Pharmaceutical Supply Chain Risks and Risk Mitigation Strategies: Systematic Literature Review (SLR) through Text-Mining

by

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Risques de la chaîne d'approvisionnement pharmaceutique et stratégies d'atténuation des risques: revue systématique de la littérature (SLR) par l'extraction de textes

Elmira MOHEBI

RÉSUMÉ

Les chaînes d'approvisionnement pharmaceutiques sont confrontées à différents types de risques et d'incertitudes et la gestion des risques est devenue un problème important avec des changements constants dans la chaîne d'approvisionnement. Pour gérer avec succès les risques, il est important d'identifier les risques et les incertitudes et de savoir comment atténuer ces risques avec une stratégie d'atténuation des risques appropriée. Le but de cette étude est d'étudier la littérature existante pour identifier les risques et les stratégies d'atténuation des risques en utilisant des techniques d'extraction de textes au lieu de l'approche traditionnelle de revue de littérature.

Les méthodes que nous avons appliquées pour effectuer une revue systématique de la littérature (SLR) consistent en l'extraction de phrases par approche lexicale et en utilisant Natural Language Toolkit (NLTK), le regroupement de similarités sémantiques (y compris la vectorisation par la méthode Universal Sentence Encoder et la méthode de matrice de similarité) et le post-traitement.

Au total, 4205 articles ont été extraits après avoir appliqué des chaînes de recherche associées dans les trois moteurs de recherche Web of Science, PubMed et Google Scholar. Enfin, après avoir effectué différentes phases de suppression des références en double, de sélection de titres et de sélection de titres et de résumés dans le logiciel DistillerSR, 278 références ont constitué les études sélectionnées de notre projet.

Les résultats démontrent que 317 risques en général sont identifiés dans 24 groupes différents de produits, logistique, matériel, approvisionnement, financier, médicament, client, technologique, inventaire, réglementation/législation, information, demande, coût, transport, marché, qualité, politique, environnemental, humain, organisationnel, international, réseau, technique, opérationnel et autre. Les trois risques principaux qui sont les plus discutés dans le littérature sont respectivement les risques d'approvisionnement, les risques opérationnels et les risques opérationnels. Les quatre groupes principaux qui présentant le plus de risques sont l'approvisionnement, les produits, les transports et les finances, avec respectivement 27, 27, 22 et 20 risques. De plus, plus de 73 stratégies d'atténuation des risques sont trouvées dans le littérature qui ciblaient différents risques dans le domaine de la capacité, des essais cliniques, de la conformité, du service client, de l'offre, de la demande, etc. Différentes études ont travaillé sur le problème des pénuries de médicaments et de médicaments. Le deuxième risque qui a retenu le plus d'attention des chercheurs est celui lié à l'approvisionnement.

Mots-clés: chaîne d'approvisionnement pharmaceutique, risques, stratégie d'atténuation des risques, SLR, extraction de textes

Pharmaceutical Supply Chain Risks and Risk Mitigation Strategies: Systematic Literature Review (SLR) through Text-Mining

Elmira MOHEBI

ABSTRACT

Pharmaceutical supply chains face different kind of risks and uncertainties and managing the risks has emerged as an important issue with constantly changes in the supply chain. To successfully manage the risks, it is important to identify risks and uncertainties and know how to mitigate these risks with proper risk mitigation strategy. The purpose of this study is to investigate the existing literature to identify risks and risks mitigation strategies by using Text-Mining techniques instead of traditional literature review approach.

The methods we applied to perform a Systematic Literature Review (SLR) consist of phrase extraction by lexical approach and using Natural Language Toolkit (NLTK), semantic similarity clustering (include vectorizing by Universal Sentence Encoder method and similarity matrix method), and post-processing.

A total 4205 papers were extracted after applying related search strings in the three search engines of Web of Science, PubMed, and Google Scholar. At last, after performing different phases of removing duplicated references, title screening, and title and abstract screening in the DistillerSR software, 278 references formed our project's selected studies.

The results demonstrate that 317 risks in general are identified in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other. Top three risks that are discussed the most in the literature include supply risks, operational risks, and quality risks respectively. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively. moreover, more than 73 risk mitigation strategies are found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines. The second risk that has received the most attention from researchers is supply-related risks.

Keywords: pharmaceutical supply chain, risks, risk mitigation strategy, SLR, Text-Mining

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LIST OF ABREVIATIONS

PSC	Pharmaceutical Supply Chain
SCM	Supply Chain Management
SCRM	Supply Chain Risk Management
SLR	Systematic Literature Review
TM	Text-Mining
AI	Artificial Intelligence
SC	Supply Chain
LR	Literature Review
CRD	Center for Reviews and Dissemination
VTM	Visual Text Mining
IV	Information Visualization
IR	Information Retrieval
IE	Information Extraction
NLP	Natural Language Processing
SVM	Support Vector Machine
USE	Universal Sentence Encoder
GSE	Google Sentence Encoder
GloVe	Global Vectors
NLTK	Natural Language Toolkit

INTRODUCTION

One of the most important human rights is accessing medicine at the right time, place, quantity, and acceptable quality. Pharmaceutical Supply Chain (PSC) is facing different kinds of risk which can waste resources and threaten patients' life by limiting access to medicines (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013). Therefore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines (Moktadir M. , et al., 2018).

In the last decade healthcare organizations have become more complex owing to different factors such as efficient customers, biomedical developments, the complication of services, and the growing number of healthcare users (Ferdosi, Rezayatmand, & Taleghani, 2020). Moreover, the complication of supply network has increased by globalization, more customer expectation, shorter life cycle for products and technologies which has led to tremendous uncertainties and risks in the PSC (Wang & Jie, 2020).

The pharmaceutical supply chain is a substantial part of the health system that entail whole procedures, resources, information, different players such as suppliers, producers, agencies, third party service providers, transportation and sales activities, financial issues and IT (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Jaberidoost M. , et al., 2015).

There are different definitions for risk but as a whole it can be defined as an uncertain event, which has the likelihood of incidence of undesirable outcomes such as late delivery, economic burden, and business loss (Moktadir M. , et al., 2018) and according to ISO31000 its effect can be positive and/or negative (Leitch M. , 2010). Supply Chain Management (SCM) is integrating the significant business processes over the supply chain with the aim of making value for clients and stakeholders. All stakeholders require establishing the correct configuration and compatibility to build best practice and to outreach the barriers in ever-increasing environment (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013).

Besides, managing of risks is a critical point to cope with different kinds of uncertainties from a supply chain context (Moktadir M. A., et al., 2018). Therefore Supply Chain Risk Management (SCRM) is a crucial part of supply chain management intends to decrease supply chain risks and vulnerabilities by mitigation strategies (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013), and to guarantee PSC flexibility and cohesion (Enyinda, Mbah, & Ogbuehi, 2010).

SC vulnerability can be defined as an exposure to significant disruption (Wagner & Bode, 2006). In other words, vulnerability is a known or unknown weakness that could harm the person, system, and company as a whole (What Is The Difference Between a Threat, Vulnerability and Risk?, 2020). In fact, lack of proper risk mitigation can destroy public health reliance, patients' safety and health, and a decrease in profit margin and stakeholder value. However, the pharmaceutical organizations can not totally remove the risks they face in their operations; they are able to make an environment favorable for reactive risk mitigation (Enyinda, Mbah, & Ogbuehi, 2010).

This research aims to explore different pharmaceutical supply chain risks and risk mitigation strategies based on the Systematic Literature Review (SLR) methodology through text-mining. There are too many risks in different parts of supply chains that stakeholders need to be aware of them. To react efficiently against those risks, it is necessary to gain knowledge about different risk mitigation strategies. Different studies and researchers have worked on identifying the risks and risk mitigation strategies in the pharmaceutical supply chain and the problem is that reading all these studies is beyond someone's ability or an organization's ability.

Therefore, the purpose of this study is to conduct a SLR methodology using Text-Mining (TM) technique to cover the gap regarding automated SLR method in the pharmaceutical supply chain. Although there are different studies working on identifying pharmaceutical supply chain and risk mitigation strategies by SLR, no one has applied text-mining

techniques so far and basically, the motivation of this study is new synthesizing research with testing different TM techniques and algorithms.

0.1 Research Issue

In the last decade healthcare organizations have become more complicated owing to different factors such as efficient customers, biomedical developments, the complexity of services, and an increasing number of healthcare users. Moreover, the complication of supply network has increased by globalization, high customer expectations, shorter life cycle for products and technologies which has led to tremendous uncertainties and risks in the PSC. Furthermore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines. Mining scientific papers has been sometimes proven useful but it also presents a headache for anyone wanting to stay up to date with the literature or hoping to mine it for insight about different topics.

In a time of increasing uncertainty, different pharmaceutical stakeholders need to make better decisions with greater urgency at higher levels of risk. For example, the Covid-19 crisis poses special risks for each pharmaceutical company. The outbreak of the coronavirus/COVID-19 has been causing structural and operational changes to the way healthcare and pharmaceutical companies operate. Changes will likely have a long-lasting impact on how they approach the different strategies. Pharmaceutical companies must look to new technologies and change their strategies in order to adapt to this new landscape. As the pharmaceutical industry is on the front lines of a battle to a global pandemic, assessing the risks tied to the company’s sourcing, manufacturing, sales, and other sectors is important to ensure sufficient backup in case of future disruptions.

0.2 Research Objectives

Systematic reviews are a widely used method to bring together the findings from multiple studies. The problem is that the growing number of published studies makes it difficult to use them in an efficient way. Exploring the literature with AI techniques could greatly accelerate researchers' ability to benefit from a wide range of studies and integrate them. Text-mining is the process of discovering knowledge and structure from unstructured data. Therefore, in order to address the mentioned problems in the previous section, this research intends to pursue the following objectives:

• Using AI techniques in Systematic Literature Review (SLR) in the field of pharmaceutical supply chain and examining different TM algorithms;
• Identifying different pharmaceutical-related risks in the supply chain through the new obtained method;
• Identifying different risk mitigation strategies and discovering the relations between strategies and risks.

Therefore, some questions are raised to explore this thesis issues and objectives as follows:
• What TM algorithms will be determined to conduct the SLR in the pharmaceutical supply chain field;
• What is different pharmaceutical-related risks in the supply chains;
• What are the different risk mitigation strategies in the pharmaceutical supply chain;
In the literature, there is a gap in terms of the lack of synthesizing mitigation strategies and related risks. This then raised an additional research question for this thesis;
• Is it possible to present a synthesized work on the identified risks and risk mitigation strategies in the existing literature.

0.3 Methodology and Contributions

To answer the research questions and achieve these research objectives, the following research methodology was designed and adopted:

A Systematic Literature Review (SLR), which mainly referred to as identification, evaluation, and interpretation of a field of research that can be reproduced with the same protocol by other researchers (Kitchenham B. , 2004) has been conducted. The applied procedure contains eight steps:

- Formulating the research problem,
- Developing review protocol,
- Searching the literature,
- Screening for inclusion,
- Assessing quality,
- Extracting data: Regarding the high volume of existing texts and documents, AI technique is more effective and efficient to extract knowledge and information comprehensively,
- Analyzing data: After obtaining data, mixing, and merging data from as many data sources as possible, preprocessing the data and data modeling will be conducted,
- And reporting the findings: Interpreting the data will be done in this phase of the methodology.

0.4 Thesis Structure

This thesis contains 4 chapters and is structured as follows:

Chapter 1 presents a literature review on definitions of risk, Supply Chain (SC), supply chain risk, Supply Chain Management (SCM), Supply Chain Risk Management (SCRM), and

Pharmaceutical Supply Chain (PSC). Also, various Literature Review (LR) methods, SLR methods, and TM techniques are discussed in this section.

Chapter 2 describes the methodology used in this research. Chapter 3 provides results, Chapter 4 presents discussion and at the end of this research, conclusion and future works are presented.

CHAPTER 1

LITERATURE REVIEW

1.1 Definitions

Risk can be defined as an uncertain event, which has the likelihood of incidence of undesirable outcomes such as late delivery, economic burden, and business loss (Moktadir M. , et al., 2018) and according to ISO31000 its effect can be positive and/or negative (Leitch M. , 2010). Besides, it is considered as the extent of uncertainty in terms of realizing the importance and/or unfortunate results of decisions (Zsidisin G. A., 2003). Supply chain is a series of processes, members, information, and assets that transform raw materials into products and services available for clients (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013).

Furthermore, supply chain risk is regarded as the probability and effect of unanticipated events or situations which unfavorably have an impact on any sector of a supply chain with operational, technical, or strategic failures. According to another definition supply chain risk is the potential varying results that lead to the reduction of value-added at any task in a supply chain (Ho W. , Zheng, Yildiz, & Talluri, 2015).

Supply Chain Management (SCM) is regarded as the integration of important business operations over the supply chain with the aim of building value for clients and stakeholders. According to the council of supply chain management SCM is also defined as planning and managing of all tasks pertain to sourcing, procurement, transformation, and logistics (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013).

Supply Chain Risk Management (SCRM) is an organizational cooperative effort using different kinds of methodologies such as quantitative and qualitative risk management to recognize, assess, mitigate, and monitor unanticipated events or situations, which might negatively affect supply chain (Ho W. , Zheng, Yildiz, & Talluri, 2015). Pharmaceutical Supply Chain (PSC) is a remarkable part of the health system with the aim of providing medicines which contains all processes, information, assets, and members such as producers, mediators, logistics tasks, trading, sales tasks, finance, and IT (Jaberidoost M. , et al., 2015).

1.2 Risks and Uncertainties

Risk and uncertainty are distinct in terms of the probability distribution. Although the risk has an unknown outcome, the probability distribution regarding that outcome is known. However, in the case of uncertainty, the probability distribution is unknown as well (De Groot & Thurik, 2018). Organizations could monitor potential risks and control likely risks using supply chain risk management as well as improving its efficiency.

1.3 Risk Mitigation Strategies

Risk mitigation can be defined as the strategic actions that are pursued by organizations to counteract the risks identified from different sources (Enyinda, Mbah, & Ogbuehi, 2010). Risks in the pharmaceutical supply chain are due to the lack of information or deviation in the flow of information and physical drug and therefore, increasing knowledge in terms of risk management is imperative.

1.4 Literature Review Methods

Systematic Literature Review (SLR) is a well-settled research method applied to integrate the top existing empirical data from systematic research (Feng, Chiam, & Lo, 2017). There are different methodologies, models, guides, protocols, and frameworks such as PRISMA,

selection methodologies, Enfoque iSR, SLR Delaware guide, protocol of the Center for Reviews and Dissemination (CRD), and three states framework (Input/ Processing/ Output) to conduct SLR (Palomino, Dávila, & Melendez, 2018). Due to SLR complexity it could be a challenging task in terms of consuming time, being labor-intensive, and open to errors if performed manually. Therefore, there are various text-mining techniques and tools that can facilitate different SLR phases and activities (Feng, Chiam, & Lo, 2017).

Text-Mining (TM) is the process of getting fascinating information, patterns, trends, and significant knowledge from textual documents (Tan, 1999). There are different TM applications such as Visual Text Mining (VTM), federated search strategy, automated document classification, and document summarization; and different TM techniques such as Information Visualization (IV), clustering, Information Retrieval (IR), classification, Information Extraction (IE), and summarization in order to automate different processes in SLR (Feng, Chiam, & Lo, 2017).

For instance, there are several TM applications in search strategy development and selecting studies. Researchers are interested in applying TM and machine learning in the screening phase since selecting primary studies such as other SLR phases could be time-intensive and labor-intensive. Abstrackr, ASReview, Colandr, DistillerAI, EPPI-Reviewer, Rayyan, and RobotAnalyst are examples of study selection TM tools (Text mining for searching and screening the literature, 2021).

In terms of validation, there are different validation methods for AI systems such as simulation, trial, model-centered validation, and expert opinion. Fully virtual simulation, hardware in the loop simulation, and system in the loop simulation form simulation method. In the trial method, the system is used in the final deployment environment or in an environment that replicates a real environment. In model-centered validation we must focus on validating the model. The expert opinion method focuses on assessing the system against experts' opinion (Myllyaho, Raatikainen, Männistö, Mikkonen, & Nurminen, 2021).

CHAPTER 2

METHODOLOGY

To answer the research questions and achieve these research objectives, the following research methodology was designed and adopted:

A Systematic Literature Review (SLR), which is mainly referred to as identification, evaluation, and interpretation of a field of research that can be reproduced with the same protocol by other researchers (Kitchenham B. , 2004). It provides trustworthy approaches and established succession to gather, evaluate, and explicate the foremost available research to address specific research questions. Although SLR is a useful and famous research method, it is a challenging, labor-intensive, and time-intensive task if performs manually (Feng, Chiam, & Lo, 2017). To that end, different Text-Mining (TM) algorithms and SLR supporting software are applied in this research to facilitate the process and make it more efficient which will be discussed in detail in the following sections.

The applied procedure contains eight steps (Kitchenham B. , 2004):

- Formulating the research problem,
- Developing review protocol,
- Searching the literature,
- Screening for inclusion,
- Assessing quality,
- Extracting data,
- Analyzing data,
- And reporting the findings.

2.1 Formulating the research problem

The pharmaceutical supply chain like any other kind of supply chain and industries faces different risks and uncertainties in different parts and therefore, the consequences are even more noteworthy than any other industry owing to the fact that it can also harm patients' health. In a time of increasing uncertainty, different pharmaceutical stakeholders need to make better decisions with greater urgency at higher levels of risk. For example, the Covid-19 crisis poses special risks for each pharmaceutical company.

Several researchers have worked on the topic of identifying, assessing, managing risks, and providing risk mitigation strategies to improve the situation in PSC. The problem is that the growing number of published studies makes it difficult to synthesize them and applying the traditional SLR method manually can be an inefficient way. To address this problem, the potential of TM techniques and its developed tools help facilitate SLR processes (Feng, Chiam, & Lo, 2017).

Accordingly, we use AI tools in different phases of SLR to address the research objectives that are synthesizing relevant papers about pharmaceutical supply chain risks and risk mitigation strategies and responses.

2.2 Developing review protocol

SLR protocol considers three phases of planning, conducting, and reporting (Kitchenham B. , 2004) that is discussed step by step.

The motivation of this research is answering the following questions:

• What TM techniques and algorithms will be determined to conduct the SLR in the pharmaceutical supply chain field;
• What is different pharmaceutical-related risks in the supply chains;

• What are the different risk mitigation strategies in the pharmaceutical supply chain;

In the literature, there is a gap in terms of the lack of synthesizing mitigation strategies and related risks. This then raised an additional research question for this thesis:

• Is it possible to present a synthesized work on the identified risks and risk mitigation strategies in the existing literature.

To find the primary studies different combination of keywords and search strings are obtained that is shown in Figure 2.1.

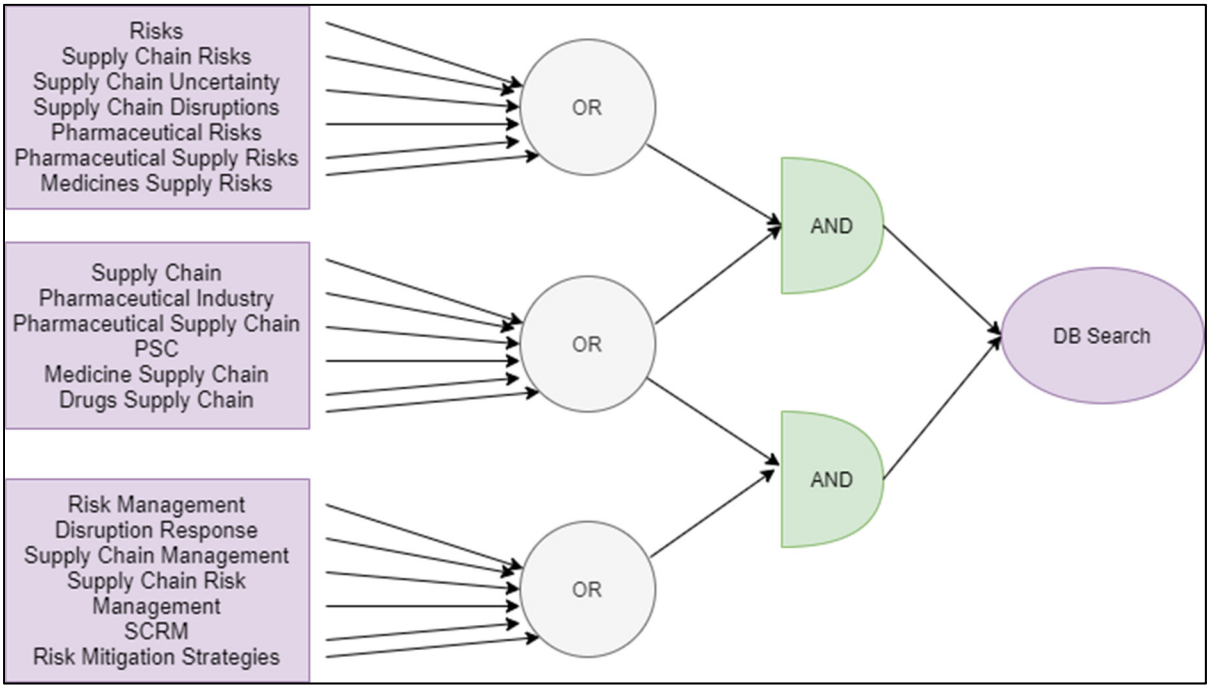

Figure 2.1 Search keywords and strings in the databases

The selected keywords are used to extract relevant research from three search engines of Google scholar, PubMed, and Web of Science. Inclusion criteria consist of all English journal papers, conference papers, and workshops between 2000 and 2021. The relevant papers are decided to be included if either those identify, assess, or analyze risks in at least one part of the pharmaceutical supply chain and the industry or identify, present, and investigate at least one risk mitigation strategy. Besides, exclusion criteria include e-books, books, thesis and also studies that worked on specific part of pharmaceutical supply chain

such as radiopharmaceutical or Biological Pharmaceutical Industry. Also, studies without full-text availability are excluded.

2.3 Searching the literature

The search strings and combinations are adapted to be applied in selected search engines. The queries result from search engines are imported in DistillerSR software. There are different software helps screening phase in the SLR to capture as many as possible relevant studies from the search set. This kind of software improves workflow by screening prioritization, and also works as a second reviewer and speeds up the screening process (Text mining for searching and screening the literature, 2021).

DistillerSR applies Natural Language Processing (NLP) to automate the screening phase through sorting and ranking results, operating as a second screener, and distinguishing the errors.

2.4 Screening for inclusion

The relevant articles are selected through two steps of title screening and abstract screening. The screening steps are performed in DistillerSR software both manually and by AI screening. Running DistillerAI gives a preview of which references will be included or excluded in terms of manually reviewed data. DistillerAI trains itself by Support Vector Machine (SVM) classifier using a percentage of the manually reviewed references and then utilize that learning to the rest of unreviewed references to automatically ascertain which references should be included or not.

2.5 Assessing quality

DistillerAI uses k-fold cross validation method to train the dataset multiple times by using a percentage of reviewed references and also ensures a diverse sample of references. Hereby, check for screening errors helps to verify if any excluded references in a previous step or even current screening step are incorrectly excluded. This method is applied in title screening and abstract screening in order to control and check the quality.

2.6 Extracting data

Titles and abstracts of all references are checked in terms of previously determined inclusion and exclusion criteria. After two steps of screening the obtained references from search engines, finding references compatible with the defined protocol, and assessing the quality, the data set will be ready to be pre-processed.

It is noteworthy that Python programming language is used in processing the data as it is a relatively simple programming language and has a big library of frameworks and it is used widely by scientific researchers. In this step the dataset requires to be pre-processed to be qualified for analyzing step. First, PDFMiner library in Python is used to convert all the PDF files into plain texts with the purpose of running algorithms. PDFMiner helps to extract PDF files' textual data and information in different levels comprising page level, blocks or paragraph level, and line level and character level.

Secondly, different rules are applied to filter and remove unwanted data. For instance, in page level if the first page ratio is different from others, it indicates that the first page is a cover and needs to be removed. Also, in blocks level if the block is placed above %95 or below %5 percent of the page height, it should be removed as it is most probably footer or a header. In line level for example it is checked that if any set of signs that imply the line is a URL or contact info, the corresponding line should be removed from the dataset. A more detailed set of rules can be observed in the Figure 2.2.

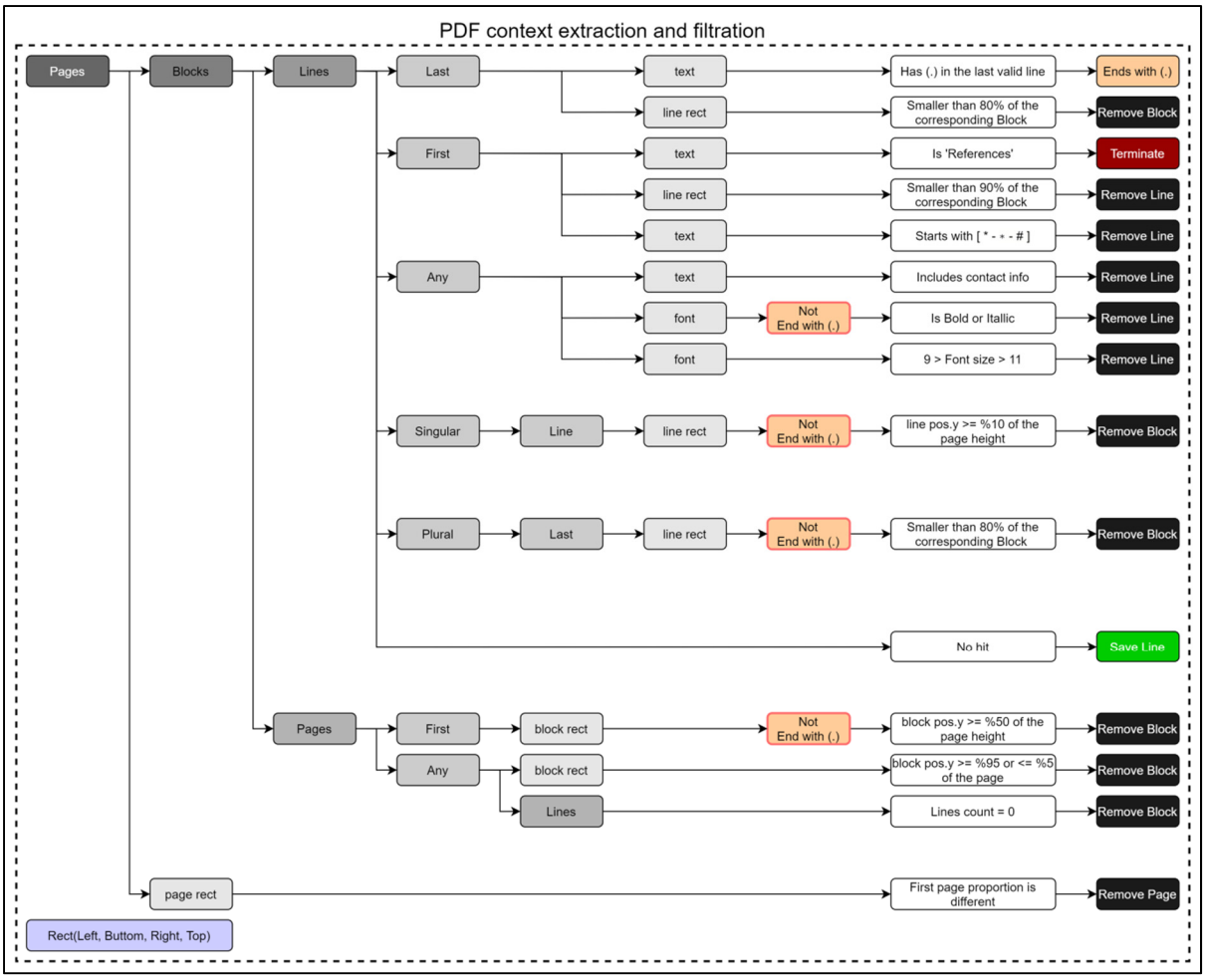

Figure 2.2 Process of PDF context extraction and filtration

Thirdly, text refinement should be done because the extracted data is not always clean and may contain many unwanted signs, characters, redundant spaces, parenthesis, and brackets. More details of the procedure are visible in the Figure 2.3.

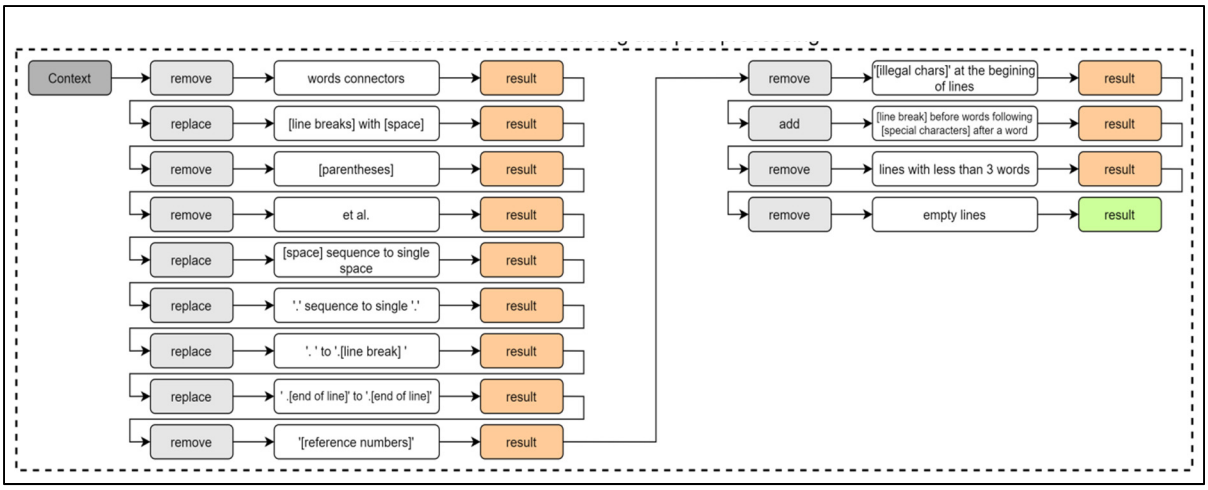

Figure 2.3 Process of extracted context cleansing and post-processing

2.7 Analyzing data

When the textual data extraction and pre-processing are completed, the next phase is data processing. In this phase data analysis and extraction of shortened noun phrases according to the best matches with provided keywords are conducted. This phase consists of these steps: phrase extraction, semantic similarity clustering, and eventually post-processing.

2.7. 1 Phrase Extraction

The purpose of this step is to acquire phrases in which they give information about aimed keywords such as risk or strategy. For example, with entering “risk” as a keyword, the program iterates through all available information and returns a list of shortened noun phrases that are about risks.

To come by a solution to that aim there are mainly two possible approaches: “semantic similarity approach” and “lexical approach”. In the semantic similarity approach, the aim is to retrieve those phrases that have the most similarity to entered keyword. This can be done

through “machine learning methods”. This is a new method in which a pre-trained neural network model scores each given phrases a number or series of numbers known as vectors. These models are previously trained with gigantic datasets to learn how words and phrases relate to each other semantically, then based on the distance of the vectors the similarity of two words or phrases are considered.

In the lexical approach, a sequence of characters is converted into a sequence of tokens. Then, rules and algorithms are defined based on the grammatical information to extract and filter potentially targeted data.

In this research, different machine learning approaches such as Universal Sentence Encoder (USE) , known as Google Sentence Encoder (GSE) in the past , and Global Vectors for Word Representation (GloVe) are tested and compared. Although machine learning approaches might seem ideal, in real-world cases they might not always be able to provide the needed results. For example, in our case, in order to acquire semantically related phrases using single words keywords, a lot of false-positive results were created, and the phrases were not considered similar or appropriate based on supervisor assessments.

According to compared results, the lexical approach is decided to be used. The process or ability of analyzing human written textual data with computer programs is called Natural Language Processing (NLP). For this purpose, we use the Natural Language Toolkit (NLTK) library in Python. The first step is to design an algorithm that would extract appropriate phrases based on the given keyword. Currently two types of keywords are supported, ‘Risks’ and ‘Strategies’, with each type supporting various keywords simultaneously.

At first, the approach searches for all individual sentences considering the given keywords, then for each keyword, the keyword position in the sentence is taken into account and the two processes are applied, one of which is moving through the rest of the sentence from the located keyword in a forward direction which is called ‘forward pass’ and the other is moving to the beginning of the sentence in the backward direction called ‘backward pass’.

As for the risk phrase extraction algorithm in the forward pass, the next token is checked to see if it is a preposition, if so, it continues further and picks individual or a set of ‘determiners’, ‘adjectives’, and ‘nouns’ in order. Then the sequence of tokens that are processed is stored in memory and the approach continues with the backward pass.

In the backward pass, individual or set of ‘verbs’ and ‘conjunctions’ are checked and skipped if provided. If there is no 'conjunction' left after skipping ‘verbs’ and ‘conjunctions’, it looks back for ‘verbs’ again to repeat the cycle if necessary, and if there hasn’t been any ‘verb’ or ‘conjunction’ at all, then it will look for individual or set of ‘prepositions’, ‘nouns’ and ‘adjectives’ similarly and in an order. Before constructing the phrase if after collecting ‘prepositions’, ‘nouns’ and ‘adjectives’ the next token is a noun the algorithm will try to repeat the cycle for the proposed pattern. Finally, when there is no ‘noun’ at the end, the sequence of tokens that are processed is stored in the memory.

For the strategy phrase extraction algorithm however, in the forward pass, the next token after the spotted keyword must be a ‘preposition’, then the program expect a ‘determiner’, after that it looks for cycles of ‘adjectives’ and ‘nouns’ which may or may not be separated by ‘conjunctions’, like the phrase “business competitiveness and future successes” which ‘business’, ‘competitiveness’, and ‘successes’ are nouns, ‘future’ is an adjective and the word ‘and’ among them is a conjunction. When there is no more adjacent ‘noun’ or ‘adjective’, the sequence of tokens that are processed is stored in the memory.

In the backward pass, if the previous token to the keyword is a ‘verb’, it will be collected and the algorithm will quit, else if a ‘preposition’ is provided, it will be collected. Either there has been a ‘preposition’ provided or not, the program looks for cycles of ‘adjectives’ and ‘nouns’ which may or may not be separated by ‘conjunctions’ as explained before, with the exception that after each cycle the program looks for a ‘determiner’ to collect. If there was a ‘determiner’ it will look for a ‘preposition’ and if it was provided the program gets back to the point where it again seeks the cycle of ‘noun’, ‘adjectives’. Finally, if there was no more

‘noun’ or ‘adjective’ at the end, the sequence of tokens that are processed is stored in the memory.

Ultimately, after the backward pass and forward pass was processed for both ‘Risks’ and ‘Strategies’, both passes will get joined together for each Risk or Strategy extracted phrase and the yielded noun phrase is stored in the database. A more detailed diagram for both forward and backward algorithms is provided in the figure.

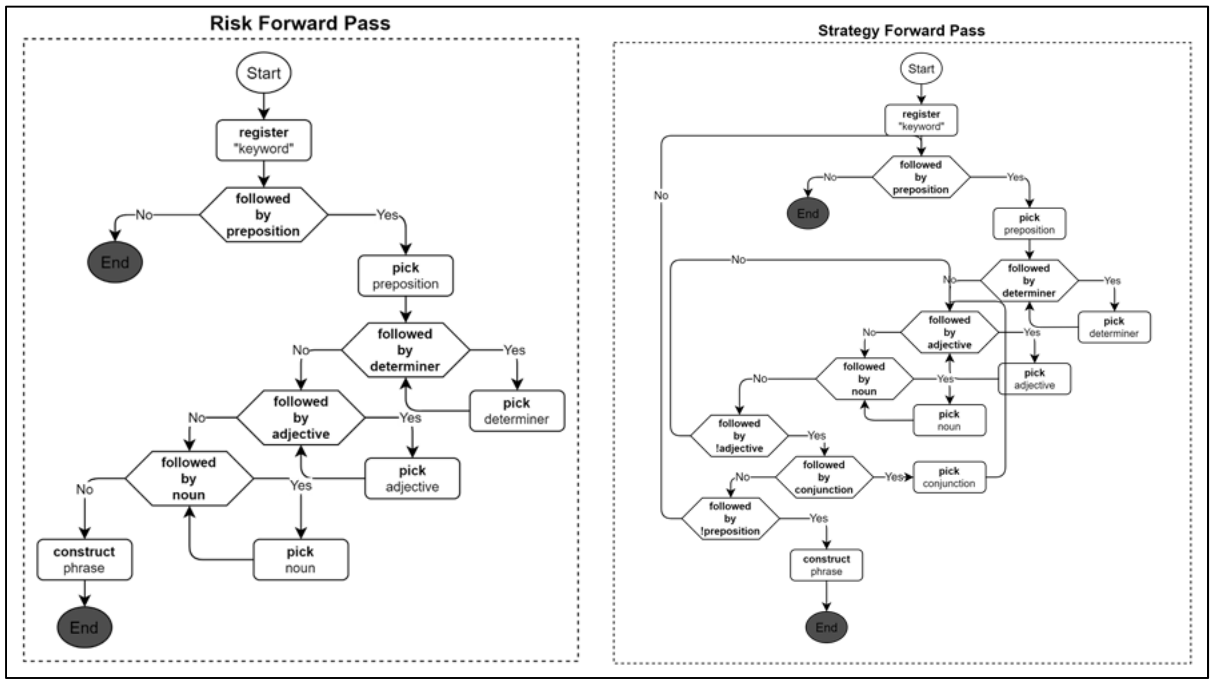

Figure 2.4 Phrase extraction algorithm for risk and strategy in the forward pass

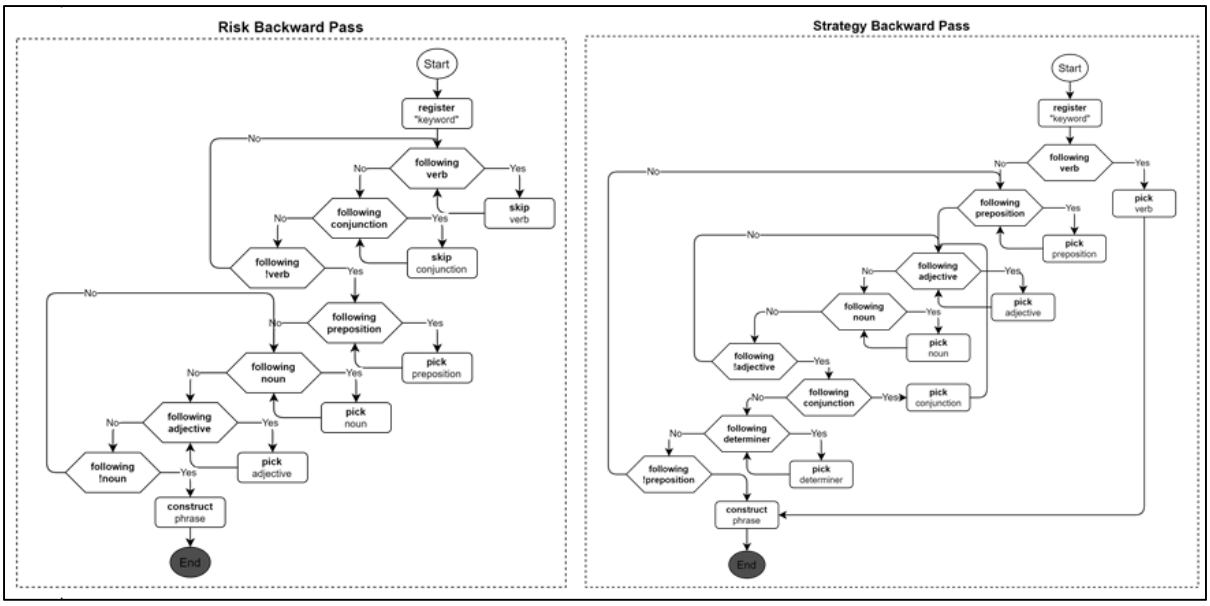

Figure 2.5 Phrase extraction algorithm for risk and strategy in the backward pass

Next step is constructing the data frame based on the yielded noun phrases. The data frame includes 8 columns, “Cluster”, “File”, “Keyword”, “Phrase”, “Sentence”, “Local frequency”, “Global frequency”, and “Files count”. Cluster indicates which group the phrase is most similar to or in another word which group of phrases shares the most semantic similarity and will be calculated later. File shows which article the extracted phrase is from. Keyword indicates which keyword resulted in extraction of the given phrase. Phrase is the extracted sequence of words that in this case is about risks and strategies. Sentence contains all sentences in a file that include the phrase in themselves. Local frequency shows the number of times the phrase is expressed in each file. Global frequency shows the number of times the phrase is expressed over all files and finally ‘Files count’ indicates the number of files that contains the phrase.

Basically ‘Local frequency’ is to show which articles more focus on a specific risk, and ‘Global frequency’ is to show how much a risk is generally important and mentioned in the literature and ‘File count’ shows how widely spoken a risk is investigated among all different articles.

2.7. 2 Semantic Clustering

Different clustering methods can be applied here and the most appropriate one can be selected base on the results. Clustering methods include MiniBatch KMeans, affinity propagation, MeanShift, spectral clustering, Ward, Agglomerative Clustering, DBSCAN, OPTICS, BIRCH, and Gaussian Mixture. Different algorithms can use different way of distance measuring that the best one should be decided to use based on the dataset characteristics. Two important measures of distance between points in vector spaces are the Euclidean distance and the cosine similarity. we can usually measure Euclidean distances in a dataset during preliminary data analysis. Some machine learning algorithms, such as K-Means, work specifically on the Euclidean distances between vectors. On the other hand, Cosine similarity between two vectors corresponds to their dot product divided by the product of their magnitudes.

In our case, the decision as to which metric to use depends on retrieval of the most similar texts to a given document, which normally function better with cosine similarity.

Next step is phrase clustering that puts similar phrases into a same group to shrink the number of phrases and focus on the content; also, it helps to relate strategies and risks that share the same words or synonyms. For example, the phrases of “supply chain risk”, “supply risk”, “global pharmaceutical supply-chain risk” and “supply chain risk management strategy” are all semantically related to “supply” as a cluster. Clustering technique in this research consists of two phases vectorizing and grouping. For vectorizing the previously described method of USE is used since it showed promising results.

For grouping k-means algorithm alongside with the similarity matrix method are tested in terms of distance calculation and clustering. K-means clustering minimizes within-cluster variances (squared Euclidean distances), but not regular Euclidean distances, which would be the more difficult Weber problem. On the other hand, Inner product spaces generalize the Euclidean spaces to vector spaces of any (even infinite) dimension, which are studied in functional analysis. Therefore, the similarity matrix method which in other word is the inner

product of vector matrix is used owing to more accurate distance calculation and grouping outcomes.

The similarity matrix is begun by the generated vectors using the USE. These generated vectors are a list of 512 decimal numbers that can be imagined as coordinates in a 512 dimensions space. We calculate a matrix of N*N which N shows the number of phrases and cell XY in this matrix shows the distance of phrase X vector with the phrase Y vector. The distance is calculated using the inner product of the matrix. All distances are normalized and inverted; hence they are all in range of (0 to 1), with 0 as the least similar or furthest away, and 1 as the most similar or closest. A threshold of 0.7 is considered and all distances above this threshold round up to 1 and ceil down to 0 for the ones below this threshold. We reached to this threshold by trial and error until the reasonable outcomes were obtained. We can also refer to the (Zahoránszky-Kőhalmi, Bologa, & Oprea, 2016) research that they considered this threshold in their study.

After having the similarity matrix, the row with the largest sum is found and all the columns which contain the numeral 1 in the selected row should be added to the group. Next step for adding objects to the current group is to take those indices from the group and repeating the previous procedure. Whenever a new group is recognized the values in the matrix are reset, but only in the rows and columns with indices of newly grouped objects. The procedure is repeated until no more numeral 1 is left in the matrix.

2.7. 3 Post-Processing

After constructing the data frame, columns such as frequencies and file names continue to be updated based on counting duplicate phrases and appending them to these columns. Subsequently faulty and unwanted rows are removed by the data supervisor. This step needs to be done only once and then the program compares the accepted and unaccepted phrases and by considering a set of tokens called “stop words” it helps the computer to automatically filter unwanted results.

2.8 Reporting the findings

In terms of validation, however automated methods have demonstrated performance in different areas, they cannot eliminate the need for reading texts by researchers and it necessitate researchers guide the process and interpret the outputs (Grimmer & Stewart, 2013).

To assess our findings' validation, a sample of ten papers are selected randomly and risks and risk mitigation strategies are extracted manually. Also, the similar way to validate results has been done in (Jones-Diette, Dean, Cobb, & Brennan, 2019) study. In the end, we compare our findings and results from algorithms with the results that are obtained manually and by reading the sample documents to see how similar they are. The findings are presented in the result section and are propounded in the discussion part of the research.

CHAPTER 3

RESULTS

3.1 Searching the Literature

Keyword phrases are searched in three search engines of Web of Science, PubMed, and Google Scholar. After searching different keywords in Web of Science, PubMed, and Google Scholar; 1551, 1370, and 1284 articles are extracted respectively. In other words, a total of 4205 papers are imported into DistillerSR software to execute two phases of title screening and title and abstract screening.

3.2 Screening the Literature

After importing 4205 articles in DistillerSR, running duplicate detection in the software helps us to find and remove all duplicate references among different search engines. As shown in Figure 3.1. duplicate detection can check any combination of fields to compare title, author, or abstract.

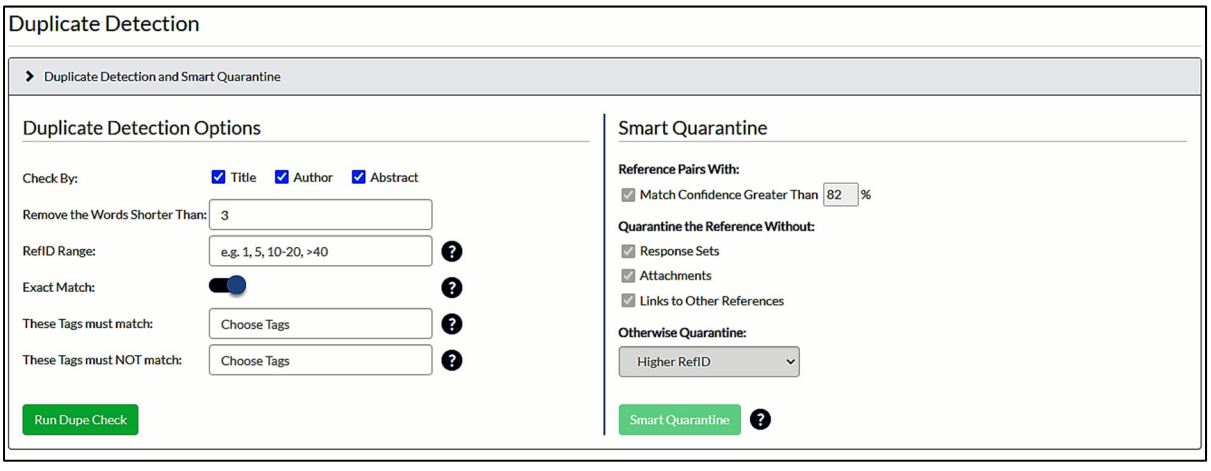

Figure 3.1 Duplicate detection of studies in the DistillerSR software

After executing this option 824 references were detected as duplicate, and 3381 references remained to do the first phase of the screening process.

3.3 Assessing Quality and Extracting Data

While the references were checked according to inclusion/exclusion criteria, the k-fold cross-validation method in DistillerSR was applied multiple times to assess the quality of included/excluded references. After conducting title screening and the next screening level of title and abstract 3103 references were excluded. As shown in Figure 3.2., in the end, 278 references were considered as our project's primary studies.

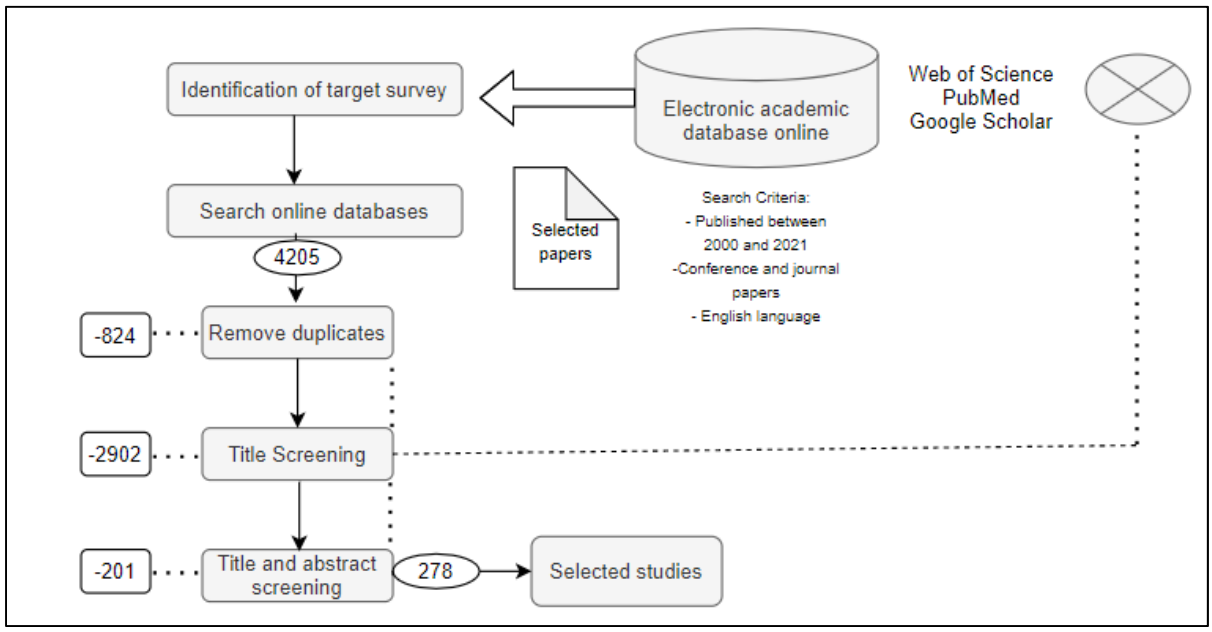

Figure 3.2 Search and selection process

3.4 Analyzing Data

As our discussion in the methodology section, two processing paths were considered to reach the results for risks and risk mitigation strategies in the pharmaceutical supply chain separately. In this section, the results are presented and discussed in two sub-sections of risk and uncertainty, and risk mitigation strategy.

3.4. 1 Risk and Uncertainty

The data frame consists of 8 columns, “Cluster”, “File”, “Keyword”, “Phrase”, “Sentence”, “Local frequency”, “Global Frequency”, and “Files count”. In the following, the columns of “Cluster” or group, “File” or reference, “Phrase” which is the risk here, and “Sentence” are regarded in a table. To avoid having too much information in the table, the result of the other columns will be discussed at the end. “Sentence” is a brief description or one of the sentences in the literature encompassing that risk and is filled for the risks that seemed unclear by itself.

It should be noted that 317 risks in general are extracted in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other.

Three risks that are more discussed in the literature according to the columns of “Local frequency”, “Global Frequency”, and “Files count” include supply risks, operational risks, and quality risks respectively. Therefore, we can infer these risks are more important in the pharmaceutical supply chain as different researchers have investigated them. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively. A summary of risks groups and risks are shown in Figure 3.3.

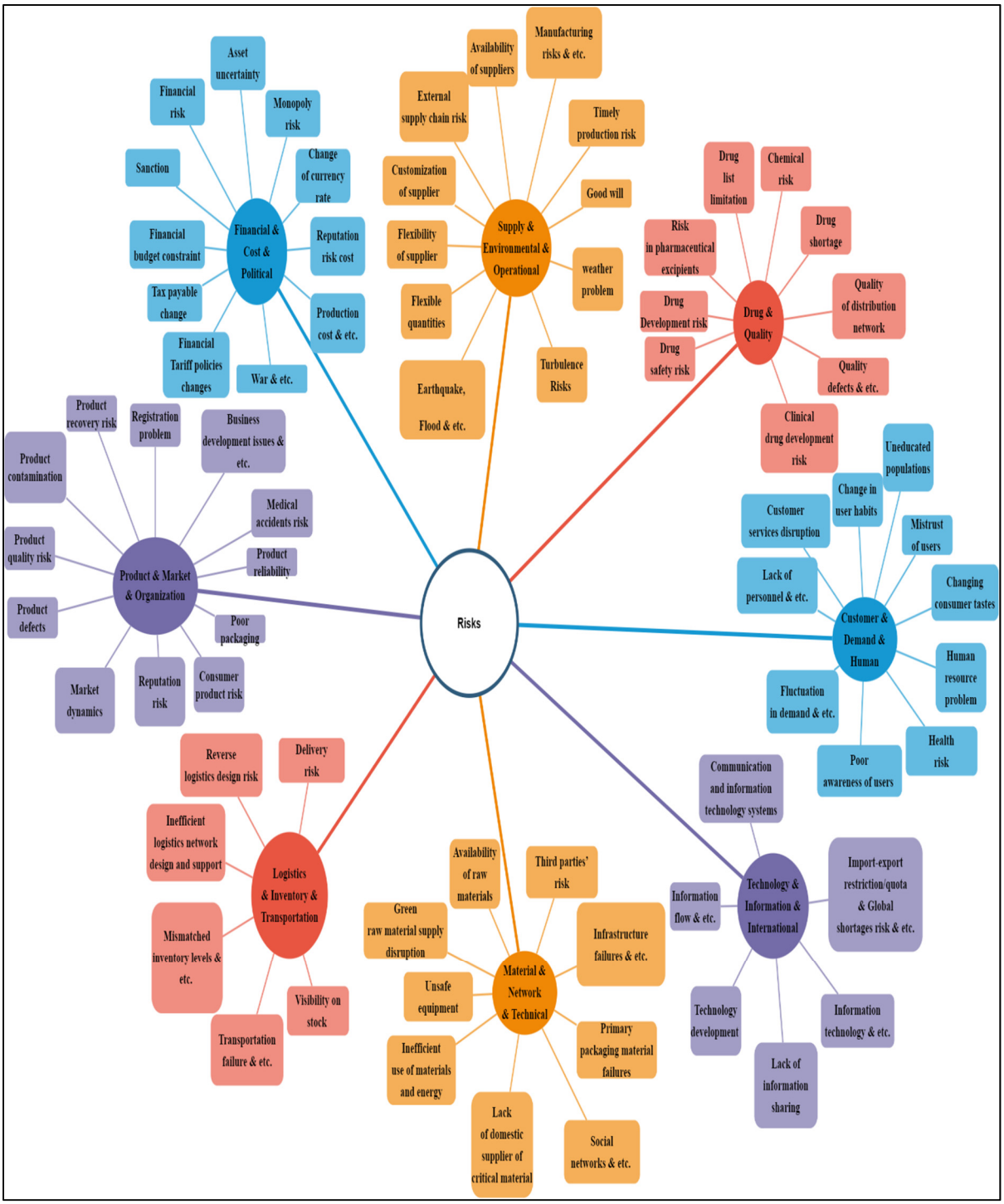

Figure 3.3 Diagram of risks and risks groups

There are a wide range of risks affecting products throughout their life cycle. Different studies have worked on products risks in different areas such as distribution, manufacturing,

contamination, regulation, quality, development, etc. to identify products related risks. For instance, (Lowman, Trott, Hoecht, & Sellam, 2012) studied about new product development, and innovation risks and problems which could arise from outsourcing this activity. As another example, we refer to (Xu, Boehm, & Zheng, 2016) research that the authors worked on pharmaceutical product quality risk that can be used by government procurement officials, to minimize the risk of degradation and dissolution failure.

Table 3.1 Product risks and uncertainties

Reference	Risk	Sentence	Group
(Davis & Abraham, 2011)	Consumer product risk	US environmental and consumer product risk regulation was more precautionary during the 1970s and early 1980s.	Product
(Enyinda & Tolliver, 2009)	Counterfeit product risk	Many companies are known to be making legitimate products at one end of the factory and counterfeit products at another.	
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Virus contamination risk		
(Gómez & España, 2020)	Cross-contamination of finished product, Poor packaging, Product contamination		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Flexibility in product variety		
(Grujić, Morača, & Fajsi, 2020)	Lack of product quality control	Management of security risks refers to the development of the work plan in pharmaceutical companies.	
(Kumar, et al., 2019)	product recovery risk	Pharmaceutical companies must pay attention to reverse logistics to enhance their effectiveness in product recovery.	
(Abbasian, et al., 2020)	Low trust in domestic products	It is shown that demand-related risks are mostly linked to low trust in domestic products, marketing issues particularly at the international level, and demand fluctuations.	
(Raka & Liangrokapart, 2017)	Registration problem	Manufacturers must be aware of IP laws, must seek approval from the FDA, and must observe drug registration laws.	
(Grujić, Morača, & Fajsi, 2020)	Patenting the product	The pharmaceutical industry is subject to a wide variety of powerful institutional and regulatory pressures	
See more product risks in Appendix I, Table-A I-1.			

There are different risks in the area of logistics that pharmaceutical firms need to be aware of them. For example, network and reverse logistics inbound and outbound infrastructure and logistics with complex nodes and ends with provision to reverse flow of products is insecure for network partners (Vishwakarma, Prakash, & Barua, 2016). Different logistics risks are gathered in the table 3.2.

Table 3.2 Logistics risks and uncertainties

Reference	Risk	Sentence	Group
(Grujić, Morača, & Fajsi, 2020)	Unfavorable location	Focuses on geographic location. Issues associated with physical and infrastructure facilities are considered	Logistics
(Huq, Pawar, & Rogers, 2016)	Accessibility of logistics provision	physical and infrastructure facilities are considered	
(Kumar, et al., 2019)	Inefficient logistics network design and support	This represents inefficiency in logistics activities in the transportation of green materials in the pharmaceutical industry.	
(Gómez & España, 2020)	Improper handling of finished product pallets		
(Kumar, et al., 2019)	reverse logistics design risk	Any flaw in designing the reverse logistics process	
(Elamrani, Benabbou, & Berrado, 2016) (Vishwakarma, Prakash, & Barua, 2016)	logistics risk		

Materials risks also can affect pharmaceutical supply chain in different cases. For example, lack of domestic suppliers for necessary materials, limited raw material supply, availability, quality, raw material prices, etc. are among the risks that can lead to negative effects for pharmaceutical organizations and in the supply chain. The findings from (Yaroson, Sharief, Shah, & Breen, 2018) research showed that lack of active ingredients is one reason of medicine shortages that has significant impacts on patients.

Table 3.3 Material risks and uncertainties

Reference	Risk	Sentence	Group
(Cundell, Guilfoyle, Kreil, & Sawant, 2020) (Moktadir M. , et al., 2018)	Availability of raw materials	Regarding the availability of raw materials, for example, drug substances, excipients, solvents, processing supplies, and packaging materials …	Material
(Kumar, et al., 2019)	Green raw material supply disruption	Disturbances in supplying of any key green raw material may disrupt the entire value chain	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Hazardous material risk	Risk of hazardous material is caused when the transported substance is contaminated due to exposure to harmful substances while transporting.	
(Kumar, et al., 2019)	Inefficient use of materials and energy	Inefficient use of material and energy may create severe ecological and social problems in healthcare sector.	
(Abbasian, et al., 2020)	Lack of domestic supplier of critical material		
(Paul, Kabir, Ali, & Zhang, 2020)	Gasoline related disruption		
(Gómez & España, 2020)	Primary packaging material failures		
(Yaroson, Sharief, Shah, & Breen, 2018)	Lack of active pharmaceutical ingredients		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Raw material quality		

Many risks are related to supply in the pharmaceutical supply chain such as availability of suppliers, customization and flexibility of supplier, inconsistency in competitive and supply chain strategies, mismatch between market demand and supplier responsiveness, partnership with supplier, etc. Different parts of supply chain could be influenced by a large diversity of risks and the SC risks can have significant effects on performance of firms in short-term and long-term.

Table 3.4 Supply risks and uncertainties

Reference	Risk	Sentence	Group
(Ouabouch & Amri, 2013) (Kumar, et al., 2019)	Supplier failure	A supplier failure, for example because of a weak logistical performance, or even a bankruptcy, is also regarded as the most critical risk factor.	Supply
(Huq, Pawar, & Rogers, 2016)	Mismatch between market demand and supplier responsiveness	One of the disturbance factors managers should be aware of while configuring their supply chains is a mismatch between market demand and supplier responsiveness.	
(Amemba, 2013)	Turbulence Risks		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Fragmentation Good will Flexible quantities Customization of supplier Flexibility of supplier	It was agreed that the top-rated risks included fragmentation of the supply chain	
(Zamora Aguas, Adarme, & Serna, 2013)	Disruptions in the supply		
(Vishwakarma, Garg, & Barua, 2019)	Inefficient supply network	Inefficient supply affects PSC competition which considers product perishability, brand differentiation of the product, as well as discarding costs.	
(Vishwakarma, Garg, & Barua, 2019)	Unawareness about PMS in supply chain	Performance measurement and metrics have an important role to play in setting objectives, evaluating performance, and determining future courses of actions.	
(Enyinda C. , 2017) (Friemann & Schönsleben, 2016) (Gómez & España, 2020) (Abbasian, et al., 2020)	Global supply chain risk	For the many pharmaceutical firms, managing global supply chain risk has become prominent in their business operation agenda.	
See more supply risks in Appendix I, Table-A I-2.			

Financial risks are always important in terms of fiscal policy, tax regimes, intellectual property rights, investments, patents, and penalties. The pharmaceutical industry has different

government liabilities regarding taxation and fees. Internal policies in the companies must be robust to change their financial structure. For instance, investment risks are increasing with high pressure on research and development which is extremely risky. Significant efforts has been made by value chain members to adapt their strategies as per variations in trade/pricing policies that could lead to the risk of frequent changes in policy effect trading capabilities of chain partners (Vishwakarma, Prakash, & Barua, 2016). Different financial risks are presented in the table 3.5.

Table 3.5 Financial risks and uncertainties

Reference	Risk	Sentence	Group
(El Mokrini, El Mhamedi, & Berrado, 2015) (Mokrini & Aouam, 2020) (Oreskovich & Gittins, 2016) (Rajagopal, Shanmugam, & Nandre, 2021)	Financial risk	Supply chain disruptions which are events that disrupt the normal flow of goods and services within a supply chain have been reported to have adverse effects on the financial and operational performance of the firm.	Financial
(Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Asset uncertainty	Two processes are related to uncertainties about the value of the project upon completion of the R&D phase (asset uncertainty) and to the uncertainty about the required investment cost (cost uncertainty).	
(Yaroson, Breen, Hou, & Sowter, 2021)	Price manipulation		
(Kumar, et al., 2019)	Financial budget constraint	This risk is related to constraints in financial budgets as research and trials of pharmaceutical products are highly expensive.	
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Tax payable change, Financial Tariff policies changes, Cash flow		
(Amemba, 2013)	Financial markets uncertainty	Risks can come from uncertainty in financial markets.	
(Yaroson, Sharief, Shah, & Breen, 2018)	Monopoly risk	Under pressure to compete in both domestic and international markets, companies need to create conditions that enable them to remain competitive and to progress and develop.	
(Moktadir M. A., et al., 2018)	Financial restriction	Poor financial plans and/or financial restrictions can hamper the smooth functioning of PSC.	

Reference	Risk	Sentence	Group
(Niu, 2017)	Interest rate fluctuation Change of currency rate	Aside from foreign exchange risk, Pfizer observes interest rate risk because the company strives to maintain a predominantly floating-rate basis position.	
(Narenjian, Riahi, & Kheirabadi, 2019)	Change of payable taxes Changing custom policies and tariffs		
(Yaroson, Breen, Hou, & Sowter, 2021)	Economic uncertainty		
(Moktadir M. A., et al., 2018)	Dynamic foreign exchange rates	Fluctuation in the foreign exchange rates can affect in profit margin of the pharmaceutical products.	
(Abbasian, et al., 2020)	Dual exchange rates		
(Grujić, Morača, & Fajsi, 2020)	External fraud Economic conditions	pranks, misuse, theft by employees, third parties, etc.	
(Kumar, et al., 2019)	Insurance risk	Risk related to high insurance/risk coverage premiums.	

Firms in the pharmaceutical supply chain have been always in danger of wasting valuable resources, unavailability of medications, safety issues, and drug shortages. One of the major risks that countries have been struggling with for a long time is drug shortage. Many factors are presented in different studies that relatively have tried to explain the complicated root causes. In research conducted by (Li, et al., 2016), the authors worked on safety, efficacy, and stability of drugs that are affected by pharmaceutical excipients and mentioned that pharmaceutical excipients create serious threats to patients.

Table 3.6 Drug risks and uncertainties

Reference	Risk	Sentence	Group
(Abbasian, et al., 2020)	Drug list limitation		Drug
(Li, et al., 2016)	Risk in pharmaceutical excipients	Supply chain risk in pharmaceutical excipients has always been the most prominent problem to threaten the safety of excipients.	
(Raka & Liangrokapart, 2017)	Drug Development risk	Risks that are associated with the new generic drug development process, which is the initial stage of the pharmaceutical supply chain, need to be considered and	

Reference	Risk	Sentence	Group
		eliminated.	
(Hartford, et al., 2006)	Drug safety risk		
(Nicholson, Peterson, & Yektashenas, 2012)	Drug risk		
(Dieck, Betger, Kracov, Manion, & Tanner, 2009)	Medicine safety	Both the pharmaceutical industry and FDA recognize that medicine safety evaluations are far from complete when a medicine is approved.	
(Ågerstrand, et al., 2015)	Chemical risk		
(Zu'bi & Abdallah, 2016) (Moosivand, et al., 2021)	Drug shortage	Pharmaceutical supply chain is susceptible to many risks leading not only to wasting valuable resources but also to disrupting the availability of medications resulting in the growing problem of drug shortages.	
(Van Bortel, et al., 2018)	Clinical drug development risk	The importance of adaptive trial designs in early clinical drug development.	
(Fleischhacker & Zhao, 2011)	Uncertainty in actual drug requirements		

Different issues put organizations under risk to meet customers' requirements and desired quality. Companies must follow the development of technologies to achieve this. It is necessary to satisfy the future requests of users in the market. Participants involved in risk assessment had major experience in customer relationships and cooperation with them. For example, there are different risks arising between doctors and users such as changes in users' habits that should be recognized. A summarization of customers' risks is shown in the table 3.7.

Table 3.7 Customer risks and uncertainties

Reference	Risk	Sentence	Group
(Blake Scott, 2006)	Public distrust risk	The drug industry found itself responding to renewed and heightened risk of public distrust, loss of patent protection, and price controls.	Customer
(Jaberidoost M. , Nikfar, Abdollahiasl, &	Customer services disruption		

Reference	Risk	Sentence	Group
Dinarvand, 2013)			
(Grujić, Morača, & Fajsi, 2020)	Change in user habits Uneducated populations	The requirements of patients are determined by assessments of their prognosis, which are continually changing.	
(Grujić, Morača, & Fajsi, 2020)	Mistrust of users	This risk factor considers the knowledge, capabilities, and roles of the people from pharmaceutical companies to contact customers and develop trust.	
(Narenjian, Riahi, & Kheirabadi, 2019)	Changing consumer tastes		
(Botelho & Reis, 2015)	Risk of adverse events	With this information, patients using these drugs can be included in individual actions of monitoring the pharmacotherapy in such a way as to reduce the risk of adverse events.	
(Vishwakarma, Garg, & Barua, 2019)	Changing patient target group	Continually growing and rapidly aging population, rapidly changing healthcare requirement would be task for pharmaceutical to respond.	
(Claycamp, 2007) (Botelho & Reis, 2015)	Health risk		
(Grujić, Morača, & Fajsi, 2020)	Poor awareness of users	Pharmaceutical companies are legally required to disclose full information to their users regarding their products' potential outcomes with the intention that such disclosures will lead to normatively better decisions when buying drugs.	

Pharmaceutical firms need to have acceptable technological capabilities including integrated information system, efficient technological infrastructure, IT applications etc. to be able to support different activities such as traceability across the SC, visibility on inventory, and so on so forth. It is noteworthy that technology can also cause different risks like failure in product traceability because of poor information system integration, hardware and software issues, improving technology level, etc.

Table 3.8 Technology risks and uncertainties

Reference	Risk	Sentence	Group
(Kumar, et al., 2019)	Cold chain technology risk		Technology
(Narenjian, Riahi, & Kheirabadi, 2019)	Communication and information technology systems		
(Kumar, et al., 2019)	Green technology related issues		
(Grujić, Morača, & Fajsi, 2020)	Information technology	Focuses on the hardware and technology associated with the software used and their cohabitation.	
(El Mokrini, El Mhamedi, & Berrado, 2015) (Mokrini & Aouam, 2020)	Technological risks		
(Vishwakarma, Prakash, & Barua, 2016)	Technology/adoption transfer risk	Timid technology/adoption transfer risk arises because small and medium enterprises were quite reluctant to new technologies to join world class manufacturing.	
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Technology development		
(Rajagopal, Shanmugam, & Nandre, 2021)	IT system breakdown risk		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Technology level		
(Ouabouch & Amri, 2013)	Outage of IT System		
(Kumar, et al., 2019)	Inefficient IT applications	Any inadequacy in IT applications in adopting GSC concepts in the pharmaceutical industry.	
(Vishwakarma, Garg, & Barua, 2019)	Dispersed IT infrastructure	The data-driven system needs complete IT infrastructure, to enhance visibility, reduce counterfeit, leads to secure and quality medicine.	
(Grujić, Morača, & Fajsi, 2020)	Technological change risk	Technological change risk comprises improvements in technology that render current technology and development efforts obsolete	

Pharmaceutical companies are faced with different risks and problems in the inventory field, and it is vital to know these risks. For example, inventory shortage is one of the important risks that need to be managed because it can threaten patients' life. From a managerial context, proper storage and handling is suggested in pharmaceutical materials to minimize loss due to expiry of the purchased or produced materials (Moktadir M. A., et al., 2018). A summarization of inventory risks is presented in the table 3.9.

Table 3.9 Inventory risks and uncertainties

Reference	Risk	Sentence	Group
(Kumar, et al., 2019)	Capacity and inventory related disruptions	Risks associated with capacity and inventory related problems in recovering pharmaceutical products.	Inventory
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Visibility on stock Inventory management		
(Grujić, Morača, & Fajsi, 2020)	Inventory	Firms may derive more benefit from establishing inventory policy parameters, increasing coordination, and reducing supplier lead times.	
(Ouabouch & Amri, 2013)	Inventory shortage		
(Moktadir M. A., et al., 2018)	Storage contamination risks	Industries are facing issues related to storage contamination during storage of raw materials and finished goods, as pharmaceutical products need to be maintained at prescribed conditions.	
(Huq, Pawar, & Rogers, 2016)	Mismatched inventory levels	Disruptions, e.g., due to quality, environmental, health or safety issues leading to untimely delivery of products or mismatched inventory levels.	

Information-related risks is also another issue that should be addressed in the SC. Providing relevant information across the SC is helpful in different parts of supply chain operations and of course, having risks simultaneously that should be managed. Therefore, different types of risks should be identified when dealing with information systems (Prater, 2005). For example, controlling the communication with suppliers and transmitting data or break in information flow can pose a company at risk of error in order processing or inventory capacity.

Table 3.10 Information risks and uncertainties

Reference	Risk	Sentence	Group
(Huq, Pawar, & Rogers, 2016)	Break in information flow Difficulty in transmitting data		Information
(Vishwakarma, Garg, & Barua, 2019)	Inefficient information system	Any firm in the pharmaceutical industry requires efficient and effective MIS to support managerial functions.	
(Rajagopal, Shanmugam, & Nandre, 2021)	Information asymmetry risk	The gap between the focal firm's perceived supplier's CSR performance and the supplier's actual CSR performance.	
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Information flow		
(Elamrani, Benabbou, & Berrado, 2016) (Mehralian, Gatari, Morakabati, & Vatanpour, 2012)	Information systems		
(Mokrini & Aouam, 2020) (Raka & Liangrokapart, 2017)	Information-related risks		
(Yaroson, Breen, & Matthias, 2017)	Lack of information sharing	Information is the foremost requirement for doing any activity. Lack of information sharing can affect the regular activity of PSC process, in terms of supplying of medicines, pricing, etc.	
(Grujić, Morača, & Fajsi, 2020)	Loss of access to information	Information has been deployed in various areas of the healthcare sector.	
(El Mokrini, El Mhamedi, & Berrado, 2015)	Strategic information leakage risk		
(Grujić, Morača, & Fajsi, 2020)	Unauthorized access to information	Course of information influences relations between managers and team.	
(Grujić, Morača, & Fajsi, 2020)	Undeveloped information structure	Information has been deployed in various areas of the healthcare sector, including structure.	
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Epistemic uncertainty	Minimizing total cost and unmet demand were aimed for a pharmaceutical case study with a high degree of epistemic uncertainty.	

Considering risks on the both supply-side and demand-side is necessary for managers to excel in their supply chains management activities such as demand forecasting and managing relationships with suppliers (Ouabouch & Amri, 2013). Inadequate and unclear information on demand causes different challenges and risks in the PSC. Researchers have considered demand risks from different aspects of minimizing cost and unmet demand, introducing inventory-routing model by regarding a deterministic demand function, estimating demand and risks of medicines demand according to price and quality of products, etc. (Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)

Table 3.11 Demand and Cost risks and uncertainties

Reference	Risk	Sentence	Group
(Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)	Bullwhip effects	The bullwhip effect makes hard for pharmaceutical companies to anticipate exact demand, which may reduce the business performance.	Demand
(Lücker, Seifert, & Biçer, 2019)	Demand risks		
(Huq, Pawar, & Rogers, 2016) (Moktadir M. A., et al., 2018)	Demand forecasting errors	Inaccurate demand forecasts will result in poor supply chain planning and may even create in gap demand and supply of products in a PSC context.	
(Elleuch, Hachicha, & Chabchoub, 2014)	Fluctuation in demand		
(Ouabouch & Amri, 2013)	Unexp. demand fluctuations		
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Cost risk		Cost
(Huq, Pawar, & Rogers, 2016)	Costs of distant production	Costs of distant production: The Sourcing Director agreed that cost is a key driver in terms of where to outsource for long-term competitiveness. Even though cost-attractive suppliers are considered, the cheapest price is not always the best due to hidden costs associated with distant production.	
(Jaberidoost M. ,	Costs related to supply		

Reference	Risk	Sentence	Group
Nikfar, Abdollahiasl, & Dinarvand, 2013)	Production cost		
(Paul, Kabir, Ali, & Zhang, 2020)	Increase of transportation costs		
(Kumar, et al., 2019)	Procurement costs risk	Risks related to disturbances in procurement of green or eco-friendly raw materials.	
(Rajagopal, Shanmugam, & Nandre, 2021)	Reputation risk cost	SC managers should not underestimate the indirect reputation risk costs imposed by the quality and unethical governance risk.	

We can point out transportation as another field that poses different risks during the transport and storage phases. For example, improper handle of pallets of finished products, poor pest control of transport vehicles, bad conditions of roads, improper fleet, damaging products because of pressure changes during transport are some of the risks in the transporting phase (Gómez & España, 2020).

Table 3.12 Transportation risks and uncertainties

Reference	Risk	Sentence	Group
(Grujić, Morača, & Fajsi, 2020)	Drug delivery	Firms may derive more benefit from establishing inventory policy parameters, increasing coordination, and reducing supplier lead times.	Transportation
(Abbasian, et al., 2020) (Elleuch, Hachicha, & Chabchoub, 2014)	Transportation risks		
(Gómez & España, 2020)	Transport and storage		
(Ouabouch & Amri, 2013)	Transportation failure Delivery chain disruptions		
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Finished goods transport	Distribute finished goods using dedicated transportation in place of common carriers.	
(Paul, Kabir, Ali, & Zhang, 2020)	Freight damage in transportation Port stoppage and		

Reference	Risk	Sentence	Group
	congestion		
(Huq, Pawar, & Rogers, 2016)	Internal transport Untimely delivery of products		
(Mehralian, Gatari, Morakabati, & Vatanpour, 2012)	Delivery risk	Delivery risk can make an important contribution to mitigate the risk of pharmaceutical industry.	
(Gatica, Papageorgiou, & Shah, 2003)	Delivery time uncertainty		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Delivery reliability, Flexibility in delivering, Timely delivery		
(Paul, Kabir, Ali, & Zhang, 2020)	Infrastructure bottleneck in port		
(Narenjian, Riahi, & Kheirabadi, 2019)	Reliability of delivery		
(Grujić, Morača, & Fajsi, 2020)	Distribution channels	The uncertainty of drug and medical service distribution channels is conditioned by the dynamic and complex market and pharmaceutical environment.	
(Raka & Liangrokapart, 2017)	Distribution problem		
(Gómez & España, 2020)	Bad road conditions, Improper fleet		
(Moktadir M. A., et al., 2018)	Increase in freight charges	From a pharmaceutical organizational context, increase in freight charges will have a significant impact on profit margins.	

Some of the risks in the supply chain are from market with different sources such as presentation and approach to market (Amemba, 2013). For instance, money market volatility, market completion as there is always a challenge between generics and branded price driven products, international marketing issues, dynamism of markets, price in the market, trade barriers, etc. are some of the market-related risks in the pharmaceutical supply chain.

Table 3.13 Market risks and uncertainties

Reference	Risk	Sentence	Group
(Ouabouch & Amri, 2013)	Decline in market prices		Market
(Amemba, 2013) (Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Market risk		
(Vishwakarma, Prakash, & Barua, 2016)	Money market volatility	Due to international trades in bulk money market risk usually high.	
(Vishwakarma, Prakash, & Barua, 2016)	Government and market related risks		
(Abbasian, et al., 2020)	International marketing issues		
(Kumar, et al., 2019)	Market dynamics	Market supply and demand affects the GSC efficiency.	
(Grujić, Morača, & Fajsi, 2020)	Market segmentation	Market segmentation and product diversification.	
(Davis & Abraham, 2011)	Pre-market risk	There may have been little need for a harmonized standard regarding pre-market risk identification and assessment.	
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Time to market		
(Vishwakarma, Garg, & Barua, 2019)	Disparity in trading partner's capability	The disparity in trading partners' capability is a major barrier to the integration of agile supply chain because partnership fails due to poor capability at partner's end.	
(Abbasian, et al., 2020)	Low international trading experience		
(Yaroson, Breen, Hou, & Sowter, 2021)	Parallel trade	In responding to parallel trade in the environment, some wholesalers and pharmacists decide to sell abroad for profit, especially when the exchange rate is favorable.	
(Huq, Pawar, & Rogers, 2016)	Problems communicating with your trading partners		
(Raka & Liangrokapart,	Trade barrier		

Reference	Risk	Sentence	Group
2017)			
(Vishwakarma, Prakash, & Barua, 2016)	Trading capability risk	The capacity and capability of suppliers to produce quality medicines is always a concern under fulfilment of sudden demands pertaining to financial loses under uncertainty.	
(Vishwakarma, Garg, & Barua, 2019)	Weakened global trade	Due to global market trading complexity small and medium enterprise has a strategic disadvantage towards growth.	

Changes of critical material and process parameters in the boundaries of the design space always yields product with desired characteristics. Also, the level of effort to handle risks must be compatible with the level of risk. By laying more emphasis on high-risk events the protection level of patient is increased. The focus on risk to the patient together with flexible development approach saves invaluable resources, increases confidence on quality and reduces compliance risk. The principle of quality risk management can be applied to different aspects of pharmaceutical quality such as product development, technology, etc (Charoo & Ali, 2013). Identified quality risks are shown in the table 3.14.

Table 3.14 Quality risks and uncertainties

Reference	Risk	Sentence	Group
(Vartak & Bhagure, 2012)	Co-coordinating quality risk	The decision makers should take the responsibility of co-coordinating quality risk management across various functions and department of organization.	Quality
(Huq, Pawar, & Rogers, 2016)	Internal quality risk Quality defects, Quality of skills, education level and talent of the labor force		
(Gray, Roth, & Leiblein, 2011)	Manufacturing-related quality risk location-related quality risk	We know of no better assessment of manufacturing-related quality risk that is available for many plants with non-identical product lines.	
(Narenjian, Riahi, & Kheirabadi, 2019)	Quality of distribution network		
(Charoo & Ali, 2013) (Ismael & Ahmed, 2020)	Quality risk	Lack of quality products can threaten human life in case of pharmaceutical products. It is important to produce the pharmaceutical products with highest	

Reference	Risk	Sentence	Group
		quality as their tendencies to directly affect the health of the patient.	
(Balmoș, Lazăr, & Burcea Dragomiroiu, 2014)	Cross contamination risk	The cleaning process of the manufacturing equipment validated is considered efficient for the removal of residues, of the degradation compounds and of the cleaning agents in order not to exist any risk related to the cross contamination of active substances	
(Gray, Roth, & Leiblein, 2011)	Single-inspection quality risk		

Table 3.15 Political risks and uncertainties

Reference	Risk	Sentence	Group
(Narenjian, Riahi, & Kheirabadi, 2019)	War Political changes of the country Sanction		Political
(Gray, Roth, & Leiblein, 2011)	Expropriation risk	The expropriation risk of our "offshore" location is essentially equivalent to the domestic location.	
(Amemba, 2013)	Political Risks	Political risks affect supply chain performance.	
(Huq, Pawar, & Rogers, 2016)	Level of political instability Societal disruptions/strikes		
(Paul, Kabir, Ali, & Zhang, 2020)	Corruption in customs, Political unrest, Terrorism		
(Raka & Liangrokapart, 2017)	Government policy problem		
(Kumar, et al., 2019)	Management of policy failures	Failure in management policies may disrupt the adoption of GSC concepts in pharmaceutical industry effectively.	
(Kumar, et al., 2019)	Failure of government policies	Failure in government policies in terms of its design and implementation would have a negative impact on GSC adoption in the pharmaceutical industry.	
(Blake Scott, 2006)	Socio-political context of risk	Socio-political context of risk construction in the pharmaceutical response to the war on bioterrorism.	

Companies operate within different environments, with various challenges, opportunities, and risks. Uncontrollable environmental circumstances, such as internationalization, technology advancement, cultural changes, natural disasters, etc. have remarkable effects on organizations. Managers should be able to identify and deal with such problems and risks.

Table 3.16 Environmental risks and uncertainties

Reference	Risk	Sentence	Group
(Narayana, Elias, & Pati, 2014) (Wang & Jie, 2020)	Environmental risks		Environmental
(Ågerstrand, et al., 2015)	Aquatic environmental risk		
(Khan, Ju, Baloch, & Uddin, 2019)	Macro-environmental risk	The results confirm the adverse effects of macro-environmental risks on organizational self-development.	
(Davis & Abraham, 2011)	Ecological uncertainty	The 'ecological uncertainty' of approving these drugs involved accepting risks that were possibly 'avoidable in exchange for expected benefits.	
(Paul, Kabir, Ali, & Zhang, 2020)	Earthquake, Extreme weather problem, Flood, Hurricane/cyclone		
(Huq, Pawar, & Rogers, 2016)	Disparity in national cultures		
(Yaroson, Sharief, Shah, & Breen, 2018)	Natural disasters	Natural disasters and uncontrollable events	

Table 3.17 Human risks and uncertainties

Reference	Risk	Sentence	Group
(Enyinda & Tolliver, 2009)	Human lives at risk	The counterfeit pharmaceutical trade supply chain is an activity that puts human lives at risk and undermines the credibility of public health systems.	Human
(Raka & Liangrokapart, 2017)	Human resource problem		
(Elleuch, Hachicha, & Chabchoub, 2014)	Human risk Lack of personnel	In spite of automating most of the production processes, still there are some disruptions leading to human risks.	

Reference	Risk	Sentence	Group
(Grujić, Morača, & Fajsi, 2020)	Inadequate coordination of professional staff Incompetent staff Injuries of employees	It considers the knowledge, capabilities, and roles of people, as well as the team structure and organizational units associated with the daily schedule.	
(Vishwakarma, Garg, & Barua, 2019)	Improper training of employees	Employee training is essential to an organization's success. Despite the importance of training, a trainer can encounter resistance from both employees and managers.	
(Rajagopal, Shanmugam, & Nandre, 2021)	Unethical behavior	Risk of unethical behavior originating at the focal firm and the upstream spillover risks such as risk of non-implementation of CSR by suppliers	
(Kumar, et al., 2019)	Scarcity of skilled labor	Lack of awareness and understanding of the concepts of GSC and its operations from labor viewpoints.	
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Personal health and safety		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Skill of workers		
(Paul, Kabir, Ali, & Zhang, 2020)	Inadequate labor/labor strike		
(Grujić, Morača, & Fajsi, 2020)	Unsafe workplace	Management of security risks refers to the development of the work plan in pharmaceutical companies. Negative effects of risk factors are health risk for people employed in company, inability to do standard work in company.	
(Grujić, Morača, & Fajsi, 2020)	Personal conflicts	Pharmaceutical products have long development life cycles, and this presents a challenge for supply-chain managers, who must manage their internal relationships with doctors.	

Operations uncertainty and risk, financial risks, and quality-related risks are among internal uncertainty and risk. The internal operations uncertainty and risk can be referred as unexpected event, outcome and/or accident during the internal processes and mainly arises within the pharmaceutical firms, such as: production planning issues, manufacturing risks, power failure, mistakes in product line, resource allocation issues, etc.

Table 3.18 Operational risks and uncertainties

Reference	Risk	Sentence	Group
(Wang & Jie, 2020)	Internal operations uncertainty	The internal operations uncertainty and risk may refer to unexpected event, outcome and/or accident during the internal processes, they mainly occurred within the pharmaceutical firms.	Operational
(Blos, Hoeflich, & Miyagi, 2015) (Azghandi, Griffin, & Jalali, 2018) (Hosseini-Motlagh, Jazinaninejad, & Nami, 2020)	Operational risks		
(Friemann & Schönsleben, 2016)	Production planning under uncertainty		
(Sreedharan, Kamala, & Arunprasad, 2019)	Production risk		
(Vishwakarma, Prakash, & Barua, 2016)	Timely production risk	The weak coordination among SC partners enhances risk of timely production of goods leads to delays and disruption with reduction in reliability and trust.	
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	GMP manufacturing		
(Yaroson, Breen, & Matthias, 2017)	Manufacturing processes	The manufacturing process of a pharmaceutical which is tagged as cumbersome is another highlighted factor that exposes the supply chain to drug shortages. These manufacturing processes may range from the failure of the product to reach the desired quality as stipulated by the regulating bodies, or the lack of raw materials which most times is sourced outside the manufacturing regions.	
(Yaroson, Sharief, Shah, & Breen, 2018) (Xu, Boehm, & Zheng, 2016)	Manufacturing risks	The FDA is the primary regulator and companies must follow FDA regulatory protocols, and the ensuing complex manufacturing activities for new drug development are highly consuming of time and money.	
(Huq, Pawar, & Rogers, 2016)	Unforeseen and random interruptions in manufacturing		

Reference	Risk	Sentence	Group
	processes		
(Moktadir M. , et al., 2018)	Power failure	Power failures will disturb the production activity and hence lower the overall efficiency of PSC	
(Grujić, Morača, & Fajsi, 2020)	A narrow product line	Product lines and narrow product lines have high risk values	
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Certificate of GMP, Waste management		
(Varma, Pekny, Blau, & Reklaitis, 2008)	Sub-optimal resource management risk, Resource allocation policies under uncertainty		
(Kumar, et al., 2019)	Irresponsible use of land and facilities Inadequacy in waste management system	This represents a case of irresponsible use of materials, land, and facilities in adopting GSC concepts in the pharmaceutical industry. Risk related to inefficiency in handling the waste in the pharmaceutical industry.	

Table 3.19 International risks and uncertainties

Reference	Risk	Sentence	Group
(Abbasian, et al., 2020)	Defect of international vision, international certification issues		International
(Moktadir M. A., et al., 2018)	Fluctuation in imports arrival	The imported raw materials of the medical products are subjected to various fluctuations, which includes delay in the arrival of the shipping, delay in customs/movement of freights.	
(Paul, Kabir, Ali, & Zhang, 2020)	Import-export restriction/quota		
(Blake Scott, 2006)	Uncontrollable global risk		
(Iyengar S. , Hedman, Forte, & Hill, 2016)	Global shortages risk	Medicines most at risk of global shortages, especially those without clinically acceptable substitutes, must be identified and prioritized for global action.	

In a dynamic market environment, organizations must understand interdependencies through distribution channels, and to identify potential risk factors and their consequences. Risks caused by a low level of identified factors can have a negative impact on a firm's sustainability and entire distribution channel. Therefore, it is necessary to establish collaboration with all participants in the network to identify and resolve problems. Also network of drug distribution to pharmacies is of great importance since to manage public health. Creating a network of pharmacies consists of selecting vendors and negotiating procurement of raw materials; arranging product distribution; accepting, checking, and transferring products; authorizing payments; and customer reception (Grujić, Morača, & Fajsi, 2020).

Table 3.20 Network and technical risks and uncertainties

Reference	Risk	Sentence	Group
(Urushihara, et al., 2014)	Public risk communication	Involvement with responsibility in public risk communication; and the need for official guidelines and a regulatory department specialized in direct communications with healthcare professionals, considering the seriousness of the risk.	Network
(Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)	Network risk		
(Grujić, Morača, & Fajsi, 2020)	Social networks	With technological advancements, global Internet and social networks reach almost every country.	
(Yaroson, Breen, Hou, & Sowter, 2021)	Misalignment of goals	The relationship between vulnerabilities and antecedents of SC resilience may sometimes lead to outcomes such as flexibility and/or power asymmetry because of misalignment of goals.	
(Vishwakarma, Garg, & Barua, 2019)	The reluctance of support of dealers, distributors		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Third parties' risk		

Reference	Risk	Sentence	Group
(Enyinda C. , 2017)	Relationship risk		
(Abbasian, et al., 2020)	Technical risk		Technical
(Gómez & España, 2020)	Vehicle's breakdowns		
(Paul, Kabir, Ali, & Zhang, 2020)	Machine, equipment, or facility failure	Failure of any machines/equipment/ facility leads to disruptions in the manufacturing process of pharmaceutical products	
(Grujić, Morača, & Fajsi, 2020)	Unsafe equipment	Health system pharmacists often struggle with issues related to patient safety with bad instruments and other work products	
(Sreedharan, Kamala, & Arunprasad, 2019)	Infrastructure failures	This represents failure in infrastructure such as facility, machines, or high-tech equipment in adopting GSC concepts in the pharmaceutical industry.	
(Grujić, Morača, & Fajsi, 2020)	Technical equipment	Technology risk considers the overall availability of the technology with its practical use.	

Different studies have worked on organizational risks and regarding them in different contexts. For example, in research by (Elamrani, Benabbou, & Berrado, 2016) the authors investigated outsourcing-related organizational risks and in the risks identification part, they mentioned different risks of poor project governance, non-supportive corporate culture, poor system of authority, poor project planning, and miscommunication as organizational risks

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Table 3.21 Organizational risks and uncertainties

Reference	Risk	Sentence	Group
(Mehralian, Gatari, Morakabati, & Vatanpour, 2012)	Reputation risk	Lack of appropriate risk reduction can destroy public health confidence and reputation.	Organization
(Grujić, Morača, & Fajsi, 2020)	Lack of company reputation	It is necessary to talk about marketing risks	
(Rajagopal, Shanmugam, & Nandre, 2021)	proactive reputation risk		
(Abbasian, et al., 2020)	Business development issues		
(Jaberidoost M. , Nikfar,	Planning issues		

Reference	Risk	Sentence	Group
Abdollahiasl, & Dinarvand, 2013)	Organization & process Mergers and acquisition		
(Rodgers & Singham, 2020)	Hospital-acquired adverse events risk	Factors which contribute to the risk of hospital-acquired adverse events and support hospital decisions on staffing, length of stay, and investments in safety.	
(Elamrani, Benabbou, & Berrado, 2016)	Organizational risk		
(Amemba, 2013)	Organizational Structure and Cultural Risks		
(Rajagopal, Shanmugam, & Nandre, 2021)	Unethical governance risk	Quality and unethical governance risks significantly impacted reputation in Pharmaceutical SC and a firm should prefer "risk avoidance" against these risks.	
(Amemba, 2013) (Vishwakarma, Prakash, & Barua, 2016)	Strategic risk		
(Grujić, Morača, & Fajsi, 2020)	Inadequate decisions management		
(Yaroson, Breen, & Matthias, 2017)	Managerial practices	The managerial practices of the firm also weaken the system which in turn makes it impossible for the system to resist drug shortages when they occur making it vulnerable to various risks.	
(Chen, Yang, & Wang, 2019)	R&D	The pharmaceutical industry is characterized by a high cost of R&D and innovation.	
(Abbasian, et al., 2020)	Single actor in the biopharmaceutical industry		

Table 3.22 Other risks and uncertainties

Reference	Risk	Sentence	Group
(Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Commercial risk	Commercial risk refers to the normal business risk any company incurs, such as the potential market size, its expected revenues, its expected cost structure, etc.	Other
(Moktadir M. A., et al., 2018)	Competitive risks	There is a tremendous competition in the local and international market of pharmaceutical products. Thus, pharmaceutical industries are under huge risks due to competitor approach and strategy in introducing new products with improved performance levels.	
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Adulteration	At every stage in the pharmaceutical supply chain, medical products are exposed to risks of "contamination, diversion, counterfeit and adulteration".	
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Security risk	Organizations should have a backup that could be used should major security risks occur within the outside parties' operations.	
(Yaroson, Breen, Hou, & Sowter, 2021)	Behavioral uncertainty	Information control within the PSC was to protect the reputation of SC actors and mitigate behavioral uncertainty such as panic buying.	
(Gómez & España, 2020)	Disruption in the cold chain		
(Raka & Liangrokapart, 2017)	FDA problem		
(Abbasian, et al., 2020)	MOH (Ministry of health) conflict of interest		
(El Mokrini, Dafaoui, Berrado, & El Mhamedi, 2016)	Risk in natural gas pipelines, social responsibility risk		
(Huq, Pawar, & Rogers, 2016)	Risk of infringement of IPR		
(Paul, Kabir, Ali, & Zhang, 2020)	Traffic accidents		

Reference	Risk	Sentence	Group
(Elleuch, Hachicha, & Chabchoub, 2014)	Compliance risk	Compliance problem related to the supplier subsystem	
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Counterfeit risks		

3.4. 2 Risk Mitigation Strategies

To address the third and fourth questions of the research, the tables 3.23 to 3.37 are presented including four columns of ‘Reference’, ‘Risk Mitigation Strategy’, ‘Risk’, and ‘Description’. ‘Risk Mitigation Strategy’ is the strategy investigated and probed to mitigate and minimize the effects of risks in the literature or to avoid the identified risk. In total 73 strategies are presented which will be discussed more in the next section. Figure 3.4. shows a summarized overview of risks mitigation strategies.

Figure 3.4 An overview of risks mitigation strategies

Table 3.23 Prescription pharmaceutical regulation risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Davis & Abraham, 2011)	Prescription pharmaceutical regulation	*Risk-managing toxic drugs*	Risk-managing toxic drugs throughout the time of post-marketing.
		Communication of risks	A main part of managing pharmaceutical risk is communicating risks on the product label with doctors and patients
		Labeling of identified risks	Performing the function of legitimating permissive regulatory by Labeling of recognized risks.

The aim of the risk mitigation plan is to treat and handle the risks that influence the firm's objectives. According to the exposure, adopting the mitigation strategy is based on the significance of risks and it depends on the risk owner to select the proper strategy. Different studies have worked on organizational-related risks and mitigating them from different aspects. For example, in a study the focus is on the identification of sources of the organizational risks related to the outsourcing project and aims to provide a guidance for the decision makers on the organizational side of the project before deciding of outsourcing a service or an activity to an external vendor vs doing it inside the company (Elamrani, Benabbou, & Berrado, 2016). Table 3.24 shows different risk mitigation strategies for different organizational risks.

Table 3.24 Organizational-related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Varma, Pekny, Blau, & Reklaitis, 2008)	Scheduling and resource allocation in pharmaceutical R&D pipelines	Resource management	Proposing SIM-OPT framework as a unified resource management tool with the aims of increasing the portfolio's expected net present value, controlling risk, and reducing drug development cycle times.
(Elamrani, Benabbou, & Berrado, 2016)	Organizational risks	Outsourcing related organizational risks	Identifying and classifying outsourcing-related organizational risks in terms of information systems, value buying, and logistics by a framework that is inspired by Enterprise Risk Management (ERM).
(Gatica, Papageorgiou, & Shah, 2003)	Capacity planning	*Mathematical programming approach*	Improving capacity planning in clinical trials uncertainty by a mathematical programming approach.

Reference	Risk	Risk Mitigation Strategy	Description
(Chen, Yang, & Wang, 2019)	Policy failure	A revenue-sharing contract or a quantity discount contract	Policy failure risk leads in a drug supply shortage if pharmaceutical companies cannot handle the financial loss caused by the price cap regulation. To minimize the risk of policy failure, policy makers can consider subsidies to the regulated company to reimburse for the loss brought by price cap regulations. For the pharmaceutical companies that benefit from regulations, one should regard supply chain coordination mechanisms, like a revenue-sharing contract or a quantity discount contract to dispense the increased profits with their supply chain partners, because the supply stoppage of associated pharmaceutical goods will have a negative effect on their performance.

In public health, drug supply networks encounter shortage challenges in different situations, such as the COVID-19 epidemic situation. Drug shortages can arise from manufacturing problems, lack of infrastructure, etc. Drug providers must regard strategies to prohibit or reduce the effect of shortages as well as disruption spreads. Table 3.25 is a summarization of studies of several researchers about the drug shortages problem.

Table 3.25 Risk mitigation strategies for drug shortages

Reference	Risk	Risk Mitigation Strategy	Description
(Moosivand, et al., 2021)	Drug shortage	1. Forming integrated Supply chain information system to manage drug inventory 2. Forming and using the databases to predict the shortage of drugs using track and trace system	
(Yaroson, Sharief, Shah, & Breen, 2018)	Shortages	Reducing bureaucracy, preventing monopolization of pharmaceutical markets, and training staff	Strategies in curbing the effects of disruptive activities: reducing bureaucracy, hindering monopolization of pharmaceutical markets, and training staff.
(Lozano-Diez, Marmolejo-Saucedo, & Rodriguez-Aguilar, 2020)	Drug shortages in epidemic outbreaks	Propose a new approach	Presenting an approach with a comprehensive view of the supply network helping fast and efficient responses to risky and changing situations.

Reference	Risk	Risk Mitigation Strategy	Description
(Iyengar S. , Hedman, Forte, & Hill, 2016)	Shortages of medicine	Advance notice systems, tracking medicines, Redistribution of supplies, evidence-based practice, developing reporting systems	Different approaches to mitigate drug shortage include: advance notice systems managed by medicine regulatory authorities, tracking medicines, and improving efficiency of the medicine supply chain, redistribution of supplies at the national level , international redistribution and exceptional regulatory approvals, prioritizing patients to get a medicine that is in shortage, evidence-based practice for optimal allocation, developing reporting systems to share information on current and emerging shortages, and improving data from medicine supply chains.
(Jia & Zhao, 2017)	Drug shortages	Drug purchase contracts	Mitigating shortages through drug purchase contracts, investigating the Pareto-improving contracts, improving the manufacturer's profit, cut government spending and providers' cost, and ensuring the GPO's profit.
(Azghandi, Griffin, & Jalali, 2018)	Drug shortage Disruptions	*Mathematical simulation model*	Proposing a mathematical simulation model to understand the behavior of the drug shortages under different disruption patterns in the pharmaceutical supply chain.
(Hatem & Habib, 2011)	Shortage of drugs (without substitute)	Forecasting, ERP, , communication, and information sharing with suppliers	
(Emmett, 2019)	Drug shortages	Better use of supply chain management, including multiple suppliers and safety stock	Better collaboration among suppliers, consumers, and government entities. Healthcare facilities should develop teams in charge for monitoring critical areas and developing contingency plans.

Table 3.26 Clinical and safety related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Rodgers & Singham, 2020)	Clinical trial study failures	*Bayesian belief networks*	It is a framework that helps practitioners assessing the probability of disruptions of their network that can help them in a clinical supply chain to make a better understanding of vulnerabilities and network behavior in the case of lack of data.

Reference	Risk	Risk Mitigation Strategy	Description
(Van Bortel, et al., 2018)	Clinical Trials	Managing Risks in Early Phase Clinical Trials	Considering knowledge, expertise and an expert team, training, and clinical pharmacology unit accreditation schemes, submitting scientific advice pre-Clinical-Trial-Authorization (CTA)
(Hartford, et al., 2006)	Safety risk	Multidisciplinary Safety Management Teams (SMT)	Safety risk management in the early stages of drug development: Safety communication pre-approval such as Early Communication with the Research and Development Team, Early Risk-Management Plans, Reporting to Regulators and Investigators, Development Safety Update Report, Communication to Patients.
(Botelho & Reis, 2015)	Safety of new drugs	Up-to-date safety strategies	Networks of population databases for surveillance, use of data mining, integrating various sources of information to promote prediction and identification of adverse events, and preparation of Risk Minimization Action Plans (RiskMAPs)
(Fleischhacker & Zhao, 2011)	Clinical trial failure	Wagner–Whitin model (W–W model)	Generalizing the Wagner–Whitin model (W–W model) to incorporate the risk of failure by balancing the tradeoff of waste and destruction versus production inefficiency.
(Charoo & Ali, 2013)	New product development	Reviewing the tools and techniques for assessing and managing the risks of new product development	
(Edwards & Chakraborty, 2012)	Safety and efficacy issues (drug safety)	Communicating risks	Effective communication needs understanding how different audiences perceive the message and what the fundamental drivers are for alerting patients and prescriber behavior to be secured. Internal communications about significant issues should be limited to those who know how to handle the risk of insider dealing from internal communications that may later be made public.
(Nicholson, Peterson, & Yektashenas, 2012)	Drug safety	Risk Evaluation and Mitigation Strategies (REMS)	Risk Evaluation and Mitigation Strategies (REMS) build a safety plan with different components, such as a medication guide, a communication plan, elements to ensure safe use and an implementation system to help guide the prescribers, pharmacists, and patients.
(Ismael & Ahmed, 2020)	Drug safety	Quality Risk Management-(QRM) approach application	Quality Risk Management-(QRM) approach application on the drug provides the safety for drug and protects it from hazards during the production process.

Table 3.27 Logistics and transportation related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Mokrini & Aouam, 2020)	Logistic risks	Developing a risk evaluation approach	Evaluating outsourcing logistics risks in the healthcare sector by developing an approach
(Paul, Kabir, Ali, & Zhang, 2020)	Transportation disruption	Resilient strategies	Proposing a model to managers for examining transportation disruptions and having resilient strategies to handle them by using Bayesian Belief Network (BBN)
(Johnson & Miller)	Pharmaceutical drug delivery	Mathematical modeling framework	A model helping managers to select the most qualified suppliers and discover the tradeoffs between costs and risks in the pharmaceutical supply chain.
(Gómez & España, 2020)	Transport and storage	Cause analysis	
(Narayana, Elias, & Pati, 2014)	Reverse logistics	Returns avoidance, improving the infrastructure, balanced risk sharing	Avoiding returns by alleviating market flooding of medicines, improving the infrastructure for quality and performance management and balancing risk sharing between the main stakeholders involved in the supply chain.
(El Mokrini, Dafaoui, Berrado, & El Mhamedi, 2016)	The persistent evolution of development and manufacturing processes put the pharmaceutical industry in a challenge.	Outsourcing logistics	Presenting a theoretical model considering outsourcing logistics risks since firms are interested in focusing on the core competencies and outsourcing logistics.

Table 3.28 Operational and technical related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Lücker & Seifert, 2017)	Operational risks	RMI, Dual Sourcing and Agility Capacity	RMI and Agility Capacity can be swapped when there is no Dual Source. Once the Dual Source is available, Agility Capacity and Dual Sourcing seem can be swapped.
(Hosseini-Motlagh, Jazinaninejad, & Nami, 2020)	Production disruption	Channel coordination	Proposing an Altered Revenue-Sharing (ARS) contract for production disruption and recall management issues.

Reference	Risk	Risk Mitigation Strategy	Description
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Operational risks	Design a resilient supply chain	Design a resilient supply chain under operational risks and disruption to mitigate the supply chain-threatening risks.
(Hatem & Habib, 2011)	Technical problems / breakdown of the machinery	Periodic maintenance, statistical process control	
(Hatem & Habib, 2011)	Compliance problem (time limit, breakage, empty or missing boxes...)	Vigilance in the reception and at the time of delivery to the care units, inspection, traceability system	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Malfunctioning of Machinery	Checking and calibrating machines at regular intervals, Selection of correct machinery	Machines are required to be checked and calibrated regularly by preventive maintenance program and have spare parts at their disposal and qualified personnel to tackle risky situations. Selection of right machinery reduces this risk.
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Wrong Packaging	Inspection, packing slips and extensive quality control checks before shipping the product	
(Friemann & Schönsleben, 2016)	Warehouse capacity planning uncertainty	Providing a practical way to improve the strategic warehouse capacity planning process	Improving the strategic warehouse capacity planning process by breaking it down to a level that warehouse managers can handle, and reducing the effort needed to ensure applicability at the same time.
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Power Shutdown	Having full power backup systems to make sure production is not halted in such a situation	

Demand-related risks could impact the ability of the organization to make products available to its customers. Studies show that the supply chain could be influenced by several demand-related risks like ban of a product that in this case, other products with similar functions come in as substitution to the banned product that leads to increase in demand of the substitute products. An epidemic outbreak can also propel to an increase in demand and competition from opponents plays an important role in demand fluctuation (Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011). In the table 3.29, different risks mitigation strategies to cope with demand risks are shown.

Table 3.29 Demand related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)	Demand uncertainty	A scenario-based Multi-Objective Mixed-Integer Linear Programming model	Developing a scenario-based Multi-Objective Mixed-Integer Linear Programming model to design a supportable CLPSC (closed-loop PSCs), which inquires the reverse flows of expired drugs in 3 classes (must be disposed of, can be remanufactured, and can be recycled).
(Hatem & Habib, 2011)	Fluctuation in customer demands	Collaboration with the manager of the care units, forecasting	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Demand risks	Building cooperation between the company and its suppliers, developing replenishment plans designed to undertake adequate product availability	

It is critical to mitigate the supply chain risk and uncertainty. Managers are usually aware of the typical risks their supply chains are exposed to because their probability occurrence is high. However, many firms that do not have a supply chain risk management in place may overlook these risks. It is difficult to provide a standard resolution to mitigate all different supply risks. However, implementing organizations capabilities and resource to manage special supply chain uncertainty and risk is possible.

Table 3.30 Supply chain related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Clauson, Breeden, Davidson, & Mackey, 2018)	Supply chain risks and cost	Block chain technology	Benefits of block chain technology for improving management of the supply chain include: 1) decreasing or removing fraud and errors, 2) decreasing delays of paperwork, 3) promoting inventory management, 4) identifying issues fast, 5) reducing courier costs, and 6) augment consumer and partner trust.
(Wang & Jie, 2020)	Supply chain uncertainty and risk	Supply Chain Visibility, Supply Chain Agility, Supply Chain Flexibility	Capability of integrating supply chain is considered as efficient risk management tools for mitigating uncertainty and risk in the supply chain.

Reference	Risk	Risk Mitigation Strategy	Description
(Roscoe, Skipworth, Aktas, & Habib, 2020)	Supply chain risks	'Wait-and-see' strategy and worst-case assumptions	Firms with different sizes implement strategies to achieve fit with an external environment disrupted by a geopolitical event: When formulating strategy, Multi-National Enterprises (MNEs) applied worst case assumptions, while large firms and small and medium sized enterprises (SMEs) used a 'wait-and-see' strategy, enabling them to reduce perceptions of heightened supply chain uncertainty. Then firms implemented reactive and/or proactive strategies to mitigate supply chain risks.
(Mahendran, Narasimhan, Nagarajan, , & Gopinath, 2011)	Import risks	Firms should book their supplies in advance with sufficient lead time based on their previous experiences to overcome delay.	
(Blos, Hoeflich, & Miyagi, 2015)	Customer Service, Inventory Management, Flexibility, Time to Market, Finance, Ordering Cycle Time, Quality, and Market	Supply chain continuity management framework	Presenting a promoted form of supply chain continuity management framework, with an efficient crisis management operational structure.

The pharmaceutical supply chain executives face ever growing uncertainty and risk within and across trade borders. Potentially, the flux in the pharmaceutical supply chain risks and the accompaniment pressure from regulatory bodies, changing legislation, exchange rate, customers, and competition are forcing many forward-looking pharmaceutical firms to perform enterprise risk management.

Table 3.31 Regulatory related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Enyinda C. , 2017)	Regulatory/legislation risk, operational risk, reputation risk, financial risk, market risk, relationship risk	Mitigate/reduce risk, retain risk, avoid risk, share risk, transfer risk	
(Salter, Kramer, &	Regulatory and/or legal jeopardy	1. Follow Established Policies and Procedures 2. Keep Compliance with	Minimizing regulatory and/or legal jeopardy

Reference	Risk	Risk Mitigation Strategy	Description
Palmer-Shevlin, 2000)		Professional Standards/Guidelines 3. Seek Peer, Senior Staff, and Outside Departmental Expert Advice 4. Seek Input from Clients 5. Do Not Practice Medicine 6. Do Not Provide Formal Consultations 7. Document Everything 8. Copyright Infringement 9. Internal Document Review	with respect to medical communications.

Table 3.32 Quality related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Rajagopal, Shanmugam , & Nandre, 2021)	Quality and unethical governance risks	Proactive mitigation strategies and assertive crisis communication, diminishment/ bolstering/rebuilding reactive crisis communication	Prefer "risk avoidance" against quality and unethical governance risks. The upstream risks affect reputation in a pharmaceutical SC comparing to the downstream risks. Proactive mitigation strategies and assertive crisis communication are considered for upstream risks while diminishment/ bolstering/rebuilding reactive crisis communication is suggested for downstream risks.
(Hatem & Habib, 2011)	Quality problem in manufacturing	Statistical quality control, inspection, quality control	
(Mahendran , Narasimhan, Nagarajan,, & Gopinath, 2011)	Risk of Inferior Quality of supply	1. Establishing high standard quality protocols and enforcing of these standards 2. Regularly vendor auditing and checking. 3. Implementing statistical quality control and step towards six sigma implementations	
(Mahendran , Narasimhan, Nagarajan,, & Gopinath, 2011)	Quality Risks	Following strict quality protocols at each stage of the supply chain	

There are different kind of environmental risks and uncertainties affecting pharmaceutical supply chain. Sudden occurrence of natural disasters like floods, earthquakes, etc. could disrupt supply. The mitigation strategies involve understanding the vulnerability points and their effect on the supply chain and developing and testing contingency plans.

Table 3.33 Environmental related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Ågerstrand, et al., 2015)	Environmental risk	1. Assessing of environmental risk even for products put on the market before 2006 2. Add obligations to assess the risk for developing antibiotic resistance 3. Run just one environmental risk assessment for each active pharmaceutical ingredient 4. Refine the tiered approach 5. Perform mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action 6. Using all available ecotoxicity studies 7. Consider environmental risks in the risk-benefit analysis 8. Reviewing environmental risk assessments on a regular basis 9. Include data from active pharmaceutical ingredients and formulations production in the risk assessments 10. Augment transparency	Presenting 10 recommendations to improve the European Medicines Agency's guidance for assessing environmental risk of human pharmaceutical products
(Mahendran , Narasimhan, Nagarajan,, & Gopinath, 2011)	Natural Disasters	Understanding the vulnerability points and their effect on the supply chain and developing and testing contingency plans	
(Huq, Pawar, & Rogers, 2016)	Endogenous, exogenous, and environment-related SC disturbance factors	SC configurations	SC disturbances affect the decision to bring production back home (reshoring) or to a closer location (nearshoring). To mitigate the effects of disturbances many BPs recalibrated their SC configurations by insourcing core products, outsourcing non-core products offshore and developing offshore insourcing capabilities through 'captives'.

Different reasons lead to human risks in the pharmaceutical industry such as negligence on part of the employee. Various risk mitigation strategies for avoiding human risks are presented such as having proper training for the personnel, setting up unions to protect employees from labor unrest, and paying attention to all their requirements. The other mitigating strategies are presented in the table 3.34.

Table 3.34 Human related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Nicholson, Peterson, & Yektashenas, 2012)	Public health risk	REMS in mitigating risks	Risk Evaluation and Mitigation Strategy (REMS) including a communication plan, a medication guide, and elements to assure safe use.
(Hatem & Habib, 2011)	Lack of personnel	Motivation, relation with labor union, reward system, appropriate appointment, career management	
(Hatem & Habib, 2011)	Human error (in manufacturing)	Training, ameliorate the working ergonomic, reward system revision	
(Hatem & Habib, 2011)	Human error (in handling and in storing the drugs)	Personnel training, investment in handling materials	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Human Risks	Providing proper training to the employees, setting up unions to look after the employees and paying heed to all their requirements	

There are various risks influencing material supply in the pharmaceutical industry. For instance, the main supplier could at once become unavailable because of different reasons like internal management problems; inability to meet appropriate quality standards, suppliers going out of business, malfunctioning of machinery etc., in such a situation the organization would encounter a shortage of raw material supply. The mitigation strategy adopted could be having secondary suppliers provide the necessary raw material to meet demand when required or having alternate suppliers for the different raw materials.

Table 3.35 Material related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Non-Availability of raw material	Having secondary suppliers to provide the necessary raw material to meet demand when needed	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Non-Availability of packaging materials	Sharing a good rapport with the packaging material supplier, prompting settlement of bills, and having enough stock since it's a non-perishable commodity	

New product research opportunities could be challenging for pharmaceutical organizations because of limited financial resources, deciding which new pharmaceutical products to develop, etc. Developing new products in pharmaceutical industry are costly and time taking since the government approval before distribution is necessary as well. Pharmaceutical product development, like the other management tasks, needs significant decisions about the tradeoffs between the available resources, as managers decide to bring what drug to market. Managers can select different risk management methods to meet their goals in the pharmaceutical industry (Kleczyk, 2011).

Table 3.36 R&D and inventory related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Kleczyk, 2011)	R&D risks	Advertising and personal promotion to healthcare providers, increased use of internet and digital media, Stochastic Dominance, Capacity Constrained NPV approach	Direct-to-Consumer advertising and personal promotion to healthcare providers also increased use of internet and digital media to inform healthcare providers and patient population of their treatment options, the expected sales and revenues can be increased. Risk management methods starting from a simple NPV of income analysis of potential product, and extending it to Stochastic Dominance, followed by the Capacity Constrained NPV approach, and the required resources

Reference	Risk	Risk Mitigation Strategy	Description
			for development and production.
(Hatem & Habib, 2011)	Theft in the stores and in the delivery sectors	Fitting out the drugstores, internal audit system	
(Lücker, Seifert, & Biçer, 2019)	Inventory	Inventory strategy, reserve capacity strategy, mixed strategy, and passive acceptance	Determining an optimal inventory level and reserving capacity production rates for a firm that is under supply chain disruption risk. Characterizing four risk mitigation strategies: inventory strategy, reserve capacity strategy, mixed strategy, and passive acceptance. Illustrating how the optimal risk mitigation strategy depends on product characteristics and supply chain characteristics.
(Narenjian , Riahi, & Kheirabad i, 2019)	Disruption, delay, prediction risks, supplier risks, risk of something which is received, capacity risk, inventory risk	Increasing capacity, increasing inventory, Alternative suppliers, increasing response speed, increasing flexibility, Tensile or integrated demand, increasing ability, having more clients	It is noted to know what factors are important to select a supplier in a supply chain to reduce the supply chain risk.

Table 3.37 Other risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Hatem & Habib, 2011)	Time limit of drugs in the medicine cabinet	Traceability system, internal audit	
(Hatem & Habib, 2011)	Transposition error of the prescription to the notebook of orders	ERP, involvement of doctors and nurses of the care units	

Reference	Risk	Risk Mitigation Strategy	Description
(Enyinda & Tolliver, 2009)	Risk of counterfeit	Public health policy makers need to secure pharmaceuticals movement in the supply chain by securing packaging, increasing vigilance and public knowledge, strengthening regulatory and enforcement oversight, building international collaboration and partnerships, increasing fees for counterfeiters, and obligating pharmaceutical firms to invest in embedded technology such as RFID tags	
(Mahendran , Narasimhan, Nagarajan,, & Gopinath, 2011)	Information Sharing Risks	ERP software	ERP software such as SAP and ORACLE can be efficient. They provide transactional tracking and global visibility of information from within a company
(Sharma & Luthr, 2021)	Medical device	Risk communication	Eliminating or reducing risks to AFAP by taking proper risk control measures against the hazards identified through communicating risk with stakeholders in different departments.

CHAPTER 4

DISCUSSION

4.1 Pharmaceutical Supply Chain Risks

It should be noted that 317 risks in general are extracted in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other. Three risks that are more discussed in the literature according to the columns of “Local frequency”, “Global Frequency”, and “Files count” include supply risks, operational risks, and quality risks respectively. Therefore, we can infer these risks are more important in the pharmaceutical supply chain since different researchers have worked on them.

For clustering the risks as we discussed in the methodology, similar phrases are placed into a same group through applying the clustering technique in two steps of vectorizing and grouping. For instance, in this technique the words consumer product risk, counterfeit product risk, product quality risk, product defects, etc. were put in a same cluster as product. In figure 4.1, the clustering phrases for four groups of supply, product, transportation, and financial is shown.

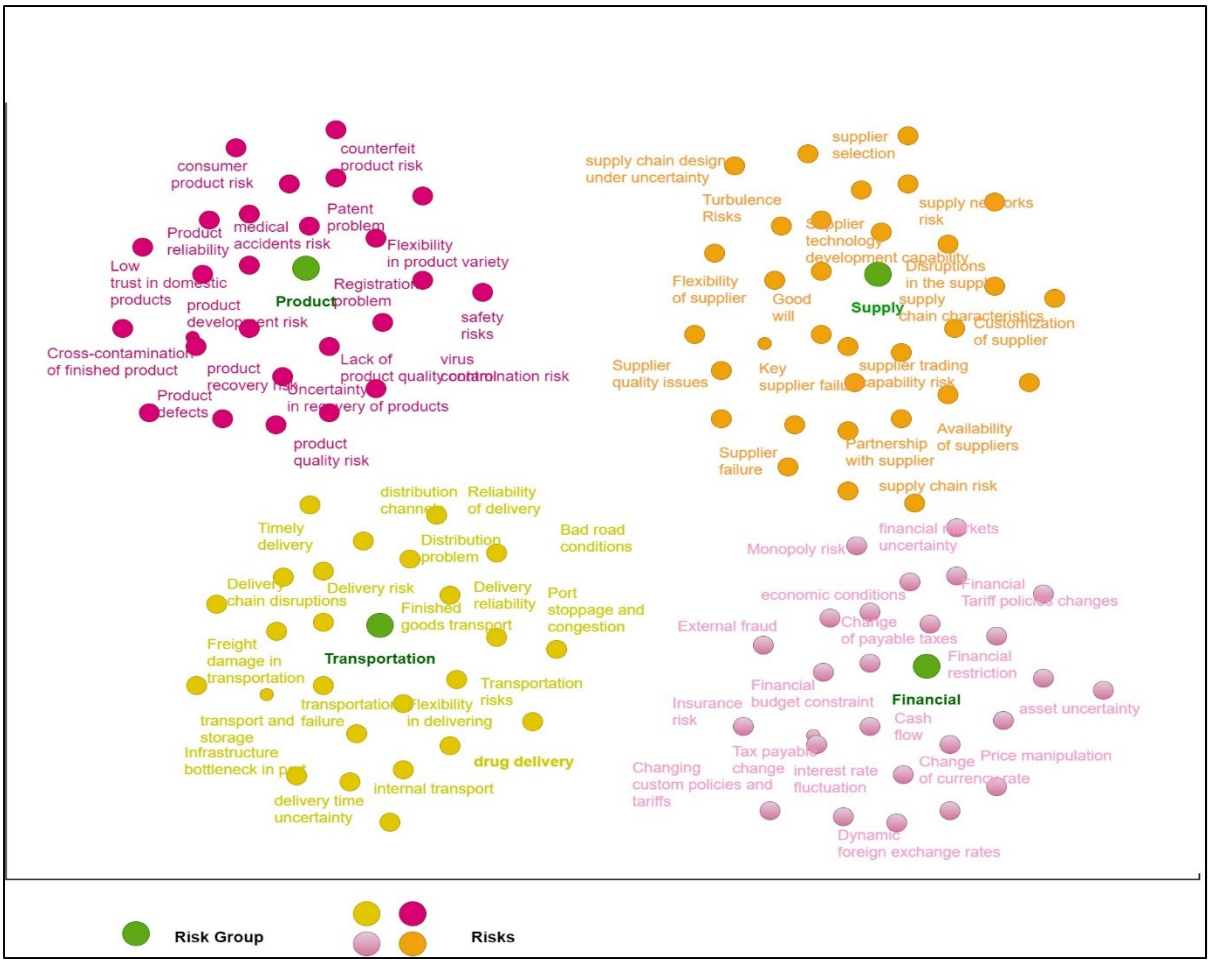

Figure 4.1 Clustering the risk phrases for groups of product, supply, transport, and finance

Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively. According to the validation process explained in the methodology 85 percent of results extracted from the text mining procedure were similar to the results extracted manually from the sample that is a promising outcome. As a comparison with other studies, we can point out to some research with text-mining techniques methodologies such as (Abeysinghe, Zheng, Hinderer, Moseley, & Cui, 2018), (Abeysinghe, Hinderer, Moseley, & Cui, 2017), (Abeysinghe, Brooks, Talbert, & Licong, 2017), and (Kobayashi, Mol, Berkers, Kismihók, & Den Hartog, 2018) that they gained an accuracy and similarity of 58%, 56%, 88%, and 55% in their results comparison respectively.

Table 4.1 Results of the automated search and manual search of extracted phrases

Searched Topics	Risk	Strategy
Manual Searches	32	9
Automated Searches	27	7
Validation	84.38%	78%

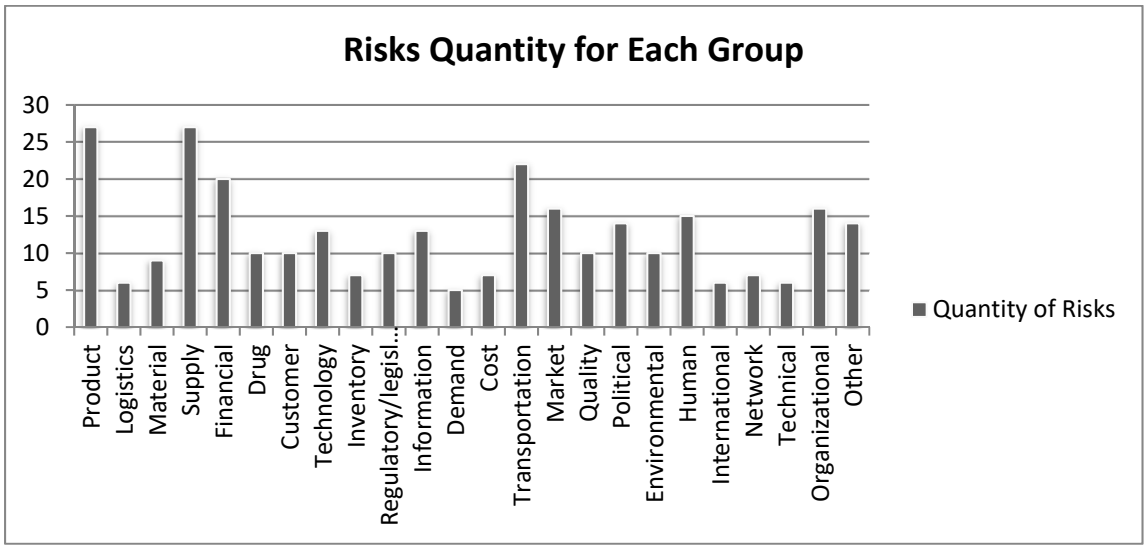

Figure 4.2 Quantity of risks in different risks groups

4.2 Risk Mitigation Strategies in the Pharmaceutical Supply Chain

According to one of the research's questions, we aimed to realize which risks in the pharmaceutical supply chain are considered in the literature to be minimized or covered by risk mitigation strategies. More than 73 strategies are found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines.

The second risk that has received the most attention from researchers is supply-related risks. Quality and safety risks have also been considered in different studies by researchers. To find

the relationship between mitigation strategies and risks the only option was reading the paragraphs that the strategies phrases were extracted. Although in terms of risk categories, researchers have almost worked on each group to discover a mitigation strategy, it does not mean that every single risk in the literature is covered. The three risk groups that have received less attention comparing others are cost, international, and political groups. An overview of different risk mitigation strategies according to each risks group is shown in the Table 4.2.

We also applied correspondence analysis to acquire a words frequency table for risk and strategy and to visualize the frequency of the words in our text. In Figure 4.3 the words are shown in blue and risk and strategy in orange color. For avoiding too much information on the plot the words with the most contribution were labeled. In this method the total inertia is the amount of the information contained in the data table. In the MCA analysis, each principal inertia values expressed as a percentage of the total inertia. These values quantify the amount of variation accounted for by the corresponding principal dimension. The variance is shown in the axe's labels of the chart. The horizontal dimension explains almost 86% of the variance in the data whereas the vertical dimension explains 13%. We can see on this map that the points vary much more on the horizontal than on the vertical, and therefore the relative variance explained of the dimension varies so greatly. This, in turn, tells us that the map represents almost all of the information in the residuals, which is good news.

We can compare row labels and column labels based on distances. As shown the words product, quality, supply is close to the word risk which is also compatible with our results, and the risks were found earlier in the dataset. Also, the words such as logistics, technical, and demand have more distance than the others which shows fewer risks in these areas. Besides, in the right part of the figure, the words supply, and shortage are around the word strategy, and the words like technology and political shows less contribution to explaining the strategy.

Furthermore, we can refer to the problem of NLP methods in our study as a limitation, in this way that none of the methods can take a sentence into account along with the previous or next sentences. In other words, we cannot remove the high need of supervising the results and extracted phrases by a human being. Therefore, the supervisor must investigate the extracted phrase's sentence in the paragraph to make sure that it is reliable. According to the validation process explained in the methodology 78 percent of results extracted from the text mining procedure were similar to the results extracted manually from the sample.

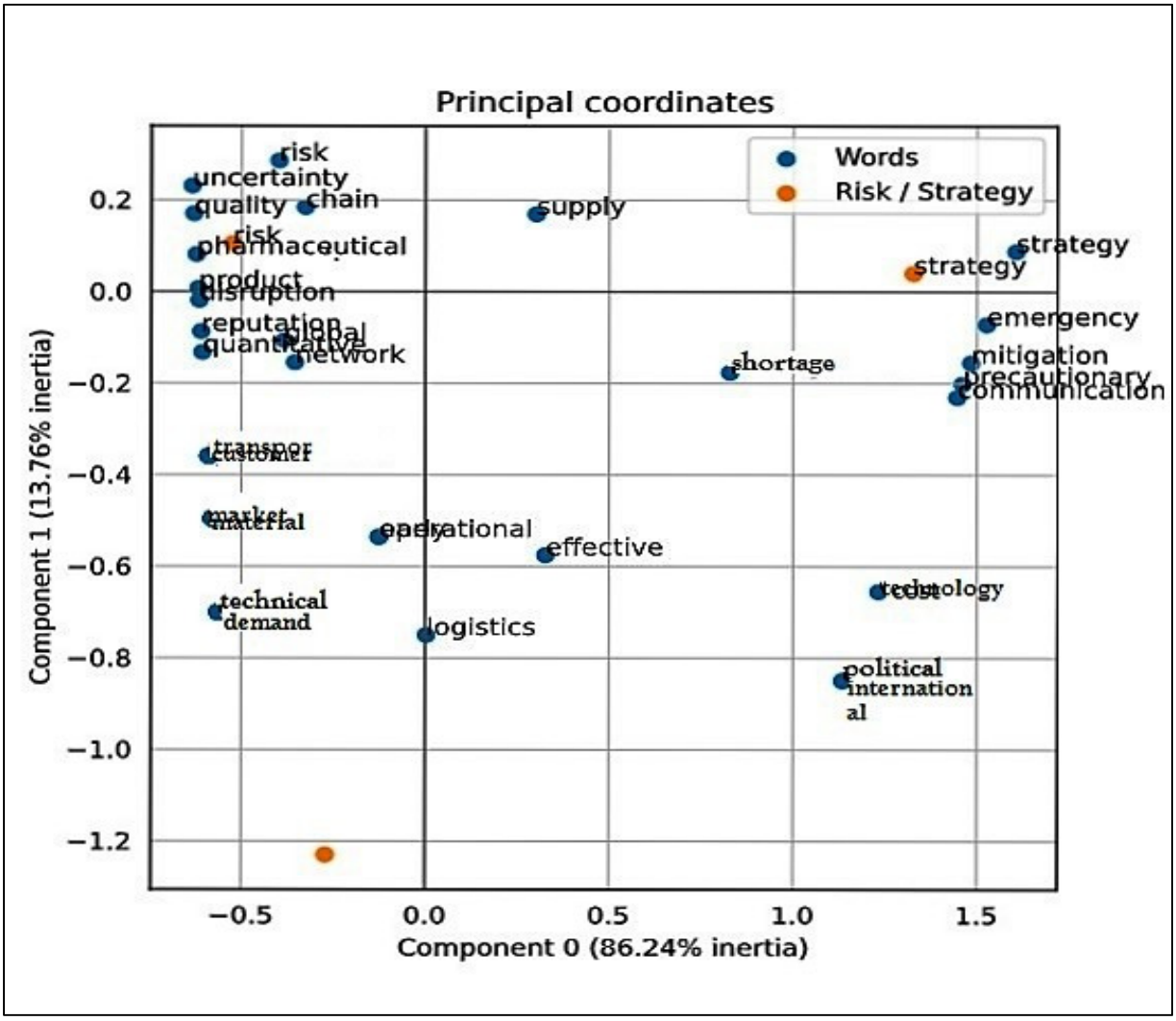

Figure 4.3 Correspondence Analysis for the words risk and strategy

Table 4.2 Risk mitigation strategies for each risks group

Risk Group	Risk Mitigation Strategy
Customer	REMS in mitigating risks
Demand	A scenario-based Multi-Objective Mixed-Integer Linear Programming model, Collaboration with the manager of the care units, forecasting, forming collaboration between the company and its suppliers, developing replenishment plans designed to assume adequate product availability
Drug & Product	Bayesian belief networks, Creating integrated Supply chain information system to manage medicines inventory in the country, Creating and using the databases to predict the shortage of medicines Using track and trace system, Reducing bureaucracy, preventing monopolization of pharmaceutical markets, and training staff, Reducing bureaucracy, preventing monopolization of pharmaceutical markets, and training staff, Propose a new approach, Managing Risks in Early Phase Clinical Trials, Managing Risks in Early Phase Clinical Trials, Risk communication, Advance notice systems, tracking medicines, Redistribution of supplies, evidence-based practice, developing reporting systems, Mathematical simulation model, Drug purchase contracts, Up-to-date safety strategies, Risk Evaluation and Mitigation Strategies (REMS), Forecasting, ERP, , communication and information sharing with suppliers, Traceability system, internal audit, Better use of supply chain management, including multiple suppliers and safety stock
Environmental	10 recommendations for improving the European Medicines Agency's guidance for environmental risk assessment of human pharmaceutical products (Ågerstrand, et al., 2015), the mitigation strategies involve understanding the vulnerability points and their impact in the supply chain and developing and testing contingency plans
Financial	A revenue-sharing contract or a quantity discount contract
Human	Multidisciplinary Safety Management Teams (SMT), Motivation, relation with labor union, reward system, appropriate appointment, career management, Training, ameliorate the working ergonomic, reward system revision, Personnel training, investment in handling materials, providing proper training to the employees, setting up unions to look after the employees and paying heed to all their requirements
Information	ERP software
Inventory	Inventory strategy, reserve capacity strategy, mixed strategy, and passive acceptance
Logistics	Developing a risk evaluation approach, Outsourcing logistics, returns avoidance, improving the infrastructure, balanced risk sharing
Material	To tackle this risk, we suggest the company to share a good rapport with the packaging material supplier, prompt settling of bills and having adequate stock since it's to a large extent a non-perishable commodity, having secondary suppliers provide the necessary raw material to meet demand when required
Network	Communicating risks
Operational	Resource management, RMI, Agility Capacity, Mathematical programming approach, Wagner–Whitin model (W–W model), Channel coordination, providing a practical way to improve the strategic warehouse capacity planning process
Organizational	Outsourcing related organizational risks, Reviewing the tools and techniques for assessing and managing the risks of new product development, Advertising and personal promotion to healthcare providers, increased use of internet and digital media, Stochastic Dominance, Capacity Constrained NPV approach

Risk Group	Risk Mitigation Strategy
Quality	Proactive mitigation strategies and assertive crisis communication, diminishment/ bolstering/rebuilding reactive crisis communication, Statistical quality control, inspection, quality control, Quality Risk Management-(QRM) approach application, Establishment of high standard quality protocols and strict enforcement of these standards (Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011), Vendor auditing should be done regularly following very strict measures of checking, Implementation of Statistical quality control will enhance the consistency and step towards six sigma implementation, Inspection, packing slips and extensive quality control checks before shipping the product, Following strict quality protocols at each stage of the supply chain
Regulatory/ legislation	Risk-managing toxic drugs, Communication of risks, Labeling of identified risks, Mitigate/reduce risk, retain risk, avoid risk, share risk, transfer risk, Adopt/Follow Established Policies and Procedures, Maintain Compliance with Professional Standards/Guidelines, Seek Peer, Senior Staff, and Outside Departmental Expert Advice, Seek Input From Customers, Do Not Practice Medicine, Do Not Provide Formal Consultations, Document Everything, Copyright Infringement, Internal Document Review, Fitting out the drugstores, internal audit system
Supply	Supply chain continuity management framework, Mathematical modeling framework, Supply Chain Visibility, Supply Chain Agility, Supply Chain Flexibility, 'wait-and-see' strategy and worst-case assumptions, SC configurations, booking supplies a bit in advance with sufficient lead time to overcome the delay
Technical	Periodic maintenance, statistical process control, Checking and calibrating machines at regular intervals, Selection of correct machinery
Technology	Having full power backup systems to make sure production is not halted in such a situation
Transportation	Resilient strategies, Cause analysis, ERP, involvement of doctors and nurses of the care units
Other	Vigilance in the reception and at the time of delivery to the care units, inspection, traceability system, Increasing capacity, Increasing inventory, Alternative suppliers, increasing response speed, Increasing flexibility, Tensile or integrated demand, Increasing ability, having more customers, Public health policy makers must intensity the need to secure movement of pharmaceuticals through the supply chain, securing packaging, increasing vigilance and public awareness, strengthening regulatory and enforcement oversight, building international cooperation and partnerships, increasing penalties for counterfeiters, and mandating pharmaceutical firms to invest in embedded technology such as RFID tags

CONCLUSION

Pharmaceutical supply chain is facing different kinds of risk which can waste resources and threaten patients' life by limiting access to medicines (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013). Therefore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines (Moktadir M. , et al., 2018).

The pharmaceutical supply chain is a substantial part of the health system that entail whole procedures, resources, information, different players such as suppliers, producers, agencies, third party service providers, transportation and sales activities, financial issues and IT (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Jaberidoost M. , et al., 2015). In a time of increasing uncertainty, different pharmaceutical stakeholders need to make better decisions with greater urgency at higher levels of risk. For example, the Covid-19 crisis poses special risks for each pharmaceutical company.

This research aims to explore different pharmaceutical supply chain risks and risk mitigation strategies based on the Systematic Literature Review (SLR) methodology through text-mining techniques. Keyword phrases are searched in three search engines of Web of Science, PubMed, and Google Scholar that resulted in a total of 4205 papers. DistillerSR software is used for the study selection phase to execute title screening and title and abstract screening. In the end, 278 references were considered as our project's primary studies.

The methodology applied in this research include different steps of extracting textual data, pre-processing, and data processing which data processing consists of phrase extraction, semantic similarity clustering, and in the end post-processing. To extract the relevant phrases, after comparing different approach results, the lexical approach was decided to be used and also, we used Natural Language Toolkit (NLTK) library in Python. Next step was phrase clustering that put similar phrases into the same groups and clustering technique in

this research consisted of two phases vectorizing and grouping. For vectorizing USE method was used and for grouping the similarity matrix method was applied owing to more accurate distance calculation and grouping outcomes.

It should be noted that 317 risks in general were extracted in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other. Top three risks that are more discussed in the literature include supply risks, operational risks, and quality risks respectively. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively.

More than 73 strategies were found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines. The second risk category that has received the most attention from researchers is supply-related risks. The three risk groups that have received less attention comparing others are cost, international, and political groups.

To sum up, our major contributions are being the first systematic literature review by text-mining in pharmaceutical supply chain discipline, providing up-to-date classifications for identified risks in the literature through semantic clustering, and reviewing risk mitigation strategies provided in the literature in all of the risk categories.

APPENDIX I

CONTINUED RISKS

Table-A I-1 Risks and uncertainties in the supply category

Reference	Risk	Sentence	Group
(Xu, Boehm, & Zheng, 2016)	Pharmaceutical product quality risk		
(Grujić, Morača, & Fajsi, 2020)	Poor design of products	Companies change product designs to meet customer wishes.	
(Gómez & España, 2020) (Gray, Roth, & Leiblein, 2011)	Product defects		
(Van Bortel, et al., 2018) (Lowman, Trott, Hoecht, & Sellam, 2012) (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Product development risk		
(Balmoș, Lazăr, & Burcea Dragomiroiu, 2014)	Medical accidents risk	To reduce the risk of severe medical accidents caused by the cross contamination, the manufacturing of certain drugs, certain strongly active drugs or non-medicamentary products must not be made in the same facilities.	
(Kumar, et al., 2019)	Product lifecycle risks	Pharmaceutical products are highly sensitive in terms of their life cycle and impacts (from introduction to withdrawal).	
(Xu, Boehm, & Zheng, 2016) (Cundell, Guilfoyle, Kreil, & Sawant, 2020) (Gray, Roth, & Leiblein, 2011)	Product quality risk		
(Narenjian, Riahi, & Kheirabadi, 2019)	Product reliability		
(Kumar, et al., 2019)	Uncertainty in recovery of products	Drugs recovered may be tampered with, and thus become unsuitable for consumption.	
(Gatica, Papageorgiou, &	clinical trials uncertainty		

Reference	Risk	Sentence	Group
Shah, 2003) (Varma, Pekny, Blau, & Reklaitis, 2008) (Fleischhacker & Zhao, 2011)			
(Abbasian, et al., 2020)	Lack of standard CROs for clinical trials		
(Raka & Liangrokapart, 2017)	Patent problem	In addition to problems with market information, patents and intellectual property are obstacles.	
(Urushihara, et al., 2014) (Hartford, et al., 2006) (Yaroson, Breen, & Matthias, 2017)	safety risks	Safety risk communication was defined as the exchange of drug information regarding safety risks by pharmaceutical companies with the aim of ensuring the rational use of drugs in practical clinical settings.	
(Abbasian, et al., 2020)	Long-term licensing process for clinical trials		

Table-A I-2 Risks and uncertainties in the supply category

Reference	Risk	Sentence	Group
(Kumar, et al., 2019)	Inconsistency in competitive and supply chain strategies	Risks related to mismatch between competitive and supply chain priorities in adopting GSC concepts in the pharmaceutical industry.	Supply
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Availability of suppliers		
(Moktadir M. A., et al., 2018)	Key supplier failure	Failure of any key supplier will disturb the functioning of a PSC in an organizational context.	
(Blos, Hoeflich, & Miyagi, 2015) (Abbasian, et al., 2020) (Wang & Jie, 2020)	External supply chain risk		
(Elleuch, Hachicha, & Chabchoub, 2014) (Hatem & Habib, 2011) (Paul, Kabir, Ali, & Zhang, 2020)	Supply networks risk		
(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand,	Partnership with supplier		

Reference	Risk	Sentence	Group
2013)			
(Elleuch, Hachicha, & Chabchoub, 2014)	Process-based supply chain risk		
(Kumar, et al., 2019) (Ouabouch & Amri, 2013)	Supplier quality issues	Raw materials and services supplied will affect the quality of the green products	
(Yaroson, Breen, & Matthias, 2017) (Mehralian, Gatari, Morakabati, & Vatanpour, 2012)	Supplier selection	Supplier selection refers to the process of selecting a supplier based on price negotiation and the ability to share in supply and demand risk.	
(Narenjian, Riahi, & Kheirabadi, 2019)	Supplier technology development capability		
(Vishwakarma, Prakash, & Barua, 2016)	Supplier trading capability risk	Supplier trading capability risk in which capacity and capability of suppliers to produce quality medicines is always a concern, under fulfilment of sudden demands pertaining to financial loses under uncertainty.	
(Yaroson, Breen, & Matthias, 2017)	Supply chain characteristics	Supply chain characteristic which depicts buyer supplier relationship includes supplier dependence and consumer dependence.	
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Supply chain design under uncertainty		
(Rodgers & Singham, 2020) (Aigbogun, Ghazali, & Razali, 2014) (El Mokrini, Dafaoui, Berrado, & El Mhamedi, 2016) (Yaroson, Breen, Hou, & Sowter, 2021) (Lücker & Seifert, 2017) (Azghandi, Griffin, & Jalali, 2018) (Li, et al., 2016) (Sreedharan, Kamala, & Arunprasad, 2019) (Van Niekerk, Niemann, Kotzé, & Mocke, 2017) (Breen L. , 2008)	Supply chain risk	Global supply chain risk that is not assessed and managed proactively can lead to many other risks.	
(Zamora Aguas, Adarme, & Serna, 2013)	Supply delays		

APPENDIX II

PAPER SUBMITTED IN OPERATION MANAGEMENT

PHARMACEUTICAL SUPPLY CHAIN RISKS AND RISK MITIGATION STRATEGIES: SYSTEMATIC LITERATURE REVIEW (SLR)

by

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ABSTRACT

To guarantee pharmaceutical supply chain resilience and permanence, it is necessary to effectively identify and evaluate risks. Lack of proper risk mitigation destroys public health reliance and validation, patients' safety and health, and a decrease in profit margin and stakeholder value.

The aim of this research is to provide a comprehensive picture of research regarding pharmaceutical supply chain risks and mitigation plans. The methodology adopted in this research is Systematic Literature Review (SLR) and after taking the screening steps 21 papers were retained as the final samples of systematic review synthesis.

One hundred thirty-seven risks are recognized which are categorized into 8 different groups and the contribution of this paper is gathering all the key risks, risk categories, and risk mitigation strategies that have been identified so far. These groups consist of supply and supplier risks, financial issues, logistics and transportation issues, market and environmental risks, operational issues, organization and strategies issues, political and cultural issues, and regulation risks. The results of risk management studies led to recognizing different

mitigation strategies in the areas of inventory and reserve capacity, global SC risk management, network management, and medicine shortage.
We illustrate what types of risks and risk mitigation strategies are identified and introduced in the pharmaceutical industry and supply chain.

Keywords: pharmaceutical risks, supply chain risks, risk management, risk mitigation strategies, pharmaceutical supply chain

INTRODUCTION

One of the most important human rights is accessing medicine at the right time, place, quantity, and acceptable quality. Pharmaceutical Supply Chain (PSC) is facing different kinds of risk which not only can spoil resources but also can menace patients' life by hampering access to medicines (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013). Therefore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines (Moktadir M. A., et al., 2018). In the last decade healthcare organizations have become more intricate owing to different factors such as efficient customers, biomedical developments, the complication of services, and the growing number of healthcare users (Ferdosi, Rezayatmand, & Taleghani, 2018). Moreover, the complication of supply network has increased by globalization, more customer expectation, shorter life cycle for products and technologies which has led to tremendous uncertainties and risks in the PSC (Wang & Jie, 2020). The pharmaceutical supply chain is a substantial part of the health system that entail whole procedures, resources, information, different players such as suppliers, producers, agencies, third party service providers, transportation and sales activities, financial issues, and IT (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Jaberidoost M. , et al., 2015).

There are different definitions for risk, but it can be defined as an uncertain event, which has the likelihood of incidence of undesirable outcomes such as late delivery, economic burden, and business loss (Moktadir M. A., et al., 2018) and according to ISO31000 its effect can be positive and/or negative (Leitch M. , 2010). Supply Chain Management (SCM) is integrating

the significant business processes over the supply chain with the aim of making value for clients and stakeholders. All stakeholders require establishing the correct configuration and compatibility to build best practice and to outreach the barriers in ever-increasing environment (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013). Besides, managing of risks is a critical point to cope with different kinds of uncertainties from a supply chain context (Moktadir M. A., et al., 2018). Therefore, Supply Chain Risk Management (SCRM) is a crucial part of supply chain management intends to decrease supply chain risks and vulnerabilities by mitigation strategies (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013), and to guarantee PSC resiliency and continuity (Enyinda, Mbah, & Ogbuehi, 2010). SC vulnerability can be defined as a disposal to significant disruption (Wagner & Bode, An empirical investigation into supply chain vulnerability , 2006). In fact, lack of proper risk mitigation can destroy public health reliance, patients' safety and health, and a decrease in profit margin and stakeholder value. However, the pharmaceutical organizations can not totally remove the risks they face in their operations; they are able to make an environment favorable for reactive risk mitigation (Enyinda, Mbah, & Ogbuehi, 2010).

Various studies have been conducted regarding identifying risks and uncertainties from various aspects of manufacturing sectors, logistics, and global network and so on. Moreover, several researchers have worked on developing mitigation strategies in the field of supply chain but not specifically for pharmaceutical supply chain. Therefore, in this research the authors conducted a Systematic Literature Review (SLR) regarding both identification of pharmaceutical supply chain risks and identification of supply chain mitigation strategies for different risks and environments. To this aim we conducted holistic research in the field of risks and related mitigation strategies in the pharmaceutical industry by the SLR technique. Therefore, we covered this gap with the aim of helping the academic researchers and practical experts to obtain a comprehensive approach regarding pharmaceutical supply chain risks and mitigation plans. The next section is dedicated to the literature review part of the study, and then the parts of results, discussion, and conclusion are described in the remainder of the paper.

CHAPTER 1

LITERATURE REVIEW

Risk can be defined as an uncertain event, which has the likelihood of incidence of undesirable outcomes such as late delivery, economic burden, and business loss (Moktadir M. A., et al., 2018) and according to ISO31000 its effect can be positive and/or negative (Leitch M. , 2010). Besides, it is considered as the extent of uncertainty in terms of realizing the importance and/or unfortunate results of decisions (Zsidisin & Ellram, An agency theory investigation of supply risk m anagement, 2003). **Supply chain** is a series of processes, members, information, and assets that transform raw materials into products and services available for clients (Jaberidoost M. , et al., 2015). Furthermore, **supply chain risk** is regarded as the probability and effect of unanticipated events or situations which unfavorably have an impact on any sector of a supply chain with operational, technical, or strategic failures. According to another definition supply chain risk is the potential varying results that influence the reduction of value-added at any task in a supply chain (Ho W. , Zheng, Yildiz, & Talluri, 2015). **Supply Chain Management** (SCM) is regarded as the integration of important business operations over the supply chain with the aim of building value for clients and stakeholders. According to the council of supply chain management SCM is also defined as planning and managing of all tasks pertain to sourcing, procurement, transformation, and logistics (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013). **Supply Chain Risk Management** (SCRM) is an organizational cooperative effort using different kinds of methodologies such as quantitative and qualitative risk management to recognize, assess, mitigate, and monitor unanticipated events or situations, which might negatively affect supply chain (Ho W. , Zheng, Yildiz, & Talluri, 2015). **Pharmaceutical Supply Chain** (PSC) is a remarkable part of the health system with the aim of providing medicines which contains all processes, information, assets, and members such as producers, mediators, logistics tasks, trading, sales tasks, finance, and IT (Jaberidoost M. , et al., 2015).

1.1 Risks and Uncertainties

(Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) presented supply chain management strategic risks with perspective of production companies and explained regulatory power effects on the quality, quantity, and delivery method, as well as medicines supply in pharmaceutical industry through conducting a systematic literature review of some studies in this area. Fifty identified risks are classified in seven categories, namely supply and suppliers, organization, and strategy, financial, logistic, political, market and regulatory issues. According to processes of production, supply and distribution, some solutions are suggested. Due to some factors such as processes, people, and functions mismanagement which are controllable through mitigation strategies, most of the risks in pharmaceutical supply chain management are considered as internal risks.

Organizations could monitor potential risks and control likely risks using supply chain risk management as well as improving its efficiency. (Breen L. , 2008) has reported risks in the pharmaceutical supply chain in terms of quantifiable measures and ratings. The author mentioned that product discontinuity, product shortages, poor performance, patient safety/dispensing errors and technological errors are possible areas of risks in the pharmaceutical supply chain. To improve public health confidence and reputation, patients' health and safety, profit margin and shareholder value, these risks must be controlled. They have focused mainly on supply chain optimization in pharmaceutical industry. Multiple aspects of external risks including economic, environmental, and political are addressed in this study.

To identify and analyze supply chain risks in the pharmaceutical industry, (Moktadir M. A., et al., 2018) conducted an integrated AHP and Delphi decision-making method. Findings show that the most important and critical risks in supply chain include supply-related risks such as fluctuation in imports arrival, lack of information sharing, failure of key supplier and non-availability of materials. Other areas of risks such as operational, financial, and demand-related risks are also investigated.

(Ferdosi, Rezayatmand, & Taleghani, 2018) have focused on implementation of risk management in healthcare organizations (HCOs) and their contribution has been a comprehensive framework or risk management which includes five stages, namely establishing the context, risk assessment, risk treatment, monitoring and review, and communication and consultation. They classified risks in terms of its sources in two groups of internal and external risks which comprise eleven internal and eleven external risks. Internal risks are such as organization or operational risks, physical structure and technological supports, communication and human resource and external risks are such as supplying, financing, and environment and ecological.

International Organization for Standardization (ISO) has published risk management rules and guidance named ISO 31000:2009 to present a foundation for enterprise risk management implementation. According to this standardization, there are five risk management processes including communication and consultation, establishing the context, risk assessment that contains risk identification, risk analysis, and risk evaluation, risk treatment and monitoring and review (Scannell, Curkovic, & Wagner, 2013).

(Wang & Jie, 2020) conducted research to investigate supply chain uncertainty and risks in pharmaceutical industry in terms of their main types in literature which are internal and external uncertainty and risks. Uncertainty is defined as the quality of being uncertain in terms of length of time, continuance, and incidence. Operational, financial, and quality-related uncertainty and risk constitute internal uncertainty and risks, whereas supply, demand and environmental uncertainty and risk are three main aspects of external uncertainty and risks. They proposed an approach to enable firms to control and manage internal and external pharmaceutical supply chain uncertainties and risks. They regarded visibility, agility, and flexibility in their framework as a supply chain integration capability to manage pharmaceutical supply chain uncertainties and risks.

(Silva, Araujo, & Marques, 2020) have identified 43 risks which are classified according to 15 dimensions of risk including capacity, demand, environmental, financial, inertia, operational, strategic, supply, and disruption, relational, legal, cultural, and informational dimensions. They stated that risk mitigation strategies must start with risk assessment in terms of consequences and probability, followed by prioritizing between these risks. The ten most important identified risks include quality, government's policy, exchange rates, intellectual property, inventory management, regulation, operations/process failure, R&D capabilities, price regulation and theft. Finally, they have presented the perception of risks and priorities in terms of different players which include industry, distributer, institutional buyer, and retail.

(Jaberidoost M. , et al., 2015) have evaluated risk factors in pharmaceutical industry in the context of Iran using Delphi panel experts considering priority, hazard, and probability of risks as the most important factors. They conducted four phases research in which 86 major potential risks were identified and classified in eleven categories, mainly associated with financial and economic areas, as well as politics and government, government, strategies, research and development, supply and suppliers, market and competitors, operation and process, logistic, human resource and disaster and accidents. Due to the local perspective of the study, the most important identified risks are identified in different management functions such as supply management function, financial management function and sales management function which are interest rate, currency fluctuation, money transfer, sanctions and inflation rate which might be interrelated to the context of the study.

(Vishwakarma, Prakash, & Barua, 2016) have identified evaluated and prioritized risks and their succedent analysis in pharmaceutical supply chain in which 24 risks were classified under five major risk categories. Financial risks, network and logistics risks, government and market related risks, Strategic risks and Supply and supplier risks are the criteria through which the risks are categorized. As illustrated in the results, the supply and supplier risks are the most important risk compared to other risks, then followed by the strategic risk which is the second most influential risk.

(Jnandev Kamath, Kamath, Azaruddin, Subrahmanyam, & Shabharaya, 2012) have presented four major risks affecting pharmaceutical supply chain in India which are regulatory risk, financial risk, inventory risk and counterfeit risk. Additionally, they investigated mitigation strategies which addresses identified risks. These strategies include outsourcing of key regulatory risks with purpose of cost reduction, inventory management logistics planning and warehousing practices for tackling inventory risk, anti-counterfeiting technologies for dealing with counterfeit risk and insuring products and facilities, increasing market share through mergers and acquisition to mitigate financial risks.

(Ayati, Saiyarsarai, & Nikfar, 2020) investigated considerable short-run and long-run effects of COVID-19 pandemic on the health market especially on pharmaceutical industry. Changes in demand, regulation revisions, research and development process changes and the shift towards tele-communication and tele-medicine are mentioned as short-term effect and decelerated industry growth, approval retardation and ethical consideration might be potential long-term effects. (Sreedharan, Kamala, & Arunprasad, 2019) have evaluated pharmaceutical supply chain risks and their effects through which 44 risks were classified under five categories namely supplier risk, production risk, demand risk, infrastructure risk and macro risk.

1.2 Risk Mitigation Strategies

(Enyinda, Mbah, & Ogbuehi, 2010) claimed in their research global pharmaceutical supply chain risk mitigation has absorbed great attention in the recent years and organizations are considering the necessity of risk management in any industry including pharmaceutical supply chain. Their research is based on empirical findings to help decision makers in terms of prioritizing the most important risk factors and then mitigating a risk portfolio. They believed that the risks in the pharmaceutical supply chain are due to the lack of information or deviation in the flow of information and physical drug and therefore, increasing knowledge in terms of risk management is imperative. The authors employed multicriteria decision making (MCDM) technique to analyze varied evaluation criteria and enable

decision makers to incorporate their preferences on analyzing different criteria. AHP methodology is applied to model risk management and this research led to identifying five risks and four decision alternatives in a developing country pharmaceutical industry. The five risks or objectives include risks arise from Food and Drug Board (FDB), counterfeit, currency, exchange rate and supplier failure and the alternatives include risk reduction/control, risk avoidance, risk acceptance/retaining, and risk transfer/funding. According to the research findings, counterfeit risk is the most important risk, which is followed by FDB, exchange rate, currency, and supplier failure. Among different risk mitigations, risk avoidance and then risk reduction is more appropriate for counterfeit. Regarding the FDB, risk reduction/control, and risk avoidance are considered as the first and second proper strategies. The overall priority results for mitigations showed that risk reduction is the most important strategy followed by risk avoidance, risk transfer, and risk acceptance.

(Lücker, Seifert, & Biçer, 2019) focused on disruption risk management in supply chains regarding inventory and reserve capacity under accidental demand. In fact, their research aimed at understanding and describing factors direct to increase risk mitigation inventory (RMI) or reserve capacity levels. They demonstrated that optimal risk mitigation strategy is related to supply chain characteristics which are agile or efficient and product characteristics which are functional or innovative. To determine which strategy is most proper for which product, they consider high level of (low) inventory holding costs with innovative (functional) products and also high level of (low) fixed cost with an agile (efficient) supply chain. Therefore, four mitigation strategies inventory strategy; passive acceptance, mixed strategy, and process flexibility strategy were recognized. Inventory strategy means regarding low inventory holding costs and high reserve capacity fixed costs for innovative products in an efficient supply chain. Mixed strategy regards low inventory holding costs and low reserve capacity fixed costs for innovative products in an agile supply chain. Passive acceptance is for the time inventory holding costs and reserve capacity fixed costs is high for functional products in an efficient supply chain. At the end process flexibility strategy

regards high inventory holding costs and low reserve capacity fixed costs for functional products in an agile supply chain.

(Manuj & Mentzer, 2008) in an article tried to discover the phenomenon of risk management and risk management strategies in global supply chain since global supply chains are more exposed to various risks disruptions, breakdowns, political changes, macroeconomic issues, and disasters. Therefore, risk management is more difficult in global supply chains as these are connected to a broad network of firms through several links. In this research, the risks that were identified in the literature are categorized as; supply risks: supplier opportunism, inbound product quality, transit time variability, risks affecting suppliers; demand risks: demand variability, forecast errors, competitor moves, risks affecting customers; operational risks: inventory ownership, asset and tools ownership, product quality and safety and other risks such as currency and security. The authors developed a model for global supply chain risk management strategies. They stated that the selection of a strategy is dependent on three factors which are temporal focus, supply chain flexibility, and supply chain environment. In general, six strategies are identified namely postponement, speculation, hedging, control/share/transfer, security, and avoidance. Those three factors and these strategies are linked by team composition and the selected strategy has an impact on the risk management results and two factors of supply chain complexity and inter-organizational learning regulate this link. Based on this model, supply chain environments are divided into level of demand risk and supply risk. For example, S_LD_H stands for low level of supply risks and high level of demand risks. Supply chains confronting S_LD_H and S_HD_H environments are more probable to get postponement strategies than the environments confronting S_LD_L and S_HD_L. Postponement strategy is considered as the factual commitment of resources to sustain delay incurred cost and flexibility. It includes labeling, packing, assembling, and manufacturing.

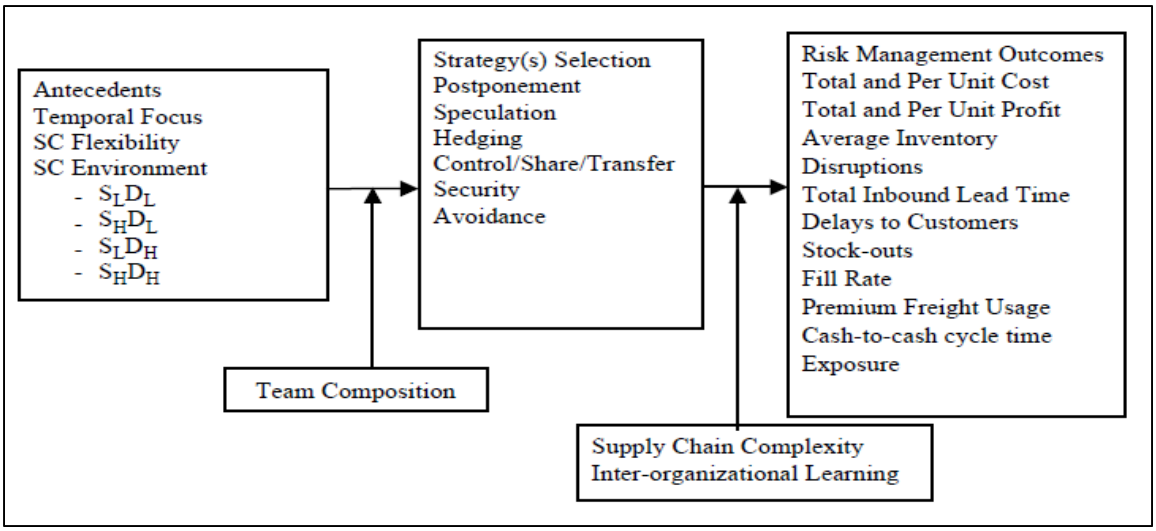

Figure-A II-1 A model of global supply chain management strategies
Taken from Manuj & Mentzer (2008)

(Huq, Pawar, & Rogers, 2016) focused on identifying disruption factors in pharmaceutical industry and to help managers make the better decision about the most proper supply chain configuration, according to the level of disruptions in their supply chain. By carrying out a literature review, the authors identified and categorized the sources of supply chain disruptions in pharmaceutical firms into firm-related disruptions (endogenous), network-related (exogenous), and location-related (environmental). Endogenous disruption factors pertain to the central firm and consist of internal process such as manufacturing processes and quality, and control such as order processing and information flow. Exogenous disruption factors turn up in the supply chain network, between the central organization and the partners. It consists of demand factors such as imbalance between market demand and supplier respond, demand forecasting complication; supply factors such as ill-timed transferring of products, imbalance inventory levels; and control factors such as hardship of connecting to the suppliers or disseminating data. Environmental factors pertain to the selection of locations or manufacturing partners and are related to production costs, hidden expenses of remote operations, man-made/natural disasters, societal disturbances, political instability, skills, and education levels and so on. Through a mixed method the results showed that there are top five disruption factors that managers should be aware of them to configure their supply chains. These five factors include quality defects, order processing

difficulties, ill-timed products delivery, random and unpredicted interruptions in manufacturing processes and an imbalance between market demand and supply amount. The paper researchers claimed that correct configuration can enhance the performance of supply chain. Besides, three supply chain configurations are identified which are insource nearshore, outsource nearshore, and outsource offshore. Finally, a supply chain disturbance framework was developed that enables pharmaceutical firms to select a proper strategy and supply chain configuration in accordance with different disturbance factors they are faced. According to this model three mitigation strategies include insourcing offshore through captives, reshoring/nearshoring core products, and outsourcing offshore noncore products.

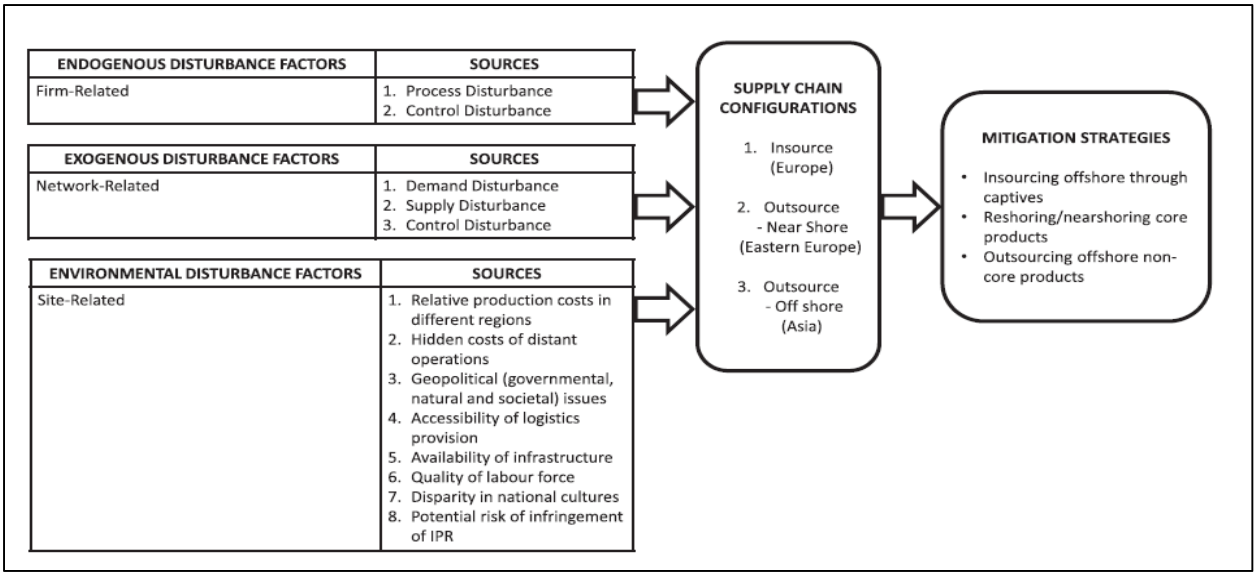

Figure-A II-2 The supply chain disturbance framework

Taken from Huq, Pawar, & Rogers (2016)

(Qazi A. , Dickson, Quigley, & Gaudenzi, 2018) conducted some research on prioritizing different risks, discovering interdependency between them, and discovering appropriate mitigation strategies in a network setting with respect to decision makers' appetite. The authors stated that efficient risk management process affects the impact of a risk network on performance measures since best selected strategies can mitigate risks consequences. In this paper different risk categories are identified as supply, demand, process, and control and the interdependencies among the risks are recognized. The mitigation strategies that were

determined during the research include contract term, quality training, perform business interruption analysis, adopt enterprise risk management process, perform Disaster Recovery Plan (DRP) testing, union relations, economics of scale, flexibility, and reduce cost. One of the competencies of supply chain risk network management is the operationalization of each phase to assist managers get an empirically assessed technique to handle the risks. Furthermore, this process gives a special integration of modeling interdependent risks, the decision maker risk appetite, and a trade-off through performance measurements. The authors stated there are various probable combinations of strategies with respect to a budget limitation and only one optimal combination. Moreover, combination of strategies would be different with the budget constraint change.

(Talluri, Kull, Yildiz, & Yoon, 2013) in an article tried to evaluate and propose effective supply chain risk mitigation strategies in accordance with different risk categories, risk sources, and different supply chain contexts (configurations). The authors incorporated the processes in a simulation model which is shown in Figure 1.3. As shown, supply chain configurations have an impact on both supply chain cost (like transportation and inventory) and SC performance measurements (like service levels and cycle times). However, cost and performance can be affected negatively by different sources and categories failure, different types of mitigation strategies decrease these negative effects.

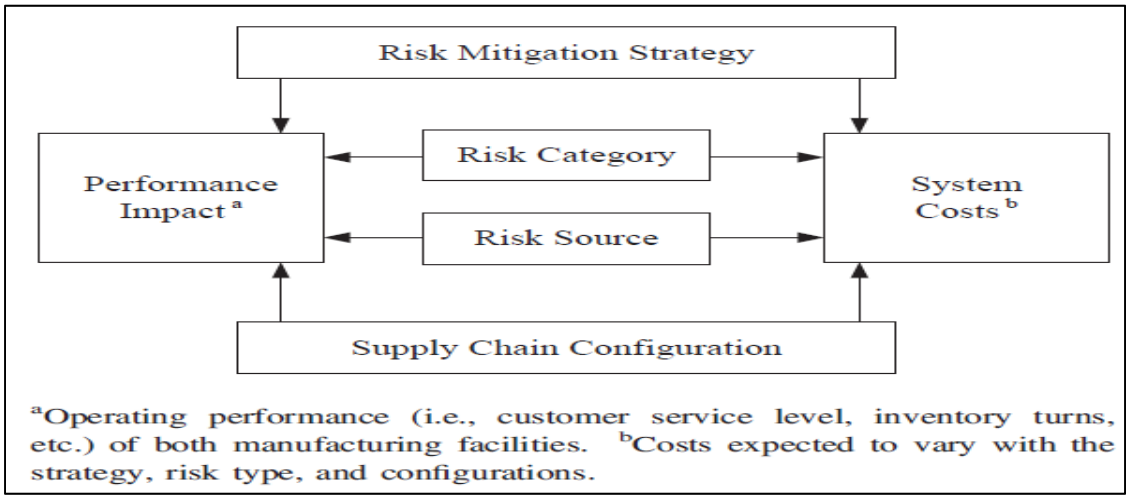

Figure-A II-3 Experimental framework

Taken from Talluri, Kull, Yildiz, & Yoon (2013)

In this paper three types of SC failures can occur from supplier, manufacturer, and customer sides which are recognized as disruption, delays, and distortion. Disruptions pertain to unpredictable drop in supply or spike in demand. Delays are related to delivering individual orders later than expected time and distortion pertains to unanticipated variations in order size. Furthermore, seven risk mitigation strategies are considered into two categories of redundancy and flexibility. Redundancy strategies consist of increasing capacity, redundant suppliers, increasing inventory and flexibility strategies include increasing responsiveness, increasing flexibility, aggregating demand, and increasing capability. In the following table different mitigation strategies are suggested with respect to different configurations and risks. For instance, if there is a risk in disruption category and it is related to supplier and also happens when the demand variability and risk likelihood is low, then the most effective strategies could be 1,3,4, and 5 which are respectively increase capacity, increase responsiveness, increase flexibility, and aggregated demand with respect to low fixed cost (Talluri, Kull, Yildiz, & Yoon, 2013).

Risk Scenario			Configuration with respect to demand variability (DV) and risk likelihood (RL)				
Risk category	**Risk source**	**Fixed costs**	**Low DV & Low RL**	**Low DV & High RL**	**High DV & Low RL**	**High DV & High RL**	**Robust for given scenario†**
Disruption	Supplier-related	Low	1,3,4,5	3,5,7	1,3,4,5	3,4,5,7	3,5
		High	1,4,5	5	1,4,5	4,5	4,5
	Internal	Low	1,3,4,5,7	3,7	3,5	3,7	3,7
		High	5	5	5	5	5
	Customer-related	Low	1,3,4,5	1,3,5,6	1,3,4,5	3,5	1,3,5
		High	1,4,5	1,5,6	1,4,5	5	1,5
	Robust for given configuration†		1,4,5	5	1,4,5	5	5
Delay	Supplier-related	Low	3,6	3,6	3,6	3,6	3,6
		High	5,6	5,6	3,5,6	5,6	5,6
	Internal	Low	3,7	3,6,7	3,7	3,6,7	3,7
		High	5	5	5,6	5	5
	Customer-related	Low	3,7	3,7	3,7	3,7	3,7
		High	5	5,7	5	5,7	5
	Robust for given configuration†		n/a	n/a	3	n/a	n/a
Distortion	Supplier-related	Low	1,4,5	4	1,4,5	1,4,5	4
		High	1,4,5	1,4,5	1,4,5	1,4,5	1,4,5
	Internal	Low	3,5	3,5	3,5	3,5	3,5
		High	5	5	5	5	5
	Customer-related	Low	4,5	3,5,6,7	1,4,5	3,5,6,7	5
		High	4,5	5	1,4,5	5	5
	Robust for given configuration†		4,5	5	1,4,5	5	5

Notes: *Strategies are numbered as follows: (1) Increase capacity, (2) Increase inventory, (3) Increase responsiveness, (4) Increase flexibility, (5) Aggregate demand, (6) Increase capability, and (7) Redundant suppliers.

Figure-A II-4 Best supply chain risk mitigation strategies for a given configuration and scenario

Taken from Talluri, Kull, Yildiz, & Yoon (2013)

(Iyengar S. , Hedman, Forte, & Hill, 2016) in their research investigated medicine shortages, its causes, and strategies to mitigate them. Several reasons affect shortages such as manufacturing matters, drastic healthcare needs, exterior political and economic elements, procurement, marketing, and SC management practices. For example, in terms of manufacturing issues, lack of raw material and confined manufacturing capacity or product quality problems can result in shortage. The authors claimed that reasons that put a medicine at risk of shortage may vary from region to region. Progressive notification systems to national medicines regulatory authorities (NMRAs) and monitoring stock levels for some special medicines enable mitigating shortages. Medicine SC data is crucial to maintain and

predict supply. Advance notice systems are mostly in high income markets and need manufacturers to instruct them for imminent shortages. Through NMRAs it is possible to recognize clinically sustainable substitute medicines, provide notice to prescribers and distributors, comfort special market authorizations for other manufacturer, and sometimes recognize other manufacturing capacities. Therefore, these kinds of systems are helpful in managing shortages, for instance, through identifying substitute sources of products. Keeping track of supply chain can also enable countries to redistribute drugs all over warehouses to handle emergency orders when is required. Besides, theoretically, different countries can mitigate shortages through sharing and redistributing warehouses by working together; however, it needs regulatory agreements and may lead to additional cost and quality risks.

(Ho W. , Zheng, Yildiz, & Talluri, 2015) tried to investigate risk types, risk factors, and risk mitigation strategies in the field of supply chain through reviewing literature. In this paper, the supply chain risks are categorized into macro-risks and micro-risks. Macro-risks include natural or man-made risks such as earthquake or war and political instability and in fact they comprise rare exterior situations which can affect negatively on companies. Micro- risks allude to sort of recurrent events that stem from internal activities in companies or communications within partners in the whole supply chain. Moreover, they can be divided into demand risk, supply risk, manufacturing risk, and infrastructural risks. Different mitigation strategies are introduced according to each risk classifications. In terms of *macro-risk mitigations* nine strategies are identified including postponement, flexible transportation, and strategic stock, make and buy flexible supply base, economic supply inducement, income management, dynamic taxonomy planning, and silent product rollover. In terms of *demand risk mitigation*, there are lots of strategies in different studies. One of the strategies refers to identifying the optimal-order placement and refilling plans to decrease the effect of demand uncertainty. We can also refer to analyzing the predicting techniques to minimize the demand risks. Risk sharing contracts, determining a same guaranteed greatest lead time to all customers under demand risks optimizing profits, presenting a dynamic system for manufacturing supply chains to handle disruptive events, and catching the demand shock are among other strategies. In terms of *supply risk mitigation*, executing behavior-based

management techniques, building supplier communications, having business continuity planning, and decreasing supply base complication can mitigate supply risks. Regarding *transportation risk mitigation*, identifying the optimal production and ordering amounts for both supplier and retailer can be beneficial. Normal hedging of currency and merchandise price fluctuations, common decision on the loan amount for the lender and borrowing organizations when one of the firms has enough low cash can be beneficial for *financial risk mitigations*. In terms of *information risk mitigation*, having a database to share data with upstream supply chain partners as well as downstream without leakage of information to rivals can help reduce uncertainty. Regarding *general risk mitigation* several strategies are suggested in different studies, for instance, increasing flexibility, building cooperation relationships among SC partners, sharing knowledge in the supply chain, managing suppliers, enhancing agility, and comprehending various cultures in organizations.

(Sweeney, 2020) surveyed about response actions after a supply chain disruption in the pharmaceutical supply chain. The authors claimed that responsive strategies to supply chain disruptions are dependent on the period since the disruption, and this affects the performance. One of the big troubles in pharmaceutical industries is about drug shortages which have tripled since 2006. Having an information processing and resource dependency perspectives has developed the construction of organizational respond to embrace the collection of disruption responds. The double strategies of buffering and bridging and generic response substitution are introduced in this research. Buffering strategies refer to establishing guard to protect a company from disruptions and bridging refers to managing risks by applying boundary-spanning and boundary-shifting acts with a substitute partner and having quick response options. The results showed that organizations with higher supply chain disruption orientation choose and implement buffering and bridging actions efficiently and superior shortage performance. The firms act differently and employ a combination of strategies in terms of environmental situation and the availability of information to have an effective shortage management strategy. The way of improving shortage management performance is illustrated in the figure 1.5.

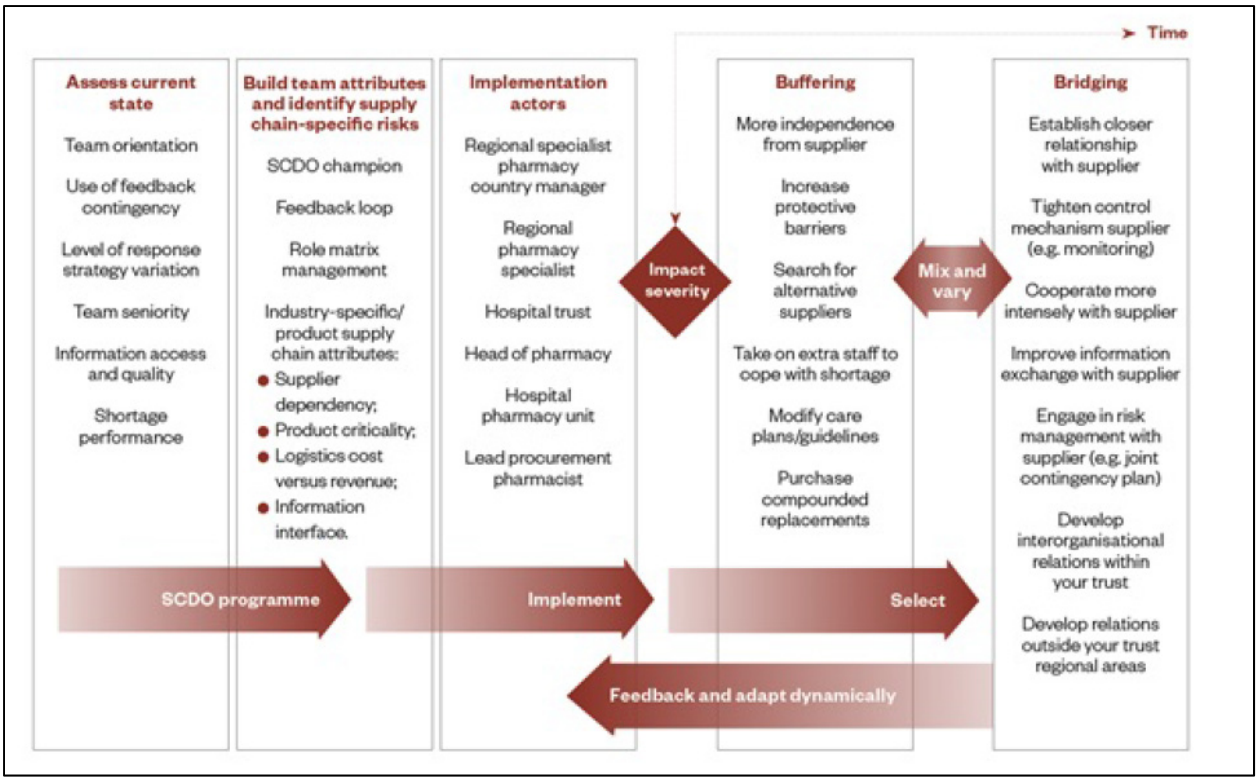

Figure-A II-5 Supply chain disruption shortage management roadmap for practice managers

Taken from Sweeney (2020)

CHAPTER 2

METHODOLOGY

In this study, a Systematic Literature Review (SLR), which mainly referred to as identification, evaluation, and interpretation of a field of research that can be reproduced with the same protocol by other researchers (Kitchenham B. , 2004) has been conducted. The applied procedure contains eight steps: formulating the research problem, developing review protocol, searching the literature, screening for inclusion, assessing quality, extracting data, analyzing data, and reporting the findings. In the first step the research questions are recognized. In the second step, all the elements of the review are defined such as inclusion criteria, search strategies, quality assessment criteria, the procedure of screening, data extraction and reporting which will be discussed in detail in the next steps. In the next step, the major sources, key words, search strings, and the search date are determined. After that, the papers are screened for inclusion based on reviewing the titles and abstracts. In the quality assessment step, the papers full texts are screened to satisfy the inclusion/exclusion criteria. In the next steps, the final data are extracted, organized based on the research questions, and finally reported as the research findings (Xie, Anumba, Lee, Tummala, & Schoenherr, 2011).

CHAPTER 3

RESULTS

The outcomes of the eight steps methodology procedure are described in this section. First, the research questions are determined as 1) what are the risks and risk categories in the pharmaceutical supply chain? And 2) what are the supply chain risk mitigation strategies in the literature? Then the inclusion and exclusion criteria were defined. For example, the articles written in English were included and master and doctoral dissertations, textbooks, book chapters and notes were excluded from the review. Some criteria are determined to filter the articles. Regarding the criteria, titles and abstracts of articles were checked to see if they cover supply chain risk topics, including risk categories, supply chain risks, pharmaceutical risks, and risk mitigation strategies. Therefore, the articles were excluded if they did not meet one of these filters. Besides, the articles with the very specific research scope such as supplier selection based on supply chain risks were excluded. The duplicate articles were also identified and removed, and accomplishment of forward and backward snowballing is considered into the process to include other related articles. In the third step, selected keywords in the shown in Figure 3.1 is applied in online databases including PubMed, Scopus, IEEE, Google Scholar and Web of Science between the years of 2000 and 2020 which 65026 records were identified. Based on duplication criterion, 35069 papers were removed. Then, 34975 papers were eliminated after performing second screening based on papers' title and abstract. In the quality and after reviewing the full text of 94 remained papers and performing forward and backward snowballing, 21 papers were retained as final sample of systematic review synthesis. We reached 12 articles out of 21 to address the first question and 9 articles to address the second question.

At last, reported results comprise 137 risks which are categorized into 8 different groups that cover all the identified categories in the reviewed literature. These groups consist of supply and supplier risks, financial issues, logistics and transportation issues, market and

environmental risks, operational issues, organization and strategies issues, political and cultural issues, and regulation risks. 37 out of 137 risks pertain to supply and supplier risks, 29 risks are related to organization and strategies issues, 18 risks for market and environmental risks, 17 risks are related to financial issues, 17 risks are related to operational issues, 9 risks are related to logistics and transportation issues, 6 risks for political and cultural issues, and 4 risks for regulation. Table 3.1 illustrates all the extracted risks and categories.

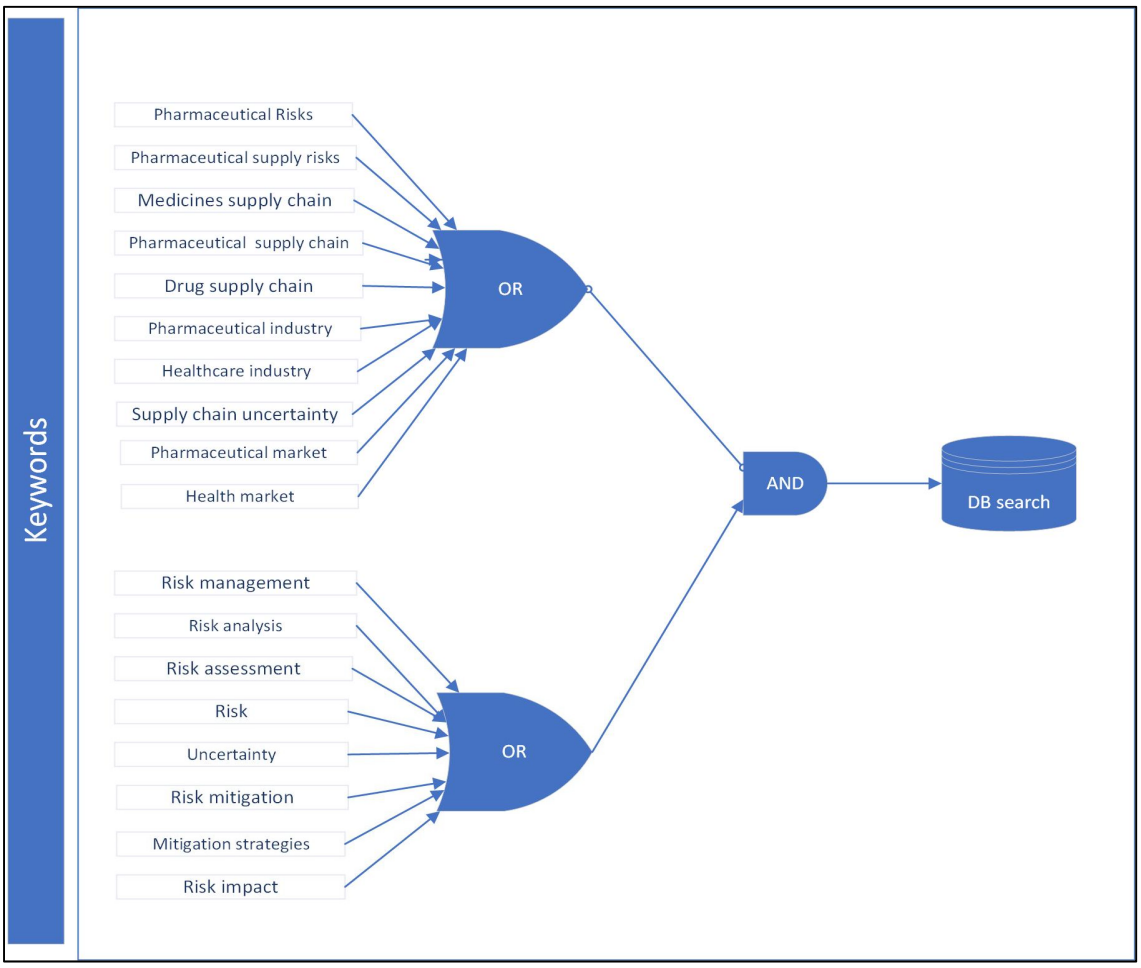

Figure-A II-6 Visualization of the key words query

Table-A II-1 Risks and risk categories in the pharmaceutical supply chain

Risk	**Category**
supply and supplier issue (Shah, 2004) (Enyinda, Briggs, & Bachkar, 2009, February) (Enyinda, Mbah, & Ogbuehi, 2010) partnership with supplier (Enyinda, Briggs, & Bachkar, 2009, February) (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) raw material quality (Enyinda, Briggs, & Bachkar, 2009, February) (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) ordering cycle time (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) contract and agreements (Breen L. , 2008) customization of supplier (Breen L. , 2008) certificate of GMP (Breen L. , 2008) (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) flexibility of supplier (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) delivery reliability (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) environmental assessment (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) technology level, information systems, goodwill (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) technology development, flexibility in delivering, flexible quantities, flexibility in product variety, timely delivery, quality management system (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) fluctuation in imports arrival (El Mokrini, Dafaoui, Berrado, & El Mhamedi, 2016) lack of information sharing (Moktadir M. A., et al., 2018) (Yousefi & Alibabaei, 2015) key supplier failure (Kieslich, et al., 2016) (Wagner, Bode, & Koziol, 2009)	Supply and supplier risks

Risk	**Category**
non-availability of materials (Ketkar & Vaidya, 2012) timid technology/adoption transfer, lack of support of SC partners, supplier trading capability (Enyinda, Mbah, & Ogbuehi, 2010) inability to handle demand changes (Sreedharan, Kamala, & Arunprasad, 2019) (Zareei, Zamani, & Tanaomi, 2014) failures to make delivery requirements (Zsidisin G. A., 2003) price of raw materials (Sreedharan, Kamala, & Arunprasad, 2019) technologically behind competitors (Zsidisin G. A., 2003) supply responsiveness (Xie, Anumba, Lee, Tummala, & Schoenherr, 2011) lack of integration with suppliers (Gaudenzi & Borghesi, 2006) supplier location (Wagner & Neshat, 2010) procurement Hubs – introduce more complexity, loss of expertise – unsophisticated purchasing/practice, short term SC planning, fragmentation of SC – no single source, multiple channels, no communication, unilateral decisions (Breen L. , 2008)	
inventory management (Blos, Wee, & Yang, 2010) (Jnandev Kamath, Kamath, Azaruddin, Subrahmanyam, & Shabharaya, 2012) (Shah, 2004) operation issues (Blos, Wee, & Yang, 2010) (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) R & D (Reschke, 2010) skill of workers (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) planning issues (Blos, Wee, & Yang, 2010) (Shah, 2004) information flow, visibility on stock (Jaberidoost M. , et al., 2015) organization and process, time to market (Blos, Wee, & Yang, 2010) mergers and acquisition (Reschke, 2010) waste management (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) demand versus capacity, manufacturing licensing/change of standards/drug recalls, inadequate buffer stock – JIT/lean, manufacturer defense tactics, diversion of manufacturing capacity, stock holding – more concentrated,	Organization & Strategies Issues

Risk	Category
dispensing/picking error – medication/packaging, prescription management, decrease in capacity linked to profit, nonstandard practice – customized policies per hospital. lack of common codes etc., storage/cold chain, reimbursement policies not consistent, response of industry to shortages – communication (Breen L. , 2008) service disruptions, myopic vision: traits of research, patents, and mergers, deficient information systems (Vishwakarma, Prakash, & Barua, 2016) system integration or extensive systems networking, lack of information transparency between logistics and marketing (Sreedharan, Kamala, & Arunprasad, 2019) intellectual property (Silva, Araujo, & Marques, 2020)	
currency rate (Enyinda, Mbah, & Ogbuehi, 2010) (Jnandev Kamath, Kamath, Azaruddin, Subrahmanyam, & Shabharaya, 2012) tariff policies changes (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) cash flow, Theft (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) interest rate (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Breen L. , 2008) increase in freight charges (Moktadir M. A., et al., 2018) financial restriction (Gandhi, Mangla, Kumar, & Kumar, 2016) dynamic taxation, money market volatility, investment risk, variations in trade/pricing policies, capital/fund management, transportation cost (Vishwakarma, Prakash, & Barua, 2016) wage rate shifts, price fluctuations, product cost and pricing due to competition lead time for internal processing and the timing of its related cash outflows (Sreedharan, Kamala, & Arunprasad, 2019) production cost (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013)	Financial Issues

Risk	Category
transportation – unavailability of fuel, congestion, weather, illness (Breen L. , 2008) counterfeit and security, storage and warehousing, network, and reverse logistics (Vishwakarma, Prakash, & Barua, 2016) transport provider's fragmentation, On-time/on-budget delivery, accidents or damages in transport, paperwork, and scheduling (Sreedharan, Kamala, & Arunprasad, 2019)	Logistics and Transportation
consumers taste (Jaberidoost M. , Nikfar, Abdollahiasl, & Dinarvand, 2013) (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) (Shah, 2004) unexpected increase in demand, lack of forecasting – customer side, demand/economics – not able to respond to demand, risk of litigation – influence on market, prioritization – conflict between patients/profits, external influences – disaster recovery (Breen L. , 2008) uncertainty in market (Moktadir M. A., et al., 2018) bullwhip effects (Craighead, Blackhurst, Rungtusanatham, & Handfield, 2007) competitive risks (Moktadir M. A., et al., 2018) (Mangla, Kumar, & Barua, 2015) market completions, demand volatility, natural disasters (Vishwakarma, Prakash, & Barua, 2016) customer dependency, deficient or missing customer relation management function, high competition in the market, order fulfillment errors, fire accidents (Sreedharan, Kamala, & Arunprasad, 2019) natural disasters and terrorism (Jaberidoost M. , et al., 2015) (Breen L. , 2008)	Market and Environmental Risks
political issues (Mehralian, Gatari, Morakabati, & Vatanpour, 2012) government's policy (Silva, Araujo, & Marques, 2020) stringent government policies and changing regulations, political instability (Vishwakarma, Prakash, & Barua, 2016) cultural grievances (Sreedharan, Kamala, & Arunprasad, 2019)	Political and Cultural Issues

Risk	Category
regulation (Enyinda, Mbah, & Ogbuehi, 2010) (Jnandev Kamath, Kamath, Azaruddin, Subrahmanyam, & Shabharaya, 2012) price regulation (Silva, Araujo, & Marques, 2020) external legal issues, government regulations (Sreedharan, Kamala, & Arunprasad, 2019)	Regulation Issues
machine, equipment, or facility failure, power failure (Finch, 2004) (Moktadir M. A., et al., 2018) quality risk, storage contamination risks (Moktadir M. A., et al., 2018) operational in/efficiencies e.g., systems operating properly, lack of knowledge regarding manufacturing process or source of supply (Breen L. , 2008) operations/process failure (Silva, Araujo, & Marques, 2020) labor disputes/strikes, skill level of the employee, inventory holding cost, production flexibility, production capabilities/capacity, technical/knowledge resources, warehouse and production disruption, insufficient maintenance, centralized storage of finished products (Sreedharan, Kamala, & Arunprasad, 2019)	Operational Issues

The second part of the literature review pertains to risk mitigation strategies in the supply chain area in which 9 articles were investigated. Researchers in these studies concentrated on different topics including analysis of risk mitigation in the pharmaceutical industry supply chain, supply chain disruption mitigating in terms of inventory and reserve capacity, global SC risk management, mitigation through investigating different SC configurations, network management, evaluating the efficiency of mitigation strategies, focusing on mitigation strategies in the field of medicine shortage, and assessing responses to disruption in the pharmaceutical SC. The authors tried to gather and review the articles that focus on different aspects of supply chain to cover various strategies. Table 3.2 illustrates the outcomes from reviewing papers related to risk mitigation strategies.

Table-A II-2 Risk mitigation strategies in the supply chain

Authors	**Research focus**	**Risk mitigation strategy**
(Enyinda, Mbah, & Ogbuehi, 2010)	Conducting an empirical finding in order to help decision makers in terms of prioritizing the most important risk factors and then mitigating a risk portfolio	Among different risk mitigations, risk avoidance and then risk reduction is more appropriate for counterfeit. Regarding the FDB, risk reduction/control, and risk avoidance are considered as the first and second proper strategies
(Lücker, Seifert, & Biçer, 2019)	describing factors direct to increase Risk Mitigation Inventory (RMI) or reserve capacity levels	four mitigation strategies inventory strategy; passive acceptance, mixed strategy, and process flexibility strategy were recognized
(Manuj & Mentzer, 2008)	discovering the phenomenon of risk management and risk management strategies in global supply chain	Selection of a strategy is dependent on three factors which are temporal focus, supply chain flexibility, and supply chain environment and six strategies are identified namely postponement, speculation, hedging, control/share/transfer, security, and avoidance
(Huq, Pawar, &	identifying disruption factors in	Three mitigation strategies

Authors	Research focus	Risk mitigation strategy
Rogers, 2016)	pharmaceutical industry and help managers make the better decision about the most proper supply chain configuration	include insourcing offshore through captives, reshoring/nearshoring core products, and outsourcing offshore noncore products are recognized
(Qazi A. , Dickson, Quigley, & Gaudenzi, 2018)	prioritizing different risks, discovering interdependency between them, and discovering appropriate mitigation strategies in a network setting with respect to decision makers appetite	The mitigation strategies that were determined during the research include contract term, quality training, perform business interruption analysis, adopt enterprise risk management process, perform Disaster Recovery Plan (DRP) testing, union relations, economics of scale, flexibility, and reduce cost
(Talluri, Kull, Yildiz, & Yoon, 2013)	Evaluating effective supply chain risk mitigation strategies in accordance with different risk categories, risk sources, and different supply chain contexts (configurations)	Defining two kinds of strategy redundancy strategies consist of increasing capacity, redundant suppliers, increasing inventory and also flexibility strategies include increasing responsiveness, increasing flexibility, aggregating demand, and increasing capability

Authors	Research focus	Risk mitigation strategy
(Iyengar S. , Hedman, Forte, & Hill, 2016)	investigating medicine shortages, its causes and strategies to mitigate them	Introducing different mitigation strategies such as advance notice systems, keeping track of supply chain, and sharing and redistributing warehouses
(Ho W. , Zheng, Yildiz, & Talluri, 2015)	Investigating risk types, risk factors, and risk mitigation strategies in the field of supply chain	Different mitigation strategies are introduced according to each risk classifications such as postponement, , pliable transportation, and strategic stock, make and buy pliable supply base and etc.
(Sweeney, 2020)	surveying about response actions after a supply chain disruption in the pharmaceutical supply chain	The double strategies of buffering and bridging and generic respond substitution are introduced in this research

CHAPTER 4

DISCUSSION

There are several Supply Chain Risk Management (SCRM) frameworks in different studies which have common elements with each other and with ISO 31000. One critical point is that ISO 31000 regards establishing the context as the first substantial step to enable comprehensive risk management. Establishing the context defines objectives, recognizes success factors, evaluates stakeholder communications, and recognizes the risk management environment. It also emphasizes the communication and engagement of stakeholders to spread risk information and identify objectives (Xiao & Watson, 2019) which is not considered in most of the reviewed papers. Furthermore, ISO 31000 framework is consisted of five processes for managing risk which are communication and consultation, establishi8ng the context, risk assessment, risk treatment, and monitoring and review. In this paper we worked on the phase of risk identification which is one of the steps of risk assessment according to ISO 31000 framework and risk treatment.

As a contribution of this paper, we can refer to gathering more risks and categories in the pharmaceutical supply chain than the other related studies. Besides, we reviewed 21 papers which are more comprehensive than the related work with the SLR methodology. Some of the reviewed papers related to risk mitigation strategies were in supply chain risk mitigations and not specifically in the field of pharmaceutical supply chain. This is a limitation of this work owing to the little previous conducted studies in pharmaceutical supply chain risk mitigation. Therefore, as future research the concentration on identifying and assessing risk mitigation strategies in the pharmaceutical supply chain can be addressed. Another suggestion for future work is working on the connection between identified risks and risk mitigation strategies in this paper which is possible through conducting a survey with the risk management experts' cooperation. Besides, it is useful to research on understanding the difference between PSC risks and other types of supply chain risks.

CONCLUSION

Pharmaceutical supply chain is encountering different types of risk which not only jeopardize resources but also menace patients' life by hampering access to medicines. To guarantee pharmaceutical supply chain resilience and permanence, it is necessary to effectively identify and evaluate risks and develop a pervasive mitigation approach. In this research the authors attempted to conduct a Systematic Literature Review (SLR) regarding both identifying pharmaceutical supply chain risks and supply chain mitigation strategies for different risks and environments. Although, there is no one specific strategy fits all firms and situations in the supply chain and might be different owing to some characteristics (Simchi-Levi, 2010), investigating different studies in this area can be helpful for academics and practical experts. Firstly, various risks and uncertainties are identified in the pharmaceutical supply chain by conducting SLR. In general, 137 risks with 8 different categorizations are recognized in the pharmaceutical industry. Secondly, we tried to present different risk mitigation strategies that were regarded in the research for various situations and parts of the supply chain.

One of the limitations of this study is that most of the papers related to risk management and mitigation strategies had not been fulfilled specifically in the pharmaceutical supply chain. And we believe that the pharmaceutical industry has some special characteristics toward other supply chains which necessitate doing more research and investigations in this area. One of the other limitations is about considering the relationship between each risk and each mitigation strategy which were not identified in most of the studies. Therefore, it is recommended to be investigated in other studies and through practical research in different pharmaceutical firms and different situations.

APPENDIX III

PAPER SUBMITTED IN OPERATIONS RESEARCH FORUM

PHARMACEUTICAL SUPPLY CHAIN RISKS AND RISK MITIGATION STRATEGIES: SYSTEMATIC LITERATURE REVIEW (SLR) THROUGH TEXT-MINING

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ABSTRACT

Pharmaceutical supply chains face different kind of risks and uncertainties and managing the risks has emerged as an important issue with constantly changes in the supply chain. To successfully manage the risks, it is important to identify risks and uncertainties and know how to mitigate these risks with proper risk mitigation strategy. The purpose of this study is to investigate the existing literature to identify risks and risks mitigation strategies by using Text-Mining techniques instead of traditional literature review approach.

The methods we applied to perform a Systematic Literature Review (SLR) consist of phrase extraction by lexical approach and using Natural Language Toolkit (NLTK), semantic similarity clustering (include vectorizing by Universal Sentence Encoder method and similarity matrix method), and post-processing.

A total 4205 papers were extracted after applying related search strings in the three search engines of Web of Science, PubMed, and Google Scholar. At last, after performing different

phases of removing duplicated references, title screening, and title and abstract screening in the DistillerSR software, 278 references formed our project's selected studies.

The results demonstrate that 317 risks in general are identified in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other. Top three risks that are discussed the most in the literature include supply risks, operational risks, and operational risks respectively. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively. Moreover, more than 73 risk mitigation strategies are found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines. The second risk that has received the most attention from researchers is supply-related risks.

Keywords: pharmaceutical supply chain, risks, risk mitigation strategy, SLR, Text-Mining

INTRODUCTION

Pharmaceutical Supply Chain (PSC) is facing different kinds of risk which can waste resources and threaten patients' life by limiting access to medicines (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013). Therefore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines (Moktadir M. , et al., 2018).

In the last decade healthcare organizations have become more complicated owing to different factors such as efficient customers, biomedical developments, the complexity of services, and an increasing number of healthcare users. Moreover, the complication of supply network has increased by globalization, high customer expectations, shorter life cycle for products and technologies which has led to tremendous uncertainties and risks in the PSC. Furthermore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines. Different studies and researchers have worked on identifying the risks and risk mitigation strategies in the pharmaceutical supply chain and the

problem is that reading all these studies is beyond someone's ability or an organization's ability.

Mining scientific papers has been sometimes proven useful but it also presents a headache for anyone wanting to stay up to date with the literature or hoping to mine it for insight about different topics. Systematic reviews are a widely used method to bring together the findings from multiple studies. The problem is that the growing number of published studies makes it difficult to use them in an efficient way. Exploring the literature with AI techniques could greatly accelerate researchers' ability to benefit from a wide range of studies and integrate them. Text-mining is the process of discovering knowledge and structure from unstructured data.

Therefore, the purpose of this study is to conduct a SLR methodology using Text-Mining (TM) technique to cover the gap regarding automated SLR method in the pharmaceutical supply chain. Although there are different studies working on identifying pharmaceutical supply chain and risk mitigation strategies by SLR, no one has applied text-mining techniques so far and basically, the motivation of this study is new synthesizing research with testing different TM techniques and algorithms.

In summary, this research intends to pursue the following objectives:

• Using AI techniques in Systematic Literature Review (SLR) in the field of pharmaceutical supply chain and examining different TM algorithms

• Identifying different pharmaceutical-related risks in the supply chain through the new obtained method

• Identifying different risk mitigation strategies and discovering the relations between strategies and risks

To achieve these research objectives, the following research methodology was designed and adopted:

A Systematic Literature Review (SLR) protocol introduced by (Kitchenham, 2004) is applied that contains eight steps:

- Formulating the research problem.

- Developing review protocol.
- Searching the literature.
- Screening for inclusion.
- Assessing quality.
- Extracting data
- Analyzing data
- And reporting the findings

The remainder of this research includes a literature review on definitions of risk, Supply Chain (SC), supply chain risk, Supply Chain Management (SCM), Supply Chain Risk Management (SCRM), and Pharmaceutical Supply Chain (PSC), various Literature Review (LR) methods, SLR methods, and TM techniques in literature review. Next sections describe the methodology used in this research followed by results, discussion and at the end conclusion.

CHAPTER 1

LITERATURE REVIEW

Risk can be defined as an uncertain event, which has the likelihood of incidence of undesirable outcomes such as late delivery, economic burden, and business loss (Moktadir M. , et al., 2018) and according to ISO31000 its effect can be positive and/or negative (Leitch, 2010). Besides, it is considered as the extent of uncertainty in terms of realizing the importance and/or unfortunate results of decisions (Zsidisin G. A., A grounded definition of supply risk, 2003). Supply chain is a series of processes, members, information, and assets that transform raw materials into products and services available for clients (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013). Supply chain risk is the potential varying results that lead to the reduction of value-added at any task in a supply chain (Ho, Zheng, Yildiz, & Talluri, 2015).

Supply Chain Management (SCM) is defined as planning and managing of all tasks pertain to sourcing, procurement, transformation, and logistics (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013). Supply Chain Risk Management (SCRM) is an organizational cooperative effort using different kinds of methodologies such as quantitative and qualitative risk management to recognize, assess, mitigate, and monitor unanticipated events or situations, which might negatively affect supply chain (Ho, Zheng, Yildiz, & Talluri, 2015). Pharmaceutical Supply Chain (PSC) is a remarkable part of the health system with the aim of providing medicines which contains all processes, information, assets, and members such as producers, mediators, logistics tasks, trading, sales tasks, finance, and IT (Jaberidoost, et al., 2015). Risk mitigation can be defined as the strategic actions that are pursued by organizations to counteract the risks identified from different sources (Enyinda, Mbah, & Ogbuehi, An empirical analysis of risk mitigation in the pharmaceutical industry supply chain: A developing-country perspective, 2010).

Systematic Literature Review (SLR) is a well-settled research method applied to integrate the top existing empirical data from systematic research (Feng, Chiam, & Lo, 2017). There are different methodologies, models, guides, protocols, and frameworks such as PRISMA,

selection methodologies, Enfoque iSR, SLR Delaware guide, protocol of the Center for Reviews and Dissemination (CRD), and three states framework (Input/ Processing/ Output) to conduct SLR (Palomino, Dávila, & Melendez, 2018). Due to SLR complexity it could be a challenging task in terms of consuming time, being labor-intensive, and open to errors if performed manually. Therefore, there are various text-mining techniques and tools that can facilitate different SLR phases and activities (Feng, Chiam, & Lo, 2017).

Text-Mining (TM) is the process of getting fascinating information, patterns, trends, and significant knowledge from textual documents (Tan, 1999). There are different TM applications such as Visual Text Mining (VTM), federated search strategy, automated document classification, and document summarization; and different TM techniques such as Information Visualization (IV), clustering, Information Retrieval (IR), classification, Information Extraction (IE), and summarization to automate different processes in SLR (Feng, Chiam, & Lo, 2017).

CHAPTER 2

METHODOLOGY

As we mentioned in introduction SLR method and the procedure by (Kitchenham, 2004) is considered as the methodology method.

2.1. Formulating the research problem

Several researchers have worked on the topic of identifying, assessing, managing risks, and providing risk mitigation strategies to improve the situation in PSC. The problem is that the growing number of published studies makes it difficult to synthesize them and applying the traditional SLR method manually can be an inefficient way. To address this problem, the potential of TM techniques and its developed tools help facilitate SLR processes (Feng, Chiam, & Lo, 2017).

2.2. Developing review protocol

SLR protocol considers three phases of planning, conducting, and reporting (Kitchenham, 2004) that is discussed step by step. The motivation of this research is answering the following questions:

RQ1: What TM techniques and algorithms will be determined to conduct the SLR in the pharmaceutical supply chain field?

RQ2: What is different pharmaceutical-related risks in the supply chains?

RQ3: What are the different risk mitigation strategies in the pharmaceutical supply chain?

In the literature, there is a gap in terms of the lack of synthesizing mitigation strategies and related risks. This then raised an additional research question for this thesis:

RQ4: Is it possible to present a synthesized work on the identified risks and risk mitigation strategies in the existing literature?

To find the primary studies different combination of keywords and search strings are obtained that is shown in Fig.1.

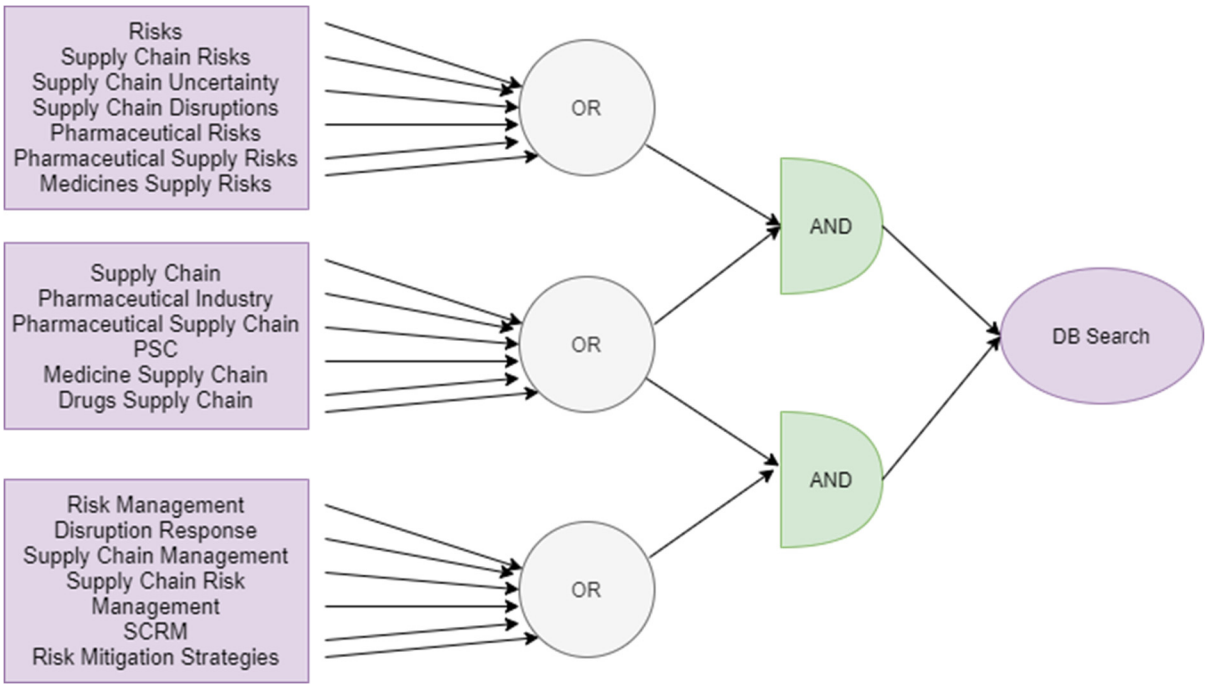

Figure-A III-1 Search keywords and strings in the databases

The selected keywords are used to extract relevant research from three search engines of Google scholar, PubMed, and Web of Science. Inclusion criteria consist of all English journal papers, conference papers, and workshops between 2000 and 2021. The relevant papers are decided to be included if either those identify, assess, or analyze risks in at least one part of the pharmaceutical supply chain and the industry or identify, present, and investigate at least one risk mitigation strategy. Besides, exclusion criteria include e-books, books, thesis, and studies that worked on specific part of pharmaceutical supply chain such as radiopharmaceutical or Biological Pharmaceutical Industry. Also, studies without full-text availability are excluded.

2.3. Searching the literature, screening for inclusion, and assessing quality

The queries result from search engines are imported in DistillerSR software. DistillerSR applies Natural Language Processing (NLP) to automate the screening phase through sorting and ranking results, operating as a second screener, and distinguishing the errors. The relevant articles are selected through two steps of title screening and abstract screening. DistillerAI uses k-fold cross validation method to train the dataset multiple times by using a percentage of reviewed references and ensures a diverse sample of references.

2.4. Extracting data

Titles and abstracts of all references are checked in terms of previously determined inclusion and exclusion criteria. After two steps of screening the obtained references from search engines, finding references compatible with the defined protocol, and assessing the quality, the data set will be ready to be pre-processed. It is noteworthy that Python programming language is used in processing the data as it is a relatively simple programming language and has a big library of frameworks and it is used widely by scientific researchers. Different rules are applied to filter and remove unwanted data. For instance, in page level if the first page ratio is different from others, it indicates that the first page is a cover and needs to be removed. Besides, text refinement should be done because the extracted data is not always clean and may contain many unwanted signs, characters, redundant spaces, parenthesis, and brackets.

2.5. Analyzing data

When the textual data extraction and pre-processing are completed, the next phase is data processing. This phase consists of these steps: phrase extraction, semantic similarity clustering, and eventually post-processing. The purpose of phrase extraction is to acquire phrases in which they give information about aimed keywords such as risk or strategy. There are mainly two possible approaches: “semantic similarity approach” and “lexical approach”

for extracting phrases. After comparing results of different machine learning approaches such as Universal Sentence Encoder (USE) and Global Vectors for Word Representation (GloVe), the lexical approach is decided to be used.

The process or ability of analyzing human written textual data with computer programs is called Natural Language Processing (NLP). For this purpose, we use the Natural Language Toolkit (NLTK) library in Python. The first step is to design an algorithm that would extract appropriate phrases based on the given keywords that in this case are 'Risks' and 'Strategies'. Next step is constructing the data frame based on the yielded noun phrases. The data frame includes 8 columns, "Cluster", "File", "Keyword", "Phrase", "Sentence", "Local frequency", "Global frequency", and "Files count" that will be discussed in the result section. Next step is phrase clustering that puts similar phrases into a same group to shrink the number of phrases and focus on the content; also, it helps to relate strategies and risks that share the same words or synonyms. Clustering technique in this research consists of two phases vectorizing and grouping. For vectorizing the method of USE is used since it showed promising results. For grouping k-means algorithm alongside with the similarity matrix method are tested in terms of distance calculation and clustering. The similarity matrix method which is the inner product of vector matrix is used owing to more accurate distance calculation and grouping outcomes.

2.6. Post-Processing and reporting the findings

In terms of validation, however automated methods have demonstrated performance in different areas, they cannot eliminate the need for reading texts by researchers and it necessitate researchers guide the process and interpret the outputs (Grimmer & Stewart, 2013). To investigate our findings' validation, we select a sample of ten papers randomly and extract risks and risk mitigation strategies manually. In the end, we compare our findings and results from algorithms with the results that are obtained manually and by reading the sample documents to see how similar they are. The findings are presented in the result section and are propounded in the discussion part of the research.

CHAPTER 3

RESULTS

After applying different keywords in Web of Science, PubMed, and Google Scholar; 1551, 1370, and 1284 articles are extracted respectively. In other words, a total of 4205 papers are imported into DistillerSR software to execute two phases of title screening and title and abstract screening. By executing duplicate option in software 824 references were detected, and 3381 references remained to do the first phase of the screening process. As shown in Fig.2, in the end, 278 references were considered as our project's primary studies.

In this section, the results are presented and discussed in two sub-sections of risk and uncertainty, and risk mitigation strategy.

3.4. 1. Risk and Uncertainty

It should be noted that 317 risks in general are extracted in 24 different groups. Top three risks that are more discussed in the literature according to the columns of "Local frequency" (number of repetitions of phrase in each file), "Global Frequency" (number of repetitions of phrase in all files), and "Files count" (number of files that contains the phrase) include supply risks, operational risks, and operational risks respectively. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively.

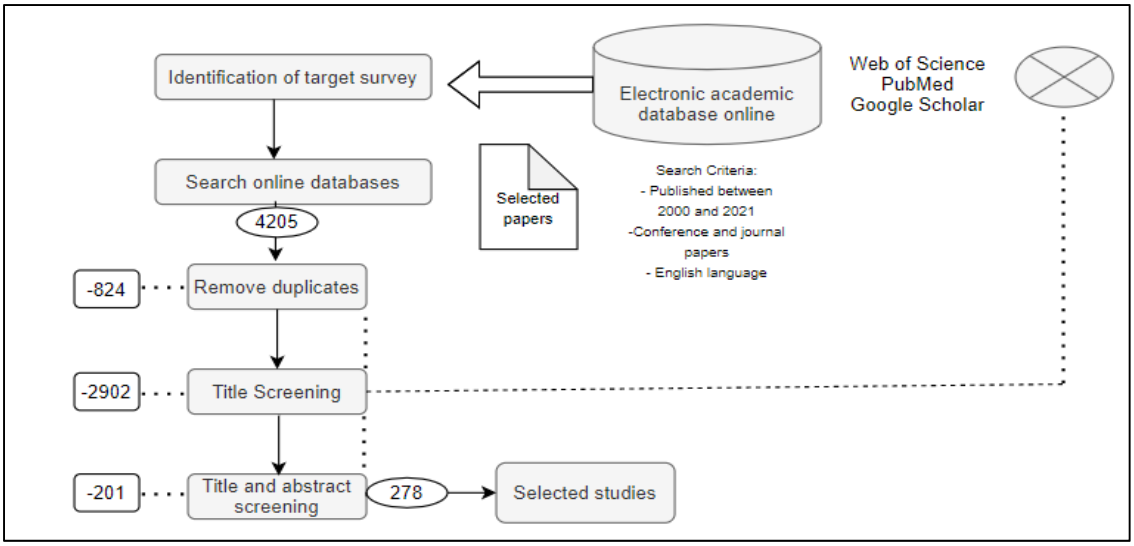

Figure-A III-2 Search and selection process

Table-A III-1 Risks and uncertainties in the product category

Reference	Risk	Sentence
(Davis & Abraham, 2011)	consumer product risk	US environmental and consumer product risk regulation was more precautionary during the 1970s and early 1980s.
(Enyinda & Tolliver, Taking counterfeits out of the pharmaceutical supply chain in Nigeria: Leveraging multilayer mitigation approach, 2009)	counterfeit product risk	Many drug manufacturing companies are known to be making legitimate products at one end of the factory and counterfeit products at another end.
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	virus contamination risk	
(Gómez & España, 2020)	Cross-contamination of finished product, Poor packaging, Product contamination	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Flexibility in product variety	
(Grujić, Morača, & Fajsi, 2020)	Lack of product quality control	Management of security risks refers to the development of the work plan in pharmaceutical companies.
(Kumar, et al., 2019)	product recovery risk	Pharmaceutical companies must pay attention to reverse logistics to enhance their effectiveness in product recovery.
(Abbasian, et al., 2020)	Low trust in domestic products	It is shown that demand-related risks are mostly linked to low trust in domestic products, marketing issues particularly at the international level, and demand fluctuations.
(Raka & Liangrokapart, 2017)	Registration problem	Manufacturers must be aware of IP laws, must seek approval from the FDA, and must observe drug registration laws.

Reference	Risk	Sentence
(Grujić, Morača, & Fajsi, 2020)	Patenting the product	The pharmaceutical industry is subject to a wide variety of powerful institutional and regulatory pressures
(Xu, Boehm, & Zheng, 2016)	Pharmaceutical product quality risk	
(Grujić, Morača, & Fajsi, 2020)	Poor design of products	Companies change product designs to meet customer wishes.
(Gómez & España, 2020) (Gray, Roth, & Leiblein, 2011)	Product defects	
(Van Bortel, et al., 2018) (Lowman, Trott, Hoecht, & Sellam, 2012) (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	product development risk	
(Balmoș, Lazăr, & Burcea Dragomiroiu, 2014)	Medical accidents risk	To reduce the risk of severe medical accidents caused by the cross contamination, the manufacturing of certain drugs, certain strongly active drugs or non-medicamentary products must not be made in the same facilities.
(Kumar, et al., 2019)	Product lifecycle risks	Pharmaceutical products are highly sensitive in terms of their life cycle and impacts (from introduction to withdrawal).
(Xu, Boehm, & Zheng, 2016) (Cundell, Guilfoyle, Kreil, & Sawant, 2020) (Gray, Roth, & Leiblein, 2011)	product quality risk	
(Narenjian, Riahi, & Kheirabadi, 2019)	Product reliability	
(Kumar, et al., 2019)	Uncertainty in recovery of products	Drugs recovered may be tampered with, and thus become unsuitable for consumption.
(Gatica, Papageorgiou, & Shah, 2003) (Varma, Pekny, Blau, & Reklaitis, 2008) (Fleischhacker & Zhao, 2011)	clinical trials uncertainty	
(Abbasian, et al., 2020)	Lack of standard CROs for clinical trials	
(Raka & Liangrokapart, 2017)	Patent problem	In addition to problems with market information, patents and intellectual property are obstacles.
(Urushihara, et al., 2014) (Hartford, et al., 2006) (Yaroson, Breen, & Matthias, 2017)	safety risks	Safety risk communication was defined as the exchange of drug information regarding safety risks by pharmaceutical companies with the aim of ensuring the rational use of drugs in practical clinical settings.
(Abbasian, et al., 2020)	Long-term licensing process for clinical trials	

Table-A III-2 Risks and uncertainties in the logistics category

Reference	Risk	Sentence
(Grujić, Morača, & Fajsi, 2020)	Unfavorable location	Focuses on geographic location. Issues associated with physical and infrastructure facilities are considered
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Accessibility of logistics provision	physical and infrastructure facilities are considered
(Kumar, et al., 2019)	Inefficient logistics network design and support	This represents inefficiency in logistics activities in the transportation of green materials in the pharmaceutical industry.
(Gómez & España, 2020)	Improper handling of finished product pallets	
(Kumar, et al., 2019)	reverse logistics design risk	Any flaw in designing the reverse logistics process
(Elamrani, Benabbou, & Berrado, 2016) (Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	logistics risk	

Table-A III-3 Risks and uncertainties in the material category

Reference	Risk	Sentence
(Cundell, Guilfoyle, Kreil, & Sawant, 2020) (Moktadir M. , et al., 2018)	Availability of raw materials	Regarding the availability of raw materials, for example, drug substances, excipients, solvents, processing supplies, and packaging materials …
(Kumar, et al., 2019)	Green raw material supply disruption	Disturbances in supplying of any key green raw material may disrupt the entire value chain
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Hazardous material risk	Risk of hazardous material is caused when the transported substance is contaminated due to exposure to harmful substances while transporting.
(Kumar, et al., 2019)	Inefficient use of materials and energy	Inefficient use of material and energy may create severe ecological and social problems in healthcare sector.
(Abbasian, et al., 2020)	Lack of domestic supplier of critical material	

(Paul, Kabir, Ali, & Zhang, 2020)	Gasoline related disruption	
(Gómez & España, 2020)	Primary packaging material failures	
(Yaroson, Sharief, Shah, & Breen, 2018)	Lack of active pharmaceutical ingredients	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Raw material quality	

Table-A III-4 Risks and uncertainties in the supply category

Reference	Risk	Sentence
(Ouabouch & Amri, 2013) (Kumar, et al., 2019)	Supplier failure	A supplier failure, for example because of a weak logistical performance, or even a bankruptcy, is also regarded as the most critical risk factor.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Mismatch between market demand and supplier responsiveness	One of the disturbance factors managers should be aware of while configuring their supply chains is a mismatch between market demand and supplier responsiveness.
(Amemba, 2013)	Turbulence Risks	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Fragmentation, Good will , Flexible quantities, Customization of supplier, Flexibility of supplier	It was agreed that the top-rated risks included fragmentation of the supply chain
(Zamora Aguas, Adarme, & Serna, 2013)	Disruptions in the supply	
(Vishwakarma, Garg, & Barua, 2019)	Inefficient supply network	Inefficient supply affects PSC competition which considers product perishability, brand differentiation of the product, as well as discarding costs.
(Vishwakarma, Garg, & Barua, 2019)	Unawareness about PMS in supply chain	Performance measurement and metrics have an important role to play in setting objectives, evaluating performance, and determining future courses of actions.
(Enyinda C. , Modeling enterprise risk management in operations and supply chain: A pharmaceutical firm context, 2017) (Friemann & Schönsleben, 2016) (Gómez & España, 2020) (Abbasian, et al., 2020)	Global supply chain risk	For the many pharmaceutical firms, managing global supply chain risk has become prominent in their business operation agenda.

Reference	Risk	Sentence
(Kumar, et al., 2019)	Inconsistency in competitive and supply chain strategies	Risks related to mismatch between competitive and supply chain priorities in adopting GSC concepts in the pharmaceutical industry.
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Availability of suppliers	
(Moktadir M. A., et al., 2018)	Key supplier failure	Failure of any key supplier will disturb the functioning of a PSC in an organizational context.
(Blos, Hoeflich, & Miyagi, 2015) (Abbasian, et al., 2020) (Wang & Jie, 2020)	External supply chain risk	
(Elleuch, Hachicha, & Chabchoub, 2014) (Hatem & Habib, 2011) (Paul, Kabir, Ali, & Zhang, 2020)	Supply networks risk	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Partnership with supplier	
(Elleuch, Hachicha, & Chabchoub, 2014)	Process-based supply chain risk	
(Kumar, et al., 2019) (Ouabouch & Amri, 2013)	Supplier quality issues	Raw materials and services supplied will affect the quality of the green products
(Yaroson, Breen, & Matthias, 2017) (Mehralian, Gatari, Morakabati, & Vatanpour, Developing a suitable model for supplier selection based on supply chain risks: an empirical study from Iranian pharmaceutical companies, 2012)	Supplier selection	Supplier selection refers to the process of selecting a supplier based on price negotiation and the ability to share in supply and demand risk.
(Narenjian, Riahi, & Kheirabadi, 2019)	Supplier technology development capability	
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Supplier trading capability risk	Supplier trading capability risk in which capacity and capability of suppliers to produce quality medicines is always a concern, under fulfilment of sudden demands pertaining to financial loses under uncertainty.
(Yaroson, Breen, & Matthias, 2017)	Supply chain characteristics	Supply chain characteristic which depicts buyer supplier relationship includes supplier dependence and consumer dependence.

Reference	Risk	Sentence
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Supply chain design under uncertainty	
(Rodgers & Singham, 2020) (Aigbogun, Ghazali, & Razali, 2014) (El Mokrini, Dafaoui, Berrado, & El Mhamedi, An approach to risk assessment for outsourcing logistics: case of pharmaceutical industry, 2016) (Yaroson, Breen, Hou, & Sowter, 2021) (Lücker & Seifert, 2017) (Azghandi, Griffin, & Jalali, 2018) (Li, et al., 2016) (Sreedharan, Kamala, & Arunprasad, 2019) (Van Niekerk, Niemann, Kotzé, & Mocke, 2017) (Breen, 2008)	Supply chain risk	Global supply chain risk that is not assessed and managed proactively can lead to many other risks.
(Zamora Aguas, Adarme, & Serna, 2013)	Supply delays	

Table-A III-5 Risks and uncertainties in the financial category

Reference	Risk	Sentence
(El Mokrini, El Mhamedi, & Berrado, 2015) (Mokrini & Aouam, 2020) (Oreskovich & Gittins, 2016) (Rajagopal, Shanmugam, & Nandre, 2021)	Financial risk	Supply chain disruptions which are events that disrupt the normal flow of goods and services within a supply chain have been reported to have adverse effects on the financial and operational performance of the firm.
(Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Asset uncertainty	Two processes are related to uncertainties about the value of the project upon completion of the R&D phase (asset uncertainty) and to the uncertainty about the required investment cost (cost uncertainty).
(Yaroson, Breen, Hou, & Sowter, 2021)	Price manipulation	
(Kumar, et al., 2019)	Financial budget constraint	This risk is related to constraints in financial budgets as research and trials of pharmaceutical products are highly expensive.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Tax payable change Financial Tariff policies changes Cash flow	
(Amemba, 2013)	Financial markets uncertainty	Risks can come from uncertainty in financial markets.

Reference	Risk	Sentence
(Yaroson, Sharief, Shah, & Breen, 2018)	Monopoly risk	Under pressure to compete in both domestic and international markets, companies need to create conditions that enable them to remain competitive and to progress and develop.
(Moktadir M. A., et al., 2018)	Financial restriction	Poor financial plans and/or financial restrictions can hamper the smooth functioning of PSC.
(Niu, 2017)	Interest rate fluctuation Change of currency rate	Aside from foreign exchange risk, Pfizer observes interest rate risk because the company strives to maintain a predominantly floating-rate basis position.
(Narenjian, Riahi, & Kheirabadi, 2019)	Change of payable taxes Changing custom policies and tariffs	
(Yaroson, Breen, Hou, & Sowter, 2021)	Economic uncertainty	
(Moktadir M. A., et al., 2018)	Dynamic foreign exchange rates	Fluctuation in the foreign exchange rates can affect in profit margin of the pharmaceutical products.
(Abbasian, et al., 2020)	Dual exchange rates	
(Grujić, Morača, & Fajsi, 2020)	External fraud Economic conditions	pranks, misuse, theft by employees, third parties, etc.
(Kumar, et al., 2019)	Insurance risk	Risk related to high insurance/risk coverage premiums.

Table-A III-6 Risks and uncertainties in the drug category

Reference	Risk	Sentence
(Abbasian, et al., 2020)	Drug list limitation	
(Li, et al., 2016)	Risk in pharmaceutical excipients	Supply chain risk in pharmaceutical excipients has always been the most prominent problem to threaten the safety of excipients.
(Raka & Liangrokapart, 2017)	Drug Development risk	Risks that are associated with the new generic drug development process, which is the initial stage of the pharmaceutical supply chain, need to be considered and eliminated.
(Hartford, et al., 2006)	Drug safety risk	
(Nicholson, Peterson, & Yektashenas, 2012)	Drug risk	
(Dieck, Betger, Kracov, Manion, & Tanner, 2009)	Medicine safety	Both the pharmaceutical industry and FDA recognize that medicine safety evaluations are far from complete when a medicine is approved.
(Ågerstrand, et al., 2015)	Chemical risk	

Reference	Risk	Sentence
(Zu'bi & Abdallah, 2016) (Moosivand, et al., 2021)	Drug shortage	Pharmaceutical supply chain is susceptible to many risks leading not only to wasting valuable resources but also to disrupting the availability of medications resulting in the growing problem of drug shortages.
(Van Bortel, et al., 2018)	Clinical drug development risk	The importance of adaptive trial designs in early clinical drug development.
(Fleischhacker & Zhao, 2011)	Uncertainty in actual drug requirements	

Table-A III-7 Risks and uncertainties in the customer category

Reference	Risk	Sentence
(Blake Scott, 2006)	Public distrust risk	The drug industry found itself responding to renewed and heightened risk of public distrust, loss of patent protection, and price controls.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Customer services disruption	
(Grujić, Morača, & Fajsi, 2020)	Change in user habits Uneducated populations	The requirements of patients are determined by assessments of their prognosis, which are continually changing.
(Grujić, Morača, & Fajsi, 2020)	Mistrust of users	This risk factor considers the knowledge, capabilities, and roles of the people from pharmaceutical companies to contact customers and develop trust.
(Narenjian, Riahi, & Kheirabadi, 2019)	Changing consumer tastes	
(Botelho & Reis, 2015)	Risk of adverse events	With this information, patients using these drugs can be included in individual actions of monitoring the pharmacotherapy in such a way as to reduce the risk of adverse events.
(Vishwakarma, Garg, & Barua, 2019)	Changing patient target group	Continually growing and rapidly aging population, rapidly changing healthcare requirement would be task for pharmaceutical to respond.
(Claycamp, 2007) (Botelho & Reis, 2015)	Health risk	
(Grujić, Morača, & Fajsi, 2020)	Poor awareness of users	Pharmaceutical companies are legally required to disclose full information to their users regarding their products' potential outcomes with the intention that such disclosures will lead to normatively better decisions when buying drugs.

Table-A III-8 Risks and uncertainties in the technology category

Reference	Risk	Sentence
(Kumar, et al., 2019)	Cold chain technology risk	
(Narenjian, Riahi, & Kheirabadi, 2019)	Communication and information technology systems	
(Kumar, et al., 2019)	Green technology related issues	
(Grujić, Morača, & Fajsi, 2020)	Information technology	Focuses on the hardware and technology associated with the software used and their cohabitation.
(El Mokrini, El Mhamedi, & Berrado, 2015) (Mokrini & Aouam, 2020)	Technological risks	
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Technology/adoption transfer risk	Timid technology/adoption transfer risk arises because small and medium enterprises were quite reluctant to new technologies to join world class manufacturing.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Technology development	
(Rajagopal, Shanmugam, & Nandre, 2021)	IT system breakdown risk	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Technology level	
(Ouabouch & Amri, 2013)	Outage of IT System	
(Kumar, et al., 2019)	Inefficient IT applications	Any inadequacy in IT applications in adopting GSC concepts in the pharmaceutical industry.
(Vishwakarma, Garg, & Barua, 2019)	Dispersed IT infrastructure	The data-driven system needs complete IT infrastructure, to enhance visibility, reduce counterfeit, leads to secure and quality medicine.
(Grujić, Morača, & Fajsi, 2020)	Technological change risk	Technological change risk comprises improvements in technology that render current technology and development efforts obsolete

Table-A III-9 Risks and uncertainties in the inventory category

Reference	Risk	Sentence
(Kumar, et al., 2019)	Capacity and inventory related disruptions	Risks associated with capacity and inventory related problems in recovering pharmaceutical products.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Visibility on stock Inventory management	
(Grujić, Morača, & Fajsi, 2020)	Inventory	Firms may derive more benefit from establishing inventory policy parameters, increasing coordination, and reducing supplier lead times.
(Ouabouch & Amri, 2013)	Inventory shortage	

Reference	Risk	Sentence
(Moktadir M. A., et al., 2018)	Storage contamination risks	Industries are facing issues related to storage contamination during storage of raw materials and finished goods, as pharmaceutical products need to be maintained at prescribed conditions.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Mismatched inventory levels	Disruptions, e.g., due to quality, environmental, health or safety issues leading to untimely delivery of products or mismatched inventory levels.

Table-A III-10 Risks and uncertainties in the information category

Reference	Risk	Sentence
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Break in information flow Difficulty in transmitting data	Any firm in the pharmaceutical industry requires efficient and effective MIS to support managerial functions.
(Vishwakarma, Garg, & Barua, 2019)	Inefficient information system	The gap between the focal firm's perceived supplier's CSR performance and the supplier's actual CSR performance.
(Rajagopal, Shanmugam, & Nandre, 2021)	Information asymmetry risk	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Information flow	
(Elamrani, Benabbou, & Berrado, 2016) (Mehralian, Gatari, Morakabati, & Vatanpour, Developing a suitable model for supplier selection based on supply chain risks: an empirical study from Iranian pharmaceutical companies, 2012)	Information systems	
(Mokrini & Aouam, 2020) (Raka & Liangrokapart, 2017)	Information-related risks	Information is the foremost requirement for doing any activity. Lack of information sharing can affect the regular activity of PSC process, in terms of supplying of medicines, pricing, etc.
(Yaroson, Breen, & Matthias, 2017)	Lack of information sharing	Information has been deployed in various areas of the healthcare sector.
(Grujić, Morača, & Fajsi, 2020)	Loss of access to information	

Reference	Risk	Sentence
(El Mokrini, El Mhamedi, & Berrado, 2015)	Strategic information leakage risk	Course of information influences relations between managers and team.
(Grujić, Morača, & Fajsi, 2020)	Unauthorized access to information	Information has been deployed in various areas of the healthcare sector, including structure.
(Grujić, Morača, & Fajsi, 2020)	Undeveloped information structure	Minimizing total cost and unmet demand were aimed for a pharmaceutical case study with a high degree of epistemic uncertainty.
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Epistemic uncertainty	

Table-A III-11 Risks and uncertainties in the demand and cost categories

Reference	Risk	Sentence
(Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)	Bullwhip effects	The bullwhip effect makes hard for pharmaceutical companies to anticipate exact demand, which may reduce the business performance.
(Lücker, Seifert, & Biçer, 2019)	Demand risks	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016) (Moktadir M. A., et al., 2018)	Demand forecasting errors	Inaccurate demand forecasts will result in poor supply chain planning and may even create in gap demand and supply of products in a PSC context.
(Elleuch, Hachicha, & Chabchoub, 2014)	Fluctuation in demand	
(Ouabouch & Amri, 2013)	Unexp. demand fluctuations	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Cost risk	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Costs of distant production	Costs of distant production: The Sourcing Director agreed that cost is a key driver in terms of where to outsource for long-term competitiveness. Even though cost-attractive suppliers are considered, the cheapest price is not always the best due to hidden costs associated with distant production.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Costs related to supply Production cost	
(Paul, Kabir, Ali, & Zhang, 2020)	Increase of transportation costs	
(Kumar, et al., 2019)	Procurement costs risk	Risks related to disturbances in procurement of green or eco-friendly raw materials.
(Rajagopal, Shanmugam, & Nandre, 2021)	Reputation risk cost	SC managers should not underestimate the indirect reputation risk costs imposed by the quality and unethical governance risk.

Table-A III-12 Risks and uncertainties in the transportation category

Reference	Risk	Sentence
(Grujić, Morača, & Fajsi, 2020)	Drug delivery	Firms may derive more benefit from establishing inventory policy parameters, increasing coordination, and reducing supplier lead times.
(Abbasian, et al., 2020) (Elleuch, Hachicha, & Chabchoub, 2014)	Transportation risks	
(Gómez & España, 2020)	Transport and storage	
(Ouabouch & Amri, 2013)	Transportation failure Delivery chain disruptions	
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Finished goods transport	Distribute finished goods using dedicated transportation in place of common carriers.
(Paul, Kabir, Ali, & Zhang, 2020)	Freight damage in transportation Port stoppage and congestion	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Internal transport Untimely delivery of products	
(Mehralian, Gatari, Morakabati, & Vatanpour, Developing a suitable model for supplier selection based on supply chain risks: an empirical study from Iranian pharmaceutical companies, 2012)	Delivery risk	Delivery risk can make an important contribution to mitigate the risk of pharmaceutical industry.
(Gatica, Papageorgiou, & Shah, 2003)	Delivery time uncertainty	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Delivery reliability, Flexibility in delivering, Timely delivery	
(Paul, Kabir, Ali, & Zhang, 2020)	Infrastructure bottleneck in port	
(Narenjian, Riahi, & Kheirabadi, 2019)	Reliability of delivery	
(Grujić, Morača, & Fajsi, 2020)	Distribution channels	The uncertainty of drug and medical service distribution channels is conditioned by the dynamic and complex market and pharmaceutical environment.
(Raka & Liangrokapart, 2017)	Distribution problem	
(Gómez & España, 2020)	Bad road conditions, Improper fleet	

Reference	Risk	Sentence
(Moktadir M. A., et al., 2018)	Increase in freight charges	From a pharmaceutical organizational context, increase in freight charges will have a significant impact on profit margins.

Table-A III-13 Risks and uncertainties in the market category

Reference	Risk	Sentence
(Ouabouch & Amri, 2013)	Decline in market prices	
(Amemba, 2013) (Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Market risk	
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Money market volatility	Due to international trades in bulk money market risk usually high.
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Government and market related risks	
(Abbasian, et al., 2020)	International marketing issues	
(Kumar, et al., 2019)	Market dynamics	Market supply and demand affects the GSC efficiency.
(Grujić, Morača, & Fajsi, 2020)	Market segmentation	Market segmentation and product diversification.
(Davis & Abraham, 2011)	Pre-market risk	There may have been little need for a harmonized standard regarding pre-market risk identification and assessment.
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Time to market	
(Vishwakarma, Garg, & Barua, 2019)	Disparity in trading partner's capability	The disparity in trading partners' capability is a major barrier to the integration of agile supply chain because partnership fails due to poor capability at partner's end.
(Abbasian, et al., 2020)	Low international trading experience	
(Yaroson, Breen, Hou, & Sowter, 2021)	Parallel trade	In responding to parallel trade in the environment, some wholesalers and pharmacists decide to sell abroad for profit, especially when the exchange rate is favorable.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Problems communicating with your trading partners	
(Raka & Liangrokapart, 2017)	Trade barrier	

Reference	Risk	Sentence
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Trading capability risk	The capacity and capability of suppliers to produce quality medicines is always a concern under fulfilment of sudden demands pertaining to financial loses under uncertainty.
(Vishwakarma, Garg, & Barua, 2019)	Weakened global trade	Due to global market trading complexity small and medium enterprise has a strategic disadvantage towards growth.

Table-A III-14 Risks and uncertainties in the quality category

Reference	Risk	Sentence
(Vartak & Bhagure, 2012)	Co-coordinating quality risk	The decision makers should take the responsibility of co-coordinating quality risk management across various functions and department of organization.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Internal quality risk Quality defects, Quality of skills, education level and talent of the labor force	
(Gray, Roth, & Leiblein, 2011)	Manufacturing-related quality risk location-related quality risk	We know of no better assessment of manufacturing-related quality risk that is available for many plants with non-identical product lines.
(Narenjian, Riahi, & Kheirabadi, 2019)	Quality of distribution network	
(Charoo & Ali, 2013) (Ismael & Ahmed, 2020)	Quality risk	Lack of quality products can threaten human life in case of pharmaceutical products. It is important to produce the pharmaceutical products with highest quality as their tendencies to directly affect the health of the patient.
(Balmoș, Lazăr, & Burcea Dragomiroiu, 2014)	Cross contamination risk	The cleaning process of the manufacturing equipment validated is considered efficient for the removal of residues, of the degradation compounds and of the cleaning agents in order not to exist any risk related to the cross contamination of active substances
(Gray, Roth, & Leiblein, 2011)	Single-inspection quality risk	

Table-A III-15 Risks and uncertainties in the political category

Reference	Risk	Sentence
(Narenjian, Riahi, & Kheirabadi, 2019)	War Political changes of the country Sanction	
(Gray, Roth, & Leiblein, 2011)	Expropriation risk	The expropriation risk of our "offshore" location is essentially equivalent to the domestic location.
(Amemba, 2013)	Political Risks	Political risks affect supply chain performance.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Level of political instability Societal disruptions/strikes	
(Paul, Kabir, Ali, & Zhang, 2020)	Corruption in customs, Political unrest, Terrorism	
(Raka & Liangrokapart, 2017)	Government policy problem	
(Kumar, et al., 2019)	Management of policy failures	Failure in management policies may disrupt the adoption of GSC concepts in pharmaceutical industry effectively.
(Kumar, et al., 2019)	Failure of government policies	Failure in government policies in terms of its design and implementation would have a negative impact on GSC adoption in the pharmaceutical industry.
(Blake Scott, 2006)	Socio-political context of risk	Socio-political context of risk construction in the pharmaceutical response to the war on bioterrorism.

Table-A III-16 Risks and uncertainties in the environmental category

Reference	Risk	Sentence
(Narayana, Elias, & Pati, 2014) (Wang & Jie, 2020)	Environmental risks	
(Ågerstrand, et al., 2015)	Aquatic environmental risk	
(Khan, Ju, Baloch, & Uddin, 2019)	Macro-environmental risk	The results confirm the adverse effects of macro-environmental risks on organizational self-development.
(Davis & Abraham, 2011)	Ecological uncertainty	The 'ecological uncertainty' of approving these drugs involved accepting risks that were possibly 'avoidable in exchange for expected benefits.
(Paul, Kabir, Ali, & Zhang, 2020)	Earthquake, Extreme weather problem, Flood, Hurricane/cyclone	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate	Disparity in national cultures	

Reference	Risk	Sentence
disturbance factors?, 2016)		
(Yaroson, Sharief, Shah, & Breen, 2018)	Natural disasters	Natural disasters and uncontrollable events

Table-A III-17 Risks and uncertainties in the human category

Reference	Risk	Sentence
(Enyinda & Tolliver, Taking counterfeits out of the pharmaceutical supply chain in Nigeria: Leveraging multilayer mitigation approach, 2009)	Human lives at risk	The counterfeit pharmaceutical trade supply chain is an activity that puts human lives at risk and undermines the credibility of public health systems.
(Raka & Liangrokapart, 2017)	Human resource problem	
(Elleuch, Hachicha, & Chabchoub, 2014)	Human risk Lack of personnel	Although most of the production processes are automated, steps are present which can lead to disruptions due to the human risk.
(Grujić, Morača, & Fajsi, 2020)	Inadequate coordination of professional staff Incompetent staff Injuries of employees	It considers the knowledge, capabilities, and roles of people, as well as the team structure and organizational units associated with the daily schedule.
(Vishwakarma, Garg, & Barua, 2019)	Improper training of employees	Employee training is essential to an organization's success. Despite the importance of training, a trainer can encounter resistance from both employees and managers.
(Rajagopal, Shanmugam, & Nandre, 2021)	Unethical behavior	Risk of unethical behavior originating at the focal firm and the upstream spillover risks such as risk of non-implementation of CSR by suppliers
(Kumar, et al., 2019)	Scarcity of skilled labor	Lack of awareness and understanding of the concepts of GSC and its operations from labor viewpoints.
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	Personal health and safety	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Skill of workers	
(Paul, Kabir, Ali, & Zhang, 2020)	Inadequate labor/labor strike	
(Grujić, Morača, & Fajsi, 2020)	Unsafe workplace	Management of security risks refers to the development of the work plan in pharmaceutical companies. Negative effects of risk factors are health risk for people employed in company, inability to do standard work in company.

Reference	Risk	Sentence
(Grujić, Morača, & Fajsi, 2020)	Personal conflicts	Pharmaceutical products have long development life cycles, and this presents a challenge for supply-chain managers, who must manage their internal relationships with doctors.

Table-A III-18 Risks and uncertainties in the operational category

Reference	Risk	Sentence
(Wang & Jie, 2020)	Internal operations uncertainty	The internal operations uncertainty and risk may refer to unexpected event, outcome and/or accident during the internal processes, they mainly occurred within the pharmaceutical firms.
(Blos, Hoeflich, & Miyagi, 2015) (Azghandi, Griffin, & Jalali, 2018) (Hosseini-Motlagh, Jazinaninejad, & Nami, 2020)	Operational risks	
(Friemann & Schönsleben, 2016)	Production planning under uncertainty	
(Sreedharan, Kamala, & Arunprasad, 2019)	Production risk	
(Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Timely production risk	The weak coordination among SC partners enhances risk of timely production of goods leads to delays and disruption with reduction in reliability and trust.
(Cundell, Guilfoyle, Kreil, & Sawant, 2020)	GMP manufacturing	
(Yaroson, Breen, & Matthias, 2017)	Manufacturing processes	The manufacturing process of a pharmaceutical which is tagged as cumbersome is another highlighted factor that exposes the supply chain to drug shortages. These manufacturing processes may range from the failure of the product to reach the desired quality as stipulated by the regulating bodies, or the lack of raw materials which most times is sourced outside the manufacturing regions.
(Yaroson, Sharief, Shah, & Breen, 2018) (Xu, Boehm, & Zheng, 2016)	Manufacturing risks	The FDA is the primary regulator and companies must follow FDA regulatory protocols, and the ensuing complex manufacturing activities for new drug development are highly consuming of time and money.
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance	Unforeseen and random interruptions in manufacturing processes	

Reference	Risk	Sentence
factors?, 2016)		
(Moktadir M. , et al., 2018)	Power failure	Power failures will disturb the production activity and hence lower the overall efficiency of PSC
(Grujić, Morača, & Fajsi, 2020)	A narrow product line	Product lines and narrow product lines have high risk values
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Certificate of GMP, Waste management	
(Varma, Pekny, Blau, & Reklaitis, 2008)	Sub-optimal resource management risk, Resource allocation policies under uncertainty	
(Kumar, et al., 2019)	Irresponsible use of land and facilities Inadequacy in waste management system	This represents a case of irresponsible use of materials, land, and facilities in adopting GSC concepts in the pharmaceutical industry. Risk related to inefficiency in handling the waste in the pharmaceutical industry.

Table-A III-19 Risks and uncertainties in the international category

Reference	Risk	Sentence
(Abbasian, et al., 2020)	Defect of international vision, international certification issues	
(Moktadir M. A., et al., 2018)	Fluctuation in imports arrival	The imported raw materials of the medical products are subjected to various fluctuations, which includes delay in the arrival of the shipping, delay in customs/movement of freights.
(Paul, Kabir, Ali, & Zhang, 2020)	Import-export restriction/quota	
(Blake Scott, 2006)	Uncontrollable global risk	
(Iyengar, Hedman, Forte, & Hill, 2016)	Global shortages risk	Medicines most at risk of global shortages, especially those without clinically acceptable substitutes, must be identified and prioritized for global action.

Table-A III-20 Risks and uncertainties in the network and technical categories

Reference	Risk	Sentence
(Urushihara, et al., 2014)	Public risk communication	Involvement with responsibility in public risk communication; and the need for official guidelines and a regulatory department specialized in direct communications with healthcare professionals, considering the seriousness of the risk.
(Sazvar, Zokaee, Tavakkoli-	Network risk	

Reference	Risk	Sentence
Moghaddam, Salari, & Nayeri, 2021)		
(Grujić, Morača, & Fajsi, 2020)	Social networks	With technological advancements, global Internet and social networks reach almost every country.
(Yaroson, Breen, Hou, & Sowter, 2021)	Misalignment of goals	The relationship between vulnerabilities and antecedents of SC resilience may sometimes lead to outcomes such as flexibility and/or power asymmetry because of misalignment of goals.
(Vishwakarma, Garg, & Barua, 2019)	The reluctance of support of dealers, distributors	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Third parties' risk	
(Enyinda C. , Modeling enterprise risk management in operations and supply chain: A pharmaceutical firm context, 2017)	Relationship risk	
(Abbasian, et al., 2020)	Technical risk	
(Gómez & España, 2020)	Vehicle's breakdowns	
(Paul, Kabir, Ali, & Zhang, 2020)	Machine, equipment, or facility failure	Failure of any machines/equipment/ facility leads to disruptions in the manufacturing process of pharmaceutical products
(Grujić, Morača, & Fajsi, 2020)	Unsafe equipment	Health system pharmacists often struggle with issues related to patient safety with bad instruments and other work products
(Sreedharan, Kamala, & Arunprasad, 2019)	Infrastructure failures	This represents failure in infrastructure such as facility, machines, or high-tech equipment in adopting GSC concepts in the pharmaceutical industry.
(Grujić, Morača, & Fajsi, 2020)	Technical equipment	Technology risk considers the overall availability of the technology with its practical use.

Table-A III-21 Risks and uncertainties in the organization category

Reference	Risk	Sentence
(Mehralian, Gatari, Morakabati, & Vatanpour, Developing a suitable model for supplier selection based on supply chain risks: an empirical study from Iranian pharmaceutical companies,	Reputation risk	Lack of appropriate risk reduction can destroy public health confidence and reputation.

Reference	Risk	Sentence
2012)		
(Grujić, Morača, & Fajsi, 2020)	Lack of company reputation	It is necessary to talk about marketing risks
(Rajagopal, Shanmugam, & Nandre, 2021)	Proactive reputation risk	
(Abbasian, et al., 2020)	Business development issues	
(Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013)	Planning issues Organization & process Mergers and acquisition	
(Rodgers & Singham, 2020)	Hospital-acquired adverse events risk	Factors which contribute to the risk of hospital-acquired adverse events and support hospital decisions on staffing, length of stay, and investments in safety.
(Elamrani, Benabbou, & Berrado, 2016)	Organizational risk	
(Amemba, 2013)	Organizational Structure and Cultural Risks	
(Rajagopal, Shanmugam, & Nandre, 2021)	Unethical governance risk	Quality and unethical governance risks significantly impacted reputation in Pharmaceutical SC and a firm should prefer “risk avoidance” against these risks.
(Amemba, 2013) (Vishwakarma, Prakash, & Barua, A fuzzy-based multi criteria decision making approach for supply chain risk assessment in Indian pharmaceutical industry, 2016)	Strategic risk	
(Grujić, Morača, & Fajsi, 2020)	Inadequate decisions management	
(Yaroson, Breen, & Matthias, 2017)	Managerial practices	The managerial practices of the firm also weaken the system which in turn makes it impossible for the system to resist drug shortages when they occur making it vulnerable to various risks.
(Chen, Yang, & Wang, 2019)	R&D	The pharmaceutical industry is characterized by a high cost of R&D and innovation.
(Abbasian, et al., 2020)	Single actor in the biopharmaceutical industry	

Table-A III-22 Other risks and uncertainties

Reference	Risk	Sentence
(Cassimon, De Backer, Engelen, Van Wouwe, & Yordanov, 2011)	Commercial risk	Commercial risk refers to the normal business risk any company incurs, such as the potential market size, its expected revenues, its expected cost structure, etc.
(Moktadir M. A., et al., 2018)	Competitive risks	There is a tremendous competition in the local and international market of pharmaceutical products. Thus, pharmaceutical industries are under huge risks due to competitor approach and strategy in introducing new products with improved performance levels.
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Adulteration	At every stage in the pharmaceutical supply chain, medical products are exposed to risks of "contamination, diversion, counterfeit and adulteration".
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Security risk	Organizations should have a backup that could be used should major security risks occur within the outside parties' operations.
(Yaroson, Breen, Hou, & Sowter, 2021)	Behavioral uncertainty	Information control within the PSC was to protect the reputation of SC actors and mitigate behavioral uncertainty such as panic buying.
(Gómez & España, 2020)	Disruption in the cold chain	
(Raka & Liangrokapart, 2017)	FDA problem	
(Abbasian, et al., 2020)	MOH (Ministry of health) conflict of interest	
(El Mokrini, Dafaoui, Berrado, & El Mhamedi, An approach to risk assessment for outsourcing logistics: case of pharmaceutical industry, 2016)	Risk in natural gas pipelines, social responsibility risk	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Risk of infringement of IPR	
(Paul, Kabir, Ali, & Zhang, 2020)	Traffic accidents	
(Elleuch, Hachicha, & Chabchoub, 2014)	Compliance risk	Compliance problem related to the supplier subsystem
(Van Niekerk, Niemann, Kotzé, & Mocke, 2017)	Counterfeit risks	

3.4. 2. Risk Mitigation Strategies

To address the third and fourth questions of the research, Tab.23 to Tab.37 is presented including four columns of 'Reference', 'Risk Mitigation Strategy', 'Risk', and 'Description'. 'Risk Mitigation Strategy' is the strategy investigated and probed to mitigate and minimize the effects of risks in the literature or to avoid the identified risk. In total 73 strategies are presented which will be discussed more in the next section.

Table-A III-23 Prescription pharmaceutical regulation risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Davis & Abraham, 2011)	Prescription pharmaceutical regulation	Risk-managing toxic drugs	Risk-managing toxic drugs throughout the time of post-marketing.
		Communication of risks	A main part of managing pharmaceutical risk is communicating risks on the product label with doctors and patients
		Labeling of identified risks	Performing the function of legitimating permissive regulatory by Labeling of recognized risks.

Table-A III-24 Organization-related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Varma, Pekny, Blau, & Reklaitis, 2008)	Scheduling and resource allocation in pharmaceutical R&D pipelines	Resource management	Proposing SIM-OPT framework as a unified resource management tool with the aims of increasing the portfolio's expected net present value, controlling risk, and reducing drug development cycle times.
(Elamrani, Benabbou, & Berrado, 2016)	Organizational risks	Outsourcing related organizational risks	Identifying and classifying outsourcing-related organizational risks in terms of information systems, value buying, and logistics by a framework that is inspired by Enterprise Risk Management (ERM).
(Gatica, Papageorgiou, & Shah, 2003)	Capacity planning	Mathematical programming approach	Improving capacity planning in clinical trials uncertainty by a mathematical programming approach.
(Chen, Yang, & Wang, 2019)	Policy failure	A revenue-sharing contract or a quantity discount contract	Policy failure risk leads in a drug supply shortage if pharmaceutical companies cannot handle the financial loss caused by the price cap regulation. To minimize the risk of policy failure, policy makers can consider subsidies to the regulated company to reimburse for the loss brought by price cap regulations. For the pharmaceutical companies that benefit from regulations, one should regard supply chain coordination mechanisms, like a revenue-sharing contract or a quantity discount contract to dispense the increased profits with their supply chain partners, because the supply stoppage of associated pharmaceutical goods will have a negative effect on their performance.

Table-A III-25 Risk mitigation strategies for drug shortages

Reference	Risk	Risk Mitigation Strategy	Description
(Moosivand, et al., 2021)	Drug shortage	1. Forming integrated Supply chain information system to manage drug inventory 2. Forming and using the databases to predict the shortage of drugs using track and trace system	
(Yaroson, Sharief, Shah, & Breen, 2018)	Shortages	Reducing bureaucracy, preventing monopolization of pharmaceutical markets, and training staff	Strategies in curbing the effects of disruptive activities: reducing bureaucracy, hindering monopolization of pharmaceutical markets, and training staff.
(Lozano-Diez, Marmolejo-Saucedo, & Rodriguez-Aguilar, 2020)	Drug shortages in epidemic outbreaks	Propose a new approach	Presenting an approach with a comprehensive view of the supply network helping fast and efficient responses to risky and changing situations.
(Iyengar, Hedman, Forte, & Hill, 2016)	Shortages of medicine	Advance notice systems, tracking medicines, Redistribution of supplies, evidence-based practice, developing reporting systems	Different approaches mitigating shortages consist of advance notice systems managed by medicine regulatory authorities, tracking medicines, and improving efficiency of the medicine supply chain, redistribution of supplies at the national level , international redistribution and exceptional regulatory approvals, prioritizing patients to get a medicine that is in shortage, evidence-based practice for optimal allocation, developing reporting systems to share information on current and emerging shortages, and improving data from medicine supply chains.
(Jia & Zhao, 2017)	Drug shortages	Drug purchase contracts	Mitigating shortages through drug purchase contracts, investigating the Pareto-improving contracts, improving the manufacturer's profit, cut government spending and providers' cost, and ensuring the GPO's profit.
(Azghandi, Griffin, & Jalali, 2018)	Drug shortage Disruptions	Mathematical simulation model	Proposing a mathematical simulation model to understand the behavior of the drug shortages under different disruption patterns in the pharmaceutical supply chain.
(Hatem & Habib, 2011)	Shortage of drugs (without substitute)	Forecasting, ERP, EDI, communication, and information sharing with suppliers	
(Emmett, 2019)	Drug shortages	Better use of supply chain management, including multiple suppliers and safety stock	Better collaboration among suppliers, consumers, and government entities. Healthcare facilities should develop teams in charge for monitoring critical areas and developing contingency plans.

Table-A III-26 Clinical and safety related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Rodgers & Singham, 2020)	Clinical trial study failures	Bayesian belief networks	A framework helps practitioners assessing the probability of disruptions to their network by Bayesian belief networks that can help them in a clinical supply chain to make a better understanding of vulnerabilities and network behavior in the case of lack of data.
(Van Bortel, et al., 2018)	Clinical Trials	Managing Risks in Early Phase Clinical Trials	Considering knowledge, expertise and an expert team, training, and clinical pharmacology unit accreditation schemes, submitting scientific advice pre-Clinical-Trial-Authorization (CTA)
(Hartford, et al., 2006)	Safety risk	Multidisciplinary Safety Management Teams (SMT)	Safety risk management in the early stages of drug development: Safety communication pre-approval such as Early Communication with the Research and Development Team, Early Risk-Management Plans, Reporting to Regulators and Investigators, Development Safety Update Report, Communication to Patients.
(Botelho & Reis, 2015)	Safety of new drugs	Up-to-date safety strategies	Networks of population databases for surveillance, use of data mining, integrating various sources of information to promote prediction and identification of adverse events, and preparation of Risk Minimization Action Plans (RiskMAPs)
(Fleischhacker & Zhao, 2011)	Clinical trial failure	Wagner–Whitin model (W–W model)	Generalizing the Wagner–Whitin model (W–W model) to incorporate the risk of failure by balancing the tradeoff of waste and destruction versus production inefficiency.
(Charoo & Ali, 2013)	New product development	Reviewing the tools and techniques for assessing and managing the risks of new product development	
(Edwards & Chakraborty, Risk communication and the pharmaceutical industry, 2012)	Safety and efficacy issues (drug safety)	Communicating risks	Effective communication needs understanding how different audiences perceive the message and what the fundamental drivers are for alerting patients and prescriber behavior to be secured. Internal communications about significant issues should be limited to those who know how to handle the risk of insider dealing from internal communications that may later be made public.
(Nicholson, Peterson, & Yektashenas, 2012)	Drug safety	Risk Evaluation and Mitigation Strategies (REMS)	Risk Evaluation and Mitigation Strategies (REMS) build a safety plan with different components, such as a medication guide, a communication plan, elements to ensure safe use and an implementation system to help guide the prescribers, pharmacists, and patients.
(Ismael & Ahmed, 2020)	Drug safety	Quality Risk Management-(QRM) approach application	Quality Risk Management-(QRM) approach application on the drug provides the safety for drug and protects it from hazards during the production process.

Table-A III-27 Logistics and transportation related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Mokrini & Aouam, 2020)	Logistic risks	Developing a risk evaluation approach	Evaluating outsourcing logistics risks in the healthcare sector by developing an approach
(Paul, Kabir, Ali, & Zhang, 2020)	Transportation disruption	Resilient strategies	Proposing a model to managers for examining transportation disruptions and having resilient strategies to handle them by using Bayesian Belief Network (BBN)
(Johnson & Miller)	Pharmaceutical drug delivery	Mathematical modeling framework	A model helping managers to select the most qualified suppliers and discover the tradeoffs between costs and risks in the pharmaceutical supply chain.

Reference	Risk	Risk Mitigation Strategy	Description
(Gómez & España, 2020)	Transport and storage	Cause analysis	
(Narayana, Elias, & Pati, 2014)	Reverse logistics	Returns avoidance, improving the infrastructure, balanced risk sharing	Avoiding returns by alleviating market flooding of medicines, improving the infrastructure for quality and performance management and balancing risk sharing between the main stakeholders involved in the supply chain.
(El Mokrini, Dafaoui, Berrado, & El Mhamedi, An approach to risk assessment for outsourcing logistics: case of pharmaceutical industry, 2016)	The persistent evolution of development and manufacturing processes put the pharmaceutical industry in a challenge.	Outsourcing logistics	Presenting a theoretical model considering outsourcing logistics risks since firms are interested in focusing on the core competencies and outsourcing logistics.

Table-A III-28 Operational and technical related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Lücker & Seifert, 2017)	Operational risks	RMI, Dual Sourcing and Agility Capacity	RMI and Agility Capacity can be swapped when there is no Dual Source. Once the Dual Source is available, Agility Capacity and Dual Sourcing seem can be swapped.
(Hosseini-Motlagh, Jazinaninejad, & Nami, 2020)	Production disruption	Channel coordination	Proposing an Altered Revenue-Sharing (ARS) contract for production disruption and recall management issues.
(Sabouhi, Pishvaee, & Jabalameli, 2018)	Operational risks	Design a resilient supply chain	Design a resilient supply chain under operational risks and disruption to mitigate the supply chain-threatening risks.
(Hatem & Habib, 2011)	Technical problems / breakdown of the machinery	Periodic maintenance, statistical process control	
(Hatem & Habib, 2011)	Compliance problem (time limit, breakage, empty or missing boxes...)	Vigilance in the reception and at the time of delivery to the care units, inspection, traceability system	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Malfunctioning of Machinery	Checking and calibrating machines at regular intervals, Selection of correct machinery	Machines are required to be checked and calibrated regularly by preventive maintenance program and have spare parts at their disposal and qualified personnel to tackle risky situations. Selection of right machinery reduces this risk.
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Wrong Packaging	Inspection, packing slips and extensive quality control checks before shipping the product	
(Friemann & Schönsleben, 2016)	Warehouse capacity planning uncertainty	Providing a practical way to improve the strategic warehouse capacity planning process	Improving the strategic warehouse capacity planning process by breaking it down to a level that warehouse managers can handle, and reducing the effort needed to ensure applicability at the same time.
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Power Shutdown	Having full power backup systems to make sure production is not halted in such a situation	

Table-A III-29 Demand related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Sazvar, Zokaee, Tavakkoli-Moghaddam, Salari, & Nayeri, 2021)	Demand uncertainty	A scenario-based Multi-Objective Mixed-Integer Linear Programming model	Developing a scenario-based Multi-Objective Mixed-Integer Linear Programming model to design a supportable CLPSC (closed-loop PSCs), which inquires the reverse flows of expired drugs in 3 classes (must be disposed of, can be remanufactured, and can be recycled).
(Hatem & Habib, 2011)	Fluctuation in customer demands	Collaboration with the manager of the care units, forecasting	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Demand risks	Building cooperation between the company and its suppliers, developing replenishment plans designed to undertake adequate product availability	

Table-A III-30 Supply chain related risk mitigation strategies

Reference	**Risk**	**Risk Mitigation Strategy**	**Description**
(Clauson, Breeden, Davidson, & Mackey, 2018)	Supply chain risks and cost	Block chain technology	Benefits of block chain technology for improving management of the supply chain include: 1) decreasing or removing fraud and errors, 2) decreasing delays of paperwork, 3) promoting inventory management, 4) identifying issues fast, 5) reducing courier costs, and 6) augment consumer and partner trust.
(Wang & Jie, 2020)	Supply chain uncertainty and risk	Supply Chain Visibility, Supply Chain Agility, Supply Chain Flexibility	Capability of integrating supply chain is considered as efficient risk management tools for mitigating uncertainty and risk in the supply chain.
(Roscoe, Skipworth, Aktas, & Habib, 2020)	Supply chain risks	'Wait-and-see' strategy and worst-case assumptions	Firms with different sizes implement strategies to achieve fit with an external environment disrupted by a geopolitical event: When formulating strategy, Multi-National Enterprises (MNEs) applied worst case assumptions, while large firms and small and medium sized enterprises (SMEs) used a 'wait-and-see' strategy, enabling them to reduce perceptions of heightened supply chain uncertainty. Then firms implemented reactive and/or proactive strategies to mitigate supply chain risks.
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Import risks	Firms should book their supplies in advance with sufficient lead time based on their previous experiences to overcome delay.	
(Blos, Hoeflich, & Miyagi, 2015)	Customer Service, Inventory Management, Flexibility, Time to Market, Finance, Ordering Cycle Time, Quality, and Market	Supply chain continuity management framework	Presenting a promoted form of supply chain continuity management framework, with an efficient crisis management operational structure.

Table-A III-31 Regulatory related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Enyinda C. , Modeling enterprise risk management in operations and supply chain: A pharmaceutical firm context, 2017)	Regulatory/legislation risk, operational risk, reputation risk, financial risk, market risk, relationship risk	Mitigate/reduce risk, retain risk, avoid risk, share risk, transfer risk	
(Salter, Kramer, & Palmer-Shevlin, 2000)	Regulatory and/or legal jeopardy	1. Follow Established Policies and Procedures 2. Keep Compliance with Professional Standards/Guidelines 3. Seek Peer, Senior Staff, and Outside Departmental Expert Advice 4. Seek Input from Clients 5. Do Not Practice Medicine 6. Do Not Provide Formal Consultations 7. Document Everything 8. Copyright Infringement 9. Internal Document Review	Minimizing regulatory and/or legal jeopardy with respect to medical communications.

Table-A III-32 Quality related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Rajagopal, Shanmugam, & Nandre, 2021)	Quality and unethical governance risks	Proactive mitigation strategies and assertive crisis communication, diminishment/ bolstering/rebuilding reactive crisis communication	Prefer "risk avoidance" against quality and unethical governance risks. The upstream risks affect reputation in a pharmaceutical SC comparing to the downstream risks. Proactive mitigation strategies and assertive crisis communication are considered for upstream risks while diminishment/ bolstering/rebuilding reactive crisis communication is suggested for downstream risks.
(Hatem & Habib, 2011)	Quality problem in manufacturing	Statistical quality control, inspection, quality control	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Risk of Inferior Quality of supply	1. Establishing high standard quality protocols and enforcing of these standards 2. Regularly vendor auditing and checking. 3. Implementing statistical quality control and step towards six sigma implementations	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Quality Risks	Following strict quality protocols at each stage of the supply chain	

Table-A III-33 Environmental related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Ågerstrand, et al., 2015)	Environmental risk	1. Assessing of environmental risk even for products put on the market before 2006 2. Add obligations to assess the risk for developing antibiotic resistance 3. Run just one environmental risk assessment for each active pharmaceutical ingredient 4. Refine the tiered approach 5. Perform mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action 6. Using all available ecotoxicity studies 7. Consider environmental risks in the risk-benefit	Presenting 10 recommendations to improve the European Medicines Agency's guidance for assessing environmental risk of human pharmaceutical products

Reference	Risk	Risk Mitigation Strategy	Description
		analysis 8. Reviewing environmental risk assessments on a regular basis 9. Include data from active pharmaceutical ingredients and formulations production in the risk assessments 10. Augment transparency	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Natural Disasters	Understanding the vulnerability points and their effect on the supply chain and developing and testing contingency plans	
(Huq, Pawar, & Rogers, Supply chain configuration conundrum: how does the pharmaceutical industry mitigate disturbance factors?, 2016)	Endogenous, exogenous, and environment-related SC disturbance factors	SC configurations	SC disturbances affect the decision to bring production back home (reshoring) or to a closer location (nearshoring). To mitigate the effects of disturbances many BPs recalibrated their SC configurations by insourcing core products, outsourcing non-core products offshore and developing offshore insourcing capabilities through 'captives'.

Table-A III-34 Human related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Nicholson, Peterson, & Yektashenas, 2012)	Public health risk	REMS in mitigating risks	Risk Evaluation and Mitigation Strategy (REMS) including a communication plan, a medication guide, and elements to assure safe use.
(Hatem & Habib, 2011)	Lack of personnel	Motivation, relation with labor union, reward system, appropriate appointment, career management	
(Hatem & Habib, 2011)	Human error (in manufacturing)	Training, ameliorate the working ergonomic, reward system revision	
(Hatem & Habib, 2011)	Human error (in handling and in storing the drugs)	Personnel training, investment in handling materials	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Human Risks	Providing proper training to the employees, setting up unions to look after the employees and paying heed to all their requirements	

Table-A III-35 Material related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Non-Availability of raw material	Having secondary suppliers to provide the necessary raw material to meet demand when needed	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Non-Availability of packaging materials	Sharing a good rapport with the packaging material supplier, prompting settlement of bills, and having enough stock since it's a non-perishable commodity	

Table-A III-36 R&D and inventory related risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Kleczyk, 2011)	R&D risks	Advertising and personal promotion to healthcare providers, increased use of internet and digital media, Stochastic Dominance, Capacity Constrained NPV approach	Direct-to-Consumer advertising and personal promotion to healthcare providers also increased use of internet and digital media to inform healthcare providers and patient population of their treatment options, the expected sales and revenues can be increased. Risk management methods starting from a simple NPV of income analysis of potential product, and extending it to Stochastic Dominance, followed by the Capacity Constrained NPV approach, and the required resources for development and production.
(Hatem & Habib, 2011)	Theft in the stores and in the delivery sectors	Fitting out the drugstores, internal audit system	
(Lücker, Seifert, & Biçer, 2019)	Inventory	Inventory strategy, reserve capacity strategy, mixed strategy, and passive acceptance	Determining an optimal inventory level and reserving capacity production rates for a firm that is under supply chain disruption risk. Characterizing four risk mitigation strategies: inventory strategy, reserve capacity strategy, mixed strategy, and passive acceptance. Illustrating how the optimal risk mitigation strategy depends on product characteristics and supply chain characteristics.
(Narenjian, Riahi, & Kheirabadi , 2019)	Disruption, delay, prediction risks, supplier risks, risk of something which is received, capacity risk, inventory risk	Increasing capacity, increasing inventory, Alternative suppliers, increasing response speed, increasing flexibility, Tensile or integrated demand, increasing ability, having more clients	It is noted to know what factors are important to select a supplier in a supply chain to reduce the supply chain risk.

Table-A III-37 Other risk mitigation strategies

Reference	Risk	Risk Mitigation Strategy	Description
(Hatem & Habib, 2011)	Time limit of drugs in the medicine cabinet	Traceability system, internal audit	
(Hatem & Habib, 2011)	Transposition error of the prescription to the notebook of orders	ERP, involvement of doctors and nurses of the care units	
(Enyinda & Tolliver, 2009)	Risk of counterfeit	Public health policy makers need to secure pharmaceuticals movement in the supply chain by securing packaging, increasing vigilance and public knowledge, strengthening regulatory and enforcement oversight, building international collaboration and partnerships, increasing fees for counterfeiters, and obligating pharmaceutical firms to invest in embedded technology such as RFID tags	
(Mahendran, Narasimhan, Nagarajan,, & Gopinath, 2011)	Information Sharing Risks	ERP software	ERP software such as SAP and ORACLE can be efficient. They provide transactional tracking and global visibility of information from within a company
(Sharma & Luthr, 2021)	Medical device	Risk communication	Eliminating or reducing risks to AFAP by taking proper risk control measures against the hazards identified through communicating risk with stakeholders in different departments.

CHAPTER 4

DISCUSSION

4.1. Pharmaceutical Supply Chain Risks

It should be noted that 317 risks in general are extracted in 24 different groups of products, logistics, material, supply, financial, drug, customer, technological, inventory, regulatory/legislation, information, demand, cost, transportation, market, quality, political, environmental, human, organization, international, network, technical, operational, and other. Top three risks that are more discussed in the literature according to the columns of "Local frequency", "Global Frequency", and "Files count" include supply risks, operational risks, and operational risks respectively. Therefore, we can infer these risks are more important in the pharmaceutical supply chain as different researchers have investigated them.

Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively. According to the validation process explained in the methodology 85 percent of results extracted from the text mining procedure were like the results extracted manually from the sample that is a promising outcome. As a comparison with other studies, we can point out to some research with text-mining techniques methodologies such as (Abeysinghe, Zheng, Hinderer, Moseley, & Cui, 2018), (Abeysinghe, Hinderer, Moseley, & Cui, 2017), (Abeysinghe, Brooks, Talbert, & Licong, 2017), and (Kobayashi, Mol, Berkers, Kismihók, & Den Hartog, 2018) that they gained an accuracy and similarity of 58%, 56%, 88%, and 55% in their results comparison respectively.

Table-A III-38 Results of the automated search and manual search of extracted phrases

Searched Topics	Risk	Strategy
Manual Searches	32	9
Automated Searches	27	7
Validation	84.38%	78%

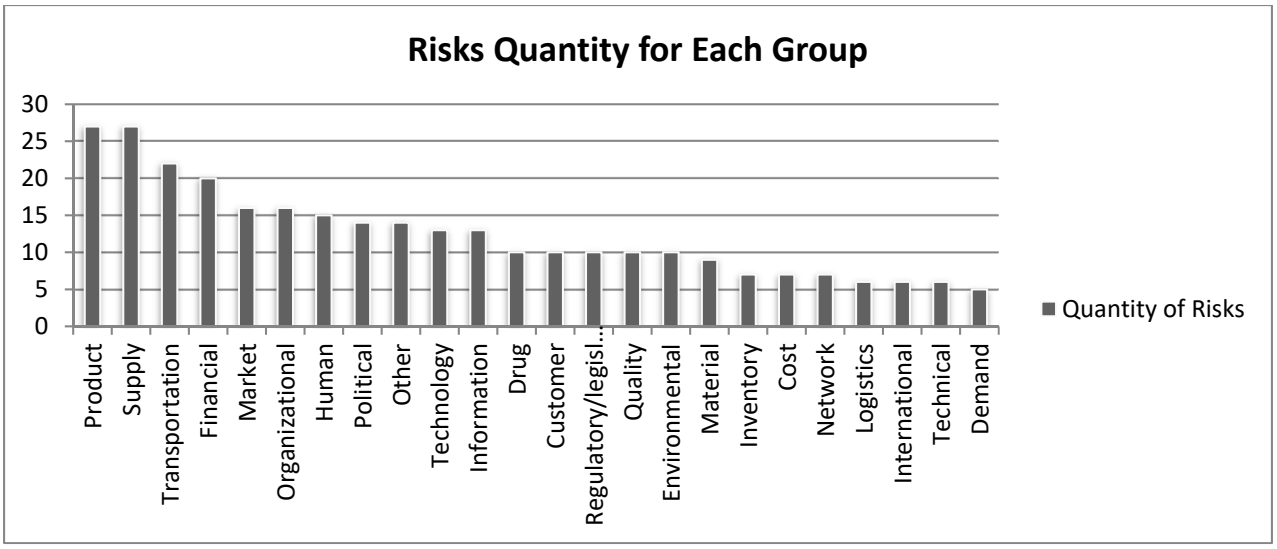

Figure-A III-3 Quantity of risks in different risks groups

4.2. Risk Mitigation Strategies in the Pharmaceutical Supply Chain

According to one of the research's questions, we aimed to realize which risks in the pharmaceutical supply chain are considered in the literature to be minimized or covered by risk mitigation strategies. More than 73 strategies are found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines.

The second risk that has received the most attention from researchers is supply-related risks. Quality and safety risks have also been considered in different studies by researchers. Although in terms of risk categories, researchers have almost worked on each group to discover a mitigation strategy, it does not mean that every single risk in the literature is covered. The three risk groups that have received less attention comparing others are cost, international, and political groups.

Furthermore, we can refer to the problem of NLP methods in our study as a limitation, in this way that none of the methods can take a sentence into account along with the previous or next sentences. In other words, we cannot remove the high need of supervising the results and extracted phrases by a human being. Therefore, the supervisor must investigate the extracted phrase's sentence in the paragraph to make sure that it is reliable. According to the

validation process explained in the methodology 78 percent of results extracted from the text mining procedure were like the results extracted manually from the sample.

CONCLUSION

Pharmaceutical Supply Chain (PSC) is facing different kinds of risk which can waste resources and threaten patients' life by limiting access to medicines (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013). Therefore, any risk that affects the PSC could also have an impact on the efficiency of health system and interrupt the supply of medicines (Moktadir M. , et al., 2018).

The pharmaceutical supply chain is a substantial part of the health system that entail whole procedures, resources, information, different players such as suppliers, producers, agencies, third party service providers, transportation and sales activities, financial issues and IT (Jaberidoost, Nikfar, Abdollahiasl, & Dinarvand, 2013) (Jaberidoost, et al., 2015).

This research aims to explore different pharmaceutical supply chain risks and risk mitigation strategies based on the Systematic Literature Review (SLR) methodology through text-mining techniques. Keyword phrases are searched in three search engines of Web of Science, PubMed, and Google Scholar that resulted in a total of 4205 papers. DistillerSR software is used for the study selection phase to execute title screening and title and abstract screening. In the end, 278 references were considered as our project's primary studies.

The methodology applied in this research include different steps of extracting textual data, pre-processing, and data processing which data processing consists of phrase extraction, semantic similarity clustering, and in the end post-processing. To extract the relevant phrases, after comparing different approach results, the lexical approach was decided to be used and, we used Natural Language Toolkit (NLTK) library in Python. Next step was phrase clustering that put similar phrases into the same groups and clustering technique in this research consisted of two phases vectorizing and grouping. For vectorizing USE method was used and for grouping the similarity matrix method was applied owing to more accurate distance calculation and grouping outcomes.

It should be noted that 317 risks in general were extracted in 24 different groups. Top three risks that are more discussed in the literature include supply risks, operational risks, and operational risks respectively. Top four groups with more risks are supply, product, transportation, and financial having 27, 27, 22, and 20 risks respectively.

More than 73 strategies were found in the literature that targeted different risks in the field of capacity, clinical trial, compliance, customer service, supply, demand, etc. Different studies have worked on the problem of shortages in drugs and medicines. The second risk category that has received the most attention from researchers is supply-related risks. The three risk groups that have received less attention comparing others are cost, international, and political groups.

To sum up, our major contributions are being the first systematic literature review by text-mining in pharmaceutical supply chain discipline, provide up-to-date classifications for identified risks in the literature through semantic clustering, and reviewing risk mitigation strategies provided in the literature without limiting to any specific risk category.

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