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Managing supply chain sustainability risks of antibiotics

A case study within Sweden

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Abstract

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Antimicrobial resistance (AMR) has been classified as one of the phenomena that belongs to the current top threats to human health. AMR is the process where bacteria become resistant to the antimicrobial drug and renders the antibiotic ineffective. This phenomenon is increasing exponentially due to misuse and overuse of antibiotics and is responsible for 700,000 annual deaths globally. If the contributing factors to AMR remain persistent, the estimated amount of annual deaths will increase to the exorbitant figure of 10 million by 2050. The inappropriate waste discharge from antibiotic manufacturing plants is the third major cause contributing to AMR. For this reason, environmental sustainability within the pharmaceutical industry is tightly linked to human health, and therefore, the importance of environmental risk management becomes crucial. Pharmaceutical supply chains are extremely complex, fragmented, and rigid due to the highly regulated environment and global distribution of the chains. Constant availability is sometimes compromised, and this leads to national shortages of antibiotics, which increase AMR. Therefore, supply chain sustainability risks (SCSRs) need to be thoroughly assessed and managed. The thesis aims to identify the sustainability risks that threaten the constant supply of antibiotics and further provide a comprehensive and sufficient framework on how to assess and manage SCSRs within the pharmaceutical industry. This research is based on the review of existing literature, followed by an empirical study that included a case study of two specific antibiotics relevant to the Swedish market. The analysis of publicly available databases, together with the qualitative interviews, revealed that the most susceptible node of the supply chain resides in the primary manufacturing stage. The most relevant SCSRs have been identified, and an adapted framework is suggested. The role of regulatory agencies has been demonstrated to be fundamental to achieve change concerning environmental progress. Further research needs to be implemented for the validation of the suggested framework within a practical context.

Key words: AMR, antibiotics, sustainability, supply chain sustainability risks, SCSR, sustainable development, pharmaceutical supply chains, supply chain management, risk management.

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Popular Science Summary

Environmental sustainability has become increasingly important during the past few years due to the severe negative consequences that caused by its mismanagement. Corporations are entities in society whose role is no longer to purely provide profits to shareholders and deliver a product or service to the market. Instead, they are being increasingly seen as responsible entities for providing value to society in different relevant forms. Environmental contamination from pharmaceutical manufacturing facilities have created real concern. Not only for greenhouse emissions, but more importantly for the contaminant waste disposals thrown directly to the environment. This gains a superior level of importance when the manufacturing plants are in charge of producing antibiotics, thereby releasing antibiotics to the environment. Throwing antibiotics to soil or water bodies increases the risk of Antimicrobial Resistance (AMR), in fact it has been discovered to be the third major cause contributing to an increased AMR.

AMR is a natural process in which bacteria develop resistance to a specific antimicrobial drug. However, this process has been accelerated exponentially through the overuse and misuse of antibiotics by humans. This increased resistance originated by external factors receives the name of acquired resistance, and it threatens medicine procedures that are commonly used nowadays. AMR poses a global threat to human health. For this reason, it is extremely important to assess and manage the environmental-related risks within corporations, especially in the antibiotic's context. This thesis identifies the most relevant environmental related risks within pharmaceutical supply chains. In addition, the study reveals the most susceptible node of the supply chain that can be responsible to compromise a constant supply. By knowing the weak parts of the supply chain and understanding the general risks that are heavier in this particular industry, better suggestions for improvement can be provided.

It is crucial to understand the importance and the "*how-to*" of assessing and managing sustainability-related risks to translate them into actions. These actions must be carried out not only by pharmaceutical corporations, but also from regulatory agencies, who have a crucial role in this industry. Now there is increased awareness for this topic, and some companies are implementing initiatives where environmental risk management is embedded in their business portfolios. Also, regulations are getting stricter concerning sustainability and efforts for creating common standards amongst countries are being made. But this is not enough if to achieve the change that is needed. Every single player from the industry needs to contribute and participate to achieve visible change. Then, the risk that AMR poses on human health will be significantly decreased, what benefits both society and the industry.

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Abbreviations & Acronyms

AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
CMDO	Contract Manufacturing and Development Organization
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FDF	Finished Dosage Form
GMP	Good Manufacturing Practices
GSC	Green Supply Chains
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
MAH	Marketing Authorization Holder
NGO	Non-Governmental Organization
PNEC	Predicted No Effect Concentration
PSCI	Pharmaceutical Supply Chain Initiative
RFID	Radio-Frequency Identification Technology
RPN	Risk Priority Number
SCM	Supply Chain Management
SCSR	Supply Chain Sustainability Risks
SSCM	Sustainable Supply Chain Management
WHO	World Health Organization

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1. Introduction

Pharmaceutical supply chains are complex and highly regulated (Access to Medicine Foundation, 2018b). In addition, most processes and operations are under confidential contracts which create a significant lack of transparency. Supply chains are fragmented and fragile, which create a risk for ensuring reliable and constant global supply (Access to Medicine Foundation, 2018b). Shortages occur at an increasing frequency. Sweden has suffered from antibiotic shortages, and efforts are being made to prevent this from happening in the future. Through a thorough assessment, the Swedish medical products agency has identified 34 antibiotics that are at risk of suffering future shortages. This research will conduct a case study of 2 from these antibiotics to track all the components from both supply chains to gain a better understanding on which are the weakest nodes from the chain. The case study that will be conducted in this master thesis is part of the collaboration with the Platform for Innovation of Existing Antibiotics (PLATINEA) project. The two main purposes of this nationally funded project are to (1) improve and secure the accessibility of important antibiotics, and (2) improve antibiotics' use. The present research will solely be involved in a task that belongs to the first purpose, which intends to map and enhance physical and logistics flows in the antibiotics' supply chains, with an additional focus on assessing environmental sustainability across global pharmaceutical supply chains.

Sustainability englobes three different yet interconnected areas: Economic, social, and environmental. A consensus for one clear definition of sustainability has not been reached amongst literature. Nowadays, corporations have increased pressure on integrating sustainable responsibility within their portfolios. However, the primary driver for changes in corporate initiatives relies on changes in regulations (Blum-Kusterer & Hussain, 2001). The pharmaceutical industry has always been especially focused on ensuring the highest standards of quality due to the nature of the products. Quality still remains the priority in this industry, but with time, environmental related regulations are getting stricter due to efforts from several stakeholders such as NGOs and regulatory agencies. This trend is the reason why some pharmaceutical companies are increasing their efforts towards achieving greater sustainability standards, both social and environmental. Nonetheless, this is not the majority of the companies in the industry.

Increasing efforts on environmental sustainability is of great importance in all industries and at a global scale, but it takes an additional level of importance within the antibiotics production and consumption context. Waste discharges from manufacturing plants are one of the primary sources that contribute to creating Antimicrobial Resistance (AMR) (Access to Medicine Foundation, 2018a; EPHA & Changing Markets, 2016; Changing Markets & Ecostorm, 2016). AMR is a process in which bacteria acquire resistance to the existing antibiotics. AMR generates a problem of global concern, which has been prioritized in global health agendas due to the threat that poses on human health (Access to Medicine Foundation, 2018a; Access to Medicine Foundation, 2018b). On the other hand, shortages of antibiotics also contribute to increasing AMR due to potential

misuse, i.e., using the non-optimal antibiotic to treat an infection as a replacement to an unavailable antibiotic (Access to Medicine Foundation, 2018a).

Supply chain sustainability risks (SCSRs) have been covered in literature, and there are several different existing theoretical frameworks on how to assess and manage such risks. However, there is no current available framework which takes into account the complexity and particularities of the pharmaceutical industry. This research aims to integrate all the components and use the empirical findings from our case study to suggest an adaptation of a framework to manage SCSRs.

1.1. Background

The background behind our study is to address antibiotics' accessibility issues which have resulted into shortages that occurred and still occur not only at a local level, but also at a global scale (Access to Medicine Foundation, 2018b). The reason for such shortages relies on the weak structure of the supply chain. The supply chain for antibiotics is complex and involves several intermediaries which are not explicitly disclosed, thereby generating a lack of transparency throughout the chain (Davies & Loewenberg, 2018). The structure of the supply chain is fragile and fragmented, meaning that there are many small companies and a few large companies (Access to Medicine Foundation, 2018b). In addition, some of the essential compounds for the synthesis of specific antibiotics, which receive the name of Active Principal Ingredients (APIs) are produced in one or very few production facilities. This means that the production for such antibiotics relies entirely on these few companies resulting in an enormous dependence leaving short to none reaction time when facing unexpected failures.

An example is an incident that happened in a Chinese production facility that suffered an explosion which was the only one in the world to manufacture the API necessary to produce piperacillin/tazobactam, a key antibiotic that suddenly became unavailable at a global scale (Access to Medicine Foundation, 2018b). High susceptibility in crucial nodes of the chain generates an enormous risk for the supply chain to collapse. The reason why there are few pharmaceutical companies producing APIs or antibiotics relies on economic reasons because the production is much less profitable compared to other drugs (Access to Medicine Foundation, 2018b; Pulcini, et al., 2017). Moreover, the regions where there is the highest demand on antibiotics are usually more impoverished populations, whose governments increase pressure on producers to lower the price, leading into even tighter profit margins (Access to Medicine Foundation, 2018b; Pulcini, et al., 2017).

Antimicrobial resistance (AMR) is an increasingly important concern which is a priority on the global health agendas of organizations such as the World Health Organization (WHO) (Access to Medicine Foundation, 2018a; Access to Medicine Foundation, 2018b). The main problem or future challenge is that if the bacteria would get resistant to all or most existing antibiotics, modern medicine would no longer exist as we know it today. Antibiotics are used for treating a variety of

infections, and also are needed for surgical procedures, transplants, giving birth, and many more (Munita & Arias, 2016). An increased and spread AMR would jeopardize all these procedures and would, therefore, imply a step backward to many of the medical advances that nowadays we take for granted. AMR is a process that takes place naturally, but the misuse and overuse of antibiotics have accelerated this process exponentially (Access to Medicine Foundation, 2018a). In addition, it has been discovered that environmental contamination resulting from the production antibiotics, in particular, antibiotic wastewater discharge, actively increases AMR (Access to Medicine Foundation, 2018a; EPHA & Changing Markets, 2016; Changing Markets & Ecostorm, 2016). There is urgent need to act and achieve change, and the PLATINEA project is the first platform in Sweden to enable the collaboration between academia/research, healthcare providers, industry, and public authorities. Coordination and cooperation among all the actors involved are crucial to being able to stop this global and complex phenomenon (Access to Medicine Foundation, 2018a).

Many changes under political, economic, social, legal, and environmental scope motivate this work. All of these changes together are the reason why AMR has gained much more awareness and has been prioritized. The production of off-patent antibiotics is not as profitable when compared to the production of other drugs, hence big pharmaceutical companies have continuously decreased or wholly abandoned the manufacturing for such (Roland Berger GmbH, 2017; Munita & Arias, 2016). In addition, high competence started to arise in Asian countries, especially China and India where they invested on big facilities for intermediates and APIs manufacturing, and the wages are lower when compared to Europe or the U.S (Roland Berger GmbH, 2017). Furthermore, the pharmaceutical industry is highly regulated, which makes the supply chain complex and rigid, but the regulations differ across the world. Asian countries have less strict regulations than those in Europe and the U.S. For this reason, many of the manufacturing plants in European and American countries outsource or off-shore the production of intermediates and APIs (Access to Medicine Foundation, 2018a; EPHA & Changing Markets, 2016). Therefore, such components are nowadays mainly produced in countries where the regulations are not so strict and imply a lower manufacturing cost, hence being in charge of supplying APIs for the global demand. This reliance, in turn, increases the political dependence on such countries, and some governments start to be concerned about these dependencies which can be a threat when a sudden increase of demand occurs in a particular moment (Roland Berger GmbH, 2018; Changing Markets & Ecostorm, 2016).

AMR is occurring at an increasing rate not only due to misuse and overuse but also because its propagation happens faster with globalization (Access to Medicine Foundation, 2018a; EPHA & Changing Markets, 2016). Misuse of antimicrobial treatments can refer either to not using the treatment properly, finish the treatment before time or when the used antimicrobial drug is not optimal to target that specific infection, all these actions contribute to decreasing effectivity and overexposure of the antimicrobial drug to the bacteria that will enable a faster-acquired resistance. Overuse refers to the excessive use of antimicrobial drugs. Antimicrobial resistance, as mentioned before, is a natural process that occurs as a result of the interaction of microorganisms with the

environment. It is the process that bacteria use to adapt and evolve following Darwin's law of natural selection and survival of the fittest (Munita & Arias, 2016). However, the resistance that is gained from typically clinical settings in an already susceptible bacteria population receives the term "acquired resistance". There are two major genetic mechanisms that bacteria use to adapt and resist the antibiotic drug: (1) Mutational resistance and (2) Horizontal Gene Transfer (Munita & Arias, 2016). Firstly, mutational resistance is gained through the mutation in the gene(s) that when in the presence of antimicrobial molecules, the mutation that happens to be resistant predominates amongst the others. The mutation that gains resistance is often associated with the mechanisms of action from the drug (Munita & Arias, 2016). Secondly, horizontal gene transfer is the process used to acquire and transfer foreign DNA material from and to other bacteria. This process is one of the most critical factors causing bacteria evolution, and the exchange of genetic material is usually the responsible mechanism for the development of AMR (Munita & Arias, 2016).

Bacteria have immense genetic plasticity; therefore, the spread of resistance happens easily, and some activities enable them to happen faster and to spread in longer distances amongst different communities. For instance, traveling enables the transmission of resistant bacteria to new hosts, which will then transfer them to other humans and propagate faster across the globe (Changing Markets & Ecostorm, 2016). Thus, AMR is a collective problem regardless of where it occurs first (EPHA & Changing Markets, 2016). Approximately, 700,000 people die worldwide every year due to an infection resistant to treatment, and the rate of deaths increases at a fast speed. By 2050 the amount of deaths due to this phenomenon is expected to increase to 10 million deaths worldwide per year (EPHA & Changing Markets, 2016). Another factor that has been discovered to influence on increasing AMR is environmental pollution at pharmaceutical production sites, which turns out to be the third major cause of AMR (EPHA & Changing Markets, 2016; Changing Markets & Ecostorm, 2016). Many factories do not appropriately manage waste discharges. The release of antibiotics into the environment, both water, and soil trigger an enhanced resistance of bacteria (Access to Medicine Foundation, 2018a). This fact gives increased importance to tackle environmental issues, which is the reason why it is the focus of our thesis.

1.2. Research purpose & contribution

The two specific antibiotics have been assigned to us by our supervisor at PLATINEA. The reason why we study these two antibiotics is because they belong to the list of antibiotics that are at risk of being unavailable in the future. Also, the case study needed to be restricted for the research to be viable within the time limits. Other antibiotics belonging to the shortages' risk list could have been assigned to us indistinctively.

The main two aims of our thesis are (1) to identify sustainability risks of two specific antibiotic supply chains which are amoxicillin and piperacillin/tazobactam and (2) to provide a suggestion how these risks could be managed in the pharmaceutical industry. During the process of achieving our main goals, we will penetrate the details of the selected supply chains by investigating all supply chain stages, stakeholders, and their relationships. This research is intended to increase the visibility of the antibiotics' supply chains and aid in the purpose to increase the attention to the third major cause of AMR, which is the environmental pollution at pharmaceutical production sites (EPHA & Changing Markets, 2016; Changing Markets & Ecostorm, 2016).

Our task will provide a modest contribution to the PLATINEA project, especially regarding availability issues, and this will be done by studying and trying to provide increased visibility for the supply chains of the mentioned antibiotics. The expectations from our research seem reasonable and indeed it is a challenge to obtain information in such a secretive industry, but this will be overcome thanks to the active collaboration from our supervisor and all the members we are working with in the project. In addition, we want to contribute to increasing academic knowledge, within a reasonable extent, of sustainable supply chain management and risk management research focused on the pharmaceutical industry. The contribution to academic knowledge will be a framework to manage SCSRs within the pharmaceutical industry.

1.3. Research questions

RQ1: What sustainability risks do the supply chains of the antibiotics have for its constant availability in Sweden?

RQ2: How can the supply chain sustainability risks be managed in the pharmaceutical industry?

1.4. Disposition

This thesis is comprised of seven chapters: Introduction, Theory, Methodology, Empirics, Analysis, Discussion, and Conclusion.

The **introduction** chapter provides a brief background and problematization of the main topics that will appear in the thesis. Here, the importance of the problem is discussed, and helps the reader understanding why it is important to study the research questions that are further presented. The correlation between the basis problem, AMR, and the research questions that guide the study is not straightforward if the reader is not familiarized with the topic. Furthermore, both practical and theoretical purpose and contributions are provided.

The **theory** chapter is divided in two sections. Firstly, a literature review is presented and secondly the theoretical framework that will be used in the thesis is displayed. The literature review shows all the relevant scientific literature that is currently available. The topics included in the literature review are those relevant to answer our research questions, which provide a foundation for our future analysis. In the theoretical framework, the most important already existing frameworks are deeply explained and discussed. Special attention and detail are provided in this sub-section because these are the frameworks that will be used as a basis and inspiration for the creation of our suggested framework.

Methodology chapter outlines the research type and method choice, as well as the steps that have been followed throughout the study. Additionally, the design of the thesis is explained, and details are provided about the research plan. The research plan is a stepwise process that shows which analytical steps have been followed to answer each research question. Ethical aspects are considered as well in this section.

Empirics presents the field material that will be used to perform the analysis and obtain our results. In this chapter, empirical material from other authors as well as our own gathered empirical material is presented. The empirics chapter distinguishes itself from the theory chapter. *Theory* is according to Kerlinger (1986) associated concepts, propositions and definitions that prove relations between variables. In our thesis, the theory chapter compares different supply chain and sustainability definitions and opposes various proposed frameworks for managing SCSRs. *Empirics* is according to Gray (2018) observations of previous researches and findings of experiments. Therefore, this empirics chapter will use observations of previous researches regarding pharmaceutical supply chains, regulations within the pharmaceutical industry, and current environmental risk management performance of pharmaceutical companies. Complementary, primary data will be gathered to be able to reconstruct the supply chain of two specific antibiotics and to identify its stakeholders and their issues.

In the **analysis** chapter displays and analyses the empirical data that was previously presented. Furthermore, the findings from the analysis are presented as well in this chapter. We develop a novel framework for how to assess and manage SCSRs adjusted to the pharmaceutical industry. This framework is presented and explained in the end of the chapter.

Discussion chapter provides an extended interpretation of our findings which are further connected to the reviewed theory. The main relevant topics are discussed separately, and an additional highlight to theoretical, managerial, policy, and ethical implications are presented. The limitations of the study are also provided in this chapter.

Finally, the **conclusions** chapter answers briefly the research questions in a direct manner. Also, an argumentation for the answers are presented, but the direct and straightforward style is predominant in this chapter to keep it direct and simple.

2. Theory

In this section, a review of the current literature on all the relevant topics to the aim of this thesis and research questions is provided. The themes that are covered within this chapter are within the field of Supply Chain Management and Sustainability. More specifically, Supply Chain Strategies, Sustainability, Sustainable Supply Chain Management, Supply Chain Sustainability Risks, and all the currently available theoretical frameworks that can be found to manage SCSRs. The chapter aims to provide a foundation for our further analysis chapter by getting acquainted with all the current relevant scientific publications.

2.1. Literature review

2.1.1. Supply chain strategies

Supply Chain Management (SCM) is the process to satisfy customer needs, and therefore, the customer receives valuable products or services. Several processes have to be linked with regard that all stages create value for the customer. Various companies and operations are involved in the supply chain, and hence, management of relationships is essential to enable a continuous flow of products and services. These collaborative activities also facilitate the upstream and downstream information flow, which is vital to delivering valuable products or services to the customer. (Slack, et al., 2015; Braziotis, et al., 2013)

Within a supply chain, there are different ways to manage the relationships between supply chain parties. The two opposite, pure strategies to manage supply chain relationships are contract and partnerships. On the one hand, contract relationships are short-term. The purchaser decides every time which supplier offers the best product or service in terms of price, quality, time to delivery, etc. On the other hand, partnerships are a long-term agreement between companies to achieve the individual goals of each partner. Additionally, both partners collaborate closely, and the supplier will be developed over time. Both strategies have different pros and cons and are suitable for different kind of situations. For instance, contract relationships have the advantage that products or services can be acquired for a lower price, and innovations can be obtained through supplier acquisition. A disadvantage could be that competitors can acquire these innovative suppliers first, and consequently, there is a high risk that innovation cannot be obtained. In contrast, partnership relationships have for instance, the advantage that the supply can be secured, and it is appropriate when innovative products depend on close collaboration. A disadvantage could be the lower flexibility. Most companies have a portfolio with different kind of relationships. In addition, suppliers are often scored and assessed to receive the best fit. Slack, et al. (2015) outlines several factors that purchaser use to score a supplier. However, environmental or social sustainability is not mentioned as an assessment factor. (Slack, et al., 2015)

Slack, et al. (2015) highlight that companies have five operations performance objectives: Quality, speed, dependability, flexibility, and cost. Depending on the company's offered product or service, a supply chain can be designed either more lean or agile. Lean supply chain is a philosophy that is originated as part of the Toyota Production System and is striving to eliminate waste within the supply chain and still be able to offer valuable products and/or services to the customer at the right time and location (Reichhart & Holweg, 2007; Garza-Reyes, et al., 2016). According to Carvalho, et al. (2017) and Corbett and Klassen (2006) waste are resources or operations that are not adding value to the product or service. Waste can be for instance related to labor, time, equipment, space, and inventory. The inventory is particularly low in the downstream part of the supply chain, i.e., close to the customer (Slack, et al., 2015). Through lean supply chain management, the cost can be reduced, and quality can be improved (Paksoy, et al., 2019). Slack, et al. (2015) state that lean supply chains are suitable for consistent products and services.

The agile supply chain is generally seen as flexible and responsive. Hence, an agile supply chain is offering a high service level because it is dynamic in adapting the operations resources in the supply chain for the customer. Therefore, an agile supply chain is more suitable for innovative products that are less predictable (Slack, et al., 2015).

2.1.2. Sustainability

Sustainability Science

Sustainability has gained increasing attention within the last decades due to global environmental changes that showcased the need to address the topic first discussed in the 1980s (Kates, et al., 2001). Sustainability is the relationship between society and nature, and sustainability science studies the interaction between ecology systems and socioeconomic systems. The world has suffered and still suffers from unintended consequences from scientific advances (Kates, et al., 2001). For instance, the exploitation from natural resources that have then become scarce, or the contamination of the environment (water, soil and, air) with all kinds of substances. Some of these contaminant compounds are chemicals whose effect on the ecosystem and their propagation patterns are unknown. In addition to that, the world is unfairly distributed with highly divided communities of people, few rich (millions of people) and many poor (billions of people). The former has surplus resources and contribute to climate change whereas the latter has shortages of resources and suffers the consequences from climate change without contributing in the same way (Kates, et al., 2001). The countries of the northern hemisphere are the ones mainly responsible for the environmental damage that affects at a global scale (Goodland, 1995).

Sustainability englobes three different but interconnected perspectives: Economic, social and environmental. The concept of economic sustainability has evolved significantly since the middle ages until the 1990s; traditionally it referred to ensure the stability of capital maintenance, from what one earns to what one consumes in terms of human-made capital (Goodland, 1995). Goodland (1995) highlighted the need to extrapolate the traditional definition solely based on human-made capital to a new one that integrates all forms of capital: Human, social, and natural capital. Taking all three forms into account, *economic sustainability* is defined as the employment of natural resources as inputs for production processes used in a responsibly and cautiously manner (Goodland, 1995). *Social sustainability* aims for global poverty decrease from qualitative development such as population stability, redistribution, and solidarity, while maintaining life-support systems; hence, being environmental sustainability a prerequisite to achieving social sustainability. Social sustainability requires community participation for the maintenance of equal rights and shared values (Goodland, 1995). Social and environmental sustainability are highly interconnected because meeting human needs requires the use of natural capital, but also needs the maintenance and protection of the environment to be able to meet those needs for a prolonged time also considering the future generations. *Environmental sustainability* is defined by Goodland (1995) as "the maintenance of natural capital", a broad but robust definition that applies consistently to all different countries, sectors and, future epochs.

Environmental sustainability: From theory to practical implementation

The need for sustainability has not always been considered; for a long time, production was solely focused on efficiency, along with increased consumerism, using natural resources as if they were infinite. The use of renewal and non-renewal resources for an increasing rate of production disregarded the finite capacity that nature can offer. Goodland (1995) defined three principles to define environmental sustainability: Output rule, Input rule, and Operational principles. *Output rule* refers to k eep the waste emissions within an assimilative capacity of the environment. *Input rule* includes renewables, which harvest rates should be kept lower concerning the generation capacity; and non-renewables where the depletion rates should be kept lower than the rate at which humans can find a renewable substitute. *Operational principles* should be within a limited scale of the economic subsystem, technological progress should focus on efficiency increasing, and renewable resources should be utilized on a sustainable fashion. *Sustainable development* should include social, environmental, and economic sustainability aspects to meet human needs and improve life quality within the carrying capacity of the ecosystems. (Goodland, 1995)

Implementing a holistic approach to sustainability within corporations and accomplish fully sustainable development is challenging. In addition, there are many definitions of or perspectives on sustainability. For instance, Hoffman's (2014) definition for sustainability is "The degree to which firms take social and ecological criteria into account beyond minimum legal requirements". This definition differs from the priory presented by Goodland (1995) in that sustainability will be

achieved purely dependent on the current laws, without assessing the integrity of such. Additionally, laws change with time; therefore, the latter definition is relative whereas the former is based on more absolute terms. What could be considered sustainable several years ago may not apply nowadays due to changes in the legal regulations.

2.1.3. Sustainability within the supply chain

Green Supply Chain Management

As stated before, lean supply chain management reduces waste in the form of operations and also resources. Through the reduction of waste, lean supply chain management is focusing next to the economic factor on the environmental impact. Due to the increased environmental concerns, green supply chains (GSC) have emerged. Green Supply Chains is the integration of environmental thinking in supply chain management (Machado, et al., 2017). Srivastava (2007) adds that environmental thinking is also integrated into the design of the product and manufacturing processes. Therefore, green supply chain management is aiming to reduce the environmental impact. The United States Environmental Protection Agency (2000) highlighted that the combination of lean and green supply chain management is reducing the costs of the investigated firms. According to Paksoy, et al. (2019) the cost reductions can be achieved through the reduction of energy consumption, recycling of products, diminished water discharge cost and increased market share through enhanced company image. Due to the increasing pressure of stakeholders such as governments, customers, and non-governmental organizations (NGOs) green practices in supply chains received greater attention. In addition, more corporations have begun to realize the economic performance improvement of the implementation of green thinking. (Paksoy, et al., 2019)

Sustainable Supply Chain Management (SSCM)

In recent times, sustainable supply chain management (SSCM) has been increasingly researched (Beske & Seuring, 2014). SSCM strives to target equally all three dimensions, i.e., economic, environment and social (Schaltegger & Burritt, 2014). Hence, when comparing with green supply chain management, one can see that the social dimension is added at SSCM. Beske and Seuring (2014) highlight that the goals of all three dimensions derivate from stakeholder and customer requirements. Schaltegger and Burritt (2014) outline that SSCM often is described as a reputational risk. For instance, the working or environmental conditions at a supplier are bad. One purpose of SSCM is to differentiate the company from others because customers increasingly include the sustainability aspect into their decision making (Schaltegger & Burritt, 2014; Beske & Seuring, 2014). Additionally, Beske and Seuring (2014) underline that studies have shown that at least an enhanced environmental performance has a positive effect on economic performance. Klassen and Vereecke (2012) state that SSCM will lead in the short-term to higher costs, but on the longer-

term, the implementation of SSCM will be a competitive advantage. However, the study of Esfahbodi et al. (2016) shows that within emerging countries an improved environmental performance does not improve economic performance. This study was conducted with Chinese and Iranian companies.

Schaltegger and Burrit (2014) differentiate between three sustainability supply chain strategies, i.e., efficiency, consistency, and sufficiency. Efficiency is to enhance economic performance while lowering the negative social and environmental impact. Consistency is to replace unnatural materials with materials coherent with nature. Finally, sufficiency is to reduce and eliminate waste, such as products and parts.

Moreover, Beske and Seuring (2014) identify five different key categories of SSCM, i.e., orientation, continuity, collaboration, risk management, and proactivity. First, orientation is that a company integrates the environmental and societal values in its strategic values. Secondly, continuity is to develop the company's partnerships and also to select and reduce them. Studies have shown that a reduced number of suppliers are better to improve environmental performance (Vachon & Klassen, 2006; Gimenez & Tachizawa, 2012). Thirdly, collaboration is a key aspect that means to increase transparency and cooperation within the supply chain through, e.g. common IT interfaces and joint development. Fourthly, risk management is to reduce the probability that, for example, non-governmental organizations raise their voice against the company due to environmental or societal shortcomings. Examples of managing the risks are to communicate to external stakeholders, implemented standards, and obtained certifications. Finally, proactivity is to conduct stakeholder management, innovation, and life-cycle assessment. For instance, stakeholder issues can be identified early when they are involved, and innovations help to reduce the negative environmental or social impact.
Schaltegger and Burritt (2014) outline that opportunities to change the environmental or social impact originate mostly from the focal company. Moreover, Roy, et al. (2018) highlight that SSCM implementation is a non-linear journey. The planned changes of SSCM are not developing as directed. Thus, it is not possible to achieve an aimed equilibrium of all three performance dimensions.

Supply chain sustainability risks (SCSR)

As already stated, within the pharmaceutical industry, there is a lack of supply chain transparency (Davies & Loewenberg, 2018; Bengtsson-Palme, et al., 2018). It is known that many intermediary parties are involved in the antibiotic supply chains and that the production of Active Principal Ingredients (API) of antibiotics is mainly outsourced (Bengtsson-Palme, et al., 2018; Roland Berger GmbH, 2018). However, it is not known which particular API suppliers are involved in each supply chain. For instance, the Access to Medicine Foundation (2018b) illustrates that of 18 investigated companies within the pharmaceutical industry, only one company has published its third-party manufacturers.

Without the visibility of antibiotic supply chains, its stakeholders cannot be easily identified. Busse, et al. (2017) outline that stakeholders of the supply chain can influence or are influenced by the organization's business. Hence, these unseen stakeholders can be negatively affected by the supply chain and can harm the supply chain in several ways (Hajmohammad & Vachon, 2016). For instance, Hajmohammad and Vachon (2016) outline consequences such as road blockages or a collective boycott organized by stakeholders what would lead to an interruption of the supply chain and consequently to financial losses. The cost of the disruption of a supply chain would be even higher in the pharmaceutical industry, specifically for antibiotic manufacturing, where such interruption could lead to a shortage of particular antibiotics and hence directly affect the health of human beings. Consequently, this would imply a hazard for the whole population affected by the shortage. Giannakis and Papadopoulos (2016) state otherwise that the negatively affected stakeholders can harm the organization without interrupting the operation. Examples can be adverse publicity, reputational loss, and expensive legal obligations (Busse, et al., 2017).

Supply chain sustainability risks (SCSRs) are a result of stakeholders criticizing and harming the focal firm of the supply chain when environmental or societal demands are not sufficiently fulfilled (Busse, et al., 2017). Hofmann, et al. (2014) outline a four-stage process of how SCSRs develop. First, negative sustainability-related conditions appear in the upstream supply chain. Secondly, stakeholders notice the adverse circumstances and accredit responsibility to the firm that initiates the supply chain. Finally, stakeholders choose to take actions that can harm the focal firm. Nowadays, SCSR can appear more often due to enhanced transparency and fast spreading information. Stakeholders have easier access to information regarding the misconduct of firms, and therefore, the probability of a stakeholder action that harms the focal firm is higher. (Busse, et al., 2017)

As described before, sustainability risks in supply chains are only feasible with the active involvement of stakeholders (Hofmann, et al., 2014). Therefore, the difference between supply chain sustainability risks and ordinary supply chain risks is that supply chain sustainability risks are triggered by stakeholders, and not by disruptions that disturb the flow of products or services.

Consequently, to be able to manage SCSRs, the different perspectives of stakeholders must be understood (Busse, et al., 2017). Furthermore, Busse, et al. (2017) highlight that not all stakeholders can be addressed. It is essential to assess the importance of each stakeholder regarding the respective risks. For instance, stakeholders can be employees, suppliers, customers, local communities, NGOs, competitors, governmental actors, owners, and also the natural environment (Busse, et al., 2017). Each stakeholder can influence different decisions within the supply chain (Meixell & Luoma, 2015). For instance, the study of Meixell and Luoma (2015) illustrates that the media has the most influence on purchasing decisions, and the competition has the most influence on operational decisions. Moreover, Muhammad Rafi-UI-Shan, et al. (2018) outline that existing frameworks to manage SCSRs share the steps risk identification, risk prioritization, and risk mitigation.

2.1.4. Current Frameworks for managing SCSRs

Busse, et al. (2017) highlight that SCSRs can be elevated by media or NGOs that communicate broadly that a company is misconducting against societal or environmental regulations or is not fulfilling stakeholders' expectations. These described supply chain sustainability risks are also often named as sustainability-related supply chain risks within the literature (Hofmann, et al., 2014; Giannakis & Papadopoulos, 2016). Hoffmann, et al. (2014) highlight that research in supply chain risk management has mostly ignored these sustainability risks. This thesis will strive to fill this research gap, and an adapted framework to assess and manage supply chain sustainability risks within the pharmaceutical industry will be proposed. Several pieces of research have already tackled this research gap (Hofmann, et al., 2014; Busse, et al., 2017; Giannakis & Papadopoulos, 2016; Foerstl, et al., 2010; Hajmohammad & Vachon, 2016). Therefore, concepts and models that seek to fill this research gap are already available. However, the proposed frameworks of previous studies are developed on different theories and disparate methods. Additionally, these studies have slightly different aims, and firms that were involved were not in the pharmaceutical industry, except for one case by Giannakis and Papadopoulos (2016) that included multiple sectors. In the following section, the differences between the available frameworks will be outlined and shown how these studies will be valuable for the thesis. Table 1 shows frameworks that have been developed recently to assess and manage supply chain sustainability risks.

Table 1 Existing Developed Frameworks | Assessing and Managing SCSRs

Authors	Method	Results	Limitations	Useful for thesis
Hofmann, et al., 2014	• Drawing on stakeholder theory • Trans-disciplinary method (joint research team of six firms) • German firms	• Framework to *manage* SCSRs – integrate sustainable concept into supply chain risk management discourse	• Requires empirical validation • Disregard opportunistic corporate behavior • No pharmaceutical company involved • It is broad: refinement needed	• Rough framework as a basis • Communicating efforts/improve-ments to the stakeholders is an important part of the framework
Busse, et al., 2017	• Recombination from prior literature and adapting view of stakeholders • Validation with a Swiss company (food industry) • Design science approach (study cannot be induced from data nor deduced from theory)	• Framework to *identify* SCSRs	• Applicability to other industries need to be validated • No pharmaceutical company involved	• Iterative process to identify stakeholders and SCSRs
Giannakis & Papadopoulos, 2016	• Adopt a risk management perspective (framework) to sustainability • Exploratory & confirmatory • Survey • Semi-structured interviews	• Framework to *manage* sustainability-related risks • Incl. risk prioritization, cause and effect, and correlations	• Only companies of two countries were part in the study (also pharmaceutical) • Risk monitoring and control not included in the analysis	• Operational risk monitoring (FMEA – to calculate risk priority numbers (RPN)) • RPN (FMEA) can be applied to prioritize risks

Foerstl, et al., 2010	• Drawing on dynamic capabilities view • Extending research framework of Ritchie and Brindley (2007) • Multiple case study approach	• Framework to *assess* and *manage* SCSRs • Described effective *capabilities* to manage SCSRs	• Only in the chemical industry	• Can be used to compare to the framework of Hofmann, et al. (2014) where the focus is more on suppliers
Hajmohammad & Vachon, 2016	• Conceptional theory building approach • Draw on resource dependency and agency theories • Literature research	• Framework to *manage* SCSRs: Four different risk management strategies (how to manage the suppliers)	• Framework limited to purchasing and supply management • Not focused on assessing risks	• Can be integrate in the framework of Hofmann et al. (2014) • Can be compared to parts of the framework of Foerstl, et al., (2010)

First, Hofmann et al. (2014) introduce a concept for managing supply chain sustainability risks based on stakeholder theory. A joint research team consisting of six German firms developed this framework. It is a rough concept, and it has to be refined. The study did not involve companies of the pharmaceutical industry, but the framework can be used as a basis for the development of our framework, i.e., to assess and manage SCSRs for the pharmaceutical industry. It is of great importance to evaluate and manage SCSRs in this particular industry due to the severity of the consequences of not addressed sustainability risks (as mentioned before).

Secondly, Busse, et al. (2017) have developed a framework to identify SCSRs for supply chains with low levels of visibility. In this framework, the stakeholders of the supply chain are utilized to identify SCSRs. This research combines previous literature and with the view of supply chain stakeholders. In addition, the framework was validated with a Swiss company within the food industry, and therefore, the applicability to other industries is not confirmed yet. However, this developed framework can be beneficial for our study, because the antibiotic supply chains have low visibility, and this framework helps to identify relevant stakeholders and consequently SCSRs.

Thirdly, Giannakis and Papadopoulos (2016) present a framework to manage SCSRs. This research is exploratory and confirmatory. Several interviews and surveys were conducted within a wide range of industries. Moreover, the study provides recommendations on how to act on different kind of sustainability-related risks, correlations between supply chain sustainability risks, and cause and effect of SCSRs. A limitation of this study is that only companies of the two

countries were included. An essential difference of the introduced frameworks proposed by Giannakis and Papadopoulos (2016) and the other frameworks is that the supply chain sustainability risks are calculated analytically and prioritized with a failure mode and effect analysis (FMEA). This method can be used in our thesis to prioritize and quantify the SCSRs.

Fourthly, Foerstl, et al. (2010) present a framework to assess and manage SCSRs based on the dynamic capabilities view. So, it is researched how the management of SCSRs is a competitive advantage for a company. The framework of Ritchie and Brindley (2007) has been extended and the effective capabilities to manage SCSRs are described within the research. The companies involved in the case studies are only of the chemical industry. The proposed framework is similar than the framework presented by Hofmann et al. (2014). The main difference is that Foerstl, et al. (2010) focus more on the supplier consequences and Hofmann et al. (2014) aim attention on communicating the management efforts of SCSRs to the stakeholders. In our opinion, the communication of efforts and results of SCSR management is of great value because SCSRs are triggered by stakeholders (Hofmann, et al., 2014).

Lastly, Hajmohammad and Vachon (2016) introduce a framework to manage SCSRs based on resource dependency agency theories. Literature research was conducted to build the framework, which is distinctively focused on four strategies to manage the company's suppliers. These strategies are based on the supplier's perceived risk and the buyer's relative power over the supplier. A limitation of the framework is that there are no recommendations on how to assess risks. This proposed concept can be integrated into a broader framework that is, for instance, also trying to identify stakeholders and assessing risks.

Muhammad Rafi-UI-Shan, et al. (2018) criticize that the proposed frameworks by Foerstl, et al. (2010), Hofmann, et al. (2014) and Giannakis and Papadopoulos (2016) consider risk and sustainability as two different concepts and that the frameworks are either based on sustainability or risk management concepts. So, it is argued that an appropriate framework is needed to manage SCSRs, as a guideline for organizations, in fashion supply chains. However, in our opinion, the prior presented frameworks are not separating risk and sustainability. The frameworks to manage SCSRs consider risks that are triggered by stakeholders. These risks are sustainable risks because stakeholders can feel provoked by the firm's supply chain if it harms the environment or the society (Hofmann, et al., 2014; Hajmohammad & Vachon, 2016). From our point of view, the available frameworks are not separating risk and sustainability, as stated by Muhammad Rafi-UI-Shan, et al. (2018).

Moreover, it is partly true that the frameworks are either based on sustainability or risk management concepts. The frameworks are also based on different concepts, e.g. stakeholder theory, and integrate the risk management or sustainability perspective. Hence, we see the opportunity to compare and adapt the frameworks that are based on different concepts. Muhammad Rafi-UI-Shan, et al. (2018) probably meant that this comparison of frameworks based on different

concepts is missing. Additionally, we accord with Muhammad Rafi-UI-Shan, et al. (2018) that an appropriate framework refined for organizations is needed. Muhammad Rafi-UI-Shan, et al. (2018) argue that the refined framework is required for the fast fashion supply chain. The fast fashion supply chain has similarities with the pharmaceutical industry. For instance, the price pressure makes outsourcing unavoidable in both sectors, and there could also be a volatile demand in the pharmaceutical industry because an epidemic could increase the need for drugs (Roland Berger GmbH, 2017). The main differences are the regulatory conditions and rigidity from the pharmaceutical industry (Access to Medicine Foundation, 2018b).

2.2. Theoretical Framework

In the following section, the most important frameworks for our thesis will be explained and discussed more thoroughly. First, the iterative framework of Busse, et al. (2017) will be used as a tool to identify stakeholders and their issues with the antibiotic supply chain (Figure 1).

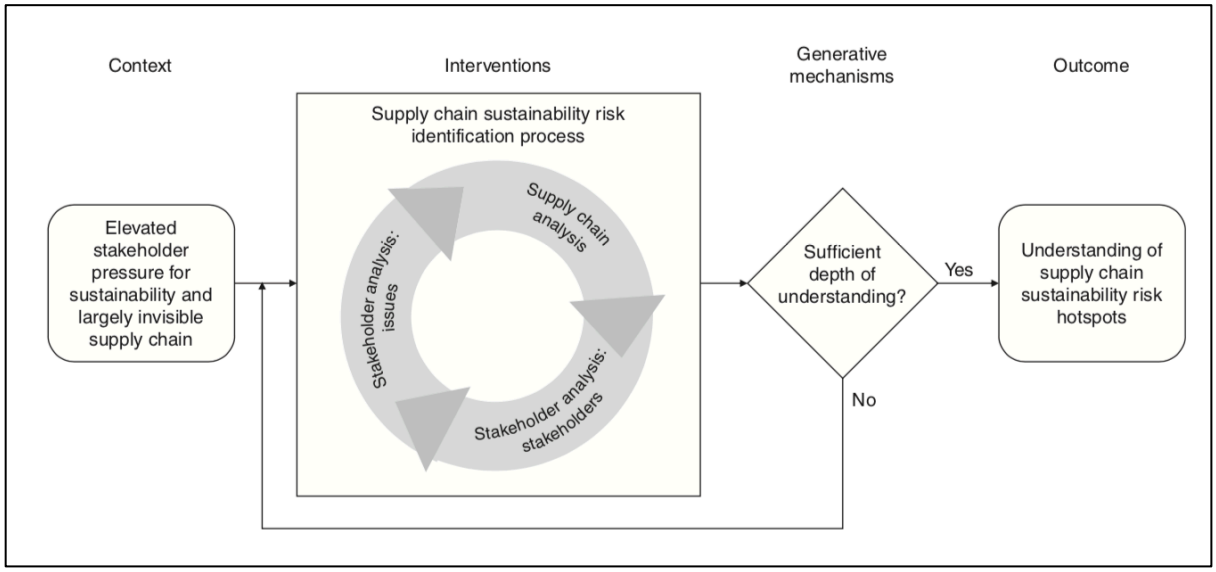

Figure 1 Procedural Model - Identifying SCSR (Busse, et al., 2017)

Figure 1 shows the procedural model for identifying sustainability-related supply chain risks. The procedural model consists of three steps. First, the supply chain should be analyzed through observation, company's internal knowledge, expert sources, and stakeholder's sources. With the prerequisite knowledge of the supply chain, the second step of the procedural model, i.e. stakeholder analysis follows. To reduce the complexity of the identification of sustainability-related supply chain risks, the most important stakeholders of the supply chain have to be identified. Most important stakeholders are critical to the business and stand out. These stakeholders can be powerless or powerful. Moreover, the identified stakeholders' expectations and topics have to be detected. Hence, sustainability-related issues that are not tolerated by these stakeholders can be identified. Finally, the iteration of these three steps will increase the

understanding of risks triggered by the most important stakeholders and therefore, supply chain sustainability risk hotspots can be identified.

Moreover, another crucial framework for our thesis is the concept for sustainability-oriented supply chain risk management developed by Hofmann, et al. (2014).

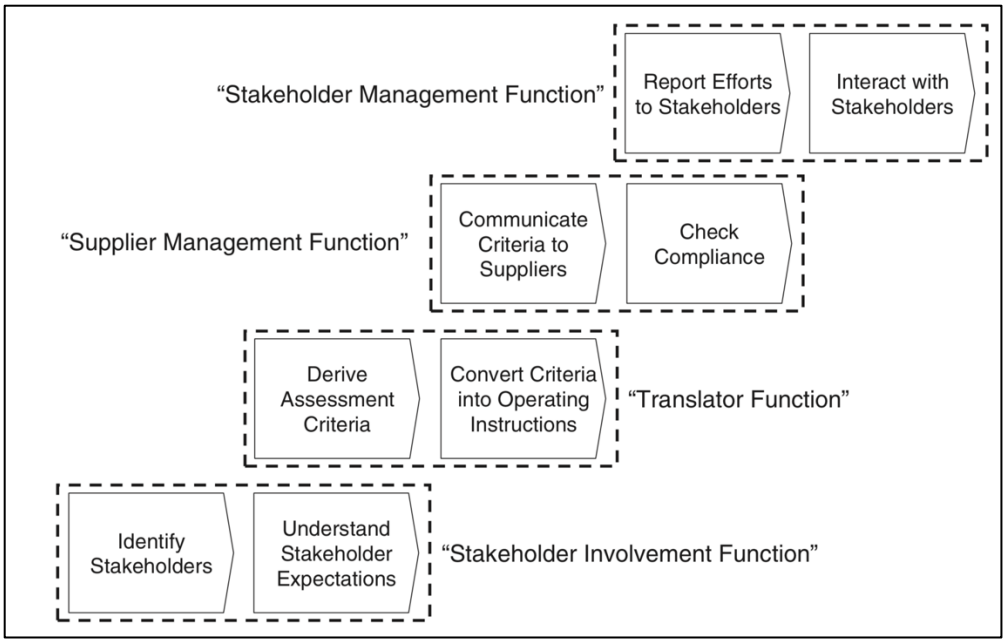

Figure 2 Concept for sustainability-oriented supply chain risk management (Hofmann, et al., 2014)

Figure 2 shows the framework that will be used as a basis for our thesis. This broad framework will be refined and adapted to the pharmaceutical industry. The framework consists of the four functions *stakeholder involvement function*, *translator function*, *supplier management function,* and *stakeholder management function*. First, the stakeholder involvement function will identify the most important stakeholders for the business and determine the stakeholder's expectations. This function is similar to step two and three of the previously introduced framework developed by Busse, et al. (2017). Secondly, the translator function will initiate specific operation instructions derived from the former detected stakeholder expectations. Thirdly, the supplier management function will communicate the new operation instruction to its suppliers and also control their compliance. The suppliers' compliance can be monitored through audits, memberships in compliance initiatives or if possible, through the inspections of incoming goods. Finally, the stakeholder management function will promote and communicate the company's efforts to its stakeholders. Hence, sustainable shortcomings and the company's effort to reduce them are presented transparently, which will avoid possible stakeholder actions.

Furthermore, the framework developed by Hajmohammed and Vachon (2016) can be integrated into the previously introduced framework of Hofmann, et al. (2014). The framework of Hajmohammed and Vachon (2016) is focusing on supplier-oriented sustainability risk management strategies and can be compared to the *translator function* and *supplier management function* of the framework of Hofmann, et al. (2014).

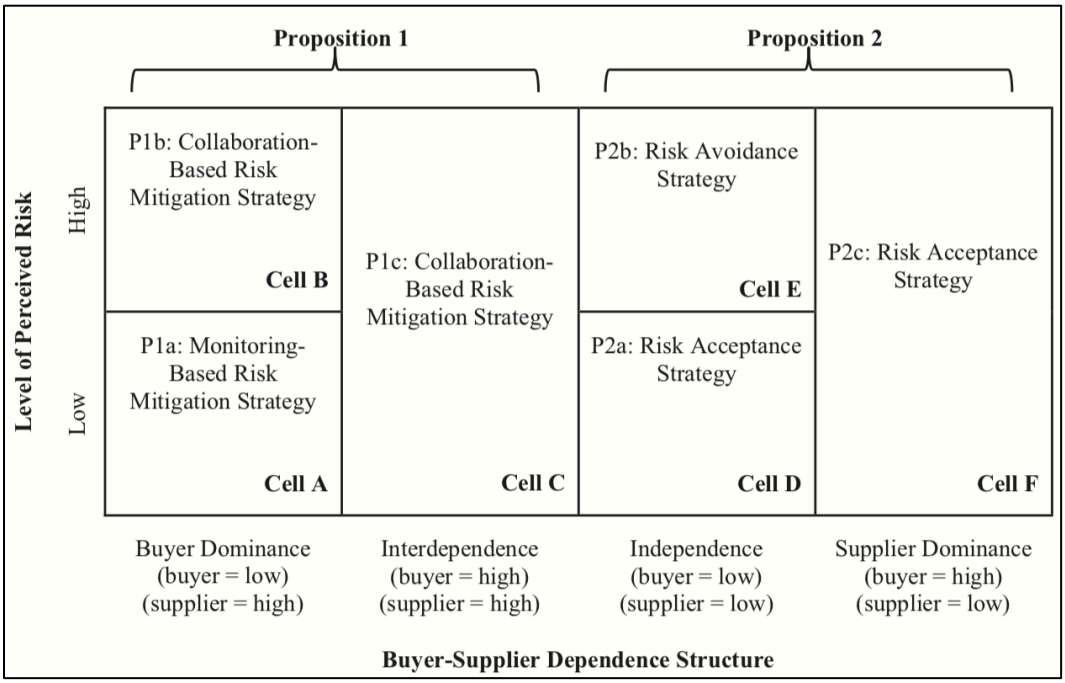

Figure 3 The Supply Manager's Choice Among Risk Management Strategies (Hajmohammad & Vachon, 2016)

Figure 3 shows the four different risks management strategies *collaboration-based risk mitigation strategy*, *monitoring-based risk mitigation strategy*, *risk avoidance strategy*, and *risk acceptance strategy*. First, the collaboration-based risk mitigation strategy intends to advance the supplier's environmental and social performance through partnership. Secondly, the monitoring-based risk mitigation strategy focuses on improving the supplier's environmental and social performance by introducing specific requirements that the suppliers have to fulfill. This strategy can be compared with the supplier management function of Hofmann, et al. (2014). Thirdly, the risk acceptance strategy is to take risks and to allocate costs to control future damages. Fourthly, the risk avoidance strategy is to prevent risks by ending the relationship with the supplier.

Moreover, the risk management strategy is chosen depending on the level of perceived risks, i.e., low or high, and the buyer-supplier dependence structure. Buyer-supplier dependence structures are buyer dominance, interdependence, independence, and supplier dominance. First, buyer dominance is when the supplier is dependent on the buyer. Secondly, interdependence is that both buyer and supplier highly depending on each other. Thirdly, independence is that supplier and buyer do not depend on each other. Finally, supplier dominance is when the buyer is dependent on the supplier. After the determination of the buyer-supplier dependence structure and level of

perceived risk, the risk management strategy can be chosen. For instance, a low level of perceived risk and a buyer dominant buyer-supplier dependence structure will lead to the strategy monitoring-based risk mitigation strategy (Cell A of Figure 3). The framework of Hajmohammed and Vachon (2016) shows that the supplier management function of Hofmann, et al. (2014) is not the only strategy to mitigate supplier-oriented sustainability risks.
Additionally, similar to Giannakis and Papadopoulos (2016), we will apply the failure mode and effect analysis (FMEA) to assess and prioritize supply chain sustainability risks systematically. We will use the *Likert scale* of Giannakis and Papadopoulos (2016) that consists of numbers from one to seven (Figure 4). Severity (S) is the effect of the risks, frequency/probability of occurrence (P) is the likelihood that the specific risk is happening, and detection of hazard (D) is how difficult it is to discover the respective risk. After evaluating the severity (S), probability of occurrence (P) and the detection of hazard (D) of a risk, the risk priority number (RPN) can be calculated as follows: $S_i*P_i*D_i$=RPN. The higher the RPN, the greater is the particular sustainability-related supply chain risk.

Scale	1	2	3	4	5	6	7
severity	No effect	Negligible effect	Minor effect	Moderate effect	Major effect	Critical effect	Catastrophic effect
Frequency of occurrence	Almost never	Rarely	Infrequently	Occasionally	Frequently	Usually	Almost always
Detection of hazard	Certain	Easy	Moderately easy	Moderate	Difficult	Very difficult	Impossible to detect

Figure 4 Risk scales (Giannakis & Papadopoulos, 2016)

It has to be noted, that the criteria we use to rank the SCSRs is up to our knowledge and perception, considering all the valuable feedback from interviewed experts, company's internal knowledge and stakeholders' sources from the industry. By no means is this intended to be taken as ground theory.

3. Methodology

In this chapter, the research type choice is shown and further explained. How the data has been collected, and the specific purpose of it is further described. Furthermore, the design of the research is displayed through a detailed research plan which purpose is to allocate how the research questions are intended to be answered through a set of analytical steps. Finally, the ethical aspects that were considered throughout our research, and data gathering are mentioned.

3.1. Research Methodology

This thesis followed *an inductive research* type. The first step was data collection. Primary and secondary data were collected regarding the structure, stakeholders, and stakeholder issues of antibiotic supply chains. Additionally, a *case study* of two important antibiotics for the Swedish market, i.e., amoxicillin and piperacillin/tazobactam were conducted as part of our data collection. This allowed us to investigate how two specific antibiotic supply chains look like in depth, which provided us with two concrete examples (Flyvbjerg, 2006). Also, the theory was reviewed regarding frameworks that suggest how to manage supply chain sustainability risks. The literature review helped to point out which data we should look for in our data collection and also which research gaps existed. The second step involved the analysis and findings of our collected data. The third step involved suggesting a theory based on previous findings. Hence, a framework to manage supply chain sustainability risks in the pharmaceutical industry has been proposed, what represents the outcome of our thesis. (Gray, 2018; Bryman & Bell, 2011)

In addition, the thesis also followed an *exploratory research* type because the following aspects had to be explored to identify SCSRs within pharmaceutical supply chains: Structure, stakeholders, and stakeholder issues of the supply chain. According to Busse, et al. (2017), it is necessary for supply chains with low visibility to use an iterative process to identify a supply chain's stakeholders and their issues. The iterative process consisted of a supply chain, stakeholders, and stakeholder issues analysis. Especially the pharmaceutical industry has low visibility (Access to Medicine Foundation, 2018b) and therefore, a different analysis of the circular, iterative process was providing different inputs which were valuable for the next analysis. For instance, the stakeholder analysis could provide input for the structure analysis of the supply chain. Hence, stakeholders were able to outline how the structure of supply chains looked like from their perspective. Consequently, the more loops of the iterative process were conducted, the higher the visibility of the antibiotic supply chain was, which facilitated the identification and assessment of supply chain sustainability risks (i.e., stakeholder issues). Furthermore, the collection and analysis of data happened simultaneously. In addition, a framework for managing SCSRs within the pharmaceutical industry was not available, and therefore, exploratory research was essential to understand the requirements for a framework to manage SCSRs within the pharmaceutical industry. Our suggested framework has a practical focus and can be used by pharmaceutical

companies. Therefore, our thesis can be considered as *applied research*. (Gray, 2018; Bryman & Bell, 2011)

Moreover, a *qualitative approach* was chosen for this thesis because this approach allowed us to interact with people through in-depth interviews, and hence, we were able to understand complex topics such as pharmaceutical supply chains. Therefore, words have been the main medium within this research, and consequently, the stakeholder's needs, goals, and issues could be investigated. The same degree of understanding of these stakeholder's issues was not likely to be achievable with, for instance, an analysis of publicly available "rigid" data. However, cons of a qualitative approach were that the data collection was time-intensive and there was a possibility that we, as the researchers, could be biased regarding the formulation of questions and interpretation of the content. Therefore, our interview questions were reviewed by our supervisor to make sure that the research resulted as objective as possible. Moreover, the interviews were *in-depth* and *semi-structured*. A check-list ensured that we covered topics that we had targeted, and still, we were open to new information and directions that the interviewee initiated. During the interviews, we took notes and recorded the sound if approved by the interviewee to ensure that we did not miss valuable information for the analysis. The only interview where we were not allowed to record the sound, we made sure that both of us were taking notes during the interview, and these were extended directly afterwards to ensure that any information was lost nor distorted. The interviewees were different stakeholders that are involved in antibiotic or pharmaceutical supply chains to receive different perspectives on the structure of the pharmaceutical supply chain and its sustainability risks. When possible, the interviewees were conducted in person; otherwise, the media we used was via phone or video call.

We conducted 5 interviews for our research (see Appendix 2). The interview participants work in diverse types of pharmaceutical companies located in various countries and have different positions. These interviewees were chosen because each of them shows a different perspective of the whole antibiotic supply chain. *The first interview participant* works in a small pharmaceutical company, which is a Market Authorization Holder (MAH) for supplying Amoxicillin/clavulanic acid to Sweden. The interviewee is the director of that small pharmaceutical company, and the company is located in the UK. *The second interview participant* works in a company which is an intermediary between synthetic antibiotic API suppliers from India and European pharmaceutical companies. The interviewee is an agent of that company, and the firm is located in Spain. *The third interview participant* is working in a multinational pharmaceutical company, which is a MAH for on-patent and off-patent drugs. The interviewee is the global head and business continuity manager of external supply operations of this firm and has expertise in environmental issues within supply chains. This big pharmaceutical company is located in Switzerland. *The fourth interview participants* work in a contract development and manufacturing organization (CDMO), which produces generic antibiotics. Two interviewees of that company have the job titles Director Corporate Projects, and one interviewee has the job title Director Global Procurement. This

company addresses efforts towards social and environmental sustainability issues and is located in Sweden. *The fifth interview participant* has been working for the last 10 years in different pharmaceutical companies in Hyderabad, India. The interviewee has experience as a business developer and with supplying finished pharmaceutical products and APIs to Europe, the US, and Middle East countries.

Furthermore, a *descriptive quantitative analysis* was chosen to measure data trends and identify the structure of amoxicillin and piperacillin/tazobactam supply chains (Gray, 2018). Hence, numbers were the main medium in this part of our research to describe which actor, in which location is producing how much and which part of the respective antibiotic. Here, the descriptive quantitative analysis allowed us to analyze a big amount of secondary data that are researcher distant and therefore, more objective. So, this descriptive quantitative analysis enabled us to use it as a knowledge foundation for our qualitative research, and the results of both analyses were utilized to achieve high-quality results. One has to consider that the data of our quantitative research was mostly based on open databases and therefore, we did not have control over the data quality and also the data could be incomplete. Nevertheless, the databases that were used are the most important ones which are publicly available. The databases that were used in this thesis are the following: *Pharmacompass.com, Chemicalregister.com, Indiamart.com, Pubchem.ncbi.nlm.nih.gov,* and *FASS.se*. Finally, this thesis was *empirical* because the research involved qualitative and also descriptive quantitative data in order to assess SCSRs and to recommend how SCSRs should be managed in the pharmaceutical industry. (Gray, 2018)

3.2. Research Plan

In the following part, our research plan is presented (Table 2) that illustrates how we answered the two research questions of our thesis. As a reminder, the two research questions are [1] "What sustainability risks do the supply chains of the antibiotics have for its constant availability in Sweden?" and [2] "How can the supply chain sustainability risks be managed in the pharmaceutical industry?". Table 2 shows the research plan for our thesis. Each analytical step has been derived from the respective research question, and it is shown how the data has been collected and analyzed.

Table 2 Research Plan

Research Question (1/2)	Analytical Step	Data Collection	Analysis Method
1	[1] Identify main actors involved in amoxicillin & pip/tazo supply chains and general pharmaceutical supply chains	• Secondary data (data bases, annual reports, literature, etc.) • Interviews	Content analysis
	[2] Outline the structure of both antibiotic supply chains and of general pharmaceutical supply chains	• Secondary data (data bases, literature, etc.) • Interviews • Iterative framework of Busse, et al. (2017)	
	[3] Identify stakeholders of pharmaceutical supply chains	• Interviews • Secondary data • Iterative framework of Busse, et al. (2017)	
	[4] Identify SCSRs (stakeholder issues) of pharmaceutical supply chains	• Interviews • Iterative framework of Busse, et al. (2017)	
	[5] Prioritize stakeholders and SCSRs	• Data of previous steps	Failure mode and effect analysis (FMEA) to prioritize SCSRs with risk scales of Giannakis and Papadopoulos (2016)
2	[6] Identify how the *SCSRs* of both antibiotics and within general pharmaceutical supply chains are currently assessed and managed	• Interviews • Annual reports • Secondary data	Content Analysis
	[7] Critical review processes of how pharmaceutical companies are assessing and managing SCSRs currently	• Secondary data • Previous data	

The first research question was answered in five analytical steps. First, the main actors of the supply chains of the two antibiotics amoxicillin and piperacillin/tazobactam and general pharmaceutical supply chains had to be detected. Secondly, it had to be investigated how these previously detected actors were interacting, and hence, the structure of both mentioned supply chains and general pharmaceutical supply chains could be found out. Thirdly, with the gained knowledge of the previous steps, the most important stakeholders of pharmaceutical supply chains could be determined. Fourthly, the issues of the formerly identified stakeholders (i.e., SCSRs) could be recognized. The analytical steps [1], [2], [3] and [4] are iterative, circular and progressive because an iterative process of these steps was a way to identify SCSRs in a supply chain with low visibility, as outlined by Busse, et al. (2017). The analytical steps [1] to [4] were repeated until we had enough understanding of the supply chain sustainability issues. In addition, within the fifth analytical step, the identified stakeholders and SCSRs were prioritized.

The data for step [1] to [4] was gathered through secondary data (i.e., databases, literature, and annual reports) and interviews. The gathered data of these steps were analyzed through content analysis. The data gathering and analysis were conducted simultaneously. For the prioritization, step [5], the previously gathered data were used. The failure mode and effect analysis (FMEA) was applied to prioritize SCSRs. Also, the *Likert risk* scales introduced by Giannakis & Papadopoulos (2016) were used as they already created them.

The second research question was planned to be answered in two analytical steps [6] and [7]. First, it was determined how different pharmaceutical companies were currently assessing and managing SCSRs. Secondly, these practices of how pharmaceutical companies assessed and managed SCSRs were critically reviewed. The data for these analytical steps were gathered mainly through interviews and also through secondary data and annual reports of pharmaceutical companies. The data were analyzed through content analysis.

3.3. Ethical considerations

This thesis aimed to provide more visibility to the supply chains of antibiotics, which from an ethical point of view, would imply an increased responsibility for each player involved. However, we provided this increased visibility by naming the kind of company that we interviewed without disclosing the company's name to avoid any potential repercussion. The ethical aspects considered in this research were encountered during the interviews. Informed consent was always provided before the interview; a summary of the research, and its purpose was delivered, in addition to the questions that we intended to ask. Privacy requirements were considered as well; before the commencement of the interview, the interviewees were asked whether the interview could be recorded or not. Some interviewees declined permission to record the interview because it concerned sensitive information. Others agreed to record the interview. Respecting the privacy of the source was the top priority for all the interviewees, all wanted to remain anonymous; hence, we naturally fulfilled the requirement. A big part of the data collection and empirical analysis has been conducted using public databases that were found on the internet. We have responsibly made use of the information by properly citing the source of each database.

4. Empirics

In the following chapter, the field material used to analyze and obtain our findings is presented. The information comes from different kinds of sources: Journals, interviews, and secondary data. Firstly, the pharmaceutical supply chains are explained in detail to gain an understanding necessary for the further identification of the two antibiotic supply chains from the case study. Furthermore, regulations and environmental law are briefly explained, given their importance in the pharmaceutical industry. Secondly, the case study is presented, which includes the study of two antibiotics: Amoxicillin and Piperacillin/Tazobactam. Both supply chains are outlined, and the stakeholders are identified. Lastly, environmental risk management performance from several companies within the pharmaceutical industry is presented to gain insight into how SCSRs are currently managed.

4.1. Supply chains in the Pharmaceutical Industry

Pharmaceutical supply chains differ and are particularly complex compared to supply chains from other industries because the products that are manufactured and distributed are not mere consumer goods but medicines, products whose goal is to improve human health. Within this industry, the main priority is to ensure patient care and safety, and the way to do so is through strict regulations to protect the integrity of the medical products throughout the supply chain (Koh, et al., 2003). Setting and guaranteeing compliance from such laws and administrative orders that regulate the industry adds a significant degree of complexity to the supply chain and also tremendous amounts of documentation that need to circulate along the chain. Documentation entails to *track*, i.e., know the physical location at all times, and to *trace*, i.e., know historical locations, times, ownership, packaging configurations and environmental conditions from the storage, for every particular drug within the supply chain (Koh, et al., 2003).

The main stages from the pharmaceutical supply chain are displayed in Figure 5, starting with the manufacturing process, following with distribution and finalizing with the commercialization process. Shah (2004) enumerates the most typical nodes that a pharmaceutical supply chain can contain: Primary manufacturing, secondary manufacturing, market warehouses, and distribution centers, wholesalers, and retailers/hospitals. There is not a unique configuration of the supply chain, but a general scheme of the typical processes involved shall be sufficient to understand the structure and order of events (Figure 5).

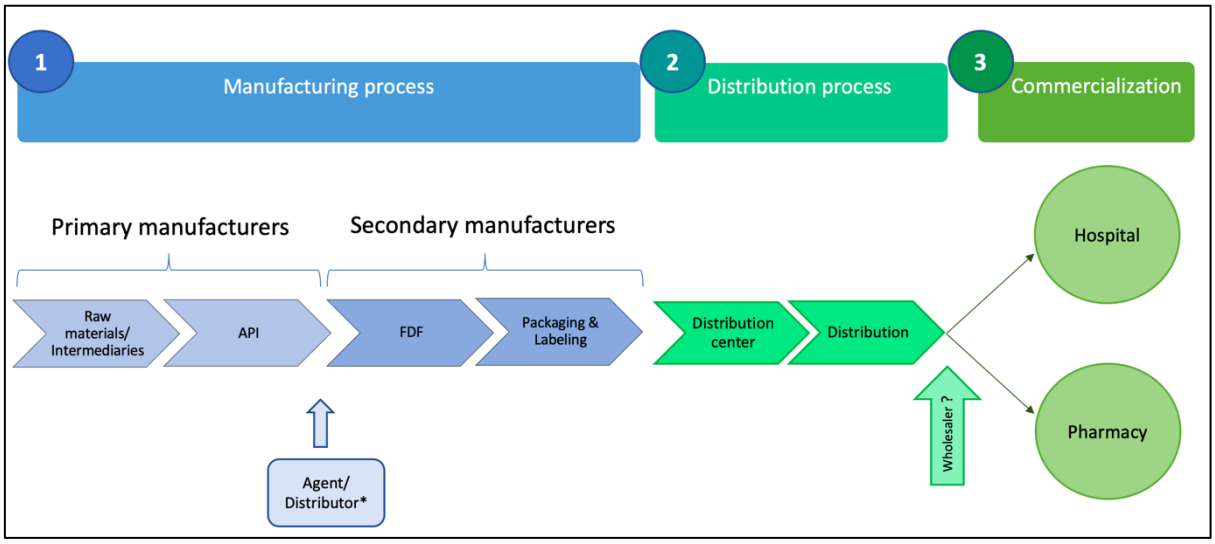

Figure 5 General scheme from the pharmaceutical supply chain

The manufacturing process is divided into primary manufacturing and secondary manufacturing. Primary manufacturers are in charge of producing the raw materials and intermediates, which are the compounds that will be used to produce the Active Pharmaceutical Ingredient (API). Stable intermediates are many times produced through a multistage process, which can result in low responsiveness and contribute to the deficient supply chain metrics characteristic from this industry (Shah, 2004). API production involves several chemical processes, and for antibiotics, these can vary between synthetic processes, fermentation processes or a mixture in between. This manufacturing process is long and requires many processing shifts (Shah, 2004). Additionally, these compounds require quality approvals to be able to continue to further phases. Some products, such as fermented antibiotics need different facilities to avoid cross-contamination. All of these factors together, make of this initial manufacturing process long and complex, which is many times outsourced to contract manufacturing companies (Shah, 2004).

Secondary manufacturers produce the Finished Dosage Form (FDF) by combining and processing the API with inactive ingredients, also called excipients, which will then be packaged (Shah, 2004). Depending on the form of the FDF (e.g., tablet, syringes, or capsules), the production requires different technologies and processes and will be manufactured in different plants. The secondary manufacturing facilities are typically located in a different place than primary manufacturing (Shah, 2004). It is quite rare to have a complete vertical integration for one product, especially for generic drugs. Also, regularly, the number of secondary manufacturers surpasses the number of primary manufacturers (Shah, 2004). After the production and packaging, the distribution stage begins. This process will depend on whether the product is manufactured in-house or outsourced. Sometimes only the API is outsourced, and the FDF is produced in-house, or the whole product is outsourced, and the commercial company (MAH) will receive the FDF. The product to be distributed will go to a market warehouse or distribution center, and from there, it

can go through a wholesaler. Finally, the medicine will be ready to be commercialized, which can be either to hospitals or retail pharmacies.

There are many different actors involved in the supply chain and, due to globalization, the chain is distributed and spread across the globe. The main players within the pharmaceutical industry are (Shah, 2004):

1) R&D-based multinationals with a global presence in branded products
2) Large generic manufacturers
3) Local manufacturing companies which commercialize only in the home country
4) Contract manufacturers
5) Drug discovery and biotechnology companies

Besides the five main players, there are several key stakeholders involved which include: Producers of intermediaries and raw materials, API manufacturers, Finished Dosage Form (FDF) manufacturers, government agencies, hospitals, distributors, pharmacy chains, retailers, research organizations, and regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (Kapoor, et al., 2018). The cooperation and coordination between all parties involved across the different stages of the supply chain are crucial for an optimal outcome. Quality is the main priority in this industry, and even the smallest irregularity from a product can cause the elimination of whole product batches and also entail civil penalties (Santos Bravo & Crespo de Carvalho, 2013). For this reason, it is more difficult to fully optimize the process into the most efficient and productive way when considering these limitations. In addition to that, companies must have not only good planning and management for forward logistics, but also for reverse logistics for product recalls, which are increasing radically (Santos Bravo & Crespo de Carvalho, 2013).

Product recalls can happen due to any possible defect on the product, which will be labeled according to a recall classification from the FDA or EMA depending on the severity of the possible consequences of the defect (Santos Bravo & Crespo de Carvalho, 2013). In addition, all the products that expire at the hospital or pharmacy shell need to be recalled as well. These two reasons, product defect, and expiration are the main causes for return in the pharmaceutical industry (Kumar, et al., 2009). Product recalls happen quite often despite going through an extensive process of quality, efficacy, and safety of each product to get the mandatory authorization by the corresponding regulatory authority how to be legally able to commercialize it (Santos Bravo & Crespo de Carvalho, 2013). However, despite happening quite frequently, the process of replacement of the product needs to be done as fast as possible to avoid any negative consequence of using a defective or expired product on a patient. For this reason, pharmaceutical companies need to have a well-planned efficient reverse logistics process.

Tracking and tracing pharmaceutical products is an essential aspect to secure safety within the supply chain; it is typically used when a product needs to be recalled. Another important use is to avoid counterfeit drugs. Counterfeit drugs are considered those drugs that have been illegally modified or mislabeled with an intentional nature and if these reach the market they jeopardize patient safety, contribute to economic loss of authorized drug manufacturers and imply a threat to national security (Koh, et al., 2003; Kumar, et al., 2009). Counterfeit products are widespread in all industries; the difference is that the consequences of a counterfeit drug can be catastrophic given the nature of the products, whereas the consequences counterfeit products in apparel or electronics industry, for instance, would not have such a negative impact (Kapoor, et al., 2018). The prevalence of counterfeit or substandard medical products is much higher in low- and middle-income countries, where it represents a 10% of their market and have severe negative consequences such as directly impacting the patient's safety or contributing to AMR and drug-resistant infections (World Health Organization, 2018).

A solution to enhance traceability and trackability of medical products would be the implantation of Radio-Frequency Identification Technology (RFID) and Electronic Product Code (EPC), which would serve to secure the supply chain (Kapoor, et al., 2018; Kumar, et al., 2009). RFID is defined as "a technology that incorporates the use of electromagnetic or electrostatic coupling in the radiofrequency portion of electromagnetic spectrum to uniquely identify an object" (BT & Henley Centre, 2004, p. 8). It is a form of AutoID tag which is manufactured as a microchip where information can be encoded and stored in electronic product code form (Kapoor, et al., 2018). The benefits are undoubted; it is a recommendation from the FDA to pharmaceutical companies to implant this technology in their products, but it implies a big economic investment. For this reason, the method has not been fully implanted, but some of the pharmaceutical giants such as Pfizer and GlaxoSmithKline have started to use it the technology for some of their most popular products as a pilot program (BioIT World, 2019).

4.1.1. Regulations within the pharmaceutical industry

Regulations play a fundamental role in the pharmaceutical industry. The purpose is twofold; to guarantee the patient's safety by ensuring minimum quality standards and also to enhance affordability by limiting medicines' outlay. These regulations force the interaction between pharmaceutical companies and the public sector. The strength of such interactions will depend on the characteristics of the specific institutional framework and healthcare systems from each country. Every country has different laws and regulatory schemes for healthcare provision. Nonetheless, the most important and common aim from regulators is to set minimum quality standards. The research and development process that a pharmaceutical firm undertakes is very costly in terms of economic resources and time. After a novel drug is developed, the pharmaceutical company will apply for obtaining the marketing authorization. The medicine needs to get approval, where the safety and efficacy of the compound are assessed, from the

corresponding regulatory agency for where the drug is aimed to be commercialized. This approval is highly difficult to earn; only 1 out of 1000 achieve success. Two of the most important regulatory agencies are the European Medicines Evaluation Agency (EMEA) for the commercialization within Europe and the Food and Drug Administration (FDA) for the commercialization in the United States. (Atella, et al., 2012; van Boxtel, et al., 2008)

Once the drug achieves the approval to allow its commercialization, other legal requirements need to be fulfilled during the manufacturing process. The Good Manufacturing Practices (GMP) requirement was instated as a minimum legal standard in 1968 (Hinz, 2006; van Boxtel, et al., 2008). The GMP requirement purpose is to ensure that all drugs are manufactured in adequate facilities, with the required equipment and control. Therefore, ensuring the quality and safety of the medicines through a controlled production process (Hinz, 2006). All manufacturers need to comply with this regulation since it became valid in 1968. The need to comply with such regulations during the manufacturing processes sums up additional efforts and time to the ordinary production processes. Moreover, it creates an environment which is opposite to innovation-friendly, thereby diminishing optimization and continuous improvement initiatives within production processes (Hinz, 2006). Any change, no matter how small, on the production method needs to get approval from the regulatory agency in charge, which involves great amounts of time and paperwork (Hinz, 2006). Hence, manufacturers avoid introducing any change to the production process method to avoid production delays.

These regulations surely create some disadvantages, and it is the reason why pharmaceutical manufacturers fall behind other industries' manufacturers in terms of efficiency in production (Hinz, 2006). However, it is crucial to keep in mind that pharmaceuticals are not ordinary consumer's products and cannot be treated as such either for its commercialization nor for its production (van Boxtel, et al., 2008). The main reason why the pharmaceutical industry differs from other industries is that all stages from the supply chain, including distribution and dispensing, require specific knowledge and expertise. Also, the defects on the drugs can cause catastrophic consequences, which include death at the most extreme case, this is why so many precautions need to be taken (van Boxtel, et al., 2008).

Harmonization trends for regulatory frameworks have for long existed. European countries did not always operate as a common market; it took around 10 years to develop the harmonization of some European countries, introduced in 1975 (Casper & Matraves, 2003). The International Conference on Harmonization (ICH) started in 1990 to establish common international regulatory standards between the largest domestic markets: US, EU and Japan (van Boxtel, et al., 2008; Casper & Matraves, 2003). The focus of ICH, which is supported by the WHO, is on technical requirements for novel medicines to find consensus on quality, safety, and efficacy standards. Another aim from this initiative is to increase the availability of generics to create more accessibility and affordability through fair competition (van Boxtel, et al., 2008).

Global bodies like WHO and the ICH initiative work on achieving global regulatory consensus and improving access to medicines in the developing world, which efforts are made towards achieving enhanced social sustainability. However, GMP does not cover environmental protection. Instead, environmental issues are ruled by national legislations. Therefore, there is enormous variability within environmental sustainability standards. Nonetheless, the WHO is aware and assumes that a special set of standards for the global regulatory environment need to be set in a gradual manner (van Boxtel, et al., 2008). The International Organization for Standardization (ISO) has current standards for environmental management, the ISO 14000 family, which are not specific or limited to a certain industry. Even though these standards are not mandatory to follow by law, it is a framework commonly used within the pharmaceutical industry. Its use allows holistically handling environmental issues and also guaranteeing external stakeholders that proper environmental management is being followed.

4.1.2. Environmental law

Corporations need to comply with legislation, it is possible that some companies decide to go one step further from legal requirements, but this is not always the case. Therefore, for the sake of understanding how the legal minimums are set within this field, environmental law should be briefly reviewed. *Environmental law* refers to the set of regulations which purpose is to protect and preserve the ecosystem and its natural resources. These integrate a prevision into the human decisional system taking into account the costs and values that are often neglected because they take place outside the formal market economy (Plater, et al., 2016). Environmental laws are often created retroactively. Typically, after a significant threat has created sudden public concern and awareness, to prevent a similar catastrophe in the future. However, also, doctrines exist to anticipate and prevent environmental disruptions (Plater, et al., 2016). Either way, the main goal is to introduce a fair process which takes into consideration real societal costs and benefits to the public or private decision-making (Plater, et al., 2016).

Environmental law is created through a utilitarian process by calculating the balance between cost versus risk or benefits. This kind of process might be not the most suitable for this matter because while costs are easy to quantify and calculate earnings or losses, environmental risks are difficult to quantify. The reason why it is highly complex to quantify environmental risks and potential damage is that it requires a long-term perspective, and the outcome is a probabilistic estimation. Scientific uncertainty does play a big role as a weakness not to have strong evidence to create a basis for the creation of a new law. This is conveniently utilized by some actors of the industry that can take advantage and use it in their favor. Furthermore, access to data is many times restricted due to confidentiality matters. Then, it results even more complex to assess risks and reach awareness when the access is so limited. Determining who should carry the burden of proof of how serious a problem is, is a critical matter. The industry claims it is the public's responsibility

to demonstrate that their emissions, use of natural resources, or any other practice they do is harmful to the environment. Challenging the industry standards is a costly procedure, so placing such burden on communities of people that lack the necessary resources is unrealistic yet beneficial for corporations. (Wargo, 2012)

There has been a significant change over the last five decades towards environment concern and law practices around this field. The field has increased in such a way that there are nowadays more environmental lawyers than labor lawyers in the U.S (Plater, et al., 2016). This trend is growing at an increasing rate due to the reality and potential from environmental issues (Plater, et al., 2016). Nevertheless, environmental law is still highly fragmented and not created in a sufficiently comprehensive and systematic way (Wargo, 2012). Funding and administration are also very fragmented; there are many different agencies involved that share such responsibility. Then, one problem can result to be handled by several various agencies which make its implementation more difficult (Wargo, 2012).

FCG, a Swedish financial consultancy, states that many businesses are increasingly including sustainability as a top priority in their portfolio (FCG, 2018). The firm believes that climate risk management will gain even more importance throughout the upcoming years provided that the environmental risks have gained awareness and importance between investors, regulators, and the public (FCG, 2018). There are a few organizations gathering efforts to accelerate this process that back up this information; for instance, the Network for Greening the Financial System (NGFS), which is a network composed by 23 central banks and supervisors. Their members state that climate change risks are a source of financial risks and further claim that “It is therefore within the mandates of the central banks and supervisors to ensure the financial system is resilient to the risks” (NGFS, 2019, p. 2). NGFS (2019) highlights the importance of performing environmental reports, hence increasing transparency and when possible, make data publicly available. This is one of multiple platforms that are increasing the efforts to make regulations related to climate change end sustainability stricter. The link between climate change risks with financial risks might be a good incentive to accelerate the process.

4.2. Case study: Antibiotics' supply chain structure & Stakeholders

4.2.1. General structure of the antibiotics' supply chain

Figure 6 and Figure 7 display the structure of amoxicillin and piperacillin/tazobactam supply chains that are resulting in Sweden. Furthermore, the Figures below show which countries are involved in all steps of the manufacturing process from the respective supply chains. The structure of amoxicillin and piperacillin/tazobactam supply chains consists of raw material/intermediates producer, API producer, FDF manufacturer, FDF supplier (MAH), distributors, and commercialization. The percentages and the fillings of the funnels represent the relative share of involved countries of each step of the supply chains. Abbreviations of countries are presented in the funnels. For instance, CN is an abbreviation for China and IN for India. The GMP symbol shows if a respective step of the supply chain must comply with the GMP guidelines. The data analysis is based on secondary data (see Appendix 1) and interviews (see Appendix 2).

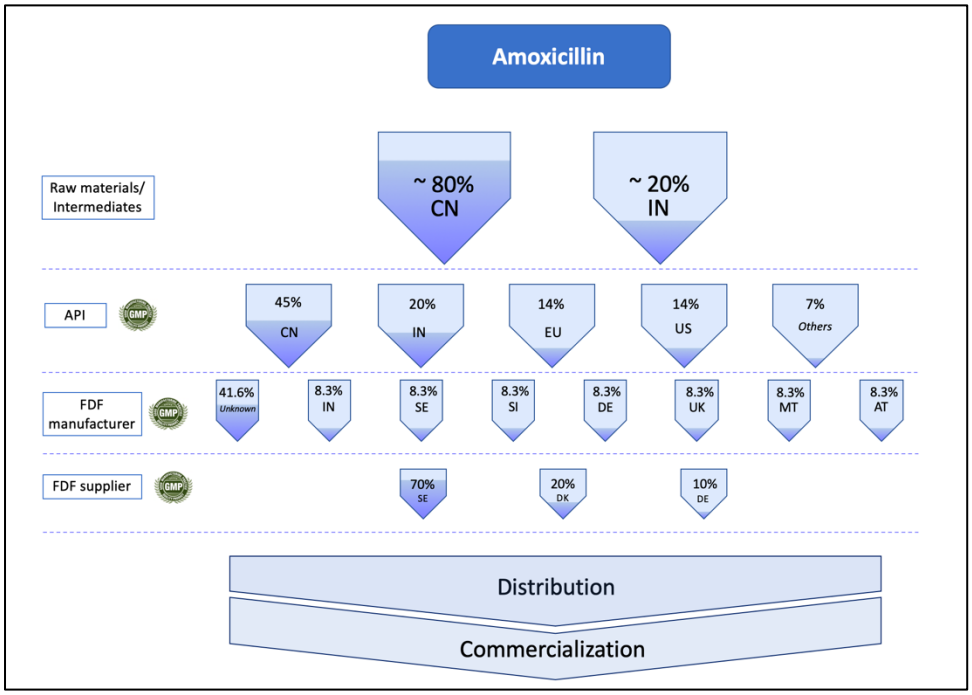

Figure 6 Amoxicillin Supply Chains to Sweden

Figure 6 shows the amoxicillin supply chains that are resulting in Sweden. To begin upstream of the supply chain, China is approximately producing 80 percent, and India is providing the other 20 percent of all raw materials necessary for amoxicillin. Therefore, one can see the dependence on especially China and India for amoxicillin production. Furthermore, no GMP certificate is required for companies that are producing these raw materials. In addition, most of the Active Pharmaceutical Ingredients (API) is also produced by China (45%) and India (20%), but the API is also produced in Europe (14%), the US (14%) and other countries (7%). Beginning from the API production, all steps need to comply with the GMP regulation. The Finished Dosage Form

(FDF) is produced in at least eight different countries with an equal share of 8.3%: India, Sweden, Slovenia, Germany, UK, Malta, and Austria. However, some FDF manufacturer could not be determined (41.6%) because a share of FDF suppliers (MAHs) did not disclose where they source their antibiotics. Additionally, Sweden is sourcing the amoxicillin FDF from the suppliers within Sweden (70%), Denmark (20%), and Germany (10%).

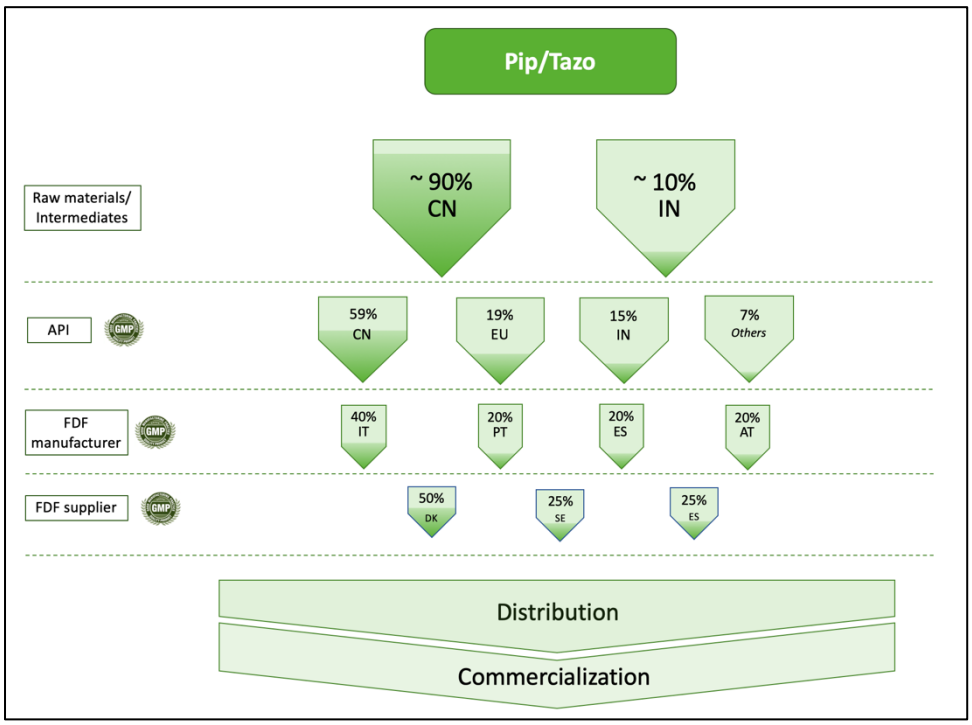

Figure 7 Piperacillin/Tazobactam Supply Chains to Sweden

Figure 7 shows the piperacillin/tazobactam supply chains that are resulting in Sweden. To begin here also upstream of the supply chain, China is producing approximately 90% and India 10% of the raw material necessary for piperacillin/tazobactam. The increased percentage for this case occurs because tazobactam's raw materials and intermediates are solely produced in China, as well as tazobactam API itself. Thus, the dependence on China is for piperacillin/tazobactam even higher in comparison to the raw material necessary for amoxicillin. Furthermore, as mentioned before, no GMP certification is necessary for raw material producers of piperacillin/tazobactam. Additionally, the Active Pharmaceutical Ingredient (API) for piperacillin/tazobactam is produced in China (59%), Europe (19%), India (15%), and other countries (7%). Starting from the API step, companies have to comply with the GMP regulations. Moreover, the Finished Dosage Form (FDF) is produced in Italy (40%), Portugal (20%), Spain (20%) and Austria (20%). Finally, the FDF suppliers are located in Denmark (50%), Sweden (25%), and Spain (25%).

4.2.2. Comparison: Amoxicillin & Piperacillin/Tazobactam

API manufacturers

Figure 8 compares the amount of amoxicillin and piperacillin/tazobactam API manufacturers. One can see that amoxicillin has the leading share with 82% and piperacillin/tazobactam has a share of only 18%. In China, there is 3.5 times more manufacturer for amoxicillin API compared to piperacillin/tazobactam API. Additionally, there are 6.25 times more amoxicillin API manufacturers in India and 17 times more manufacturers in the USA. Hence, it clearly shows that piperacillin/tazobactam has significantly less API manufacturer than amoxicillin.

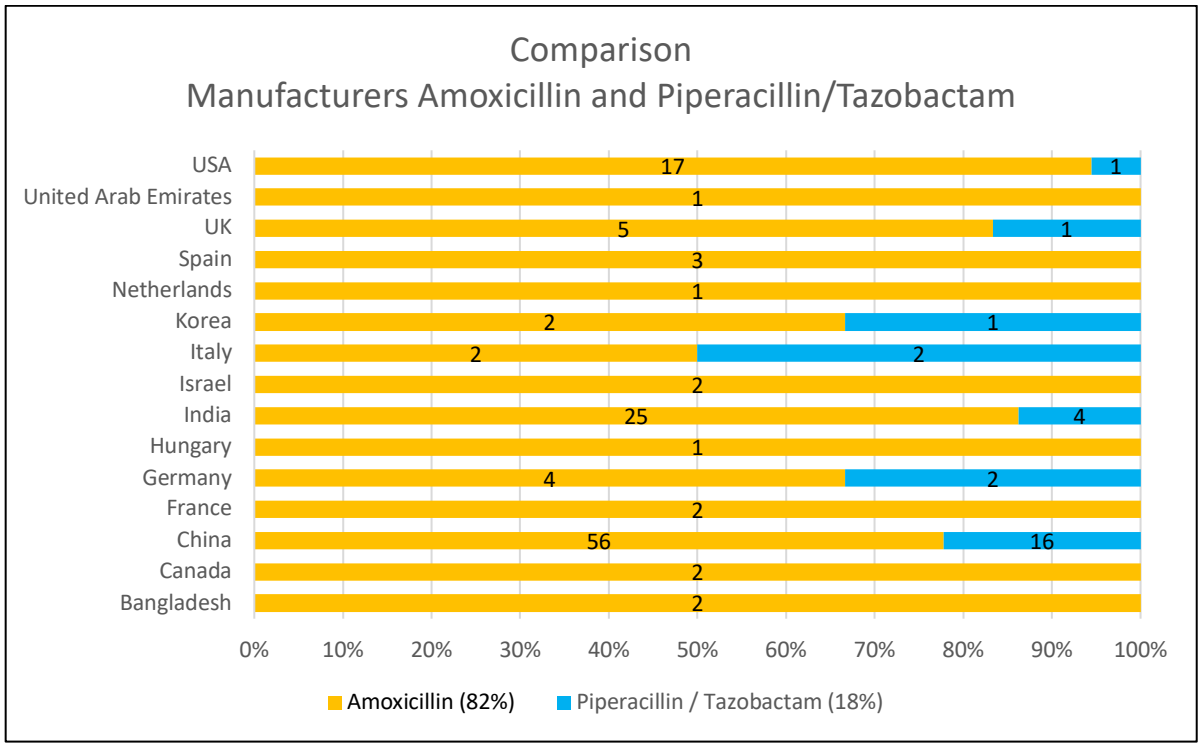

Figure 8 Comparison Manufacturers Amoxicillin and Piperacillin/Tazobactam

FDF suppliers (MAHs distributing to Sweden)

Figure 9 shows that Sweden has seven times more amoxicillin FDF suppliers than piperacillin/tazobactam suppliers. Hence, Sweden is more depended on piperacillin/tazobactam FDF suppliers of other countries compared to amoxicillin. In addition, Sweden is sourcing from a share of 71% of amoxicillin FDF suppliers and a share of 29% of piperacillin/tazobactam FDF suppliers.

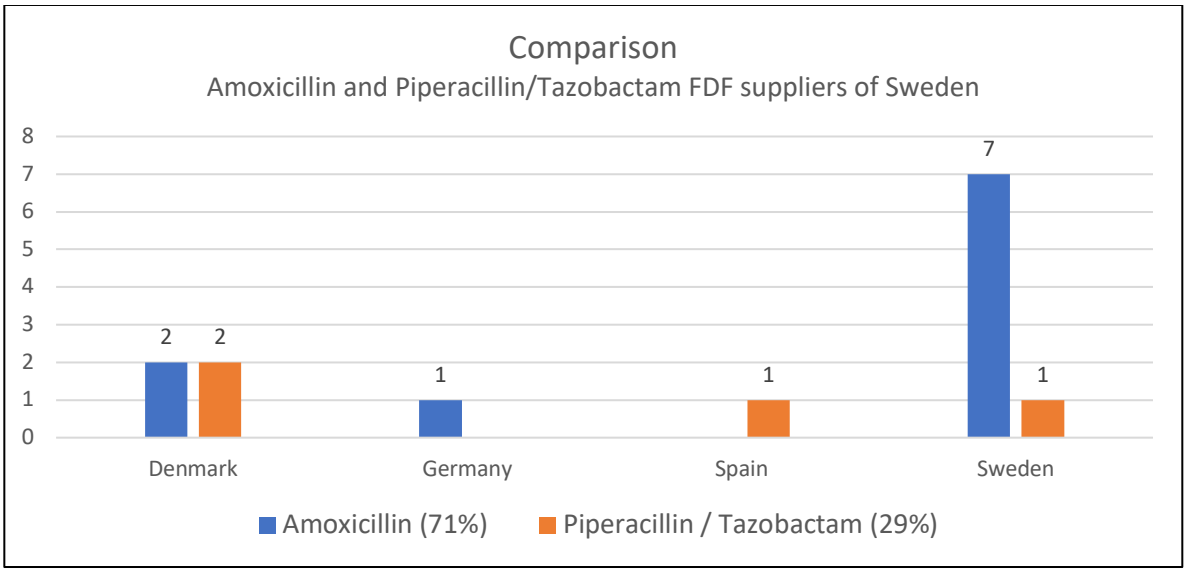

Figure 9 Comparison Amoxicillin and Piperacillin/Tazobactam FDF suppliers of Sweden

4.2.3. Stakeholders identified in the supply chain

From the interviews that have been performed, the general stakeholders have been identified along with a further categorization of most influential stakeholders, and the most susceptible stakeholders to be negatively affected by the supply chain. SCSRs as those risks triggered by stakeholders due to environmental and societal deficiencies have also been identified along with other more general supply chain risks. Also, how companies are currently managing SCSR in their business portfolio. From a total of 5 participants integrated by diverse roles within the supply chain such as generic pharmaceutical company, antibiotics' intermediary or agent, Marketing Authorization Holder (MAH), Contract Manufacturing and Development Organization (CMDO), and API supplier. Each one represents a different node from the supply chain. The gathered information aims to provide an overall insight from the antibiotics' supply chains seen from different perspectives.

General stakeholders involved in antibiotics' supply chains

There is a variety of stakeholders involved in the antibiotics' supply chains (Table 3). To begin with, all the stakeholders involved in upstream supply chain operations such as intermediate/raw material producer, API manufacturer, and FDF manufacturer. Then, the distributor, agent, and wholesaler would be part of some of the downstream supply chain operations. The MAHs are the ones authorized and have the documentation to produce and commercialize a certain drug, crucial stakeholders within the chain. Because the pharmaceutical industry is so highly regulated, all the stakeholders involved in regulatory activities are also taking part of it such as governmental authorities or medical and environmental agencies (e.g., FDA, EMA, WHO). On the other side of the chain, we would find the consumers, i.e., the patients. To finalize, external stakeholders involved which are relevant to secure that companies act responsibly are: Media, investors, academia, and NGOs. The last identified stakeholders are those indirectly affected, the local communities living near the manufacturing plants.

Table 3 Stakeholders of antibiotic supply chains

Stakeholders
Raw materials/Intermediate Supplier
API manufacturer
FDF manufacturer
Distributor
Agent
Wholesaler
MAH
Governmental regulatory authorities (e.g. FDA, EMA)
Global health authorities (e.g. WHO)
Environmental agencies
Patients
Local communities
Investors
Media
NGOs
Academia

Most influential stakeholders involved in antibiotics' supply chains

The most influential stakeholders in the antibiotic's supply chain are governmental regulatory authorities and global health authorities and suppliers. Firstly, the reason why regulatory agencies are such influential stakeholders is clearly because the industry is so highly regulated. These agencies are the ones that have most the power and responsibility within this industry because they are the ones that set the rules and the standards for the whole industry. Secondly, suppliers are also very influential in the supply chain, especially strategic raw materials and intermediate suppliers. They are influential because the whole production chain relies on them; therefore, there is a high dependency. In addition, for some antibiotics, some compounds are produced by very few suppliers, this aggravates the situation by increasing the dependency on just a few suppliers that have sudden uttermost power. A clear example of that showcase is the situation for one of the antibiotics in this study, piperacillin/tazobactam. This is a combined medicine where the antibiotic is piperacillin and tazobactam is a β-lactamase inhibitor. Piperacillin has several suppliers; on the contrary, tazobactam has very few (see Appendix 1). In addition, the few suppliers that are manufacturing the product are solely located in one country, China. This generates a situation of high dependency and power, which can be associated with higher risks to the constant global supply of medicine. The reason why it is complex to change this scenario is that China has the expertise and technology for producing raw materials and intermediates with a profit. Raw materials are often very cheap; the profit margins are extremely low. Hence, they have to be manufactured in very high volumes to generate a profit and sell them at a competitive price.

Most susceptible stakeholders involved in antibiotics' supply chains

The most susceptible stakeholders to be negatively affected by the antibiotic's supply chains are local communities that live near the manufacturing facilities and patients. The former group represent the people living near the production sites where the waste is not properly managed and hence generate soil or water contamination. People are exposed to this contamination with the negative consequences these entail. The latter group are the end-consumers, i.e., the patients; specifically, patients from emerging countries. If something goes wrong within the supply chain and ends up in delays or interruption of the supply, the ultimate affected are those who cannot get the medicine they were in need for. The negative consequences can become life-threatening in countries that do not have as many resources and do not have access to alternative treatment options. Even when the consequences are not so extreme, they are still hazardous and imply a threat in people's health such as contributing to AMR, when encountering themselves forced to use a not so effective or appropriate antibiotic for instance.

4.3. Stakeholder Prioritization

Table 4 Prioritization of Stakeholders

Most influential stakeholders (powerful)	Most susceptible stakeholders (powerless)	Stakeholders that can elevate SCSRs
Raw materials/Intermediate Suppliers	Local communities	NGOs
Governmental regulatory authorities	Patients	Media
-	-	Academia

Table 4 shows the prioritized stakeholders. As defined before, most important stakeholders for sustainability-related supply chain risk identification are stakeholders that are critical for the business and stand out. Most influential and powerful stakeholders are raw materials/intermediate suppliers and governmental regulatory because they are critical to the business. Raw material/intermediate suppliers are producing strategic raw materials and governmental regulatory authorities set the rules and standards for the whole industry. In addition, most susceptible and powerless stakeholders are local communities living near the production facilities and patients because they stood out during analyzing of secondary data, literature and interviews. Other important stakeholders for SCSRs identification are stakeholders that can elevate SCSRs, i.e. communicating environmental and social drawbacks to powerful stakeholders (Busse, et al., 2017). We identified NGOs, media and academia as stakeholders that can influence the opinion of especially governmental regulatory authorities.

4.4. Current environmental risk management performance of pharmaceutical companies

Access to Medicine Foundation (2018a) has compared pharmaceutical companies regarding environmental risk management. This benchmark consists of 18 companies: 8 large research-based pharmaceutical companies and 10 generic medicine manufacturers. The following three points are analyzed: The companies' environmental risk management performance (see Figure 10), the compliance with GMP practices, and the degree of disclosure of companies' information about environmental risk management.

First, Figure 10 shows the environmental risks management performance benchmark of the 18 companies that are in the scope. The depth illustrates if the company has an environmental risk management *strategy*, if the company verifies the strategy through *audits* and if the strategy includes discharge *limits* for specific antibiotics. The breadth shows which sites are included in the strategy, audits and limits. These sites are *own manufacturing sites*, *third-party manufacturing sites of API and Drug Products*, and *external waste treatment plants*.

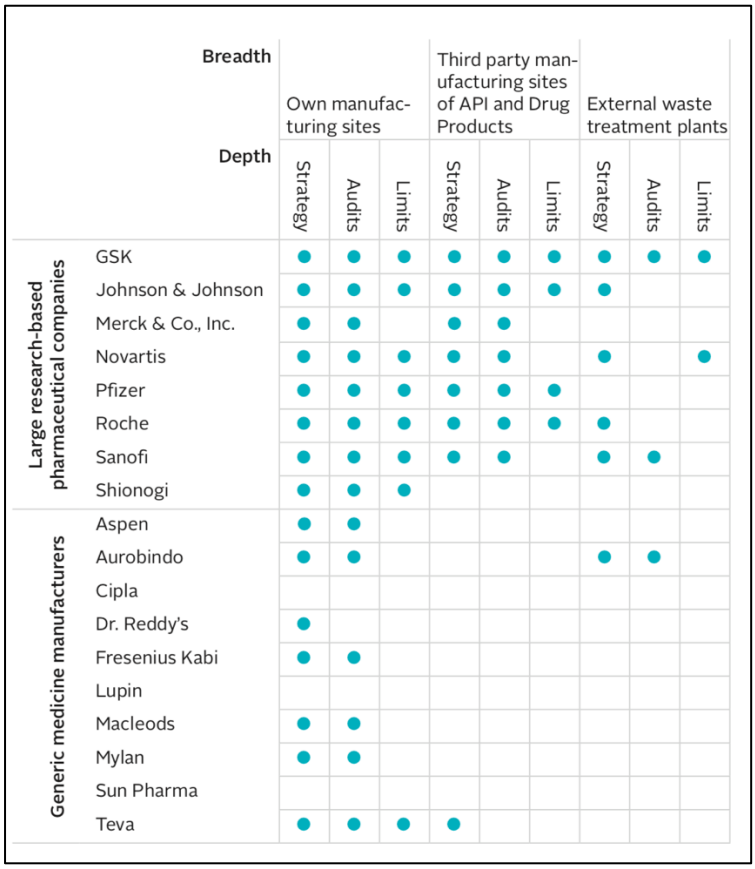

Figure 10 Environmental risk management performance benchmark (Access to Medicine Foundation, 2018a)

Almost all companies have an environmental risk management strategy. However, the depth and breadth of these strategies vary significantly. Beginning with the depth *strategy*, one can see that 15 of 18 companies have an environmental risk management strategy that includes its manufacturing sites. Only 8 of these 15 companies are including third parties in their environmental risk management strategy, and just 6 of these 15 companies also include external waste treatment plants in their strategy. Moreover, the depth *auditing* shows a similar tendency. 14 of 18 companies are auditing their environmental risk management strategy at their manufacturing plants, 8 of these companies are also auditing third parties, and only 2 companies are auditing external waste treatment plants. Furthermore, the depth *limits* show that 8 of 18 companies have discharge limits for their manufacturing plants, only 4 companies have limits for their third parties, and 2 companies have limits for external waste treatment plants. In addition, Figure 10 exemplifies clearly that large research-based pharmaceutical companies strive to integrate their environmental risk management strategy also outside their manufacturing sites. In contrast, generic medicine manufacturers are focusing nearly solely on their manufacturing plants.

So, particularly 6 companies are leading regarding environmental risk management performance: GSK, Johnson & Johnson, Company C, Pfizer, Roche, and Sanofi. However, audits of external waste treatment plants and the availability of discharge limits at third parties and external waste treatment plants should be extended in the companies' risk management strategies. Furthermore, the Access to Medicine Foundation (2018a) outlines that Pfizer also includes improvement plans in their environmental risk management strategy. That means that suppliers that do not meet environmental expectations have to improve or the particular supplier will be avoided. This performance aspect was not part of the benchmark, though, but Pfizer is an excellent example that suppliers are obligated to comply with the client's environmental performance plans.

Companies' disclosure regarding its environmental risk management strategies and companies' compliance with GMP

12 of the 15 companies that have an environmental risk management strategy are disclosing it. Nevertheless, just one biopharmaceutical company publishes identities of third-party manufacturers, which is The Medicines Company (Access to Medicine Foundation, 2018a). GSK and Roche are the only companies that reported predicted no-effect concentrations (PNECs) (F. Hoffmann-La Roche AG, 2018; Access to Medicine Foundation, 2018a). That means other companies are not publishing limits for antibiotic discharge because the companies would have to take responsibility for antibiotic discharges over a specific limit. In addition, 13 of 18 companies comply with GMP at all production sites, 2 companies comply with GMP only at their production sites, and the other 3 companies do not have evidence that they comply with GMP at all. That means that most of the companies within the scope comply with GMP what represents that these companies are manufacturing high-quality antibiotics. However, Lupin, Mylan and Pfizer have received warning letters for violating the GMP agreements in 2017. Disclosing information about companies' environmental risk management procedures is important because it allows companies to learn from other companies that will lead to a lower contribution to the environment and AMR. In addition, a revelation of antibiotic discharges and limits will allow researchers to understand the impact of antibiotic manufacturing and antimicrobial resistance better.

5. Analysis

In this section, the analysis of the empirical data is performed, and the findings are presented. Firstly, the supply chain sustainability risks for both antibiotics from the case study are identified and explained with corresponding examples. Then, a prioritization from those SCSRs is performed through risk weight quantification. Following, how SCSRs are assessed and managed from all the companies that were interviewed is explained. Every company that was interviewed represents one kind of player in the industry, aiming to provide a broad picture considering all different perspectives. Finally, the adapted framework for how to assess and manage SCSRs in the pharmaceutical industry is presented and explained in detail.

5.1. SCSRs from Amoxicillin and Piperacillin/Tazobactam

SCSRs are the risks triggered by stakeholders with an environmental or social underlying reason. Within this group, we find reputational risks (triggered by ecological and social risks), authorities', and safety risks. After analyzing both amoxicillin and piperacillin/tazobactam supply chains, the following SCSRs were identified:

- **Reputational risks:** The threats to the firm's name and generalized public view or opinion. The reputation of a company represents an intangible asset which needs to be well managed for generating profits and avoiding losses. Risks associated with reputation can be generated directly or indirectly, hence the crucial need of developing a strategy to deal with both of them. Reputational risks are triggered through various matters of social and environmental issues. Maintaining a good corporate reputation is of even greater importance in the pharmaceutical industry because the products have the purpose of improving people's health. Therefore, an industry with the ultimate purpose of enhancing people's health is more susceptible to harder public judgment.
- **Ecological risks:** Those which consequences would be harmful to the ecosystem. One example amongst the factors that can trigger this risk is when the waste is not managed or disposed correctly. This risk can have an impact on human health as a consequence of environmental contamination, as in the case of antibiotics' waste thrown in water bodies surrounding manufacturing facilities. The spread of resistant bacteria increases and propagates through the population. Additionally, other contaminants thrown to the environment can cause very harmful diseases due to the toxicity nature of the chemical not properly disposed.
- **Social risks**: These risks represent a hazard for local and global communities of people. Labor issues, workers' human rights violations, and corruption are examples of social risks. A particular example we came across during the interviews is the mafias that have emerged from local communities in India. Local communities claimed monetary compensation for the contamination they were being exposed due to the waste disposal to the environment surrounding chemical manufacturing sites. The manufacturing companies gave money as compensation for such exposure to the abnormal toxicity levels that had caused severe diseases

to some people. Since then, mafias were created to bribe the companies and get money regularly. The companies agree and deal with it as another expense they have to spend on production. Social risks go hand in hand with reputational risks both for the manufacturing company as well as the company contracting its services. In addition, a potential interruption of the supply chain could occur as a consequence of poorly management towards this situation.

- **Authorities-related risks:** The pharmaceutical industry is highly regulated. Pharmaceutical companies and suppliers must comply with the legislation to be able to commercialize the products. Auditions to supervise regulatory compliance are done regularly. Regulations within the pharmaceutical industry are especially stricter to ensure good quality of the medicines for the patients' safety. However, general to all industries, also environmental sustainability regulations are getting increasingly stricter. Therefore, by acknowledging that regulatory agencies are putting more focus on environmental sustainability to combat climate change is an increasing trend, it remains clear that the risk is increasingly higher. A remarkable example is a situation in China. Many factories that produced raw materials and intermediates, amongst others, are being shut down by the government due to a change in their regulations. Regulations have become much stricter, and many factories that did not fulfill the requisites or could not adapt in time to the new legislation have been shut down. For this reason, a big part of the market share that China has lost has been transferred to India.
- **Safety risks:** These refer to occupational hazards such as potential accidents that could occur through the production process. Safety standards differ between countries; hence, the risk might increase depending on the location. The chemicals used, like solvents, and the reactions involved, such as *thermal runaway* chemical reactions imply high hazards. This is why safety risks need to be seriously considered and managed to avoid explosions or undesired adverse outcomes. In addition to safety-related hazards, an interruption of the supply chain would be an additional negative consequence.

5.2. Prioritization of SCSRs

Table 5 Prioritization of SCSRs / Through determination of the Risk Priority Number (RPN) with help of the risk scales by Giannakis and Papadopoulos (2016) see Figure 4

SCSR	Risk level			RPN (S_i*P_i*Di)
	Severity (S)	Frequency (P)	Hazard detection (D)	
Ecological risks (directly linked to reputational risks)	*5*	*7*	*4*	-
Social risks (directly linked to reputational risks)	*5*	*4*	*6*	-
Ø Reputational risks	Ø5	Ø 5.5	Ø5	Ø137.5
Authorities-related risks	7	3	6	126
Safety risks	6	2	4	48

Severity: 1=no effect; 7=catastrophic effect; Frequency: 1=almost never; 7=almost always; Hazard detection: 1=certain; 7=impossible to detect

Table 5 shows the results of the prioritization of the identified supply chain sustainability risks. As mentioned before, the assessment and prioritization of SCSRs are based on our knowledge and perception, taking into account the valuable feedbacks from interviewed experts, company's internal knowledge and stakeholder's sources form the pharmaceutical industry. The RPN is the product of severity (S), frequency (P), and hazard detection (D). The higher the RPN, the greater is the sustainability-related supply chain risk. The risk scales overview can be seen in the table description above, and in Figure 4 (p.21), the complete risk scales are displayed.

As shown in Table 5, the reputational risks are the greatest SCSR with an RPN of 137.5. The reputational risks are resulting from the ecological and social risks because these risks are directly linked to reputational risks as explained before. Therefore, the reputational risk levels severity (S), frequency (P), and hazard detection (D) are the average of the ecological and social risk levels. Moreover, authorities-related risks are the second greatest risks with an RPN of 126. The RPN of reputational and authorities-related risks are relatively close together with a difference of 11.5 RPN. In addition, safety risks are the third greatest risks with an RPN of 48. The RPN difference between safety risks, and the second greatest risk, authorities-related risks, are relatively high with a gap of 78 RPN. In the following section, the reasons for choosing the particular specific risk levels are justified.

First, **ecological risks** have the severity *major effect,* the frequency *almost always,* and the hazard detection *moderate*. The severity is rated as major effect because the detected ecological risks, such as contaminants thrown in water bodies surrounding manufacturing facilities, affect the local community and consequently, the local community pressures the crucial raw material producers as the Indian supplier (see Appendix 2 – Interview #5) outlined. The example outlined by the

Indian supplier shows that the local community receives bribes from the companies to ensure the production of the raw material. Bribing the local community can lead to reputational risks for the primary manufacturer and consequently for the FDF manufacturer who buys from the primary manufacturer. These reputational risks can lead to financial losses for the FDF manufacturer because a buyer, i.e., an FDF supplier (MAH), can choose another FDF manufacturer that has a better reputation. Hence, the FDF manufacturer would lose a customer, which leads to lower revenue. In addition, frequency is rated as almost always because the analysis of pieces of literatures (e.g., Access to Medicine Foundation, 2018a; SumOfUs, 2015) and interviews outline that it is well known that waste of pharmaceutical production, i.e., raw material and API manufacturers, are disposing contaminants into nearby water bodies. However, it is difficult to replace these manufacturers because secondary manufacturers depend on these primary manufacturers. Moreover, the hazard detection is rated as moderate because customers of these primary manufacturers need to travel to China or India what makes the hazard detection time-consuming. However, if the customers are traveling to the locations of primary manufacturers, then it is fairly easy to detect ecological drawbacks. Therefore, the hazard detection gets the rating moderate, which represents the middle of the Likert scale.

Secondly, **social risks** have the severity *major effect*, the frequency *occasionally*, and the hazard detection *very difficult*. The severity is as the ecological risks rated as major effect because identified risks such as bribing mafia and bad working conditions are linked to reputational risks. As mentioned in the previous paragraph, reputational risks can lead to losses for the focal company. The frequency is rated as occasionally because these risks were less prominent in our research in comparison to environmental risks. For instance, only one source (see Appendix 2 – Interview #5) outlined the bribing issue of locals. The social risks are rated as very difficult because it is very hard to detect bribing because it is not conducted publicly. Additionally, working conditions are relatively simple to detect when the customer, i.e., secondary manufacturer, is traveling to the primary manufacturers to observe the existing labor conditions. However, from a distance, it is difficult to detect social risks. The hazard detection of social risks is rated as more difficult as environmental risks, mainly due to the challenging to detect corruption.

Thirdly, as mentioned before, **reputational risks** are linked to social and ecological risks and therefore, the risk levels of reputational risks are the average of the risk levels of ecological, and social risks. Thus, reputational risks have the severity *major effect*, the frequency *between frequently and usually*, and the hazard detection *difficult*. Generally, the hazard of reputational risks is difficult to detect because it is hard to identify how the information about social or environmental grievances will spread and influence powerful stakeholders such as governmental regulatory authorities. Pharmaceutical supply chains are not transparent and thus, links between primary manufacturers, that have social or environmental shortcomings, and secondary manufacturers, that buy from the primary manufacturers, are not clear. Therefore, stakeholders that reveal these links and shortcomings, i.e., NGOs, media, and academia, are a key factor that

determines how much powerful stakeholders are aware of and are influenced by these social or environmental issues. For instance, if the media is uncovering and reporting intensively about social or environmental shortcomings, it is more likely that a specific problem is more visible. This visibility of shortcomings will presumably affect the stakeholder MAH more because the respective issue is well-known in society. For example, an interviewee with the position Global Head HSE and BCM External Supply Operations at Company C outlined that she was part of a German television show around 1.5 years ago. The television show highlighted that big pharmaceutical brands such as TEVA and Ratiopharm have its production in Asia. Consequently, that announcement damaged the mentioned company's reputation.

Fourthly, **authorities-related risks** have the severity *catastrophic effect*, the frequency *infrequentl*y, and the hazard detection *very difficult*. The severity is rated as a catastrophic effect because new governmental regulations can lead to shutting downs of companies what causes directly drug shortages because the essential raw materials cannot be produced anymore. For instance, in China, due to new implemented environmental regulations by the government, many factories had to shut down because these factories did not comply with these new regulations. The frequency is rated as infrequently because governments do not introduce rapidly new regulations regarding sustainability due to the fragmented environmental law as described before (see 4.1.2 Environmental law). However, there is an increasing trend of environmental laws, and consequently, the risk level of authorities-related risks will rise in the future. The hazard detection is rated as very difficult because initiations and decisions about new regulations are not predictable.

Fifthly, **safety risks** have the severity *critical effect*, the frequency *rarely*, and the hazard detection *moderate*. The severity is rated as a critical effect because, e.g. explosions of a critical factory can interrupt the supply chain what leads directly to antibiotic shortages. An example is the explosion of the Chinese factory that was the only one in the world to manufacture the API necessary to produce piperacillin/tazobactam. The severity is a bit lower than the severity of authorities related risks because newly introduced regulations can affect more factories to shut down than an explosion. The frequency is rated as rarely because it is unlikely that a factory that is the bottleneck of raw material or API is exploding. The hazard detection is rated as moderate because it is fairly easy to detect safety risks within a factory, but it requires time for the secondary manufacturer to travel to the primary manufacturer to audit the safety risks.

5.3. How SCSRs are currently assessed and managed

Table 6 Assessment and management of SCSRS depending on the company type

Company Type	How are SCSR assessed & managed
Pharmaceutical company (MAH) – Small size (*Company A*)	• Assessing external impact of the supply chain once a year (not mention how)
Pharmaceutical company (MAH) – Big size (*Company B*)	• Initial internal training to decrease risks • Members of PSCI: International platforms that share, train, and enhance capabilities to improve social, health, safety and environmentally sustainable outcomes within the supply chains • One step forward
CDMO	• Initial audition→ ensure GMP and laws are complied Submit a CSR questionnaire (including environmental sustainability) but it is not mandatory for the supplier to comply with – The outcome of the CSR questionnaire does not affect the decision of contracting their services or not
Agent	• Customer of API (MAH or CMDO) audits the supplier • Focus on supplier's reliability: Initial assessment of risks that could produce a stop in the supply chain (initial risk assessment by the agent) • Risk assessment to ensure constant supply o Track all the steps of the supply chain up to the basic intermediates and raw materials→ Raw materials and intermediate producers are the riskiest supplier selection o Try to avoid Chinese suppliers when possible (bad reputation-low reliability)
API supplier	• Comply with the client's (MAH) requests/regulations (e.g. GMP) • Increasing efforts towards ISO standards (does not ensure a practical outcome) • When supplying for a powerful client (big pharmaceutical company) they go one step forward – comply with increasing efforts/demands from the client

How SCSRs are assessed and managed within a company differs significantly depending on three factors: The kind of company, the size, and the role they have in the industry. Our analysis intends to cover and explain the different perspectives. It is also important to point out that the mentioned factors correlate with power/influence and dependency level.

To begin with, the pharmaceutical companies can be differentiated between *Research-based* pharmaceutical companies, which focus on patented drugs; and *Generics* medicine companies, which manufacture off-patent drugs. Both of these are MAHs, which determines the right to produce the drugs from which the marketing authorization is owned. However, Research-based pharmaceutical companies have higher power compared to Generics because the profit margins in their production are much higher and have no competitors whilst the patent is valid. The bigger the company, the bigger the power and influence within the industry and over suppliers. Shall we first compare the management of SCSR between the interviewed pharmaceutical companies, one of them is small and focuses on few generic drugs (company A); the other is one of the pharmaceutical giants where they focus on patented drugs (company B), but also have a division for generics.

The differences between how company A and B assess and manage SCSRs are enormous. The public online information regarding the sustainability of Company A is limited to a two-page letter regarding antislavery policies. Contrary, Company B provides a full detailed sustainability report where they communicate their key areas and actions within corporate responsibility covering social and environmental sustainability. Considering the publicly available information plus the information gathered from the interviews, the differences between both companies become obvious. Company A solely sticks to the regulations they are obliged to comply with, without any visible assessment or management of SCSRs. In contrast, company B shows that great efforts are invested towards social and environmental sustainability, aiming to go one step further from the legal minimum standards. A thorough assessment of SCSRs within the supply chain with a plan to achieve specific goals is performed. They also collaborate in PSCI, a platform to share and learn knowledge within all actors involved in the supply chain, including external suppliers.

The third company to discuss is a CMDO, which provide manufacturing and developing services to pharmaceutical companies that own the rights to manufacture and commercialize a specific drug (MAHs). This kind of company is highly dependent on the client's requirements. This company has a strong culture where sustainability-related ideals are embedded. For this reason, they go a step further than what the law requires, but many times, this is not translated into tangible actions or results, because they do not have the final word. They, however, advice the client which of the external suppliers would be best to hire, and typically when it is not tied to an increase in cost the client agrees. However, this only works at the time of finding a new supplier, since changing an existing supplier is not possible because the contracts are based on long-term relationships and

cannot be easily broken. The window where they can promote change is rather small. Nevertheless, they have a complete sustainability report where they show with transparency the efforts that they implement in their production facilities.

The agent is an intermediary between the external suppliers and the pharmaceutical company. This role within the industry does not have too much power or influence. SCSRs are not assessed, not managed. The focus is on guaranteeing the reliability of supply, and whenever this is attached to sustainability matters, then it will be contemplated for choosing one supplier or another.

Finally, the API supplier does not perform a systematic assessment nor management of SCSRs. However, they are flexible, depending on the requirements of the client (MAH). When the client demands to increase the efforts and set higher standards of environmental sustainability, they apply them with to keep the client. The clients that demand and increase environmental standards are typically giant pharmaceutical companies that have the power and influence to do so.

5.4. Adapted framework

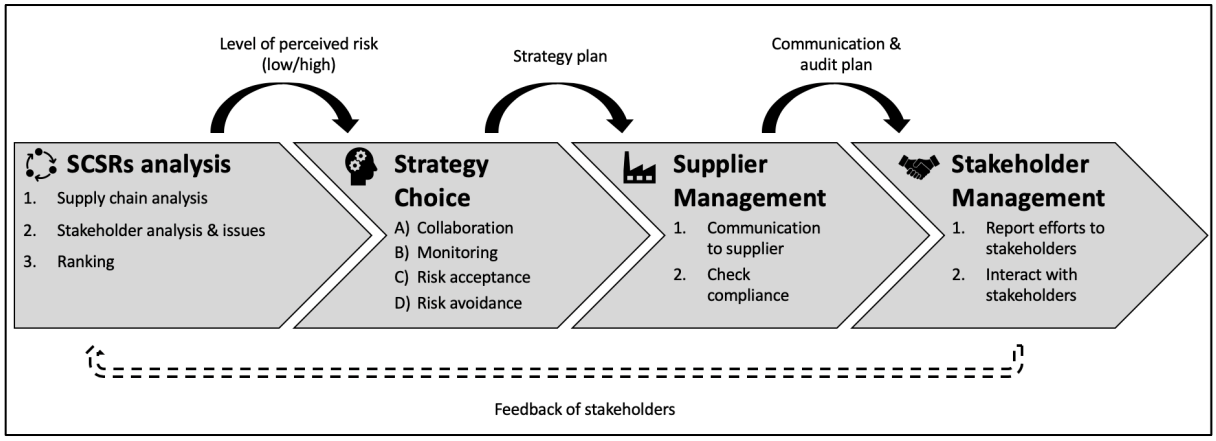

Figure 11 Proposed framework to manage SCSRs

The suggested framework to assess and manage SCSRs has been adapted to the pharmaceutical industry (Figure 11 Proposed framework to manage SCSRsFigure 11) considering all the particularities with the input of the interviews and secondary data. For the inspiration of the framework, we have considered Busse, et al. (2017), Hajmohammad & Vachon (2016), and Hofmann, et al. (2014). The suggested framework consists of 4 sequential steps, where the output of the previous step is used as the input for the next step. In addition, there are some parts that are iterative aiming to achieve continuous improvement, this circular approach is taken in the second sub-step of the first stage (*1b*) and in the last stage (*4*), where the output can be used as new input for the first step, hence achieving continuous improvement and update for the whole process. The steps and sub-steps of the frame are explained in detail below.

1. **<u>Supply chain sustainability risks analysis</u>**

   a) *Supply chain analysis*:
   Perform a thorough analysis of the whole supply chain by identifying all the stages, processes, and players involved within the chain to get insights of the broad picture and your position in it.

   b) *Stakeholder & Stakeholder issues (SCSRs) analysis – (*iterative process)*
   - Categorize stakeholders: Differentiate between *direct* and *indirect* stakeholders regarding the relationship and impact you have towards them and vice versa
   - Identify stakeholder issues (SCSRs)
   - Allocate SCSRs to stakeholders
   - Categorize stakeholders between influential/powerful and susceptible/powerless. With this, an insight on who can potentially affect you and who you can potentially affect is gained

c) *Ranking*

- Rank SCSRs with the FMEA model, which considers the severity, frequency, and hazard detection of the risks. Risk scales of Giannakis and Papadopoulos (2016) can be used (see Figure 4)
- Selection and prioritization of SCSRs and stakeholders: After ranking SCSRs, focus on the risks that have resulted in the highest value from the FMEA method (i.e., highest risk priority number). The most important will be the risks that have a higher value than the median of all the risk values (i.e., high level of perceived risk). Then, identify the stakeholders that are responsible for the selected SCSRs, these are the ones you must prioritize and include in your future strategy

2. <u>Strategy choice</u>

The strategy choice integrates and makes use of Hajmohammad & Vachon' (2016) *"Buyer-Supplier dependence matrix"* to find the optimal strategy in relation to the dependencies between the buyer and the supplier and the level of perceived risk (see Figure 3). The dependencies between buyer and supplier need to be assessed for the company considering the previous supply chain analysis in step *1a.* The level of perceived risk has been calculated in step *1c.* The focus needs to be put on high risks, but lower risks can also be considered, and a different strategy will be determined using the matrix. There are four different strategies to use: (1) *Collaboration-based risk mitigation strategy*, (2) *Monitoring-based risk mitigation strategy*, (3) *Risk avoidance strategy*, and (4) *Risk acceptance strategy*. After assessing which strategy is best for the evaluated SCSRs, another dimension, which is reputational susceptibility, needs to be revised. Some companies are more susceptible to reputational issues than others. After the strategy selection, it is important to double-check that the strategic plan does not compromise the reputation of the company when its' potential impact on the entire business is high. If it does, an additional evaluation of strategy choice needs to be performed.

3. <u>Supplier management</u>

- Communicate your strategy/action plan to your supplier (if involved)
- Check compliance on improvement plans

4. <u>Stakeholder management</u>

- Report efforts and long-term objectives to stakeholders
- Interact with stakeholders: Communication and collaboration with stakeholders are highly beneficial. Seek feedback and find updated needs from the stakeholders. Then, use this as a new input for the first step, i.e., SCSR analysis, to start the process again. This is a way to achieve continuous improvement and keep the management and assessment updated

6. Discussion

In this chapter, the interpretation of our findings in connection to the previously reviewed theory is presented. This section is characterized by critical thinking that has been applied to all the presented problems and suggested solutions/alternatives. The discussion is divided into five sections: Pharmaceutical supply chains, case study, theoretical contribution, managerial implications and limitations, policy implications, and ethical implications.

Pharmaceutical supply chains

From the review of *supply chain strategy* literature, two clear different strategic positions can be identified: Contract relationships and partnerships. The common *modus operandi* within the pharmaceutical industry is focused on long-term agreements with suppliers. Hence, partnership strategies are mainly adopted. Moreover, suppliers need to be selected carefully because once the focal company starts working together with a supplier, it is extremely difficult to change suppliers even when desired. The amount of documentation, necessary quality auditions, and confidentiality agreements amongst them is enormous; this is why it makes it so hard to change a supplier. This adds a tremendous rigidity; thus, the flexibility of the supply chains is very low.

In addition, the operations performance objectives always follow the same order of prioritization in this industry, which highly determines the strategic choice. Quality always is the most important operation performance objective, followed by cost and speed (time-to-market). Flexibility and dependability remain in the background. Therefore, agile strategies are not suitable in this industry. The lean strategy would be, in theory, highly suitable for pharmaceutical supply chains since it intends to reduce costs and lead times while increasing quality. Nevertheless, considering how fragmented and complex the supply chains are, the implementation would be highly complicated to achieve, especially for the generics industry, due to the greater outsourcing trends. Perhaps this issue could be addressed by changing the geographical location of the whole supply chain. If all the stages from the supply chain were located in a restricted geographical space, a lean approach could gain better odds to succeed, and consequently gain better lead times, quality, and cost savings.

The alternative of locating the totality of the supply chain within a restricted geographical location, let us consider Europe for the sake of this example, would come along with numerous benefits. To begin with, the risk of shortages would be lower if the production was placed locally because European countries would not be dependent on a few global suppliers located in Asia. Thus, political dependencies would be reduced, and with it, potential risks would be diminished, since there would not be such strong reliability on other countries. In addition, the environmental impact would be considerably reduced for several reasons. Environmental regulations in European countries are much stricter than in Asian countries. This is important because GMP does not cover environmental issues. Instead, national environmental regulations should be followed. Hence, by

transferring the production plants to a place where more measures need to be applied to comply with the law, the environmental impact would highly decrease. Furthermore, PNEC levels for antibiotic discharges in Europe are much more regulated, and the authorized levels are lower than those compared to other regions of the world. Therefore, the contribution to AMR through discharges from manufacturing plants could be decreased through achieving a better controlled waste management system. Lastly, the transportation of the products would be highly reduced if the production was more local. Thus, the air pollution from the greenhouse emissions that the transportation implies would be decreased, thereby helping in the fight for global warming.

This suggestion, however, would imply a tremendous increase in production costs for drugs. Economic pressures are very high, which would make it extremely complicated to implement. Also, affordability of the products would, by consequence, be reduced, and increased accessibility for medicines could be compromised, which is one of the most important aspects when considering social sustainability. Besides, the countries that are currently in charge of most of the production of drug components, especially APIs and raw materials, would suffer a considerable decrease on the amounts of jobs that are sustaining many people's lives. This is an extremely complex problem where many factors are involved, and the solution is not trivial because any change would come at a cost. Any related decision should take into account all economic, social, and environmental aspects.

Regarding the manufacturing processes efficiency, the pharmaceutical industry has always fallen behind in comparison to other industries. The reason is again, the immense rigidity and of the supply chain and highly regulated environment. Every operational process needs documentation and approval from regulatory agencies. If a change were to be implemented, no matter how small, a long process for granting the corresponding approval from regulatory agencies would be required. Hence, manufacturers avoid introducing changes when it is not necessary, to stay away from production delays and dealing with an enormous amount of paperwork. Consequently, efficiency in production processes through innovation is hindered. Nonetheless, the reasons behind are comprehensible, which rely on the nature of the products. Medicines are not mere commodities, and their production and commercialization cannot be treated as such. They need special regulations to be able to grant safety and quality for the ultimate customer, the patient.

Environmental sustainability progress within pharmaceutical chains is also affected by its characterized fracture, rigidity, and complexity. Big research-based pharmaceutical companies are the most powerful players within the supply chain excepting regulatory and authority agencies. Therefore, they are the ones that can promote change concerning sustainability issues most effectively. Indeed, big research-based pharmaceutical companies are the ones that have deeper and broader environmental risk management strategy programs in place. However, much more could be done within this field, especially concerning third-party manufacturers and external waste treatment plants. Defining discharge limits for third-party manufacturers and external waste

treatment plants is crucial for enhanced environmental performance, yet very few companies are doing it. Also, increasing audits of external waste treatment plants should be performed by all companies. Another aspect that should be managed better is to publish the predicted no-effect concentration (PNEC) levels for antibiotic discharge. Increasing transparency concerning this aspect would be highly beneficial for all the companies to learn from each other and set a suitable common standard of discharge, which would not contribute to gain increased AMR. However, the implementation of this suggestion comes with a dilemma to the companies. If they make information publicly available, they are more susceptible to public criticism and would position themselves on the spotlight for media and NGOs.

Many of the necessary changes that need to be implemented will not come from the initiatives of the corporations. Even if some have current initiatives, the effort needs to be done by all the players in the industry to achieve visible change. The suggestions that were previously discussed were based on the presumption that some efforts were already being implemented, which is the case for big research-based pharmaceutical companies. But smaller research-based companies, generic pharmaceutical companies, CMDOs, and others, have a much lower current environmental risk management performance by far. Therefore, the only possible way to ensure proper environmental sustainability management is through regulations, which has been proven to be the primary driver for change regarding environmental issues. The role of regulators will be further discussed below in *policy implications*.

Case study: Analysis on antibiotics supply chains

The ***weakest nodes*** we have discovered in the amoxicillin, and piperacillin/tazobactam supply chains are located upstream in the supply chain at the primary manufacturing sites. These primary manufacturing sites, i.e., raw materials/intermediates and API manufacturers, are mainly located in China and also in India. In the following section it is aimed to discuss why primary manufacturers are located in China and India, the disadvantages of these locations, how these disadvantages are contributing to AMR, why the location of these manufacturing sites are difficult to change, and why it is important to focus especially on environmental sustainability in the pharmaceutical industry.

Firstly, primary manufacturing sites of amoxicillin and piperacillin/tazobactam are located mainly in China and India due to the ***low costs***. In China and India, the production costs are low due to low labor costs, economies of scale, and less strict audits. In Sweden, there is a high price pressure for antibiotics, and therefore MAHs want to have low costs for antibiotics they offer. Chinese and Indian manufacturers have the capability, i.e., knowledge and technology, to produce a high amount of, e.g. raw materials what leads consequently to lower costs. Moreover, less strict environmental and safety audits facilitate the ability to produce high quantities.

Secondly, the ***disadvantages of these locations*** are that the Swedish market is dependent on China and India to obtain high-quality APIs for antibiotics and also high SCSRs which are ecological risks, social risks, reputational risks, safety risks and authorities-related risks. These mentioned disadvantages are a risk for constant API supply. Hence, the whole antibiotic supply chain of amoxicillin and piperacillin/tazobactam is mainly relying on bottleneck raw material/intermediate manufacturers what means that the supply will be interrupted in case these key manufacturers could not produce as much or the high-quality as needed in Sweden. In our case study, we identified that GMP audits that examine the quality of production, are not conducted in the first production step at the raw materials/intermediates manufacturing sites. One can criticize that the quality of antibiotics cannot be ensured if the raw materials/intermediates are not checked regarding its production quality. Moreover, ecological risks and social risks were identified in our case study. Ecological risks are, for instance, the contamination of water bodies that are located nearby the manufacturing sites, and social risks are for example that locals are demanding monetary compensation due the contamination they are exposed to. These risks lead to reputational risks for the primary manufacturer and also for the clients, i.e., the second manufacturer. Hence, clients could choose another antibiotic manufacturer with a better reputation what will lower the revenue of the manufacturer with a bad reputation. In addition, safety risks are high at raw materials/intermediates manufacturers because no GMP audits are conducted, and chemicals are possibly not handled as they should be. For instance, this led to an explosion of a key factory in China, and therefore, the whole supply chain for tazobactam/piperacillin was interrupted. Finally, authorities-related risks are high in China and India because implementation of new environmental regulations can lead to a shutdown of factories with low environmental standards and bottleneck raw material/intermediate manufacturers can be part of it. For instance, in China, many raw material/intermediate factories were shut down by the government due to new environmental regulations.

Thirdly, the outlined ecological, supply, and safety/quality risks are ***contributing to AMR***. For instance, one of the ecological risks is the waste discharge in water bodies near the manufacturing sites. Thus, APIs of antibiotics can be and are frequently part of the waste discharge due to the mismanagement in factories. Hence, bacteria acquire resistance against existing antibiotics and are present in the respective water bodies. Furthermore, these antibiotic-resistant bacteria can spread through meat, food crops if the respective water was used to irrigate these food crops, and human contact, which means the resistant bacteria can travel globally with humans as carrier and transmitter. Additionally, supply risks and consequently a shortage of a specific antibiotic type can lead to not completed treatments or usage of another more effective antibiotic type instead. Both instances give the bacteria the chance to get resistant against the used antibiotic, and for the latter instance, it means that the patient could be resistant against the more effective antibiotic which could not be used for a worse sickness in the future. Moreover, safety/quality risks could imply the production of a counterfeit or substandard drug, i.e., the manufacturing of inferior antibiotic

quality with a lower API dose than it should contain. The usage of this too low dosed antibiotic can accelerate the development of antibiotic resistance in bacteria.

Fourthly, the ***weakest nodes are difficult to change*** due to the antibiotic price pressure, missing expertise/technology, long-term partnerships, and the highly regulated industry. As explained before, the antibiotic price pressure is the main reason for having primary manufacturing sites in China and India. In addition, other countries do not have the capacity and expertise to manufacture antibiotics on a large scale which can also lead to supply risks. Moreover, the relationships between primary manufacturers and secondary manufacturers are long-term because of the highly regulated industry. For instance, it is very difficult to obtain approval from a corresponding regulatory agency and all manufacturing sites beginning from the API manufacturer must comply with GMP. These approvals are very time demanding, hence the contract agreements between buyer and supplier are long-term. Changing suppliers would imply repeating this time-consuming process over again, which could lead to production delays and higher costs. Furthermore, having as a primary manufacturer, more suppliers implies also that the cost is rising for each supplier due to audits and approvals. Therefore, having more backup solutions for primary manufacturers are not an option due to the enormous price pressure of antibiotics.

Finally, it is especially crucial nowadays to ***focus more on environmental sustainability*** due to the current environmental awareness and the fact that AMR is occurring at an increasing rate. Environmental awareness, such as climate change, leads to new environmental regulations. Additionally, the third major cause of AMR is the environmental pollution at pharmaceutical production sites, which indicates that especially in the pharmaceutical industry, new environmental regulations will be implemented. Therefore, it is important to improve the environmental standard at the primary manufacturing sites to ensure constant antibiotic supply and lower the contribution to AMR. In addition, when pharmaceutical companies tackle environmental issues, the companies' reputation will be improved, and consequently, more clients can be acquired.

<u>Theoretical contribution: Adapted SCSR Framework</u>

Initially, supply chain risk management had mostly ignored sustainability risks. Therefore, some pieces of research have tackled this research gap and proposed a different kind of frameworks to assess and manage SCSRs. However, while developing these frameworks, no firms within the pharmaceutical industry were part of the research, and therefore, we aimed to develop a framework to assess and manage SCSRs within the pharmaceutical industry. In the following part, it will be outlined how our proposed framework differs from the others.

We used the framework of Hofmann, et al. (2014) as the basis for our framework. The steps of this framework are very broad, and hence, our proposed framework has more defined steps tailored to the pharmaceutical industry. The framework of Busse, et al. (2017) was integrated into the basic framework to be able to identify and prioritize SCSRs in an industry that has a low supply chain visibility. Additionally, to assess SCSRs more analytical, the FMEA method with risk scales developed by Giannakis and Papadopoulos (2016) was integrated into the basic framework. Moreover, to specify the strategy to mitigate SCSRs, 4 specific supplier management strategies developed by Hajmohammad and Vachon (2016) are included in the framework. Inputs to determine the specific strategy are the prior determined level of risk, the buyer-supplier dependence structure, and we added the consideration of the company's susceptibility to reputational issues. If a chosen strategy is jeopardizing the company's reputation considerably, then another supplier management strategy should be chosen. In addition, we integrated an iterative approach in our proposed framework. SCSRs are triggered by stakeholders, and therefore, efforts to mitigate these risks should be communicated to them. Through this interaction with stakeholders, recommendations, and considered problems can be used as input for the first step of our framework, i.e., SCSRs analysis.

The adapted framework that we deliver integrates all the necessary aspects for the complete assessment and management of SCSRs. Any of the existing frameworks are not sufficient alone for further practical implementation. The pharmaceutical industry needs to take stakeholders, especially into account while finding a good balance between social, environmental, and economic aspects. Stakeholders' feedback is further integrated to accomplish continuous improvement. Our framework intends to serve as a guideline to achieve a balance between these three fundamental aspects taking into account the specific characteristics and necessities of any firm within the pharmaceutical industry. Both internal necessities of the firm and external necessities from the stakeholders are taken into account. In addition, the suggested model is iterative, thereby ensuring adaptability towards a dynamic environment and continuous improvement. To sum up, the proposed adapted framework contributes to academic literature within the *Sustainable Supply Chain Management* and *Environmental-related Risk management* field and also contributes to further practical implementation.

Managerial implications and limitations from the proposed framework

When applying this framework in a company, ***SCSRs will be tackled*** and also the probability of a ***constant supply of antibiotics*** or other drugs will be increased. For instance, if the antibiotic discharge at primary manufacturing sites would be assessed as a high-level risk, then a supplier management strategy would be chosen to address this issue. The supplier management strategy could be, e.g. the collaboration-based risk mitigation strategy depending on the buyer-supplier dependence strategy and the company's susceptibility to reputational risks. Furthermore, a communication and audit plan will be created for the suppliers, and afterward, the stakeholders

who are triggering this SCSR will be informed. The stakeholders could be here, e.g. the government where the primary manufacturing sites are located, and the stakeholder's feedback will be then utilized for the first step of our framework, SCSRs analysis. Hence, the supply risk of, e.g. antibiotics, would be lowered due to the proactive interaction with the stakeholders that could jeopardize the supply. Also, the SCSR, in this case, the antibiotic discharge, will be tackled, and therefore, the environmental sustainability will be improved. Consequently, the ***contribution to AMR would be lowered*** because antibiotic discharge is the third major cause of AMR. In other cases, social issues could be tackled depending on the respective prioritization of SCSRs. Another advantage of applying our proposed framework is that through the communication to stakeholders, the ***transparency regarding the company's sustainability issues will be increased***.

As mentioned before, advantages when applying the proposed framework are especially a higher probability of constant supply and a structured process to address SCSRs. Hence, environmental issues are tackled, and environmental performance will be improved. Studies showed that companies could improve their long-term economic performance when the company's environmental performance is enhanced (Beske & Seuring, 2014; Klassen & Vereecke, 2012). However, one has to consider that the short-term costs will be higher because more resources are necessary when environmental sustainability issues are assessed and managed. Additionally, a study showed that within emerging countries, better environmental performance is not leading to better economic performance (Esfahbodi, et al., 2016). In the case of antibiotic supply chains, the environmental shortcomings are occurring in emerging countries, and therefore, the change of environmental conditions has to come from companies located in non-emerging countries which also have the most influence in pharmaceutical supply chains.

Our proposed framework to assess and manage SCSRs has following limitations. First, the framework requires validation from the industry. The framework has to be presented to and used by companies within the pharmaceutical industry to confirm that the proposed framework is adequate and effective. Secondly, the application of the framework is time-intensive, and current employees need to be retrained if the capacities are available, or new employees have to be employed. Finally, the step "supplier management" of the framework can lead to a dilemma if the buyer-supplier dependence structure is supplier dominant. According to the risk management strategy matrix by Hajmohammad and Vachon (2016), the strategy "risk acceptance strategy" would result. However, if environmental or societal shortcomings are excessive, it is difficult to decide how to act in this situation. This is the case with amoxicillin and piperacillin/tazobactam because the suppliers of raw materials/intermediates and APIs which are vital for the production of antibiotics are dominant regarding the buyer-supplier dependence structure. This supplier dominance result is due to having rare capacities to produce these raw materials/intermediates and APIs in great amounts at low costs. Either, buyers are accepting the risk and consequently accepting the environmental or societal shortcomings, or they have the ability to convince the supplier to collaborate to improve these conditions.

Policy implications

As mentioned before, the only feasible way to improve environmental sustainability within the pharmaceutical industry would be through regulations. Reducing environmental impact needs of the participation of all players in the industry, not just a few. Therefore, the way of achieving so is through the implementation of common international environmental regulations, provided that the pharmaceutical supply chains are global. Interestingly, the stricter environmental regulations are placed in the countries where the production processes constitute a very reduced fraction of the whole. Therefore, it is crucial that stricter environmental regulations are implemented in the countries where most of the manufacturing facilities are located since these are the source of the highest rates of contamination. The process of creating and implementing new environmental laws is slow. However, the current trend is to increase such regulations as it has been seen in the past few years. There are two important aspects to consider: Implementing stricter environmental regulations and achieving further global harmonization. Both are important, but we believe that the latter needs more urgent implementation.

Previous efforts from the WHO and ICH have already achieved a set of common standards for the major markets: Japan, EU, and the US. These efforts need to be extended onto other markets and to environmental-related issues because the already common standards are sole with regards to quality and safety. Nonetheless, we regard environmental protection as a safety standard, given the tight interrelation between them. The clearest example is antibiotics disposal; discharge of antibiotics to the environment increases AMR, which in turn affects and creates a direct risk to human health. Other environmental examples do affect human health, but in many cases, the consequences are more visible at a long-term period, which should not be misunderstood for less necessary or urgent. Since it has been proven that regulations are the primary and fundamental driver for achieving successful change, regulatory and authorities' agencies hold the responsibility to force change in behalf of society. We do, however, acknowledge the efforts that are currently being addressed, and understand that it is a gradual process.

Ethical implications

During the past recent years, a strong belief has grown amongst a society that companies have the moral obligation to provide value to society and act as good corporate citizens. Corporations provide economic growth and development to nations, but this comes along with the responsibility of participating in the social and environmental challenges that we as a whole, face nowadays. From an ethical perspective, there are four processes that need to be taken into account: Awareness, taking responsibility, critical thinking, and action. Awareness has been raised concerning the importance of social and environmental issues, and it is increasingly growing. The second step, which is taking responsibility, includes two different perspectives: *Forward* and *backward* responsibility. The former occurs when the sight is focused on the future, from something that has provided awareness, how can that be avoided in the future. The latter implies retroactive thinking where the action that has brought awareness needs to be reflected upon and find out what was wrong and who was responsible for that to happen.

The degree of *causality* from an action refers to the strength level from which A is responsible for B to happen. This relationship can be stronger or weaker, more or less direct, depending on the context of the events. The degree of causality is a relevant condition that affects the process of allocating responsibility. The stronger the degree, and the more direct one action has been responsible for causing the next action, the stronger the responsibility. This factor is what has made society realize that corporations need to take a proactive involvement towards societal and environmental issues. Given that corporations create consequences to both society and the environment, they have to take accountability for their actions. When considering the process of taking responsibility, there are other conditions that influence, and these are *capacity* (ability to act), *knowledge*, and *freedom to ac*t. We assume that all companies within the pharmaceutical industry have the capacity, knowledge, and freedom to act as responsible entities. Therefore, focusing on the future, *forward responsibility* is allocated to corporations. Corporations have a consequent obligation to act upon the issues they are responsible for and where they can contribute to creating a better society.

For this reason, integrating corporate social responsibility within companies' business portfolios has become increasingly common, yet it has not been accomplished by all firms. This has happened mainly as a consequence of the harder demands from society; the outcome from corporations is no longer acceptable to purely return to shareholders and products. The public perception and reputation of a firm affect its operational capability. Hence, the more susceptible a company is from its reputation, the higher the efforts that will be implemented towards sustainability. The pharmaceutical industry has also embraced this trend; however, more barriers are encountered in this particular industry due to higher expectations from society and also due to the complexity and rigidity of the supply chains. The social responsibilities that are entitled to corporations are harder in the pharmaceutical industry because the products are medicines, and hence are not judged like any other simple commodity. The root cause for a harsher judgment towards the pharmaceutical

industry is the common belief that access to health is a human right. Therefore, the social burden carried by corporations from this industry ends up being higher.

Then, having a strong CSR program in pharmaceutical companies become also an opportunity due to the importance that stakeholders link to it. This will provide a competitive advantage to the company and by consequence increased turnovers. This ideal *win-win* situation is however, hard to implement. If we consider the example mentioned earlier in the discussion chapter, a change in the geographical location on the upstream of the supply chain could have many benefits concerning environmental aspects, but then would compromise other social aspects like accessibility to medicines. Naturally, achieving good economic performance is fundamental for the company to exist and continue developing new drugs. Finding the right balance between social and environmental sustainability and good economic performance for the company is extremely complex. Something we find very important is to increase transparency within the supply chains. If direct and third-party suppliers were openly disclosed, everyone involved in that supply chain would take care that the actions from everyone follow a similar ethical style as its own. The reason is that any malpractice made by a third-party could be linked to the focal company, even indirectly. The reputation would be affected, and hence, it would be desirable to avoid any malpractice for the good of all. Nevertheless, this would position companies on the spotlight, and the susceptibility of the corporation would highly increase, thus the reason why they want to remain less transparent.

7. Conclusions

RQ1: What sustainability risks do the supply chains of the antibiotics have for its constant availability in Sweden?

*We have concluded that the antibiotics' SCSRs are**: Reputational risks, ecological risks, social risks, authorities-related risks,** and **safety risks**. Also, the stage in the supply chain that poses the heaviest risk for ensuring constant supply is **the primary manufacturing phase** of the supply chain.*

This research aimed to identify the sustainability risks from antibiotics' supply chains that compromise the constant availability of antibiotics in Sweden. From the case study findings, we were able to identify SCSRs involved in amoxicillin and piperacillin/tazobactam supply chains. The findings from the analysis of secondary data provided additional insights for a broader variety of antibiotics. Taking both findings into consideration, we can conclude that the antibiotics' supply chain sustainability risks are: Reputational risks, ecological risks, social risks, authorities-related risks, and safety risks. In addition, based on the thorough analysis from the antibiotics' supply chain structure we conclude that the most susceptible node from the whole supply chain is located upstream in the supply chain, i.e., primary manufacturing phase. More specifically, the stage where raw materials and intermediates are manufactured poses the most vulnerable node of the totality of the chain.

RQ2: How can the supply chain sustainability risks be managed in the pharmaceutical industry?

*SCSRs can be effectively and fully managed by companies in the pharmaceutical industry using the **adapted framework** that we have developed.*

We explain how SCSRs in the pharmaceutical industry can be managed. For this purpose, different available frameworks for assessing and managing SCSRs were explored and analyzed. Furthermore, we identified the singularities and barriers encountered in the pharmaceutical industry. As a result, an adapted framework for assessing and managing SCSRs within this industry was developed. Therefore, the **adapted framework** that is proposed suggests an iterative process with four main stages where (1) SCSRs are identified and analyzed, (2) the strategy that best fits is chosen, (3) management of suppliers and (4) management of stakeholders is performed. The latter stage takes the feedback from the stakeholders and uses it as input to start the process again. Therefore, constant improvement and update of stakeholder issues are ensured. This framework shall be followed by companies within the pharmaceutical industry and intends to serve as an assistive tool to achieve effective management of SCSRs, and hence improve overall sustainability.

Nevertheless, our findings also suggest that sustainability-related change is primarily driven by regulations. Therefore, the stakeholders that can influence the most in achieving higher environmental and social sustainability standards are regulatory authorities. More specifically, stricter environmental regulations should be installed in the manufacturing process stages to achieve sustainable development. Given that antibiotic supply chains have low visibility and are complex, results would become unlikely to achieve otherwise.

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Appendices

Appendix 1: Identified main actors involved in both supply chains & Outlined structure

Amoxicillin

Primary Manufacturers

I. Intermediate Manufacturing: 6-APA

The fermentation of the intermediate 6-APA forms the basis for amoxicillin production (Roland Berger GmbH, 2018). Roland Berger GmbH (2018) illustrates that there are six relevant 6-APA producers in total. However, four of the six 6-APA production sites are in China. This shows a strong dependence on China for the intermediate 6-APA. Conducted interviews (e.g. Interview #2) show that most likely the other two relevant 6-APA producers are located in India.

II. API Manufacturing

Table 7 Location of API manufacturer (Amoxicillin)

Location of API manufacturer (Amoxicillin)	Amount
Hungary	1
Netherlands	1
United Arab Emirates	1
Bangladesh	2
Canada	2
France	2
Israel	2
Italy	2
Korea	2
Spain	3
Germany	4
UK	5
USA	17
India	25
China	56
Grand Total	**125**

The table above shows that China has the most API manufacturer for Amoxicillin, followed by India and USA. One can see that other countries have significantly fewer API manufacturers for Amoxicillin. For instance, the UK have only 5 Amoxicillin API manufacturers and China has 56 manufacturers. So, China has 11.2 times more Amoxicillin API manufacturer than the UK, and the UK is according the data analysis the fourth biggest Amoxicillin API producer.

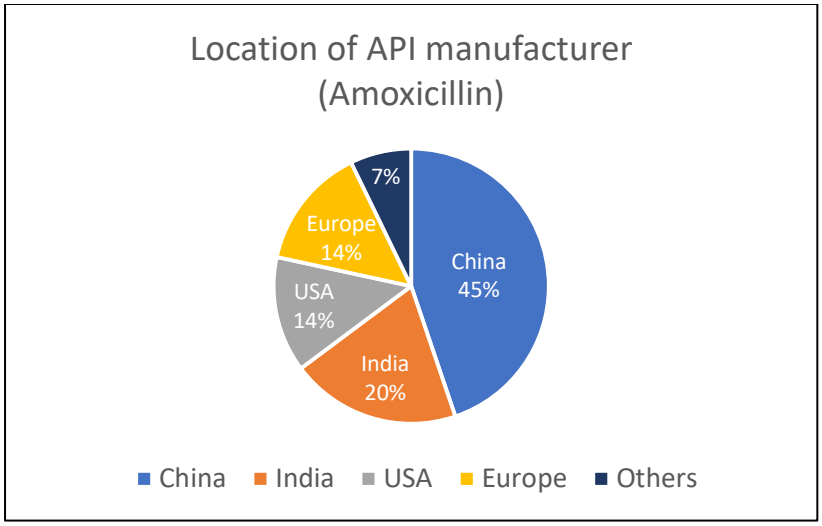

Figure 12 Location of API manufacturer (Amoxicillin)

The pie chart above shows that China has a share of 45% of all Amoxicillin API manufacturer. This means that almost half of all Amoxicillin API manufacturers are Chinese. India has a share of 20% and has therefore the second most Amoxicillin API manufacturers.
Figure 12 illustrates that USA and Europe have both a share of 14%. Hence, the amount of all European Amoxicillin API manufacturers is the same as Amoxicillin API manufactures of USA. Other countries, such as Israel and Canada, have only a share of 5%.

III. FDF manufacturer (supplying to Sweden)

Table 8 Location of FDF manufacturer (Amoxicillin)

Location of FDF manufacturer (Amoxicillin)	Amount
India	1
Sweden	1
Slovenia	1
Germany	1
UK	1
Malta	1
Austria	1
Unknown	5
Grand Total	**12**

Table 8 illustrates the Finished Dosage Form manufacturers where Sweden's suppliers are sourcing from. The sum of Table 8 has with an amount of 12, two more manufacturers as suppliers of Table 9. This is because two Amoxicillin FDF suppliers are sourcing from two different manufacturers. Table 8 illustrates that there is only one Amoxicillin FDF manufacturer within Sweden. One manufacturer is located in India, other five manufacturers are spread within Europe and the location of five manufacturers is unknown.

IV. FDF suppliers (distributing to Sweden)

Table 9 Location of Finished Dosage Form suppliers (Amoxicillin)

Location of FDF suppliers (Amoxicillin)	Amount
Denmark	2
Germany	1
Sweden	7
Grand Total	**10**

In Sweden, Amoxicillin is provided by ten different companies. Seven suppliers of Amoxicillin FDF are located in Sweden. These suppliers represent 70% of all suppliers Sweden are sourcing from. Sweden is purchasing from two Danish Amoxicillin FDF suppliers and from one German supplier.

Primary Manufacturers and Distributors

I. Intermediate Manufacturing
II. API Manufacturing

Table 10 Location of API manufacturer (Piperacillin/Tazobactam)

Location of API manufacturer (Pip/Taz)	Amount
Korea	1
UK	1
USA	1
Germany	2
Italy	2
India	4
China	16
Grand Total	**27**

The table above illustrates that there is a total of 27 Pip/Taz API manufacturers. China has with an amount of 16 the most production sites for Pip/Taz API. India has four production sites and has therefore the second most Pip/Taz API manufacturers. Moreover, Italy and Germany have each two production sites for Pip/Taz API and hence share the third place for having the most Pip/Taz API manufacturers. Table 10 emphasizes that China has four times as many manufacturers for Pip/Taz API as India.

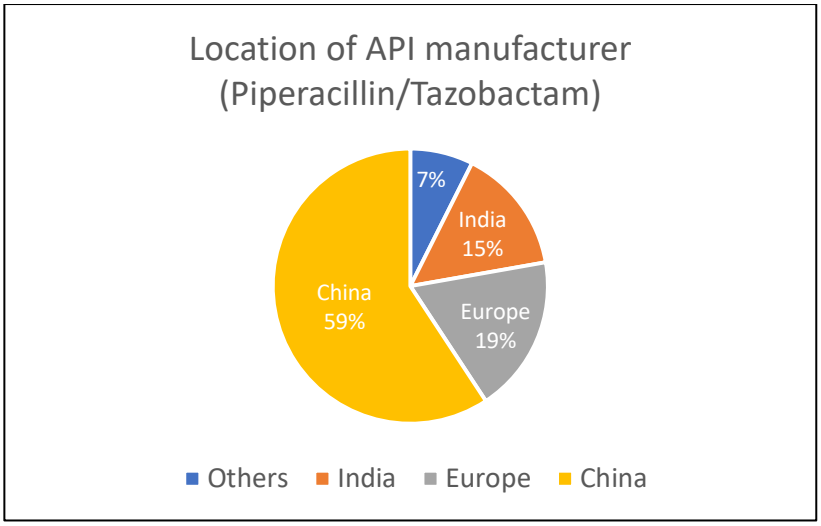

Figure 13 Location of API manufacturer (Piperacillin/Tazobactam)

The pie chart above shows that China has the biggest share of 59% of Pip/Taz API manufacturers, Europe has the second biggest share with 19%, followed by India with a share of 15%. Other countries, i.e. Korea and USA, have a share of 7%.

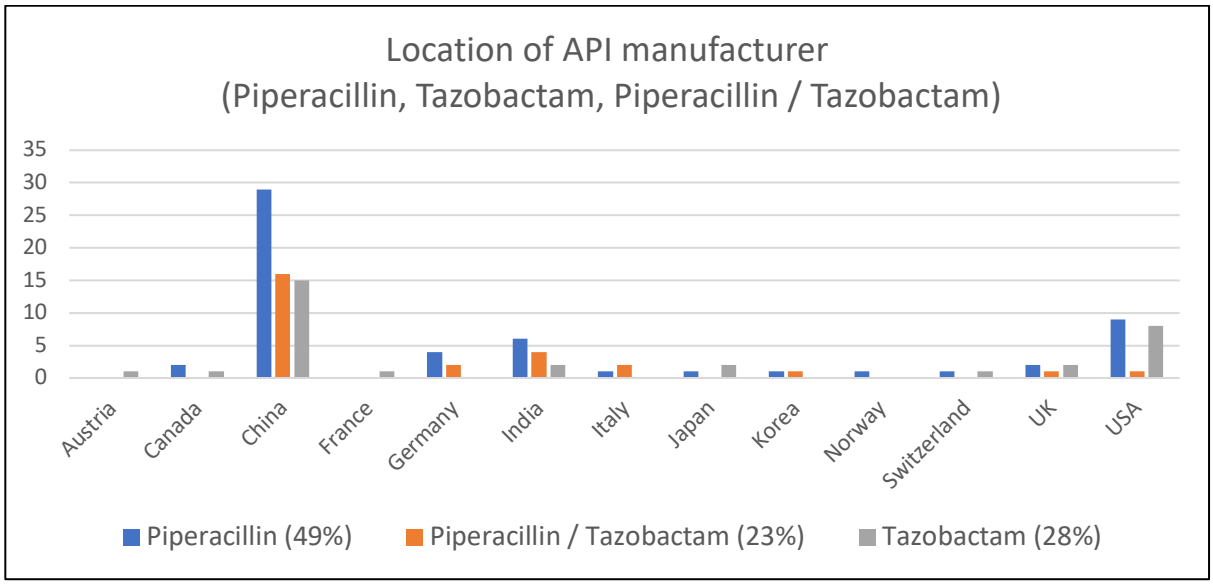

Figure 14 Location of API manufacturer (Piperacillin, Tazobactam, Piperacillin / Tazobactam)

Figure 14 compares the amount of API manufacturers of Piperacillin/Tazobactam, and of Piperacillin and Tazobactam separately. Piperacillin has the most manufacturers with a share of 49%. The three countries that have the most manufactures for Piperacillin are China, USA and India. In addition, Tazobactam has the second most manufacturers with a share of 28%. The countries that have the most manufacturers for Tazobactam are China and USA. India, Japan and the UK have each two Tazobactam manufacturers and share the third position for having the most Tazobactam manufacturers. Hence, Tazobactam is less produced than Piperacillin and Tazobactam

is therefore the bottle neck for producing Piperacillin/Tazobactam. Moreover, Piperacillin/Tazobactam has the least manufacturers with a share of 23%.

Secondary Manufacturers and Distributors

III. FDF manufacturers (supplying to Sweden)

Table 11 Location of Finished Dosage Form manufacturer (Piperacillin/Tazobactam)

Location of FDF manufacturer (Piperacillin/Tazobactam)	Amount
Italy	2
Portugal	1
Spain	1
Austria	1
Grand Total	**5**

Table 11 illustrates the Finished Dosage Form manufacturers where Sweden's suppliers are sourcing from. The sum of Table 11 has with a sum of 5, one more manufacturer as suppliers. This is because one Piperacillin/Tazobactam FDF supplier is sourcing from two different manufacturing companies.

IV. FDF supplier (distributing to Sweden)

Table 12 Location of Finished Dosage From suppliers (Piperacillin/Tazobactam)

Location of FDF suppliers (Piperacillin/Tazobactam)	Amount
Spain	1
Sweden	1
Denmark	2
Grand Total	**4**

In Sweden, Piperacillin/Tazobactam is provided by four different suppliers. One supplier is located in Sweden, two in Denmark and one in Spain.

Appendix 2: Interviews

Interview #1 – Director Pharmaceutical company (MAH) – Small size (Company A)

About the interviewee: The interviewee is the director from Company A, responsible for managing the division in UK, Ireland and Nordic countries, and used to be country manager at Company X
The company: Generic pharmaceutical company based in the UK with headquarters in Uxbridge. Company A is an independent division from Company X It is a small company with a manufacturing site in Bangalore, India.
Relevance: Company A is an Amoxicillin/Clavulanic acid supplier for Sweden.

No.	Desired Outcomes	Questions	Answer
Questions for theoretical framework			
1	Identify main actors involved in Amoxicillin & Pip/Tazo supply chains	What main actors are involved in the Amoxicillin supply chain that is delivering to Sweden?	The supply chain that is involved in the supply to Sweden for Amoxicillin/Clavulanic acid is: The 2 APIs for this antibiotic are outsourced. Amoxicillin API is contracted from India and/or China, and Clavulanic acid is purchased in Mexico. The finished product is manufactured in the facility they own in Bangalore, India. Then it is sent to the UK to check the quality and then it is sent to Swedish facility to do the distribution.
2	Outline the structure of both antibiotic supply chains + Supply chain control	Can you outline the structure of this amoxicillin supply chain? As a part of Company A mission/vision statement in the web, it says that the company specializes in providing quality and added value by "a guaranteed, reliable and controlled pharma supply chain". How is the supply chain controlled? Do you monitor the external supplier sites? Environmental aspects?	(India/China + Mexico → Bangalore (India) → UK → Sweden) Outsource production of both APIs. Particularly, Amoxicillin API can come either from China or India. Clavulanic Acid can come from Mexico or Austria (Biotica, Sandoz). They do not control the third-party sites, because it is manufacture. He does not think that anyone would have an intention to disrupt the supply chain. They have their own water management system. He does not regard any risk.
3	Identify Stakeholders of both supply chains	What are the stakeholders that influence or are affected by this supply chain?	No aswer.
4	Identify SCSR (stakeholder issues) of both supply chains	What are current stakeholder issues (sustainability supply chain risks) of this supply chain?	He does not see any risks regarding to stakeholders.

5	Identify how the SCSR of both antibiotics are assessed and managed currently	In the CSR section of your webpage you only address anti-slavery policies. Do you consider more aspects of social responsibility besides anti-slavery? If yes, which ones? **How do you assess and manage these SCSR currently? So, how are the risks prioritized and managed?	They assess once every year if there is any external impact on the supply chain. It is a constant process where they keep assessing every year and reassess 2 different molecules every month (from 14 molecules they have in total, which 10 are API or intermediaries so there are no issues there), but for the other 4 they keep assessing it. If there is any package 'rip?' always trying to keep 2 different suppliers
Additional Questions			
6	Company A role in the Amoxicillin supply chain	Is Sweden producing the API or the end product of Amoxicillin? Or is Company A only a distributor? (You commercialize in many countries in the EEA (EU) like France, Portugal, Spain... what differences are there with the countries you have a facility like in Sweden and the ones that not?)	Every country's regulatory requirements are different, so they look at the requirements from each country and also the product and what is launched. Based on that they do it one way or another.
7	Relationship to COMPANY X	Is COMPANY X producing the API for amoxicillin? Still active relationship with COMPANY X?	They are a division from COMPANY X but independent in the sense of managing and controlling their work.
8	Recommendations for other interviewees	Do you have some recommendations for other persons that could be helpful for this study?	Can't disclose names.

About the interviewee: Company B works as an intermediary for several medicine compounds including synthetic antibiotics. He is connecting especially the Indian supply with the European demand. His company is only dealing with synthetic, excluding semi-synthetic and fermented antibiotics. The reason is that synthetic antibiotics can be produced in the same plants as other products, since semi-synthetic and fermented antibiotics need different manufacturing plants because it requires a different process to produce and to avoid cross-contamination.
The company: Consultancy (2 employees). It is a very small company focused on providing intermediary services between Indian manufacturers and Spanish pharmaceutical companies, and also consultancy services for Spanish pharma that want to grow across different markets. The company is formed by the father who had been working for 30 years in the pharmaceutical industry, and then realized he wanted to do work by his own, knowing the industry and having some contacts. His son then joined the company (our interviewee).
Relevance: Experience with work relationships with Indian API suppliers and European pharmaceutical companies. Insight to understand such relationships.

No.	Desired Outcomes	Questions	Answer
Questions for theoretical framework			
1	Identify main actors involved in Antibiotic supply chains	What main actors are involved in the antibiotic supply chain?	**Chinese manufacturers**: producing the *basic intermediaries/raw materials*. They are focused on mass production, are therefore cheaper and also have low labor cost. Additionally, the advanced intermediaries are either produced also in China or in India. **Indian manufacturers:** supplying the *API (2 or 3 batches a year, depending on the customer).* India has been stricter in terms of environmental regulations. **Other country's manufacturers** are also supplying the APIs for the antibiotic (e.g. Spain and Italy). However, China and India have the biggest market share. **Company that produces finishes dosage:** imports the API and finishes the product. SPAIN: If it has the commercial capability, then the drug will be named or if not, then another company will be licensed that commercializes it. GERMANY: distribution through tenders. So, there is a transparent competition between suppliers and the best suppliers (in regard of price, quality, etc.) will be chosen. USA: finished dose will go to the wholesaler (e.g. Walgreen) and then it will be delivered to pharmacies/hospitals.

			Agent: connecting two points and getting commission. **Distributor:** buys and sells.
2	Outline the structure of the antibiotic supply chains + Supply chain control	Can you outline the structure of the antibiotic supply chain? How is the supply chain controlled? Do you monitor the external supplier sites? Environmental aspects?	**Based on activities:** 1. Route of synthesis: raw material → add step by step additional intermediary (every intermediary has its own name) → API 2. API sold to the company that produces the finished dosage form 3a. Finished dosage form will be commercialized (if commercial capability) 3b. Finished dosage form will license another company to commercialize it 4.. Spain: Product sold to pharmacies/hospitals. **Based on countries (biggest share)**: China (raw material) → India (API) → agent/distributor → Europe (finished dosage producer); but nowadays in China factories had to shut down within the last year due to environmental regulation introduced by the government. So, India is relatively producing now more raw material than in India. **Control of supply chain:** The company that produces the finished dosage (*the customer*) has to audit the supplier (i.e. the API producer), need the written confirmation (specific audit for each product) and it is compulsory in Europe that the supplier has the GMP certification. **Environmental aspects:** Suppliers put effort to improve environmental/societal conditions to show the effort and improvements to the customer. India was stricter than China in term of environmental regulations. Since last year, China has new environmental requirements and many pharmaceutical factories had to shut down. Part of the industry moved from China to India. **Supplier selection (1=most important; 5=least important):** 1. Reliability 2. Technical knowledge 3. Environmental behavior 4. Price If the API is exclusive, the customer (company that produces the finished dosage) wants to make it secret who the supplier is. So, other customers cannot offer higher prices and take away their supplier.

3	Identify stakeholders of both supply chains	What are the stakeholders that influence or are affected by this supply chain?	1.Government (regulations) 2. Supplier (regulations and demands) 3. Agent (decides which are the most reliable)
4	Identify SCSR (stakeholder issues) of both supply chains	What are current stakeholder issues (sustainability supply chain risks) of this supply chain?	Government China - introduction of regulations
5	Identify how the SCSR of both antibiotics are assessed and managed currently	How do you assess and manage these SCSR currently? So, how are the risks prioritized and managed?	The API customer is auditing the supplier or assigns an auditor to do it. He, as an agent, is looking for reliability, and is therefore regarding the risks that could interrupt the supply chain. He saw what in China happened due to the environmental regulations, and therefore is also moving towards Japan.
Additional questions			
6	Company's role in the antibiotic supply chain	What is the company's role within the supply chain?	Agent between API producer and company that produces the finished dosage.
7	Identify API producers	Which are the factories that you buy the API from?	Only mentioned countries: India (most of it), China and Japan. You can look at https://www.aemps.gob.es/home.htm who is supplying piperacillin/tazobactam or amoxicillin in Spain.
8	Recommendations for other interviewees	Do you have some recommendations for other persons that could be helpful for this study?	Supplier from India. We can meet the supplier from the 6th to the 10th of April.

About the interviewee: The interviewee has been working mostly in sustainability issues in supply chains for pharmaceuticals for the last 4 years. Currently working at Company C.
The company: Company C is a multinational pharmaceutical company based in Basel, Switzerland. The subdivision from Company C that produces generic pharmaceuticals is Sandoz and is one of the biggest antibiotic producers in the world.
Relevance: Highly valuable insight. She is one of the best at her position in the industry, with expertise in environmental issues within supply chains.

No.	Desired Outcomes	Questions	Answer
1	Important factors when choosing an external supplier	What factors do pharmaceutical industries consider during a decision-making process? Is it only the cost factor that matters?	- Location - Finance - Reliability - Quality - Technology level - Environmental health & safety and labor rights
2	Rank important factors mentioned before in generics industry	On a scale from 1 to 5, with 1 being the least considered factor and 5 the most, how would you rate the factors implanted in generic supply chains?	5- cost 4- good at supplying, quality & reliability 3- responsibility of the supplier
3	Multiple outsourcing possibilities when considering time-to-market	As time-to-market is a critical factor in the pharmaceutical industry, is there a possibility that an MAH will outsource its operations to more than one contract manufacturing organization in order to achieve faster lead-times?	Yes, dual source supply is a common strategy to secure the system. Specially for intermediates or starting materials. But then it implies a double inspection, more effort, but risk reduction.
4	Outsourcing possibility rating for generics and on-patent pharmaceuticals	Could you rate how often this outsourcing possibility exists in both branded and generic supply chains?	High frequency. Especially raw materials like chemicals and solvents, strategic raw materials and intermediates. API depending on the involved technology may want to do it in-house. The more advanced the drug is, the more you want to keep it in-house to keep control of it.
5	Advantages and risks associated to off-shoring operations	What are the possible risks that are associated with offshoring operations? Can you also talk about the advantages?	Advantages: - Mutual learnings - Innovation - Cost reduction Risks: - Ecological risks

			- Authorities risks - Safety risks - Quality risks - Reputational risks - "Oversight" risks - Supply risks
6	Rate off-shoring risks	Which risks would you rate to be the highest, lowest and moderate?	Hard to rate. **Quality** is always highest risk. Internal trainings to decrease risk. Pharmaceutical Supply Chain Initiative (PSCI), platform for sharing and training and enhancing capabilities. **Commitment of supply** risk is another important one, to deliver on-time in-full (DIFOT). **Data security** is another big topic. Hard to monitor **environmental** risks online because the follow-up is made in paper documents→ not too much reliability.
7	Profit distribution at upstream supply chain: generics vs. on-patent pharmaceuticals	How does profit distribution vary in the upstream supply chain among different operations with regards to branded or generic drugs manufacturers?	In general, for Company C the profit is 32% for the entire business but the generics is much lower. How each packet is distributed she does not know.
8	Outsourcing frequency for generics and on-patent pharmaceuticals	How often is it outsourced from the unpatented drugs? Like API, we have an assumption that the branded drug manufacturers have most of their processes in-house because it is a new drug and maybe they don't want to get it out due to exclusivity, so how often are API manufacturing (primary manufacturing) and formulation (secondary manufacturing) processes outsourced by unpatented drug producers?	When the patent expires, so it becomes a **generic**, the trend is to move towards outsourcing including formulation. For **on-patented drugs** the aim is to have control over the production, the API is preferable to keep it in-house also, but perhaps some of the previous steps can be outsourced. There is, however, an increasing trend for outsourcing. Depends also on the special technology that is required for the production. Sometimes if the pharma company does not have the technology there is possibility to out-source to avoid risks of lacking knowledge. For strategic drugs the development is kept close by so that there is an increased control over it.
9	Core activities' differences between on-patent and off-patent pharmaceuticals	How do core activities of an innovator company and generic drug company vary?	2 completely different mindsets. **ON-patent pharmaceutical companies:** move slower, time plan. High investment in the upfront sales. It is a long process whilst the patent is on so no worries about competitors. Changes are done slow and steady. **OFF-patent pharmaceutical companies:** (generics) have to move

			really quickly. Rapid decision-making and usually these two people don't understand each other. Also, the resources at the generic facilities have less manpower than in patented drugs facilities
10	Optimization of core operations	Are outsourcing or offshoring decisions made by companies to optimize their core operations?	Yes, it is to optimize the core operations. One of the examples I said before was about technologies, when you don't have it in-house. Another offshoring that could happen is when you need to release a drug in a country and that country says you need production here, so then you might need to find a partner in that country, some countries have these requirements, that you need to be present in the country, like Bangladesh for instance.
11	Outsourcing core activities in on-patent pharmaceuticals?	How often are these decisions influenced by the choice to focus on core operations in the branded drug market? Can you rate them?	Not that often, it happens, but it would be more in the generics business.
12	What motivates a company to out license?	Out Licensing is more prominent in branded drug market, what are the different factors that motivate the focal firm to brand other manufacturers license to manufacture their product in different countries?	Yes, when it comes into the different markets so maybe you have a partner that markets your drug in the U.S. because you don't have the sales channels for example, so there is a lot of crossover happening. Here in Basel for example there is a company called Roche and Company C sell their product but in a different market, so we are partners rather than competitors.
13	Vertically integrated supply chain profitability in generic vs. patented pharmaceuticals	Is vertically integrated supply chain profitable in generic drug market when compared to a branded (patented) market?	It needs to be profitable otherwise they don't survive. If you look at these Chinese and Indian suppliers for example, they are completely vertically integrated. They have the entire supply chain in-house and they also go for huge volumes. So, I think you can see to their volume production, I mean the production plant of that, but they do a big investment to do the whole vertical integration of the supply chain

14	Most patented producers operate in vertical-integrated fashion?	Do most on-patent drug producers operate in a very vertically integrated fashion?	Not sure, but it feels like it. It feels like they've got all of the steps, the ones I have seen have got everything in-house, with many customers as well, but many of them actually release their drugs in their own name to the local market.

About the interviewee: Three employees from the company participated in the interview. Two employees have the job title *Director Corporate Projects*, and one has the job title *Director Global Procurement*.
The company: Company D is a Swedish Contract Development and Manufacturing Organization (CDMO), a company that provides services from drug development and manufacturing to other pharmaceutical companies which are Marketing Authorization Holders.
Relevance: Company D has addressed efforts towards social and environmental sustainability issues since their beginnings. Their experience in sustainability, integrated in the company's portfolio since the start and part of their culture, provides highly valuable insight.

No.	Desired Outcomes	Questions	Answer
Questions for theoretical framework			
1	Structure of antibiotics supply chain. Specific information on amoxicillin and Pip/Tazo supply chains.	Can you outline the structure of the antibiotics supply chain (if possible: amoxicillin and piperacillin/tazobactam)?	**Piperacillin/Tazobactam:** The main suppliers of the starting materials are located in China, and a couple of companies of the whole Pip/Tazo API are in India, but still many purchase the intermediators from China. The number of suppliers for Pip/Tazo are much less when compared to Amoxicillin. In addition, the number of suppliers for Piperacillin alone are more abundant than for Tazobactam alone, there are very few suppliers of Tazobactam, and they are located in China. When choosing suppliers, it is important to assess the reliability – Risk management. Some suppliers have the final mix, but it is interesting to see where their raw materials come from, also for price. Company D as a CMO recommends changes and if they are not too costly to implement the client, i.e., MAH, usually accepts the change. Once you choose a supplier, it is a long-term commitment very hard to change. If they have ISO 14001 you know that they checked upstream. This is useful when they search for a new supplier for instance, it gives security and trust. Now it is more often that their customers have 2 audits separately, for Company D is more of a hygiene

			aspect. Tazobactam alone is very limited in suppliers→ Fushine and Qilu are the main (or only?) that produce big amounts (tones) of Tazobactam. These companies follow a tendency into full vertical integration, so produce everything in-house to become more independent. They do have their own brand, but they also now sell the final dosage form to the U.S market. Apparently, this is quite common in the penicillin market. Fresenius Kabi has the biggest share in the European market for Pip/Tazo, their source is from Qilu pharmaceuticals. China controls the world market for Piperacillin/Tazobactam. **Amoxicillin:** Much more spread production: China, India, and also big ones in Europe. Centrient has 3 sites in Europe, Sandoz, and a smaller one called Antibioticums. Amoxicillin does not have single sourcing problems such as in the case of Tazobactam, the threat of Amoxicillin is AMR due to misuse (humans and agriculture); pollution. If Centrient shows an excellent performance for fighting pollution → good for reputation/ more customer – on the other way an argument for higher price. The customer chooses them because they are the 'good guys' so it is a leverage for them to act sustainably responsible.
2	Most important environmental aspects	Which environmental aspects do you consider as most important? (For instance: product waste, pollution, emission of greenhouse gases, energy consumption, etc.)	Not at that level yet, for now focus on comply with regulations. Top one for the group is CO2. Emission of greenhouse gases + energy consumption – these go hand in hand. In India and china water consumption is also a concern.
3	Most relevant and/or challenging environmental aspects	Which environmental aspects do you consider most relevant when monitoring external supplier	The audit group has a CSR questionnaire, but it is not mandatory. Right now, they check that the laws are

	from an external supplier site	sites? Which ones do you think are most challenging to achieve?	complied with. Pollution needs to be avoided. Normally standard at suppliers is very high and in line with Company D priorities.
4	Control of further steps (suppliers of the direct supplier) on the supply chain	How do you control if your supplier is supervising environmental and social standards from their external suppliers?	Through acknowledgement of our Supplier Code of Conduct and at Quality audits.
5	Which stakeholders are: - The most influential - Negatively affected by the supply chain - Can jeopardize the supply or damage the company's reputation	Which stakeholders do you consider as most influential within pharmaceutical (and especially antibiotic) supply chains? Which stakeholders do you think could be negatively affected by pharmaceutical (and especially antibiotic) supply chains? Which stakeholders of Company D (antibiotic) supply chains do you think can jeopardize the supply and/or damage the reputation of the company?	Company D considers a wide variety of stakeholders in their supply chains: 1. Customers and patients to secure supply 2. Authorities (Medical Agencies and Environmental) to ensure compliance 3. Other external stakeholders, e.g. media, investors, securing that we act in a responsible way and avoid negative exposure due to inappropriate practices - **Influential→** economic involved incentives most important. Price and quality most important in this industry. Healthcare authorities is where the pressure starts and also depends on governmental regulations. - **Negatively affected→** People living near to the production site where the waste is not properly managed (ground/river/soil contamination) - **Jeopardize→** Academia and customer groups
6	Reputational risks management	How do you assess and manage supply and reputational risks triggered by stakeholders?	Through our Sustainability work, where risk management is an integrated aspect
7	Benefits from sustainability-related risk assessment and management	In which ways do you think it would be beneficial for a company to have a more thorough sustainability-related	Good for business; and safe and efficient products. The integrated risk assessment is a tool to identify and mitigate risks.

		risk assessment and management?	
8	Operations distribution across Company D facilities located across the globe	Company D has 20+ development and manufacturing plants across Europe, USA and India. How do you distribute the operations across these facilities in different counties? Which criteria was used to decide such distribution? (For instance: experience, technology from acquired facilities, cost, regulation standards, etc.)	None of the facilities are greenfield, consequently the most important aspect is the legacy portfolio and manufacturing footprint.
9	Key to achieve sustainability success	Company D is one of the leading pharmaceutical companies when it comes to sustainability. What would you say is the key to achieve so and why do you think other companies don't?	Board + Senior management attention and Sustainability having a chair in the Executive Team. For big pharmaceutical companies they do it because their reputation is on the public eye and also have more resources for caring about sustainability and some do have really good initiatives. For CMOs it is very rare that they care about sustainability issues, especially when the company is also smaller like in Company D case. The two owners from Company D knew since the beginning that they wanted to incorporate sustainability in their portfolio, so it is very embedded in the company's culture. The only way for smaller companies to consider sustainability issues is through requirements from the customers or through regulations, otherwise it is not worth it for them and they do not do it. However, now there is much more pressure from big pharma companies which has changed a lot from 5 years ago.
10	How is cultural change managed across employees	How do you manage the cultural change across the employees that are used to comply with lower environmental standards than the	Company D CSR responsible assures they have never faced any issues regarding this.

		ones you implement with ISO-14001?	They start applying their code of conduct, but it is not a mandatory requirement to follow so it depends. Incentive for good environmental behavior depends on the requirements from customers. Suppliers that produce for the European market have higher standards (the factories look very similar to the European ones) than those that produce for local market which have to comply to lower standards and different customer requirements and the price is also different, for instance in India.

Interview #5 – Indian API supplier (Company E)

About the interviewee: He has been working for the last 10 years in different pharmaceutical companies in Hyderabad, India. His role was pharmaceutical business developer, supplying finished products and APIs to Europe, US, and Middle-east countries.
The company: He lives in Hyderabad, Telangana. API is a huge business in India, and the industry is concentrated in 3 states: Gujarat, Telangana & Andhra Pradesh, and Mumbai, Maharashtra & Goa. He had been working in a company that manufactured 300 metric tons of Ciprofloxacin antibiotic, the rest of the experience is with other drugs.
Relevance: Highly experienced in the pharmaceutical industry. First-hand information from the situation in India, where most of API suppliers are located.

No.	Desired Outcomes	Questions	Answer
Questions for theoretical framework			
1	Most influential stakeholders and the ones that can result most negatively affected	Within the pharmaceutical/antibiotic supply chain, which stakeholders do you think are more influential? And which are the ones that could result most affected by?	*Most influential:* intermediate producers providing the key starting materials for the production of APIs. The hub of these producers is located in China, but now many companies are being shut down due to environmental issues/pollution. The market is moving to India. *Most negatively affected:* end consumers, i.e., patients. If the production stops for whatever reason and it is not possible to be supplied, the

			patient can be at risk of not getting the cured (example Africa).
2	Top 3 risk factors for interrupting the supply chain	Which are the top 3 risk factors that can stop the production of a compound?	*Risks to stop production:* • Environmental • Cost • Government regulations
3	Most important environmental aspects	Which environmental aspects do you consider as most important and/or challenging to achieve? (For instance: product waste, pollution, emission of greenhouse gases, energy consumption, etc.)	Chemical disposal because of the toxicity nature from the components. Also, it is very important that the surrounding areas of the factories are NOT surrounded by lakes or any kind of water bodies. The Indian government (pollution control board) requests zero-discharge facilities. For example, when they reuse the chemicals it has to be disposed by the third-party or within the facility without licking it across the water bodies. So, all the chemicals need to be either stored, the waste, and given to the 3rd party who takes care and process it elsewhere otherwise you have to have zero-discharge in the facility.
4	Differences between UE/EU clients vs. local (Indian)/ emerging countries clients	Producing for European clients must be very different than producing to local clients. Which are the most relevant differences that you have seen?	There are 2 aspects involved: • **Impurity levels**: much more stringent from UE/EU than from Emerging countries • **Environmental**: EHS law required from UE/EU clients. If Pfizer wants to manufacture in India, they will come to the facility and they will audit them from the EHS perspective. Only if they pass the audit then they will be allowed to supply the product to US/EU.
5	Indian suppliers' point of view on environmental-related certifications	Do you consider that having an environmental-related certification such as ISO-14001 provides a competitive advantage to the supplier or not so much?	Yes, definitely it gives a competitive advantage. Most of the companies are having ISO and WHO-GMP. Everyone is complying to these requirements now and also pollution control board is insisting in these certifications.
6	Indian suppliers' perception on pharmaceutical	Would you think that the clients from suppliers, i.e., pharmaceutical companies	They give importance to the environmental actions, now it is very important otherwise the facilities are

	companies' efforts on environmental issues	(MAH) give great importance to environmental aspects or just to stick to law?	getting closed, and also NGOs are now fighting because lots of water bodies are getting affected and people suffer direct consequences, such as cancer. This is not only from the pharma industry, also from other industries that discharge chemicals. Not every company tries to go one step further than law requirements with environmental efforts, but few of them yes. The big companies like Johnson & Johnson, Company C, Pfizer they do go a step further to show that they are committed to the environment
7	Consequences on the blacklisted supplier companies located in India	Have you seen repercussion in the blacklisted companies from these white papers published by NGOs such as 'Changing markets'?	They do get blacklisted but in India and China is all about corruption. If someone would come and say guys you cannot manufacture starting from tomorrow, next week I can put money on the table to get to manufacture again. The NGOs report and blacklist goes to the big media, the pollution board goes and gives them a warning but after 2 weeks it is forgotten. We are short-time memory, today we have a situation and after 2 weeks there is a new sensation. It's not registered in the minds of people.
8	Locals' (Indians) reaction about the contamination from the companies	How do companies deal with locals' reaction about the contamination they produce?	He mentioned an example of a company that got 200 people from a village blaming them for the diseases they had and asking for money. The company distributed money to them and since then, they go every 2-3 months to get more money. This has become a common thing to do and it is a big mafia in India right now.

Appendix 3: Identified stakeholders and SCSRs of both supply chains

Number of interview/ Category	**Most important/influential stakeholders**	**Most negatively affected stakeholders**	**Other stakeholders**	**SCSR** (risks triggered by stakeholders due to environmental and societal deficiencies)	**Other supply chain risks**	**How is it managed?**
#1: Generic pharmaceutical company	-	-	• API producer • FDF produce • Quality department • Distributor	• No risks regarded	-	• Assessing once a year if there is any external impact on the supply chain • Reassessment of two molecules every month
#2: Antibiotics intermediary	• Government • Supplier • Agent	-	• Intermediate producer • API producer • FDF producer • Distributor • Agent • Wholesaler	• Government (e.g. China's introduction of stricter environmental regulations)	-	• The API customer is auditing the supplier or assign auditor to it • An agent is looking for reliability, and is therefore regarding the risks that could interrupt the supply chain

Number of interview/ Category	**Most important/influential stakeholders**	**Most negatively affected stakeholders**	**Other stakeholders**	• **SCSR** (risks triggered by stakeholders due to environmental and societal deficiencies)	**Other supply chain risks**	**How is it managed?**
#3: MAH	-	-	-	• Ecological risks • Authorities' risk • Safety risks • Reputational risks	• Quality risks (highest risk) • "Oversight" risks • Supply risks • Commitment of supply risks • Data security	• Internal training to decrease risks • PSCI: Pharmaceutical Supply Chain Initiative - platform for sharing, training and enhancing capabilities

Number of interview/ Category	**Most important/influential stakeholders**	**Most negatively affected stakeholders**	**Other stakeholders**	**SCSR** (risks triggered by stakeholders due to environmental and societal deficiencies)	**Other supply chain risks**	**How is it managed?**
#4: Contract Development & Manufacturing Organization	• Healthcare authorities/ Governmental regulatory bodies	People living near production sites where waste is not managed properly (ground/soil/water contamination)	• Customers & patients to secure supply • Authorities (medical agencies and environmental) to ensure compliance • Other external stakeholders (media, investors, etc.) securing that companies act in a responsible way and avoid negative exposure to inappropriate practices	Environmental: • Top one for the group is CO2. Emission of greenhouse gases + energy consumption • In India and china water consumption is also a concern	• Cost • Quality	The audit group has a CSR questionnaire, but it is not mandatory. Right now, they check that the laws are complied with. Pollution needs to be avoided. Normally standard at suppliers is very high and in line with Recipharm priorities.

Number of interview/ Category	**Most important/influential stakeholders**	**Most negatively affected stakeholders**	**Other stakeholders**	**SCSR** (risks triggered by stakeholders due to environmental and societal deficiencies)	**Other supply chain risks**	**How is it managed?**
#5: API Supplier	Intermediate producers (hub located in China, but currently market share moving to India)	• End consumers, i.e. patients (especially the patients from emerging countries) • Locals communities	• NGOs, • Media • API producer • MAH	• Environmental/ social (local community is suffering from chemical disposal) • Governmental regulations (China as an example)	• Cost	• GMP and ISO When the client is a big pharma company like Johnson & Johnson, Novartis or Pfizer, they go one step forward in sustainability efforts to show they care about environment as a business strategy for increasing reputation