk (scores 25 and 30).

The example of the scoring is provided in Appendix 4.

4.3 Piloting the Risk Assessment Tool

After the risk assessment tool was improved, as described in chapter 4.1 and its sub-chapters, its piloting began. First, during May – June 2024, it was decided how to update the risk assessment tool, what kind of information about materials and suppliers has to be collected. Supply chain risks were pre-defined and the structure how to score materials according to their criticality for the drug was created. Second, information about all materials and suppliers was started to be collected in June through July 2024. Following this, during August and the beginning of September, 2024 the materials were scored for supply chain risks based on their importance for drug manufacturing, and scored according to their criticality for the drug.

The risk assessment approach was designed to have a systematic approach – materials were grouped, and impact scores were assigned based on materials' criticality to the manufacturing process. The likelihood of pre-defined risks was also defined in a structured manner. This systematic approach establishes the framework for the risk assessment process. It ensures that anyone can conduct a risk assessment once it is described in the SOP.

When the materials scoring was completed in early September 2024, the tool highlighted the most critical materials for the drug manufacturing. Some highlighted materials had already been recognized as critical before, and their importance was again affirmed.

Following the tool's piloting, the meeting was held on September 13th, 2024 with the Procurement Manager and the Supplier Quality senior specialist to review and discuss the results. It was decided to present the tool to the Procurement department director and Supply Chain director. Another meeting was arranged on September 19th, 2024, where the risk assessment tool was presented and explained to the directors. In this meeting, the risk assessment tool and its results were approved. It was decided that the risk assessment tool and its results would serve as the risk assessment for the year 2025. Following this, the next steps were to schedule meetings to discuss mitigation actions and the risk assessment procedure preparations.

4.4 Mitigation actions

After the directors' approval to use the improved risk assessment tool, the mitigation actions were discussed and agreed in the meeting. The meeting regarding this took place on October 9th, 2024 (see Appendix 1). During the meeting, the possible mitigation actions for each color-coded group were discussed, focusing primarily on the most critical materials (red color-coded materials). Over 600 materials were evaluated, and 8 of them were identified as the most critical. Considering the significance of these materials, the selected mitigation action was to implement a safety stock. The decision was based on the materials' importance to drug manufacturing. Keeping pre-determined safety stocks helps Company X guarantee sufficient material levels when needed to cover unexpected delays or supply shortages. It was also important to estimate the size of the safety stock should be, indicating how many months it should cover in case of disruptions. Currently, the safety stocks for materials are guaranteed for roughly three months or even less, depending on the material group. Moreover, re-assessing current levels of safety stocks was seen as necessary, particularly when the manufacturing is being scaled up. Implementing safety stocks requires collaboration among various departments and/or teams. The production planning team plays a role in providing materials' consumption estimations, while the finance team provides financial impact, evaluates potential storing costs, ensures everything aligns with budgets, etc. Additionally, the warehouse team might be needed to provide information regarding the occupancy of the warehouse and whether there is enough space to store materials stocks.

In addition to the previous mitigation action, fostering close relationships with suppliers of the most critical materials was deemed a supporting measure alongside safety stocks. During the last few years, a focus on building supplier relationship management (SRM) in Company X was given more attention. The relationship with vendors is maintained through regular communication – by having business review meetings (BRM) that involve key teams from both sides. The frequency of the meetings can range from annual or quarterly to monthly, biweekly, or weekly, depending on the vendor's role and the business requirements. Meetings can cover different topics, and they also foster an environment to strengthen the partnership, boost performance, and proactively address any issues. The topics on the meeting agenda are usually related to but not limited to materials quality issues (e.g., defective items, reclamations), supply chain (e.g., lead times, inventory levels if stored at the vendor's location), cost management (e.g., pricing review, payments), any changes related to the manufacturing of material in question, communication topics (e.g. communication effectiveness, feedback), long term partnership goals, any unresolved issues, and any other topic which is deemed important at the time of the meeting. Some suppliers have noted that the more accurate and longer-term oriented (ideally up to 18 months) the Company's X forecast of the need of materials is, the more reliable the supply from their side can be. In addition to the regular meetings, some suppliers have also proposed to hold planning sessions once or twice a year in order to identify potential supply constraints from their side, so Company X could also adjust its safety stocks based on the outcomes of those meetings.

4.5 Establishing the Risk Assessment Procedure

Establishing the risk assessment procedure in the form of an SOP started soon after the mitigation topic was covered. The meeting to discuss what should be covered in the procedure was held on October 22nd, 2024 (see Appendix 1). The established procedure will mandate that a risk assessment is performed every year at the same time. The SOP describes the way the process has to be followed, which ensures the consistent process. The SOP gives step-by-step instructions on how to carry out a risk assessment and this way helps to eliminate subjective opinions and interpretations. Everyone has to follow the same instructions and perform the risk assessment the same way what further guarantees that there are no variations in performance in employees who do the risk assessment. The SOP defines key topics, such as purpose and objectives, scope, and responsibilities allocated, and provides a detailed description of the risk assessment process and how to do it using the risk assessment tool. The roles in the SOP are clarified by defining assigned departmental responsibilities, which also helps to reduce ambiguity. The first draft of the SOP was completed in November 2024 and sent for review to the Procurement Manager and Supplier Quality senior specialist. After the feedback was received, the procedure was finalized in January 2025. As per standard Company X practice, all procurement SOPs must be reviewed and approved by the Supplier Quality team. The SOP was approved on February 11th, 2025, and made effective on March 12th, 2025. When the SOP is made effective, it means that it is officially implemented and must be followed from that date onwards.

The online questionnaire to get feedback and evaluate the risk assessment tool and procedure was delivered to the recipients on February 26th, 2025.

5 Results

5.1 Brief summary of the Risk Assessment development

The problem of the development project was stated as “a lack of a formal risk assessment procedure prevents identifying critical manufacturing materials and makes the business vulnerable and subject to supply chain disruptions”. This problem was tackled by improving a risk assessment tool and creating a risk assessment procedure. The whole development project process reflected the risk management cycle (as shown in Figure 5 in section 3.2). Supply chain risks were pre-defined, materials were scored, mitigation actions, suitable for Company X, were applied. Monitoring, that is an ongoing and continuous process, was also taken into consideration in regards to the risk assessment procedure’s establishment. The existing risk assessment tool was improved by applying theory found in relevant literature sources regarding risk assessment. For the tool’s improvement, primarily literature related to 5x5 risk matrix methodology and risk control was used, while other sources served as supportive materials.

5.2 Evaluation based on objectives

At the beginning of the development project, three objectives were established. The first one was to review existing industry standards and guidelines for risk assessment for manufacturing materials. It is known that pharmaceutical industry must adhere to strict regulatory requirements, however, the review of industry guidelines and standards revealed the absence of specific requirements for pharmaceutical companies to have a formal risk assessment procedure for materials in procurement activities. In this case, a set of general international standards for risk assessment, ISO31000, evaluation applies. The standards are valid for any organization of any size in any field, because the approach set in the standard is not industry-specific. These general principles were taken into account during the development project implementation.

The other two development project objectives were related to designing, piloting and establishing a risk assessment procedure. The objectives were successfully achieved. The Excel-based tool was improved and also combined all material and their supplier data. The design of a risk assessment tool was implemented with a help of an academic literature, which put an emphasis on a structured risk assessment, and from there a methodology of 5x5 risk matrix was applied to score materials for pre-determined supply chain risks. Also, scoring materials according to their criticality for the drug was created using the binary scoring system which was based on the specific selected categories from the collected information about the materials and suppliers. After the improvements to the risk assessment tool were done, the tool was piloted. The piloting revealed the most critical materials which some of the them had already been recognized as critical before, and their importance was again affirmed. The establishment of the risk assessment procedure was successfully implemented as well as an SOP that was made effective on March 12th, 2024, and after that recognized as one of the procedures in the Company X that must be followed.

5.3 Evaluation based on metrics

To measure the successful integration of a risk assessment tool, an online close-ended questions questionnaire (Appendix 5) was delivered to four recipients: procurement manager, senior supplier quality specialist (they were directly involved in the risk assessment procedure), procurement specialist and supplier quality specialist (they were introduced to the procedure after its completion). Using the questionnaire, respondents expressed their opinion regarding the risk assessment procedure effectivity, usability, easiness of use, and overall satisfaction. The findings were based on a very small sample size, with the response rate of 50%. However, while the response rate is low, the responses came from people who were relevant to the development project and their insight gave a perspective on the risk assessment tool. Both responses showed similar attitudes towards the risk assessment tool and procedure, what indicates a positive trend and a lack of variations in opinions. Even though a low response rate is considered as a limitation, it was influenced by factors such as participant’s willingness to respond.

The general effectiveness of the procedure together with the risk assessment tool was rated as good to highly satisfactory with a score of 3,5. Respondents recognize it as effective in identifying critical materials and providing a clear and structured approach. Usability and ease of use of the procedure were seen as above average and good, with a score of 3,25. The satisfaction with the new procedure and performance of the risk assessment tool was seen as good to highly satisfactory with a score of 3,75. However, the procedure being user-friendly received a slightly lower score of 3 compared to all other questions. The new procedure received positive feedback, however in the future it might require a focus on improving user-friendliness. Even though the findings are based on a small number of respondents, the scores represent a favorable insight of the new procedure.

Table 5. Numeric evaluation of questionnaire results.

Statement	Questions	Scores				Score of the question	Final score for the statement
		1	2	3	4		
General effectiveness	The new procedure identifies critical materials well.	Disagree	Partly agree	Mostly agree	Fully agree	3,5	3,5
	The tool provides a clear and structured approach to risk assessment.	Disagree	Partly agree	Mostly agree	Fully agree	3,5	
Usability and ease of use	The new procedure is user-friendly.	Disagree	Partly agree	Mostly agree	Fully agree	3	3,25
	The new procedure is clear and understandable.	Disagree	Partly agree	Mostly agree	Fully agree	3,5	
Overal satisfaction	I am satisfied with the new procedure.	Disagree	Partly agree	Mostly agree	Fully agree	3,5	3,75
	I am satisfied with the overall performance of the risk assessment tool.	Disagree	Partly agree	Mostly agree	Fully agree	4	

The average result showing the overall satisfaction towards the newly established procedure was calculated as described in section 2.4 (see the calculation below):

$$Average = \frac{42}{6 \text{ x } 2} = 3{,}5$$

The average satisfaction is 3,5, indicating good to highly satisfactory satisfaction with the newly established procedure.

5.4 Reliability and limitations of the development project

For the development project mainly qualitative research methods were used with a supplement of quantitative method that was in a form of a questionnaire with close-ended questions. Unstructured interviews were the main method used in the development project when preparing the risk assessment tool improvements and establishing a risk assessment procedure. Unstructured interviews, that were held in a form of a conversation, helped to respond and ask questions at the moment, based on the meeting topic. This way it fostered flexibility where more and additional, supplementing information, related to the development project process, could be shared. As Chauhan Rahul S. (2022)

emphasized, unstructured interviews are a suitable method when collecting information.

Another qualitative method used was document review. This research method was beneficial, because the documents reviewed were fixed and could be reviewed multiple times, and it eliminated a subjective interpretation. However, it is also very important in what quality, how accurate and completed documents are. If the documents were lacking information, it might have been challenging and that might even have hindered their interpretation.

Reliability of the development plan was increased by adding a quantitative method - closed-ended questions questionnaire. The questionnaire prepared this way made data easier to analyze. As it was noted by Rashid Mehal (2024), close-ended questions representing Likert scale are commonly used to measure opinions, what in this case suited the purpose of a questionnaire very well. Despite of this advantage, there was a drawback of online questionnaire which is related to respondents' willingness to participate and provide answers. Only two out of four respondents, to whom the online questionnaire was shared, provided their answers.

For establishing a risk assessment procedure at Company X, the use of 5x5 risk matrix was a suitable method that offered a clear framework for assessing manufacturing materials for pre-defined risks. According to the literature, this method is widely used in risk management because it offers structured and visual representation of risks severity. Further, in order to avoid subjectivity in scoring materials, the scoring criteria were set based on materials importance in the manufacturing process. Another approach used was utilizing a binary scoring system in order to identify the most critical manufacturing materials for the drug. The score of either 0 or 5 was given to materials based on the selected criteria, for example, lead time, manufacturing sites, etc., what helped to avoid subjectivity and provided a reliability.

The development project objectives were met leaving no gaps to be addressed. A challenge of the development project, which did not affect the results, was how to design the whole risk assessment tool so it satisfies the needs of Company X. Since the risk assessment tool was about scoring the manufacturing materials, it was a little bit challenging of adapting the generic 5x5 risk matrix to this specific need. To ensure a practical applicability of the risk assessment tool, it required a thoughtful selection of risk factors and objective scoring criteria, and also that everyone working on this task would be on the same page.

Another limitation, faced in the end of the development project, was related to a low response rate of the questionnaire to gather feedback of the risk assessment procedure. The online questionnaire was distributed to four recipients and only two provided responses, resulting in 50% response rate. However, the low response rate was beyond my control.

6 Conclusions

6.1 Key achievements

The development project aimed to find a solution to tackle business problem regarding the absence of a formal risk assessment procedure in procurement department. The problem was resolved by improving and further developing an Excel-based risk assessment tool and establishing a risk assessment procedure in an SOP format. The whole process was related to risk management and reflected the risk management cycle: risk identification, assessment, control, and monitoring. The risk assessment tool was improved by applying primarily the theoretical framework of the 5x5 risk matrix. The possible supply chain risks were pre-determined, materials assessed and scored, risk mitigation actions applied, and the risk assessment procedure established.

6.2 Relevance for Company X

The implementation of a risk assessment procedure benefits Company X, because previously there was no standardized procedure for manufacturing materials' evaluation, and evaluation itself used to be inconsistent. From now on, with the new procedure all the manufacturing materials will be systematically scored. Also, the establishment of the risk assessment procedure does not prevent the risk assessment tool to be continuously improved when needed. The risk assessment procedure prioritizes materials that need immediate attention. This helps to shift the focus and resources on the most critical materials that are prone to disruptions in case of supply chain disturbances. Due to the applied risk control strategy that was focusing on safety stocks, the risk assessment can also serve as a mean for improving inventory management. Another positive aspect is that by paying attention to critical materials and their suppliers, this way the risk assessment procedure contributes to maintaining better supplier relationships. In conclusion, the structured risk assessment procedure helps Company X to make strategic decisions for proactive risk management.

6.3 Reflection and lessons learned

The development project process was a valuable learning experience when theoretical knowledge merged with a real-life problem and its resolution. The development of the procedure showed the importance of having a structural approach for risk assessment and also challenges of designing a tool that had to align with a real-word Company X needs. One of the outcomes from the development project was that even though, according to pharmaceutical industry guidelines, a risk assessment was not required to be applied in procurement, however having it helps to see the critical materials, what in turn helps for decision making and even for possible supply chain disruptions.

One of the lessons learned is that identification of risks and critical manufacturing materials is more effective than reacting to supply chain disruptions. By identifying critical materials early enough, mitigation actions can be taken to avoid and prevent possible delays or disruptions. When delays or disruptions happen, Company X would face significant consequences. Another lesson learned was that having a clear and structured framework led to consistent and reliable materials assessment and without that there possibly would have been gaps and inconsistencies in identifying critical materials.

The risk assessment procedure is not standing still. As there are changes in Company X needs regarding the growth, for example, new materials or suppliers are introduced, or there are shifts in the supply chain, or additional improvement ideas appear, the procedure will be reviewed accordingly. This shows the last step of risk management cycle – monitoring, what ensures that the risk assessment procedure remains relevant, practical and effective.

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Appendix 1: Research related meetings

Date and length of the meeting	Participants	Topic(-s) discussed	Documented as
February 2nd, 2024 1 hour	Participant 1, Procurement manager	The initial meeting for thesis proposal preparation. The meeting addressed the following areas, such as the current state of manufacturing materials and the risk of purchasing them from a single supplier, the challenges of introducing back-up suppliers, and the absence and the need to have a risk assessment procedure.	Notes
Risk assessment tool improvement and risk assessment procedure preparations			
May 15th, 2024 1.5 hours	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	I received an introduction to the current risk assessment tool (Excel file). We discussed about the importance of materials and how to determine their criticality. Additionally, we also discussed about suppliers, manufacturers and their sites. We agreed on further action to improve the existing risk assessment tool and to assign scores to the each of the manufacturing materials by doing material ranking using 5x5 risk matrix.	Notes
May 24th, 2024 1 hour	Participant 1, Procurement manager	Training on how to use the ERP system and collect the necessary information for a risk assessment.	Notes
May 29th, 2024 1.5 hours	Participant 1, Procurement manager	Improvements to the risk assessment tool were suggested, such as incorporation of supply chain risks and scoring the criticality of each material for the	Notes

Date and length of the meeting	Participants	Topic(-s) discussed	Documented as
	Participant 2, Supplier Quality senior specialist	manufactured drug. We also agreed to start filling in the information related to each material, and start scoring materials using 5x5 risk matrix.	
July 2nd, 2024 1.5 hours	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	We discussed about the new scoring method for material ranking. Additional materials' ranking type, based on binary scoring of materials was introduced, which lets us to see the most critical materials.	Notes
August 15th, 2024 1 hour	Participant 1, Procurement manager	We discussed about the scores given to the materials, some corrections were done in the risk assessment tool. Since the risk assessment tool is very comprehensive and have around 600 items, the discussion was set to continue in the next meeting.	Notes
August 27th, 2024 1 hour	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	The previous discussion continued.	Notes
September 13th, 2024 0.5 hours	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	Remaining questions about the risk assessment tool and materials information in it are answered.	Notes

Date and length of the meeting	Participants	Topic(-s) discussed	Documented as
September 19th, 2024 0.75 hours	Participant 1, Procurement manager Participant 2, Director of the Procurement team Participant 3, Director of Supply and Logistics department	An improved risk assessment tool was presented and discussed with the directors. The risk assessment tool was accepted as suitable for further use.	Notes
October 9th, 2024 1 hour	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	The meeting was dedicated to discuss about mitigation actions for the materials after they were scored. Possible mitigation actions for each color-coded group were discussed. The main attention was paid to the most critical, red color-coded, materials.	Notes
October 22nd, 2024 1 hour	Participant 1, Procurement manager Participant 2, Supplier Quality senior specialist	The purpose of this meeting was to discuss the writing process of the risk assessment procedure and what has to be mentioned, when it is expected to be written.	Notes

Appendix 2: Visual representation of materials and suppliers' data collection

	A	B	D	E	F	G	H	I	J	K	L	N	O	P	Q	R
3				Material and supplier data												
4	Component name	ITEM ID	Vendor	Product step	Material classification as per SPE	Supplier (sole/single/dual source)	Supplier specified in SPE	Supplier manufacturing site location - ISO3166 2-digit country code (CN, US, JP, etc.)	Standard/ Customized item (S/C)	Standard item available (Y/N)	Lead time (Days)	Contract (supply agreement) in place (Y/N/In Progress)?	Notification period for contract termination in months?	Back-up supplier in place (Y/N)?	Is there a second production site? (Y/N)	Supplier Contingency Plan. Has second production site been approved (Y/N)

			Material and supplier data												
Component name	ITEM ID	Vendor	Product step	Material classification as per SPE	Supplier (sole/single/dual source)	Supplier specified in SPE	Supplier manufacturing site location - ISO3166 2-digit country code (CN, US, JP, etc.)	Standard/ Customized item (S/C)	Standard item available (Y/N)	Lead time (Days)	Contract (supply agreement) in place (Y/N/In Progress)?	Notification period for contract termination in months?	Back-up supplier in place (Y/N)?	Is there a second production site? (Y/N)	Supplier Contingency Plan. Has second production site been approved (Y/N)
Medium for cells	001	Vendor 1	Upstream/Analytical	Raw material	Single	Supplier 1	UK	S	Y	42	In progress		N	N	N
Hepes reagent	002	Vendor 2	Analytical	Material used in analytical work	Single	Supplier 2	UK	S	Y	7	In progress		N	N	N
L-Glutamine reagent	003	Vendor 2	Upstream/Analytical	Raw material/Material used in analytical work	Single	Supplier 2	UK	S	Y	7	In progress		N	N	N
PBS reagent	004	Vendor 2	Upstream/Analytical	Raw material/Material used in analytical work	Single	Supplier 2	UK/US	S	Y	14	In progress		N	Y	Y
Penicillin/streptomycin	005	Vendor 2	Analytical	Material used in analytical work	Single	Supplier 2	US	S	Y	14	In progress		N	N	N
Sodium Chloride	006	Vendor 3	Analytical	Material used in analytical work	Single	Supplier 3	US	S	Y	21	Y	6	N	N	N
Trypan blue stain	007	Vendor 2	Upstream/Analytical	Material used in analytical work/Other	Single	Supplier 4	US	S	Y	14	In progress		N	N	N
Sodium dodecyl sulphate	008	Vendor 4	Analytical	Material used in analytical work	Single	Supplier 5	US	S	Y	14	Y	18	N	N	N
Cell Counting Kit	009	Vendor 5	Analytical	Material used in analytical work	Single	Supplier 6	JP	S	Y	14	N		N	N	N
Cuvette Cleaning Solution	010	Vendor 3	Equipment	Material used maintain facility/equipment	Single	Supplier 7	DE	S	Y	7	Y	6	N	N	N
Conductivity standard	011	Vendor 3	Analytical/Equipment	Material used in analytical work/Material used maintain facility or equipment stat	Single	Supplier 8	IE	S	Y	7	Y	6	N	N	N
Ethanol	012	Vendor 6	Facility	Material used maintain facility/equipment status	Single	Supplier 9	UK	S	Y	90	Y	6	N	N	N
Cleaning agent	013	Vendor 6	Facility	Material used maintain facility/equipment status	Single	Supplier 9	UK	S	Y	90	Y	6	N	N	N
Cell culture flask	014	Vendor 3	Upstream/Analytical	Product contact plastic/materials used in analytical work	Single	Supplier 2	DK	S	Y	21	Y	6	N	N	N
Cell culture flask 2	015	Vendor 3	Upstream/Analytical	Product contact plastic/materials used in analytical work	Single	Supplier 2	DK	S	Y	42	Y	6	N	N	N
Cryotubes	016	Vendor 3	Upstream/Downstream/Analytical	Product contact plastic/materials used in analytical work	Single	Supplier 2	DK	S	Y	21	Y	6	N	N	N
Cell scrapers	017	Vendor 3	Analytical	Material used in analytical work	Single	Supplier 2	US	S	Y	21	Y	6	N	N	N

Appendix 3: Visual representation of supply chain risks

	SUPPLY CHAIN RISKS (Likelihood vs Impact)												
Component name	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Suppliers historical supply issues or capacity constraints(shortages)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Geopolitical factors (in the continent, country, political situation)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Logistics and transportation (e.g.,poor logistics performance that causes delays, scheduling errors, transport disruption due to weather conditions, traffics, custom)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Historical quality issues and complaints on products	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	AVERAGE of Supply Chain risks

	SUPPLY CHAIN RISKS (Likelihood vs Impact)												
Component name	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Suppliers historical supply issues or capacity constraints(shortages)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Geopolitical factors (in the continent, country, political situation)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Logistics and transportation (e.g.,poor logistics performance that causes delays, scheduling errors, transport disruption due to weather conditions, traffics, custom)	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	Likelihood (1-5) 1-rare, 2-unlikely, 3-moderate, 4-likely, 5-certain Historical quality issues and complaints on products	Impact (1-5) 1-insignificant 2-minor 3-significant 4-major 5-severe	Evaluation	AVERAGE of Supply Chain risks
Medium for cells	1	4	4	2	4	8	1	4	4	2	4	8	6
Hepes reagent	1	4	4	2	4	8	1	4	4	2	4	8	6
L-glutamine reagent	1	4	4	2	4	8	1	4	4	2	4	8	6
PBS solution	1	4	4	2	4	8	1	4	4	1	4	4	5
Penicillin/streptomycin	1	4	4	2	4	8	1	4	4	1	4	4	5
Sodium Chloride	1	4	4	2	4	8	1	4	4	1	4	4	5
Trypan blue stain	1	5	5	2	5	10	1	5	5	1	5	5	6
Sodium dodecyl sulphate	1	4	4	2	4	8	1	4	4	1	4	4	5
Cell Counting Kit	1	4	4	3	4	12	1	4	4	1	4	4	6
Cuvette Cleaning Solution	1	2	2	1	2	2	1	2	2	1	2	2	2
Conductivity standard	1	5	5	1	5	5	1	5	5	1	5	5	5
Ethanol	1	2	2	2	2	4	1	2	2	2	2	4	3
Cleaning agent	1	2	2	2	2	4	1	2	2	2	2	4	3
Cell culture flask	2	4	8	1	4	4	1	4	4	2	4	8	6
Cell culture flask 2	2	4	8	1	4	4	1	4	4	2	4	8	6
Cryotubes	1	4	4	1	4	4	1	4	4	1	4	4	4
Cell scrapers	1	3	3	2	3	6	1	3	3	1	3	3	4

Appendix 4: Visual representation of materials criticality for the manufactured drug

	Criticality for the drug						
Component name	Sole supplier YES - 5 NO - 0	Second manufacturing site YES - 0 NO - 5	Lead times >80 days - 5 ≤80 days - 0	Custom item - 5 Standard item - 0	Expipient or primary packaging product YES - 5 NO - 0	Raw material YES - 5 NO - 0	Criticality for the drug FINAL RESULT

	Criticality for the drug						
Component name	Sole supplier YES - 5 NO - 0	Second manufacturing site YES - 0 NO - 5	Lead times >80 days - 5 ≤80 days - 0	Custom item - 5 Standard item - 0	Expipient or primary packaging product YES - 5 NO - 0	Raw material YES - 5 NO - 0	Criticality for the drug FINAL RESULT
Medium for cells	0	5	0	0	5	5	15
Hepes reagent	0	5	0	0	0	0	5
L-glutamine reagent	0	5	0	0	5	5	15
PBS solution	0	0	0	0	5	5	10
Penicillin/streptomycin	0	5	0	0	0	0	5
Sodium Chloride	0	5	0	0	0	0	5
Trypan blue stain	0	5	0	0	0	0	5
Sodium dodecyl sulphate	0	5	0	0	0	0	5
Cell Counting Kit	0	5	0	0	0	0	5
Cuvette Cleaning Solution	0	5	0	0	0	0	5
Conductivity standard	0	5	0	0	0	0	5
Ethanol	0	5	5	0	0	0	10
Cleaning agent	0	5	5	0	0	0	10
Cell culture flask	0	5	0	0	0	0	5
Cell culture flask 2	0	5	0	0	0	0	5
Cryotubes	0	5	0	0	0	0	5
Cell scrapers	0	5	0	0	0	0	5

Appendix 5: A questionnaire with close-ended questions and assigned numeric values

	Statements	Answers			
		Scores			
		1	2	3	4
General effectiveness					
1	The new procedure identifies critical materials well.	Disagree	Partly agree	Mostly agree	Fully agree
2	The tool provides a clear and structured approach to risk assessment.	Disagree	Partly agree	Mostly agree	Fully agree
Usability and ease of use					
3	The new procedure is user friendly.	Disagree	Partly agree	Mostly agree	Fully agree
4	The new procedure is clear and understandable.	Disagree	Partly agree	Mostly agree	Fully agree
Overall satisfaction					
5	I am satisfied with the new procedure.	Disagree	Partly agree	Mostly agree	Fully agree
6	I am satisfied with the overall performance of the risk assessment tool.	Disagree	Partly agree	Mostly agree	Fully agree