UNIVERSITY LJUBLJANA
FACULTY OF ECONOMICS

MASTER'S THESIS

RISK MANAGEMENT IN THE DISTRIBUTION PROCESS OF BIOSIMILAR PRODUCTS IN THE PHARMACEUTICAL INDUSTRY

Ljubljana, July 2016 KAJA KELHAR

AUTHORSHIP STATEMENT

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INTRODUCTION

Optimization and improvement of planning procedures, inventory turnover and on time deliveries are processes which support and enable supply chains to reach their goals, targets and supply markets on time and enable companies to stay competitive on the market for longer periods. One of the important processes of the supply chain is the distribution process itself and the shipment system within, which the company has in place. To be able to supply the market, a company needs to be able to maintain and enhance its shipment processes, to deliver the goods on time, within which the quality of products remains uncompromised. With supply networks spread all over the world and risks present at every step, designing a good distribution system is a complex and important process and if done properly, it can offer significant opportunities for the company and creates a strategic advantage.

Distribution process and its complexity are directly related to particularities of goods being distributed. In today's global supply chains we can see an increasing trend where temperature-controlled supply chains are coming to the forefront. Their goal is being able to effectively supply different products in temperature controlled environment from beginning to end. Since supply networks are globally spread, this means that they need to consider and address differences in environmental conditions, custom regulations, longer transportation routes and possible changes in transport means along the way. Overall we are talking about highly complex processes and as such all possible risks along the line should be identified and tackled as soon as possible. Between 2004 and 2014, the market of temperature-sensitive products has grown by more than 50% and such trend will also be seen in the future (Lipowicz & Basta, 2014), which is why nowadays having an implemented shipment conformance system in the distribution process is one of the top priorities.

In my thesis I will shift my focus to cold chain distribution process. This refers to the transportation of products that in order to uphold their integrity must be transported within a certain temperature range. Cold chain products and processes related to them are coming to the forefront, not only in the chemical and food industry, but also in the pharmaceutical industry. Significant increase in demand for cold chain infrastructure in pharmaceutical industry is also seen due to the emergence of bioscience, since cold chain products such as biologics, vaccines and blood products must be maintained in controlled temperature environment that lies in the range between 2˚C and 8˚C. Any variation out of the specific temperature, can partially or wholly, cause irreversible effect of the product; this is why it is required to consider and implement very strict guidelines, which must be followed to enable the product's quality, safety and viability.

Cold chain healthcare logistics is currently faced with two major growth drivers; the growing demand for quality on one side and the fact that drugs are becoming more cost effective, due to increased competition on the market and due to the emergence of generic drugs. At the same time lack of adequate cold chain infrastructure and improper procedures, present major

obstacles in this field. Any temperature excursions in transportation of heat sensitive products can cause an adverse reaction to the product if consumed (Transparent Market Research, n.d.). The ability to maintain the correct temperature environment over the whole transportation period becomes crucial. One of the challenges that companies in the pharmaceutical industry are currently facing, is the distribution of cold chain products to different countries across the globe. Many companies add multiple linkages to their global supply chain, not assessing the risks that the extension of the cold chain and its subsequent complexity brings (Szuhaj, Vohra, Raizada, & Windnagel, 2013, p. 1).

To know what to expect is a great advantage that should already be recognized by companies today. This is why I would like to emphasise the importance of risk management in the distribution process. Since pharmaceutical supply chain industry heavily relies on controlled and uncompromised transport and is working towards establishment of process which maintain shipment integrity, I decided to explore distribution process of cold chain products, with emphasis on biosimilars. This is also an area in which I was involved in a multinational company for two years, so I want to combine theoretical knowledge with my practical knowledge by doing a risk assessment of the distribution process of biosimilars, followed by analysis of gathered data to try and identify when, why and how main risks, which companies are facing when distributing biosimilar products, occur. Since global supply chains are long and complex due to many factors involved, I will focus solely on distribution process of biosimilars from the company to the wholesaler, without additional intermediates in between and with strong emphasis on the delivery process (preparation and loading of goods, the physical shipment of the goods, and their unloading and further storage).

My purpose in this thesis is to provide pharmaceutical companies a fast, simple and more organized way on how to recognize and evaluate main risks encountered in the distribution process. I want to find out the hidden challenges that companies can face when first setting-up the shipment process for biosimilars or for any other temperature sensitive products. By doing so, hopefully the proposed steps and the risk management tools used could provide a generic framework for risk assessment for others working in this field, which they could apply in practice. At the same time I would also like to provide an overview of current literature in the field of risk management.

My goal in this master thesis is to analyse the shipment process of biosimiliar products with the help of risk management tools. Companies should be aware that any failures in their distribution process can lead to shipment delays in the best case scenario or worse to rejections of the batch and its destruction, which can lead to stock outs on the market, unforeseen destruction costs, additional replenishment orders and decrease of the company's brand image. Thus having an implemented shipment conformance system in the distribution process is one of the top priorities. I wish to identify risks and provide proposals which would enhance and improve the distribution process. With the review of existing literature in the first part I will try to get the necessary theoretical background which I will then use in combination

with my practical knowledge to conduct a risk analysis of the distribution process. I will tackle the problem of risk in biosimilar shipment process with the use of different risk management tools but will focus on the application of Failure Mode and Effect Analysis (hereinafter: FMEA). The research questions which I would like to address through my analysis are stated below.

- What are the specifics of the biosimilar cold chain process, compared to the ''general'' pharmaceutical products?
- Could FMEA and other risk management tools be used to identify the main risks in the distribution process of biosimilars and evaluate their negative effects on the company's performance?
- How can we decrease these risks in a company and therefore improve the process and make it more compliant?
- Could steps taken in this analysis be used as a general framework for other companies which would like to conduct similar analysis and which are dealing with biosimilars or other temperature sensitive products?

The analysis presented in this master thesis is done by using the combination of the theoretical and empirical approach. First, the theoretical part is presented, based on using a descriptive approach where introduction to supply chain risk management and pharmaceutical industry are provided. Key sources of literature are taken from published research and expert literature from different publications, books, magazines and on- line resources. In the empirical part a risk analysis of the distribution process in multinational pharmaceutical company, which was taken as a benchmark and general model, is conducted. Here I used assembled theoretical knowledge and data from the first part as well as my practical knowledge and experiences which I received while working with cold chain products, which helped me identify most suitable steps on how to approach the problem and conduct the analysis. The findings which derived from the analysis are then further analysed to provide us with manageable end data which I was than able to interpret and explain to such extent that they helped me answer my research questions.

Master thesis comprises from 3 main chapters. The first and second chapter present theoretical part of my thesis and are the base for my practical part, by providing the reader with main theoretical background needed for understanding the thesis topic. In the first chapter the existing literature review of concept of supply chain, supply chain management and supply chain risk management are presented. Emphasis are given to risk management process, its steps and risk management tools which were later on used in my practical part when conducting the analysis. In the second chapter I focused on the concept of pharmaceutical supply chain and the specifics of biosimilar products. This part provides the reader with an introduction to cold chain process as well as information about the importance of maintaining the cold chain at all time. The practical part begins in the third chapter where all stages of the distribution process of biosimilars on the benchmarked process, are firstly

described and also presented visually with the help of a flowchart, to provide the reader with a better overview of the process. A short compilation of risk management tools and methods which are recommended in the literature for purposes of such analysis were used, to gather data needed for conducting my own analysis. After gathering the needed data, steps of conducting FMEA on my distribution process is presented. In my thesis I describe how I approach the analysis and how rankings, specifically for this case were developed. The final subchapter in the practical part is devoted to risk control step and in which I, based on results of analysis, provide proposals for improvements in the process. In the conclusion also answers to my research questions are given, as well as short review of my method is provided. Limitations that I thought could arise during the application of the analysis were, that the quantity and the complexity of data which would be acquired during FMEA process, could be overwhelming and special attention would need to be given to make sure that the data would be well managed and organized. I think this was well tackled with my FMEA sheet in appendixes, where I was able to state all data in organized, visual and reader friendly way.

1 SUPPLY CHAIN RISK MANAGEMENT

This chapter aims to introduce in detail the supply chain, supply chain management and supply chain risk management concepts. It will provide the reader with basic information and knowledge from these fields and at the same time enable them to better understand my analysis which follows. Since this master thesis will bear focus on risk management, this concept is also explained in more detail.

1.1 Definition of supply chain and supply chain management

Supply chain consists of different parties which are involved with each other directly or indirectly working towards the same goal, which is trying to fulfil customers' requests. These parties can all be a part of one single firm, so risk is easier to control, or they can be collaboration between many independent firms. Supply chain as such is a network of organizations; from manufacturers, producers of raw materials and components, to assemblers, wholesalers, retailers, transportation companies, warehouses etc. (La Londe & Masters, 1994, p. 38). We can identify different degrees of complexity which were proposed by Mentzer et al. (2001, p. 4). The most basic supply chain is a ''direct supply chain'' which consists of a direct supplier, a company and an end customer. The more evolved supply chain is an ''extended supply chain'' which includes tier 1 and tier 2 supplier as well as tier 1 and tier 2 customer. The most evolved and also most complex supply chain is an ''ultimate supply chain'' which includes numerous organizations in one supply chain which are linked with each other. In all 3 degrees of complexity, all parties are involved in all upstream as well as downstream flows of services, products, finances and information; which run from ultimate supplier to the end customer.

Traditionally all functions in a supply chain were independent and pursuing their own goals, which were sometimes even contrary to each other. Such supply chains lacked synchronization of all parties involved, were not working as a whole and did not enable coordination of the in- and outflows of materials. In time, a traditional supply chain evolved and recognized the need for a two way information flow, planning and execution in time and importance of the horizontal and vertical connections of all companies and parties involved. We can define a supply chain as a network of different companies that are linked through different processes and activities which creates linkages between processes from beginning stages of planning and supplying (upstream linkages), through their manufacturing, reworking and alternation processes (internal supply), to their final stages of warehousing and storing them and then distributing them to the final customer (downstream linkages) (Christopher, 2011, p. 17). All these activities produce value for the end customers in form of services or products.

In the literature we stumble upon two different terms, the term supply chain and the term supply network which are used by authors interchangeably. The distinction between them is that supply chain refers to more focused area, with more linear and stable structure design and with more predictable and stable operations with lower complexity, whereas supply network is referring to a broader and more complex concepts, not focusing only on products and services but also on the relationships among involved parties. Its structure is more dynamic with high complexity and multiple interactions between network members (Braziotis, Bourlakis, Rogers, & Tannock, 2013, pp. 644–652). The concept of supply networks is more visible in complex and technologically advanced industries, such as IT or pharmaceutical industry; therefore I will use the term 'supply network' from this point forward.

Supply network on its own exists if it is managed or not, but to achieve long-term lasting competitiveness of a company it needs to be managed in such a way that it is more effective and more efficient than its competitors. To be able to do so and remain competitive on the market, only having a good supply network is not enough. As stated by Lambert and Cooper (2000, p. 65) companies today do not compete as solely autonomous entities, but more as supply network versus supply network. A manager's job is to find a way how to capture, exploit and manage business process excellence and the synergies of intra-company and intercompany integration. Companies need to work non-stop to try to improve their performance in an area of customer focus, process management and to increase stakeholder value. Such management is called supply chain management (hereinafter: SCM). Over the past decades there is an increasing emphasis on SCM, since companies are starting to realize more and more the problems as well as the benefits that accompany an integrated supply chain (Katunzi, 2011, p. 110).

In the literature, a consistent explanation of what SCM really is has not yet been suggested. In the past, academics as well as practitioners often used the term SCM as a synonym or

extension of logistic management (Cooper, Lambert & Pagh, 1997, p. 1). In reality SCM is much more than just logistic due to the fact that a high level of coordination within and between all involved parties is necessary to be able to provide the end customers with high quality and services and products delivered in time. This was also recognized by the Council of Logistic Management in 1998 and the definition of logistics was changed, by indicating that logistic management is a subset of SCM and a part of a supply chain process (Cooper, Lambert, & Pagh, 1998, p. 1). Stock and Boyer (2009, p. 706) proposed this definition of SCM: »The management of a network of relationships within a firm and between interdependent organizations and business units consisting of material suppliers, purchasing, production facilities, logistics, marketing, and related systems that facilitate the forward and reverse flow of materials, services, finances and information from the original producer to final customer with the benefits of adding value, maximizing profitability through efficiencies, and achieving customer satisfaction.«

Customers nowadays demand products to be of high quality, delivered in time and without any damages. To be able to do so, corporations are striving towards closer collaboration with suppliers as well as distributors to meet customer demands. Time and quality are two of the main factors in which today's corporations are competing. Due to globalization, global sourcing, importance of cost efficiency and high quality as well as an increasing uncertainty in the environment, most firms have now suppliers spread all over the world. There are several levels before a company can evolve from domestic purchasing towards global one. The network of the supply chain as such is consequently becoming more and more complex and globally spread. To coordinate all parties involved and to be able to compete with other competitors is becoming harder with time, since even a small problem within one of the supply network links can cause problems in the whole network stream. To be able to remain and grow in a market with rapidly changing technology and environment, as well as the changing economic conditions and customer preferences, priorities of the supply network itself must also change. This means that firms need to have flexible, effective and efficient supply networks to be able to quickly respond to upcoming changes (Katunzi, 2011, p. 110). Companies which have already integrated global supply chain networks, must at the same time integrate global supply chain management and at this stage a company has to be able to proactively integrate and coordinate common sources, materials, processes, designs, technology and suppliers not just domestically but also globally on the highest level (Trent & Roberts, 2009, p. 16).

1.2 Definition of supply chain risk management

As mentioned above an effective supply network is a crucial component of a firm no matter the industry in which it operates. Without it, a firm is not able to fulfil customer demands in time and as efficiently as it could. Nowadays when supply networks are becoming larger,

more complex and dynamic in structure and global competition is intensifying, the likelihood of not achieving desired performance is increasing.

One consequence is that supply network effectiveness can be decreased due to unplanned events or disturbances that may occur inside or outside the supply network process. Such events arise from risk and they are associated with any undesirable loss, damage, danger, uncertainty or negative consequences. The supply chain risk leadership council defined supply chain risk quite broadly, as the likelihood of events and their consequences that occur from beginning to the end of supply network (The Supply chain risk leadership council, 2011, p. 4). More narrow definition was proposed by Tummala and Schoenherr (2011, p. 474) in their paper, where they conceptualized supply chain risk as an event, which adversely affects all supply chain operations and desired performance measures, such as costs, service level and responsiveness. They also presented main supply chain risk categories and their triggers. The main risk categories identified in their paper are demand and delay risk, disruption risk, inventory risks, manufacturing break down risks, physical plant risks related to capacity, system risks, sovereign risks and transportation risks. The triggers in each category are different. To name just a few, which are also linked to my field of research; the main triggers in demand risks are order fulfilment errors, inaccurate forecasts, seasonality, production shortage, etc. For the delay risk the main category triggers are transportation break downs and border crossings and for transportation risk category the triggers are paperwork, late deliveries and higher costs of transportation.

Globalization, increase in network complexities and intensifying competition are all factors which are causing networks to be more vulnerable and more receptive to risk. This was also identified by Sodhi and Tang (2012, p. 7) in their book Managing supply chain risk, where they identified three main reasons why networks became more receptive to risk. First and second reason being, that due to the fact that supply networks are becoming larger and more interconnected, this causes multiplication of points where possible disruption may occur and therefore, they are less transparent which makes decision making process and response slower and risks harder to detect and identify. The third reason is that by having larger networks, the solutions to retain risks on local level can cause disruptions and occurrence of new risks in other parts of its network.

Implementation of strategies on how to identify, asses and mitigate risk, to manage everyday as well as exceptional risks which are occurring along the supply network is called supply chain risk management process (hereinafter: SCRM). It is a function that aims to identify the potential sources of risk, and to implement appropriate actions to avoid or contain such risks. In complex supply networks, risk is increasing and also shifting around the whole supply network, therefore managers need to identify as well as manage risks from a more diverse range of sources and contexts. Effective risk management enables organizations to perform well and compete in an environment which is full of uncertainty. The International Organization for Standardization is a worldwide federation of national standards bodies. In

ICH Q9 (ICH, 2005, p. 9) risk management is defined as: “The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risks.”

When identifying risks Harland, Brenchley and Walker (2003, pp. 52–53) suggest that supply chain management should be concerned with two essential aspects; which are the probability that an event will occur and if it does, what are the consequences and losses associated with it and how significant this effect will be on the process or business. In terms of significance of consequences, they are referring to tangible consequences such as financial loss as well as intangible consequences such as loss of credibility and reputation. In relation to that they identified 6 different types of losses which are financial loss, performance loss, physical loss, psychological loss, social loss and time loss. Probability is trickier to identify and quantify, since future is uncertain. Van der Vorst & Beulens (2002, p. 413) defined that supply chain uncertainty is referring to situations when decisions need to be made, but the involved parties which need to make a decision, do not know definitely how to decide. The reason behind that is that they are indistinct about the objectives, because they are lacking information about supply network environment, effective control actions and processing capacities. Therefore we can conclude that probability of occurrence in reality cannot be defined so accurately. Taking this into account, we can determine probability by using both, the objective approach for example based on historical data, if they are available, as well as using subjective approach based on our gut feeling, knowledge, intuition and experiences. In practice both approaches are usually used together.

While probability and the consequences that risk has on a company are most commonly and widely discussed aspects of risk in literature, Manuj and Mentzer (2008, p. 196–197) highlighted two more dimensions of risk which are important in global supply networks. One of them is the speed of detection, since due to long and complex supply chain networks, lead times and physical distances are increased. This causes lesser overall control over the whole network, leading to the increase of the magnitude of the problem, if not detected soon. The other one is the frequency of risk, since one time disruption could in some cases be treated as acceptable, but frequent disruptions can lead to a decrease of a company’s reputation and image on the market. To sum up, the losses that happen per unit of time are determined by the speed and frequency of disruptions that occur.

1.3 Phases of risk management process

We cannot abolish risk from everyday life, but companies can manage and decrease risk by being prepared for it. In connection to the above reasons, we can see especially in the last decade that more and more companies are starting to use proactive approach towards identifying and managing risk. This subchapter is devoted to the presentation of main approaches and strategies which can be used to manage such risks.

SCRM is engaged in trying to manage the disruptions that are occurring in the supply chain. Its role is to try and identify main risks, analyse and evaluate them and then implement proactive approaches to mitigate risk or to decrease the effects that risk may have on company's processes if it occurs. To achieve the SCRM process' effectiveness, company's managers need to make sure that it will be an integrated part of a business and will also be supported by top level management (Wu & Blackhurst, 2009, p. 1). If doing it right, SCRM process and strategies obtained from it could even lead to increased competitive advantage for the company, since not all companies devote a lot of resources to this field.

In today's global and dynamic environment, changes are in fact the only constant, so SCRM needs to be an ongoing process, to really reap its benefits. The key challenges of SCRM are the identification of possible disruption events or risks and then development of strategies for managing these risks. These strategies are called mitigation strategies and they are basically a systematic approach of how to handle occurrences of unwanted events. These strategies enable companies to avoid, decrease, redirect or postpone risks, in terms of decreasing the possibility of risk occurrence or/and in terms of decreasing the negative impact that it may have. One of the possibilities is also that the firm actually accepts risk, by only acknowledging it and with it also the consequences that it bears. The SCRM process therefore begins with risk identification in internal and external environment. To be able to identify risks, firms firstly need to have criteria, which risks really pose a threat to their operations. Once this is in place identification and assessment of risks can take place. These processes include external and internal risks identification, risk analysis, risk evaluation and risk prioritization. Steps to protect a firm's supply network are then created, as well as treatment plans which will provide a framework on how to respond to cases where risks cannot be avoided. Plans must be prepared in a way that they enable the firm to continue operating and fully recover from these disruptions. Through the whole risk management process companies must continually monitor, review and communicate the process steps, evaluate the effects of risk treatment, respond to any changes that are affecting the elements of supply chain and identify opportunities for improvement (The Supply chain risk leadership council, 2011, p. 27). Most authors therefore propose the next key process steps that need to be taken in SCRM:

- risk identification,
- risk analysis and evaluation,
- decision on use of different strategies and their implementation,
- risk monitoring.

In literature concerning SCRM we also find two terms used interchangeably by authors, which are risk management and quality risk management. The difference which I could distinct between these two terms is, that risk management is a systematic process of identifying and managing all risks in the whole supply network and it focuses on the effects of

probability and consequences that uncertainty brings, whereas quality risk management focuses more on domestic manufacturing requirements and the ones abroad, on international standards and on different government regulations. At the high level they are both relaying on cause and effect analysis techniques to be able to identify corrective and preventive measures. They both share a common ground and holistic approach to quality and risk and combined they can provide synergies to the company (Guidance for Industry: Q9 Quality Risk Management, 2006, p. 3). Quality risk management supports a practical and scientific approach to decision making and provides documented and transparent methods, which enable us to accomplish steps needed in the process to be able to assess risks. If companies have an integrated effective quality risk management in place they can provide regulators with a greater assurance that a company is able to deal with potential risks. Quality risk management should be integrated into existing operation by each firm, since it provides greater understanding of decision-making process (The Supply chain risk leadership council, 2011, p. 28). Due to this, I decided I will rely more on a quality risk management process proposed in Guidance for Industry: Q9 Quality risk management, when conducting my analysis. Quality risk management process in this respect proposes three main steps with one additional in between step that needs to be taken, when conducting a risk assessment:

- risk assessment, which includes:
  - risk identification,
  - risk analysis,
  - risk evaluation.

- risk control, which includes:
  - decision which strategy will be used (risk reduction strategies or risk acceptance strategy),
  - implementation of these strategies.

- output stage, which is an in between step, where the results of the quality risk management process are communicated and documented.

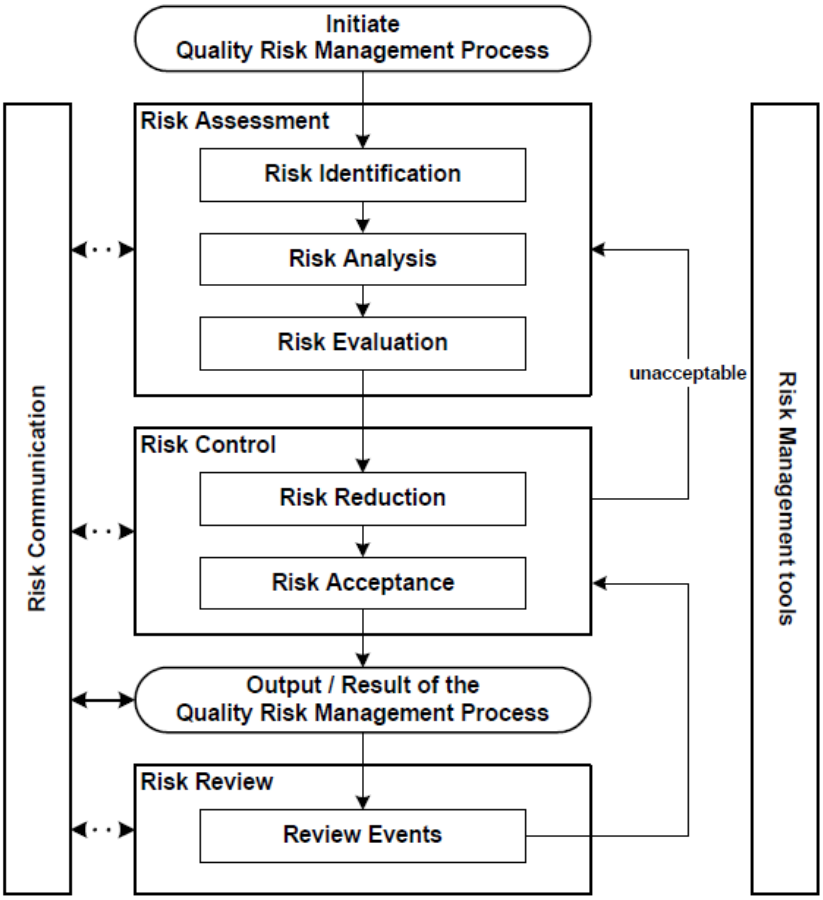
- risk review, which includes:
  - review of risk events and outcomes of implemented strategies.

Based on defined steps, we could say that the last step is in fact already the starting point of a new circle of quality risk management process, making quality risk management process an ongoing one. Basic overview of the above defined steps is also shown in Figure 1 and also more exactly presented in the upcoming paragraphs.

In my practical part I will conduct risk assessment steps and provide proposals for strategy implementation, but actual implementation and review of them will not be conducted, since

my analysis will be done based on a generic, benchmarked process, so actual implementation of proposed strategies and their review, is out of the scope of this work.

Figure 1. Overview of a typical quality risk management process



Source: *Guidance for Industry: Q9 Quality Risk Management*, 2006, p. 3.

1.3.1 Risk assessment (risk identification, risk analysis and risk evaluation)

The risk assessment is done firstly by establishing a context, which defines what actually is at risk, followed by the risk identification step. In the beginning stage companies try to identify potential risks within their supply network in a structural way. This step involves a determination of potential risks associated with a given problem. All affected areas need to be clearly identified and understood as well as interrelationship between these risks. Threats and resources must be considered, where threats refer to a large variety of forces that could produce reverse result and resources refer to people, assets or earnings which could be affected by this threat. The chosen method how risks identification will be done may depend on industry practice, culture and compliance. Techniques of risk identification can be quantitative, such as pure facts, variables, measurements and analysis results; or qualitative or informal, such as trends, observations and experiences that we have, as well as they can be

based on our own predictions. In this way some events which are reoccurring could be identified by using historical data, if available, whereas this technique is not applicable for one-time events. The risk management tools used at this stage will be presented in more depth in the following subchapter.

Risk assessment usually begins with the well-defined problem description and fundamental risk questions such as: What might go wrong? What is the probability (likelihood) that something will go wrong? What would be the consequences and/or the severity if this does happen? Can we detect these risks before they happen? In this assessment process it is important that decisions are made carefully when potential impact or severity and probability of occurrence are determined (ICH, 2005, p. 3). After risks have been identified, this enables the firm to understand the basic nature of the risk more easily, to be able to appropriately manage it. This part is called risk prioritization part and is done by analysing risks based on their likelihood of occurrence and consequences and severities that they have, which was already mentioned in the beginning of this chapter. By doing this, a company has a better understanding of how to allocate resources which will be dedicated to properly develop strategies for managing risks. Based on risk management tools used in this phase, some also incorporate the factor of being able to detect the risk, called detectability (Guidance for Industry: Q9 Quality Risk Management, 2006, p. 3).

Risk evaluation represents the second part which is a process where risks, after being analysed, are evaluated against an appropriate risk criterion. This risk evaluation considers all the fundamental risk questions mentioned above and in this phase, risks are assigned with rankings, such as low or tolerable, medium and high or intolerable. In theory they are classified into four major types, taking into account the consequences they bring, the characteristics of frequency that they have and severity and predictability associated with them. Based on Tummala & Schoenherr (2011, p. 476), risk can be categorized into four groups related to consequences associated with them:

- **Trivial consequences –** This group consists of risks that are predictable, have high frequency of occurrence and their severity is low. Such risks are part of everyday business and companies need to be aware of and prepared for them.
- **Small consequences –** This group consists of risks which are only reasonably predictable, still have quite high level of frequency but their severity is low. For these risks companies need to monitor and make sure that the frequency of such risks does not grow.
- **Medium consequences –** This group consists of risks which are only partially predictable, the frequency of their occurrence is lower than with trivial and small consequence grouping, but their severity is medium. For these risks, companies should incorporate mitigation strategies after identification to be able to detect them on time and to avoid or at least decrease severity of the consequences that they would have.
- **Large consequences –** This final group consists of risks which are hard to predict, they do have low frequency of occurrence, but their severity is high. Risks which fall in this

category should be immediately taken into account and examined in more detail, since if they occur, they could have catastrophic consequences for the company in short or in long term.

In risk assessment stage we can use different quantitative or qualitative techniques proposed in literature. In my thesis I will concentrate on the use of FMEA, which is presented in more detail later on. Overall we can sum up that the process of risk assessment after having been finalized should provide us with a list of identified risks based on their probability, severity and detectability. In this way, after completing the risk assessment stage, we are able to determine the risk profile of the company and prioritize risks within it.

1.3.2 Risk control (decision on/and implementation of different strategies)

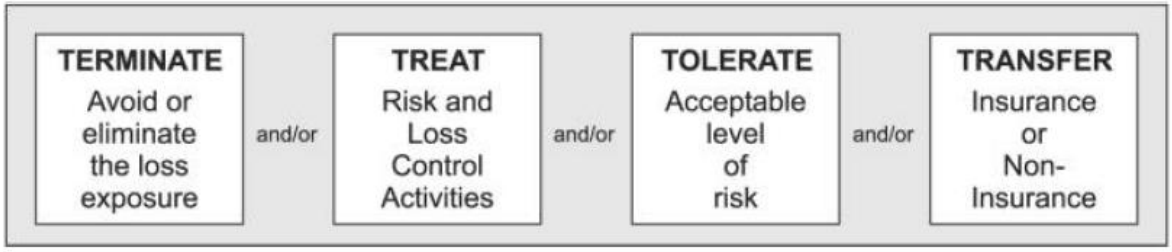
The following step after risk assessment is risk control, which is actually a stage within which the risks which were identified and prioritized in risk assessment stage are being managed. Once a risk is identified and assessed, we have different options how this risk can be managed, from doing nothing at all, to try and fully eliminate the risk. Risk control is important since it includes decision making to reduce or accept the risk. Before this step can be taken, companies should classify what is the acceptable risk level for them. Here, firms should classify acceptable, tolerable and unacceptable risks. The purpose of this control is to reduce risks to an acceptable level and the amount of effort put into this risk control should be proportional to the significance of the specific risk. At this point processes such as cost-benefit analysis can help, so that the risk control remains optimal (ICH, 2005, p. 4).

Risk can be managed with several different strategies, which include risk acceptance or retention, risk avoidance or elimination, risk sharing or transferring, and risk reduction or control. These strategies represent different development of risk response action plans and can also be similarly presented as the "four T's" model. This model proposes four different ways how companies can deal with risks which are acceptable or unacceptable for them. All four T's are summarized below (Olson & Wu, 2008, p. 33) and also shown in Figure 2:

- **Take/Tolerate a risk (acceptance):** Companies do not incorporate any strategies to mitigate risk; they accept it as it is and only acknowledge the risk, may it be positive or negative and try to find a balance between the possible negative risk and the benefit that this operation could bring. This category contains risks where risk management practices might not work in a sense that risk could be fully eliminated.
- **Transfer a risk (sharing):** Companies will share its risk and the measures to reduce risks with another party (insurance companies, use of different contracts, etc.). In this way any loss or benefit from these risks will be carried by both parties.
- **Terminate a risk (avoidance):** Companies will discontinue all the activities which made them exposed to the risk.

- **Treat a risk (control):** Companies take a direct action to reduce the impact and the likelihood of the risks, which exceed the specified acceptable risk.

Figure 2. Four T's



Source: R. Williams, B. Bertsch, B. Dale, T. van der Wiele, J. van Iwaarden, M. Smith, & R. VIsser, *Quality and risk management: what are the key issues?"*, 2006, p. 71.

Once a company decides on how their risk will be managed, appropriate controls for measuring each risk have to be implemented. Based on the nature of the risk, if needed, the mitigation strategies also need to be approved by the appropriate level management before any implementation can begin. After approval the implementation can start, following all the planned methods which were decided for mitigating the effects of the risk (The Supply chain risk leadership council, 2011, p. 7).

1.3.3 Output stage (risk communication and results of the quality risk management process)

After risk assessment and control stages are finalized, the important aspect is also risk communication in a sense, that all relevant information about identified and analysed risks, as well as risk management decisions taken need to be communicated between decision makers and other stakeholders in the company. Referring to Figure 1, risk communication is actually a process which is done throughout the whole quality risk management process, between all parties involved. But at this stage, all final outputs of the quality risk management process need to be appropriately documented and also officially communicated to all involved/interested parties.

For appropriate flow of communication, stakeholders are usually divided into four different categories also shortly called RACI. Here individuals are each assigned one of the four roles, based on their responsibilities in quality risk management process. Responsibilities between categories differ as seen below (Jenkins et al., 2010, pp. 23–24):

- **Responsible** – Stakeholders who need to achieve the task. In most cases we only have one person who is directly responsible and few which are delegated to assist them.

- **Accountable** – Stakeholders which could be also called final approvers. Per each task inside the risk management process, only one accountable person should be identified. Their role is to approve the work done by the responsible person.
- **Consulted** – Here we are actually referring to the two way communication done during the process and involved stakeholders whose opinions were sought.
- **Informed** – Stakeholders who need to be kept up to date with the progress of the process, usually only at key milestones and on completion stage. Here communication is usually only one-way.

Communication overall should relate to the identified risk, their nature, probability, severity and detectability, as well as the information on implementation strategies, treatments, controls etc. Such communication should be carried out for all assessed risk (Guidance for Industry: Q9 Quality Risk Management, 2006, p. 6).

1.3.4 Risk review (Review of risk events and outcomes of our implemented strategies)

Since no initial risk management plan is perfect, it should be repeated periodically, at least annually or more, to be able to implement possible changes based on the practice, experiences and actual results of the initial plan. Conformity and effectiveness of the implemented plan need to be checked and if deviations occur, corrective actions need to be taken, so that in the end the desired supply chain performance is achieved (The Supply chain risk leadership council, 2011, p. 27). This review should include ongoing reporting of any occurred deviations from the desired outcomes, any disruptions or abnormal cases. At the same time new risks can appear and review and monitoring is needed, due to the fact that no environment is static, so risks in a company can start to change or move away from already identified ones. Here different SCRM systems software's are also available and can provide easier control.

1.4 Risk management tools

In this subchapter some risk management tools proposed from theory will be presented, which can help us identify and assess risks. From compilation of the tools described below, some of them, which I feel are most appropriate for my case, will also be used in the practical part of the thesis.

As we identified in the previous subchapter in the risk assessment stage, companies try to identify all possible risks which can appear in their supply network. But before we can take a step towards risk identification, we first need to get a better overview of the process, its steps and correlations between them. When starting a risk assessment, risk managers must also define clear boundaries of the processes on which risk assessment will be done, to truly focus on the correct areas in the supply network.

In the past a variety of informal ways were used for risk assessment, such as past data observations and trends. This way of assessing risk is still valid, but nowadays assessment and management of risk is also done with the use of risk management tools. We can use a combination of statistical tools and risk management methods. In theory and practice we have many different approaches how to identify risks. Two that are widely used prior and during the risk identification work are supply chain mapping and flowcharting. These charts can also be used as pre-requisition before the use of other methods.

- **Supply chain mapping** is a visual approach, a map that shows the supply chain and its flow of goods, money and information from the upstream suppliers to the downstream customers (Tummala & Schoenherr, 2011, p. 476). It shows their interrelation and provides us with a clear presentation of all involved steps in the supply chain process.
- **Flowcharting** is similar approach to supply chain mapping. It is a pictorial representation of the chosen process. It helps present all the steps and parts of a chosen supply network, which provides better understanding and overview of the processes. In this way it helps us to identify steps in the process that do not add additional value, duplication of work or unnecessary work, and possible outliers where failures can occur.

After clear context regarding the focus area is provided, the risk identification stage can begin. This stage is concerned with identification of uncertain events within pre-established context that could result in harm or in benefits. Here we could use approaches such as:

- **Objective-based risk identification approach**, where any event that can cause a threat to achieving this objective can be defined as a risk.
- **Scenario based risk identification**, where any event which triggers undesired scenario can be identified as a risk.
- **Common risk checking,** where list of known risks is available and each risk is checked separately.
- **Brainstorming technique** is also a commonly used technique which incorporates a group of people that try to find a solution to a problem together. This method enables us to get a wide spectrum of ideas from people working in various disciplines. Its advantages are that it requires little resource and training, it is fast and simple and can lead to identification of areas which were not considered before. It also has some disadvantages such as that large quantities of ideas can be provided but a lot of them may not be directly relevant to our problem, and it can also lead to loss of focus, if not managed properly (Jenkins et al., 2010, pp. 46–47).

For evaluating and recording how often some failure contributed to a specific event that occurs, use of check sheet or check list is appropriate. They are used to gather standardized data based on which different charts such as histogram or others could be prepared.

- **Pareto chart** which is a problem solving tool and is directly referred to as Pareto principle. Pareto principle states that a small number of causes are the reason for large proportion of effects that cause problems. A Pareto chart is a bar chart which categorizes multiple factors in a descending order, based on their effect frequency, magnitude or impact. Ordering by magnitude is done, since it helps us prioritize problems and enables us to concentrate on those factors which have the greatest impact. It helps us recognize the major few, from the trivial many and in this case identify major quality problems, unsafe acts, major reasons for not meeting targets and many more (World Health Organization, 2012b, p. 4).
- **Heat-maps** that show risks in a matrix, which is defined by the likelihood and the consequences. This technique provides good visual representation of critical risks which should be immediately taken under investigation (The Supply chain risk leadership council, 2011, p. 17).

Companies need to be careful here and also keep in mind the difference between actual risk, which can be measured by its impact and probability, and the actual uncertainty which cannot be avoided.

When identifying risks, different models and analysis are also widely used techniques in practice. Different graphical diagrams here show that the correlation between probability and consequences is applicable, since they enable us to conduct an analysis of consequences linked to specific decisions taken (Tummala & Schoenherr, 2011, p. 476).

- **Fault tree analysis (hereinafter: FTA) and event tree analyses (hereinafter: ETA)** are graphical diagrams where each focuses on a different side of undesired events, showing them graphically. Both methods are complimentary and are in some cases even used together. The FTA is used for analysing supply chain failures, which if they occur might lead to an event. ETA on the other side is analysing the possible events which failures may trigger and how to stop them from escalating.
- **Fishbone diagram or Ishikawa diagram** is a similar cause and effect diagram. This diagram is easier to conduct than FTA and ETA and it enables us to state all possible causes that a specific event may bring. It uses a single effect and states multiple causes. It graphically represents the relationship of the causes to the specific event and also to each other (Guidance for Industry: Q9 Quality Risk Management, 2006, pp. 12–13). The major branch in the diagram shows the effect and the minor branches present detailed causes. The diagram is created by brainstorming what could be the causes of the stated main event which occurred. It can help us recognize different factors that may contribute to an effect, default or error. These identified factors or causes that lead to the main event, help us to focus on the areas which need to be improved.
- **Scatter diagram or scatter plot** is a graphical presentation, which detects correlations between two examined variables and it is used to determine cause and effect. The diagram shows two main variables and correlations between these two by using dots. In cases

where dots do not create a similar to straight line shape, the two variables have no correlation. On the other hand, if a straight line is seen, that means that variables are in correlation.

Once risks are identified, the next stage in the process is to analyse them, based on their likelihood, so the probability and the frequency of the risk. Assessments can take place quantitatively or qualitatively (Williams et al., 2006, p. 70). Occurrence ranking uses statistical information of past data and if it is not available it is harder to determine it. In most cases past data is available and the evaluation is done based on it, but if we are talking about new processes, than usually data of other companies, which already have similar processes in placed, are taken as a benchmark in the evaluation process. Other possibility is also the use of subjective information, judgment and beliefs. Techniques such as expert focus group or Delphi method could be used or even probability encoding. It is important to mention that company needs to try to assess what would be the consequence if the risk occurs? Risks should be carefully assessed and prioritized, since using too much time and money on risks, which are not likely to occur, can divert resources form those which should be managed. By doing so, a company has a better awareness of possible upcoming events, which could cause disruptions in their process.

1.5 Failure Mode and Effect Analysis

One of the overall risk assessment tools frequently proposed in literature, is FMEA. FMEA is a quality improvement tool which does not require complicated statistics, but can provide significant savings for the company. It is a systematic proactive method that helps us identify possible risks during a specific process and enables us to analyse as well as asses what might go wrong and how severe the consequences would be and how we could prevent this process problems before they occur (Carlson, 2014, p. 1). It is focused on preventing defects, enhancing safety and ultimately increasing customer satisfaction. It should be a part of a comprehensive quality system in each company (McDermott, Mikulak, & Beauregard, 2009, p. 1). FMEA takes a systematic approach with which weaknesses in the processes are identified, it assesses the affects these weaknesses have on our current process and it provides possibility of fixing them, before an event even occurs (Department of Defense Patient Safety Center, 2004, p. 1). In practice it is usually used in combination with the tools already mentioned above, since some are complimentary to FMEA.

The main objective of this tool is to specifically look for possible ways in which process could fail and putting fixes in right places that enable elimination or reduction of the risk of the failure mode, which in the end results in a safer and more efficient system. Failure is an event, error or condition, which refers to the ending of the ability to perform the desired function of an object or process (Šolc, 2012, p. 1906). Failures are limited not only to the process but also to other factors involved in the process, such as people and mistakes that they

could make. In the healthcare industry most of FMEA's are conducted on processes already in place. This kind of FMEA analyses the actual processes in place and not the ideal processes. The scope of it should be well defined and clear definitions of the process, which is being studied, need to be written and well understood, to prevent the possibility of focusing on the wrong aspect of the process. The scope should be manageable and focused on a specific part of process or sub-processes and critical failure modes should be identified within those process boundaries (Department of Defense Patient Safety Center, 2004, p. 7).

As McDermott et al. (2009, p. 23) specified, it should be conducted based on 10 step processes outlined below:

- **Step 1:** Review the process or product.
- **Step 2:** Brainstorm potential failure modes.
- **Step 3:** List potential effects of each failure mode.
- **Step 4:** Assign a severity ranking for each effect.
- **Step 5:** Assign an occurrence ranking for each failure mode.
- **Step 6:** Assign a detection ranking for each failure mode and/or effect.
- **Step 7:** Calculate the risk priority number for each effect.
- **Step 8:** Prioritize the failure modes for action.
- **Step 9:** Take action to eliminate or reduce the high-risk failure modes.
- **Step 10:** Calculate the resulting risk priority number, as the failure modes are reduced or eliminated.

First step should be the review of the whole process which is taken under observation. Here additional management tools such as flowcharts can come in handy for better visualisation and understanding of the process. Flowcharts as already mentioned are also a tool which helps us narrowing the scope of the process, which should be determined by the first and final steps in the process. The process should be flowcharted as it is, not as the ideal one or as we wish it would be.

The second step includes identification and listing of potential failure modes, using a flowchart for help as well as questions such as "what could go wrong at this step?" During this analysis we need to keep the desired outcome of our process in mind and what could happen that would prevent this outcome. Some steps may not possess any failure modes, whereas some can possess several of them.

The third step is the listing of potential effects of each failure mode. Here we should ask questions such as ''If failure does occur, what could be the consequences of this failure?''. In this step again tools such as check sheets, cause and effect diagrams, histograms and others can be helpful.

After each failure mode and its effects are listed, hazard analysis is conducted that allows us to estimate and prioritize each risk of identified failure modes. This is done in steps four to six, by determining the occurrence or probability ranking, severity of the affect and detection ranking to each failure mode. The ranking method usually uses a numerical scale from 1 to 5 or from 1 to 10, where for probability and severity ranking 1 means low and 5 or 10 means high, and for detectability ranking 1 means very high possibility of detection and 5 or 10 very low or even not possible to detect. Each risk factor is then ranked by its occurrence, severity and detectability. We need to note that when determining the severity of the impact or consequences, also the severity of occurrence if risk cannot be mitigated needs to be evaluated. The severity of the impact is the evaluation of the consequences, the effect of all potential risks which were defined and the magnitude of the impact this effect would have on the resources. Effects could be the interruption of service level, schedule delays, poor process performance, damage to assets, loss of income, etc. When determining probability ranking, historical data can be used. The last to be determined is the detectability ranking, which is done based on possibility of detecting this risk before it occurs. Here companies take into account measures already taken in the process, which enable them to see, discover and anticipate the risk before it happens.

Risk prioritization is done in the seventh and eighth step, where all assigned rankings are multiplied for each failure mode to get an index number. This is called a risk priority number or RPN factor and is the most widely accepted formula for risk quantification. Based on the calculations, prioritization of risks is then done, by listing risks from the ones with the highest hazard score to the ones with the lowest hazard score. Here we need to determine the RPN cut off number, which allows us to focus on failure modes which have the highest impact and set aside the ones, which have an acceptable level of risk.

Once above risk assessment has been completed, a company's risk profile can be determined. This profile shows the scale and complexity of risks that a company is facing as well as what is its risk exposure. The risk exposure defined by Williams et al. (2006, p.70) should be equal to the risk capacity and risk appetite of the organization, where risk capacity of a company presents the overall maximum number or level of resources, that the organisation is willing to put at risk and on the other side the risk appetite is referring to the amount of risk that the organisation is willing to comprehend and take.

In step nine, the actions plans are determined and put into place. An action plan is determined for each potential failure mode, which would eliminate or reduce the risk of that cause. When developing action plans, we need to keep in mind also what effect each action will have on the whole process not just the failure mode, since the goal is to reduce specific cause without possibility of creating new failure modes in this or any other process.

The last step is the review and monitoring step, where again each failure mode is reassessed based on the actions already taken and risk priority numbering is repeated. By doing so, the

review of our work is done, providing us with information if and which failure modes were reduced or even totally mitigated and which were not.

2 SUPPLY CHAIN IN PHARMACEUTICAL INDUSTRY

Supply processes are different from company to company depending on size, activities, arrangements, assortments and quantity of production need, etc. Though the supply chain process is not the same from company to company, overall it does have its basic form and it is unwind in a certain order and degrees which follow one and other (Završnik, 2008, pp. 33–60). Pharmaceutical industry is a branch of chemical industry and is defined as a complex of operations, processes and public as well as private organizations that are involved in discovery, development and manufacture of drugs and medicines. Pharmaceutical industry also has several unique characteristics, one of which is that the demands regarding quality are exceptionally high and the second is that the volume and range of the production and sales are determinate by morbidity (Shah, 2004, p. 929).

In this chapter, the specifics related to pharmaceutical industry and its supply chain will be investigated further. Firstly, the key players in pharmaceutical industry will be identified as well as specific risks which are related to pharmaceutical industry, identified from literature. Furthermore, a subchapter where specific differences between branded and generic drugs will be presented, followed by more in depth presentation of biological and biosmilar product concept. Here the distinctions between "regular" pharmaceutical drugs and biosimilars will be defined, since these specifics will directly influence how I will conduct my risk analysis in a sense of which risk factors will be given a greater weight. Then I will continue with a subchapter on regulatory requirements in this industry, focusing on cold chain products specific requirements, where also some of them will be highlighted. I will conclude this chapter with specifics of cold chain process and requirements that accompany this process. Since process from manufacturing to administering the drug to a patient is long, complex and involves several different parties, I will concentrate in my thesis solely on the distribution process; therefore factors related to this area are presented in greater detail.

2.1 Key players in the pharmaceutical industry

The key players of pharmaceutical supply chain as mentioned by Shah (2004, pp. 931–932) are primary, secondary and tertiary manufacturers which could also include contractor sites, the distribution centres, wholesale distributors and at the end the pharmacies and hospitals. Below they are described more thoroughly.

- **Primary, secondary and tertiary manufacturers**

In the pharmaceutical industry we have three manufacturing stages. Firstly, primary manufacturing is manufacturing of and active pharmaceutical ingredient or API and different intermediates from basic chemical and also biological substances. API is an ingredient which is manufactured from raw materials and has to undergo chemical and physical process. It depends on the complexity of the required molecule but generally the synthesis of API requires a range of processing technologies and requires many complex steps of chemistry. Final API is an active compound which produces a therapeutic effect. API manufacturers must comply with strict safety and quality standards, which are set by the country where API will be used (The API Industry at a Glance, 2013). Primary manufacturers can face high fluctuations in demand due to the bullwhip effect which occurs as a consequence to disturbances on one end of supply network, which then amplifies backwards to the other end. API manufacturers are mostly spread around Asia as companies are increasingly outsourcing API manufacturing, since by doing so they eliminate cost which would be needed for investments in equipment and infrastructure (Sousa, Liu, Papageorgiou, & Shah, 2011, p. 2396).

Once API is produced, the secondary manufacturing is the next stage. In this stage the product is prepared to be suitable for the final consumers in a form of a tablet, capsule, injection, etc. Here we are talking about large-scale processing of the finished dosage forms or FDFs. This production requires modern and precise equipment with high speed, to be able to produce large quantities of pills, capsules, liquids etc. The secondary stage is in fact less technically demanding than the primary stage, but it has to be completed in such a way that the product complies with prescribed specifications and with Good Manufacturing Practice standards. These secondary sites are usually separated geographically from API manufacturers; there are more of them and they usually serve regional and local markets.

The last stage is tertiary manufacturing which is limited to formulation, packaging and labelling of finished products or repackaging of bulk finished products received from primary and secondary manufacturing. This production also addresses the specifics of the market and local needs, regarding packaging, labelling etc. At this final stage the initially established quality in the earlier phases must be maintained (Management Science for Health, 2012, p. 7.3).

- **Distribution centres**

Distribution centre is a warehouse that is stocked with products which are waiting to be distributed to the wholesalers, retailers or directly to final customers. They are the foundation of the supply network and can be located at a logistic centre or not. Pharmaceutical distribution centres are thought of being demand driven. All centres have 3 main areas which are specialized. They have a receiving docks, where goods are received from the shipper and

unloaded, a storage area where goods are stored and a shipping dock, an area where goods are prepared to be loaded for shipping to the final customer, the hospital, etc.

To be appropriate for pharmaceutical industry, these warehouses and distribution centres must be specialized. To be able to store pharmaceuticals they need to be of appropriate size and are also obliged to meet demands that pharmaceutical industry has regarding storage of drugs. Such centres must take into account high importance of safety stock levels and frequencies of supply from product manufacturers and onward delivery to the final customers as well as seasonal re-supplies from manufacturers to be able to meet markets demand (World Health Organization, 2014, p. 8).

All employees in such centres need to be educated and trained regarding drug specifics and their storage requirements. For example, some drugs need to be specially treated; such as narcotics and psychotropic products, which need to be locked down in a special area with restricted access; hazardous materials, inflammable, radioactive or explosive materials, where special handling and storage conditions need to be obliged and temperature controlled products, where specific temperature regime needs to be maintained at all times. All these safety regulations need to be implemented to prevent accidents, theft and misuse of these products (World Health Organization, 2011, p. 341).

These warehouses also need to be able to provide special temperature-controlled regimes which are required for time and temperature sensitive pharmaceutical products. Such products have to be transported and stored within the predefined environmental conditions as well as within time limits; otherwise its effect is decreased to the extent that it does not perform as originally intended.

- **Wholesale distributors**

A certified wholesale distributor is a company that handles shipments from the manufacturers to the hospitals, retailers, or final customers. A wholesale distributor has a distribution centre, which was already described above and ships goods, in our case pharmaceuticals, to the final customers. A wholesaler works directly with manufacturer on one side and with retailers, other wholesale distributors or final customers on the other side.

All the above mentioned factors are key players in a pharmaceutical chain or network, between which supply and demand flow is created. But these factors can also be distinguished between each other in a different way. Shah (2004, p. 929) also mentioned specific characteristic which divide key players in the industry into five different groups. The first are the research and development–based multinationals that have branded products and are present worldwide with manufacturing sites in different locations. They usually market with their own branded products, which can be available with prescription (RX products) as well as without the prescription or so called over the counter drugs (OTC products). Then we have

generics manufacturers that produce RX and OTC products which are already out-of-patent. The term patent will also be clearly presented in the following subchapter. The third key player are manufacturing companies that operate locally and produce generic as well as branded products, but both under licences or contracts. We also have contract manufacturers that produce product by providing outsourcing service to other companies and the last ones are often new start-ups with little manufacturing capacity, such as biotechnology companies and drug discovery companies.

2.1 Main risks in pharmaceutical industry

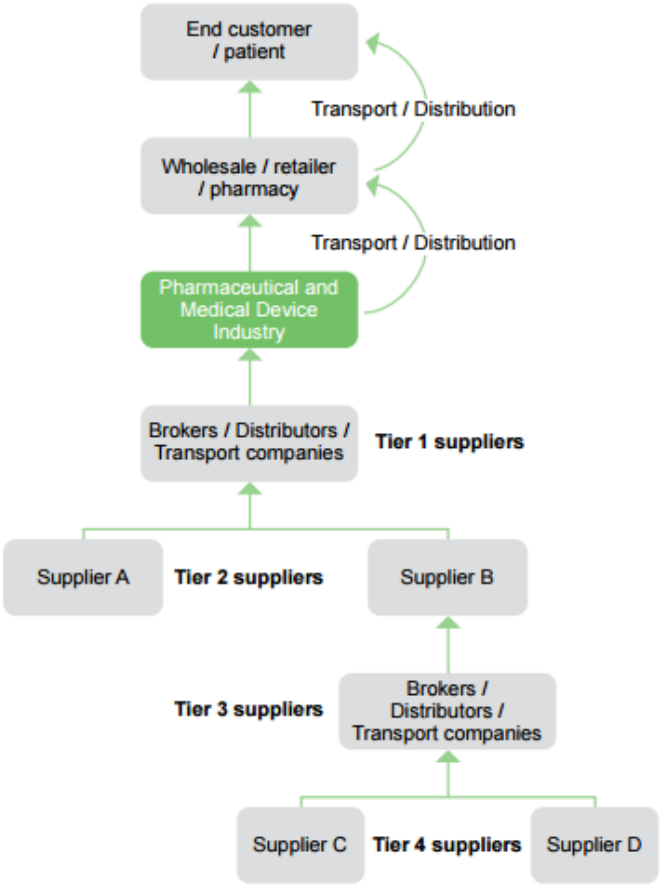
One of the main objectives of the global healthcare system is that every human has to have a right to access medicines. In connection to this, every pharmaceutical supply chain should be able to provide medicines, with acceptable quality and the right quantity, to the right place and time. All of this should be done in consistence with the health system's objective by making benefits for the stakeholders and with optimum costs (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013). Pharmaceutical industry is a highly competitive branch where the main players mostly have globally spread networks, to be able to reap cost benefits and to be close to their customer base. By having a globally spread network with many inter-related connections, chances and points where risk can be encountered, is increased. This is seen especially in cases, when companies are supplying medicine products to developing countries, which have high economic, social and political instability. Main risks upon which we stumble in the pharmaceutical industry are the risk of product shortage, adulteration to quality of products or services, poor performance, theft, counterfeiting, the risk of product becoming unfit for use doing storage, shipping and handling and system disruptions (Breen, 2008, str. 193). We cannot avoid risks in fully, but it is important that we have processes and measures in place which help us to identify and manage appropriate risks in time, so that patients and other involved parties can enjoy the reliable supply of medicines.

In pharmaceutical industry the risk associated with quality assurance and security of supply is one of the most important ones. Based on World Health Organisation (hereinafter: WHO), from available drugs on the market, there is likely that 1 % of them are counterfeit (Medicines and Healthcare products Regulatory Agency, 2008, p. 5). Companies are responsible to ensure that products are quality compliant and fit for use by the end user, through the whole product lifecycle. Inefficient quality control over the whole supply network can result in harm for the patient or in worst case scenario it can lead to death of the patient. Occurrence of such events is not acceptable, and risks need to be identified and mitigate on time, otherwise this will lead to the loss of the company's brand image, its integrity, as well as to a significant financial loss.

To preserve the impeccable quality of a product through the whole network is quite a challenge, since pharmaceutically supply network is usually spread globally, encountering

different variations in standards and controls used, making it harder to control. As presented in Figure 3, in the pharmaceutical complex supply chain or network, suppliers and end customers can be far apart. Events associated with risks can be present in any process throughout the whole supply network, from the source of raw materials to the correct usage at the end.

Figure 3. Typical supply chain hierarchy



Source: J. Jenkins, J. Ahern, D. Cock, S. Shutler, R. Smalley, & S. Hooper. *A Guide to Supply Chain Risk Management for the Pharmaceutical and Medical Device Industries and their Suppliers*, 2010, p. 14.

Events associated with risks, can even be increased by further steps, making events become visible only in a later stage of supply. As mentioned above, the worst case scenario is that the products can already be released to the market or administrated to patients, before actual event is identified (Jenkins et al., 2010, p. 14). This is why the importance of risk management in pharmaceutical industry is only growing and increasing over time. It is becoming a vital need for every pharmaceutical network, since medicines are highly regulated products, which are under tight controls and limitations of public regulatory authorities. It is in everyone's interest, that every possible event which could lead to risk is managed through every tier of the whole supply network.

2.2 Branded and generic drugs

Due to the strong competition between main rivals in this industry, one of the most important drivers to which companies are striving, is to be on time on the market. By being the first, companies can secure high returns with a successful drug, before the entry of another competitor with a similar drug.

In pharmaceutical industry we have generic and branded drugs. Branded drugs are drugs which have patented name and are made by pharmaceutical companies such as Pfizer and Novartis. These are drugs which have exclusivity on the market, meaning that no other drug can enter the market to compete with it. Related to this fact, these drugs are also more highly priced. The reason behind such exclusivity and price is that companies use millions of dollars and years of research for development and clinical trials. In cases where the drug shows as efficient and safe, Food and Drug Administration (hereinafter: FDA) approves it, meaning that it can be released to the market. A company can then cover its expenses, which it had with producing the drug, from sales revenues and it can also contribute to research and development department (hereinafter: R&D) for drugs it wants to develop in the future. Brand products are the ones which drive innovation in the pharmaceutical industry (Baltazar, n.d.).

After exclusivity or in other words patent for a brand drug expires, other companies such as Teva and Sandoz can enter the market with their own drug, which is in a sense a replica of the original branded drug. A generic drug can be developed and manufactured faster and cheaper than the branded drug, since these companies only copy the recipe from the original drug and do not need to spend the same amount of money for R&D. These companies also have to prove that their active ingredient in their drug is an exact replica of the branded drug, before FDA approves it. In the past few years the number of generic drugs on the market has increased, which is due to consumers increasing education and knowledge, that the generic drug is as good as the branded one and it also comes at a more affordable price (Stoppler, n.d).

Pharmaceutical industry has become more and more challenging over the past decades. It has become harder to maintain the responsiveness of the supply chain due to establishment of regulatory authorities and the maturity of the market. Due to the aging population, governments put a lot of pressure on prices and encourage the use of generics instead of branded drugs, which force companies to decrease their margins. All of this has led to the decrease of productivity in R&D activities and increase in the cost that company has in stages of development of a new drug and clinical trials, which also led to shortening the patent period of a product (Sousa, et al. 2011, p. 2396).

2.3 Biologics and biosimilars

Biologic medical product is any medical product which was derived from living material, so from biological source (World Health Organization, 2009, p. 13). These medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies and fusion proteins. They are large molecules, very complex in structure and are used in a diagnosis, treatment and prevention of disease. Biosimilars are similar to originator biologic, but are not identical copies. They are generics, meaning that minor differences in active ingredient are expected due to the complexity of the molecule. They have comparable properties such as quality, efficiency and safety as the brand name drugs and are approved via very strict regulatory pathways (O'Donnell, 2009).

We have several definitions of what biosimilar product actually is and some of them are presented below:

- The WHO defines biosimilar as a: "Biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product." (World Health Organization, 2009, p. 6).
- The European Medicines Agency (hereinafter: EMA) definition is: "A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise."(European Medicines Agency, 2013, p. 4).
- The U.S. FDA defines it as: "A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product."(U.S. Food and Drug Administration, 2015, p. 4).

They are in other words copycat drugs, meaning that biosimilars could only be introduced to the market after the patent, which was held by innovator biologic drug expires. Today these drugs are used to help patients with serious illnesses such as cancer, auto-immune disease, blood conditions, etc. (Amgen Inc., 2014, p. 5). Compared to other chemical based pharmaceutical drugs, biosimilars are less stable and more sensitive to changing temperature conditions, which is the reason they require maintenance of cold chain (2˚C to 8˚C) at all times (Veeda Clinical Research, n.d.). We can see the rise of generic drugs on the market, amongst which are also biosimilars, largely due to lower cost and increased awareness that the generic drug is as good as the branded one.

The EMA was the first agency that issued the regulatory framework and guidelines for biosimilars and by doing this it set the rules and procedures for quality, effectiveness and

safeness of the biosimilars. Europe's framework, for approving biosimilars, was established in 2004 and 3 biosimilar molecules were introduced to EU market till 2010 (Ledford, 2010). Later on, 4 additional biosimilar molecules were approved and to this date 19 biosimilars were approved by EMA for use in Europe (GaBi Online, 2016). Not so long ago, in 2012 US FDA also accepted guidelines for biosimilars, but they were quite wade comparable to EMA's, so in May 2014 FDA came out with more detailed 17-page draft guidance (U.S. food and drug administration, n.d.). This regulatory framework is a step further for the biosimilar market and its growth, since it will enable companies to further develop such medicines and decrease the cost of therapy. Based on Rickwood and Di Biase (2013) biosimilar market will expand dramatically. Just some of the indicators are that firstly many branded biological drugs will lose their patent and with that the exclusivity on the market, secondly biologic drugs had lower volume share then biosimilars in Europe in 2012 and thirdly that in 2013, 76 % of all the prescription drugs were the generic ones and only 24 % branded ones. The market expansion can be seen even more if we look at only those drugs which have the generic equivalent available and in this group there were 92 % of the generic drugs dispensed, which is even higher.

As in any supply chain and its distribution process the pharmaceutical industry is also facing many risks. But before we can define risks, we firstly have to be aware that biosimilars have different characteristics comparable to other chemical based drugs. They are lifesaving drugs, are more expensive, have shorter life span and are less stable, thus cold chain should be maintained at all time (Veeda Clinical Research, n.d.). These characteristics have a direct effect on ordering process, storage and transport process as well as costs. Firstly, these characteristics increase risks associated with inventories, since increase stock levels combined with the high cost of the product and its short shelf life, increases the write off risks, compared to the risk associated to other pharmaceuticals, which have longer shelf life and are less expensive. Secondly, the biosimilars should be strictly temperature controlled and monitored from the time they are manufactured until the administration to the patient (Veeda Clinical Research, n.d.). This characteristic has a direct effect on storage of such products, since they require special facilities and refrigerators, as well as temperature monitoring systems. There is high emphasis on controlling the storage ambient, since any deviations in temperature can cause irreversible effect on products efficiency leading to write-offs.

Introducing biosimilars to the market should increase access to the biologic medicines as well as reduce the cost of them. In emerging markets there is less intellectual property protection, so developers of biosimilars are trying to launch their products in such markets as soon as possible to assure their market share (Global biosimilars market "will see exponential growth", 24.September 2015). Based on the expected growth and importance of this market, the increased pressure on cold chain process, its continuity, reliability and cost efficiency will be even more visible.

2.4 Regulatory requirements

Companies which manufacture and distribute biosimilars and therefore must maintain cold chain at all-time, need to be aware of the industry and regulatory guidance documents, standards and regulations which are shaping this industry (Wodrich, 2011). One of the biggest risks seen in pharmaceutical and growing biotechnology supply chain is the risk of being non-compliant with the federal standards, guidelines and regulations.

International conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use (hereinafter: ICH) is an organization which was founded by the FDA and European Community in 1990. ICH is an international entity which involves the US, Japan and European Union. Its goal is to create a harmonized approach across the globe, which would enable understanding and application of technical guidelines for drug manufacturers. In this way, the replication of regulatory processes could be avoided, cost could be decreased and it would enable an organization to promote globally efficient methods of manufacturing, processing and distribution (Vaisala, 2012, p. 1).

At this point the manufacturers and the distributors have to be acquainted with several different regulations, documents and standards, since there is currently no single guidance, document or standard, which would include and sum up regulated cold chain per region. Current regulatory environment in the cold chain management is quite fragmented and includes many different standards, guidelines and documents, which need to be followed with the cold chain products. Just some of them are:

- WHO working document, QAS/04.068 on Good Distribution Practice (GDP) and EU GDP Commission guideline 2013/C 343/01. They are applicable to all persons and companies involved in supplying medical products to the public. These guidelines were published so that the quality and the integrity of the product would not be compromised due to the lack of adequate control over the products. This document applies to manufacturers, brokers, importers, suppliers, distributors and wholesalers, transport companies involved in the process, forwarding agents and persons that are authorized or entitled to supply medicines to the public (European Commission, 2013 pp. 1–14).
- Good Storage Practice or GSP and Good Manufacturing Practice or GMP principals need to be followed. They provide standards and regulations on manufacturing and storage of medicine products.
- A pharmaceutical quality system (ICH Q10), which extends to any outsourced activity as well as quality of purchased materials and it also defines the responsible organisation which is responsible to incorporate controls and reviews of these activities. ICH Q10 also states that every process should have in place Quality risk management process as was defined in ICH Q9, which was already presented in previous chapter (Jenkins et al., 2010, p. 8).

- US and European Pharmacopoeia which covers active substances, excipients and preparations of chemical, animal, human or herbal origin, homoeopathic preparations and homoeopathic stocks, antibiotics, as well as dosage forms and containers. It also includes texts on biologicals, blood and plasma derivatives, vaccines and radiopharmaceutical preparations (World Health Organization, 2012a, p. 11).
- CDC Guidelines for Maintaining and Managing the Vaccine Cold Chain which provides data of timing and spacing, administration, safety precaution, storage and handling of vaccines.
- WHO Guidelines on the international packaging and shipping of vaccines.
- PDA Technical Report 39: Cold chain guidance for medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. This document provides approach to develop specialized packages and systems, which will enable protection of temperature-sensitive products during the whole transport.

2.5 Specifics of cold chain

Cold chain products need to be temperature-controlled throughout the whole supply chain. Thus notion "cold chain" refers to the process which is used to maintain the optimal temperature conditions from the manufacturer site, until drug is administrated to the patient (BC Centre for Disease Control, 2013). In the past years pharmaceutical companies devoted a lot of their time and resources, to try and implement efficient cold chain practice. Cold chain products often require deep frozen/refrigerated storage, but the specific temperature tolerances are different from product to product. Products such as vaccines, biologics, insulin, serums, blood products, etc. are complex structure molecules and are very sensitive to conditions to which they are exposed during manufacturing process and until they are administrated to individuals. The most common range used for the cold chain pharmaceutical products is therefore 2˚C to 8˚C. The reason behind this is that traditionally all of the historical stability data acquired for developing vaccines were in this range and as a consequence, due to the lack of testing, such products at a wider temperature range, also developed biological products fell into the same temperature category. If these medicines are exposed to freezing temperatures or heat it could lead to loss of efficiency of the products.

Since I will concentrate solely on a distribution process of biosimilars in my analysis, from the company to the wholesales, looking in more detail at processes such as preparation and loading of goods, their physical shipment and processes of unloading and further storage, I believe more exact presentation of directly related processes should also be given. In the subchapter below I will therefore present some specifics which are related to storage and logistics of temperature sensitive products, identified with the help of published literature. Specifics related to proper storage and labelling of cold chain products will also be presented, as well as specialized equipment related to their transportation. Here I am referring to

specialized active and passive systems, which are used in the distribution of such products, as well as specialized trucks and data loggers, which are already a necessity when dealing with cold chain products. The second subchapter will then be devoted to presentation of the main risks which are specific to the cold chain distribution and which are also important in relation to my risk assessment. With this, I will also conclude my theoretical part and move on to the practical.

2.5.1 Storage and logistics of temperature sensitive products

A boost of the health care logistics is expected in the coming years, due to the changing epidemiological profile of people worldwide. The field is expected to grow to 13,4 billion dollars by 2020, based on the world's leading research and advisory firm IMARC Group, which can also be partially contributed to the industry intensified production development of biologic based drugs (Global Healthcare Cold Chain Logistics Market Report & Forecast (2016-2020), 2015). This will show in increased demand for chronical disease drugs, cardiovascular drugs, vaccines and others. Major restrains which the health care logistic market will face is the lack of funds and cold chain infrastructure in underdeveloped and in developing countries (Transparent Market Research, n.d.). Overall, the complexity of the supply chain is increasing due to the push for being cost effective and the globalization itself. Consequences of these trends can be seen in reduction of knowledge as well of good understanding of the exposure to risk that this might bring. Due to several hands-off points, such as transporters, customs and airlines, even short routes such as shipment of goods from the warehouse to the nearby customer can cause exposure to temperature fluctuations. The more complex the shipping route becomes, the higher is the possibility of risk exposure. The GDP directives aim to ensure supply chain integrity until the drug is administered to the patient, which involves the internal manufacturing process, as well as transportation and distribution activities. Companies must ensure compliance and maintain quality throughout the whole transport chain including the ones which were outsourced to their logistic service providers (8^{th} World cargo symposium, 2014).

In the past few years several companies have expanded their cold chain logistic, distribution and storage capabilities, due to the growing market of cold chain health care logistics. Some of the biggest healthcare cold chain logistic companies include World Courier, DB Schenker, FedEx Corporation, Kuehne and Nagel International AG, Continental Air Cargo, DHL, etc. With tighter regulatory controls and the market expansion, pharmaceutical companies are faced with many challenges in how to preserve the right temperature during the transfer of cold chain products through the whole distribution process. Some of such challenges are also presented below.

- **Storage**

Biopharmaceutical drugs are of a fragile nature and any chemical or physical instability can contribute to loss of efficiency of the products. Careful attention is needed in storage and

handling of these products to minimise the potential possibility of physical instability. The major factor that contributes to maintaining the quality and integrity of biopharmaceutical drugs and biosimilars, is the careful control of storage and transportation temperatures of these products (Hoffman, n.d., p. 2).

All environmental conditions such as temperature, light, humidity etc. should be monitored in all storing, holding, receiving and transferring areas. Temperature-controlled storage in warehouses ensures that cold chain products are stored correctly. First of all, the facility where cold chain products or in our case biosimilars are stored, should be equipped with a power failure alarm so that they can continue to operate independently in case of a power failure. Biosimilars are usually stored in large refrigerators or walk-in cold rooms in cases where volumes of the goods are higher. Refrigerators and cold rooms should be purpose-designed for the storage of cold chain products (World Health Organization, 2011, p. 340). These units should be serviced at last once a year and the internal air temperature distribution should be mapped and checked annually. The temperature mapping needs to be repeated in case of occurrence of any significant changes like repair, replacement or changes in internal storage layout. These refrigerators or walk-in cold rooms need to be fitted with an electronic temperature recording device, which is able to measure the load temperatures. The probes need to be placed in such a way that alarm is not triggered every time the doors of the cold room open.

At any time, the system should also allow the temperature to be seen outside the cold room. Alarm should be triggered in case the temperature drops below +1°C or rises above + 9°C, during the day and during the night. These alarms which are used for monitoring the temperature should be checked regularly meaning, they need to be manually checked at least twice a day, once in the morning and once in the afternoon/evening. Each monitoring needs to be documented and stored in a way it could be accessible at any time if needed (WHO, 2011, pp. 361–362).

A calibrated max/min thermometer should also be placed inside the unit as a backup use for confirming the temperature. All electronic and manual recording devices should be calibrated at least annually against a traceable reference device. Records of pre-calibration as well as post-calibration should also be archived and kept. When positioning goods inside the cold room, products extremely sensitive to temperatures higher than 8°C should be stored away from the door, and products susceptible to temperatures lower than 2°C should be placed away from the refrigerated unit airflow.

- **Labelling**

Prior to shipping, the labelling and the documentation also needs to be put into place. Labels should be applied to shipping containers, pallets and transport units prior to shipping. Content identification needs to be stated on the label as well as any warning statements and controlled

temperature transport storage conditions of the products, according to IATA regulations. A notice is also needed whether the materials are to be transferred to a specific storage condition upon receipt at the receiving end.

- **Passive and active systems**

The global healthcare cold chain logistics market can be categorized by products and by techniques. By products, we have three major cold chain groups which are vaccines, biopharmaceuticals and clinical trial materials. By techniques, we have possibility of using dry ice, gel packs, liquid nitrogen or use of electrical power source (Transparent Market Research, n.d.). Validated packaging solutions can help maintain and safeguard products during transit. As cold chain logistic and transportation of drugs across multiple continents is growing and the demand for tighter temperature control and prolonged delivery times is increasing, the importance of packaging materials is coming to the forefront (Hager, 2011, p. 98).

Active systems are systems which use electricity or any other fuel source to maintain mandatory temperature environment inside an insulated enclosure. They also have a thermostatic regulation in place. This group includes temperature–controlled trucks, refrigerated ocean containers and refrigerated air containers (World Health Organization, 2011, p. 329). Systems which are used to maintain mandatory temperature environment inside an insulated enclosure, using only preconditioned coolant such as dry ice, frozen gel packs or phase change materials, are passive systems. This group contains different kinds of coolers and insulated containers which are usually portable. They are not appropriate for shipment on long routes or in very extreme weather conditions. They may or may not have thermostatic regulation in place (Australian Government Department of Health and Ageing, 2013, p. 31).

- **Transport vehicles**

Vehicles and containers used for pharmaceutical product storage, transportation and distribution should be able to provide contamination prevention and required environmental conditions, as well as package and label integrity (Good Storage and Distribution Practice, cold chain safety and validation, 2012).

With transportation of cold chain products it is mandatory to use qualified equipment and vehicles, which are equipped with temperature monitoring equipment, that must be calibrated regularly, which enables maintenance of temperature within acceptable limits through the whole transport. They have sensors located at points which present the highest temperature extremes and are equipped with alarms, which alerts the driver in case of breach of temperature at any time. Monitoring sensors must be accurate to ± 0.5 °C and need to record temperature of at least six times per hour. All specification and documentation of transit temperature of internal or external shipment needs to be accessible and stored. Doors on these

vehicles are also equipped with security seals and locks, which provide protection from unauthorized access. These vehicles are capable of maintaining the temperature which range was predefined by the system, over known distribution routes, when vehicle is parked or in motion and are able to safely transport the goods in compliance, which can be presented to regulatory authorities or other parties if needed (World Health Organization, 2011, p. 345).

- **Temperature monitoring**

Temperature data loggers are small electronic devices which can come in different shapes and sizes and are a self-contained miniature computer. They are portable devices, which can be reusable or not and are used to measure temperature at pre-determined intervals and record temperatures at 10-15 minute intervals during storage and transportation. They measure temperature electronically and can provide numerical format data or chart records, which also include information of the max and min temperatures and excursions outside that predefined range. The data measured by a data logger is stored by the monitoring system and can also be downloaded onto the computer at the end of the route once turned off (Australian Government Department of Health and Ageing, 2013, p. 20).

Data loggers are used for accurate indication of temperatures and can be also used for investigations or to map extreme temperature spots. They are usually used when more detailed tracking is required, like it is the case with biosimilars. They should be positioned on the pallet before loading begins and at the end of shipment they should be turned off in the cold room and data downloaded to the computer. In case of any excursions outside the temperature range, data should be evaluated and documented by personnel. Corrective actions should be taken if needed and documented (Hager, 2011, p. 99).

In the complex supply chain, the company has to be able to distribute, store and handle biosimilars within the prescribed temperature range through numerous involved parties and risks that occur along the way. Logistics which used to be only a back-office function is nowadays coming to the forefront very fast. Logistics now requires a deep understanding of not only the shipping, handling and storage part of the process, but also understanding of and training in the field of temperature control. In the past the GDP already specified that temperature sensitive products need to be distributed through the supply chain under specified conditions, but these requirements have intensified recently with regularity scrutiny and different industry initiatives. As a consequence logistic partners now demand strict following to compliant processes, extensive training in temperature control processes and they need to be alert for any changes in regulatory mandates (Clark, 2006). Since shipments can be delayed or even rejected at arrival due to non-conformance, a number of countries now require temperature controlled product shipments, which uses a recorder that covers the entire transport lane, as well as the conformance process with label claim temperature and additional security measures, to be able to mitigate the risk of counterfeiting and theft.

2.5.2 Cold chain risk management

In the past, firms could get away with reacting to risk only after it already emerged, but traditional risk buffering approaches are no longer sufficient to deal with this new environment. The value of risk prevention and not merely reaction to it needs to be understood and recognized by firms now days. Risk is a part of every business environment and companies need to try and prevent problems before they even emerge and not react to them, only after they already happened (Giunipero & Eltantawy, 2004, pp. 698–699).

The principals and tools for quality risk management are also being increasingly applied to pharmaceutical industry and its quality systems. Cold chain management field focuses on the development and implementation of the cold chain shipment conformance process and cold chain management process. The development of such quality system includes planning and implementing processes, steps and methods of efficient control and temperature monitoring that is necessary to meet the product and regulatory requirements. The goal is to optimize the product quality and safety at each step within the production, storage and distribution of the product (Montero, 2010).

As stated above, cold chain is a process of maintaining prescribed temperature range from the manufacturing site to the patient. Within this process many different risk can occur which need to be taken into consideration. One of them is that cold chain transport is more expensive, thus distribution of cold chain products is more costly compared to distribution costs of other pharmaceuticals. Characteristics of biosimilars also have an effect on the ordering process, since buyers who are in vicinity usually order smaller quantities to maintain low inventory, meaning that the frequency of orders is higher. On the other hand, if buyer is located further, this means that such specific transport will also have higher costs and to decrease the number of shipments to lower the cost, the ordered quantities are usually bigger and with that also the value of the load increases. Some of these risks need to already be taken into consideration when planning the cold chain distribution process. Risk associated with biosimilars should already be tackled when making a decision about which route to choose, which provider to choose and if they have the right equipment to manage this kind of cargo, which is the most suitable means of transport, are all parties educated on how to handle the cold chain products, are the storage facilities suitable, etc. (ABB, 2009).

Overall, the commonly encountered risks are seen where the human factor is involved, as well as when the product is being transferred – hand on and hand off point, when one is not able to see the product (transport), but also when shipping high value load, when using a new route, or when transferring a product from country to country (Hoffman, n.d., pp. 14–15). These risks have a common ground which is the shipment process. These risks are common to all supply chains, but are multiplied when dealing with the cold chain products. In delivery process of cold chain products; which comprises of preparation and loading of goods, the physical shipment of the goods, and their unloading and further storage, shipping

conformance process presents the basis for evaluation of the entire shipping process. Shipping conformance process is a process that is used periodically after qualification and implementation of temperature monitoring is established. It consists of three stages which are pre-transportation, transportation and post-transportation stage. It enables us to confirm that our shipment process is performing as intended, confirms shipment conformance and enables us to also identify needed improvements. In our case it should be specialized to specifics of cold chain products. When dealing with cold chain products such cold chain shipping conformance process should be established at a company since it presents guidance to the cold chain distribution process. Its development and implementation, if done properly, then ensures sustainability (Montero, 2010). Thus the main risk in cold chain is establishing a shipment integrity, since the biggest challenges seen are related to preservation of the temperature conditions through the process of storage and handling as well as documenting the storage conditions throughout the supply chain and at the same time maintaining the safety of the products through the whole process, to avoid counterfeiting, damages and theft (Hoffman, n.d., p. 9).

Manufacturers of cold chain products have a direct responsibility for the product from manufacturing to administrating it to the patient. After products reach their first point of shipment, however, manufacturers have only indirect influence on correct handling with the products and they can only indicate to distributors how such products need to be stored and handled (Hoffman, n.d., p. 3). Understanding of how supply network works and is managed is important before any risk management can be put into practice, but once implemented it will protect the continuity of the product supply. In pharmaceutical industry we can see raised awareness of temperature maintenance during transit, since regulations are different from country to country and the requirement for shipping can rapidly change and become stricter (8^{th} World cargo symposium, 2014). This is why risk management in the distribution processes should be in place. It enables and increases the possibility to preserve quality, safety and efficiency of the product throughout the whole route. It enables us to understand the distribution process which company has in place and provides tools to reduce risk and overall improve the effectivnes of the process.

Main risk sources in the distribution process can therefore be divided into equipment, processes, people and external factors. We can not influence the external factors, but other groups are in our domain. ‘Equipment’ consists of storage, transport vehicles or shipping containers and packaging, which were described in more depth alredy in the previous subchapter. Process group can be defined as pre-shipping process, in-transit and post-shipment process and main risk identified here is related to people, more precisely to unskilled people and their lack of knowledge. The biggest issues occurring during the shipping process are temperature excursions, damages to the product and delays at customs, which in the end results in delivery delays or even destruction of a product and they directly impact the cold chain integrity. All these issues are a consequnce of possible failures in the process steps, may it be misscomunication, technical failure or operational error (8^{th} World cargo symposium, 2014).

3 RISK ASSESSMENT OF THE DISTRIBUTION PROCESS OF BIOSIMILARS

Many companies realize the flaws in their cold chain process only after it has already reached a level of complexity that is difficult to simplify. Further development and production of these products will increase the importance of cold chain process even more also due to increasing distance between destinations to which the products are shipped. As with any other process, correct planning and execution is critical, but with the cold chain, where we are talking about high value and lifesaving products, to have unbroken cold chain through the whole process is of outmost importance. Overall, due to the complexity of the process, all possible risks in the cold chain distribution process should be identified and tackled as soon as possible. Since the pharmaceutical supply chain industry relies heavily on controlled and uncompromised transport and is working towards establishing the process which will maintain the shipment integrity, I decided to focus as already mentioned, on the distribution process of cold chain products. Since the term 'distribution process' is wide and complex in supply networks, to be able to conduct my analysis, my focus area will be limited to distribution process from the company and its distribution centre to the wholesaler, without additional intermediates. I will also put a stronger emphasis on the delivery process within the distribution process and in relation to this fact, only this part of the process will be presented in more depth.

As already stated at the beginning, my analysis will be conducted with the help of FMEA tool and will be done based on generic, benchmarked process, so actual implementation of proposed strategies and their review, is out of the scope of this work, however I will conduct risk assessment steps as well as provide proposals for strategy implementation. For this purposes this chapter is divided into five subchapters.

In the first subchapter the process and the stages of the distribution process of biosimilars in a pharmaceutical company are descriptively and graphically presented. Here the distribution process which is currently established in one of multinational pharmaceutical company is used as a benchmark. This subchapter will enable the reader to get a better overview and understanding of the process and will provide a context to my risk assessment process based on which FMEA will be conducted. In the second subchapter the risk identification will be done. Here I will gather the necessary data and identify potential failure modes and associated effects and causes of a failure mode, which will later on serve as a base and input data for further analysis of the process. This data will be gathered using a compilation of risk management tools and methods which are recommended in the literature for purposes of such analysis and were already introduced in the previous chapter. In the third subchapter, I will focus on the analysis of gathered data. In it, I will describe my approach to conducting the analysis and the rankings which were developed for this specific case. Each risk factor will be given its ranking, based on its severity, occurrence and its detectability. These rankings will serve as a mean to calculate the RPN factor in my fourth subchapter, where I will also

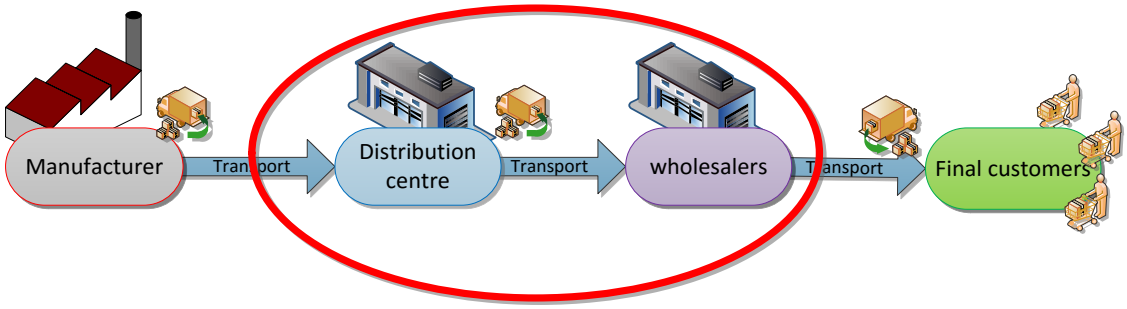
prioritize all risks based on their relevance. In the final, fifth subchapter I will conclude with my analysis, by analysing all the highest ranked failure modes and provide recommended actions, which I believe they would need to be implemented as soon as possible, to make the process more compliant and to enable the company to avoid, decrease or at least to some extent control the risks encountered in the process.

3.1 Mapping of the distribution process from the company to the wholesaler

As mentioned several times, "cold chain" refers to process where temperature control needs to be maintained from the manufacturer site, until the drug is administered to the patient. Biosimilars fall in the category of "cold chain goods", so all rules and regulations referring to the cold chain specifics need to be adhered to also when dealing with biosimilars.

To be able to identify problems that we could face in distribution of biosmilars and in the shipment process established within, a distribution process will be presented with the help of an already established process in a multinational pharmaceutical company, which will serve as a benchmark. This company already has some years of experience with distribution of biosimilars. It does not yet manufacture biosimilars, but it is working as a hub, meaning that it receives products from other companies in its division and is then storing and distributing them further on. Distribution takes place toward other dislocated warehouses in different countries as well as towards end customers which are in our case wholesalers. To undertake the risk assessment on the whole supply network would be, due to its complexity, overwhelming at this stage. To narrow the scope of the process, the risk assessment which will be conducted in this paper, will therefore be done only on one part of the whole distribution process, which is the part of the process which includes the distribution from the company and its distribution centre towards the wholesalers. The process boundaries are represented on one side, with receipt of customer order at the company end and on the other side with the receipt of goods and their release on the wholesaler side. These process boundaries are also graphically illustrated in Figure 4.

Figure 4. Scope of the analysis



The chosen part on which analysis will be conducted includes all the high risk processes; such as preparation of the shipment, transport, loading and unloading of the goods. These processes

were identified in the literature as the ‘more risky’ steps, due to high interaction with the load and in this part of the process, weaknesses are shown and deviations which can jeopardize product safety, quality and integrity are most likely to occur. I believe however, that the steps taken and the methodology of the risk assessment used in this thesis could be at the end generalized in such a way, that this approach and included steps would be appropriate for use, for all parties at any stage in the distribution process of cold chain products, with minor changes.

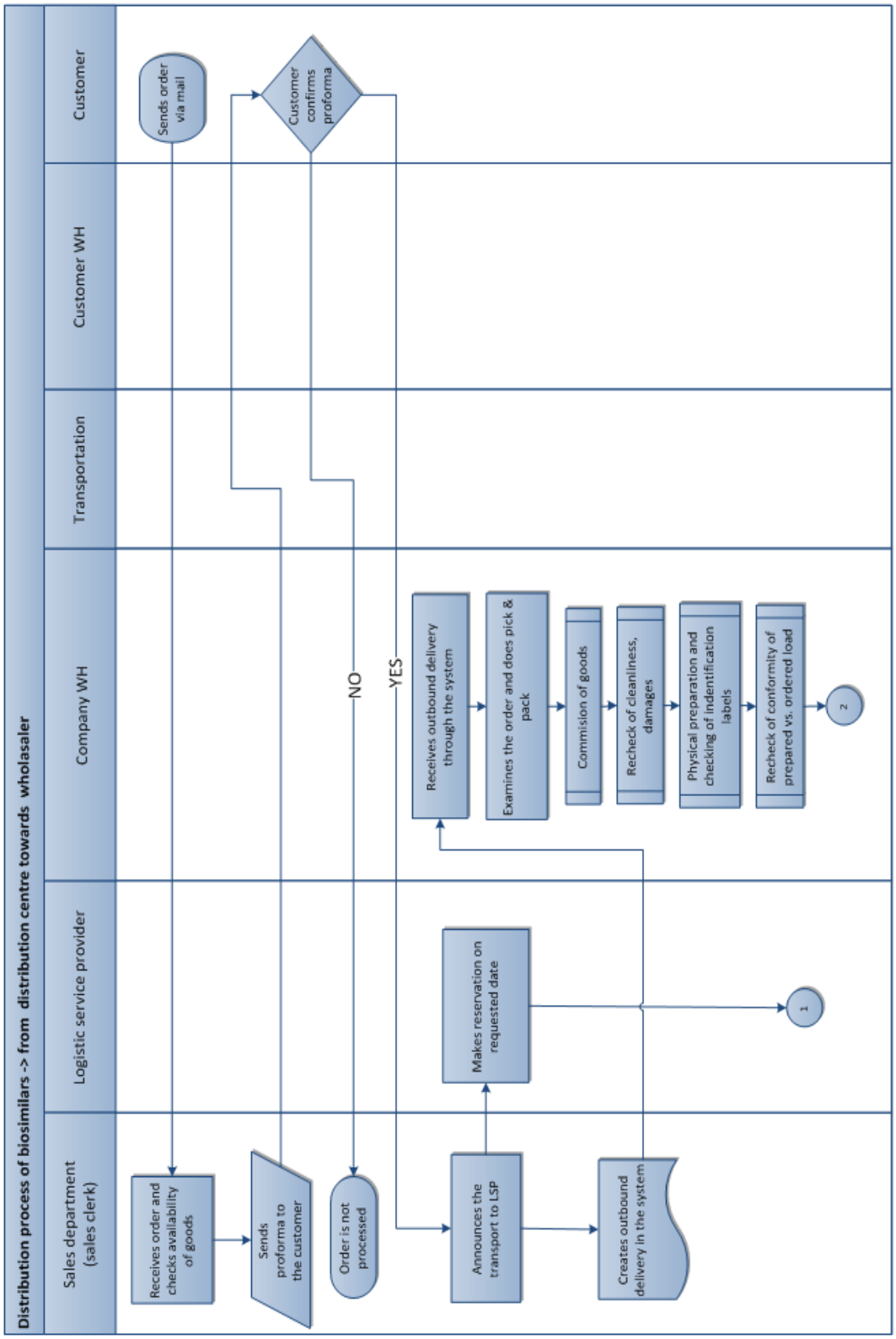
The distribution process of biosimilars from the company and its distribution centre to the wholesalers incorporates different activities which are shown in Figure 5; from the dispatch order to the physical delivery of goods to the customer, which in our case is the wholesaler. The process begins when the wholesaler places the order, then the sales clerk from the company processes the order through the system and informs the logistic service provider about the expected transport date. The logistic service provider then finds an appropriate carrier and a suitable truck. The distribution centre warehouse takes care of the physical preparation of the shipment based on clerk’s order and carries out the loading of the goods to the carrier who transports the goods to the wholesaler’s warehouse. The wholesaler’s warehouse then unloads the shipment and takes care of further storage of the goods at their end.

Figure 5. Activities in distribution process from the distribution centre to the wholesaler

My purpose in this risk analysis is to try and identify the main risks that can be found in this process. To be able to start with my risk assessment, firstly I need to get a good overview of the process and of each stage that the process consists of. This is also the starting step in FMEA analysis. By doing this, the basic context of my analysis scope will be well determined and will serve as a base to which I will return during further analysis process. In literature, one of proposed methods with which we can present the process graphically, is by using a flowchart technique, which sometimes enables faster and easier overview of the process than a descriptive way. I therefore flowcharted the process, with the help of Microsoft Visio tool and in Figure 6 this flowchart is also presented. I believe it provides us with a good visual overview of all the steps included in the process.

With this graphical technique, the focus area is provided, all steps of the process and their correlations are determined, as well as the start and the end of the process, which present the boundaries for my analysis.

Figure 6. Flowchart of the process



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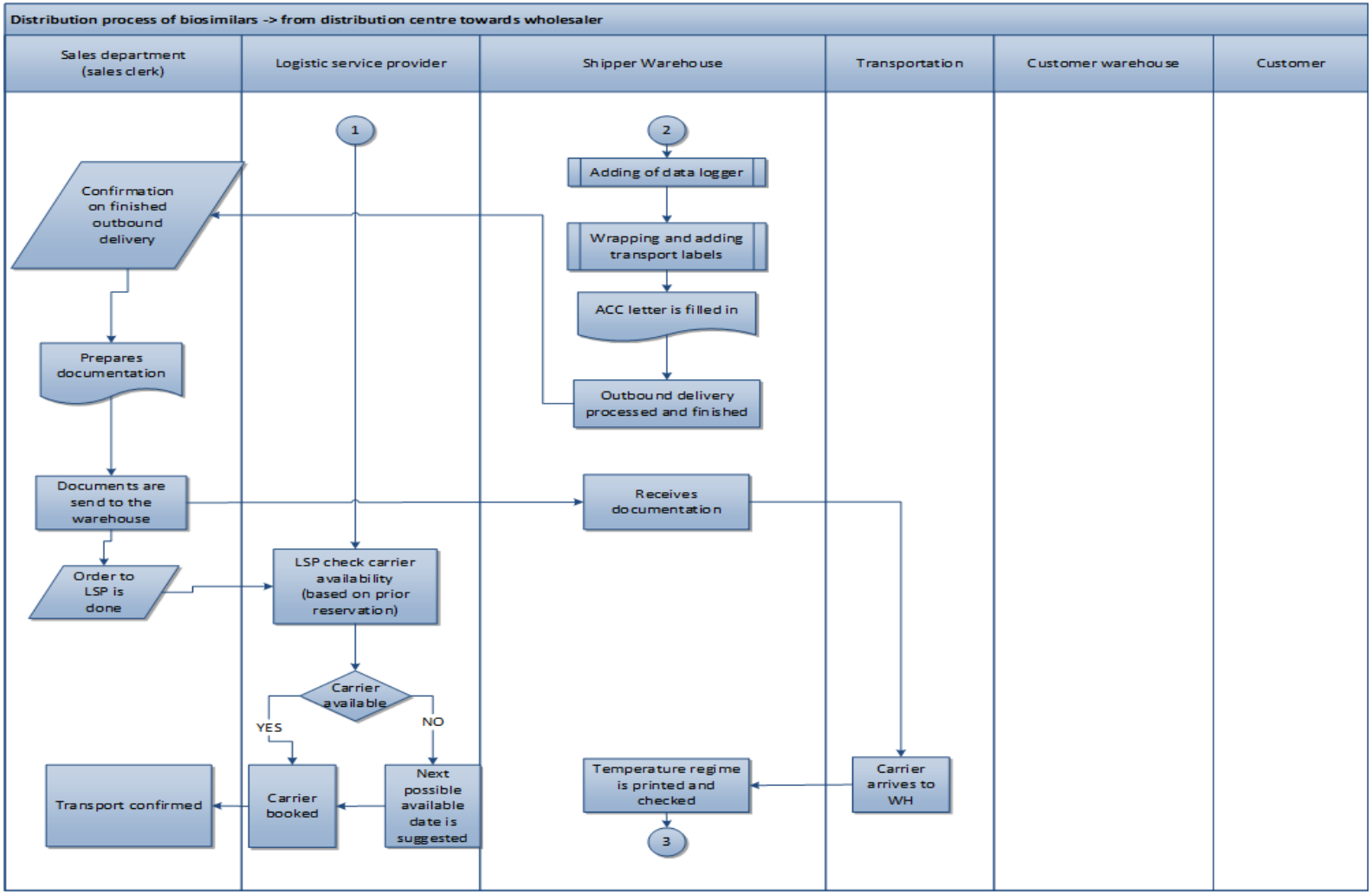

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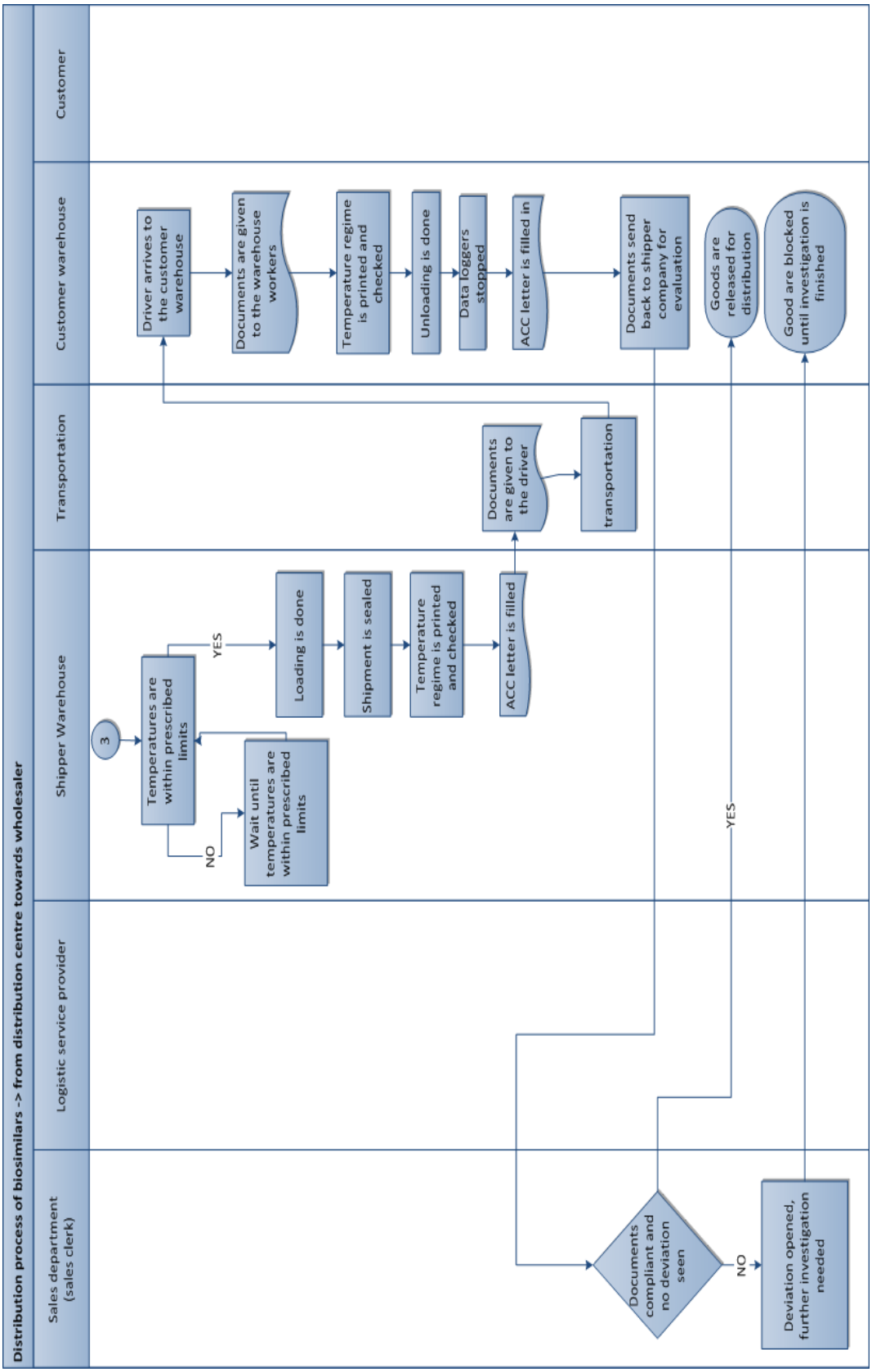

Distribution process of biosimilars -> from distribution centre towards wholesaler
Sales department (sales clerk)
Logistic service provider
Shipper Warehouse
Transportation
Customer warehouse
Customer
3
Temperatures are within prescribed limits
NO
Wait until temperatures are within prescribed limits
YES
Loading is done
Shipment is sealed
Temperature regime is printed and checked
ACC letter is filled
Documents are given to the driver
transportation
Driver arrives to the customer warehouse
Documents are given to the warehouse workers
Temperature regime is printed and checked
Unloading is done
Data loggers stopped
ACC letter is filled in
Documents send back to shipper company for evaluation
Goods are released for distribution
Good are blocked until investigation is finished
YES
Documents compliant and no deviation seen
NO
Deviation opened, further investigation needed

Graphical presentation, even though it provides a good overview of the process and comprising steps, it unfortunately does not provide enough detailed information about each step. For this purpose in continuing paragraphs, the whole flowcharted process is also broken don to 6 main steps, which are described below in more detail. The first and the third step are in the following paragraph described together, since they are directly related to activities, which are conducted by the sales clerk.

- **Customer order processing and customer order finalization**

As seen from the flowchart, firstly the order from the wholesaler is received by the sales clerk, who then initiates the dispatch order and takes care of the dispatch preparation activities, such as informing the logistic service provider about the upcoming transport; it prepares all the necessary documentation and provides information to the warehouse.

- Order from the customer is received by sales clerk via mail.
- The sales clerk checks available quantity of stock and provides the customer proforma invoice with desired quantities and batches.
- Based on the proforma document, the customer then confirms the order to the sales clerk via mail.
- The sales clerk then announces the transport to the logistic service provider. With the cold chain shipment, the sales clerk also needs to check the availability of the cold truck with the logistic service provider.
- The announcement to the transport company has to include the information of the payer for the transport, chosen route, dispatch warehouse address, shipment date, number of pallets, unloading point, country of the recipient, means of transport, temperature regime, e-mail and number of the client, the requested date of loading and the date of the arrival to the client as well as the urgency of the shipment.
- Logistic service provider makes the reservation on the requested dispatch date.
- Sales clerk also sends in parallel the information about the shipment and the order to the warehouse for preparation – outbound delivery number via system (which includes all the information about the order, dispatch date, comments about cold chain shipment, adding of the data loggers, etc.) based on which he can then find all the necessary data in the system to prepare the shipment.
- After the sales clerk receives the confirmation that shipment is prepared for dispatch in the warehouse, they prepare the sales documentation. Sales documentation comprises from invoice, disposition, delivery note, analysis documents, origin document, packing specification, accompanying letter or ACC letter, which is the document that helps track that the cold chain process of loading, shipment and unloading was done correctly and loading document, which helps the warehouse worker identify the driver, truck and the loading regime and without this document, truck is not allowed to be loaded. It also includes information about the grouping of the shipments, the cargo, the

number of the pallets, gross weight, cost centre, postal number, ADR mark (if we are talking about dangerous goods), UN number (in which dangerous group the goods fall under), additional instructions with notes and customs house where/if truck will leave EU and customs documents. The base for this information is the outbound delivery which is created through the system and the order is done via system e-booking.

- Sales clerk than sends all the documents to the warehouse.
- When the outbound delivery is finalized from the warehouse side, the sales clerk also places an order for the transport to logistic service provider.
- The logistic service provider then needs to assure the carrier with suitable transport means (based on the order from the sales clerk) and the driver. Since the sales clerk already announced the need for transport prior to ordering it, logistic provider already planned the carrier and transport means in advance. This decreases the possibility that truck would not be available on requested date.
- The confirmation or transport booking is sent to the sales clerk. If none of the carriers have free capacity or suitable transport means for the date that sales clerk requested, then the first possible date when transport could be arranged, is proposed to the sales clerk.

- **Preparation of shipment in the warehouse**

At the same time as the transport is announced, the sales clerk sends outbound delivery (order information) through the system, which then is received by the warehouse worker. In the system the outbound delivery number provides the worker with all necessary data about the shipment, to be able to physically prepare it.

- Receiving and examination of the order (outbound delivery) and documentation, number of positions and special notes are done. Under special notes, the requirement for transport between 2 ˚C to 8 ˚C needs to be stated from the sales clerk's side.
- All operations except loading should be done and finalized in the cooling room.
- Commission of the goods and recheck/control based on received documentation (order from buyer).
- Recheck of cleanliness, possible damages and conformity of the load with the order.
- Physical preparation of the load, based on SKU of the material, batch and order quantity.
- Identification labels are checked for the pallets or cartons (if smaller quantities are ordered) and printout of the pallet marking is done.
- If shipment is within the country, due to small order quantities, cooling transport units are used. If the shipment is done outside the country, order quantities are larger and goods are shipped on pallets.
- Recheck of prepared versus order load is done based on quantity, SKU and batch and then the packaging specification is signed.

- Shipment is finally prepared for transport – adding pallet identification markings.
- Adding of data loggers, if possible always in a spare carton, if not, then additional small box is added on the pallet where the data logger is stored. One data logger per molecule but not more than one on one pallet. For shipments within the country one data logger per cooling unit.
- All shipping units for data loggers and data loggers need to be cooled down prior to shipment.
- After data logger is activated still within the cold room, its ID number also needs to be added to the online tracking database. This is an online database, which stores the temperature readings of the data logger throughout the whole shipment.
- A yellow sticker which states that temperature recorder is added to the shipment needs to be added.
- Then the pallet is wrapped with foil. In case of cooling units, no wrapping with foil is needed.
- The shipment is marked with shipping transport label.
- Warehouse then processes and finishes the outbound delivery in the system.
- Warehouse workers receive all necessary documentation for the shipment from the sales clerk and wait for the driver.

- **Loading process**

After the preparation of shipment is finalized and goods are prepared for transportation, the warehouse worker waits for the carrier to arrive, to be able to load the goods.

- Loading of the goods is done only after the driver confirms that the temperature regime is assured, by printing the truck temperature read out.
- Under supervision of the warehouse worker the loading is then done as fast as possible, but still in such a way that it is safe. No stops on the loading zone are done.
- Warehouse worker supervises that loading is done correctly and that goods are loaded in the right order and in such a way that they could not be damaged during the transport.
- Warehouse worker signs the loading document and seals the shipment.
- ACC letter has to be filled out during the loading process.
- The driver again needs to print out the truck temperature record to confirm that the temperature regime is maintained.
- Necessary documents are given to the driver with filled out ACC letter.

- **Distribution (transportation of goods)**

When the carrier arrives, the goods are loaded onto the truck and transported to the customer.

- The measuring system in the truck has to cool down the load throughout the whole shipment.
- No damages to the load should be seen during transport.
- The doors of the truck should not be opened until the goods arrive to the customer. An exception could be made if the truck is delivering outside the EU, since there is a possibility that border checking will be required.

- **Unloading process**

At the arrival of the truck to the customer warehouse, the goods are unloaded and stored in a refrigerator or a cold room and the documentation is properly filled out and checked for any temperature excursions.

- The customer needs to be informed by the sales clerk, prior to arrival of the truck, that the cold chain shipment should be expected.
- Driver has to provide all the documents, which he received from the dispatch warehouse to the customer, including the ACC document.
- The receiving warehouse has to be familiar with handling of cold chain goods.
- The truck doors should be opened and pallets/cooling transport boxes unloaded directly to the cooling room.
- Process should be handled fast to not break the temperature regime, but still in compliance with all the rules and regulations and in a safe way.
- The necessary data should be filled out on the ACC letter.
- Data logger needs to be stopped only after goods already arrived to the cold room.
- The truck temperature report needs to be printed from the driver's side and checked.
- Data of the data loggers needs to be uploaded to the online database if available.
- All documents should be sent to the quality personnel at shipper side and until they receive confirmation of release and further distribution of the goods, goods need to be put in quarantine.

This descriptive presentation, combined with graphical overlook of the process above is very important, since it provides the main frame and information on the process steps, based on which my risk assessment and evaluation will be done later on. Overall, I think this subchapter serves as a good input base for starting the risk assessment process, from which the data will be used when conducting FMEA further on in the following subchapters.

3.2 Risk identification stage

Now the risk identification stage begins where activities, which are part of step 2 and 3 in the process of conducting FMEA, will take place. These steps include identification of potential failure modes and also identifying the risks, of each failure mode which can occur during the process and their causes. This part will be done with the help of different techniques provided in literature and already presented in chapter of risk management tools and based on my own knowledge. At this stage, I will still return to my descriptive and graphical presentation, since they serve as a basis for my analysis.

But before we can move forward with the identification of risks, we firstly need to distinguish between failure, failure mode, failure cause and failure effect concept. For better understanding a short explanation of differences between these terms is provided below:

- **Failure** is any state or a condition that does not meet the intended or desirable objective. In our case, for example failure is that the product quality is compromised.
- **Failure mode** is a way by which a certain failure occurs. It is a description of what is wrong, a failure state of an item or function. It is the result of the failure cause. Failure modes should be prevented. Here questions such as "What could possibly go wrong with this equipment/part or part of the process?" should be asked. In our case the failure mode could be the temperature excursion.
- **Failure cause** is a brief description why it went wrong. A cause is the reason that failure mode occurs. "Why would the failure occur?" In our case the failure cause could be the warehouse worker, which did not follow procedures and left the goods in loading zone for a longer period, instead of directly loading them from the cold room to the truck.
- **Failure effect** is the direct consequence of a failure. Here questions such as "What will happen if the failure mode occurs?" should be asked. In our case the failure effect could be that due to temperature excursion, the product quality is compromised to such an extent that it has to be destroyed.

Now that we have explained the differences between the above terms, the risk identification process can begin. Risk identification stage is concerned with identification of uncertain events which could appear in the predefined process above. Designed flowchart provides us with an overview of the process but before we can identify main risks which can occur during this process and their rankings, we firstly need to define all potential failure modes, their effects and causes which lead to specific failure mode. To identify them, I consulted the literature review and used my own knowledge concerning the cold chain distribution. I also used some different tools that enabled me to better identify failure modes, effects and causes:

- Brainstorming process, with the help of which I brainstormed and identified possible failure modes and their effects.

- Fishbone diagram or Cause and effect diagram, with which I brainstormed all possible failure causes that could lead to the main unwanted effect in our process which is that the product quality is compromised.
- Structure tree, with which I categorized and summed up the main failure causes that could lead to a failure mode in our process by categories that will enable me to list possible causes in a more manageable way.

To gather all the data in a structural way I designed my own FMEA sheet, in which all the necessary data for conducting analysis will be gathered. This FMEA sheet is also attached in appendixes. As stated below, it is comprised of several columns which are:

- **Column A: Process steps and sub process steps** → In this column all process steps will be listed and they will also correspond to the flowcharted process steps presented above.
- **Column B: Potential failure mode(s) → What could go wrong?** → In this column all potential failure modes for a specific step will be identified with the use of my own knowledge and past failure modes, which I encountered in my line of work.
- **Column C: Potential effect(s) of failure→ What are the consequences if failure mode occurs?** → Here all possible effects which could arise due to failure modes will be listed.
- **Column D: Severity**→ In this column the severity ranking will be given, which will directly relate to severity rating scale developed for this case and presented in the following subchapters.
- **Column E: Potential cause(s) of failure→ Who/what, why did the failure mode occurs**? → Here causes that lead to a failure mode will be identified. Identification of possible causes will be done with the use of cause and effect diagram. To be able to easier manage the data and to find the main root causes for each of the failure modes and break down high level causes and directly link them to specific failure modes, I will also help myself with a structure tree. With it, the grouping of detailed causes on higher level will be done, for easier data management.
- **Column F: Occurrence**→ In this column the occurrence ranking will be given, which will directly relate to occurrence rating scale developed for this case and presented in following subchapters.
- **Column G: Current process controls** → Here process controls which our benchmarked company already has in place will be listed**.**
- **Column H: Detection**→ In this column the detection ranking will be given, which will directly relate to detection rating scale developed for this case and presented in following subchapters.
- **Column I: RPN score** → All listed rankings for each failure mode, will be multiplied, which will provide me with risk priority number or RPN score, based on which I will then be able to prioritize them. This risk prioritization will also be conducted in more detail in the risk evaluation subchapter.

- **Column J: Criticality** → Results of multiplication of severity and occurrence ranking will be stated here.
- **Column K: Recommendations/actions to reduce failure mode** → Here recommended actions which would in my opinion reduce, mitigate or enable us to avoid risk completely, will be stated. To this specific part, the last subchapter is dedicated in more detail.

Our FMEA scope is the distribution process of biosimilars from the company to the wholesaler, without additional intermediates in between and our goal in this analysis is the identification of possible risks which can arise during the process and their prioritization based on the severity, occurrence and detection ranking. FMEA sheet prepared for this case is added in Appendixes C to H. In Figure 7 also the partial view of a blank FMEA sheet is presented for better visualisation.

Figure 7. FMEA sheet

FMEA scope and goal:	**Scope of FMEA:** Distribution process of biosimilars from the company to the wholesaler, without additional intermediates in between. **Goal of FMEA:** Identification of possible risks which can arise during the process and their prioritization based on the severity, probability and detection ranking.									
A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	Potential failure mode(s) -> What could go wrong?	Potential effect(s) of failure -> What are the consequences if failure mode occurs?	Severity	Potential cause(s) of failure -> Who/what, why the failure mode occurs?	Occurrence	Current process controls	Detection	RPN score	Criticality	Recommendations/ actions to eliminate or reduce failure mode

The first step in conducting FMEA is to state all observed process steps and sub process steps. Since this process comprises from quite some steps, the FMEA sheet in Appendixes from C to H was therefore further divided in to 6 main process steps and to in total of 37 sub process steps, which were more in detail already presented in the previous subchapter where mapping of the distribution process from the distribution centre to the wholesaler was presented. This was done, so that the reader will be able to easily navigate through my analysis.

In Figure 8 also all main steps, which are customer order processing, preparation of shipment in the warehouse, customer order finalization, loading process, distribution process and unloading process as well as their associated sub process steps are presented. All of them will be more in detail analysed through the process of conducting FMEA.

Figure 8. Distribution process of biosimilar → main process steps and their sub process steps

DISTRIBUTION PROCESS OF BIOSIMILARS	
Process element: customer order processing	**Process element: customer order finalized**
customer sends order via mail	sales clerk sees processed outbound delivery in the system
sales clerk checks availability of stock	sales clerk reserves transport with LSP
sales clerk sends proforma	LSP checks carrier availability, books and confirms the transport
customer confirms proforma	sales clerk/outbound logistics prepares the documents for custom
sales clerk announces transport to LSP	**Process element: loading process**
sales clerk creates outbound delivery	transport arrives to the WH
sales clerk prepares ACC document and sends it via mail to WH	readouts of the truck temperature data are printed before loading
Process element: preparation of shipment in the warehouse	loading is done
WH receives outbound delivery and ACC letter	selling of the shipment
WH examines the order/goods to be shipped	readouts of the truck temperature data are printed after loading
use of transport cooling units	ACC letter is filled in
WH does pick & pack	documents are given to the driver
data logger is added in a special box (or in rest box if enough space)	**Process element: distribution (transportation of goods)**
data logger is added in a special box (or in rest box if enough space)	shipment to the customer
data logger is connected to the online tracking database	**Process element: unloading process**
data logger is activated	at arrival documents are given to the customer
data logger label added	readouts of the truck temperature data are printed before unloading
transport label added	unloading is done
ACC letter is filled in	ACC letter is filled in
outbound delivery processes and finished	data logger is stopped and uploaded to the online tracking database *if customer has no access to the online tracking database, it has to send read outs of the data logger to the seller
	documents related to shipment are send by customer to QA for evaluation and final release of goods to the market

In column A in my FMEA sheet in appendixes, I therefore firstly stated all process steps and sub process steps from Figure 8. Each step was entered in a separate row in the FMEA sheet, due to the fact that each step will be analysed for possible failure modes separately. For instance, as seen in Figure 9, one of the first sub process steps is a step in which customer send order via mail and this process step was entered in column A in its own row. The same was done also for all other steps and sub process steps and the full list is available in FMEA sheet in Appendixes from C to H in column A.

Figure 9. Example of FMEA sheet analysis: listing of process steps

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail										

The starting point of my risk identification stage is the identification of failure modes, so after all process steps were entered in the FMEA sheet I tried to identify in each step all possible failure modes that could occur. I helped myself with my own knowledge and past experiences which I have with distribution of biosimiliras as well as with literature review, which helped me to identify possible failure modes more easily. Based on the detailed descriptive and graphical presentation above I went through each step asking myself "What could possibly go wrong with this equipment/part or step of the process?" to try and identify all possible failure

modes scenarios that could occur during each step. In this step the failure modes were identified whether or not they are likely to occur. For each sub processes one or several failure modes were identified and in total of 81 failure modes were stated. As an example in Figure 10, for the first sub process step which is that customer sends order via mail, failure mode, that the order is not received by the sales clerk, was identified and stated in column B. The same was done for all sub process steps and the full list is available in FMEA sheet in Appendixes from C to H in column B.

Figure 10. Example of FMEA sheet analysis: listing the failure modes

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	Potential failure mode(s) -> What could go wrong?	Potential effect(s) of failure -> What are the consequences if failure mode occurs?	Severity	Potential cause(s) of failure -> Who/what, why the failure mode occurs?	Occurrence	Current process controls	Detection	RPN score	Criticality	Recommendations/actions to eliminate or reduce failure mode
customer sends order via mail	order is not received by sales clerk									

For instance in customer order processing step, I identified for different sub process steps 14 possible failure modes. This were besides the one stated in Figure 10 also that mistake could occur when identifying available stock, that transport is not correctly announced, that the outbound delivery is not created or received by the warehouse workers or that there could be problems related to documentation. The full list of those identified failure modes is available in Appendix C in column B. In the second step, where goods are prepared for shipment in the warehouse, I identified 23 possible failure modes, which are that the wrong SKU, batch or quantity could be prepared, that data logger is not added, activated or cooled down, that wrong transport labels could be added or again issues related to documentation could be seen. The full list of those identified failure modes is available in Appendix D in column B. In the customer order finalization step, I identified 7 possible failure modes, related to transportation booking and documentation and they are listed in Appendix E in column B. During the loading process, 18 failure modes were identified which were directly related to the carrier, the loading process itself and the properly filled documentation. Failure modes related to loading process are in detail presented in Appendix F in column B. During the process of distribution of goods, I identified 4 possible failure modes, which could be that temperature excursions occur or that goods are damaged during transportation. Failure modes related to transportation process are seen in Appendix G in column B. In the last step, which is unloading of the goods at the customer side, additional 15 failure modes were identified, which are similar to the ones identified in the process of loading of goods and the full list is available in Appendix H in column B.

The next step in conducting FMEA analysis is to identify and describe the effects which can arise from each failure mode. The effect is the result of a specific failure mode of the process or function. The effects should be stated and described in terms of what internal or external customer could see or feel as a consequence. Here I tried to identify all possible effects of

risks in our distribution process of biosimilars, by asking myself "If the failure occurs, what could be the consequences?" Based on the above descriptive and graphical presentation I went again through each step and brainstormed all the possible scenarios that could occur, if our predefined failure modes would happen. Here I helped myself again with my own knowledge working closely with biosimilars and being involved in their distribution process. All identified possible risks effects are stated based on their correlation to each step and failure mode. Note that more than one effect can arise from one failure mode, and in some cases the same effects could be seen even if related to different failure modes.

For instance in Figure 11, for the first sub process step and its corresponding failure mode, I identified as a possible effect of this failure mode, that order would not be processed. The effect was also stated in column C. The same was done for all failure modes and their effects and the full list is available in FMEA sheet in Appendixes from C to H in column C.

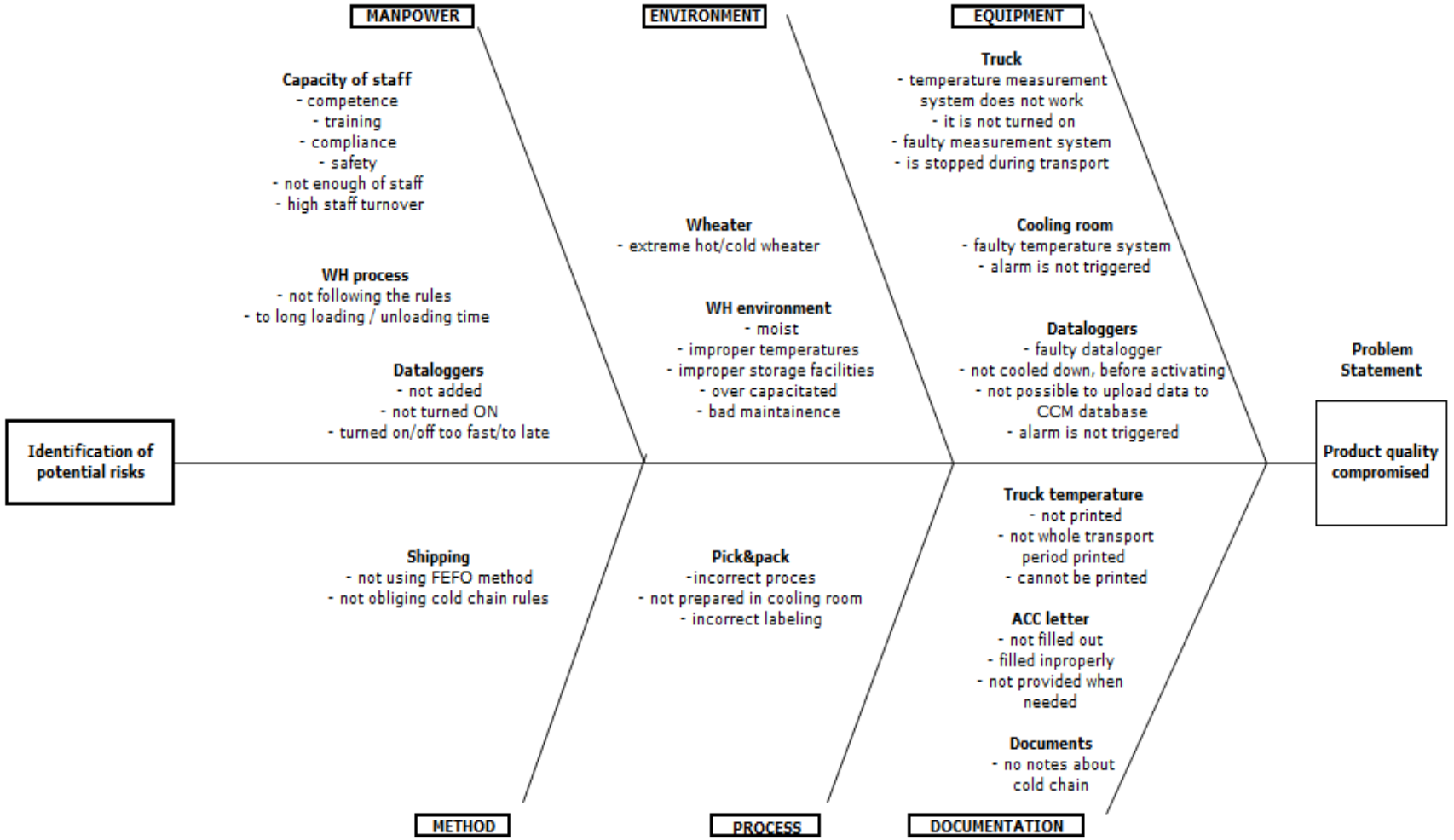
Figure 11. Example of FMEA sheet analysis: listing the potential effects of the failure mode

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed								

In all 6 main process steps I identified several possible effects which could arose from failure modes if they would occur. In overall effects could be seen and felt by the customer as delay in shipment, possible damages that could be done during loading, possible temperature excursion which would compromise the quality of goods, additional delays in release of the product, additional work which would be related to incorrectly filled documentation, frustration at the customer side and many more. They range from minor effects, which in overall would not present a big threat to the shipment and release of the goods, to the severe ones, where the whole shipment and its release could be endangered.

Next step in FMEA process is the identification of possible causes, which could lead to identified failure modes. Failures causes by themselves are in our case seen as process weakness, which may result in a failure. With the use of cause and effect diagram, I firstly brainstormed and tried to identify main failure causes that could lead to our undesirable effect. Due to wide spectre of possible failure causes, it is wise to firstly arrange the failure causes to the categories they belong to. In this way, we can then define causes within each category in more detail. In our case in Figure 12, firstly the main problem, the unwilling effect is stated, which is that the quality of the product is compromised. Then I identified additional categories which are presented as branches coming out of the main branch. Within these categories, possible failure causes were identified that could lead to the main problem.

Figure 12. Cause and effect diagram



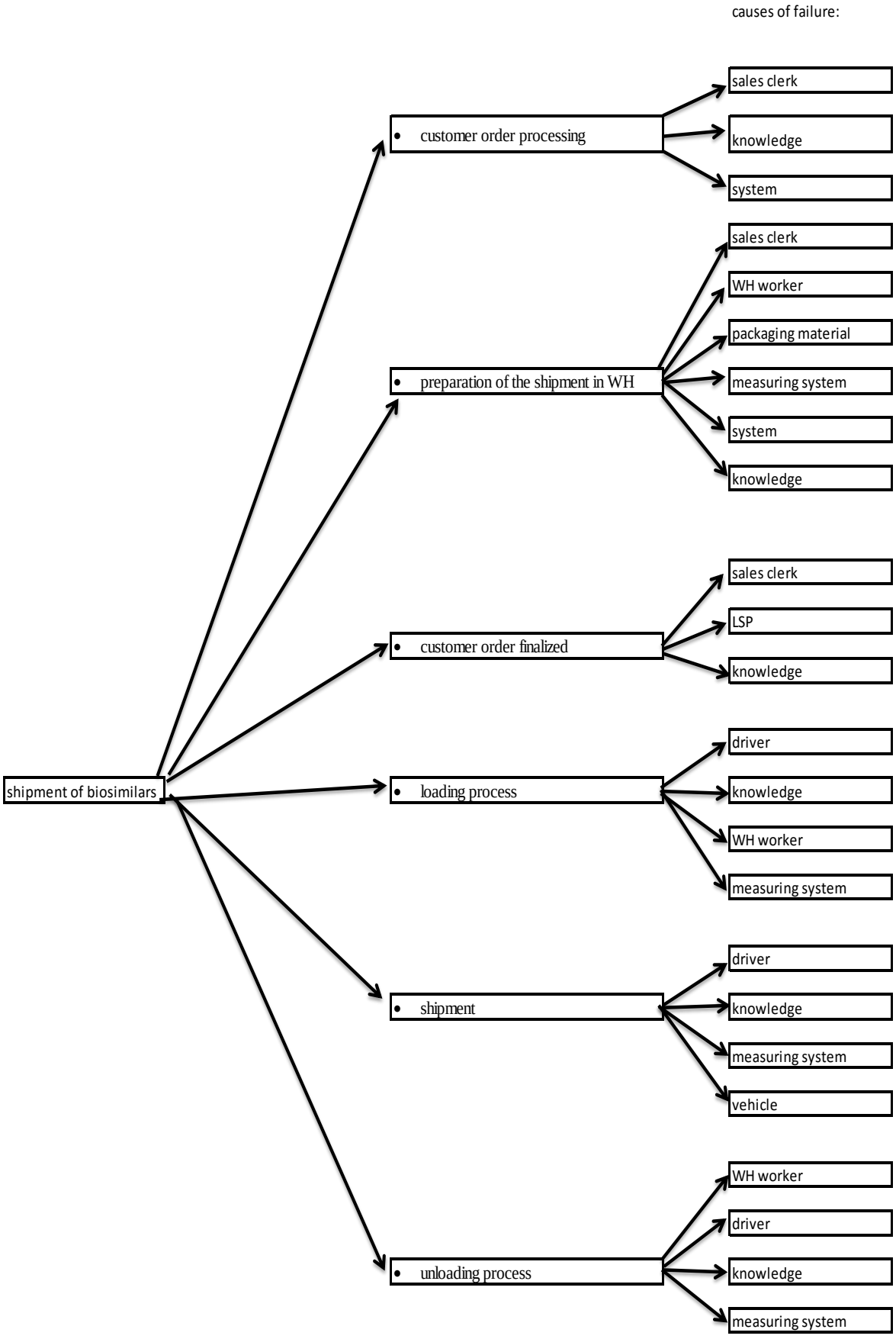
In our case, the main categories are manpower, processes, equipment and environment. To be able to search for root causes in more detail, the process category is actually extended to the method and the documentation category. Brainstorming by categories, provided in each category several main failure causes that could lead to an undesired effect. They are identified as shown in Figure 12. For manpower category the main failure causes identified were the staff themselves and their competences, warehouse processes that are not being adhered to and incorrect use of data loggers. In the environment category, weather as external cause and warehouse environment as internal cause were identified. Under equipment category main equipment such as unfit trucks, cooling rooms and data loggers were identified as possible failure causes. Documentation category presented several causes that could lead to an unwilling effect, but they are mainly centralized around the fact that documentation is not properly filled out. In the last two categories of processes and methods, the main causes leading to an effect were directly related to the fact that incorrect steps are used in the process or due to lack of knowledge over the process itself.

Cause and effect diagram provided me with the main broad possible causes that could lead to an undesirable effect, which is that the product quality is compromised. These causes should now be directly presented in relation to our process and all involved steps, to see where and due to which reason this causes can in fact can be realized in the actual process. Our distribution process descriptively and graphically presented at the beginning of this chapter is comprised of 6 main steps or categories into which it could be divided. These categories are also stated and seen in our FMEA sheet, as main process steps and they divide the whole process into manageable steps. These steps as already mentioned above are:

- customer order processing,
- preparation of shipment in the warehouse,
- customer order finalized,
- loading process,
- distribution (transportation of goods),
- unloading process.

With the help of a structure tree I tried to get an even better insight into the main failure causes in each step of the process in a way it would enable me to get more summarized and structural data, with which I can operate later on. Here I oriented myself based on our detail presentation of distribution process above and also based on data gathered from the Cause and effect diagram. For better understanding and easier evaluation of what caused the failure to occur, main failure causes are in a broader sense presented in structure tree in Figure 13.

Figure 13. Structure tree



In the category customer order processing the main failure cause is presented by the sales clerk, instructions that they are given, their knowledge and system itself. In the category of the preparation of the shipment in the warehouse the main failure causes are again the sales clerk and instructions, documents that they provide, warehouse worker and their knowledge, correct use of packaging and measuring systems and again the system itself. In the third step which is customer order finalization, as the main failure causes identified, are the sales clerk and the instructions, documents that they provide and the logistic service provider. In the loading process category the main failure causes are presented in the form of a driver and warehouse worker involved in the process, the knowledge that they have and instructions that they follow as well as the measuring systems which are used in the process. During the shipment, vehicle used and the driver are identified as the main failure causes. In the last category during the unloading process, the warehouse worker at receiver side, the driver and measuring system as well as the knowledge and following given instructions are identified as major possible failure causes. To sum it up based on our structure tree, basic possible failure causes that can lead to an effect which is that product quality could be compromised, can be categorized to:

- people involved in the process (sales clerks, warehouse workers and the drivers) and instructions that they follow or give,
- knowledge they possess,
- measuring equipment,
- transport equipment,
- system used by the company.

With identified broad failure causes, I went through each step in the process and the list of already identified failure modes and identified all possible failure causes that could lead to that specific failure mode. All possible causes listed were directly related to already identify main causes in structure tree analysis.

For example as seen in Figure 14, for the first sub process step and its corresponding failure mode, I identified as a possible cause that could lead to this failure mode, a system error, such as connection problem and it was stated in column E. In parenthesis the main cause from our structure tree is stated, followed by more detail description of the cause.

Figure 14. Example of FMEA sheet analysis: listing the potential causes of the failure mode

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed		• (system) connection problem						

The same was done for all failure modes and their causes and the full list is available in FMEA sheet in Appendixes from C to H in column E.

Overall in this chapter, my main goal was to try and present possible failure modes, effects that they could have on the process and their causes, in the most possible structured and understandable way. By using literature and the knowledge of the process I posses and observed failures in the past, have helped me to be able to produce a managable list of all failure modes, their effects and their causes. I believe this was achieved through this chapter.

3.3 Risk analysis stage

Next stage is the risk analysis stage which in relation to FMEA 10 step process proposed by McDermott et al.(2009), includes step 4, 5 and step 6 in the process of conducting FMEA. These steps are directly related to assigning different rankings to each identified failure mode. This part is done by analysing risks based on their likelihood of occurrence, consequences or severities that they have and how detectable they are, which was already mentioned at the beginning of the chapter. By doing this, a company has a better understanding of how to allocate resources which will be dedicated to properly develop strategies for managing risks.

To be able to rank all failure modes, risk rating scales firstly need to be determined. Rating scales enable us to rank the failure modes based on their importance in the analysis, for example if they would only have minor consequences or a catastrophic consequence for the customer. This enables us to prioritize failures and address the most important ones first. The scales need to be established before the actual rating begins and the proper way is to present them numerically and descriptively. Each numeric number also should have its own description, so that each rating is fully understandable. Ranking method can use a numerical scale from 1 to 5 or from 1 to 10, where 1 means low and 5 or 10 means high. For detectability on the other hand, 1 means high possibility of detecting risk before it occurs, whereas 5 or 10 means unlikely to detect it with current controls the company has in place. The scale 1-10 enables better precision and estimation than 1-5 and it is also most commonly used in practice since it provides a wider variation in scores.

In our case, the severity rankings were determined first. Severity in our FMEA tells us how severe and serious the outcome can be if the failure mode and its effects occurred and remained undetectable. Based on past data and experiences, we can easily assess the seriousness of the effect, but in processes where past data are not available, estimations are given based on the knowledge of all involved parties and from data, which is gathered from other references, and similar benchmarked processes. Here effects are rated and not the failure modes, meaning that if we have several effects for one failure mode, several effects are rated separately. Severity is ranked from 1-10, whereas 1 represents no severity at all and where 10 represents dangerously high. In our case the severity rankings developed for this case are

available in Table 1, which was developed specifically for this case. Each description and ranking was defined based on possible outcomes that failure mode effects could have.

Table 1. Severity ranking

Description	Severity	Allocated rank
• Failure would **not compromise** the quality of the products. • It would have **minor effects on the internal process** (additional work, minor delay). • Would **not be noticeable** to the customer.	None	1
• Failure would **not compromise** the quality of the products. • It would have **medium effects on the internal process** (additional work, delay) • Failure would have **small effects on the shipment process** (delay in delivery, additional work needed). • Would **not be noticeable** to the customer or to very small extent.	Low	2-3
• Failure would **not compromise** the quality of the products. • It would have **high effects on the internal process** (additional work, delay) • Failure would have **medium effects on the shipment process** (additional work, corrections). • Failure would **be detected by customer** (delay in shipment, medium delay in release, possible claims from customer).	Low to Moderate	4
• Failure **could compromise the quality** of the products **– short to medium long investigation.** • It would have **high effects on the internal process** (additional work, delay) • Failure would have **medium effects on the shipment process and to the customer** (delay in delivery, additional work needed and delay in release). • Failure would **be detected by customer** (delay in shipment, medium delay in release, possible claims from customer).	Moderate	5-6
• Failure **could compromise the quality** of the products – **return of samples, products for further investigation.** • It would be **greatly felt by customer** (substantial delay in delivery and/or release, unable to sell in time and within obligations, brand image of the customer decreased) • **Brand image** of the company would be decreased, possible loss of market share.	High	7-8
• Failure **did compromise the quality** of the products - **destruction of products.** • It would be **greatly felt by customer** (substantial delay in delivery and/or release , unable to sell in time and within obligations, patient would not receive their treatment, brand image of the customer decreased) • **Brand image** of the company would be decreased, loss of market share. additional destruction costs	Dangerously high	9-10

On the basis of my severity ranking table, all effects which were already listed in our FMEA sheet in appendixes have been ranked. I went through each identified step in the process and their failure modes and related effects, asking myself for each of them a fundamental risk question which is: "What would be the consequences, the severity, if the failure mode and its effect really do happen?

For instance as presented in Figure 15, in our first sub process step, the effect of order not being processes, was ranked with severity of 3. The reason behind why rank 3 was chosen is that in cases were customer sends its order and does not receive feedback in a day or two, would most probably contact the sales clerk to verify if order was received. In cases where the order was actually not received, customer would resend its order and effect which he and the shippers company would felt, would be seen as additional work, to try and process the order as quickly as possible, to try and decrease delay in delivery which was caused by the order not being received, when first send.

Figure 15. Example of FMEA sheet analysis: ranking identified effects by their severity

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed	3	• (system) connection problem						

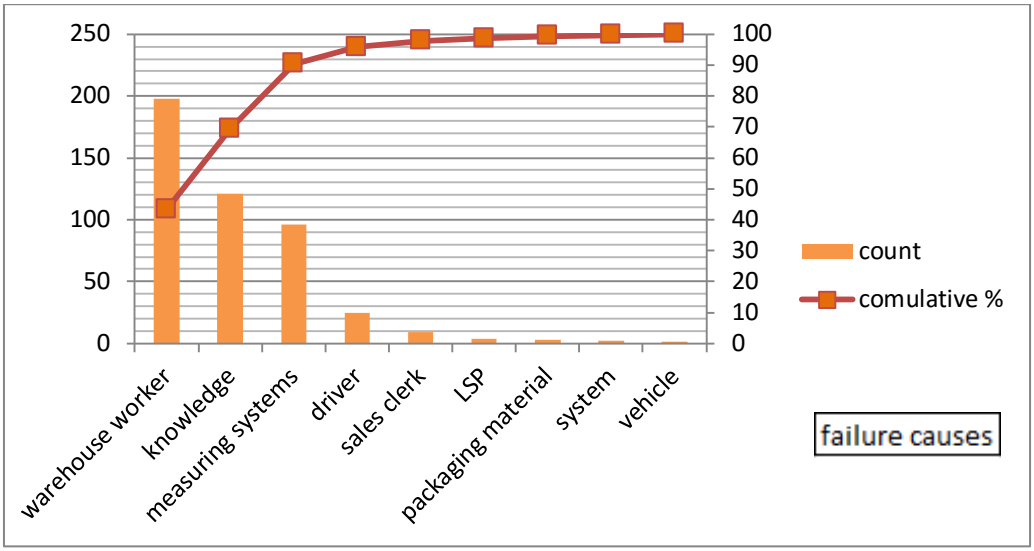
In the same sense as described above, I went through each step, its failure mode and related effects and ranked them on their severity, based on my severity ranking table developed for this case. The full list of ranked effects by their severity could be seen in Appendixes from C to H in column D under Severity. After the rankings were stated I noticed, that failure modes and their effects which directly relate to the fact that temperature excursions could occur or that temperature was not monitored during the whole process, were identified as the most severe ones, since the result could be that the quality of goods has been compromised. At the same time also failure modes and effect related to damage of goods, were ranked the highest.

Next ranking which should be in place is the occurrence or probability ranking. The occurrence ranking is a number which is associated with the probability that a failure mode and its associated cause will be realized in the process being analysed. It has a relative meaning, rather than an absolute value. It considers the percentage chance that a failure can happen in a defined period in a process. This assessment can be done quantitatively or qualitatively and the rankings are determined without regard to the already established severity rankings, or likelihood of detection that will be presented later on. The rankings should be as objective as possible, this is why in most cases the past data is used or the data gathered from similar processes. This is possible when we are doing risk assessment on already implemented processes. Here we can also use our own experiences and other sources of information. At this stage, to assess probability of occurrence, I therefore used the data which I gathered during my two years working in this field. Based on my data analysis, the occurrence ranking for our case was also developed.

While working in the area directly related to the distribution process of biosimilars, I monitored 495 shipments shipments of biosimilars. From all the shipments, in 47% of them

different failure modes occurred which lead to different effects, from minor, which were easily corrected and were not felt by the customer, to the severe ones, where additional investigation needed to be done or in some cases the product even had to be destroyed, since its quality was compromised, to such an extent that it was not safe for use anymore. We need to keep in mind that more than one failure mode could occur during one shipment, which is why the number of failure modes observed is not the same as the number of shipments within which we observed these failure modes. In total 459 different failure modes occurred. Categorizing those failure modes by main causes that were also identified previously in Figure 13 in the structure tree, showed that from all failure modes which occurred, more than 80% were caused due to warehouse workers, may it be at the shipper's or the receiver's side, due to not following the instructions or human error and most of others, due to lack of knowledge, or malfunction and improper use of measuring systems. This data is also graphically shown in Figure 16.

Figure 16. Frequency of failure mode causes



As seen from the graph, from 459 failure modes almost 200 of them were by their cause directly related to warehouse workers, 121 failure modes, were directly related by their cause to the knowledge that involved parties possess and 96 were directly related to measuring systems and their proper usage. Based on this observation, we can see in the graph, by looking at the cumulative line, that there is more than 40 % chance that if failure mode occurs, the cause for its occurrence would be directly connected to the warehouse worker handling the goods. We can also identify that in almost one third of cases where failure modes occur, their causes could be directly related to knowledge and in one fifth of the cases, causes could be directly related to the measuring system.

The data provided above will now help me to generate an occurrence ranking table more easily. Occurrences were ranked from 1-10, whereas 1 represents unlikely to appear, meaning

that the failure cause, which would lead to the failure mode occurs very rarely, almost never, and where 10 presents high possibility of happening, for example almost in every shipment. The occurrence rankings developed specifically for this case are seen in Table 2.

Table 2. Occurrence ranking

Description	Occurrence	Allocated rank
Failure occurs in less than 5% of shipments	Remote, failure very rarely happen	1
Failure occurs in less than 10% of shipments	Low, failures are unlikely	2
Failure occurs in 10-20% of shipments	Low to moderate, failures are few and far apart	3
Failure occurs in 20 - 40% of shipments	Moderate, failures occur	4-5
Failure occurs in 40-60% of shipments	Moderately high, frequent failures	6-7
Failure occurs in 60-90% of shipments	High, repeated failures	8-9
Failure occurs in more than 90% of shipments	Very high, failure is almost inevitable	10

All possible causes that lead to our identified failure modes are already listed in our FMEA sheet and are available in Appendixes from C to H. All of those listed causes have now been ranked based on above occurrence ranking table. Here I went again through each identified step in the process, failure modes and their causes, asking myself for each of them a fundamental risk question which is: "What is the probability (likelihood, occurrence) that something will go wrong?"

An example of one of such ranking is seen in Figure 17, where I ranked the cause of failure mode to occur, due to system error or more exactly due to connection problem with ranking 1. Ranking 1 was chosen, since such cases happen very rarely.

Figure 17. Example of FMEA sheet analysis: ranking identified causes by their occurrence

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed	3	● (system) connection problem	1					

In the same manner I went through all listed failure modes and their causes and ranked them one by one, using my occurrence ranking table for guidance. The full list of ranked failures by their occurrence is available in Appendixes from C to H in column F under occurrence. In total all failure causes were ranked from 1 to 6, meaning that in current process I have not identify a failure cause which I believe would occur in almost every shipment and would be highly repeated or even inevitable. The failure causes which directly related to the warehouse workers were identified as the ones, which occur most commonly. At the same time insufficient knowledge of all involved parties was identified as the one of most commonly occurred causes of failure mode.

The last ranking which needs to be put in place is the detectability ranking. Detectability number tells us if the failure is detected only when the failure already occurs, or is it likely to be detected and stopped before. We can rank detectability once we know what kind of controls we already have in place for all of the failure modes. In this step I firstly listed all process controls that are already in place. Since I used a process from a multinational company for benchmark, I listed here controls that the observed company already has in place. To sum them up from the whole list, which is available in Appendixes from C to H in column G under current process controls, the company has a very strong IT service and support as well as that the company has several local super users in each department. They have many standard operating procedures which are in place and employees are trained based on their relevance to their work. These documents are also at all time available to all employees. The company also trains all new employees, which arrive to the company, based on their relevant standard operating procedures as well as that every employee is monitored by a supervisor for a specific time period, until it becomes independent in their work.

After listing all current controls, I developed a general detectability ranking table, which can be different from company to company, based on the controls that each company has in place and based on the process which is being analysed. Detectability is also ranked from 1-10, whereas 1 means that current controls will detect the potential cause that can lead to an effect and whereas 10 presents a high possibility that controls will not detect the failure mode and subsequently also its failure in the process, or even that no controls are currently in place. For purposes of my analysis I will use detectability ranking developed specifically for this case and those data are available in Table 3.

Based on the developed detection ranking table, I again helped myself with my own knowledge and the past data information on shipments which I monitored, to be able to rank each failure cause by its detectability. I went through each of identified steps in the process and their failure modes and current process controls, asking myself for each of them a fundamental risk question which is "Can we detect these risks before they happen?"

Table 3. Detectability ranking

Description	Detectability	Allocated rank
Current controls almost certain to detect the failure mode. Reliable detection controls are known with similar processes.	Almost certain	1
High possibility that current controls in process will detect the failure mode.	Very high	2 -3
Moderate possibility that current controls in process will detect the failure mode, failure mode will however be detected by later controls in the process.	Moderate	4-5
Low possibility that current controls in process detect the failure mode, they will maybe be detected by later controls in the process.	Low	6-7
Current controls in process will not detect the potential failure mode, they will in low % be detected by later controls in the process.	Very low	8-9
Current controls in process will not detect the failure mode until the process is finalized.	Absolute uncertainty	10

For instance, for our failure mode, which is that order is not received by the sales clerk due to connection problems, a strong IT service support and several local super users based in the company were identified as current process controls, which are already in place in the company. Due to this fact, the detection ranking was given a value of 1, since current controls present in the company would almost certain identify system problems and resolved them quickly to enable business process to unwind smoothly. This case is also presented in Figure 18 and additional data were added to column G and H.

Figure 18. Example of FMEA sheet analysis: ranking identified causes by their occurrence

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed	3	● (system) connection problem	1	● strong IT service and support and several local super users	1			

In the same sense, I went through all of our listed failure modes and added the detection ranking to each line. The full list is available in Appendixes from C to H in column H. In overall the highest ranked failure modes were the ones, where detection is low or sometimes even impossible. This is true for the processes, where system controls are not in place and where knowledge of the process itself and taking correct steps is the most important prevention measure. Even doe the company has instructions and operating procedures written down and employees are trained by them, if they do not follow them, we in many cases are not able to detect a possible failure mode. Based on the analysis it is shown, that the lowest detectability of possible failure modes is seen in the processes of preparing and loading of goods in the warehouse, as well as later on during their unloading. These are processes, which include physical handling of the goods and are carried out by the warehouse workers. Here unfortunately we can detect a high possibility of human error.

In this chapter I presented ranking tables which were developed specifically for this case. Based on them all listed failure modes, causes and effects were also ranked numerically. At this point we have all the prerequisites to start with the next stage in the risk assessment, which is the risk evaluation stage. This stage will be described more in depth in the following subchapter. In it, all the data gathered up to this point will enable us to do the evaluation and prioritization of the possible risks which could be encountered in the whole process.

3.4 Risk evaluation stage

Risk evaluation represents the next part in risk assessment stage, which is a process where risks, after being identified and analysed, are evaluated against an appropriate risk criterion. This step is also related to step 7 and 8 based on McDermott et al. (2009), 10 proposed steps of conducting FMEA. It considers the calculation of risk priority number for each of our identified failure modes which are than prioritized for action by assigning them with rankings, such as tolerable, medium and high or intolerable. Based on already available rankings, RPN is calculated by multiplying severity, occurrence and detection rankings associated with each failure mode, its effect, cause and detectability. In this way I went through each of the identified steps in the process and calculated specific RPNs. For instance as seen in Figure 19, for the first process step, the resulting RPN score is 3, which was received from multiplying severity ranking value of 3, with occurrence ranking value of 1 and detectability ranking value of 1. This was done for all identified failure modes in FMEA sheet in the same manner. The full list is available in the FMEA sheet in Appendixes from C to H in column I. In overall, our scores range from 3 to 360 in total.

Figure 19. Example of FMEA sheet analysis: RPN rankings

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
customer sends order via mail	order is not received by sales clerk	order is not processed	3	• (system) connection problem	1	• strong IT service and support and several local super users	1	**3**		

Now that we have all RPN scores in place, we need to prioritize them based on the received result. But before we move forward we need to be aware that focusing only on RPN results could provide us with an incomplete list of all failures. The reason behind is that FMEA helps us to identify big and small risks, whereas we need to give higher priority to those risks that can cause maximum damage. So firstly, we need to focus on effects of the failure, so on failure modes which could have the most severe effects. The following actions are then related to occurrence rankings and only the last to detection. Due to this reason we have several different approaches on how to conduct prioritization of risk. I decided that in my case I will conduct prioritization based on 3 steps, which are presented below:

- **Step 1:** All cases where we have the severity ranked as 9 or 10 will be prioritized.
- **Step 2:** All cases where the combination between the cause and associated effect of failure mode (multiplication of severity and occurrence ranking) results in a high score, will be prioritized.
- **Step 3:** All cases are prioritized based solely on the highest RPN number.

In step 1, I prioritized all cases which were given the highest severity ranking. This provided me within a scope of 81 identified failure modes, with 9 failure modes and 10 possible highest effect cases which need to be prioritized as first. For purpose to be able of distinguish them from other RPN values, their RPN score in FMEA sheet was marked with red colour and number.

In step 2, all cases which resulted in a high score between severity and occurrence ranking were prioritized. For this purpose, I added scores in a separate column J in my FMEA sheet, entitled criticality. Multiplication of only severity and occurrence ranking was done and for better data organization, scores were calculated directly to FMEA sheet. I ranked criticality score on 4 levels. Acceptable risk level incorporates the lowest 15% of scores and an unacceptable risk incorporates the highest 30% of scores. In between we have two more categories, which are high priority and 'monitor and review' at appropriate time. Heat map related to these criticality scores is shown in Figure 20.

Figure 20. Severity-occurrence heat map

		SEVERITY					
		Dangerously high (10,9)	High (8,7)	Moderate (6,5)	Low to Moderate (4)	Low (3,2)	None (1)
OCCURRENCE	Very high (10)	Risk not acceptable (90-100)	Risk not acceptable (70-80)	High priority (50-60)	Monitor and review at appropriate time (40)	Monitor and review at appropriate time (20-30)	acceptable risk (10)
	High (8,9)	Risk not acceptable (72-90)	High priority (56-72)	High priority (40-54)	Monitor and review at appropriate time (32-36)	Monitor and review at appropriate time (16-27)	acceptable risk (8-9)
	Moderately high (6,7)	High priority (54-70)	High priority (42-56)	Monitor and review at appropriate time (30-42)	Monitor and review at appropriate time (24-28)	Monitor and review at appropriate time (12-21)	acceptable risk (6-7)
	Moderate (4,5)	High priority (36-50)	Monitor and review at appropriate time (28-40)	Monitor and review at appropriate time (20-30)	Monitor and review at appropriate time (16-20)	acceptable risk (8-15)	acceptable risk (4-5)
	Low to moderate (3)	Monitor and review at appropriate time (27-30)	Monitor and review at appropriate time (21-24)	Monitor and review at appropriate time (15-18)	acceptable risk (12)	acceptable risk (6-9)	acceptable risk (3)
	Low (2)	Monitor and review at appropriate time (18-20)	Monitor and review at appropriate time (14-16)	acceptable risk (10-12)	acceptable risk (8)	acceptable risk (4-6)	acceptable risk (2)
	Remote (1)	acceptable risk (9-10)	acceptable risk (8-7)	acceptable risk (6.5)	acceptable risk (4)	acceptable risk (3-2)	acceptable risk (1)

For better visualisation, the data in my FMEA sheet was also marked with the corresponding colour from the heat map presented above. In total, 62 failure modes have criticality ranking of acceptable risk and 19 of them which fall into the category 'monitor and review' at appropriate time. None have critically score high enough to fall into the category 'high priority' or 'unacceptable risk'.

The third and last step taken in the RPN prioritization is prioritizing failure modes only based on the RPN score, without taking into account which of the available three rankings should be weighed higher compared to others. In total, our RPN score ranges from 3 to 360 in value. When conducting FMEA, taking into account all failure modes and propose actions to eliminate mitigate or decrease risk for all of them, is just too overwhelming. At the same time, if we look at all failure modes, we can spent too much time on low risks, which do not threaten our process to a large extent, and not enough time on risks, which can severely harm our process, business and the company's brand image. Due to all these reasons, when conducting FMEA and after we have all RPN scores in place, a RPN cut off number/border is determined, which provides us with a more manageable number of risks, where immediate action is needed. The cut off number can differentiate from one FMEA to another and from company to company. Since rankings are also done mostly based on subjective thinking, here the same approach is used. In practice, the most common approach is that the overall range of RPN results is checked and based on this, the cut off number is determined. Checking the literature, I discovered that in many cases score 200 is used as a cut off number. In our case the cut of number will be set at 150 to also include some lover ranked risks, which I think are important and should be examined. In total, from 81 identified failure modes, 14 of them, from which one already ranked the highest in previous group based on severity ranking, fall into this category and were also marked with a red number, to be able to separate them from other failure modes, which have resulting RPN number below the cut of number.

After all 3 steps in prioritization were done; we now have a manageable number of risks presented also in Figure 21, where actions to eliminate or reduce risk, should be taken immediately. Based on the above criteria, from total of 81 failure modes, 22 of them need to be examined firstly. The number 22 was received, since one failure mode ranked the highest by both criteria, and one failure mode had two different possible effects which both were ranked with the same RPN number. In total, this means that from all identified failure modes, around 25 % should be examined firstly and corrective measures should be taken as soon as possible. In overall almost all process steps where all high ranked failure modes appeared, are steps which are carried out in the warehouse, may it be on the shipper's or the customer's side. Some steps are duplicated in a sense that similar process steps and tasks need to be performed on both sides; the shipper's and the customer's side.

Figure 21. Highest ranked failure modes

Process steps and sub process steps	Potential failure mode(s) -> What could go wrong?	RPN score	Criticality
use of transport cooling units	transporting cooling units are not used	50	10
	transporting cooling units are not cooled down prior to shipment	180	18
data logger is added in a special box (or in rest box if enough space)	data logger is not cooled down prior to adding it	250	25
	data logger box is not cooled down prior to inserting data logger	160	16
	data logger added without a box and not in rest cartoon	72	9
data logger is activated	data logger is not activated	70	10
ACC letter is filled in	ACC letter is wrongly filled from WH side	240	24
readouts of the truck temperature data are printed before loading	readouts are forgotten to be printed	180	18
loading is done	loading can take too much time	270	30
	goods are damaged during loading	100	10
selling of the shipment	shipment is not sealed	50	10
ACC letter is filled in	ACC letter is wrongly filled from WH side	240	24
	ACC letter is not filled at all	180	18
shipment to the customer	high temperature excursions during transport	100	10
	medium temperature excursions during transport	360	36
	goods are stolen	10	10
	damages during transport	100	10
readouts of the truck temperature data are printed before unloading	readouts are forgotten to be printed	150	15
unloading is done	unloading can take too much time	250	25
ACC letter is filled in	ACC letter is wrongly filled from customer side	360	36
	ACC letter is not filled at all	240	24
documents related to shipment are send by customer to QA for evaluation and final release of goods to the market	wrongly filled documents sent	252	36

From Figure 21 we can identify, that main highly ranked failure modes mostly occur during 3 main process steps in our distribution process, which are the process of preparing the shipment in the warehouse, loading of the goods and during unloading of the goods. All three processes are the ones, within which there is a lot of steps where direct handling with the goods is necessary. Most of them are also directly or indirectly related to maintaining and monitoring temperature environment of the goods during the distribution process. Meaning that from provided data, we can agree as already stated in the literature several times, that the maintenance of temperature environment during the process of distribution is one of the most important aspects. In our case main identified failure modes directly related to this fact are that transport cooling units are not cooled down prior to shipment, or worse, not even used, or that the data loggers are not cooled down or activated. Also failures modes such as that loading and unloading can take too much time and possible temperature deviations during

shipment can occur, were identified as one of the highest ranked failure modes. At the same time also failure modes in the documentation process were identified as the more critical ones. If ACC letter is wrongly filled or not filled at all, was shown as one of the more important failure modes.

Now the risk assessment stage is finalized we need to move on to the next stage. The last subchapter is dedicated to the risk control stage, where actions to eliminate or reduce risk in identified high risks failure modes should be proposed and actions also taken in practice.

3.5 Risk control stage

The risk control stage is a process where risks, after being analysed and evaluated against an appropriate risk criterion, are then examined and actions to eliminate or reduce the high risk failure modes are proposed and put into practice. This step is related to step 9, based on McDermott et al. (2009) 10 proposed steps of conducing FMEA. It considers not only proposals but also implementation of the proposed best actions in practice. In our case, this second part - the implementation of proposed actions is out of the scope of this thesis, since the risk assessment was done on benchmarked process and the actual implementation will not be possible. Consequently step 10 in conducting FMEA; which relates to recalculation of resulting RPN scores, after actions were implemented in practice, will also not be possible. However, the first part, where proposals and recommended actions are being assigned to each of our high priority failure modes, will be conducted in the following paragraphs.

At this stage, I went again through my identified failure modes in the process which are stated in FMEA sheet in appendixes, but in this case I examined in detail only the ones which were identified as high risk failure modes. From 81 identified failure modes, 22 ranked the highest by prior established risk prioritization criteria and therefore actions related to those failure modes were proposed. During my examination I went through each position; so I rechecked the failure mode, effect which it may have on the process, the cause that led to the failure mode and all belonging rankings for each of them. With the help of my own knowledge and the past data information on shipments which I monitored, I then assign to each highly ranked failure mode one or several recommendations which should be be taken. These identified recommendations or actions should reduce to some extent or even eliminate the identified high risk failure modes. The full list of all recommendations, directly related to specific failure mode, is available in Appendixes from C to H in column K.

Till this point, I used sub process where customer sends the order to sales clerk and related failure mode, that order is not received by sales clerk, as an example to show how I did this in practice in my FMEA sheet in appendixes, but since in this case the resulting RPN was not high enough, to fall in the group of failure modes, which present the highest risk, I will in this case as an example use process step during which loading is done. For instance, as seen in

Figure 22, the failure mode identified was that loading can take too much time; the possible effect of this failure mode is that goods can be exposed to temperature deviations and the cause of this failure mode was identified as the warehouse worker, which was not experienced enough. Currently all warehouse workers are trained by standard operating procedures in place in the company, but that does not mean, that human error could not be seen. Since all rankings are quite high, also resulting RPN score is high. My recommendations for this specific failure mode were stated in column K, and for this specific case they are, that the company should organize an additional training, where all employees which handle biosimilar products should be trained. This training would be repeated at least once per year, it would take place in a warehouse and it would be presented as a practical example of correctly followed through process. During such training, workers could learn when, which and how some steps should be approached and due to their involvement during training, they would probably also remember and learn more, then just by listening or reading instructions, which the company currently has in place. The second suggestion coming from my side would be that the whole loading process should be re-examined by a team of expert colleagues, which should try to find optimization possibilities within the process itself.

Figure 22. Example of FMEA sheet analysis: listing of proposed recommendations

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
loading is done	loading can take too much time	exposure to temperature deviations	6	● (WH worker) not experienced enough	5	● standard operating procedures are in place and employees are trained based on their relevance to their work ● training of all new employees is done as well as monitoring by supervisor for specific time period	9	270	30	→ On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Current process of loading of goods should be re-examined and optimization in process steps should tried to be achieved.

At this point, where our FMEA is already finalized, I am also able to provide an overlook of my recommendations which were proposed in the FMEA sheet in appendixes in more detail. Some of my recommendations can be referred to and used on more than one process step and relating highest ranked failure modes in the process. This enabled me to extract the most important pieces of information and provide a summarized conclusion which will be understandable to all parties involved. Therefore I summarized my recommendations in Figure 23. The list in total provided 13 recommendations, which I would propose to the company and which, after conducting the analysis, I believe once implemented, would greatly decrease or even prevent occurrence of failure modes, which poses the most risk to the current process. They all mainly fall in the risk response strategy of treating a risk, so trying to control the identified risk, by reducing the impact and the likelihood of the risks itself.

Figure 23. Summarized list of recommendations/actions which should eliminate or reduce failure mode

	Recommendations/actions to eliminate or reduce failure mode
1	Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end.
2	On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. Same training and sharing of best practice should be done also for customers.
3	Additional lines added to ACC letter: - Box must me checked if transport boxes or pallets were used, based on the type of shipment (domestic, international). - Box must me checked if printouts were printed and to which temperature the truck was cooled down prior and after loading it.
4	Check sheets (several copies) stored in visible site (ex. on the door, beside the cooled room, etc.) and on them all important steps in correct order are stated. WH worker would use this sheet at every shipment, to make sure no steps are forgotten.
5	Analysis should be done to determine the maximal number of transport units, data loggers and data logger boxes used per week (based on past data shipments). Based on results from analysis, this maximal number of transport units, data loggers and data logger boxes, should be stored in cooled room with the goods at all time. Also weekly rechecking and refiling of them should be implemented as a standard process.
6	Search for new data logger provider, which uses smaller and thinner data loggers that would not require that much space and would be specifically designed, that they could be added in any box or on the side of the box (damage proofed). Related to new data logger provider also cost and benefit analysis should be conducted, that would provide us with information, if this change would be beneficial or not.
7	A visual sign should be placed on the box where data loggers are stored, stressing importance that data loggers need to be activated prior to shipment.
8	Example of correctly filled ACC letter should be placed on visual place in the cooled room, loading or unloading zone at all time. It would provide WH worker helpful possibility to quickly check how they should fill the ACC letter related to the current shipment.
9	Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.
10	Current process of loading and unloading of goods should be re-examined and optimization in process steps should tried to be achieved.
11	Search for additional packaging materials should be done, which would provide additional precaution against possible damages during loading process, transport itself and unloading process.
12	For all currently used transport providers, analysis should be conducted, which would provide information, how many temperature deviations or damages occur during transportation of goods. Based on received results, only those providers, who had minimal and / or acceptable temperature deviations or % of damages, would be used for shipments of biosimilar products.
13	Search for new transport provider which is specialized for transportation of cold chain goods should be done. Cost - benefit analysis needs to be conducted, to provide information, if choosing a new provider, which may be more expensive, is acceptable.

All recommendations stated in Table 23, are mostly related to the fact, that the company should provide detailed training to all relevant parties in the process of the distribution of biosimilars. Sometimes companies do not stress the importance of continuing training as much as they should. In our case, where many steps are done by employees however, I identified the lack of knowledge as the main source or risk. It is directly related to the fact how steps in the process are taken and how measuring equipment is used, which was already recognized as the main cause that could lead to a failure mode in my previous chapter, where I was analysing data from my past processes observation. For instance, all employees who are at some point included in the distribution process of biosimilars, should be involved in additional trainings, may it be practical or theoretical, where they would refresh their knowledge several times per year. Such trainings are important, since importance of specific steps and rules during a process can fade with time, if not repeatedly stressed.

Also the background of why such high demands are required during the distribution process of biosimilars should be explained and presented to all involved parties. For example, in our analysed process, wrongly filled documentation was highlighted as related to some of the most highly ranked failure modes. If employees, who are responsible to correctly fill this documentation, would be educated of its importance and about the processes to which this documentation has a direct impact on, they would almost certainly make sure that in the future they really do their best to correctly fill it out.

I also suggested some simple tricks which should be implemented in the company's warehouse area, such as placement of visual signs and examples of properly filled documentation in a visible spot in the warehouse. This are easy and low cost methods, that would constantly remind warehouse workers of proper steps which need to be taken in the process and since they would serve as a constant reminder, they would in time become embedded in workers mind.

Referring directly to highly ranked failure modes related to transport cooling units and data loggers my recommendation includes proposition that they would be at all time stored in the cooled room. If this would be implemented in the company, we would eliminate several failure modes instantly, since all cooling units and data loggers would be cooled down at all time and at the same time, they would be placed besides products which require their use, during shipment, meaning that possibility of forgetting to use them in the process would be decreased to a large extent.

I also came to the conclusion, that sometimes companies rely too heavily on their long term partners, such as transport providers and providers of measuring equipment used in this process, while it would maybe be wise to screen the market once more to see if maybe better, more reliable partners are available, which could offer the company more than the current ones.

CONCLUSION

An effective supply chain management is a must have in the current competitive global environment. Customers demand products to be of high quality in perfect condition and delivered on time, which is a goal that is becoming harder and harder to achieve. Reasons preventing companies to achieve these goals are risks. Risks are present everywhere, at any time and we could say they are actually the only constant in today's fast changing environment. With suppliers and customers spread all over the world, a simple supply chain has grown and evolved to a complex supply network consisting of multiple linkages. This global evolution of supply chain has not only forced companies to change their organizations, mentality and how they do their business, but has also presented them with new and unknown risks, with which companies have not dealt with before. The complexity, which somewhat became a necessity for globally competing companies, therefore also presents one of the main sources of risks. These risks, if identified too late or if being ignored and not proactively tackled, could result in disastrous consequences. Unfortunately many companies start shifting their focus to risk and related risk management practices only after a risk event already realizes in practice and harms a supply chain in a different dimension.

Risk management awareness is therefore consequently growing in its importance and is becoming an area to which companies are dedicating more resources, energy and time. Effective and incorporated risk management in an organization can enable companies to efficiently compete and grow on a global market. For many companies the risk management service is frequently a forced action, which is a consequence of the increased demands of the governmental and regulating authorities. But even so, companies are starting to realize that without a good control over risks, they cannot build on trust and have control over their own performance volatility. Management decisions taken without a well-grounded consideration and estimation of possible evolved risks can have severe consequences (Rogachev, 2008, pp. 82-84). It is to be expected that, due to increased pressures to be more cost effective and continuing increasing supply and market complexity that the significance of the risk management field will only grow in years to come.

Even though the risk management field is just starting to rise in its significance in theoretical as well as in practical environment; we have to know that without it companies will not be able to sustain. In this master thesis the importance of implemented and effective risk management processes and tools, related to pharmaceutical industry were presented more in detail in the first part. To be able to properly implement and reap benefits from risk management, broader understanding is needed of what a risk actually is, what the sources of risks are and which categories of risk exist. As we learned through this thesis, risk management process consists of the risk assessment stage, the risk control stage, the output stage and the risk review stage. Risks identified during this process can then be categorized based on their consequences as trivial, small, medium or large consequence risks. Only after we truly know the sources of risk and understand the features, significance and related

consequences that identified risk bear, we are able to efficiently and effectively prepare a compilation of possible strategies, with which these risks will be managed. As we have learned, we can manage risks with 4 different approaches, which are, that we can accept and tolerate risk, we can transfer it, terminate it or treat it. All approaches from theory can be used, but based on the specifics of the process which is under examination in the company, some approaches are more appropriate than others. This can be directly related to implementation difficulties, financial ability or compatibility with a company vision.

In the main part of the master thesis we also presented risk related directly to pharmaceutical industry and to biosimilar products in more detail. As we found out, biosimilar products differ from other pharmaceutical drugs, by being in large proportion more expensive, are lifesaving drugs, have shorter life span, should be kept under specified temperature conditions and are extremely sensible to any damages or temperature excursions. Related to all these characteristics we learned that identified risks in processes involving biosimilar drugs, can have much higher severity and consequently effects related to their occurrence, compared to cases where we would be dealing with other pharmaceutical drugs. Especially due to high risks involved in the process of handling with biosimilar products, this theme was chosen to be explored in more detail and presented in this thesis, since any disruptions in the process could have severe effect for the final customer. This important notion gives the process of biosimilar distribution additional relevance and priority in the company and should be closely monitored at all times.

In our case, we took an example of distribution process of biosimilar products from a multinational company as a benchmark. This was needed, so that we were able to break the whole process down into manageable pieces and conduct a risk analysis on it. The process taken under observation was only a part of the whole process, since conducting analysis from beginning to the end of the process, would be overwhelming. In any case, we included in our scope the process parts, which are the main risk source based on theory and practice. The reason behind this is that many different parties are involved, a high portion of the process is directly related to the physical handling of the goods and the main steps are being done by employees, where there is a high possibility of human error. Through analysis conducted in this thesis, we were able to identify all involved parties from broken down steps and through FMEA also identify all possible risks, their effects and causes. By using different management tools we were in the end able to prioritize the risk based on their highest rankings and provide a manageable number of risks, which would in mine opinion urgently needed to be tackled and mitigated. In our case, highly ranked risks which were identified evolved as predicted around processes where there is no system support and steps are conducted based on the knowledge and experience of employees. Proposed recommendations which resulted from our analysis stress importance of proper education and training for all employees in the company as well as regular refreshment courses. During analysis some other steps in the process were identified as steps, where additional optimization would be needed, by maybe trying to challenge the process which was always done the same, to try and search

for better ways of doing it. At the same time, search for a new partner in relation to measuring equipment involved in the process and a new logistic service provider would be highly recommended. In many cases companies have partners, with whom they have already worked for several years, but we need to be aware, that even though we could have good relations with them, on the market we could maybe find a better, more cost effective, more technologically updated and reliable partner, than we currently have.

Unfortunately, the actions could not be put into practice in our case, since only benchmarked process was analysed, but in overall the conducted FMEA showed that with the steps which were taken, we were able to identify main risks in the distribution process of biosimilars as well as evaluate possible negative effects that their occurrence, if realized, would have on company's performance. Recommendations and actions were proposed, which I believe, if implemented properly would in time improve the process and make it more compliant. However, we need to stress that the risk management process is an ongoing process which never ends. We need to monitor and re-evaluate risks all the time, so that all new appearing risks are also included and to make sure that we constantly improve the process. This is the only way for a company to really have a process under control and to be able to compete on the market and be seen as a trustworthy, reliable and strong company.

I believe steps taken in this master thesis present and show how we can tackle and conduct FMEA on the chosen process in a company. With the approach and steps which I proposed, I believe that such analysis can be done by any company which would like to analyse and identify risk in their processes related to biosimilar products. Furthermore, these steps could in my opinion be taken as guidance for conducting FMEA analysis in any company on any process.

As a possible improvement, I believe my analysis could be conducted even more in depth, by trying to break the whole process down into even smaller steps, really taking into account each and every possible variable which can appear. I am sure that by conducting such analysis with a team of experts, we would be able to identify additional hidden risks, which in our case remain unidentified, since experts would have had more in depth knowledge from their field, which I do not possess. If I would tackle a similar problem in the future, I would also strongly recommend the use of a computer programme with which risk analysis would be done, since it would provide a much better organization of high number of data which result during FMEA and also better traceability and correlation between different variables.

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APPENDIXES

TABLE OF APPENDIXES

Appendix A: Povzetek

Optimizacija in izboljšave na področju planiranja, hitrost obračanja zalog in pravočasne dobave so vse procesi, ki podpirajo in omogočajo oskrbovalnim verigam, da ne le dosežejo svoje cilje in oskrbujejo kupce pravočasno, temveč jim tudi omogočajo, da so fleksibilne, rastejo in podjetjem omogočajo, da so na trgu vidni kot močni konkurenti. Eden izmed bolj pomembnih procesov v oskrbovalni verigi, je sam proces distribucije, ki je v podjetju postavljen. Dobro zastavljena distribucijski mreža omogoča podjetjem, da oskrbujejo kupce po celem svetu odzivno in da dostavljajo pravo blago, ob pravem času, na pravo mesto, ter da je blago neoporečne kakovosti. V današnjem času, ko so oskrbovalne mreže razširjene preko kontinentov, je tveganje toliko večje, saj je prisotno na vsakem koraku. Prav iz tega razloga je dobro zasnovana distribucijska mreža dandanes še toliko bolj pomembna in če ima podjetje le to dobro zastavljeno, mu lahko nudi številne prednosti in možnosti, kot tudi omogoči strateško prednost pred drugimi podjetji.

V moji magistrski nalogi,sem posebno pozornost posvetila izdelkom, ki so zelo občutljivi na temperaturne pogoje. V to skupino izdelkov spadajo vsi izdelki, ki morajo biti hranjeni in transportirani skozi celoten življenjski cikel pod določenimi temperaturnimi pogoji. Med letom 2004 in 2014, je trg le teh zrasel za več kot 50 % in tak trend naj bi bil viden tudi v prihodnosti (Lipowicz & Basta, 2014). Izdelki kot so biološka zdravila in cepiva zahtevajo nadzorovano temperaturno okolje, ki je vzdrževano med 2˚C in 8˚C. Kakršnakoli odstopanja od predpisane temperature, lahko povzročijo, da zdravilo postane neuporabno. Ena izmed največjih težav s katerimi se podjetja trenutno srečujejo, je distribucija izdelkov, ki sodijo v le to skupino. Veliko podjetji, doda številne člene v svojo oskrbovalno mrežo, brez da bi presodila tveganja, ki jih ta dodatna kompleksnost oskrbovalne mreže lahko prinese (Szuhaj et al., 2013, str. 1,). Vedeti kaj pričakovati, je dandanes velika prednost, ki bi jo številna podjetja že morala prepoznati. Prav iz tega razloga sem se odločila, da bom v svoji magistrski nalogi posvetila pozornost managementu tveganja, bolj natančno managementu tveganja v procesu distribucije biološko podobnim zdravilom v farmacevtski industriji. Moj namen v tej nalogi je, da bi farmacevtskim podjetjem lahko ponudila hiter, enostaven in organiziran način, kako prepoznati in oceniti glavna tveganja s katerimi se lahko soočajo v svojem procesu distribucije zdravil, ki zahtevajo posebne temperaturne pogoje. Stremim k temu, da bi moj proces in koraki, ki jih bom uporabila v tej nalogi, bili videni kot okvir ali smernice, ki bi jih posamezniki ali podjetja lahko uporabila na kateremkoli procesu, kjer bi želela identificirati glavna tveganja. Moj cilj v tej nalogi je analizirati primer distribucijskega procesa biološko podobnih zdravil s pomočjo analize možnih napak in njihovih vplivov (ang. FMEA), ter ostalih tehnik, ki se uporabljajo pri managementu tveganja. Skozi nalogo si želim odgovoriti na spodnja vprašanja:

- Kakšne so posebnosti biološko podobnih zdravil v primerjavi z ostalimi zdravili?

- Ali bo moja analiza možnih napak in vplivov le teh napak, ter druge uporabljene tehnike res identificirale glavna tveganja v distribucijskem procesu biološko podobnih zdravil in ocenila možne negativne posledice, ki jih identificirana tveganja lahko imajo na podjetje in na njegovo delovanje?
- Kako lahko zmanjšamo tveganja v procesu in tako izboljšamo proces in ga naredimo bolj skladnega.
- Bi lahko moji koraki v procesu analize bili uporabljeni kot vodilo za ostale posameznike ali podjetja, ki bi želeli izvesti podobno analizo in prav tako poslujejo z biološko podobnimi zdravili ali ostalimi izdelki, ki zahtevajo določeno temperaturno okolje?

Preden se lahko lotimo analize, moramo najprej razumeti kaj management oskrbovalne verige pravzaprav je, kot tudi, kaj zajema management tveganja oskrbovalne verige. Stock in Boyer (2009, p. 706) predlagata razlago, da je management oskrbovalne verige pravzaprav management mreže različnih odnosov znotraj organizacije in med ostalimi odvisnimi organizacijami, ki je sestavljena iz dobaviteljev, nabave, proizvodnih obratov, logistike, marketinga in ostalih podobnih sistemov, ki skrbijo za pretok materialov, storitev, financ in informacij od osnovnega proizvajalca do končnega kupca, z dodatnimi koristmi, ki dodajo vrednost, povečujejo dobičkonosnost skozi učinkovitost in dosegajo zadovoljstvo kupcev. Management tveganja pa se tako ukvarja z identifikacijo tveganj, ki se v procesu oskrbovanja kupcev lahko pojavijo in kako se le tem tveganjem izogniti, jih odpraviti ali vsaj imeti pod nadzorom in zmanjšati njihove posledice, v kolikor se tveganja uresničijo. Prav zaradi vedno bolj obširnih in razpredenih oskrbovalnih mrež, bi moral biti management tveganja integriran v obstoječe procese v vsakem podjetju. Proces managementa tveganj je sestavljen iz več sklopov. V svoji nalogi bom sledila enemu izmed predlaganih procesov, ki deli management tveganja na 4 stopnje. Prva stopnja je ocena tveganja, znotraj katere je potrebno tveganja najprej identificirati, nato analizirati in na koncu le ta tveganja oceniti. Naslednji korak je obvladovanje tveganj, kjer se glede na identificirana tveganja odločimo katere strategije za zmanjšanje teh tveganj bomo uporabili. Znotraj tega koraka se predlagane strategije implementira tudi v praksi. Naslednji korak je dokumentiranje celotnega procesa in ugotovitev. Zadnji korak v managementu tveganja pa nato vključuje ponovni pregled tveganj, kjer se zopet preuči na začetku identificirana tveganja, kot tudi izboljšave, ki so jih v proces prinesle vpeljane strategije. V moji nalogi se bom osredotočila samo na prva dva koraka, torej na oceno tveganj in njihovo obvladovanje. Sama se bom le tega lotila s pomočjo analize možnih napak in njihovih vplivov. Le ta analiza je orodje, ki ne zahteva zahtevne statistike, vendar pa lahko prinese številne pozitivne rezultate za podjetje. Gre za proaktivno metodo, ki nam pomaga identificirati tveganja znotraj analiziranega procesa in nam omogoča oceniti tveganja v procesu, njihovo resnost, ponovljivost in možnost zaznave le teh na trenutnem procesu. Odkrije šibkosti v procesu in omogoča njihovo odpravo.

V moji nalogi se bom osredotočila na farmacevtsko industrijo. Ena izmed specifičnih karakteristik, ki jih le ta industrija ima je, da so zahteve glede kvalitete izjemno visoke, ter da je obseg in razpon zdravil odvisen od obolevnosti prebivalcev (Shah, 2004, str. 931–932). Glavni akterji vključeni v farmacevtsko industrijo so primarni, sekundarni in terciarni

proizvajalci, distribucijski centri in veledrogerije, bolnišnice ter lekarne. Vsi našteti so člani oskrbovalne verige, med katerimi se poraja potreba po oskrbi in povpraševanju. Prav tako pa lahko ločimo organizacije v farmacevtski industriji na drug način. Shah (2004, str. 929) je omenil tudi specifične značilnosti, ki delijo glavne akterje v 5 različnih skupin. Prva so raziskovalna in razvojna podjetja, ki proizvajajo originalna zdravila in imajo svoje proizvodne obrate locirane po celem svetu. Le ta trgujejo z lastnimi znamkami zdravil, ki so lahko na voljo z ali brez recepta. Nato imamo generike, oziroma podjetja, ki proizvajajo generična zdravila. Generična zdravila so zdravila, ki so po sestavi zelo podobna originalnim zdravilom, le da za njih podjetje ni porabilo več let raziskav, temveč je vzelo recepturo, kako proizvesti le to zdravilo od originalnega proizvajalca. Prav tako lahko ta podjetja vstopijo na trg s svojimi zdravili šele ko poteče patent, ki ga je imelo podjetje, ki je prvo prišlo na trg z originalnim zdravilom. Tretja vrsta, so proizvodna podjetja, ki proizvajajo tako originalna zdravila kot tudi generična, vendar znotraj pogodbene obveznosti ali preko licence. Na trgu imamo nato prisotna tudi podjetja, ki ponujajo drugim podjetjem le svoje storitve in zadnja so novo nastale organizacije, ki imajo malo proizvodne infrastrukture, kot so na primer biotehnološka podjetja ali podobna raziskovalna podjetja.

V svoji nalogi se bom osredotočila na biološko podobnim zdravilom, ki so skoraj identične kopije bioloških zdravil, le da so njihovi generiki. Biološka zdravila, so vsa zdravila, ki so bila pridobljena iz bioloških materialov. Biološkim podobna zdravila imajo tako enake karakteristike kot biološka zdravila, kot so kvaliteta, učinkovitost in varnost, le da imajo malo drugačno aktivno sestavino. V primerjavi z ostalimi zdravili, so tako kot biološka zdravila, izjemno občutljiva na spremembe v temperaturi in zato zahtevajo hrambo in transport pod določenimi temperaturnimi pogoji. Kot omenjeno zgoraj, so za biološko podobna zdravila zahtevani temperaturni pogoji od 2˚C do 8˚C ves čas, od začetka njihove proizvodnje, pa vse dokler jih pacient ne uporabi.

V nalogi, bom tako poskusila na procesu distribucije biološko podobnih zdravil s pomočjo analize možnih napak in njihovih vplivov identificirati glavna tveganja, ki se porajajo v procesu in predlagala izboljšave s katerimi bi le ta tveganja lahko izničili, se jim izognili ali jih vsaj imeli pod nadzorom. V mojem primeru, bom za analizo vzela proces distribucije biološko podobnih zdravil, ki ga ima trenutno vpeljano podjetje, ki sicer bioloških ali biološko podobnih zdravil še ne izdeluje, vendar pa je vključeno v njihovo distribucijo. Za namene svoje analize, se bom osredotočila na proces, ki vključuje distribucijo blaga od distribucijskega skladišča, pa do končnega kupca, ki bo v našem primeru veledrogerija. Analizirati celoten proces, ki bi vključeval vse akterje od proizvajalca do končnega kupca, z vsemi vmesnimi distributerji, bi bilo v našem primeru preobsežno. Kljub temu naš izbran del procesa vsebuje vse korake, ki so se preko pregleda literature izkazali za najbolj tvegane. Naše območje analize je tako omejeno na eni strani s kupčevim naročilom in na drugi strani s sprejemom blaga pri kupcu in tako vsebuje samo pripravo blaga za odpremo, naklad, transport, razklad in nadaljnjo hrambo blaga pri kupcu. Proces torej vsebuje vse korake, pri katerih so tveganja največja, saj so v proces vključeni številni ljudje, zatorej je možnost

človeške napake toliko višja, sam proces pa zahteva v veliki meri tudi rokovanje s samim blagom.

Naš proces je sestavljen iz 6 glavnih korakov ki so, sprejem kupčevega naročila in njegova izvedba, pri katerem kupec pošlje naročilo referentu, ki nato naročilo obdela preko sistem, pošlje potrebne podatke v skladišče, rezervira in naroči transport in ko je blago s strani skladišča že pripravljeno, pripravi tudi potrebno dokumentacijo. Naslednji korak je sama priprava blaga v skladišču. Ko skladišče preko sistema prejme potrebne podatke o naročilu s strani referenta, skladiščnik pripravi blago glede na prijeta navodila in poskrbi, da je blago opremljeno s pravilnimi dokumenti in merilniki temperature. Nato sledi sam proces naklada blaga. Ko je blago pripravljeno za odpremo, skladiščnik počaka na voznika. Po prihodu le tega, je blago naloženo na tovornjak v skladu s pravili, ki narekujejo pravilni naklad biološko podobnih zdravil. Transport blaga se izvrši, ko prevoznik prispe in je blago naloženo, ter le tega odpelje do namembnega kupca. Zadnji korak je nato sam razklad blaga. Po prihodu tovornjaka h kupcu, je blago razloženo s tovornjaka v skladu s pravili, ki narekujejo pravilni razklad biološko podobnih zdravil.

V moji nalogi, sem se tako lotila analize s pomočjo FMEA orodja. Da bi lahko zbrala vse potrebne podatke na strukturiran in pregleden način, sem pripravila svojo FMEA tabelo, kjer bodo vsi podatki tekom analize tudi zbrani. Sama tabela je priložena h prilogam. Naše območje analize obsega proces distribucije bioloških podobnih zdravil v farmacevtski industriji. Naš cilj je, da bi preko le te analize identificirali verjetna tveganja, ki se lahko pojavijo v procesu, ter le ta tudi razvrstili glede na samo resnost posledic, verjetnost pojavitve in zmožnost zaznave tveganja, predno se le ta realizira. Po McDermottu et al.(2009, str. 23) lahko analizo možnih napak in njihovih vplivov razdelimo v sklop desetih korakov. Preko teh korakov sem tako v nalogi najprej pregledala celoten proces in ga tudi grafično predstavila in opisala. Nato sem v svojo FMEA tabelo vnesla vse korake in pod korake v procesu čemur je sledila identifikacija vseh tveganj, ki se v procesu lahko pokažejo, nadaljevala sem z identificiranjem posledic, ki se lahko realizirajo, če do le teh napak pride, kot tudi identificirale vse možne vzroke, ki lahko vodijo do le teh napak. Naslednji korak je vključeval pripravo lastnih tabel na katerih bodo temeljile moje ocene resnosti posledic, kako pogosto se tveganja v procesu pojavijo in kakšna je njihova možnost zaznave napak preden se le te uresničijo. Vsem identificiranim tveganjem sem nato pripisala primerno vrednost. Ko so bile vse vrednosti določene, sem izračunala RPN vrednost. RPN število je zmnožek ocen resnosti, pogostosti in zaznave vsakega identificiranega tveganja. Na podlagi prejetih rezultatov, sem nato tveganja razvrstila po pomembnosti in preko celotne analize tako identificirala 22 tveganj, pri katerih bi bila potrebna takojšnja implementacija akcij, ki bi omogočila, da se le tem tveganjem izognemo, jih zmanjšamo ali vsaj nadzorujemo. Sama implementacija priporočil, ki bi izboljšala proces v našem primeru žal ni mogoča, vendar sem kljub temu pripravila spisek predlogov, ki bi jih glede na analizo, svetovala podjetju, da jih implementirajo.

Moji predlogi in ugotovitve so bile, da bi bilo potrebno dodatno izobraževanje in treningi zaposlenih v podjetju, katerih delo vključuje rokovanje z biološko podobnimi zdravili. Priporočala bi jim treninge, ki vključujejo aktivno sodelovanje zaposlenih, saj bi le preko njih bili vsi zahtevani postopki in procesi res upoštevani. Ugotovitve analize so tudi pokazale, da bi podjetje morda moralo ponovno preučiti trenutne partnerje s katerimi sodeluje in mogoče razmisliti o pridobitvi novih ponudb in novem partnerstvu.

Mislim, da sem preko analize prišla do identifikacije glavnih tveganj, kot tudi pripravila primerni sklop predlogov, ki bi podjetju lahko omogočil izboljšavo trenutnega procesa. Mislim, da bi lahko postopki in koraki, po katerih sem se lotila same analize, lahko bili videni kot okvir oziroma navodila, kako lahko katerikoli posameznik ali podjetje poskusi podobno analizo izvršiti na svojih procesih.

Appendix B: List of Abbreviations

ACC letter → Accompanying letter
EMA → European Medicines Agency
ETA → Event tree analysis
FDA → U.S. Food and Drug Administration
FTA → Fault tree analysis
FMEA → Failure Mode and Effect Analysis
GDP → Good Distribution Practice
GMP → Good Manufacturing Practice
GSP → Good Storage Practice
ICH → Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use
R&D → Research and development
RPN → Risk Priority Number
SCM → Supply Chain Management
SCRM → Supply Chain Risk Management
WHO → World Health Organisation

Appendix C: FMEA sheet → Process element: Customer order processing

FMEA scope and goal:	**Scope of FMEA:** Distribution process of biosimilars from the company to the wholesaler, without additional intermediates in between. **Goal of FMEA:** Identification of possible risks which can arise during the process and their prioritization based on the severity, probability and detection ranking.

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
DISTRIBUTION PROCESS OF BIOSIMILARS										
Process element: customer order processing										
customer sends order via mail	order is not received by sales clerk	order is not processed	**3**	● (system) connection problem	**1**	● strong IT service and support and several local super users	**1**	**3**	**3**	
sales clerk checks availability of stock	stock is identified even doe not physically there	outbound delivery cannot be created if goods are not on stock, but proforma can be	**3**	● (knowledge) sales clerk checked the wrong batch/SKU ● (system) system failure ● (knowledge) sales clerk identified stock which is expected to be released in time for shipment	**2**	● following approved standard operating procedures goods which are not on stock should not be identified as available ● system does not allow sales clerk to define stock if not available, however this step can be overridden manually in cases where expected batch release should be done in time for shipment	**1**	**6**	**6**	
	stock is not identified even doe physically there	outbound delivery cannot be created	**4**	● (system) system failure	**2**	● strong IT service and support and several local super users	**1**	**8**	**8**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
sales clerk sends proforma	customer does not receive proforma via mail	order is processed with delay when received by customer and confirmed from their side	**2**	• (system) connection problem • (customer) wrong e-mail address	**2**	• strong IT service and support and several local super users • mail generates feedback note if mail is not delivered, monthly recheck and maintenance of correct contacts on share point	**1**	**4**	**4**	
	sales clerk forgets to send proforma	order is processed with delay once proforma send	**2**	• (sales clerk) sales clerk forgot to send it, due to too much work • (knowledge) sales clerk did not know that proforma needs to be send	**1**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**5**	**10**	**2**	
customer confirms proforma	customer does not confirm proforma	order is processes without confirmation	**4**	• (sales clerk) sales clerk did not know he needs to get final confirmation from customer, before processing the order	**1**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**4**	**16**	**4**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
sales clerk announces transport to LSP	sales clerk forgets to announce the transport	possibility of delay of shipment, due to not announced transport prior to actual ordering of it	**4**	● (sales clerk) sales clerk forgot to send it, due to too much work ● (knowledge) sales clerk did not know that transport needs to be announced prior to booking	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**5**	**20**	**4**	
	sales clerk announces the transport, but forgets to specify that cold truck is needed	delays in shipment, due to rebooking of correct truck	**3**	● (knowledge) sales clerk did not know that for cold chain shipment also type of truck needs to be specified ● (sales clerk) sales clerk forgot to add note when announcing the transport	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● additional corrections possible during final ordering	**7**	**63**	**9**	
sales clerk creates outbound delivery	outbound delivery not created	order is not processed or processed with delay	**4**	● (sales clerk) sales clerk forgot to send it, due to too much work	**1**	● no process control	**10**	**40**	**4**	
	outbound delivery not received by WH worker	order is not processed or processed with delay	**3**	● (system) connection problem	**1**	● strong IT service and support and several local super users	**3**	**9**	**3**	
	outbound delivery created with wrong data	order processed, with wrong materials and batches (not the ones confirmed on proforma)	**4**	● (knowledge) sales clerk wrongly processed outbound delivery	**1**	● no process control	**10**	**40**	**4**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
sales clerk prepares ACC document and sends it via mail to WH	ACC document not send	shipment processed without the ACC document - no traceability, can cause problems with final release of the goods	**6**	● (knowledge) sales clerk did not know he needs to fill it ● (knowledge) WH worker did not know he needs this document for cold chain shipments	**2**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**9**	**108**	**12**	
		WH worker requests it, additional work	**1**	● (knowledge) sales clerk did not know he needs to fill it ● (sales clerk) sales clerk forgot to send it	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● WH worker needs to request it before he prepares the shipment	**4**	**12**	**3**	
	ACC document send but i it s wrongly filled in	wrong data on the document can cause problem in process of releasing the goods	**3**	● (knowledge) sales clerk did not know how to properly fill it	**2**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**7**	**42**	**6**	
		WH worker requests correction, additional work	**1**	● (sales clerk) sales clerk worked to fast and used wrong data	**2**	● sales clerk and WH worker are are trained based on standard operating procedures, if sales clerk sends wrongly filled ACC letter, WH worker needs to request corrections before he prepares the shipment	**4**	**8**	**2**	
	ACC document send but to wrong recipients	ACC not received by correct employee	**3**	● (sales clerk) sales clerk send it to the wrong recipients due to too much work ● (knowledge) sales clerk did not to whom to send it	**2**	● no process control	**10**	**60**	**6**	

Appendix D: FMEA sheet → Process element: preparation of shipment in the warehouse

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
Process element: preparation of shipment in the warehouse										
WH receives outbound delivery and ACC letter	WH worker missed received outbound delivery	quantities prepared with delay, possible delay in shipment	**4**	• (WH worker) WH worker did not check the system due to too much work	**1**	• daily monitoring of opened outbound delivery in place	**1**	**4**	**4**	
WH examines the order/goods to be shipped	damages not discovered when goods are examined	damaged goods shipped to the customer, possibility of claim form customer	**6**	• (WH worker) WH worker did not check properly, mistake due to hurry • damages were hidden, WH worker could not see it	**2**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**120**	**12**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
use of transport cooling units	transporting cooling units are not used	high possibility of temperature deviation of goods	**10**	● (knowledge) WH worker did not know he needs to use them ● (management) not enough ordered transport cooling units, not on stock	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● monthly checking of available stock of transport units	**5**	**50**	**10**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. →Additional line added to ACC document, where box must me checked if transport boxes or pallets were used, based on the type of shipment (domestic, international). → Check sheets (several copies) stored in visible site (ex. on the door, beside the cooled room, etc.) and on them all important steps in correct order are stated. WH worker would use this sheet at every shipment, to make sure no steps are forgotten.
	transporting cooling units are not cooled down prior to shipment	possibility of temperature deviation of goods	**6**	● (WH worker) WH worker made mistake due to hurry ● (knowledge) WH worker did not know he needs to cool them down first	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**180**	**18**	→ Analysis should be done to determine the maximal number of transport units used per week (based on past data shipments). Based on results from analysis, this maximal number of transport units should be stored in cooled room with the goods at all time. Also weekly rechecking and refiling of transport units should be implemented as a standard process.
WH does pick & pack	use of wrong SKU and batch used	order processed, with wrong SKU and batch - customer rejects delivery or claim is raised	**8**	● (WH worker) WH worker made mistake due to hurry ● (system) system failure	**2**	● recheck of physically prepared goods versus ordered goods in outbound delivery ● possible human error	**6**	**96**	**16**	
	wrong quantity prepared	order processed, with wrong quantity - customer opens a claim	**4**	● (system) system failure ● (WH worker) WH worker made mistake due to hurry	**3**	● for not full cartoons -manual counting where 2 different persons need to count the rest cartoons	**6**	**72**	**12**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
data logger is added in a special box (or in rest box if enough space)	data logger is not added	data logger added later, additional work	**1**	● (WH worker) WH worker forgot due to hurry	**5**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● during the preparation and loading of the goods ACC letter should be filed in, where information related to data loggers are requested	**4**	**20**	**5**	
		shipment shipped without data logger, no temperature monitoring, possibility of rejection of batch	**8**	● (knowledge) WH worker did not know he needs to add data logger	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● during the preparation and loading of the goods ACC letter should be filed in, where information related to data loggers are requested	**5**	**40**	**8**	
	not enough data loggers are added	if we have more than one customer and unloading points, possibility of problems with final release, due to missing temperature monitoring through whole shipment, for each customer	**5**	● (knowledge) WH worker did not know he needs to add specific number of data logger ● not enough data loggers on stock	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● monthly checking of available stock of data loggers in place	**6**	**90**	**15**	
	data logger is not cooled down prior to adding it	possible temperature deviation until data logger cooled down, possibility of problems with final release	**5**	● (knowledge) WH worker did not know he needs cool down the data logger ● (WH worker) WH worker did not let it cool down for enough time ● (WH worker) WH worker forgot due to hurry	**5**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**250**	**25**	→ Analysis should be done to determine the maximal number of data loggers used per week (based on past data shipments). Based on results from analysis, this maximal number of data loggers should be stored in cooled room with the goods at all time. Also weekly rechecking and refiling of data loggers should be implemented as a standard proces

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
data logger is added in a special box (or in rest box if enough space)	data logger box is not cooled down prior to inserting data logger	possible temperature deviation until box and data logger cooled down, possible problems with final release	**4**	● (WH worker) WH worker forgot to cool down the box ● (knowledge) WH worker did not know he needs cool down the data logger	**4**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**160**	**16**	→ Analysis should be done to determine the maximal number of data loggers boxes used per week (based on past data shipments). Based on results from analysis, this maximal number of data loggers boxes should be stored in cooled room with the goods at all time. Also weekly rechecking and refiling of data loggers boxes should be implemented as a standard proces → Search for new data logger provider, which uses smaller and thinner data loggers that would not require that much space and would be specifically designed, that they could be added in any box or on the side of the box (damage proofed). Related to new data logger provider also cost and benefit analysis should be conducted, that would provide us with information, if this change would be beneficial or not.
	data logger added without a box and not in rest cartoon	possibility of damaging / loosing data logger	**9**	● (packaging material) not enough boxes on stock ● (knowledge) WH worker did not know he needs to add data logger	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● any box can be used to insert data logger in, but it has to be cooled down first	**8**	**72**	**9**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Check sheets (several copies) stored in visible site (ex. on the door, beside the cooled room, etc.) and on them all important steps in correct order are stated. WH worker would use this sheet at every shipment, to make sure no steps are forgotten.
		data logger exposed to temperatures, which do not simulate temperatures within a cooled down box - possibility of problems with final release,	**8**	● (packaging material) not enough boxes on stock ● (knowledge) WH worker did not know he needs to add data logger	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**8**	**64**	**8**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
data logger is connected to the online tracking database	data logger is not connected to the online tracking database	temperature of goods is not recorded during transport, possible problems with final release process	**7**	● (WH worker) WH worker forgot to connect the data logger to online tracking database	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ●used data loggers enable also PDF print of the recorded temperature	**8**	**56**	**7**	
	online tracking database is not working	delay in shipment	**5**	● (system) system failure	**1**	● strong IT service and support of contractual party	**1**	**5**	**5**	
data logger is activated	data logger is not activated	temperature of goods is not recorded during transport, possible problems with final release process	**10**	● (WH worker) WH worker did not know or forgot to activate the data logger	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● during the preparation and loading of the goods ACC letter should be filed in, where data and hour of data logger activation are required	**7**	**70**	**10**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Check sheets (several copies) stored in visible site (ex. on the door, beside the cooled room, etc.) and on them all important steps in correct order are stated. WH worker would use this sheet at every shipment, to make sure no steps are forgotten. → A visual sign should be placed on the box where data loggers are stored, stressing importance that data loggers need to be activated prior to shipment.
	data logger is activated to late	temperature during lading of the goods is not recorded during transport, possible problems with final release process	**5**	● (WH worker) WH worker remembered later that data logger needs to be activated	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● during the preparation and loading of the goods ACC letter should be filed in, where data and hour of data logger activation are required	**7**	**35**	**5**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
data logger label added	no data logger label added	customer believes no data logger was added - possibility of problems with final release, if data logger not discovered	**8**	• (WH worker) WH worker did not know he needs to add the label	**2**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**6**	**96**	**16**	
	data logger label added on the wrong box	customer needs to search for data logger, frustration	**4**	• (WH worker) WH worker added it to the wrong box, due to hurry	**2**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**80**	**8**	
transport label added	no transport label added	customer can reject the shipment, due to no information on the boxes what is in the shipment	**8**	• (knowledge) WH worker did not know he needs to add the label	**1**	• standard operating procedures are in place and employees are trained based on their relevance to their work	**2**	**16**	**8**	
	wrong transport label added	customer can reject the shipment, due to impression that wrong goods were shipped and mismatch of data	**8**	• (system) system failure • (WH worker) WH worker added wrong label due to hurry	**1**	• strong IT service and support and several local super users • standard operating procedures are in place and employees are trained based on their relevance to their work	**2**	**16**	**8**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
ACC letter is filled in	ACC letter is wrongly filled from WH side	wrong data on the document can cause problem in process of releasing the goods	**6**	● (knowledge) WH worker did not know how to fulfil the ACC letter ● (WH worker) WH worker was in a hurry and made mistake	**4**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**240**	**24**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill the ACC letter related to current shipment. → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.
	ACC letter is not filled at all	shipment processed without the ACC document can cause problems with final release of the goods	**6**	● (knowledge) WH worker did not know that ACC letter needs to be filled ● (WH worker) WH worker was in a hurry and made mistake	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work also based on prior steps in the process, they should receive it already partially filled from sales clerk	**7**	**126**	**18**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
outbound delivery processes and finished	WH worker forgets to finish the outbound delivery in the system	sales clerk does not get information that shipment is prepared, possibility of delay of shipment	**4**	• (WH worker) WH worker forgot to finalized the outbound delivery due to hurry • (knowledge) WH worker did not know he needs to finalize the outbound delivery also in the system	**1**	• daily monitoring of opened outbound delivery in place	**1**	**4**	**4**	
	our outbound delivery processed and finished in the system by mistake instead of another one	sales clerk reserves the transport, possibility that transport arrives, shipment promised to the customer, but shipment not yet prepared in the WH - frustration, additional costs, delay in shipment	**5**	• (WH worker) WH worker made mistake in the system, due to hurry	**1**	• outbound delivery cannot be finalized if several previous steps related to shipment are not done in the warehouse within the system	**1**	**5**	**5**	

Appendix E: FMEA sheet → Process element: customer order finalized

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
Process element: customer order finalized										
sales clerk sees processed outbound delivery in the system	sales clerk does not check if outbound delivery is finalized	delay in shipment	**4**	● (knowledge) sales clerk did not know he needs to recheck the system	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● daily monitoring of opened outbound delivery in place	**2**	**8**	**4**	
		WH workers frustrated, since prepared shipment is taking up space in WH	**4**	● (sales clerk) sales clerk forgot due to too much work	**2**	● daily monitoring of opened outbound delivery in place	**2**	**16**	**8**	
sales clerk reserves transport with LSP	sales clerk forgets to reserve transport	delay of shipment, customer not pleased, shipment takes room in WH	**5**	● (sales clerk) sales clerk forgot due to too much work	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**5**	**25**	**5**	
	sales clerk reserves the transport with wrong vehicle	loading not possible (cold truck needed),delay in shipment	**5**	● (sales clerk) sales clerk did not know which vehicle is correct ● (sales clerk) sales clerk forgot to add comment that cold truck is needed when reserving the transport	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**6**	**90**	**15**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
LSP checks carrier availability, books and confirms the transport	transport cannot be booked for desired date	postponements of shipment	**4**	● (LSP) carrier does not have free vehicles ● (sales clerk) sales clerk did not give announcement, on desired date no vehicles available	**3**	● announcement prior to reservation provided to LSP, so it can predict needed available trucks	**5**	**60**	**12**	
sales clerk/outbound logistics prepares the documents for custom clearance, shipment, etc. and send them to WH	wrong documents send to WH	possible delay in shipment, since correct documents need to be send to the warehouse	**4**	● (sales clerk) sales clerk made a mistake, due to too much work	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**4**	**16**	**4**	
	sales clerk forgets to send the document	possible delay in shipment, since documents need to be prepared (if not yet) and send to the warehouse	**4**	● (sales clerk) sales clerk forgot due to too much work	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**4**	**16**	**4**	
	documents cannot be issued due to system error	possible delay in shipment	**4**	● (system) system failure	**1**	● strong IT service and support and several local super users	**1**	**4**	**4**	

Appendix F: FMEA sheet → Process element: loading process

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
Process element: loading process										
transport arrives to the WH	transport does not arrive	delay in shipment	**5**	● (driver) driver got lost, LSP gave driver wrong date, sales clerk gave LSP wrong date	**3**	● sales clerk can check at any time with LSP to get information on truck location ● in case of longer delay LSP informs sales clerk about it, so he/she is able to inform the WH and customer	**5**	**75**	**15**	
	transport arrives late	possible delay in shipment	**4**	● (driver) traffic jam	**6**	● sales clerk can check at any time with LSP to get information on truck location ● in case of longer delay LSP informs sales clerk about it, so he/she is able to inform the WH and customer	**5**	**120**	**24**	
	transport arrives too early	driver needs to wait if WH is overloaded	**4**	● (driver) driver did not follow directions ● reserved truck was on another assignment and came directly to warehouse	**5**	● in case of sooner arrival LSP informs sales clerk about it, so he/she is able to inform the WH and customer	**3**	**60**	**20**	
	transport arrives, but not with correct vehicle	new vehicle needs to be ordered, additional costs, delay in shipment	**6**	● (sales clerk) sales clerk ordered the wrong vehicle ● (LSP) LSP send the wrong vehicle	**2**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● ordering done wia LSP system where all specific related to the transport are stated from ordering party	**7**	**84**	**12**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
readouts of the truck temperature data are printed before loading	readouts are forgotten to be printed	no evidence that goods were loaded to correctly cooled truck	**6**	● (knowledge) WH worker did not know printouts need to be examine before loading	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● measure of temperature done by WH worker ● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**180**	**18**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Additional line added to ACC document, where box must me checked checked if printouts were printed and to which temperature the truck was cooled down prior to loading it.
	readouts printed, but with wrong date and hours	no evidence that goods were loaded to correctly cooled truck	**6**	● (driver) driver made a mistake when printing	**1**	● WH worker always rechecks the print out and if needed requests a new or correct one ● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**3**	**18**	**6**	
	printer in the truck doesn't work	no evidence that goods were loaded to correctly cooled truck	**6**	● (system)system problems	**2**	● LSP has possibility to provide temperature data of each truck in their fleet base from their system ● measure of temperature done by WH worker	**1**	**12**	**12**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
loading is done	loading can take too much time	exposure to temperature deviations	**6**	● (WH worker) not experienced enough	**5**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● training of all new employees is done as well as monitoring by supervisor for specific time period	**9**	**270**	**30**	→ On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Current process of loading of goods should be re-examined and optimization in process steps should tried to be achieved.
	goods are not directly transported to the cooled vehicle	exposure to temperature deviations	**6**	● (knowledge) WH worker did not know he should directly load to truck	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● training of all new employees is done as well as monitoring by supervisor for specific time period	**5**	**30**	**6**	
	goods are damaged during loading	damaged goods not seen, goods shipped to customer, claim from customer could be received	**8**	● (WH worker) not experienced enough	**2**	● training of all new employees is done as well as monitoring by supervisor for specific time period	**9**	**144**	**16**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
loading is done	goods are damaged during loading	goods cannot be shipped	**10**	● (WH worker) WH worker was not careful enough or was in a hurry	**1**	● training of all new employees is done as well as monitoring by supervisor for specific time period	**10**	**100**	**10**	→ On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Current process of loading of goods should be re-examined and optimization in process steps should tried to be achieved. → Search for additional packaging materials should be done, which would provide additional precaution against possible damages during loading.
	goods are damaged during loading	damaged goods should be replaced, delay of shipment, exposure to temperature deviations	**10**	● (WH worker) WH worker was not careful enough or was in a hurry	**1**	● training of all new employees is done as well as monitoring by supervisor for specific time period	**10**	**100**	**10**	→ On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Current process of loading of goods should be re-examined and optimization in process steps should tried to be achieved. → Search for additional packaging materials should be done, which would provide additional precaution against possible damages during loading.
selling of the shipment	shipment is not sealed	possibility of tampering with goods	**10**	● (knowledge) WH worker was not informed shipments need to be sealed	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● photo of loaded goods and sealed truck need to be done	**5**	**50**	**10**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn.

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
readouts of the truck temperature data are printed after loading	readouts are forgotten to be printed	no evidence that goods are loaded and that the vehicle is correctly cooled down prior to shipment	**4**	● (knowledge) WH worker did not know printouts need to be examine after loading	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**120**	**12**	
	readouts printed, but with wrong date and hours	no evidence that goods are loaded and that the vehicle is correctly cooled down prior to shipment	**4**	● (driver) driver made a mistake when printing	**1**	● WH worker always rechecks the print out and if needed requests a new or correct one ● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**40**	**4**	
	printer in the truck doesn't work	no evidence that goods are loaded and that the vehicle is correctly cooled down prior to shipment	**4**	● (system)system problems	**1**	● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**40**	**4**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
ACC letter is filled in	ACC letter is wrongly filled from WH side	wrong data on the document can cause problem in process of releasing the goods	**6**	● (knowledge) WH worker did not know how to fulfil the ACC letter ● (WH worker) WH worker was in a hurry and made mistake	**4**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**240**	**24**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill the ACC letter related to current shipment. → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.
	ACC letter is not filled at all	shipment processed without the ACC document can cause problems with final release of the goods	**6**	● (knowledge) WH worker did not know that ACC letter needs to be filled ● (WH worker) WH worker was in a hurry and made mistake	**3**	● standard operating procedures are in place and employees are trained based on their relevance to their work also based on prior steps in the process, they should receive it already partially filled from sales clerk	**10**	**180**	**18**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers) is done step by step once a year, which will enable employees to refresh their knowledge, ask questions and learn. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill the ACC letter related to current shipment. → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
documents are given to the driver	wrong documents given to the driver	shipment rejected in customs	**5**	● (knowledge) WH worker did not know that documents should be given to the driver	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work, driver also request them	**4**	**20**	**5**	
	document are not given to the driver	shipment rejected in customs	**5**	● (WH worker) WH worker was in a hurry and forgot	**1**	● driver Request them	**4**	**20**	**5**	

Appendix G: FMEA sheet → Process element: distribution (transportation of goods)

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
Process element: distribution (transportation of goods)										
shipment to the customer	high temperature excursions during transport	temperature deviations arose, which can cause problems with final release of the goods	**10**	● (truck) cooling unit in the truck malfunctioned	**1**	● yearly recalibration and maintenance of all vehicles is done by transporting company	**10**	**100**	**10**	→ For all currently used transport providers, analysis should be conducted, which would provide information, how many times temperature excursion occur during transportation of goods. Based on received results, only those providers who had minimal and/ or acceptable deviations are used for shipments of biosimilar products. → Search for new transport provider which is specialized for transportation of cold chain goods, should be done. Cost - benefit analysis needs to be conducted if choosing a new provider, which may be more expensive, is acceptable.
	medium temperature excursions during transport	temperature deviations could be seen, which can cause problems with final release of the goods	**9**	● data logger reacts to small changes in temperature ● (driver) driver opened the door in custom	**4**	● stability studies for all product in place	**10**	**360**	**36**	→ For all currently used transport providers, analysis should be conducted, which would provide information, how many times temperature excursion occur during transportation of goods. Based on received results, only those providers who had minimal and/ or acceptable deviations are used for shipments of biosimilar products. → Search for new transport provider which is specialized for transportation of cold chain goods, should be done. Cost - benefit analysis needs to be conducted if choosing a new provider, which may be more expensive, is acceptable.

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
shipment to the customer	goods are stolen	shipment cannot be delivered to the market, loss of sales	**10**	● (WH worker) not sealed truck	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work ● trucks are sealed	**1**	**10**	**10**	→ No actions.
	damages during transport	customer sends claim for damaged products, costs	**6**	● (driver) careless driver	**2**	● no process control	**10**	**120**	**12**	
	damages during transport	goods can be damaged to extent where selling them is not possible	**10**	● (driver) careless driver	**1**	● no process control	**10**	**100**	**10**	→ For all currently used transport providers, analysis should be conducted, which would provide information, how many damages occur during transportation of goods. Based on received results, only those providers who had minimal and/ or acceptable % of damages seen are used for shipments of biosimilar products. → Search for new transport provider which is specialized for transportation of cold chain goods should be done. Cost - benefit analysis needs to be conducted if choosing a new provider, which may be more expensive, is acceptable.

Appendix H: FMEA sheet → Process element: unloading process

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
Process element: unloading process										
at arrival documents are given to the customer	wrong documents are given to the customer	customer needs to request correct ones, frustration	**4**	● (driver) driver mixed up the papers	**1**	● no process control	**5**	**20**	**4**	
readouts of the truck temperature data are printed before unloading	readouts are forgotten to be printed	no evidence that goods were delivered in properly cooled down truck	**3**	● (knowledge) WH worker did not know printouts need to be examine before unloading	**5**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically ● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**150**	**15**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers at customer side) is done step by step once a year, which will enable customers to refresh their knowledge, ask questions and learn. Sharing of best practice with our customers. →Additional line added to ACC document, where box must me checked if printouts were printed and to which temperature the truck was cooled down after loading it.
	readouts printed, but with wrong date and hours	no evidence that goods were delivered in properly cooled down truck	**3**	● (driver) driver made a mistake when printing	**1**	● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**5**	**15**	**3**	
	printer in the truck doesn't work	no evidence that goods were delivered in properly cooled down truck	**3**	● (system)system problems	**1**	● LSP has possibility to provide temperature data of each truck in their fleet base from their system	**10**	**30**	**3**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
unloading is done	unloading can take too much time	exposure to temperature deviations	**5**	● (WH worker) not experienced enough	**5**	● no process control	**10**	**250**	**25**	→ On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers at customer side) is done step by step once a year, which will enable customers to refresh their knowledge, ask questions and learn. Sharing of best practice with our customers. → Current process of unloading of goods should be re-examined and optimization in process steps should tried to be achieved.
	goods are not directly transported to the cooled room	exposure to temperature deviations	**6**	● (knowledge) WH worker did not know he should directly load to cold room	**1**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	**10**	**60**	**6**	
	goods are damaged during unloading	goods can be unsellable	**8**	● (WH worker) not experienced enough	**1**	● no process control	**10**	**80**	**8**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
ACC letter is filled in	ACC letter is wrongly filled from customer side	wrong data on the document can cause problem in process of releasing the goods	6	● (knowledge) customer did not know how to fulfil the ACC letter ● (WH worker) WH worker was in a hurry and made mistake	6	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	10	360	36	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers at customer side) is done step by step once a year, which will enable customers to refresh their knowledge, ask questions and learn. Sharing of best practice with our customers. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill t → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.
	ACC letter is not filled at all	shipment processed with partially filled ACC document can cause problems with final release of the goods	6	● (knowledge) WH worker did not know that ACC letter needs to be filled in ● (WH worker) WH worker was in a hurry and made mistake	4	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	10	240	24	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers at customer side) is done step by step once a year, which will enable customers to refresh their knowledge, ask questions and learn. Sharing of best practice with our customers. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill t → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
data logger is stopped and uploaded to the online tracking database *if customer has no access to the online tracking database, it has to send read outs of the data logger to the seller	data logger stopped but not uploaded to the online tracking database	searching temperature data in database based on shipment number	**1**	● (WH worker) WH worker did not know that data logger needs to be uploaded to the database or pdf files sent	**3**	● data can be at any time downloaded from online tracking database ● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	**10**	**30**	**3**	
	data logger is not found	no information on temperatures during shipment (if data logger was added on the shipper side, no information till when did it monitor temperature of the goods)	**8**	● not enough data loggers added when preparing the shipment - several unloading points ● no data logger added on the shipper side	**1**	● standard operating procedures are in place and employees are trained based on their relevance to their work	**10**	**80**	**8**	
	data logger not stopped	data logger stopped later	**1**	● (WH worker) WH worker did not know that data logger needs to be stopped	**1**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	**3**	**3**	**1**	

table continues

continued

A	B	C	D	E	F	G	H	I	J	K
Process steps and sub process steps	**Potential failure mode(s) -> What could go wrong?**	**Potential effect(s) of failure -> What are the consequences if failure mode occurs?**	**Severity**	**Potential cause(s) of failure -> Who/what, why the failure mode occurs?**	**Occurrence**	**Current process controls**	**Detection**	**RPN score**	**Criticality**	**Recommendations/actions to eliminate or reduce failure mode**
documents related to shipment are send by customer to QA for evaluation and final release of goods to the market	documents not send	documents send later, delay in release	**4**	● (knowledge) customer did not know that document need to be send to QA	**2**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically ● shipper requests the documents	**4**	**32**	**8**	
	only partial documents send	all documents send later, delay in release	**4**	● (knowledge) customer did not know which documents need to be send to QA	**3**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically ● shipper requests the documents	**4**	**48**	**12**	
	wrongly filled documents sent	documents need to be corrected, delay in release or possibility of blockage of goods until all discrepancies are resolved	**6**	● (knowledge) customer did not know how to properly fill the documents	**6**	● customers are trained on proper steps that need to be taken, from shipper side and are done periodically	**7**	**252**	**36**	→ Quarterly trainings based on standard operating procedures, (not just self-study -reading) but with actual test examination at the end. → On site practical presentation of the whole process of biosimilar shipment (directly related to WH workers at customer side) is done step by step once a year, which will enable customers to refresh their knowledge, ask questions and learn. Sharing of best practice with our customers. → Example of correctly filled ACC letter should be placed on visual place in the cooled room at all time. It would provide WH worker helpful possibility to quickly check how they should fill t → Additional training should be done once a year, where relevant stakeholders from shippers and customer WH would be educated on release process steps for biosimilar products and through it also the importance of correctly filled ACC letter.