Drug Shortages Mitigation of Supply Chain in the Canadian Hospital Pharmacy

by

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Pénuries de médicaments Atténuation de la chaîne d'approvisionnement dans la pharmacie hospitalière canadienne

Tarek ABU ZWAIDA

RÉSUMÉ

La pénurie de médicaments est un problème complexe à l'échelle mondiale, qui a également plusieurs répercussions négatives sur l'ensemble de la chaîne d'approvisionnement pharmaceutique du Canada en raison de divers facteurs, notamment une augmentation imprévue de la demande, des difficultés à obtenir des matières premières ou de la main-d'œuvre directe, des problèmes de production soudains, des problèmes de fabrication de sources uniques, des problèmes législatifs et réglementaires, des facteurs de distribution et des catastrophes naturelles. En outre, la gestion actuelle des stocks avec des opérations manuelles et la gestion des stocks dans la pharmacie de l'hôpital ne peuvent pas empêcher la pénurie de médicaments. En fait, cette question est très critique dans les systèmes de soins de santé canadiens, ce qui appelle récemment plusieurs enquêtes et recherches pour atténuer l'impact négatif et le risque pour le système de soins de santé.

Afin de mettre en évidence les facteurs critiques qui pourraient conduire à des pénuries de médicaments et affecter la chaîne d'approvisionnement et les stratégies de gestion des stocks dans les pharmacies hospitalières canadiennes, notre thèse vise tout d'abord à fournir une image complète des pharmacies hospitalières canadiennes en présentant une analyse de la pénurie de médicaments au Canada de 2016 à 2021 et une revue systématique de la littérature (RSL) pour extraire les facteurs critiques en effectuant un large examen des pharmacies hospitalières canadiennes et pour comprendre comment la perturbation continue s'est produite dans ce processus et a affecté les pénuries de médicaments. Nous avons utilisé les données ouvertes de la base de données de l'Association médicale canadienne (AMC) et des méthodes stochastiques analytiques pour illustrer les résultats de l'enquête.

Sur la base de cette étude approfondie, nous abordons ensuite le modèle pratique de pénurie de médicaments dans la chaîne d'approvisionnement hospitalière (HSC), dans lequel nous proposons un modèle d'optimisation pour éviter le problème de pénurie de médicaments dans un hôpital et une méthode d'apprentissage pour gérer automatiquement l'inventaire. Plus précisément, un mécanisme d'apprentissage par renforcement profond (DRL) est conçu sur la base du modèle d'optimisation pour gérer l'inventaire en ligne, la décision de réapprovisionnement en médicaments étant automatiquement déterminée en fonction de l'observation du prix, de la demande et du niveau actuel des médicaments. Un coût de pénalité est également ajouté à la fonction objectif afin de minimiser non seulement le problème de pénurie de médicaments, mais aussi la situation de surapprovisionnement.

De plus, dans cette thèse, un résultat numérique a été présenté pour vérifier la performance de l'approche proposée qui surpasse les benchmarks en ligne tels que (Over-provisioning, Ski-rental, et Max-min) en termes de coût de remplissage et de taux de pénurie.

Pour conclure, nous nous concentrons dans cette thèse sur la pénurie de médicaments au Canada afin de fournir une analyse approfondie sur une longue période de temps, de 2016 à 2021. Nous contribuons à l'étude de ce sujet en utilisant un ensemble de données réelles et des approches analytiques stochastiques. Nous proposons une étude documentaire intensive comme suivi de l'analyse afin d'esquisser le tableau de la pénurie de médicaments dans la chaîne d'approvisionnement pharmaceutique de l'hôpital. Les résultats de l'étude et de l'enquête nous aideront à approfondir notre recherche en construisant un modèle d'optimisation de la gestion des stocks. En outre, et sur la base du DRL, une stratégie d'apprentissage profond a été développée pour gérer de manière autonome les stocks de la pharmacie de l'hôpital afin de prévenir les pénuries de médicaments.

Mots-clés: chaîne d'approvisionnement, pharmacie hospitalière, optimisation, pénurie de médicaments, et Canada

Drug Shortages Mitigation of Supply Chain in the Canadian Hospital Pharmacy

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ABSTRACT

Drug shortage is a complicated issue worldwide, which also causes several negative impacts to the whole Canada's pharmaceutical supply chain because of various factors that include an unforeseen increase in demand, trouble obtaining direct raw materials or labour, sudden production problems, sole sourcing manufacturing issues, legislative and regulatory problems, distribution factors, and natural disasters. Furthermore, the existing inventory management with manual operation and inventory management in the hospital pharmacy cannot prevent drug shortage. In fact, this issue is very critical in the Canadian healthcare system which is recently calling several investigation and research to mitigate negative impact and risk to the health care system.

In order to highlight the critical factors which could lead to the drug shortages and affecting the supply chain and the inventory management strategies in Canadian hospital pharmacies, our thesis is firstly to contribute a whole picture of the Canadian hospital pharmacies by presenting an analysis of Drug Shortage in Canada from 2016 –2021 and a comprehensive Systematic Literature Review (SLR) to extract the critical factors performing a wide review of the Canadian hospital pharmacies and to understand how the continued perturbation occurred in this process and affected to the drug shortages. We have used the open data from Canadian Medical Association (CMA) database and analytical stochastic methods to illustrate the survey result.

Based on the intensive survey, we next go in the practical model of drug shortage in the Hospital Supply Chain (HSC) in which we contribute an optimization model to avoid the medicine shortage problem in a hospital and propose a learning method to automatically manage the inventory. Specifically, a Deep Reinforcement Learning (DRL) mechanism is designed based on the optimization model to operate the inventory under an online fashion in which refilling drug decision is automatically determined based on the observation of price, demand, current level of drugs. A penalty cost is also added in the objective function to minimize not only the drug shortage issue but also the over-provisioning situation.

Furthermore, In this thesis, a numerical result has been presented to verify the performance of the proposed approach which outperforms the online benchmarks such as (Over-provisioning, Ski-rental, and Max-min) in terms of the refilling cost and the shortage rate.

To conclude, we focus on the medication shortage in Canada in this thesis to provide an extensive analysis over a lengthy period of time, from 2016 to 2021. We contribute to the study of this topic by using an actual data set and stochastic analytical approaches. We propose an intensive literature study as a follow-up to the analysis to sketch the drug shortage picture of the hospital's pharmacy supply chain. The findings of the study and survey will aid us in furthering our research by constructing an inventory management optimization model. Besides that, and based on DRL, a deep learning strategy was developed to manage autonomously inventories in the hospital pharmacy in order to prevent drug shortages.

Keywords: supply chain, hospital pharmacy, Optimization, drug shortages, and Canada

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

LIST OF ALGORITHMS

LIST OF ABREVIATIONS

DSC	Drug Shortages Canada
CHPSC	Canadian Hospital Pharmacy Supply Chain
HSC	Hospital Supply Chain
FIP	International Pharmaceutical Federation
AI	Artificial Intelligent
ML	Machine Learning
CPhA	Canadian Pharmacists Association
CSHP	Canadian Society of Hospital Pharmacists
CMA	Canadian Medical Association
RD	Research and Development
SLR	Systematic Literature Review
ETS	École de Technologie Supérieure
NSERC	Natural Sciences and Engineering Research Council of Canada
WHO	World Health Organization
FDA	Food and Drug Administration
CDC	Centers for Disease Control
US	United States
ASHP	American Society of Hospital Pharmacists
UUDIS	University of Utah Drug Information Services

API	Active Pharmaceutical Ingredients
COPD	Chronic Obstructive Pulmonary Disease
HCQ	Hydroxychloroquine
ISMP	Institute for Safe Medication Practices
CPSI	Canadian Patent Safety Institute
ATO	Assemble-To-Order
CPU	Central Processing Unit
RL	Reinforcement learning
MDP	Markov decision process
DNN	Deep Neural Network model
DR2O	Dynamic Refilling Drug Optimization
ADCs	Automated Distribution Cabinets
PCIP	Pharmacy Computerized Inventory Program
ADDSs	Automated Drug Dispensing Systems
RFID	Radio Frequency Identification
DRL	Deep Reinforcement Learning
AI/ML	Artificial Intelligent/Machine Learning

INTRODUCTION

Throughout the COVID-19 pandemic, shortages of drugs worsen in most nations in the world. Several countries and the World Health Organization (WHO) have evaluated the causes leading to drug shortages and considered solutions that may be beneficial at the local and global levels to avoid, mitigate the drug shortage impacts. As one of the world's best healthcare systems, Canada acknowledges the vital concerns and escalating danger created by drug shortages, thus the Canadian healthcare system always makes significant efforts to avoid shortage circumstances to deliver strong and wealthy healthcare services. Canada's federal and provincial governments have developed several initiatives and projects ranging from research to business that may use innovative technology into healthcare systems ranging from supply chain to inventory systems. Following this crucial trend, our thesis investigates a comprehensive survey of the drug shortage in Canada's hospital pharmacies, which includes challenges and solutions and focuses on proposing two-fold contributions including (i) a systematic literature review to collect data and research papers in drug shortages, (ii) a drug shortage survey, which studies the drug shortage problem in the Canadian's hospital pharmacy, and (iii) an optimization and learning solution to manage the pharmacy inventory system in order to deal with drug shortage.

0.1 Background

In general, drug shortage can be defined as the situation where the manufacturers that set out the identification number assigned for a certain drug are not able to meet the drug's demand (Elbeddini *et al.*, 2020). Several factors drive the problem of drug shortage which include delays, approval issues, and discontinuations. Drug shortages contribute to increased errors, patient non-adherence, and adverse effects and can cause substantial stress for pharmacists and patients. Before and after COVID-19, drug shortage had rapidly grown with the hallmark of scarcity rising beyond control with the strike of the Coronavirus in late 2019 (Moosivand *et al.*, 2021). The shortage of drugs used to treat life-threatening conditions deserves attention from the government and pharmaceutical industries CDC (2019). Drug shortage is a complicated issue worldwide and then more specifically in the hospital pharmacy by Zu'bi & Abdallah (2016); Badreldin & Atallah (2021). Although healthcare systems have established contingency plans and practices refining preparation for unexpected drug shortage crises, medicine supply remains a major issue of concern across the globe. Many countries such as Europe, Australia, Canada, and Germany among others have experienced drug scarcity thus influencing medicine supply in the world (Rhodes *et al.*, 2016).

Focusing on Canada's health care system, drug shortages are also a critical challenge for pharmacists, health caregiver and more importantly, their patients in the hospitals; the frequency of drug shortages caused a call for improved management better supply chain management (Swangkotchakorn *et al.*, 2009). The drugs range from acetazolamide to levetiracetam to valproic acid syrup and Valsarta™ (Canada). Reportedly 74% of the 23 non-seizure related drugs have been subject to shortages up to and including the first half of 2016. Medicine anticancer medicines have been subject to prolonged back order or discontinuation. Discontinuations are a subcategory of drug shortages, which refers to the drug that simply is not manufactured any longer regardless of people still using the drugs. Since 2010, Canadian pharmacists, physicians, and patients have been wrestling with shortages in drug supply, primarily for generic drugs (Donelle *et al.*, 2018), which account for 70% of Canadian prescriptions. Although the drug shortage problem affects every life of clinicians and patients, there is paucity of literature specifically describing the experienced problems and their clinical consequences, as pointed out by Videau *et al.* (2019b), International Pharmaceutical Federation (FIP), and Drug Shortage Canada (Canada).

Efforts have been made to establish effective techniques for strengthening the supply chain strategy in order to avoid drug shortages (Canada, 2021). According to Drug Shortage Canada, this system discloses all circumstances of the drug shortage in Canada with detailed information.

The Canadian Pharmacists Association (CPHA) has taken the lead in addressing drug shortages in Canada. They continue to push for drug shortage research as well as worldwide cooperation to address and resolve drug supply challenges. The CPHA and Health Canada's Multi-Stakeholder Steering Committee, comprised of industry and healthcare representatives, are working together to improve drug shortage response and communication strategies, as well as identify strategies to help mitigate and prevent disruptions to the Canadian drug supply. In order to allow students, professors, and experts in Canadian universities to reach their goals in drug shortage, many research platforms e.g., MITACS; NSERC have offered funds, scholarship, and sharing communities for discussion, analysis and implementation.

0.2 Motivation

According to the literature, the paradigm "drug shortage" might signify a variety of things. "It is a circumstance in which the overall supply of all clinically interchangeable versions of an FDA-regulated medicine is insufficient to fulfill the present or predicted demand at the patient level" according to the Food and Drug Administration (FDA). While it also defines a medically required medicine as "a product used to treat or prevent a serious disease or medical condition for which no other alternative drug, available in adequate supply, is determined to be a suitable substitute by medical personnel". The following definition was suggested by De Weerdt *et al.* (2017a): situations in which a planned or present user-demand for medication is not satisfied. The phrase 'drug scarcity' is used in the current study to describe the situation. Because of the complexities of drug shortages in terms of causes and consequences, research for drug shortages remains both promising and challenges.

In addition to the more well-known effects, the recent studies found that higher readmission owing to medication shortage-related treatment failures accounted for approximately 10% of the reported unsatisfactory patient outcomes. Thirty-eight percent of the surveyed pharmacy directors stated claimed their organization has received at least one patient complaint concerning shortages, with roughly 20% of those revealing the actual number of complaints man. Therefore, from the federal government to the local province, Quebec, there are several research proposals and projects that aim to deal with drug shortages (MITACS; NSERC). Implementation of a shared database system Canada requires a large investment to monitor and collect data from different pharmacies and organizations. However, many hospitals are reluctant to change the layout of the storage area because of this cost. In addition, sharing their own data is always a hesitant decision of each organization when their private data is disclosed in the network to be used and analyzed. To understand major challenges and potentials, a comprehensive survey of drug shortage in the Canada's pharmacy supply chain can help us to draw a precise picture from different angles. It can also help us to find solutions to deal with the drug shortages.

Among potential recent solutions to avoid and tackle the drug shortage, intelligent methods based on artificial intelligence (AI) and machine learning (ML) have been widely used to analyze, predict and learn valuable information of user data to enhance the performance of the pharmacies supply chain . Many forward-thinking pharmaceutical companies are seeking to employ AI in order to improve their medication management and development of the supply chain process. Insilico Medicine, for example, used AI and deep learning to create, manufacture, and assess a novel pharmaceutical candidate in 46 days – 15 times faster than previously anticipated Insilico. Pharmacy system may acquire real-time data and be sensitive to changes in medication legislation across regions by going entirely digital. AI and data analytic can be facilitated to expedite learning collection from publicly accessible and commercial data sources. They can support to handle large volumes of data, even unstructured data, in a fraction of the time it takes humans . AI and ML can "learn" what patterns and developments to search for in data and only notify humans to the important information. With plenty of potentials, they strongly motivate us to apply stochastic analysis methods under supporting of data mining and ML framework in order to reduce the possibility of the drug shortage in the hospital's pharmacy inventory. To study benefits of ML approaches applying for the pharmacy inventory management, in the chapter 4 of this thesis, we develop an efficient learning method to automatically operate and prevent drug shortages in the inventory management system of the hospital pharmacies.

0.3 Objectives

This thesis starts with a thorough analysis of longitudinal study, from 2016 to 2021. Using an actual data set and stochastic analytical techniques, we add our following contributions to the literature. First, as a follow-up to the research, we present an systematic literature review to study the hospital's pharmacy supply chain's medicine shortage in Canada (Abu Zwaida *et al.*, 2021a). The study helps us further in our research by accurately providing related work of the drug shortage in the hospital pharmacy inventory. We can also obtain related work that used optimization and ML techniques to automatically manage the inventory system. As our best of knowledge, we firstly contribute to the study of the inventory drug shortage problem by proposing a deep learning solution that can autonomously manage inventory in the hospital pharmacy in order to reduce medicine shortages (Abu Zwaida *et al.*, 2021b).

Even though there exist open databases for drug shortages in Canada, the literature has little work that makes survey about the drug shortage in the hospital pharmacy systems in order to precisely understand, evaluate and make decisions to prevent medicine shortages. Differences of concepts and paradigms of pharmacy systems are discussed and defined in our thesis to present a clear picture of drug shortages. We aim to build a systematic literature review to collect precisely research papers related to drug shortage in Canada. In addition, we aim to summarize operation mechanisms and models of the inventory management system in the pharmacies along with a numerical analysis to illustrate how the current systems copes with the drug shortages. A process flow is developed to show the steps involved in managing inventory. Based on that, we can characterize the hospital's pharmacy supply chain design in terms of drug shortage, identify critical factors in hospital's pharmacy supply chain design and illustrate potentials as well as challenges. Finally, we aim to develop an automation inventory management to minimize the operational cost in terms of the penalty cost caused by drug shortages (Shaban *et al.*, 2018; Shukar *et al.*, 2021). ML techniques are combined with optimization methods to make inventory decisions based on user behaviors, environment conditions (such as, price, remaining level of stocks). The output of ML are continuously observed, measured, and trained to reinforce the performance.

In summary, the specific objectives are as follows:

- To provide a comprehensive survey about drug shortages in the Canadian hospital's pharmacies supply chain;
- To understand and raise potentials as well as challenges in the topic of drug shortages in the Canadian hospital's pharmacies supply chain;
- To propose an optimal drug inventory management by applying ML and optimization techniques to prevent the drug shortages.

To fulfill these objectives, our research thesis aims to find the solutions for the following research questions:

- Q1: How can we obtain precisely research work related to the drug shortage topic in the Canadian's hospital pharmacy?
- Q2: What are the major challenges and current strategies to deal with drug shortage in the Canadian's hospital pharmacy?
- Q3: What and how can AI/ML methods be applied to mitigate or to avoid the drug shortage situation?

0.4 Methodologies

In this thesis, the research methodologies are presented through three main contributions, from the comprehensive survey to the applied-learning implementation. Focusing on the drug shortage situation in Canadian hospital's pharmacy supply chain, we first use a systematic literature review (SLR) that is performed to determine the main and current challenges of the hospital supply chain of drugs in Canada, and understand how these supply chain disruptions contribute to drug shortages.

- Designing a comprehensive survey process: This helps us extensively and intensively make a survey based on prior research;
- Defining a search procedure: Due to several works in different approaches from inventory management systems to pharmacy supply chains, we propose a search procedure to precisely obtain papers in the survey;
- Validating the search procedures: We filter and validate considerable and valuable research results to present in our survey;
- Conducting literature search: this is the final step but is very important to raise conclusions. We have used expert's opinions and comments from our supervisors to conduct literature research.

In addition, the research thesis conducted a SLR which unveils issues and factors such as raw materials availability and increases in demand which cause drug shortages. The proposed systematic methodology in the survey seeks to highlight possible solutions to the supply chain management issues which could cause drug shortages in Canada. Various solutions are explored and discussed with the relevant information being obtained from studies conducted on how to mitigate the impact on supply chain management.

Based on the proposed SLR, we make a comprehensive survey of drug shortage in Canadian's hospital supply chain system. We have applied survey methodologies by identifying and select potential research materials, collecting data from those which have confident results, evaluating and presenting pros and cons of their research papers, comparing and concluding their results to present in our work. Based on that, we review various models of the pharmacy supply chain and inventory managements to draw a picture of the drug shortage in Canadian's hospital supply chain system.

In the third contribution, we focus on the implementation in which an optimization and ML methods are studied. Specifically, we take into account the online methodologies of the automation control system that can be applied to automatically manage the inventory system. Based on observation information, a reinforcement learning method is applied to make inventory decisions without human interactions in order to prevent drug shortages. A deep learning model is employed in the implementation to address the high complexity of the observation environment which cannot be solved by the traditional reinforcement learning method. Our results in the learning method also convince that the machine learning approaches will be very potential in future to cope with the drug shortage as well as reduce significantly human interactions in inventory management.

0.5 Discussion

Solving the drug shortage in the Canadian's hospital supply chain system is not a trivial issue which really need strong effort from several organizations in both research and industry. There are a number of studies in the state of the art focusing on the inventory system and supply chain methodologies to deal with the drug shortages. However, as our best knowledge, this thesis is the first study going deeply on the specific system of the Canadian's hospital supply chain system with specific aspects. We aim to limit our work in a narrow area instead of covering a general drug shortage in the world in order to draw a precise picture and understand clearly the system in the Canadian hospital pharmacies. Based on that, we attempt to provide to the research and industry usable contributions and promising solutions that can be applied in the real system. Our work studying the drug shortage in the Canadian's hospital supply chain system which has limitations. In fact, the big difficulty in this research topic is the open and available data set. Even though the shortages of drugs cause several impacts on the health care system, hospital's pharmacies hesitate to disclose their data and information. Privacy-preserving procedures make us frustrated to understand issues and collect data. Open access papers and documents are mostly collected from the ETS library and Canada drug shortage website Canada. Practical experience in the reality of the hospital pharmacies should be added in the future to add more contributions for our work. Besides, to order and to fill missing data, we have used methods to generate data based on seeds of data collected from drug. Even though the data is not fully gathered in the real system, the results of our thesis are still significant to contribute for both research and practice.

In addition, our learning model is designed based on the following assumptions:

- Assumption 1: Considering the huge amount of drugs managed in the hospital pharmacy inventory, there is a need to introduce an automation system to manage the inventory in terms of reducing drug shortages;
- Assumption 2: Considering the hospital pharmacy inventory in Canada, there are some local characteristics that are presented in the specific data of Canada drug shortage (Canada);
- Assumption 3: Considering a discrete time slot system to manage the inventory, we assume that at each time slot (e.g., a day, a week), the system makes an inventory decision based on the current observation (e.g., the amount of remaining drugs in the stock, and price, etc.);
- Assumption 4: Because of the multiple uncertainties aspects causing drug shortages, we assume that the situation of the system can be formed with a finite states and from a state to another state, it follows the Markov chain process.

0.6 Key contributions

The main contributions of our research thesis are as follows:

• Article 1 (Chapter 3). To the best of our knowledge in the first article, analyses highlight current knowledge gaps that exist with regard to the factors which affect the supply chain, and the inventory management strategies that are utilized by hospital pharmacies in Canada which could lead to drug shortages. The result of this research is contained in a systematic search methodology which consists of four main tasks, namely: a) building an optimal review process, b) defining search procedures, c) validating the search procedures, and d) conducting literature search. Furthermore, we conducted a SLR which unveiled issues and factors such as raw materials availability and increases in demand which cause drug shortages.

• Article 2 (Chapter 4). In the second article, we cover the drug shortage in the Canadian hospital pharmacy supply chain, which is described as a situation in which the total supply of regulated drugs fails to meet the projected or current demand at the patient level. This research is based on the SLR to have a precise comprehension literature review. Although it is hard to have all data and relevant research results, the SLR can help us to draw key factors and challenges in this system to contribute to drug shortage research.

• Article 3 (Chapter 5). In this article, we study an optimization model of the Canadian hospital pharmacy inventory. To the best of our knowledge, we are the first, who propose the optimization model for the Canadian hospital pharmacy inventory. Based on the SLR and the comprehensive literature review, we can understand the Canadian hospital pharmacy inventory to model an optimization management problem. With a given input information such as the price of a drug, amount of demand in the history, we aim for an automatic management system that can automatically make inventory decision to minimize the drug shortage situation. We advocate the learning method based on Deep Reinforcement learning to solve the designed problem under an online mechanism

0.7 Conclusion

Going through our thesis, the two-survey research provides useful aspects for us to support the implementation of the ML-based framework to prevent the drug shortage. They also show that to avoid drug shortages, we leverage modern technologies into the daily inventory management. Meanwhile, the ML-based implementation illustrates potential cutting-edge technologies to deal with the drug shortage. In Canada, the pharmaceutical sector has traditionally prioritized innovation. The need for innovative medications is stronger than ever to identify several emerging issues which contribute to this thesis. In the scope of our thesis, even though we cannot cover all issues and aspects of the drug shortage in the Canada hospital pharmacies, we have contributed to the research by conducting extensive surveys and implementing a numerical evaluation to demonstrate the promising performance of our solution. We illustrated that there is a need for more thorough and in-depth investigation into the causes that cause drug shortages in hospital pharmacies. We have surveyed existing models and architectures of inventory managements and supply chains in Canadian hospital's pharmacies. However, there is a scarcity of available data and knowledge about the variables that cause active ingredients, drug prices, user demand, and pharmacy behaviors in response to drug shortages. Therefore, our research thesis still has gaps that need to be fulfilled and enriched by future more intensive research. We aim to collaborate with a hospital in the future to establish a connection between our theoretical study and the actual reality. As a consequence, we will be able to incorporate relevant hospital resources into our complete research, both in terms of data and outcomes. In order to optimize and benefit their system, we will also try to adapt our solution to a real pharmacy.

CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

Ventola (2011); Chen *et al.* (2021) opined that prescription drugs play a significant role in enhancing patients' lives by promoting positive health outcomes. The globe reels from a drug shortage that has affected low, middle, and high-income nations. Health practitioners, such as doctors and nurses, remain committed to assisting patients by identifying illnesses and prescribing the necessary medication. However, Iyengar *et al.* (2016) opine that in many instances, patients find that their prescribed medication cannot be found in their local pharmacies. Gagnon (2012) opines that the unavailability of drugs in pharmacies augments patients' health risks by making it challenging for patients' health to be improved. Without drugs, Hoffman (2012); McLaughlin *et al.* (2013); Tucker *et al.* (2020), patients' health outcomes cannot be improved. This essay evaluates drug shortages by evaluating drug shortages in general, particularly from a global perspective. The paper also discusses Canada's drug shortages, justification of drug shortage in Canada, drug shortages in the hospital pharmacies, and the shortage of drugs in Canada before and during COVID-19. It will also discuss Canada's drug supply chain and the critical factors influencing the supply chain.

1.2 General Review of Literature

According to Shukar *et al.* (2021), the American Society of Hospital Pharmacists (ASHP) and the University of Utah Drug Information Services (UUDIS) define drug shortage as a supply predicament that hinders the pharmacy's preparation and dispensation of a drug product to the extent that patient care would only be possible by prescribing a substitute agent. According to Phuong *et al.* (2019) cited in Shukar *et al.* (2021), drug shortage, as outlined by the FDA in the United States, constitutes an interval when the drug supply cannot meet the demand.

Variable	Canada (n = 84)	
Quantitative profile		
No. of drug manufacturers with ≥ 1 shortage	28	
Duration of drug shortage, days†		
Mean ± SD	55 ± 61	
Median (range)	32 (0–402)	
No. of drug shortages from generic manufacturers	48	(57)
No. of shortages involving parenteral drugs	41	(49)
Therapeutic class‡		
Anti-infective agents	15	(18)
Central nervous system agents	13	(15)
Cardiovascular drugs	7	(8)
Antineoplastic agents	1	(1)
Gastrointestinal drugs	3	(4)
Skin and mucous membrane preparations	9	(11)
Hormones	5	(6)
Anesthetics, local	5	(6)
Antihistamines	3	(4)
Autonomic drugs	6	(7)
Diagnostic agents	3	(4)
Electrolytic, caloric, and water balance agents	2	(2)
Ointments, ophthalmic agents	3	(4)
Serums, toxoids, vaccines	2	(2)
Smooth muscle relaxants	1	(1)
Vitamins	1	(1)
Radioisotopes	0	(0)
Enzymes	0	(0)
Blood formation and coagulation agents	0	(0)
Blood derivatives	0	(0)
Expectorants and cough preparations	0	(0)
Other	5	(6)

Figure 1.1 Drug shortages by manufacturers in Canada
Taken from Videau *et al.* (2019b)

There is a drug shortage when manufacturers of specific drugs cannot supply sufficient drugs to match the existing demand in Canada. Drug shortage negatively influences patients because it denies them the opportunity to access their prescribed drugs. One needs to understand that a drug shortage can be long term or short-term. Regardless of the shortage's duration, there are some factors responsible for drug shortages. These factors include a manufacturing delay or issue, challenges acquiring the necessary ingredients or raw materials, a sharp rise in demand, a pandemic, a natural disaster, or drug's discontinuation (Canada, 2022). There is a need to understand these factors if a country is to handle drug shortages effectively. A persistent drug shortage can jeopardise people's lives. This essay evaluates drug shortage in the Canadian supply chain hospital. It will evaluate the prevalence of such a shortage and the factors responsible for the shortage. A study conducted in Canada in 2018 indicated that the country experienced 84 drug shortages (Videau *et al.*, 2019b). Additionally, the research indicated that Canadian hospitals had a median of 32 days where drug shortages were concerned (Videau *et al.*, 2019b). Parenteral administration formed the majority of drugs affected by short supply. However, the major therapeutic classes influenced by drug shortages constituted anti-infective agents, which formed 21.1 per cent, followed by the agents of central nervous system at 11.3 per cent, antineoplastic agents at 7.5 per cent, and cardiovascular drugs at 8.2 per cent (Videau *et al.*, 2019b).Furthermore, by manufacturer, out of 84 drug shortages, Apotex had 10, Aspen Pharmacare had five, GSK had four, Pfizer (18), Pharmascience (12), and Teva Pharmaceutical(11). From the research, findings indicate that at 98 per cent, wholesalers formed the largest source for drug shortage identification (Videau *et al.*, 2019b). In 2012, Canada experienced a severe drug shortage that forced the policy makers to generate a database where drug manufacturers can report shortages (Lau *et al.*, 2022). It is important to establish inventories to track drug use and demand in order to identify instances of drug shortage (Dillon *et al.*, 2017b). In 2017, Canada's drug companies were obligated to report actual and anticipated shortages (Lau *et al.*, 2022). However, the evolution of the COVID-19 pandemic severally affected drug availability as it hurt the supply chain. Additional research found that 13329 drug products were at an augmented shortage risk at 44.7 per cent (Lau *et al.*, 2022). The pandemic elevated the demand of some drugs, thereby generating an unprecedented demand and pharmacies and manufacturers had to seek alternatives to provide the drugs to clients (Lau *et al.*, 2022). However, with some drugs' demand increasing, others did not indicate a rise in demand during the pandemic (Lau *et al.*, 2022). This can be attributed to the fact that the inability of people to access health care services could have led to a decreased demand in some pharmaceutical drugs (Lau *et al.*, 2022).

1.2.1 Drug shortage in Canada

According to Canada.ca (2017), a drug shortage occurs when a drug manufacturer fails to supply sufficient drugs to meet Canadian drug orders. When there is a drug shortage in Canada, the public cannot access their prescribed medication because the drug is 'stocked-out' or back order. As per Ireland (2018), Canada continues to experience drug shortages, whereby one adult in every four persons has been affected by drug shortage since 2015. According to pharmacists.ca (2018), The Canadian Pharmacists Association conducted a survey to determine the prevalence of drug shortage in Canada. In the survey, the Canadian Pharmacists Association interviewed 1,500 adult Canadians (the youngest was 18 years) between November 9 and November 13, 2018. A majority of the participants (69 percent) were concerned about Canada's drug shortage. The 69 percent of participants concerned about Canada's drug shortage situation comprised 28 percent who were extremely concerned and the 41 percent who were somewhat worried about the deficit. The figure below shows the participants' concern regarding drug shortage in Canada.

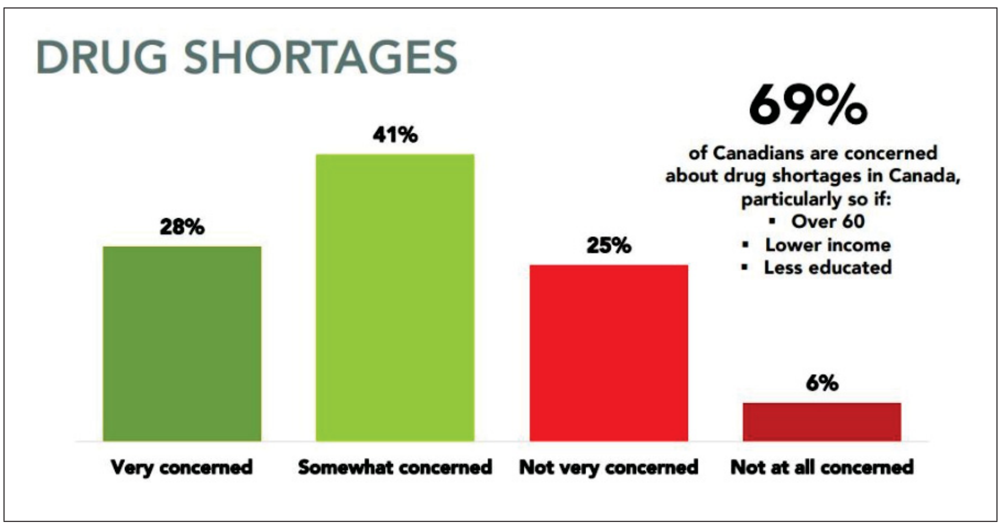

Figure 1.2 The participants' concern regarding drug shortage in Canada
Taken from pharmacists.ca (2018)

The figure can represent Canadians that the majority are concerned about the drug shortage issue affecting the country. With only 6 percent of the participants not concerned at all about the shortage, one can deduce that the drug shortage issue is prevalent in Canada to the extent of worrying most Canadians. Figure 1.3 below indicates the percentage of participants who have experienced drug shortages

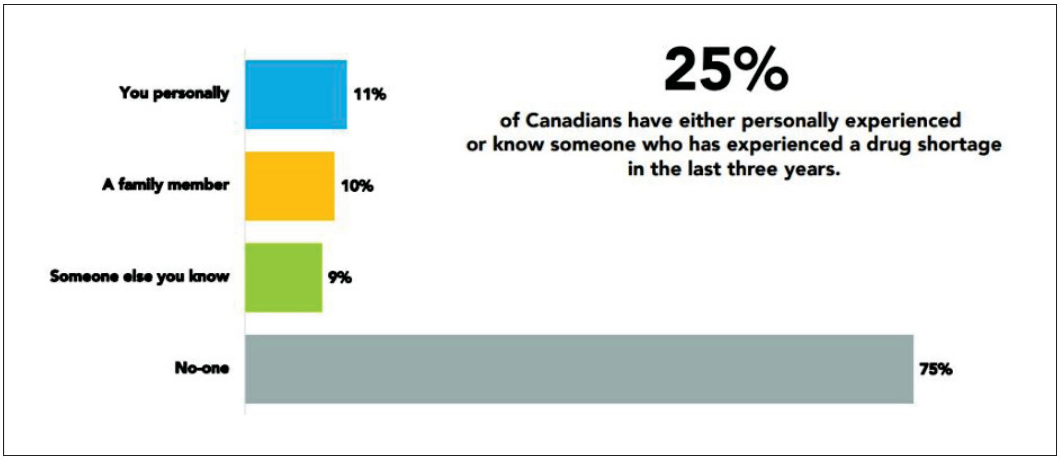

Figure 1.3 The percentage of participants who have experienced drug shortages
Taken from pharmacists.ca (2018)

From figure 1.3, 25 percent of the participants have either experienced drug shortages personally or can identify someone who could not find a drug they were supposed to get in the last three years. Eleven percent of the surveyed participants had personally experienced a drug shortage, whereas 10 percent had had a family member experience a drug shortage. Nine percent of the participants knew someone who had experienced a drug shortage. Even though 75 percent of the participants had not experienced or did not know any individual who experienced a drug shortage, the fact that 25 percent of the participants experienced drug shortage either personally or by knowing someone who did, the issue cannot be overlooked. The Canadian Pharmacists Association (2022) and Elbeddini *et al.* (2020) opine that the pharmacist's daily routine incorporates the management of drug supply challenges, thereby denying them the opportunity to serve the needs of Canadian patients by providing them with the necessary drugs. When the drugs are in short supply, Canada's pharmacists cannot play their role in influencing positive health outcomes by providing the required medications. In contrast, drug supply challenges force pharmacists to assume a new role in managing the supply issues while finding out how the unavailable drugs could be made available to meet the patients' needs. In major instances where there is a drug shortage, the Canadian Pharmacists Association (2021) opines that pharmacists liaise with physicians while also tracking down the supply to identify and provide appropriate alternatives to drug therapy to guarantee continuity in the provision of proper care to patients. According to Ireland (2018), the drug shortages problem in Canada has worsened recently to the extent that the medication shortages' frequency is unparalleled. In 2017, Ireland (2018) declares that Canada faced an acute EpiPens shortage, thereby jeopardizing the lives of many Canadian children living with life-threatening allergies. In November, Canada experienced another shortage when patients could not access Wellbutrin from their local pharmacies due to its shortage. Wellbutrin is a popular and necessary antidepressant drug. Furthermore, Ireland (2018) opines that Canada continues to experience shortages of various medications to evaluate blood pressure (such as the angiotensin receptor blockers, ARBs).

1.2.2 Justification for research on Drug Shortage in Canada

In Canada, Zhang *et al.* (2020) stated that one of the factors causing drug shortage is the lack of an active ingredient. There is a need to understand that specific ingredients are used to manufacture drugs. According to Zhang *et al.* (2020), active ingredients play a significant role in making prescription drugs, without which the drug would not be achieved. In Canada, there are issues with the unavailability of active ingredients, which leads to the unavailability of the drug. Additionally, Zhang *et al.* (2020) opined that Canada also experienced instances where shipping the drug was highly delayed. Delays in shipping the drug meant that the people could not access their prescribed drugs until the drug entered the country. According to Zhang *et al.* (2020), drug shortages also occurred in Canada due to increased demand. When the demand is high, the number of people in need of a specific drug surpasses the available quantity of the drug. According to Ireland (2018), recalling some drugs also contributed to the drug shortage. For example, Some Chinese-manufactured batches of EpiPen were recalled after it emerged that they were impure. Investigations on EpiPen found that some batches contained valsartan, which is believed to be carcinogenic. Ireland (2018) opines that EpiPens are significant drugs used by children with life-threatening allergies. In addition to the fact that the recalling of some batches caused EpiPens' shortage, other factors such as manufacturing issues experienced by pharmaceutical companies also led to the deficit. Ireland (2018) declares that some pharmaceutical companies made marketing blunders which led to the shortage. Some pharmaceutical companies make ineffective distribution decisions (Ireland, 2018). This adversely affects drug availability. The inefficient drug distribution decisions meant that some drugs could not reach specific regions within the expected time. Furthermore, distribution decisions could also mean failing to supply sufficient drugs to all pharmacies. Locations with high prevalence rates of particular diseases would require an adequate supply of the necessary drugs. However, if distribution decisions fail to cater to that specific population's proportion, there would be a shortage because the relevant individuals would not receive the drugs because of their short supply. Fagan (2019) cites that Canada has experienced an intensive shortage of Wellbutrin, a prescribed drug for the treatment of depression. Wellbutrin, sold under the Effexor brand name, is used as an antidepressant. The shortage meant that people with depression could not access the drug. In its place, pharmacists recommended other Wellbutrin versions, which had extreme adverse effects (Mertz (2018). According to Fagan (2019), the primary cause of the Wellbutrin shortage is lack of an active ingredient.

1.2.3 Drug shortages in hospital pharmacies

The Canadian Pharmacists Association (CPHA) conducted a survey involving 427 pharmacists who submitted their survey responses. In the survey, the majority of the pharmacists were located in Quebec at 32.9 percent, followed by Ontario and Alberta in that order at 21.4 percent and 11.7 percent, respectively. The locations with the fewest pharmacies based on the participants include Newfoundland, Prince Edward Island, and Territories, at 1.2 percent each. The participants were asked whether they encountered challenges locating medications for prescriptions during their last shift. In answering this question, about 81.2 percent of the participating pharmacists (nationally) agreed to have experienced challenges locating medications. In Ontario, 97.8 per cent of the participating pharmacists experienced challenges locating specific medications for their patients' prescriptions, while in Quebec, 57.2 per cent of the participating pharmacists could not find their patients' prescribed drugs. Figure one below shows the percentage of pharmacists who had trouble locating prescription drugs.

Last shift	National (n=427)	Ontario (n=91)	Quebec (n=140)	Rest of Canada (n=196)
Yes	81.2	97.8	57.2	89.3
No	18.3	2.2	40.7	10.7
Unknown	0.5	--	2.1	--

Figure 1.4 Percentage of pharmacists who had trouble locating prescription drugs
Taken from Canadian Pharmacists Association (2010)

Figure 1.5 below shows the number of prescriptions that the pharmacists could not find

Last shift	National (n=427)	Ontario (n=91)	Quebec (n=140)	Rest of Canada (n=196)
Median response	3	3	2	3

Figure 1.5 The number of prescriptions that the pharmacists could not find
Taken from Canadian Pharmacists Association (2010)

For the participants who experienced challenges finding specific drugs, figure 1.5 shows that about three types of prescriptions could not be found nationally, the same as in Ontario. However, only two types of prescriptions could not be found in Quebec pharmacies. The pharmacists were asked whether they had had challenges locating prescriptions in the last week. Nationally, 93.7 percent indicated they experienced challenges locating medications. In Ontario, 97.8 per cent of the pharmacists experienced challenges finding prescriptions in the last week, while in Quebec, 86.4 per cent of pharmacists had challenges locating prescriptions, as shown in figure 3 below. Figure 1.6 shows the percentage of pharmacists who had trouble locating medications in the last week.

Last week	National (n=427)	Ontario (n=91)	Quebec (n=140)	Rest of Canada (n=196)
Yes	93.7	97.8	86.4	96.4
No	5.6	2.2	11.5	3.1
Unknown	0.7	--	2.1	0.5

Figure 1.6 The percentage of pharmacists who had trouble locating medications in the last week
Taken from Canadian Pharmacists Association (2010)

1.2.4 The shortage of drugs in Canada before COVID-19

Before COVID-19, mainly between January 8 and February 2, 2018, Videau *et al.* (2019b) opined that Canadian hospitals experienced 84 shortages. This drug shortage issue during the identified period involved 28 manufacturers. Figure 1.6 below shows the drug shortage scenario in Canada before COVID-19. From figure 1.6, the number of drug shortages from generic manufacturers in Canada was 48, while the number of shortages involving parenteral drugs was 41. Under the therapeutic class, Canada had a shortage of 15 anti-infective agents. The number of central nervous system agents in short supply was 13, while that of cardiovascular drugs was 7. Antineoplastic agents had a short supply of one drug, while gastrointestinal drugs had a shortage of 3 drugs in Canada. In Canada, skin and mucous membrane preparation drugs emerged among the leading ones in short supply, with nine drugs unavailable.

1.2.5 Drug shortage during COVID-19

According to Badreldin & Atallah (2021); Kanji *et al.* (2020), during COVID-19, the need for specific drugs increased due to the pandemic's impact on people's health. For example, the demand for Tocilizumab increased in Canada during COVID-19. Tocilizumab's demand increased because the entire country (Canada) depended on one manufacturer. According to Verma *et al.* (2021), Tocilizumab is necessary for the treatment of various rheumatologic conditions. Verma *et al.* (2021) opine that Tocilizumab can also be used to manage cytokine release syndrome, a common and potentially deadly impediment of chimeric antigen receptor.

Variable	Country; No. (%) of Shortages*					
	Canada (*n* = 84)	France (*n* = 62)	Belgium (*n* = 46)	Spain (*n* = 28)	Switzerland (*n* = 98)	Total (*n* = 318)
Quantitative profile						
No. of drug manufacturers with ≥ 1 shortage	28	30	19	16	42	135
Duration of drug shortage, days†						
Mean ± SD	55 ± 61	35 ± 83	51 ± 47	51 ± 63	186 ± 301	91 ± 186
Median (range)	32 (0–402)	9 (2–437)	37 (1–263)	25 (0–240)	68 (0–1771)	31 (0–1771)
No. of drug shortages from generic manufacturers	48 (57)	28 (45)	4 (9)	12 (43)	33 (34)	125 (39.3)
No. of shortages involving parenteral drugs	41 (49)	29 (47)	31 (67)	17 (61)	73 (74)	191 (60.1)
Therapeutic class‡						
Anti-infective agents	15 (18)	18 (29)	7 (15)	8 (29)	19 (19)	67 (21.1)
Central nervous system agents	13 (15)	11 (18)	1 (2)	5 (18)	6 (6)	36 (11.3)
Cardiovascular drugs	7 (8)	7 (11)	3 (7)	1 (4)	8 (8)	26 (8.2)
Antineoplastic agents	1 (1)	6 (10)	1 (2)	5 (18)	11 (11)	24 (7.5)
Gastrointestinal drugs	3 (4)	0 (0)	4 (9)	0 (0)	3 (3)	10 (3.1)
Skin and mucous membrane preparations	9 (11)	0 (0)	4 (9)	4 (14)	7 (7)	24 (7.5)
Hormones	5 (6)	0 (0)	6 (13)	2 (7)	1 (1)	14 (4.4)
Anesthetics, local	5 (6)	2 (3)	5 (11)	0 (0)	2 (2)	14 (4.4)
Antihistamines	3 (4)	1 (2)	0 (0)	0 (0)	0 (0)	4 (1.3)
Autonomic drugs	6 (7)	1 (2)	1 (2)	1 (4)	3 (3)	12 (3.8)
Diagnostic agents	3 (4)	0 (0)	3 (7)	0 (0)	3 (3)	9 (2.8)
Diagnostic agents	3 (4)	0 (0)	3 (7)	0 (0)	3 (3)	9 (2.8)
Electrolytic, caloric, and water balance agents	2 (2)	4 (6)	3 (7)	0 (0)	5 (5)	14 (4.4)
Ointments, ophthalmic agents	3 (4)	1 (2)	2 (4)	0 (0)	3 (3)	9 (2.8)
Serums, toxoids, vaccines	2 (2)	3 (5)	0 (0)	0 (0)	9 (9)	14 (4.4)
Smooth muscle relaxants	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Vitamins	1 (1)	0 (0)	0 (0)	1 (4)	1 (1)	3 (0.9)
Radioisotopes	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (0.3)
Enzymes	0 (0)	1 (2)	0 (0)	0 (0)	1 (1)	2 (0.6)
Blood formation and coagulation agents	0 (0)	1 (2)	3 (7)	0 (0)	4 (4)	8 (2.5)
Blood derivatives	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (0.3)
Expectorants and cough preparations	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (0.3)
Other	5 (6)	6 (10)	3 (7)	0 (0)	10 (10)	24 (7.5)

SD = standard deviation.
*Except where indicated otherwise.
†For drugs with an estimated date of return to the market later than February 2, 2018, the end date was arbitrarily defined as February 2, 2018, for purposes of calculating the duration of shortage.
‡According to the classification of the American Hospital Formulary Service.

Figure 1.7 Drug shortage problem in hospitals in many countries
Taken from Videau *et al.* (2019b)

According to McLemon (2021), Switzerland's Hoffman-La Roche is the only Tocilizumab manufacturer. For Canadian residents to access Tocilizumab, the Swiss Company need to have produced and distributed sufficient batches of the medication. One can deduce that if one location is responsible for generating drugs for use by the entire country, the supply needs to be effective. Distributors need to have the necessary resources and capability to transport the drug from its manufacturing location to where it is required.

1.3 Challenges of drug shortages in the Canadian hospital pharmacies

According to Moosivand *et al.* (2019), some of the challenges affecting the pharmaceutical supply chain include legal, political, social, technical and political. Other challenges include production costs, compliance, and augmented generic competition. Moosivand *et al.* (2019) also opines that pharmaceutical companies also struggle with forecasting accuracy, customer satisfaction, and inventory levels, which also hinder the effective access to the necessary medication by their customers.

1.4 Literature analysis

Table 1.1 Literature analysis

Authors/Year	Title	Methodology	Approaches	Weakness	Strength
Videau *et al.* (2019b)	Drug shortages in Canada and selected European countries: A cross-sectional, institution-level comparison	Descriptive cross-sectional study	Evaluating one hospital in each of five countries such as Canada, Belgium, Spain, France, and Switzerland.	Could not provide comprehensive information about drug shortage in each of the countries because it only included data from one hospital in each country. Such an approach hinders the researcher from getting comprehensive information regarding drug shortage. One cannot take information from a single hospital to represent the general population. Therefore, it may be challenging to use the information about drug shortage from one hospital and use it as a representative of the entire country.	Succeeded in providing information from different countries regarding drug shortage in specific hospitals. One can use that information to deduce the extensive nature of drug shortage in various countries.
Shukar *et al.* (2021)	Drug shortage: Causes, impact, and mitigation strategies	Literature review	Narrative review	Does not have any new information because it is not based on the researchers' original research	

Continued on next page

Table 1.1 Literature analysis (Continued)

Authors/Year	**Title**	**Methodology**	**Approaches**	**Weakness**	**Strength**
Badreldin & Atallah (2021)	Global drug shortages due to COVID-19: Impact on patient care and mitigation strategies	Literature review	Narrative review	Does not contain any new information that could have been associated with original research.	Contains extensive information regarding the potential effect of drug shortages due to COVID-19 on patient outcomes. It also informs on the role of pharmacy policymakers and that of pharmacists in addressing this challenge.
Burbidge *et al.* (2001)	Drug design by machine learning: Support vector machines for pharmaceutical data analysis	Descriptive		It is limited to a specific target. Not everyone can understand because it uses terms and vocabularies that only people who understand machine language can understand the article.	It clearly shows the potential of the support vector machine (SVM) classification algorithm. It uses a mathematical approach to prove the SVM's superiority to additional machine learning techniques such as the MLP, the C5.0 decision tree, and RBF network.
Calatayud *et al.* (2018)	The self-thinking supply chain	Multi-disciplinary, systematic literature review	Narrative review	The target audience is limited to people who understand artificial-intelligence and the use of RFID technology.	Indicates how disadvantaged and poor countries can fully take part in global supply chains.

Continued on next page

Table 1.1 Literature analysis (Continued)

Authors/Year	**Title**	**Methodology**	**Approaches**	**Weakness**	**Strength**
Chen *et al.* (2021)	Drug shortage management: A qualitative assessment of a collaborative approach	Qualitative	Semi-structured interviews	-Probability of bias is high because the researchers led the focus groups with shortage approaches discussion and a list of probable resource ideas. -Community members were unfamiliar with drug shortage management. -Small sample size which could not represent rural hospitals.	Highly knowledgeable participants. -Participants' responses revealed massive problems associated with education and external communication.
Hoffman (2012)	The drugs stop here: A public health framework to address the drug shortage crisis	Literature review	Descriptive review	Does not present new information from original research.	The article fills the existing gap of having little information on drug shortage on the law review literature. The article thoroughly evaluates the origins and effects of the drug shortage issue and articulates a multi-layered solution.

Continued on next page

Table 1.1 Literature analysis (Continued)

Authors/Year	**Title**	**Methodology**	**Approaches**	**Weakness**	**Strength**
Sadraoui & Mchirgui (2014)	Supply chain management optimization within information system development	Literature review	Descriptive	Information is limited to information already in public and not new findings from a study that the authors conducted.	The simulation of the software indicated the effectiveness of forecast accuracy in enhancing control performance, thereby contributing to the supply chain's efficient management.
Zhang *et al.* (2020)	Factors associated with drug shortages in Canada: A retrospective cohort study	Retrospective cohort study	Evaluating the availability of prescription drugs in the market between 14th March 2017 and 12th September, 2018.	The method could only be effective if pharmacists entered the correct records regarding drugs in short supply. -Researchers did not have each DIN's utilisation data.	Findings are significant in showing the extent of drug shortage in Canada since 2017. -It also identifies factors leading to Canada's drug shortage.

1.5 Potential of using machine learning to deal with drug shortage

According to Castellanos & Journal (2019) machine learning can play a significant role in dealing with the drug shortage problem. Castellanos & Journal (2019) further opine that some companies such as Merck KGaAcontemplate employing machine learning and analytics to forecast and prevent medication shortage. According to Kavakiotis *et al.* (2017); Burbidge *et al.* (2001), machine learning entails the use of a scientific technology to allow machines to learn from experience. Kavakiotis *et al.* (2017), opine that scientists are using machine learning through biomarker identification to predict Diabetes Mellitus. Kavakiotis *et al.* (2017) declare that machine learning employs data mining methods, which identify risk factors that could define that an individual is at risk of getting diabetes. Based on the understanding that machine learning is applied in biotechnology, mainly in the detection and management of diabetes, there is a potential in the application of machine learning to detect and prevent drug shortage. Pharmacists can employ machine learning to determine probable medication that is highly likely to be in short supply based on specific patterns such as increased demand.

1.6 Supply chain optimization techniques

Calatayud *et al.* (2018); Kumar & Shoghli (2018), state that one of the most effective techniques of optimising supply chain processes is the establishment of effective communication between retailers and suppliers. In the medical field, such communication means that supplies would inform retailers of any issues associated with specific drugs. For example, one may argue that where effective communication exists, suppliers of Tocilizumab could communicate with retailers and pharmacists to inform them of the shortage to enhance proper planning.

1.7 Discussion

Even before the pandemic, Canada grappled with drug shortages (Videau *et al.*, 2019b). After the emergence of COVID-19, Canada still experienced drug shortage, although at a lesser state than previously did (Lau *et al.*, 2022). This new development could be attributed to the pandemic's effect on people's movement, thereby restricting the number of people who could access hospitals for the required drugs (Gaudette, 2020). Notably, policy makers in Canada have devised strategies of ensuring drug shortage is tracked effectively by demanding for the reporting of anticipated and actual drug shortages by manufacturers (Lau *et al.*, 2022). Furthermore, there is a need to continue employing the RO models to determine uncertainty and enhance coping with computational problems. Relevant stakeholders should embrace the Action "Medicines Shortages" which entail evaluation of disruptions in the manufacturing of medicines, disruptions in procurement and provisions, impact of drug shortages on healthcare system and patients, and clinic-pharmacological needs (de Miranda *et al.*, 2019).

1.8 Conclusion

The issues of drug shortage are global and may continue affecting the world if appropriate measures are not taken to remedy it. Sometimes, necessary ingredients to manufacture drugs are unavailable, thereby leading to drug shortages. In other instances, problems arise in the supply chain, limiting the availability of drugs, while sometimes; demand for a specific drug surpasses the available batches. The COVID-19 pandemic increased demand for specific drugs, leading to drugs shortage, although Canada, and major global regions were experiencing drug shortages before the pandemic. Various researchers have studied the drug shortage issue and there is potential in using machine learning to detect and address drug shortages.

CHAPTER 2

METHODOLOGIES

Our thesis presents the whole story of the drug shortage problem in the Canadian hospital's pharmacy supply chain from the comprehensive survey to a specific use-case to apply optimization and machine learning methods to mitigate the drug shortages. In this chapter, we present all the methodologies that are used in our thesis according to each contribution.

2.1 Introduction

Drug shortage is a global pandemic that many nations from the low middle and high-income countries experience. Therefore, several prior works focus on this problem to predict the future shortage, to analyze the reasons of this crisis, to manage and control the inventory system in order to mitigate the impact of drug shortage. In this thesis, we begin from the systematic literature review to a specific learning solution for avoiding the drug shortage situation.

Since our thesis covers from the comprehensive survey to a specific use-case application, published studies and other peer-reviewed articles will be used. The aim of the study is to use the research design approach with justifications to describe the link between what are the best methodologies as solutions and strategies to solve or mitigate drug shortages in Canada. According to Van Wyk (2012), a research design approach is the overall plan that is used to connect conceptual research challenges to the achievable and pertinent empirical investigation. Different logic studies are employed for different types of studies. The approaches to be discussed in this section include analysis approach, systematic literature review, optimization, simulation as well as machine learning.

As depicted in Fig. 2.1, we propose a systematic literature review in Chapter 3 where we use different methods to extract, analyze and compare drug shortage data. In Chapter 4, we continue with survey methods to draw a picture of the drug supply chain in Canada based on various search strategies. The literature review and survey chapters provide significant aspects and variables to help us build an inventory management optimization model in Chapter 5 in which we apply the combinatorial optimization method. To solve this proposed problem in an online fashion, we study a learning framework, reinforcement learning method.

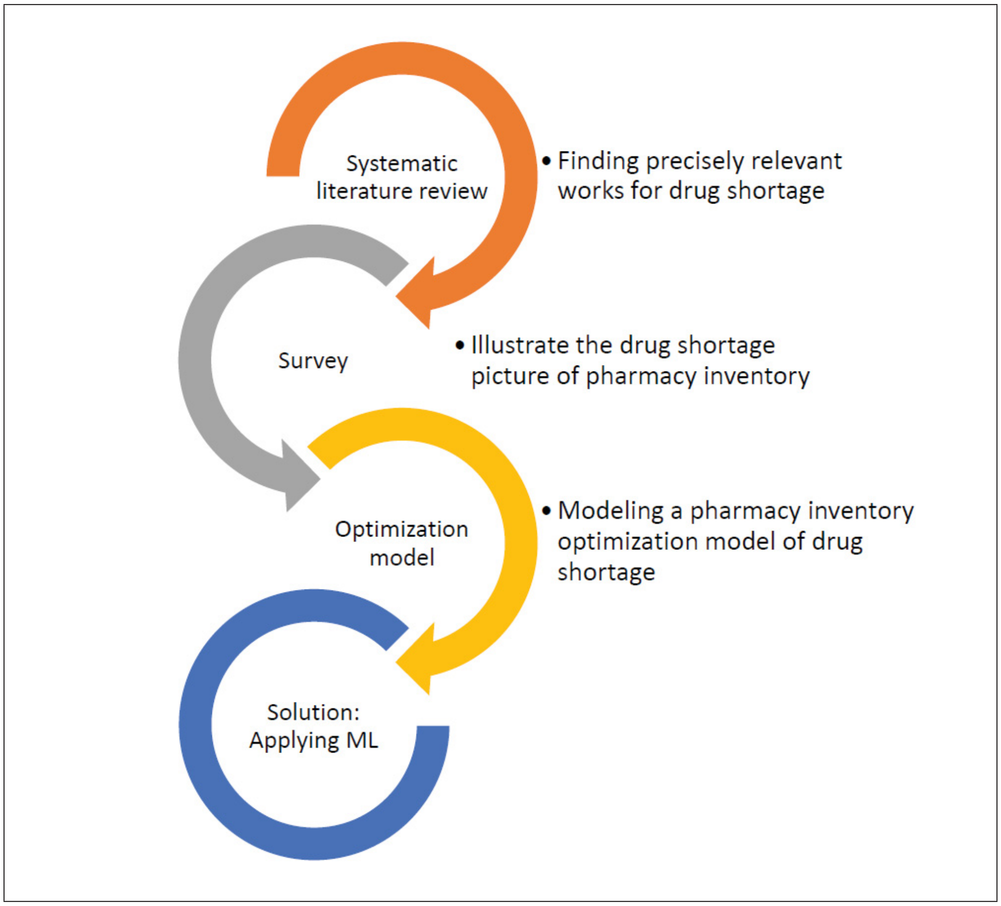

Figure 2.1 Summary of thesis methodologies

2.2 Analysis Approach

The analytical process of thinking and approach to solving problems involves the critical breakdown of the elements of a problem and determining the probability to solve it (Van Wyk, 2012). To mitigate the drug challenge in Canada, it is imperative to first assess, analyze and break down the problem into elements that can be solved easily. This includes breaking down the drug supply and management chain and systematically addressing the particular issues in each stage. For instance, analyzing and addressing problems facing the production of drugs and resolving labor conflicts that may hinder drug production and distribution (Shukar *et al.*, 2021). This can include finding trusted and reliable manufacturers and paying them accordingly so that they can deliver drugs on time and meet the rising demand. Below is the schematic representation of the drug supply and management in Canada.

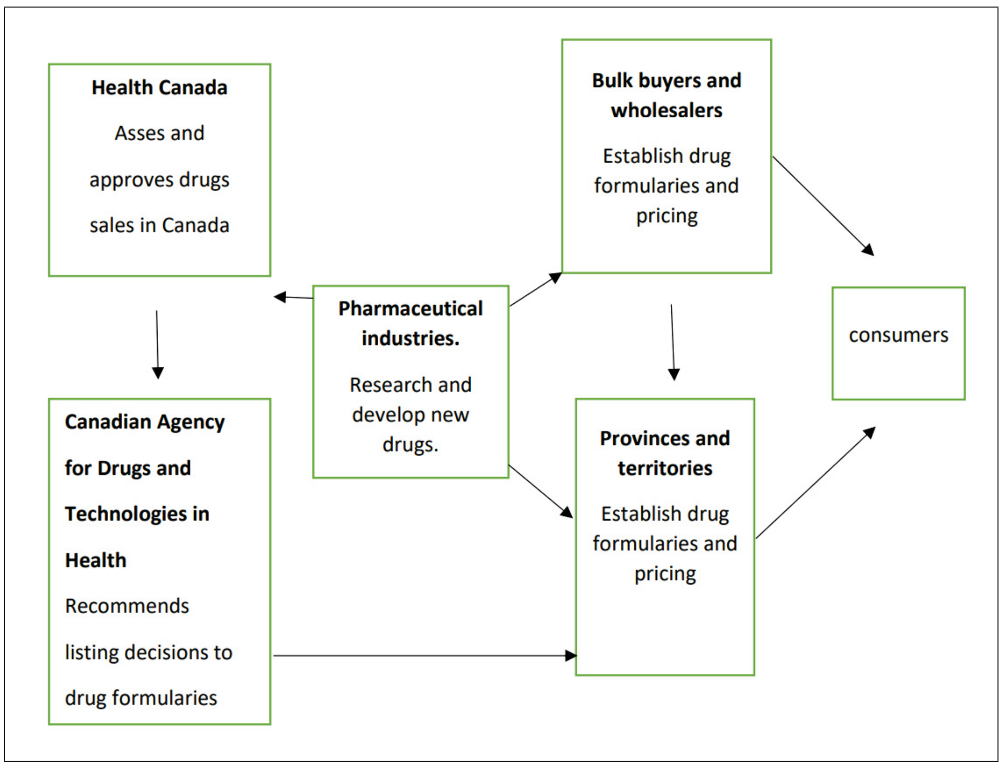

Figure 2.2 The schematic representation of the drug supply and demand management in Canada

2.3 Methodologies of the systematic literature review

In the systematic approach, drug shortages are managed by collection, analysis and summarization of the available literature and identifying the gaps in the drug supply chain. According to Offermann *et al.* (2009), systematic reviews can be used in problem identification as it specifies the literature question and verifies the practical relevance of the problem identified. Research, for instance, learning about the available drugs and the trends in pharmacy can help get other drugs that are substitutes to the current ones. According to AlAzmi & AlRashidi (2019), a robust system is critical for maintaining an effective and viable supply chain. Besides, in hospitals, systematic approach can be used reasonably by recommending alternative medication to the patients, contracting other suppliers with similar medication and updating the formula (Panic *et al.*, 2020).

When planning and implementing strategies to curb drug shortages in Canada, mathematical simulation models can be used to assess, analyze and predict the effects of the interventions to be implemented. Mathematical simulations can be used to manage the complex drug supply chains that are not only complex but difficult to manage due to the frequent disruptions that occur limiting drug access by various healthcare centers in Canada. To mitigate such disruptions, it is critical to use mathematical simulation to predict the consequences of product recalls taking into account various disruption profiles, such as the spread in space and time, and the options of decision makers on drug shortages to determine how these shortages might be reduced by altering inventory policy choices (Azghandi *et al.*, 2018). Additionally, simulations can be utilized to assess the impacts of various policy trajectories on supply chain disruptions using two performance indicators: inventory levels and product shortages at hospitals (Myers *et al.*, 2010). The efficient frontier (optimal inventory policies) is then characterized by variable cost ratios of the two performance measures as they correspond to the various disruption patterns by policymakers using a method akin to data envelopment analysis (Chen *et al.*, 2022). This analysis sheds light on what happens when an incorrect inventory policy is chosen in the presence of disruptions. A proper drug inventory is essential to manage medication due to the large amounts of drug data in most hospitals that are difficult to optimally manage.

2.4 Methodologies to formulate the Canadian hospital pharmacy inventory model

In Chapter 5, we aim to model the hospital pharmacy inventory system in Canada based on obtained knowledge in our previous survey. Although our proposed model could not cover every aspect, it is comprised of basic parameters and control variables to manage the inventory system. To do that, we use the combinatorial optimization method to model the system.

Finding the best solution from a finite set of objects is the objective of the branch of mathematics known as combinatorial optimization (Korte, Combinatorial Optimization), where the feasible solution is discrete or may be reduced to a discrete set. For example, the travelling salesman problem (TSP), the minimal spanning tree problem (MST), and the knapsack problem are well-known combinatorial optimization problems studied in the state of the art. Exhaustive search is frequently impractical to solve issues of this kind of problems, including those already described. As a result, approximation techniques or learning algorithms (Korte, Combinatorial Optimization) that quickly exclude significant portions of the search space must be used.

Combinatorial optimization has important applications in different areas such as AI, ML, network, software engineering, theoretical computer science. In the state of the art, combinatorial optimization has been widely used in supply chain optimization, logistics, invention problems. Several works consider discrete optimization as the combinatorial optimization problems, although they are closely intertwined. The main problem of the combinatorial optimization is the operational search that is related to the complexity theory.

There is a tonne of research on polynomial-time techniques for the particular combinatorial optimization class. It is mostly brought together by the notion of linear programming. Shortest routes and shortest-path trees, flows and circulations, spanning trees, matching, and matroid problems are a few examples of combinatorial optimization issues that are addressed by this approach. Recently, each basic problem has special heuristic algorithms to address. For NPcomplete combinatorial optimization problem, the current research focuses on polynomial-time solutions for special cases, approximation solutions that is close to optimal, and learn-to-optimize solutions that use learning methods to obtain near optimal solutions (e.g., RL to solve the TPS, or to mimics the behaviors of the branch and bound algorithm).

2.5 Background of combinatorial optimization method

Basically, a combination optimization problem P is comprised of a tuple (I, f, m, g) where:

* I : a set of instances;

* An instance $x \in I$ has a finite set $f(x)$ of feasible solutions;

* given an instance i, and a feasible solution y of x, we denote $m(x, y) > 0$ as the mesure of y;

* g is the objective function, which aims to maximize/minimize.

Hence, we have

$$m(x, y) = g\{m(x, y')|y' \in f(x)\} \tag{2.1}$$

It means that we aim to find an instance y' in the feasible solutions $f(x)$ to maximize/minimize the objective function $g(.)$.

2.6 Methodologies to solve the combinatorial optimization problem

For a particular combinatorial optimization problem, there is a corresponding decision problem. We can often easily find an initial feasible solution $m\{0\}$ to satisfy all the problem constraints but it is difficult to obtain an optimal solution in polynomial time. For example, in the knapsack problem, we can randomly pick items to fill into the knapsack depending on the remaining space. We can also sort the items based on their dimensions to have a good strategy to fill them into the knapsack. However, these heuristic algorithms in polynomial time do not guarantee an optimal solution.

The field of approximation algorithms deals with algorithms to find a near-optimal solution to hard problems. The usual decision version is then an inadequate definition of the problem since it only specifies acceptable solutions. Even though we could introduce suitable decision problems, the problem is then more naturally characterized as an optimization problem.

2.7 Machine learning methods to solve the combinatorial problem of the Canadian hospital pharmacy inventory problem

With the advent of technology, it is possible to use Artificial intelligence and the internet to manage drug supply and management (Zhu *et al.*, 2021). This is possible through the incorporation of technologies such as blockchain technology. According to Younis *et al.* (2021), blockchain technology can be incorporated into pharmacies to monitor the demand and supply of drugs across Canada as it can easily merge data and monitor the transit of medication from the producers to the consumers. In other words, a trustworthy legal defense for the delivery of medicinal drugs and their tracking could be provided using blockchain technology in pharmacies (Abbas *et al.*, 2020). Such a method could significantly simplify pharmaceutical product audit and control. Healthcare and pharmaceutical sectors can use blockchain to improve privacy and secrecy, expedite operations, increase the safety of patients and give clients better clinical treatment. Blockchain technology has the highest level of transparency, speed, and accuracy in dealings (Ada *et al.*, 2021).

In this thesis, we apply the reinforcement learning method to solve the proposed optimization model. Based on the current supply inventory situation, such as price, remaining drugs in the store, and the amount of demand, we use the Markov decision process (Howard, 1960) to model the state of the system. An agent of the learning model can will make inventory decisions to optimize the cumulative reward.

2.8 Summary of the proposed thesis methodologies

The proposed research methodology will involve carrying out a descriptive study for the drug shortages during certain time in the Canadian hospitals, next a systematic literature review will investigate more issues and what are the most critical factors influence drug shortages, eventually an optimization model will be proposed to mitigate this problem which is exist in many levels of the supply chain including the inventory management issue that has high affect in drug shortages. According to Mousazadeh *et al.* (2015), the pharmaceutical supply chain network design is a complex optimization problem. Therefore, to ensure effective and efficient supply along the network, several criteria and factors should be considered. Mousazadeh *et al.* (2015) argues that both the demand coverage pattern and supply facility locations should include a number of factors such as reliability, accessibility and capacity of supply facilities (Myers *et al.*, 2010). The proposed model will help hospital pharmacies make best decisions regarding the location of pharmaceutical supply facilities and demand coverage pattern.

More precisely, this methodology will involve three main phases as shown in Fig. 2.3. In Phase 1, we describe the research study of the drug shortage in Canadian hospital pharmacy. we collect relevant data to analyze. Based on this result, we propose the systematic literature review in phase 2 in which we define search procedure, and search terms to obtain an optimal review. We also use this systematic literature review present challenges, and aspects of drug shortage in Canada. Both phase 1 and phase 2 provide a foundation and motivate us to model a drug-shortage inventory management model to mitigate the shortage situation in Phase 3. We use a methodology of combinatorial optimization and a learning solution to address it. Specifically, deep reinforcement learning method, which is based on Markov Decision Process (MDP), is used to address the proposed optimization problem in an online fashion.

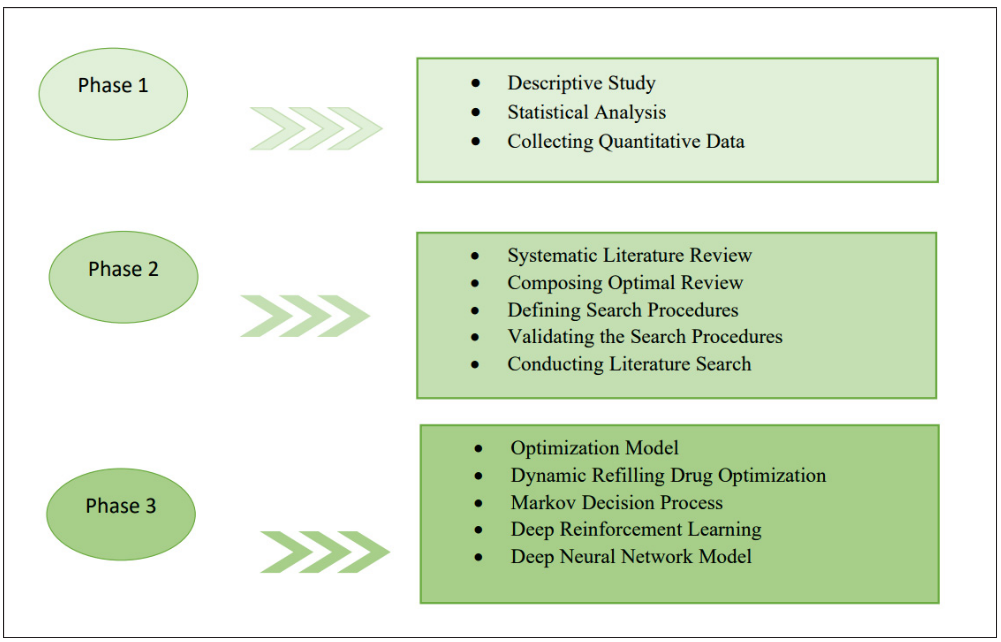

Figure 2.3 Research Design

CHAPTER 3

ANALYSIS OF DRUG SHORTAGE IN CANADA FROM 2016–2021

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Abstract:

Researchers consider drug shortages to be a complicated issue worldwide, with various causes that include an unforeseen increase in demand, trouble obtaining direct raw materials or labor, sudden production problems, and sole sourcing.

Aim The general objective of this study is to describe Canada's drug shortage situation between January 2016 and January 2021 and to elaborate on the issue of shortages during the COVID-19 global pandemic. Therefore, the aim of this study is to quantify the number of drugs in short supply per annum and the period of these drug shortages, and to address this knowledge gap. The secondary objective seeks to describe the number of drugs in short supply by therapeutic class and manufacturer.

Subject and method Many indicators point to the growing need to focus on drug shortages in Canada and the world at large. Although the drug shortage problem affects every life of clinicians and patients, there is paucity of literature specifically describing the experienced problems and their clinical consequences. A descriptive statistical analysis on publicly available data on reported drug shortages from pharmaceutical companies in Canada, moreover, the quantitative data was collected from McKesson Canada, one of Canadian drug wholesalers, and the official Drug Shortages Canada website.

Results and conclusion The findings show that the country has encountered more than 3123 shortages at national level. The leading shortages were from the central nervous system drugs remain the largest category of the period starting from 2016 to 2019 and another shortage during pandemic to reach 2436 drug shortages. The study reveals that drug manufacturers in Canada have continued to record increasing drug wastages between 2016 and 2021. Besides knowing the sources of wastages in the country, both policy makers and manufacturers lack powers to reduce wastages at the national level.

Keywords: Drug Shortages; Manufacturer; Inventory Shortage; Hospital; COVID-19.

3.1 Introduction

A drug shortage is defined as a situation in which a drug maker is unable to meet the demand for the medication. Researchers consider drug shortages to be a complicated issue worldwide, with various causes that include an unforeseen increase in demand, trouble obtaining direct raw materials or labor, sudden production problems, and sole sourcing (Tucker *et al.*, 2020; Videau *et al.*, 2019a; Zwaida *et al.*, 2019). The consensus among health professionals is that the global COVID-19 pandemic has worsened the drug shortage concerns (Bookwalter, 2021). Like most industrialized countries, Canada requires that pharmaceutical companies declare any foreseen and actual shortages to the relevant regulatory bodies (Videau *et al.*, 2019b). We can adapt this data to carry out a descriptive statistical analysis of drug shortages in Canada.

Since 2010, Canadian pharmacists, physicians, and patients have been wrestling with shortages in drug supply, primarily for generic drugs (Donelle *et al.*, 2018), which account for 70% of Canadian prescriptions. Although the drug shortage problem affects every life of clinicians and patients, there is paucity of literature specifically describing the experienced problems and their clinical consequences, as pointed out by (, FIP; Canada, 2019a; Videau *et al.*, 2019b). To address this knowledge gap, the general objective of this study is to describe Canada's drug shortage situation between 2016 till 2021, and subsequently discuss this concern in the Canadian context. The findings are expected to inform effective operational management of Canada's pharmaceutical system, especially hospitals' procurement and inventory management units.

The study will help managers in planning and monitoring activities associated with procurement and inventory management of essential drugs (medicines), critical actions to enhance the availability of drugs and hence, positive health care outcomes. The study will serve as a platform where health care professionals and policymakers can discuss, plan and effectuate measures to facilitate the management of current problems, predict and tackle future drug shortage problems in Canada. Moreover, the findings of this study will help the relevant agencies in making informed strategic decisions about pharmaceutical manufacturing and distribution centers. Quality of health care is ultimately expected to improve as is the utilization of public care facilities by health care clients.

The scientific contribution of this paper is extensive; it provides a qualitative analysis on the nature, causes, and effects of medical shortages across the country and allows for the data to further the field of study by examining a previously unexplored area. Providing this data will further our knowledge of medical shortages within Canada by categorizing and analyzing the information in a single place. Moreover, it examines a time period previously unexamined by other studies.

3.2 Literature Review

Medicine shortage, according to the (, FIP) is a drug supply issue influencing patient care, and thus requires a change using an alternative agent. Fox *et al.* (2009a); Fox & McLaughlin (2018) describes a drug product shortage a supply issue that informs how the pharmacy dispenses or prepares a drug product(s) or affects patient care when prescribers have to use an alternative agent (Ventola, 2011). This description shows Health Canada's definition of drug shortage as a scenario in which a drug authorization holder is not able to meet the demand for the drug. Videau *et al.* (2019b) point out those drug shortages can include permanent or temporary disruptions in the generation and supply of a drug. Drug shortages are recognized by researchers and medical practitioners alike as a potential threat to public health. It can result to adverse delay or compromise medical procedures and drug therapy in addition to resulting in medical errors, delayed supply, rationing, and sometimes denial of treatment (Fox & McLaughlin, 2018; Fox & Tyler, 2003; Lynas, 2013; Postma *et al.*, 2018; Vaillancourt, 2012). As of March 25, 2019, Health Canada sees drug shortages as a complicated global concern, with various causes, including but not limited to sole sourcing, production problems, challenges in acquiring raw materials and a rapid increase in demand for a specific drug. Many indicators point to the growing need to focus on drug shortages in Canada and the world at large. For instance, 70 to 115 articles published with the key word “drug shortages” were indexed in PubMed, a free engine to search MEDLINE database, since the year 2011, relative to 24 to 30 per annum for the period between 2002 and 2010 and less than 10 per annum prior to 2002 (Videau *et al.*, 2019b). Most regulatory authorities such as (, EMA; Canada, 2019b; Food & Administration, 2018; Fox *et al.*, 2009b; Pauwels *et al.*, 2015) have created specific pages of their web portals dedicated to the drug shortages problem. Furthermore, many countries, such as France, the US and Canada since 2017 (Pauwels *et al.*, 2015), demand a declaration of anticipated and actual drug shortages to the pertinent regulatory authority (Jensen *et al.*, 2002; Videau *et al.*, 2019b).

Even before the outbreak of COVID-19, Drug shortages have been an ongoing issue for the medical community for decades (Fox & Tyler, 2003; Phuong *et al.*, 2019). Several empirical studies focused on the cause of drug shortages have reported one or more causes (Tucker *et al.*, 2020; Videau *et al.*, 2019b). They can be classified into either 1 proximate, 2 capacity and supply chain dynamics, 3 regulation, and 4 economic factors. However, in most cases, the root causes of short supply remain unknown or go unreported mainly because of the proprietary implications of drug manufacturing (Videau *et al.*, 2019b).

A systematic review by Bookwalter (2021) confirms that the global pandemic has exacerbated drug shortage concerns. Drug manufacturers will often adhere to standard business practices that allow them to make a profit. Researchers have consistent evidence that pharmaceutical companies typically operate on a just-in-time model and manufacture products when there is demand for it to keep costs down and remain efficient (Bookwalter, 2021; Sen-Crowe *et al.*, 2021; Socal *et al.*, 2021) If there is a disruption to supply or a surprising demand, then a shortage can occur (Acosta *et al.*, 2019; Badreldin & Atallah, 2021).

A great deal of anxiety is provoked among patients who are unable to access trusted medications for chronic conditions as a result of drug shortages (Barthélémy *et al.*, 2013). For the health care team and pharmacists, shortages in drug supply often demand frustrating and time-consuming searches for alternatives (Bochenek *et al.*, 2018; Yang *et al.*, 2016). For patients, shortages result in the harm and stress of delayed treatments and surgeries (Barthélémy *et al.*, 2013; Hall *et al.*, 2013; Morgan & Persaud, 2018). For governments and policymakers, they skyrocket healthcare expenditures to obtain the limited products or innovator substitutes or their replacement from other sources (Donelle *et al.*, 2018; Liang & Mackey, 2012; Vaillancourt, 2012).

Drug shortages, according to the Organization *et al.* (2016), are becoming, if not already, a complex global problem. It a product of many factors including but not limited to challenges in acquiring raw materials (AlRuthia *et al.*, 2017; Berry, 2014; Bochenek *et al.*, 2018; Holm *et al.*, 2015; Lukmanji *et al.*, 2018; Abu Zwaida *et al.*, 2021b), regulatory issues and manufacturing problems (Fox *et al.*, 2009a; Fox & Tyler, 2003; Phuong *et al.*, 2019) as well as many other disruptions along the supply chain (Postma *et al.*, 2018; Abu Zwaida *et al.*, 2021b). Countries across the globe have reported shortages in drug supply and subsequent problems that affect both developed and developing countries (De Weerdt *et al.*, 2017b).

Drug shortages occur at an alarming rate in Canada. Association *et al.* (2010) conducted a survey in 2010 of 427 pharmacists. Their finding suggested that shortages in drug supply had significantly increased in the previous 12 months, as reported by 89% of the respondents (Association *et al.*, 2010). Furthermore Lukmanji *et al.* (2018); Lynas (2013), pointed out that in 2012, another national European compromising of 1070 members of the Canadian Society of Hospital Pharmacists and Canadian Medical Association CSHP and CPhA corroborated this finding, revealing that there was a further increase in drug shortages since 2010, according to 66% of the respondents. Similar results were also observed in the US which registered a 435% (from 23 to 123 drugs) increase in the prevalence of emergency medicine drug shortages between 2008 and 2014 (Hawley *et al.*, 2016). Canada experienced a serious shortage of the level 1 critical antiepileptic drug (AED) clobazam, a shortage that lasted between May 2016 and October 2016 (Association, 2010). The result of this shortage was complete clobazam depletion in most parts of the country (Lukmanji *et al.*, 2018). The root of this shortage, according to Lukmanji *et al.* (2018), was multifactorial such as changes in quality standards, shortage of active ingredient and increased clobazam. Patients suffering from epilepsy can, for example, face treatment interruptions as a result of shortages. Based on the proof from non-adherence studies (Hovinga *et al.*, 2008), treatment interruptions can cause increased seizures or relapse of epilepsy that was previously well-controlled.

When there are shortages in drug supply patients are often subjected to a situation where they cannot refill their full drug prescription. This necessitates or increases the demand for more frequent refilling (Bussières *et al.*, 2011; Fleet *et al.*, 2015; Lukmanji *et al.*, 2018; Zwaida *et al.*, 2019). Not only do drug shortages impact patients' physical and mental health, but also subject health care professionals to a situation characterized by lack of, inadequate if any, information on drug shortages, and the urgent need to find appropriate solutions. This causes pressures on both hospital and primary care, as had long been observed by McCartney (2015), as well as cost increases (Bussières *et al.*, 2011; Lücker & Seifert, 2017; Tucker *et al.*, 2020).

In any health care system, drugs are considered as strategic products. It is for this reason that the public regulatory authorities (Zu'bi & Abdallah, 2016) highly regularly and tightly control drugs. Protecting the integrity across the pharmaceutical supply chain requires regulatory frameworks to cover many operational areas to ensure both quality and successful product manufacturing while also maintaining oversight on drug distribution system, as pointed out by (Bussières *et al.*, 2011; Fink, 2016; Zu'bi & Abdallah, 2016). Despite such, however, government regulations can result to shortages in drug supply because of stringent quality requirements, which McKenna (2011); TOSCHI (2017) perceive as costly and major constraints from wholesalers and manufacturers perspectives. Increased government oversight to ensure quality assurance reflected in far-reaching regulations about good manufacturing practices and quality control issues result in increased costs and time to supplemental applications, approval decisions and approval of new facilities' processes due to risk mitigation (Zu'bi & Abdallah, 2016). In this view, manufacturers see regulation as working to limit their capacity to create reliable production schedules, which according to De Giorgi *et al.* (2018); Fleet *et al.* (2015); Gulbis *et al.* (2013); Ventola (2011) insufficient resources and internal policies could compound. Therefore, it would be important to assess how legislative and regulatory processes affect drug shortages in Quebec.

Canada has a complex drug supply chain, with different roles and responsibilities among various players including governments, health care practitioners, hospitals, wholesalers and manufacturers. Shortages in drug supply can occur at any point within the drug supply chain. Azghandi *et al.* (2018) observed that just like other supply chains, pharmaceutical supply chains are exposed to disruption risk. Because of shortages in drug supply in a product in one or many disruptions within the pharmaceutical supply chain, other researchers, including Gu *et al.* (2011) has expressed their doubts on whether it can be possible to prevent disruptions.

Drugs can be recalled for varying reasons such as defects in the container, defective products or mislabeling (Azghandi *et al.*, 2018). The occurrence of a recall in the pharmaceutical supply chain removes the inventory of some, if not all, members of the supply chain. Beyond recalls, Azghandi *et al.* (2018) noted that the temporary manufacturing plants shut down for some period can also befall pharmaceutical supply chains. One of the researchers' major challenges is to design a supply chain that is resilient enough to withstand different types of disruptions (Azghandi *et al.*, 2018). This leaves a research gap that scholars in supply chain risk management need to address. Lücker & Seifert (2017); Abu Zwaida *et al.* (2021b) suggested keeping more inventory one of the solutions to avoiding shortages because this ensures the availability of more inventories to treat patients even in the event that drugs are recalled. Azghandi *et al.* (2018); Engelberg *et al.* (2016); Tucker *et al.* (2020); Abu Zwaida *et al.* (2021b), however, contend arguing that holding more inventory only results in additional costs incurred in the supply chain, and as such, may not be attainable for most health care centers because of budget and storage limitations. Considering the need to balance the costs and benefits of retaining inventory, it is become more important to have strategic decisions regarding inventory policies along the supply chain. Furthermore, in their study aimed at describing and finding a model for Quebec's challenging biomedical specimen transportation. Anaya-Arenas *et al.* (2014) found that the province currently has a decentralized supply chain design current supply chain with independent decisions made on each laboratory and pharmaceutical departments about the required and used transportation services. The current design, thus, does not recognize the uncertainties on the demand and supply sides, the consequence of which is shortages in drug supply. Beyond resulting in management issues, such shortages oncology, inpatient pharmaceuticals, and injectable drugs account major clinical risks including medical errors and forced withdrawal from critical medical surgeries, according to (Anaya-Arenas *et al.*, 2014).

3.3 Methodology

The paper proposes a generalized methodology for analysis of drug shortage in Canada. This methodology can be processed for any given duration. However, for sake of proof of concept, the duration of the study has been selected as recent years from 2016 – 2021. The outcome of the study includes: the type of drugs in a short supply, the period of shortages, as well as the shortage during the pandemic of COVID-19. Meanwhile, the outcome of this research study is to address the knowledge gap in both types and duration of the drug shortages in Canada.

It can be seen in the figure 3.1 a flow diagram of the proposed methodology for analysis of drug shortages in Canada. In this research, the duration of the study has been selected for 2016-2021.

As the main target for this analytical research paper is to focuses on drug shortage data available within the period between January 1, 2016 and January 31 2021. This 73-month period is targeted primarily as a follow-up to some previous studies (Bussières *et al.*, 2011; Tucker *et al.*, 2020; Videau *et al.*, 2019b), which analyzed drug shortage in Canada during specific time as shown in figure 5.

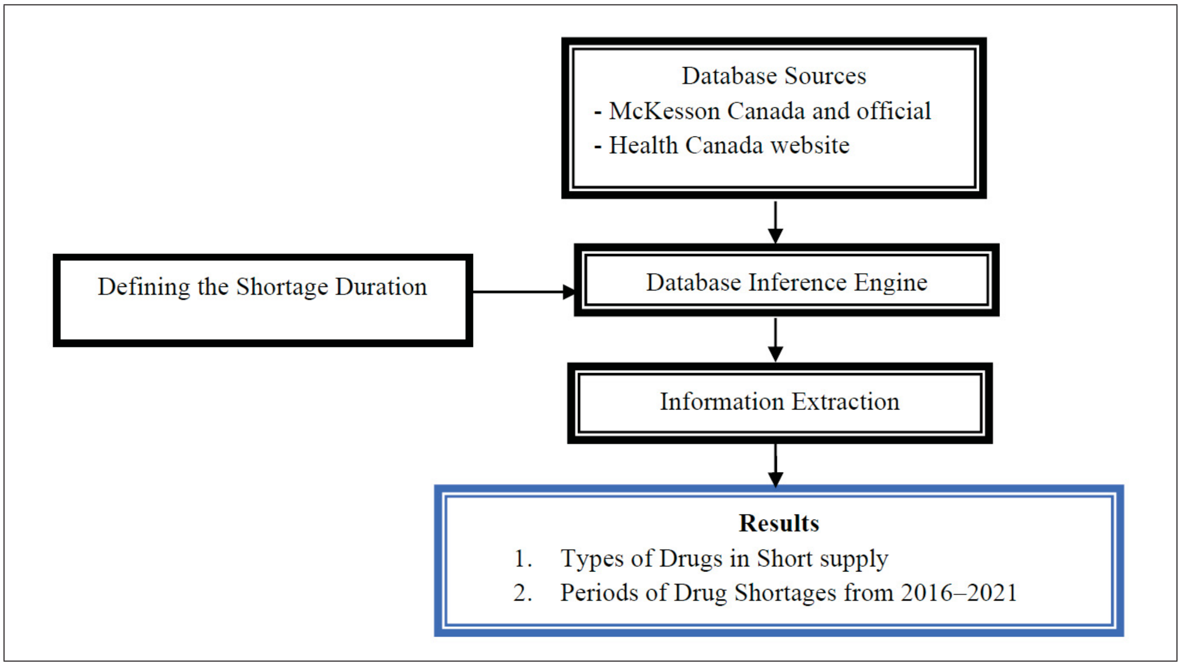


Figure 3.1 Generalized Flow Diagram of the Proposed Study Analysis

3.4 Data Sources and Extraction:

In this research paper, the data was collected from McKesson Canada, one of the major drug wholesalers for healthcare facilities in Canada. Its official Health Canada website designed to record drug shortages. McKesson, in addition to its position as a major drug wholesaler, covers a wide geographical range with thirteen distribution centers across seven provinces in Canada. Therefore, its data can provide a representative of the situation in Canada (This is why I chose McKesson over other companies. Health Canada website for reporting drug shortages is another credible information source about Canadian drug shortage situation in light of the fact that anticipated and real drug shortages are reported to the relevant regulatory authority, as asserted by (Videau *et al.*, 2019b).

Several records in each of the databases may represent a shortage in drug supply for a specific product. For each drug product in short supply, the researcher identified the dates when the shortages started and ended where the end date is either the date of withdrawal from the market or return to stock. Notably, the actual start and end dates of the drug shortage was used only when known. The duration of the shortage would otherwise be calculated by using the approximated date when the shortage started and the time it took to return to stock. For drugs products with an expected return date on market after August 31, 2019, the end data is arbitrarily set as August 31, 2019. Moreover, for each drug product in short supply, the researcher identified the manufacturer, the manufacturer type (generic or innovative), the therapeutic class as stipulated by the American Hospital Formulary Service clarification and the administration route (parenteral or otherwise). Information regarding the cases of drug shortages, when known, was collected using the Canadian drug shortage database.

For every drug that was in shortage for example, the study considered the manufacturer of the drug as well as the nature of manufacturer whether it was generic or innovative. Other factors of consideration included looking at the therapeutic category (according to the classification provided by the America Hospital Formulary Service classification as well as the route of administration whether it is by the parental or otherwise. In case it is known, the study went ahead to collect information concerning what causes shortages in drugs. The data was collected from the Canadian drug shortage database because McKesson database failed to store such information.

3.5 Data Analysis

From the descriptive study, it can be observed that several drugs are in short supply in Canada. It is interesting to note that even some of the drugs, which can be considered ‘common’ such as the anti-nauseates are no longer being supplied after their supply, were discontinued. This statement means that the drugs remain ‘unavailable’ in pharmacies and hospitals, which can highly affect patients. Notably, the health sector in Canada seems to be in jeopardy because there seems to be no solution for the discontinued supplies.

Additionally, it can also be observed that patients ailing from diseases of the central nervous system suffer most because drugs, which could otherwise have assisted them, are in short supply.

Furthermore, drugs associated with cardiovascular ailments are also in short supply and this can greatly affect the health status of people.

3.6 Results

n this research paper, there are two periods of drug shortages, starting from 2016 to 2019, which show specifically two different data bases, one from Canada drug shortage database and the other one is from McKesson Company Database. Whereas the other period covers 13 months during the COVID-19 pandemic, in which the data was extracted from Canada drug shortage data base in general.

It can be seen from the Figure below the drug shortage issue in Canada by brand between 2016 and 2019 from the drug shortage Canada website database and McKesson Database, which shows the fluctuation numbers in the years between two categories.

According to the table above, an additional data from the McKesson database also indicates drug shortages in Canada. From a list of about 2,129 shortages, shortage for drugs for the central nervous system was at 26.4%, cardiovascular drugs shortage was at 12%, anti-infective agents at 11.2%, gastrointestinal drugs at 7.9% and 7.4% for antineoplastic agents.

The following table shows the percentage of the drug shortage in Canada between 2016 and 2019.

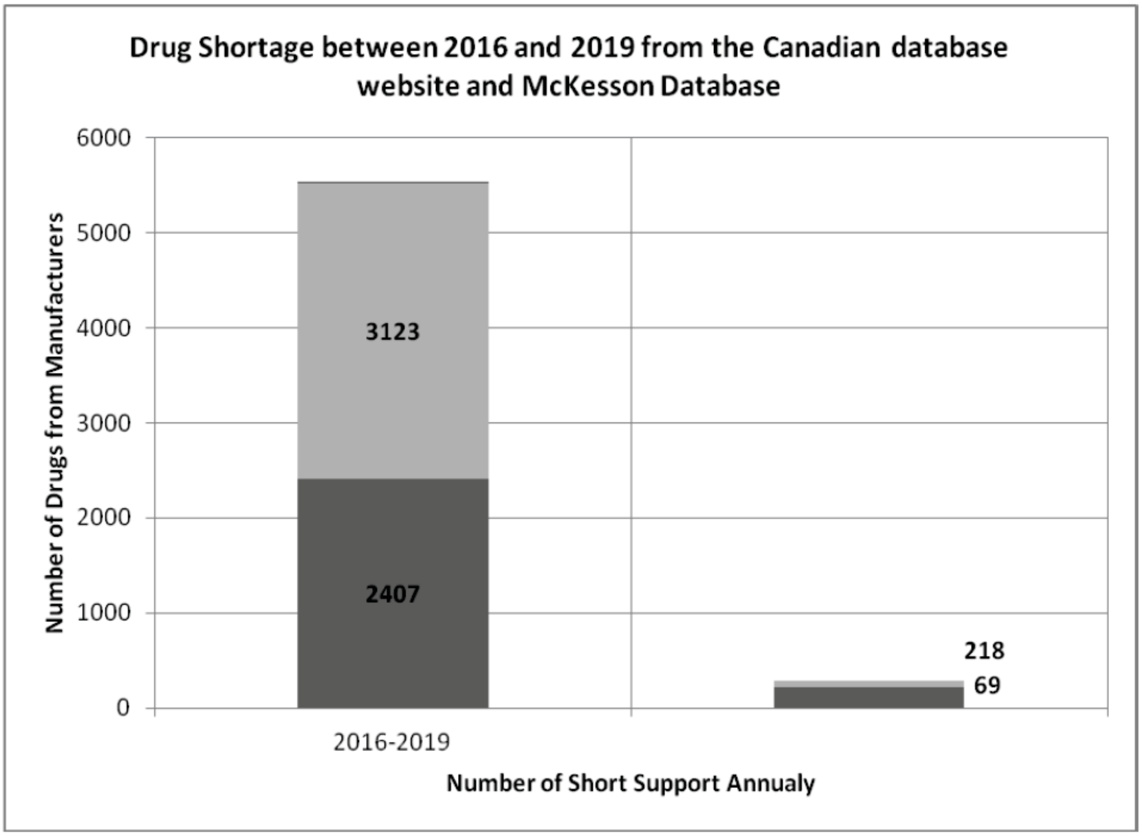
The McKessson database indicated a total shortage of 26.4% in the central nervous system over a period between 2016 and 2019. While on the other hand, the Canadian drug shortage database showed that we had a total of drug manufacturer at 43 with McKesson averaging 68 within the Canadian drug shortage. More important, it is apparent that a majority of suppliers included generic drugs. For example, McKesson accounted for 84% while the shortage database accounted for 80%. Furthermore, 24% (151/582) for all the shortage within the Canadian database. All the products were being used for parental products. Even though it is understandable that a majority of the products were affected by shortages, the central nervous system drugs remain the largest

Table 3.1 Drug shortage by brand between 2016 and 2019 from the Canadian database website and McKesson Database

Variable	**Drug Shortages Canada Website Database 2016-2019**	**McKesson Database**				
		2010-2011	2015-2016	2016-2017	2017-2018	2018-2019
Number of drugs in short support annually	3123	429	483	583	612	729
		Total from 2010 till 2019 = 2836				
Number of drugs from manufacturers	69	41	40	43	56	79
Duration of drug shortage (days, mean)	134	103	172	160	172	183
Duration of drug shortage (days, media)	90[3,865]	Not determined(ND)	112[6,880]	93[3,1235]	ND	ND
Central nervous system drugs	801(31.9)	104(24.2)	108(22.4)	154(26.4)	166(27.4)	171(29.5)
Cardiovascular drugs	655(21.9)	44(10.3)	59(12.2)	70(12.0)	75(10.4)4	82(14.0)
Anti-infective agents	189(8.4)	69(16.1)	59(12.2)	65(11.2)	69(10.2)	71(13.2)
Gastrointestinal	142(6.6)	31(7.2)	13(2.7)	46(7.9)	49(8.9)	87(6.9)
Antineoplastic agents	120(5.2)	31(7.2)	21(4.3)	43(7.4)	48(8.4)	54(6.4)
Electroltic, caloric and water balance	89(4.8)	29(6.8)	37(7.7)	34(5.8)	34(5.8)	34(5.8)
hormones	86(4.1)	31(7.2)	22(4.6)	38(6.5)	58(7.5)	64(6.5)
Skin and mucous membrane preparations	70(3.8)	16(3.7)	33(6.8)	34(5.8)	43(5.8)	66(5.8)
Automic drugs	66(3.2)	22(5.1)	23(4.8)	26(4.5)	26(5.5)	26(6.5)
Others	47(2.4)	8(1.9)	15(3.1)	10(1.7)	10(1.7)	11(1.8)

Table 3.2 Percentage of drug shortage in Canada during 2016 till 2019

Drugs	**Percentage of drug shortage**
Central nervous system drugs	26.4%
Cardiovascular drugs	12%
Anti-infective agents	11.2%
Gastrointestinal drugs	7.9%
Antineoplastic agents	7.4%



Canadian Drug Shortage Website database	3123	69
McKesson Database	2836	218

Figure 3.2 Drug Shortage between 2016 and 2019
from the Canadian database website and McKesson Database

category of the period starting from 2016 to 2019. Other drugs in shortage included those used for the purposes of cardiovascular (12%), anti-infective agents (11%), gastrointestinal drugs (8%), and antioplastic agents (7%).

Drugs shortage in Canada cannot be categorized as challenge facing only the few existing drug manufacturers. It is a problem facing the pharmaceutical sector. There are several reasons for this shortage. A large percentage of about 85% has been caused by many reasons such like late shipments, excess demand and disruptions during manufacturing. These shortages are

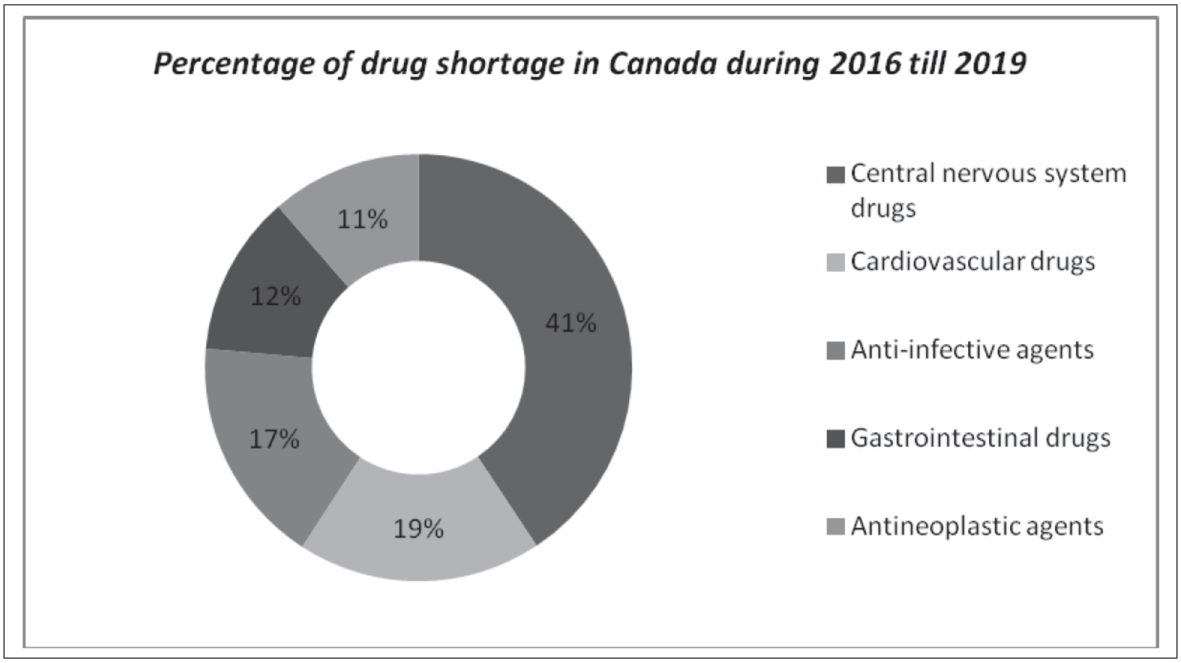


Figure 3.3 Percentage of drug shortage in Canada during 2016 till 2019

basically caused by forces of demand supply. There are several causes, first is the relocation of the production services; second is the unfavorable structure of the pharmaceutical market; third is the challenges that associate with supply and demand; fourth is the legal frameworks that limits the operations of their pharmaceutical industries; fifth is the presence of sudden fluctuation in demand, revisiting of the drug downward reimbursement rules; and the sixth cause involves mergers by manufacturing and anticipation of certain things in the international market.

The limited number of pharmaceutical companies and the size of the market have led to limited sources of drugs in Canada. Due to this, some countries have undertaken some policies to deal with the shortage of drugs nightmare. They have put in place legal policies for the manufacturers and distributors to avoid shortage of drugs. Countries have put in place drug shortage management plan. A good example is France, when there is a shortage of certain drugs such drugs cannot be exported to foreign countries at all. Canada lacks such measures.

Even if such measures are undertaken, lack of transparency among the pharmaceutical manufacturers will hinder the anticipation of any shortage. For example, pharmaceutical industries are not allowed to give any information about the production sites of certain drugs. This makes it a hard task to come up with virtual models, which can help in forecasting any scarcity of drugs. The public does not know issues of drug, only a few scenarios are publicized via media. The Drugs Strategic Plan has helped has played a big in preventing drug shortages. In recent past, the body has actually saved the country from facing a drug shortage of about 280 drugs. It has accomplished this by notifying other companies increase production, importing drugs, reviewing the strategic plans of manufacturing companies among others. Canada should undertake similar measures undertaken by the US Food and Drug Administration FDA (2018) in order to deal or prevent any drug shortage in the country.

3.7 Drug Shortages in Canada during COVID-19 Pandemic:

In order to conduct this study during the current situation of COVID-19, the researcher adapted a data set that is regularly posted on the official Health Canada drug shortages website. Overall, there is a big interest in resolved or ongoing shortages on record and ignored ones that were anticipated or avoided. The study focused on drug shortage reports from January 1, 2020, to January 31, 2021, which would allow us the data over the targeted period of 13 months. For each reported shortage, we identified the reason for the shortage, the manufacturer and their type (generic or innovative), the drug dosage form, and the status of the shortage (actual shortage or resolved). The duration for each drug's lack of supply was calculated using the actual start date and actual end date when present. If the two dates were not present, the anticipated start and end dates were used to approximate the shortage duration. We also identified their therapeutic class for each drug shortage using the Anatomical Therapeutic Chemical (ATC) classification code under the WHO Collaborating Centre for Drug Statistics Methodology. Furthermore, the data was analyzed, and the total number of drugs in shortage was also calculated during the 13 months, the proportion of drugs in shortage by reason, the proportion of drugs in short supply from generic and innovative drug companies, the average duration of shortages, the proportion of drugs in shortage by dosage form (tablet, solution, capsule, powder, and others) and the proportion of drugs in shortage by therapeutic class. Given the chronological nature of the data, it was also possible to analyze the monthly numbers of drugs in short supply and the duration of drug shortages for the 13 months. We should note that only descriptive statistical analysis was performed during the study.

Thus, as a result from this study, the data from the official Health Canada drug shortages reporting website showed a total of 2,436 drug shortages, averaging 77 (standard deviation [SD] = 104) days. The median duration of drug shortage was 45 days with min-max short supply duration of 0-1827 days. Overall, the number of drug companies with at least one drug shortage within the 12 months was 105 on the official drug shortages website. The majority of drugs in short supply were from generic drug manufacturers (79.8%). Sixty-one percent (1,501/2,436) of the reported shortages were caused by disruption of the drug's manufacturer. Other prominent reasons for drug shortages were demand increase for drugs (14.4%), delays in shipping the drugs (13.2%), other or unspecified (6.2%), reasons related to compliance (2.1%), shortage of an active ingredient (1.4%) and shortage of an inactive component (1.0%). We found at least one drug shortage for each therapeutic class in the WHO's ATC index. The leading classes identified from the analysis were central nervous system agents (26.8%), cardiovascular drugs (23.0%), anti-infective agents (7.9%), dermatological agents (7.2%), and gastrointestinal drugs (6.9%). A majority of shortages affected drugs in tablet form (57.5%), followed by solutions (14.4%), capsules (12.7%), other (10.3%), and powder (5.0%). The top 10 drug companies with drugs in short supply during the period under study were Teva (24.0%), Apotex (13.8%), Sandoz (6.7%), Auro (4.5%), Taro (4.1%), Pfizer (2.5%), Mylan (2.3%), BGP pharma (2.1%), Sanis (2.1%) and Ranbaxy (1.9%).

3.8 Discussion

In this descriptive study, we characterized drug shortages across Canada 5 years between 2016 and 2021. Meanwhile including the COVID-19 period starting from January 2020 till March 2021.

Table 3.3 Drugs in Short Supply by Therapeutic Class

Therapeutic Class	**Number of Drug Shortages**	**Proportion of Drug Shortages**
Central nervous system agents	652	26.8%
Cardiovascular drugs	561	23.0%
Anti-infective agents	192	7.9%
Dermatological (skin) agents	176	7.2%
Gastrointestinal drugs	168	6.9%
Genitourinary (genital and urinary tract) agents	127	5.2%
Antineoplastic and immunomodulation drugs	123	5.0%
Blood and blood forming products	99	4.1%
Hormone based drugs	76	3.1%
Musculoskeletal system drugs	74	3.0%
Respiratory tract drugs	69	2.8%
Sensory organ drugs	63	2.6%
Other	50	2.1%
Antiparasitics	6	0.2%

According to calculated drug shortages, the majority of them were in April 2020 (306), March 2020 (282), and January 2020 (264). Our analysis also found that about fifty-percent (105/212) of drug manufacturers in Canada had at least one report of a drug shortage during the period under study, which is in line with previous studies (Videau *et al.*, 2019b,a). While this shows that the issue is prevalent in Canada's pharmaceutical industry, we should note that more than half of the reported shortages were from just five of the 105 drug manufacturers.

Several studies recommend increasing financial incentives or modifying regulation to enhance competition in the pharmaceutical industry. They claim that this might encourage new entrants into the market to spread out drug manufacturing and increase supply (Azghandi *et al.*, 2018; Socal *et al.*, 2021). The descriptive analysis also found that the main cause of drug shortages was disruption to the manufacture of drugs. Anticipatory purchasing of pharmaceutical products worldwide due to the uncertainty of COVID-19 led to an unprecedented level of demand (Badreldin & Atallah, 2021; Bookwalter, 2021). Meanwhile, manufacturers had to shut down their plants to mitigate the pandemic's spread, resulting in the current short supply.

During the period under study, the median duration for drug shortages was 45 days, which suggests that in most cases, unavailability is long-term. Drug companies can reduce the frequency with which these shortages occur by increasing stock levels in their warehouses (Azghandi *et al.*, 2018; Socal *et al.*, 2021). However, Figure 1 shows that the number of shortages and duration of drug shortages decreased in frequency as time went by. The most likely reason for the drop was due to the adoption of novel approaches during the pandemic, like having manufacturers from different industries produce protective gear and ventilators so that drug companies could shift their focus back to producing medication (Badreldin & Atallah, 2021).

Even in normal circumstances, certain types of medications are known to be more vulnerable to shortages than others (Zheng *et al.*, 2020). The analysis found that most drug shortages were for cardiovascular drugs, particularly an agent known as Teva-Diltiazem, which had the longest drug shortage duration (1827 days). In most cases, these drugs either have complex manufacturing processes or cost significantly more to produce (Phuong *et al.*, 2019). Redirecting investment from new drug development to the more prevalent generic drug market would help foster competition. Regulatory bodies should de-incentivize the overuse of high-cost, low-value brand medication without a generic peer (Badreldin & Atallah, 2021; Sen-Crowe *et al.*, 2021).

3.9 Comparative studies

There are a number of differences between the four papers as shown in the figure 5. First, the original paper by Jean-Francois Bussieres, Andre Chiveri, and Denis Lebel specifically looked at the number of medication shortages that occurred within the year in the province of Quebec between 2006 and 2010. More specifically, they focused their study on the regions of Montreal, Laval, and other Eastern Townships in Quebec. Additionally, they examined the number of inventory shortages, the mean annual duration of the shortages, and the number of out-of-stock days. Much of this was conducted through calculations by therapeutic class and manufacturer. Second, Videau *et al.* (2019b) indicated in their study that there are a high number of shortages in Canada during 2016 and 2017 due to manufacturing disruptions, shipping delays and increased demand, moreover certain drugs are registered to have the high number such as the nervous

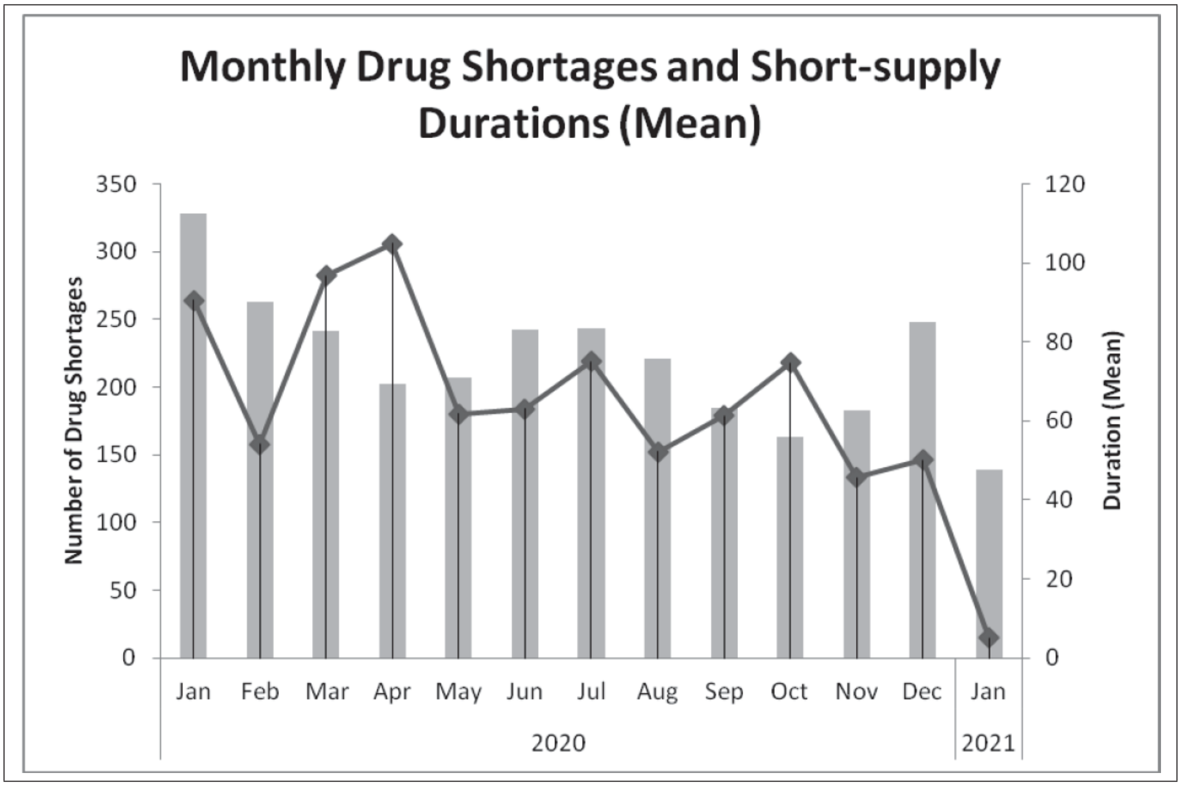


Figure 3.4 Monthly drug shortages and average short-supply durations

system drugs, cardiovascular drugs and anti-infective agents. Third, the paper which was written by Tucker *et al.* (2020), pointed out the big number of Shortages which have main impact for patients, high costs, and in the health sector in general. These comprehensive studies, targeted than 430 papers to show clearly the impact and high number of shortages, this research paper covers the period from January 2001 and May 2019. In contrast, my paper highlights the number of drug shortages between 2016 and 2021 and shortages during the pandemic COVID-19, in addition to the duration of those shortages, and what the causes and impacts of the shortages were in hospitals and patients. Additionally, my paper examined the number and type of drug in shortage by the manufacturer. Where the original paper was primarily focused on the province of Quebec, my paper conducted a nationwide study of companies, yet provided less statistics than the original paper. Thus, while the original paper can provide more nuanced answers on the medical shortages of a particular region in a particular province, my study provides a wider scope of analysis by examining the companies and shortages on a macro level.

Table 3.4 below shows specifically what are the methods that have been used and results during each period.

3.10 Study Limitations

Apart from the findings presented in the above section, the current study also experienced some limitations. The study applied descriptive research approach only. The study collected secondary data from two sources only. Such non-exhaustive of data fails to reflect on a true picture about drug shortage across Canada. One of the data sources involved a database that operates by distributing single drug type to different health facilities across Canada. The second source of data was from a website that falls under the control of multiple stakeholders. The website has operated for a short period. By collecting data from the two sources, this study failed to acknowledge the extent of drug shortage across Canada. Therefore, a shortage in one manufacturer could not reflect a true picture of different drug shortages in the country.

3.11 Recommendations

This study recommends that any other study that seeks to focus on this topic or a similar topic must incorporate different sources of secondary data. Furthermore, the study recommends that future studies must expound on their research objectives by understanding the sources and causes of drug shortages in the country. Such a focus would help explore a number of strategies to control drug shortages. In addition, future studies should apply inferential analysis to understand the correlation between drug shortages and livelihood of people living in communities.

3.12 Conclusion

The current descriptive research has succeeded in highlight the percentages of drug shortages in Canada over the period between 2016 and 2021. In overall, the study found that the country recorded 3123 shortages at national level. The current study has also succeeded in showing that

Table 3.4 Number of shortages from four different research papers during 2001 till 2021

Articles	Article Title	Methodology	Results
Jensen *et al.* (2002)	FDA's role in responding to drug shortages.	Literature Review	Discussing FDA's scope of responsibilities in drug shortages. and pointing out the ways in resolving drug shortages at FDA.
Fox & Tyler (2003)	Managing drug shortages: Seven years' experience at one health system	Descriptive and quantification report to study and manage drug shortage from 1996 to 2002	Detailed information on drug shortages monitored by UUHSC DIS Am J Health-Syst Pharm—Vol 60 Feb 1, 2003 253 REPORTS Managing drug shortages from 1996 to 2002 indicated a trend toward more frequent shortages.
Bussières *et al.* (2011)	Perspective sur les ruptures d'approvisionnement de médicaments en établissement de santé de 2006 à 2010.	Descriptive Retrospective Study Examined Drug Shortages during 2006 till 2020.	There are 2400 Inventory Shortages for 56-month period.
Videau *et al.* (2019a)	Drug shortages in Canada: Data for 2016–2017 and perspectives on the problem.	This Descriptive Study Highlights the High Number of Shortages in Canada in2016—2017.	This paper highlighted the high number of drug shortages in Canada in 2016—2017 with a total of 2129 shortages at the national level.
Tucker *et al.* (2020)	The Drug Shortage Era: A Scoping Review of the Literature 2001–2019.	Systematic Reviews and Meta-Analyses-Scoping Reviews.	There are 430 papers show drug shortages due various causes.
Abu Zwaida *et al.* (2021b)	Optimization of Inventory Management to Prevent Drug Shortages in the Hospital Supply Chain	Deep Reinforcement Learning (DRL) model	Large number of drugs in the model system, the result is: - convergence Evaluation, - evaluation of the Refilling Cost, - evaluation of the Shortage Situation, - evaluation of the Unexpected Rate.

despite the continued shortage in the country; we should not be surprises by such an occurrence since it has been there for several years.

However, during the COVID-19, we highlighted the significant issue of drug shortages in Canada between 2020 and 2021, with a total of 2,436 drug shortages. The shortages have a median duration of 45 days, which suggests that in most cases, unavailability is long-term. We found that the drug shortages were mainly due to disruption to the manufacturing process, whereby they shut down their plants to mitigate the spread of the pandemic, resulting in the current short supply. Furthermore, the number of shortages and the duration of drug shortages decrease in frequency as different authorities reduce COVID-19 restrictions worldwide. Drug manufacturers should ramp up production to ensure they have enough stock in times of sudden disruption to supply or a surprising demand that might translate to shortages. It is worth noting that the recent formulation of legislation that requires every drug manufacturer to declare their drug status will play a major role on reducing drug shortages in the future. In addition, it is important to point out that even though causes of such shortages are already known, manufacturers as well as policy makers have remained powerless in preventing drug shortages. There is a need for policy makers and government agencies to mobilize for resources to help educate people on the importance of quality and case. All stakeholders need to get involved in this matter to yield substantive results.

CHAPTER 4

THE CHALLENGES OF DRUG SHORTAGES IN THE CANADIAN HOSPITAL PHARMACY SUPPLY CHAIN - A SYSTEMATIC LITERATURE REVIEW

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Abstract:

Aim The aim of this paper is to highlight current knowledge gaps that exist with regard to the factors which affect the supply chain, and the inventory management strategies that are utilized by hospital pharmacies in Canada which could lead to drug shortages.

Subject and method This research implements an optimal SLR (systematic literature review) method on drug shortages based on CHPSC (Canadian hospital pharmacy supply chain) literature and databases. This makes it possible to perform a wide review of the Canadian hospital pharmacies and understand how continued disruption occurred in this process and caused drug shortages.

Results and conclusion The result of this research is contained in a systematic search methodology which consists of four main tasks, namely: a) building an optimal review process, b) defining search procedures, c) validating the search procedures, and d) conducting literature search. Furthermore, the researchers conducted a SLR which unveiled issues and factors such as raw materials availability and increases in demand which cause drug shortages. In conclusion, the proposed systematic methodology seeks to highlight the possible solutions to the supply chain issues which could cause drug shortages in Canada.Various solutions are proposed and explored,

with the relevant information being obtained from studies conducted on how to mitigate the impact on supply chain management.

Keywords: Hospital Supply Chain, Drug Shortages Prevention, and Inventory Management.

4.1 Introduction

This paper proposes an optimal systematic search methodology for literature review with regard to drug shortages in the Canadian hospital pharmacy supply chain. This contribution aims to propose a systematic methodology for carrying out a comprehensive review of the main and current challenges with regard to the hospital supply chain in Canada and how these supply chain disruptions contribute to drug shortages, the significant factors to consider in a hospital's supply chain management, and what the current hospital pharmaceutical inventory management and systems are. In order to perform this task, a series of key words — "drug shortages", "Canadian hospital pharmacy", "Inventory management" and "supply chain management"—were entered into relevant search engines such as PubMed and other relevant websites. Relevant information and key findings are summarized in a series of tables for better clarity.

4.2 The drug supply chain in Canada

In Canada, drug shortages defined as a situation whereby, an authorization holder of a particular drug is unable to meet the demand for the drug in question. it is believed that drug shortages are more prevalent in generic medications than in brand name marketed drugs in Canada (Videau *et al.*, 2019b). Discontinuation of drugs may have an impact on the delivery of health care services and on the financial resources that have to be needed in order to obtain these drugs from alternative supply routes (Stecca *et al.*, 2016). A survey by canadian Association for Pharmacy Distribution Management (2018) demonstrated that drug manufacturers were often not willing to disclose information with relation to shortages of a particular product as descried by the Association *et al.* (2010). As shown in Figure 4.1, an assessment and approval of a drug requirements by Health Canada involves the following process: a) Development of new drugs by the pharmaceutical industry and submission, b) Recommendation and listing of decisions to drug formularies by the Canadian Agency for Drugs and Technologies in Health, and c) Establishment of drug formularies and pricing by each province including bulk purchases from the pharmaceutical agencies and directly to the consumers (Health-Canada, 2016).

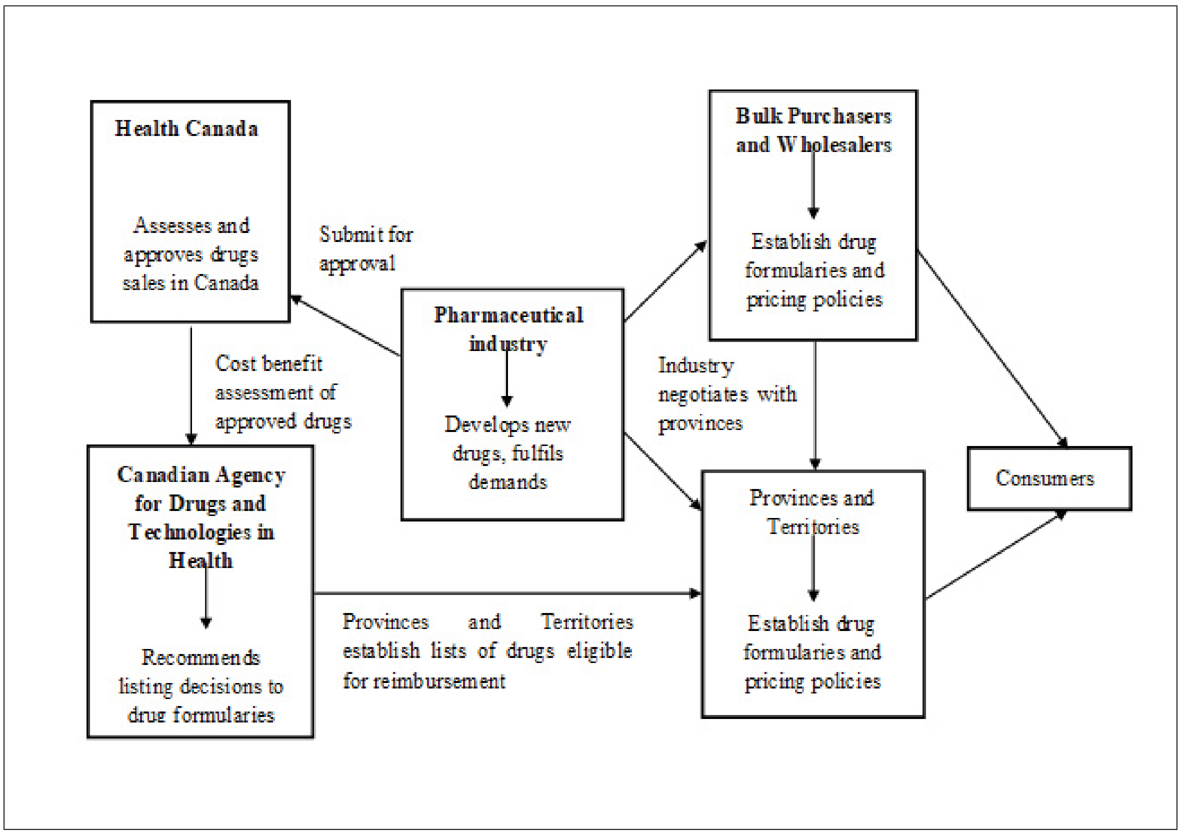

Figure 4.1 A schematic representation of the drug supply chain in Canada
Taken from Health Canada

Among the whole pharmaceutical industry in Canada, it can be seen from the canadian Association for Pharmacy Distribution Management (2018), there is a big support to the whole stakeholders of pharma supply chain, starting from the manufacturers by providing services in inventory management, merchandising support, access and support, to the retail pharmacy as well as hospital pharmacies in order to offer extra healthcare regularly to all Canadians, ending up to the patience to receive the medication on time, the right one with certainty in the safety and quality of their medicines. Drug shortages have been a cause of growing concern not only Canada but worldwide. The number of published articles in PubMed on “drug shortages” has increased exponentially from about 20 to about 450 since the year 2000. The supply of medication to the hospital and to the patients involves a complexity of the supply chain mechanism with the aim of ensuring that the medication needs of pharmacies and patients are met (Ahtiainen *et al.*, 2020). The supply chain of pharmaceutics to hospitals and patients is frequently surrounded with many risks that might lead to the disruption and availability of medication leading to the shortage of drugs (Amerine *et al.*, 2017). Given the complex nature of pharmaceutical supply chain management, it is most often difficult to identify the factors that play a role in drug shortages (Labuhn *et al.*, 2017). In conclusion, the root causes of drug shortages might be due to manufacturing issues, legislative and regulatory problems, distribution factors, natural disasters, problems with inventory and human factors as well as business and market related issues (Ottino *et al.*, 2012). The problems within each of these factors can be due to other issues such as the scarcity of raw materials needed during the manufacturing process, mergers and acquisition as well as labor disputes can have a direct disruption on the supply of drugs, lengthy approval of drugs by competent regulatory bodies as well as the breakout of pandemics that can affect the supply of these drugs to target groups such as pharmacies, hospital pharmacies and the patients in need of these medications (Barthélémy *et al.*, 2013; Bowles, 2019).

4.3 Proposed Systematic Methodology

The proposed systematic search methodology is presented as shown in the block diagram of Figure 4.2, as illustrated, it consists of four main tasks, namely: 1) composing optimal review phrases, 2) defining search procedure, 3) validating the search procedure and 4) conducting literature search. Each task consists of sub-tasks with the results of each task utilized to narrow down articles containing relevant information to be included in the systematic review.

4.4 Method

The basic concept of this methodology is based on an initial literature search which is performed in the first task of the article review followed by the establishment of golden bullets. These

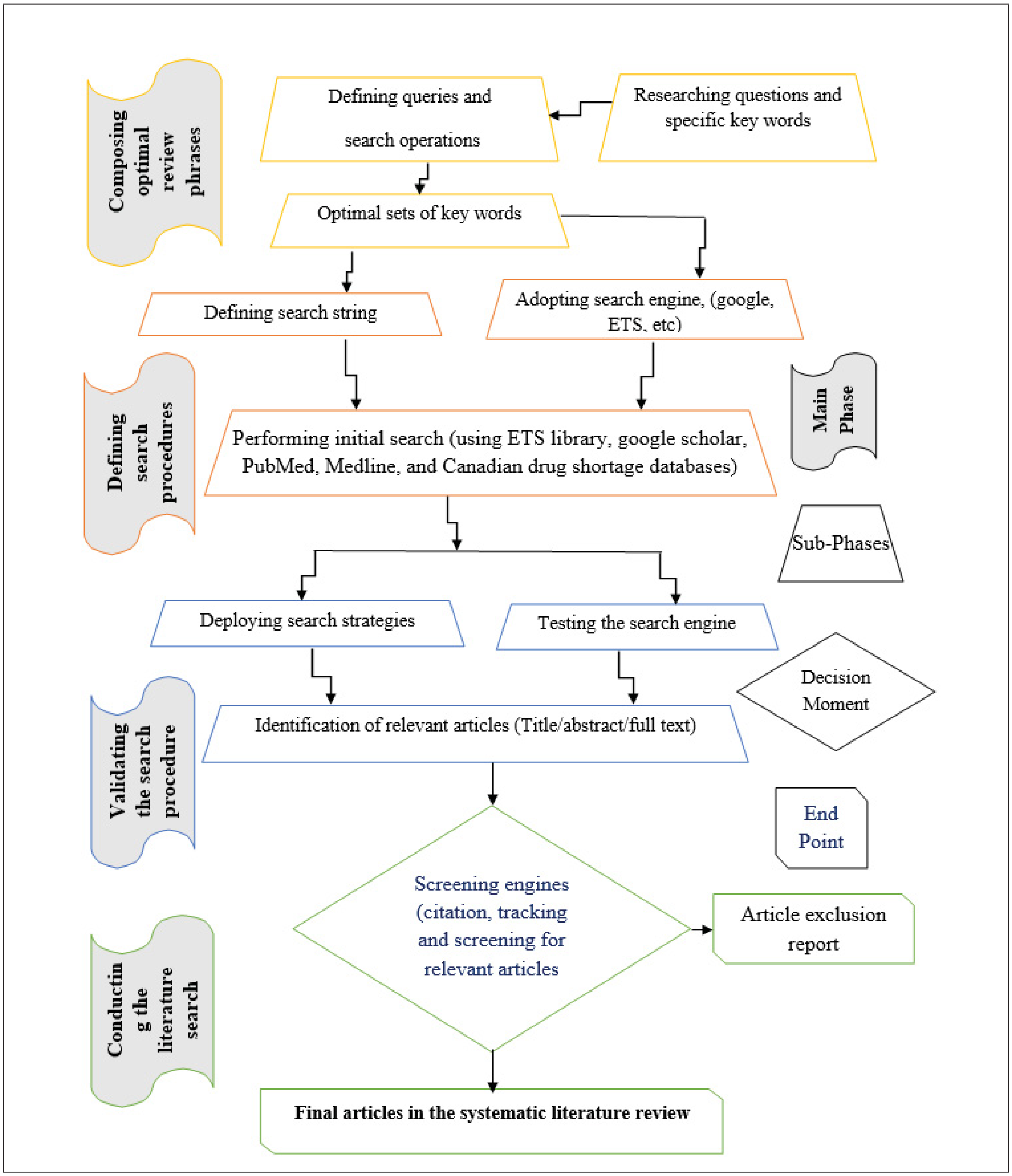

Figure 4.2 The proposed systematic literature review methodology

bullets are analyzed using a series of MeSH terms and databases such as ETS, PubMed, Google scholar and PubReminer. Validation of the search strategy is then performed by verifying if the golden bullets identified in the second task of the iterative search strategy can be identified.

The search is then performed using relevant databases followed by screening and selection of relevant articles to be included in the systematic review using predefined eligibility criteria. The description of each task is covered in details in the following subsections.

4.4.1 Task 1: Composing optimal review phrases

This task develops the optimal composition of review questions. The process starts by an initial sets of review questions, keywords, syntax, and terms that best describe the bibliographic medical database such as Health Canada, Canadian drug shortage, PubMed, and Pro Quest. The process includes the following:

- brain storming: defining the keywords, and describe the business domain;
  - words and alternative best describe the information;
  - keywords to be excluded from the searching (include and exclude key words);
  - synonyms keywords.
- defining queries;
  - filtering the most relevant keywords to achieve a list of optimal keywords;
  - database searching operators such as parentheses, Boolean operator (AND), (OR), and (NOT), synonyms (, -); exact phrase " ", and fine-tuning operators;
  - fact-based information such as publication proceedings, place, year, etc.

4.4.2 Task 2: Defining search procedures

This task builds the search strings based on the optimal keywords that were achieved from the Task 1. It consists of the following procedures:

- evaluating the matches on the search results by taking into the account, all possible medical database, and google specialized;
- utilizing search engine such as blogs, scholar, ETS, etc;

- performing the initial search.

4.4.3 Task 3: Validating the search procedure

This task allows to validate the search procedure in Task 2. Users check all possible search syntax which can be identified within the results of the search. Otherwise, the process should be adjusted and refined. This task consists of the following activities:

- testing the search engine;
- deploying search strategies;
- identification of relevant articles (Title/abstract/full text).

4.4.4 Task 4: Conducting the literature search

This final task consists of the following activities:

- screening engine (citation tracking and screening for relevant articles);
- article exclusion report;
- final articles in the systematic literature review.

4.5 Literature Analysis Guidelines

The guidelines that were used for the analysis of literature review are outlined as follows:

- defining of the topic area;
- defining specific questions;
- identifying and considering most important ideas;
- finding logical structures;

- searching the literature;
- performing the search consistency.

4.6 Search strategies

The online bibliographic database PubMed was used to extract literature relevant to the subject matter and literature published until October 1st 2019. According to Wu *et al.* (2012); Tsao *et al.* (2014), it is recommended to conduct a search strategy for relevant articles using multiple databases with the search terms and syntaxes to be tailor-made to the unique characteristics of the search engines used. This is due to the fact that various search engines render different results and conclusions highlighting the importance of using different search engines (Wu *et al.*, 2012). Based on the study by Zwakman *et al.* (2018), the utilization of Palliative Care Literature review iterative method (PALETTE) to conduct a search strategy for inclusion in a literature review is based on four tasks: the first task involves firstly developing a review question, building a search strategy, validating the search strategy and then performing the search using citation tracking tools and Boolean searching performed with utmost transparency (Zwakman *et al.*, 2018).

In order to carry out knowledge-driven systematic reviews for articles search strategies must offer some form of transparency. This can be performed through thorough explanation as to why certain databases were utilized to conduct the literature search, and how tracking of literature containing relevant information with respect to the topic at hand was performed (Finfgeld-Connett & Johnson, 2013; Tsao *et al.*, 2014). Search procedures were performed using an integrative approach with the use of the search terms "drug shortages" Canadian hospital pharmacy", "Inventory management" and "supply chain management" All literature abstracts were read and classified into three main categories: relevant, not relevant, and uncertain. During the final inclusion criteria process, abstracts of all relevant articles together with the articles in the uncertain category were read and a final decision was made on whether to include these articles in the systematic literature review. For the articles that met the inclusion criteria, the bibliographies were also obtained and searched for relevant articles.

4.7 Inclusion and Exclusion

In order for articles to be **included** in the systematic review, they have to contain at least one or more of the following information: (1) drug shortages in Canada (2) information on hospital supply chain management and (3) information on hospital inventory management of drugs in Canada. On the other hand, the articles that did not contain information on factors affecting drug shortages were **excluded**. Articles without in-depth knowledge on inventory management in a hospital or pharmaceutical setting were also excluded. Lastly, articles had to contain sufficient information on the hospital supply chain management process in order to be included in the reviewing process.

4.8 Data extraction

From the included papers, the following information were extracted: a) Key factors affecting drug shortages in Canada and in developing countries in the European Union, the United states of America and in countries such as Japan, China and other densely populated countries, b) How these factors contribute to lead to drug shortages, c) Possible solutions on factors affecting drug shortages, d) if information was present, the factors affecting the inventory management system in a hospital setting in Canada and other major developed countries such as the United States, e) Possible solutions to the factors affecting the inventory management system in a hospital and f) Factors affecting the hospital supply chain management that can lead to drug shortages and possible solutions to this problem.

4.9 Results

This systematic literature review is performed in order to determine the main and current challenges of the hospital supply chain of drugs in Canada and how do these supply chain disruptions contribute to drug shortages. The significant factors to consider in a hospital's supply chain management and what are the current hospital pharmaceutical inventory management and systems. Initially, a series of search terms computed in the PubMed search database were used and 3421 articles were identified when using the search term “drug shortages”. In this paper, the duration of the literature review covers the period from 2000 till 2019.

When the search term “drug shortages in Canada” was used, 128 articles were obtained of which only 30 articles were deemed relevant to the topic. The articles in question were published from 2012 to 2019 When the term “pharmacy supply chain management” was searched on PubMed, 202 articles were obtained of which only one article adequately described pharmacy supply chain management in Canada. When the term “hospital pharmacy inventory management” was used, 367 articles were obtained of which only 20 were relevant for this systematic review.

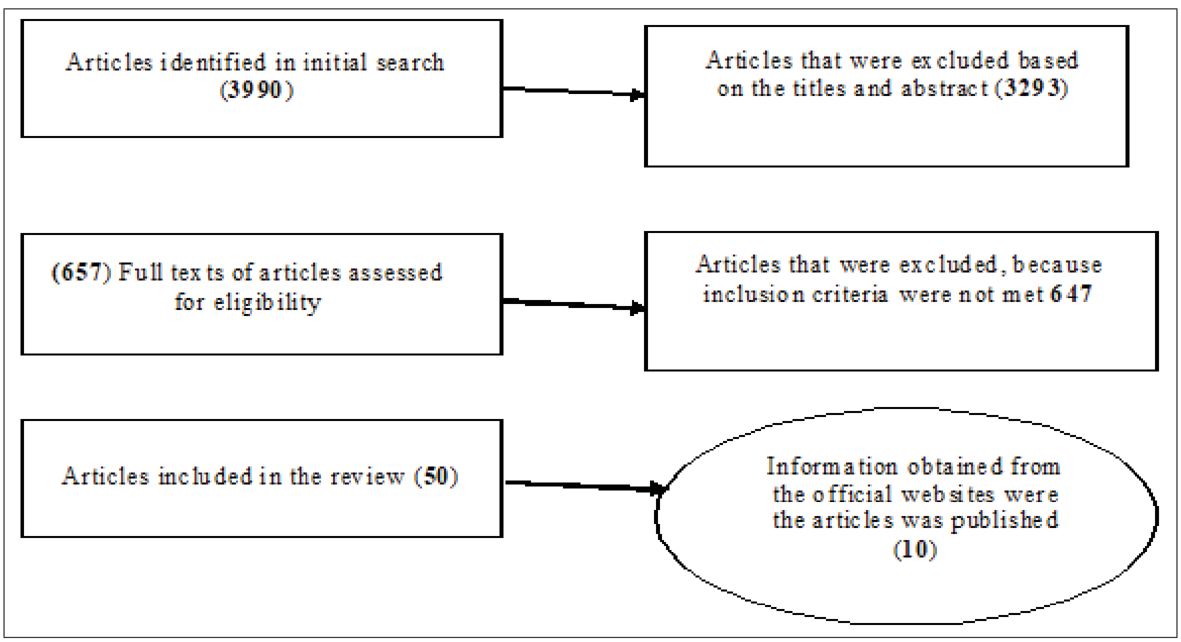

Figure 4.3 Flow step diagram on the literature search and number of articles in each step

Figure 4.3 depicts the flow chart on the literature search and the number of articles included in each step. As indicated, out of 3990 articles, only 50 articles were deemed to contain sufficient data to be included in this review. All articles were included after appraisal of the abstract, methodology, and result sections for sufficient information on drug shortages in Canada, hospital pharmacy inventory management and supply chain management in Canada. All bibliographies were read with paper extraction. Lastly, a summary of factors that are affecting drug shortages, pharmacy inventory management and pharmacy supply chain management in Canada and potential solutions to these problems are summarized in Table 4.1, 4.2 and 4.3.

4.10 Drug shortages

According to the international pharmaceutical federation, the drug shortage defined as a drug supply issue that requires a change. Drugs shortage might be classified as either temporal or permanent discontinuation in the production and supply of a specific medication (Videau *et al.*, 2019b). There are several exist factors that might influence the availability of drugs to healthcare providers and patients as well. These factors are the following: unavailability of raw materials, labor disputes of pharmaceutical manufacturing personnel, an unexpected increase in demand for a particular drug and natural disasters. In 2011, it was reported a severe shortage in anesthetizing agents by the Canadian Anesthesiologist association. Several causes of drug supply disruption were reported, this was notably due to a reduction or interruption in the production process of a particular drug (Association *et al.*, 2010). It was observed that generic medication has a small margin of profit thereby making it difficult to source the raw materials needed for the production of these generic medication (Heiskanen *et al.*, 2017). As such, most manufacturers simply chose to terminate the production of less profitable generic medication (Bowles, 2019). Additionally, the merging of two pharmaceutical companies might lead to the consolidation and change in the production of a multisource product into a single-source product (Gagnon & Volesky, 2017; Tyler *et al.*, 2002; Woodcock & Wosinska, 2013). Additional, stricter enforcement of the drug regulatory process has led to a delay in the approval of several new medications. This result mainly was due to the rise of counterfeit medication and the contamination of products produced in China. Generic medication manufacturers have additionally stated that outsourcing of active pharmaceutical ingredients were usually from the foreign sources such as China and India which has resulted in instability in the global supply chain (Rinaldi *et al.*, 2017).

The different causes of drug shortages have shown in Figure4.4 with the shortages and have observed when other components used for the manufacturing of the drugs have developed some faults leading to a halt in the production of drugs. This accounts for about 35% of drug

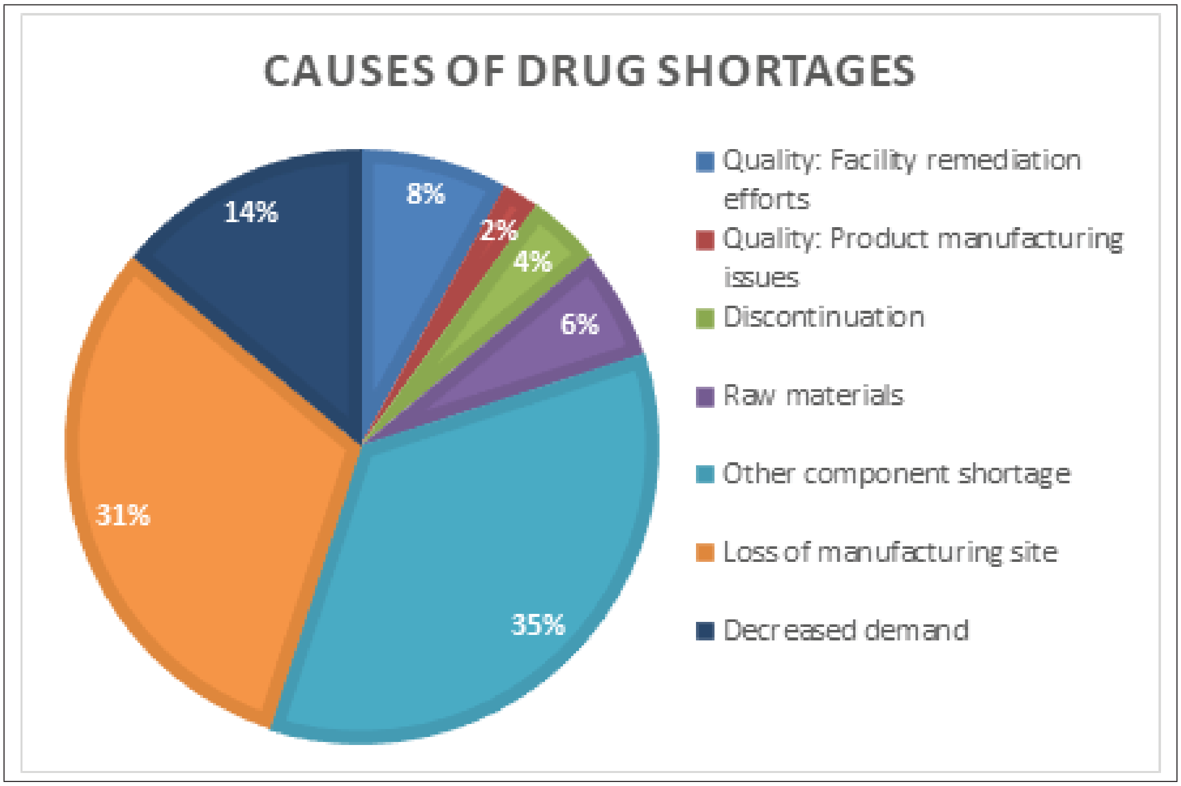

Figure 4.4 Causes of drug shortages. Source: US Food and Drug Administration

shortages Loss of the manufacturing sites for the drugs; which can be due to the natural disasters, is the second most important cause for drug shortages and accounts for about 31% for drug shortages. Decreases in demands for drugs accounts for about 14% of shortages while product manufacturing issues, discontinuation of drug production and unavailability of raw materials accounts for less than 8% of the causes for drug shortages.

Table 4.1 Factors affecting drug shortages and possible solutions in Canada

Articles	**Article title**	**Factors affecting Drug shortages**	**Possible solutions**
•Jensen *et al.* (2005) •Fox *et al.* (2009b)	•An overview of the FDA drug shortage program •Recent trends in drug shortages: an update from the 2003 report	•Active ingredient obtained from a single source supplier •Contaminated raw materials and non-conformity of established regulatory standards	•A process for the approval of alternative therapies for the healthcare organization experiencing drug shortages should be put in place
•Association *et al.* (2010)	•Canadian drug shortage survey	•Unanticipated increase in the demand for a particular drug product •Changes in production formulations and limited manufacturing capacity	•Improve the collaboration between manufacturers and other important stakeholders •Government incentives to the manufacturers to prevent the discontinuation of a particular drug

Continued on next page

Table 4.1 Factors affecting drug shortages and possible solutions in Canada (Continued)

Articles	**Article title**	**Factors affecting Drug shortages**	**Possible solutions**
•Farrukh *et al.* (2019) •MSSC-Canada (2017)	•Valsartan recall: a global regulatory overview and future challenges. • Preventing drug shortages: identifying risks and strategies to address manufacturing related shortages in Canada.	• Voluntary recall of a particular product due to possible contamination of raw materials	•Establishment of robust quality control measures, reportable quality measures such as fail rates of key processes in sterility, stability and batch failure.
• Acosta *et al.* (2019) • Health-Canada (2016)	• Medicine shortages: gaps between countries and global perspectives. • Drug shortages in Canada	• Loss of a large number of patents by pharmaceutical companies resulting in industry mergers and discontinuation of a particular drug.	• Updating regulation and procurement policies in order to ensure the acquisition of a particular product from different manufacturers

Continued on next page

Table 4.1 Factors affecting drug shortages and possible solutions in Canada (Continued)

Articles	**Article title**	**Factors affecting Drug shortages**	**Possible solutions**
• Gagnon & Volesky (2017)	• Merger mania: mergers and acquisitions in the generic drug sector from 1995 to 2016.		
• Markowski (2014)	• Drug shortages: the problem of inadequate profits.	• The strict enforcement of good manufacturing processes by drug regulatory bodies may play a role in drug shortages	

Table 4.2 Factors affecting the hospital pharmaceutical inventory management and possible solutions

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
• Alegria *et al.* (2016)	• Prospective inventory management systems for preempting problems related to medication unavailability	• Untimely delivery of backordered medication from wholesalers and inefficient scheduling and inventory management by the pharmacy technician	• Pharmacy practice coordinators schedule, carry out inventories of limited medications and forward this information to pharmacy technicians that are in charge of notifying hospital pharmacy managers on the potential unavailability of a particular medication. • Use of an automated dispensing cabinet system that allows pharmacy technicians to be updated on the remaining quantity of each medication that is dispensed.

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Table 4.2 Factors affecting the hospital pharmaceutical inventory management and possible solutions (Continued)

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
• Fung *et al.* (2009)	• Do automated dispensing machines improve patient's safety?	• Inventory shrinkage due to employee theft and robberies	• Use of automated dispensing machines as well as cabinets that provide secure medication storage on patient care units and provide electronic tracking of the use of controlled substances and narcotics.
• Jurado *et al.* (2016)	• Stock management in hospital pharmacy using chance-constrained model predictive control	• Overstocking of medication and unjustified forecasting techniques.	• Use of a chance constrained model of predictive control that determines how and when an order should be placed.
• Awaya *et al.* (2005)	•Automation in drug inventory management saves personnel time and budget	•Lack of reliable information technology support and automation in drug inventory management.	•Use of reliable information technology software systems such as the radiofrequency identification microchips or tags

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Table 4.2 Factors affecting the hospital pharmaceutical inventory management and possible solutions (Continued)

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
			which are intended to store information about the pharmaceutical product from the manufacturing date until arrival on site at the pharmacy warehouse till expiration date of the product
• american Society of Health-System Pharmacists *et al.* (2011)	• ASHP statement on bar-code verification during inventory, preparation, and dispensing of medications	• Inefficient barcoding during inventory, preparation and dispensing of medication.	• Effective use of barcoding technologies will ensure the adequate distribution and correct preparation of patient doses as well as to ensure that the products are in date and have not been recalled.
• McCarthy Jr & Ferker (2016)	• Implementation and optimization of automated dispensing cabinet technology	• Prevalence of infrequently prescribed medication and product expiration.	• Use of an automated dispensing technology will lead to cost saving and reduced pharmacy technician labor.

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Table 4.2 Factors affecting the hospital pharmaceutical inventory management and possible solutions (Continued)

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
			• A substantial reduction in the weekly stockage percentage. • An improvement in the average medication turnaround time.

Table 4.3 Factors affecting the hospital pharmaceutical supply chain management and possible solutions

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
• Holm *et al.* (2015)	• Medication supply chain management through the implementation of a hospital pharmacy computerized inventory program in Haiti	• Lack of available supply of medication	• Use of a pharmacy computerized inventory program led to an increase in medication transaction that permitted the tracking and identification of critically low medication supplies
• Labuhn *et al.* (2017)	• Supply chain optimization at an academic medical center	• Increased stock outs per month leading to medication depletion and shortages in the hospital pharmacy.	• Upgrading and re configuring carousel technology within an expanded central pharmacy footprint. • Implementation of a technician workflow design and algorithm to right size the ADC inventory.

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Table 4.3 Factors affecting the hospital pharmaceutical supply chain management and possible solutions (Continued)

Articles	**Article title**	**Factors affecting inventory management**	**Possible solutions**
• Duong *et al.* (2019)	• Stakeholder role in facilitating access to essential medicines	• Logistics management and therapeutic decision making were managed by separate entities. • Stakeholder intended control mechanisms increased the level of complexity of the supply chain.	• Need for improved and innovative stakeholder management strategies • Include hospital formulary pharmacists and wholesale distributors in the therapeutic selection committee decision making process could improve the procurement of medication processes.

4.11 Factors affecting the inventory management of a hospital pharmacy

There are several existing factors that can have an impact on the effective management of the inventory of the healthcare sector in general and specifically in the hospital pharmacy. These include the following; some cost elements such as the ordering cost the cost of product, holding cost of the central pharmacy inventory, unclaimed prescriptions, returned product policies, inventory shrinkage, and the use of outdated formularies (Ali, 2011; Stecca *et al.*, 2016). Thus, It is essential to carry out a monthly review of the pharmacy stock in order to search for already expired medication and ascertain that the quantity of a particular medication is not running low (Jurado *et al.*, 2016). Generic products have lower acquisition cost than brand named products and might be an alternative to minimizing product purchasing and inventory cost (Conti *et al.*, 2018). The sseveral factors such as the raise in healthcare expenditures impose growing pressures to improve efficiency in healthcare industry. Most products have policies in place by the vendors or wholesalers with regards to returned and unused products (Cetinkaya & Lee, 2000). This might include credits for future purchasing of products, cashback policies and product replacement policies (Macarthur, 2000). Inventory shrinkage might occur as a result of theft, shoplifting by a customer or a pharmacy employee. Formularies are utilized in hospital pharmacies in order to enhance inventory management. Stockpiling and speculative purchasing in the event of a drug shortage can lead to a disruption of efficient supply and drive up storage and handling costs and may not be absorbed during the normal usage of the product (Ventola, 2011).

4.12 The hospital supply chain management system

The hospital pharmacy supply chain is an instrumental in providing optimum patient care through the adequate supply of essential medication. However, complex issues might arise in the supply chain management of the hospital pharmacy that might lead to drug shortages (Martin *et al.*, 2000). Using technologies such as carousel and automated distribution cabinets (ADCs) to reduce storage errors and facilitate the picking up of medication has helped ease the manual delivery burden and medical errors with respect to allocations of wrong medications to patients.

The supply chain management of medication to the hospital pharmacies involves the following processes: planning of medication supply, request of a purchase order, reception of medication, validation of package deliveries, fitting and sorting of deliveries, storage at onsite hospital warehouse facilities, preparation for distribution of medicines to primary and secondary pharmacies and to automated distribution cabinets and finally reverse logistics (Romero & Lefebvre, 2015).

Stocking of medication in the ADC is essential in streamlining the pharmacy workflow and allowing pharmacy technicians to be allocated to other duties within the hospital pharmacy. In the United Kingdom, a low-unit-of-measure replenishment of ADCs has led to a decrease in carrying requirements of the hospital central pharmacy (Labuhn *et al.*, 2017). In Haiti, a Pharmacy Computerized Inventory program (PCIP) was established in order to optimize medication availability and decrease drug shortages. The PCIP system incorporated drug ordering, filling drug requests, distribution and dispensing of medication to the various departments of the hospital. An increase in the number of medication transaction and mean logins per day increased exponentially, thereby permitting the effective tracking and identification of medication that were in low supply in the hospital pharmacy (Holm *et al.*, 2015).

4.13 Factors affecting the supply chain management in a hospital

The following factors have been observed: inadequate management of hospital inventory systems which might lead to excessive losses in the form of thefts and misplaced medication, intensive manual labor strategies, time-consuming product recalls and lengthy procurement cycles (Clubb *et al.*, 2018). The receipt of the wrong medication that does not correspond to the purchase order of the medication that was purchased, the receipt of altered or counterfeited medication and the improper use of logistics and supply technologies which might arise as a result of the fact that most hospitals do not use the same bar-code for supporting their internal logistics processes might be some of the factors decreasing the efficiency of the supply chain management in a hospital (Lim *et al.*, 2013; Al-Qatawneh, 2006). At the reception point of medications, pharmacy technicians identify and manage medication distribution based on the medication labels with validation of the purchase order being performed manually as well (Ahtiainen *et al.*, 2020). In Quebec and most notably Ontario, the effect of supply chain management on drug shortages was principally due to the lack of oversight both by the local government and third parties on drug supply management. As such, the drug supply is largely dependent on the on the drug market. Additionally, it was observed the reluctance of the individual manufacturers to give access to information with regards to which drugs are facing disruptions in the manufacturing and supply process. As such, it is most often difficult to predict when drug shortages occurs (Association *et al.*, 2010). As it can be seen from the table 4.4, it shows the key differences in the supply management of drugs in the pharmaceutical and hospital pharmacies which are highlighted in table 4.3.

Table 4.4 Differences between pharmaceutical and hospital supply chain management

Pharmaceutical Supply Chain Management	**Hospital Supply Chain Management**
Production and supply of active ingredients	Acquisition of medicines directly from wholesalers or directly from pharmaceutical manufacturing companies.
Production of medicines	Production and dispensing of drug formularies as per patient prescription
Distribution of medicines to wholesalers	Distribution of medication to patients using manual or automated distribution systems
Storing and packaging of medicines by wholesalers	Storing and packaging on site in the hospital warehouse facilities
Distribution of medicines to hospitals	Automated drug dispensing systems (ADDSs) to the nurses then to the patients.

4.14 Discussion

Drug shortages have been observed as a global phenomenon in a variety of developed countries. Bond *et al.* (2004), indicated that in the United States, alone drug shortages have caused numerous difficulties for clinicians, healthcare practitioners, caregivers and patients. In 2011 alone, a total of 211 drugs were tracked and labeled as being in short supply (Ventola, 2011). The drugs shortages were principally observed for cancer and heart medication, intravenous electrolytes and many others. In Canada, shortages in propofol, cardiovascular medication, leucovorin and supplies needed in radiology and nuclear medicine were also observed (Jenks, 2011; Videau *et al.*, 2019b; Phuong *et al.*, 2019).

As a result of the various factors that have been known to exacerbate the problem of drug shortages in Canada and globally as a whole: This literature review identified the major causative factors of drug shortages. The major factors included the unavailability of raw materials or active pharmaceutical ingredients from which these medications are manufactured. A solution to this problem was to the use of alternative medications used to treat the diseases for which medication is in short supply (Barthélémy *et al.*, 2013). A second factor was the discontinuation of generic draws by pharmaceutical industries in order to enhance the sale of more expensive brand-name medication as well as the expiration of drug patents (Fox *et al.*, 2009b).

A solution to this problem was to apply for longer patent protection of a particular drug before the generic version of the drug can be released. Low profit margins of generic drugs have led to shortages due to the generic drug being manufactured by a single supplier. The application of stringent regulations during the drug manufacturing process has led to manufacturing quality control breakdowns. The mergers of pharmaceutical companies as well was observed to be some of the factors that have led to the discontinuation in the production of a particular drug (Gagnon & Volesky, 2017).

It is worth noting that the Drug shortages in a hospital pharmacy might arise due to the poor inventory management systems. Previously, the inventory management and distribution of drugs in the different departments in a hospital by pharmacy was performed manually which was labor intensive and led to medication mishandling and loss of revenue. To solve these issues, an automated distribution system and inventory management software should be introduced. This will lead into the reduction of inventory shrinkage, increasing savings on inventory cost and faster prescription processing times (Martin *et al.*, 2000; Jurado *et al.*, 2016; Stecca *et al.*, 2016).

Guidelines for decision making in the management of drug product shortages were proposed (Fox *et al.*, 2009a; Fox & McLaughlin, 2018). This involved carrying out an operational assessment to validate drug shortages, determine the stock at hand, identify alternative supply sources, identify the population that will be affected by these drug shortages, carry out a shortage impact analysis, effectively communicate to all stakeholders involved in a timely manner about the drug shortage and finally implementation of inventory changes and bar-coding practices (Barthélémy *et al.*, 2013). The majority of information on strategies to combat drug shortages clearly demonstrate that efficient handling of hospital pharmacy inventories and supply chain management should be performed using automated systems and inventory management software systems that has proven to be the cost effective (Findlay *et al.*, 2015; Al-Qatawneh, 2006). A proposal to curb the effect of drug shortages will be to invest in the production and manufacturing of generic medication to plug in the shortages of brand-name medications that are the major sources of drug shortages. Focus will be on the development of new generic medication manufacturing plants to increase the production and supply of generic medication at lower costs to the consumer patient population.

This systematic review has indicated that there is a clear lack of research being carried out on the effect of supply chain issues and inventory management shortfalls that results in drug shortages in Canada. Most articles on supply chain and inventory management were based on research conducted in the United States and Various European and Asian countries such as Belgium and Japan. The review conducted by Romero (2013) on the inventory management strategies in Canadian pharmacies demonstrated that the use of track and trace systems for medication inventory management such as bar-coding and RFID technology was still in its infancy. A survey carried out in four hospital pharmacies demonstrated that pharmacy technicians and pharmacists responded positively and clearly outlined the advantage of using such technologies for effective inventory management (Romero & Lefebvre, 2015). Adopting an RFID and barcoding system for effective inventory management in hospital pharmacies might aid in reducing medical errors and keep a handle on not only the shelf-life of a particular medication but likewise the drug shortages (Lim *et al.*, 2013).

4.15 Recommendations

From the Canadian Hospital's Pharmacy Supply Chain perspective, there are many challenges of the hospital supply chain in Canada. There is a need to focus more on the implementation of automated systems in hospital pharmacies in Canada, as such these systems of inventory management used as a means of reducing drug shortages.

It can be seen clearly that the most articles on supply chain and inventory management were based on research conducted in the United States, various European and Asian countries such as Belgium and Japan; whereas as there is a lack of research being carried out on the effect of supply chain issues and inventory management shortfalls that results in drug shortages in Canada. Hence, there is a big need for more literature review research to demonstrate the types of supply chain system being utilized by hospital pharmacies in Canada.

4.16 Conclusion

The prevalence of drug shortages is a global phenomenon. In Canada, during 2016 and 2017, there were 2129 drug shortages which was reported by the Canadian drug shortage website, furthermore, about 234 drug shortages were reported for 2018 alone with this quantification set to dramatically increase in the upcoming years, and in 2019, more than 260 drugs were reported as being in short supply. Drug shortages occurred mainly as a result of the unavailability of raw materials (active pharmaceutical ingredients), natural disasters, increase in the demand of certain drugs and other factors.

The scientific contribution of this paper is to propose an optimal systematic search methodology for literature review on drug shortages in the Canadian Hospital's Pharmacy Supply Chain. The aim of this proposed systematic methodology is to carry out a comprehensive review on the main and current challenges of the hospital supply chain in Canada.

To conclude, this systematic review has highlighted a clear lack of research being carried out on the effect of supply chain issues and inventory management shortfalls that results in drug shortages in Canada. The literature searches clearly demonstrated that there was a lack of knowledge on the types of supply chain system being utilized by hospital pharmacies in Canada.

CHAPTER 5

OPTIMIZATION OF THE INVENTORY MANAGEMENT TO PREVENT DRUG SHORTAGES IN THE HOSPITAL SUPPLY CHAIN

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Abstract: Drug shortage is always a critical issue of inventory management in healthcare systems since it potentially invokes several negative impacts. In supply chain management, the optimization goes hand in hand with inventory control to address several issues of supply, management, and use of drugs. However, it is difficult to determine a shortage situation in a hospital due to multiple unpredictable reasons, such as manufacturing problems, supply and demand issues, and raw material problems. To avoid the shortage problem in a hospital, an efficient inventory management is required to operate the system in a sustainable way, and maximize the profit of the organization in the Hospital Supply Chain (HSC). In this work, we study a refilling drug optimization problem, such a general model for drug inventory management in a hospital. We then investigate a Deep Reinforcement Learning (DRL) model to address this problem under an online solution that can automatically make a refilling drug decision in order to prevent a drug shortage. We further present a numerical result to verify the performance of the proposed algorithm which outperforms the baselines (e.g., Over-provisioning, Ski-rental, and Max-min) in terms of the refilling cost and the shortage rate.

Keywords: Hospital Supply Chain, Drug Shortages Prevention, and Inventory Management.

5.1 Introduction

In the healthcare system, the drug-inventory management represents a significant portion of the costs, especially in the hospital supply chain in order to efficiently control and satisfy usage requirements Kaakeh *et al.* (2011). However, the general healthcare system is faced with the following challenges of increasing efficiency and reducing waste. First, the implication is that no healthcare facility is immune to drug shortages Fox *et al.* (2014). Most of hospitals have experience of drug shortage or were affected by this on their systems. Drug shortages are caused by many reasons and forced healthcare organizations to purchase a more expensive alternative to operate their systems in a sustainable way. Second, an over-provisioning mechanism is often employed in the hospital as a solution referred to as safety stock William *et al.* (2018). The safety stock is a value that is calculated taking into account the variability of demand during lead time as well as the variability of delays in getting the ordered goods. Indeed, this method can mitigate the shortage situation in a hospital, but it often causes a high cost to buy and store medicines in the hospital since it is unaware of high costs to buy and maintain them in the system. Specifically, a high imported volume of drugs without taking into account the user demand might also result in a high cost to store and prevent damage. Some drugs require special storing conditions while most of the others have specific expiration which cannot be used after that.

An efficient inventory management is considered as a solution to improve the quality of customer services and the organization in the Hospital Supply Chain (HSC). Investigating the drug shortage problem, Holm *et al.* (2015) stated that there can still be nationwide drug shortages. In fact, a danger of a drug shortage can be caused in one area, but it might be a domino effect to other regions, even they are not in the same part of the health system. However, a local optimal system can mitigate this negative impact. The creation of clear lines of communication, gaining transparency into the cause of the shortages, and continually accessing in-stock and low-cost alternatives are the best mitigation process for developing the balanced inventory (Chabner, 2011). The Food and Drug Administration (FDA) has developed the Innovation Act and Strategic Plan to help mitigate drug shortages. The World Health Organization (WHO) has recognized drug shortage as a global problem (Mazer-Amirshahi *et al.*, 2014). Integrating manufacturers, suppliers, wholesalers, and store to produce and distribute the right quantities of drugs to the right time in the right place to satisfy service-level requirements and minimizing system-wide cost is termed as supply chain management.

Therefore, the optimization is needed, and goes hand in hand with the supply chain management about inventory control to address how medicines and drugs are supplied, managed, and used. Understanding the underlying causes of drug shortages is the most critical aspect that any hospital or health system to be acquainted with to help mitigate these outcomes (Postacchini *et al.*, 2015). By doing this, it is also easy to come up with proactive measures with the available resources. Determining the exact cause of drug shortages has appeared to be difficult, in general, it has been categorized to be falling into three categories such as manufacturing problems, supply and demand issues, and raw material problems (De Weerdt *et al.*, 2015a). Hence, in this study, we focus on the supply and demand issues, which means that given the information of the supply chain system, we aim to control the drug inventory based on the uncertainty of user demand and drug prices. Our model aims to make an automated decision in order to answer the following questions, which have little research focusing on: i) *Should we refill drugs*? and ii) *How much drug should be refilled*?

More precisely this research aims to study an inventory drug optimization problem, which can capture requirement constraints of drug demands, storage capacity, and refilling conditions while minimizing the refilling costs in the system. Since our designed problem is NP-Hard, it is impossible to find a solution in polynomial time. To deal with this problem, we advocate a Markov decision process (MDP) to model the drug inventory system in order to address the shortage problem. Based on that model, we propose Deep Reinforcement Learning (DRL) framework model that combines the Reinforcement Learning (RL) (Sutton & Barto, 2015) method and the Deep Neural Network model (DNN) (Goodfellow *et al.*, 2016) to automatically make a decision in a finite horizon.

Basically, RL is modeled as an MDP in which it is comprised of three concepts, such as a state, an action corresponding to a state, and a reward for that action. Following the loop of actions and observations, the agent in MDP often refers to a long-term consequence. Thus, RL is particularly well-suited to control the drug inventory in a finite horizon. Furthermore, the combination between RL and DNN can figure out the strict requirement of MDP about the exact knowledge of the state space of MDP, and DRL is able to find a near optimal solution of a large MDP model as shown in DR2O. With a large number of drugs in the system, it might be unsolvable for a classical dynamic programming method.

All of the contributions of our work are summarized as follows:

- First, we investigate the supply chain model of drugs in a hospital to formulate an optimization drug shortage problem, named as the Dynamic Refilling dRug Optimization (DR2O). We model an objective function that aims to minimize the refilling costs, comprising of the costs to buy, to store medicines, and the penalty cost due to shortage. Furthermore, we consider supplying constraints to refill drugs, such as storage capacity, and budget constraints.

- Second, we propose a deep learning method based on RL and DNN, named as the Deep Reinforcement Learning model for Drug inventory (DRLD), where the situation of drugs is formed as a state in a Markov Decision Process (MDP) Sutton & Barto (2015). Depending on each state, we look for a suitable action to make a refilling decision in order to minimize the objective cost function. Based on the MDP model, we design an online method to control the system, where a reward and Q-matrices are built to evaluate an action corresponding to each state. Due to a large searching state space in RL, we introduce a DNN model that can approximate the Q-values after training that is able to learn behavior of the system.

- Finally, we consider an intensive simulation to conduct our work. In detail, we make a comparison between our method and three baseline approaches, including Over-provisioning, Ski-rental (Karlin *et al.*, 1994), and Max-min (Mjelde, 1983). Our method outperforms in most evaluations, especially in reducing the refilling cost and shortage situation.

The rest of our study is organized as follows. In Section 5.2, we discuss selected prior works that relate to our study. In Section 5.3, we present the problem formulation of the supply chain model of drugs in a hospital. Section 5.4 discusses the reinforcement learning framework to deal with DR2O. We then present the simulation result in Section 5.5. Finally, we conclude our work in Section 5.6.

5.2 Related work

This section reviews the existing literature related to inventory management and how optimization of it can be used to prevent drug shortages in the hospital supply chain. In order for this goal to be realized, we will commence by defining several terms that are associated with the topic; Inventory Management and Hospital Supply Chain (HSC). In addition, we aim to expound on the importance of optimizing inventory management to prevent drug shortages of HSC. Ultimately, the section illustrates how healthcare institutions are minimizing drug shortage costs in their hospital supply chains.

5.2.1 Defining Inventory Management and Hospital Supply Chain

In line with Qiu *et al.* (2019); Rand (2001), inventory management is connected with the procedure of requesting, storing and utilizing an institution's inventory. This involves the management of primary products, components as well as end products. It also consists of warehousing and processing such items. However, Muller (2019) depicts it as a systematic approach to sourcing, storing and selling inventory, that is, both finished goods (products) and raw materials (components). A supply chain, on the other hand, is composed of stages that are either indirectly or directly involved in accomplishing a customer's request (Ageron *et al.*, 2018). According to Moons *et al.* (2019), it basically involves the producer, supplier, transport operators, warehousing, retailers, third party logistics providers and lastly the customer. Moons *et al.* (2019) denotes that, the supply chain is responsible for ascertaining that there is an adequate connection of hospital institutions, operations and the revenue cycle.

5.2.2 The importance of optimizing the inventory management to prevent drug shortages of the hospital supply chain

Health care institutions across the globe are in search of methods that would prove effective in improving the efficiency of operations, that is inventory management while reducing expenditures that will in no way affect medical care and services (Wild, 2017). Bradley *et al.* (2018) illustrated that, the material requirements for provision of health care delivery are multifarious, generating a complex distribution network of relationships from the distributor to the customer. Furthermore, health care budgets are very stringent and thus health care providers are attempting to optimize their inventory management which will eventually lead to reduction of costs incurred whilst providing health care (Qiu *et al.*, 2019).

Additionally, Kritchanchai *et al.* (2018) denoted that, an effective supply chain management is one that intends to optimize the full value created as opposed to the profit produced in a specific supply chain. The hospital supply chain sometimes referred to as the pharmaceutical supply chain (PSC) is intricate, and comprises of numerous organizations that perform varying but sometimes superimposed roles in the contraction and distribution of drugs (Tiwari *et al.*, 2018). In line with Loftus (2017), price variation among the various types of users is considered to be a regular phenomenon owing to its degree of complexity. Thus, it becomes significantly more complicated for policy makers to evaluate and comprehend the supply chain (Kees *et al.*, 2019). According to Ageron *et al.* (2018), increased discernment of said issues associated with policymakers is considered to take a role in making logical policy decisions for Medicare programs.

An ineffective hospital supply chain is associated with product shortages, product discontinuity, decreased patient safety, poor performance, distribution flaws and technological mistakes that result in stock shortages in hospitals (de Kok *et al.*, 2018). Abdulsalam & Schneller (2019) stated that increasing the productivity of Supply Chain Management is key to obtaining a more robust, safer and lower-cost for hospital operations in Public Hospital Medicine Management Units. This is achieved by optimizing the supply processes, enhancing satisfaction and patient safety as well as reducing errors. However, the Michigan State University University (2019) observed that an extensive distribution arrangement to transfer pharmaceutical commodities and other medical equipment from the medical stores to the service points is still lacking in most hospital systems. This lack of appropriate distribution systems creates a considerable bottleneck, often making it very difficult to access said products and supplies Tiwari *et al.* (2018).

5.2.3 Minimization of Drug Shortages in Hospital Supply Chains

The Canadian pharmaceutical supply chain, consisting of governments, manufacturers, wholesalers, distributors, pharmacists, and physicians, acknowledges the significance of a reliable medication supply Association *et al.* (2010) Moreover, it is obvious that there is insufficient information from accessing the drugs due to different issues, for instance, distribution system in the manufacturing Zwaida *et al.* (2019). However, there are instances when drugs do not reach the intended locations due to glitches in the distribution system. In instances where clients cannot access important drug products, practitioners have a responsibility of knowing the reasons for the product's unavailability, the time when the product is available, available alternatives to the unavailable drug product and the involved costs, how to obtain the unavailable product from alternative sources, and additional information detailing patients' needs and healthcare providers' needs. However, it is worth noting that it is unacceptable for hospitals to experience drug shortage Shiau (2019), along with the associated costs.

There are various factors which could cause pharmaceutical supply disruptions and they include unexpected increased demands in the drug's utilization leading to an impermanent shortage. Such a shortage ends only when the manufacturing capability increases to a level that meets the identified demand. Supply pharmaceuticals disruptions are also caused when products are voluntary recalled or discontinued by a manufacturer. Disruptions also occur when Health Canada withdraws drugs from the market or when natural disasters such as floods and storms occur. These causes are responsible for the shortage costs experienced in the hospital supply chain inventory management. One needs to understand that the costs emanate from the fact that a client could not access the required drug product at the expected time. Additionally, the costs also include the time taken to purchase the drug product from alternative sources or acquiring alternative medications representing the unavailable drug product. The inventory process needs to be planned effectively to ensure that even in instances of unpredictable natural calamities, the duration of drug shortage is minimized Silver *et al.* (2016).

Indecorous medical inventory management and drug shortages severely disrupt the HSC which eventually leads to health services that are impoverished while increasing costs Loftus (2017). Kees et al. in Kees *et al.* (2019) elucidated that, many hospitals and pharmacies are subjected to numerous problems as they aim to achieve proper inventory control. This is on account of the fact that; they have hardly addressed how medicinal products are administered, supplied and utilized to improve health as well as to save lives. An additional crucial issue in the HSC as illustrated by VanVactor (2017) is unidentified occurrences. Such disasters generate enormous losses. In order to enhance the dependence of a HSC for disasters, Feibert *et al.* (2017) proposed an inventory control model that utilizes mathematical programmable methods. The suggested model takes into account multiple forms of medications, ordering size, processing time, expiration dates of products and customer service level not to mention the holding and storage cost Dillon *et al.* (2017a). The equivalent answer or solution ascertains the optimum period of preparation and inventory level in the disaster formulation phase with the lowest overall cost. However, Kritchanchai *et al.* (2018) elucidated that, this method permits a handful of measuring points to distort the prediction and neglects to account for seasonal changes and other variables. Thus, hospitals are left exposed to high costs and avoidable waste. Bradely et al. in Bradley *et al.* (2018) supports this argument illustrating that mathematical and statistical methods are proving to be inadequate in optimize the HSC.

Additionally, Cardinal Health Health (2017) has found that manual processes and workflows in medication inventory management are not just slow and troublesome but are actually insufficient at collecting intelligent information. According to Alia (2019), when a hospital's personnel are entrusted with the task of manually monitoring, logging and restocking the inventory, the results are either imprecise, as human errors are bound to happen, or insufficient whenever the proper processes were not followed to the letter. Hence, as mentioned by Zhou *et al.* (2017), the use of Machine learning (ML), which is a type of training algorithm (or artificial intelligence (AI)) where algorithms are constantly processed as additional data enables them to be more predictive, is gaining momentum in HSC management. Wild showed how ML can help HSC management to become more refined while making it less cumbersome Wild (2017). By swiftly processing enormous volumes of data in order to discern patterns and uncover insights that may be too complex or hidden to human perception (even to those with considerable experience), ML has the capacity to enable health care providers to steadily provide the right provisions, at the right cost, place and time Brynjolfsson & Mitchell (2017).

Drug shortages can also be caused by increased demand or decreased supply Organization *et al.* (2016). Increased demand, particularly where the parties in the pharmaceutical supply chain employ just-in-time inventory control Organization *et al.* (2016), has been found to be the cause of shortages close to 13% of the time Ventola (2011). That same study has found that drug shortages caused by decreased supply due to manufacturing problems, at about 23%, surpasses drug shortages caused by increased demand Ventola (2011).

Not only are genuine real-time computerized systems utilized to streamline the performance of tasks for medication inventory management, they also present a historical reporting that is accurate, complete and real-time Zhou *et al.* (2017). This is achieved through RL.This method is considered to be a subset of ML consisting of adopting appropriate action so as to maximize the rewards in a certain condition Feibert *et al.* (2017). However, Brynjolfsson & Mitchell (2017) illustrated that when an instruction dataset lacks information, it is bound to ascertain the missing information from its past experience. Pharmacy staff and purchasing managers utilize this information in order to optimize inventory so as to prevent drug shortages as well as to give priority to patient safety while cutting unnecessary costs Dillon *et al.* (2017a).

The mathematical programming model can be used in the determination of automated refilling decisions. For example, a mathematical model considers the various types of drugs, ordering sizes, shortages and holding costs. Therefore, a hospital can use the model to compute these aspects, as well as determining the specific refilling schedule of drugs in supply. If there is a drug shortage, the costs caused by the shortage can be automatically anticipated to determine the necessary amount of refilling drugs. To the best of our knowledge, the studies presented to date do not have a learning model to deal with the shortage issue. Therefore, in this work, we propose a deep learning model to formulate and develop a dynamic inventory model for drugs in a hospital setting.

5.3 System model

We consider an enterprise supply chain to provide drugs to a hospital. This supply chain consists of a set of drugs $\mathcal{I}$ managed during period T. To simplify the problem formulation, all the notations are presented in Table 5.1. We assume that the system works in a time-slotted fashion, spanning time slots $1, 2, ..., T$, with an index t that corresponds to a week or a month defined by the hospital.

Each drug $i \in \mathcal{I}$ has a storage capacity $C_i(t)$ and an expired function $e_i(t)$ that is used to measure the amount of expired drug i at time t. With different types of drugs, the storage capacity units could be different (e.g., box, bottle, etc.) so that our model could flexibly define the capacity unit for each specific drug i. To make a refilling decision, we consider a refilling cost $p_i(t)$, which can be measured or collected by prediction methods. In this work, we simply model this function by the regular (or base) price $\underline{p}_i(t)$ and the penalty price $\beta_i(t)$ due to the emergency demand. The function is calculated as follows

$$p_i(t) = \underline{p}_i(t) + \beta_i(t), \forall i \in I, t = 1, 2, ..., T. \tag{5.1}$$

Practically, we are unaware of the price in advance and, therefore, cannot make a long-term plan. In this work, we presume that the price parameters are given before making a refilling decision at time t. We also denote the budget B_i that is used to buy drug i during time T.

5.3.1 Problem formulation

We aim to design an online solution that dynamically determines when to refill drugs over the entire running span T while satisfying all requirements with a minimum *refilling cost*. Especially, we aim to avoid a shortage situation in the system, which could lead to a domino effect. There is a general trade-off between cost optimization and any shortages due to unknown patient demand:

Table 5.1 Notations

Symbols	Description
$\mathcal{I}$	Set of drugs
i	Drug index.
t	Time index.
T	Spanning time.
$e_i(t)$	An amount of expired drug i at time t.
$p_i(t)$	The refilling cost of drug i at time t.
$\psi(.)$	The penalty function of drug i.
$\underline{p}_i(t)$	The base price of drug i at time t.
$\beta_i(t)$	The penalty price of drug i with an emergency demand.
B_i	The budget of drug i.
$\mathbb{B}$	The total budget.
α_i	The weight parameters of drug i.
$R_i(.)$	The storage cost function of drug i.
$r_i(t)$	The storage cost of drug i at time t.
$\lambda_i(t)$	The amount of demand of drug i at time t.
$e_i(t)$	The amount of expiration at time t.
$v_i(t)$	The remaining volume of drug i at time t.
$C_i(t)$	The storage capacity of drug i.
$\underline{C}_i(t)$	The lowest volume requirement of drug i.
$\underline{\rho}_i(t)$ & $\bar{\rho}_i(t)$	The upper and lower bound refilling of drug i at time t.
Variables	
$\boldsymbol{x}$	The decision refilling volume variable.
$x_i(t)$	The refilling volume of drug i.

by refilling more drugs, the shortage situation may be avoided, but the cost will be increased, and vice versa. In this work, we combine these dual goals in the objective function by using weighted parameters to weight the priority of each aspect.

We design a main variable $\boldsymbol{x} = \{x_i(t)\}_{\forall i \in \mathcal{I}, t=1,2,...,T}$ to represent the amount of drug i to refill at time t. The refilling cost model in this work contains the following parts:

- **Medicine cost.** We consider the first term as the medicine cost depending on the amount of drugs being ordered: $\sum_{t=1}^{T} \sum_{i \in \mathcal{I}} \alpha_i p_i(t) x_i(t)$, where $\alpha_i \in (0, 1]$ is the weight parameter of drug i and $p_i(t)$ is the amount of money required to purchase the required amount of drug i. Depending on the drugs' priorities, α_i is set with a high or low value.

- **Storage cost.** We design the second term as the storage cost incurred when the hospital stores drugs. Hospitals may incur a variety of costs associated with safely storing medicine, and some must utilize third-party storage. In this work, we generally model the storage cost as a function $R_i(v_i(t), r_i(t))$ depending on $v_i(t)$, the amount of drugs, and $r_i(t)$, the storage cost. The volume of drug i at time t can be obtained by

$$v_i(t) = v_i(t-1) - \lambda_i(t) - e_i(t) + x_i(t), \tag{5.2}$$

  where $v_i(t-1)$ is the remaining volume of drug i at time slot $t-1$, $\lambda_i(t)$ is the amount of the demand and $e_i(t)$ is the amount of the drug available before expiration at time t.

- **Penalty cost.** A penalty cost $\psi(v_i(t))$ is assigned to prevent a shortage situation in the system. This cost depends on the volume and the minimum requirement for the drugs at time t. Without a loss of generality, we refer this cost to a quadratic function to formulate our model. As shown in Fig. 5.1, the quadratic penalty cost increases when the volume of drug i reaches the bounded values $\underline{C}_i$ and $\bar{C}_i$. In other words, the penalty cost function aims to prevent both the shortage and overstock problems.

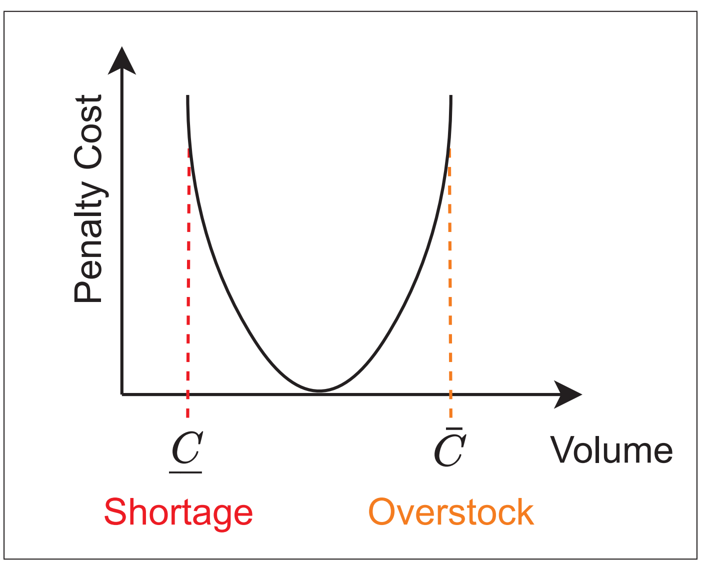


Figure 5.1 A quadratic function of the penalty cost

Consequently, the objective function in our model is to minimize the cost incurred when the hospital makes a refilling decision. The objective function is expressed as follows:

$$\min \sum_{t=1}^{T} \sum_{i\in\mathcal{I}} \alpha_i p_i(t) x_i(t) + R_i(v_i(t), r_i(t)) + \psi(v_i(t)) \tag{5.3}$$

We next formulate the set of constraints that the decision variables should respect. First, we consider the capacity constraint to ensure that the refilling decision will not exceed its storage capacity $C_i(t)$. Furthermore, the system has to ensure the lowest volume $\underline{C}_i(t)$ of each drug i to avoid a shortage. Hence, we formulate the constraint as follows:

$$\underline{C}_i(t) \le v_i(t) = v_i(t-1) - \lambda_i(t) - e_i(t) + x_i(t) \le C_i(t), \forall i \in \mathcal{I}, t = 1, 2, ..., T. \tag{5.4}$$

Second, we consider the budget constraints of the hospital for purchasing drugs during time T as follows:

$$\sum_{t=1}^{T} \sum_{i\in\mathcal{I}} x_i(t) p_i(t) \le \mathbb{B}. \tag{5.5}$$

In addition, there is a budget for each medicine i at time t, which is considered by the following constraint

$$x_i(t) p_i(t) \le B_i(t), \forall i \in \mathcal{I}. \tag{5.6}$$

Finally, at each time slot t, the hospital could have a specific refilling range for each drug i in order to provide for a specific requirement in the hospital. We formulate this constraint as follows:

$$\underline{\rho}_i(t) \le x_i(t) \le \bar{\rho}_i(t), \forall i \in \mathcal{I}, t = 1, 2, ..., T, \tag{5.7}$$

where $\underline{\rho}_i(t)$ and $\bar{\rho}_i(t)$ are the lower and upper bound refilling volumes, respectively, of drug i at time t.

5.3.2 A dynamic refilling drug optimization model

Based on the aforementioned objective and constraints, the dynamic refilling drug optimization (DR2O) model is presented as follows:

$$
\begin{aligned}
\min_{\mathbf{x}} \quad & \sum_{t=1}^{T} \sum_{i \in \mathcal{I}} \alpha_i p_i(t) x_i(t) + R_i(v_i(t), r_i(t)) + \psi(v_i(t)) \\
\text{s.t} \quad & \underline{C}_i(t) \le v_i(t) = v_i(t-1) - \lambda_i(t) - e_i(t) + x_i(t) \le C_i(t), \forall i \in \mathcal{I}, t = 1, 2, ..., T, \\
& \sum_{t=1}^{T} \sum_{i \in \mathcal{I}} x_i(t) p_i(t) \le \mathbb{B}, \\
& x_i(t) p_i(t) \le B_i(t), \forall i \in \mathcal{I}, \\
& \underline{\rho}_i(t) \le x_i(t) \le \bar{\rho}_i(t), \forall i \in \mathcal{I}, t = 1, 2, ..., T.
\end{aligned}
\tag{5.8}
$$

In general, this problem can be seen as a variant of the classic ski-rental problem Karlin *et al.* (1994). Specifically, a drug i is similar to the person in the classic ski-rental problem, who is going to ski but does not know how long the snow will last. He therefore has to make a decision every day as to whether to buy (so he will not need to pay for the next days) or to rent skis to minimize the overall cost. In our problem, we have to decide whether to buy a drug or not at time t, and we do not know the user demand in advance which could result in a shortage in the next period. A hospital might spend a good portion of its budget buying and storing a high volume of medicines that may not be used until their expiration. However, a hospital could fall into a shortage crisis if it manages a low supply of drugs. To address this problem, we advocate a learning method to deal with the following issues: i) the uncertainty of demand that affects the decisions at every time slot, and ii) the automation mechanism that can automatically make a decision to adapt to the environmental situation.

Theorem 1. *DR2O is NP-Hard.*

Considering a knapsack problem with N items where each item has a non-negative weight w_i and a value p_i. There is a bound W to select a subset S of items where $\sum_{i\in S} w_i \leq W$. The objective is to select a subset of maximum total value $\sum_{i\in S} p_i$, subject to the boundary constraint. Using a binary variable x_n to indicate item n is selected in the subset S, the problem formulation of the knapsack problem is as follows:

$$\max \quad f(\boldsymbol{x}) = \sum_{n\in N} p_n x_n \tag{5.9}$$

$$\text{s.t.} \quad \sum_{n\in N} x_n w_n \leq W, \tag{5.10}$$

$$x_n \in \{0, 1\}. \tag{5.11}$$

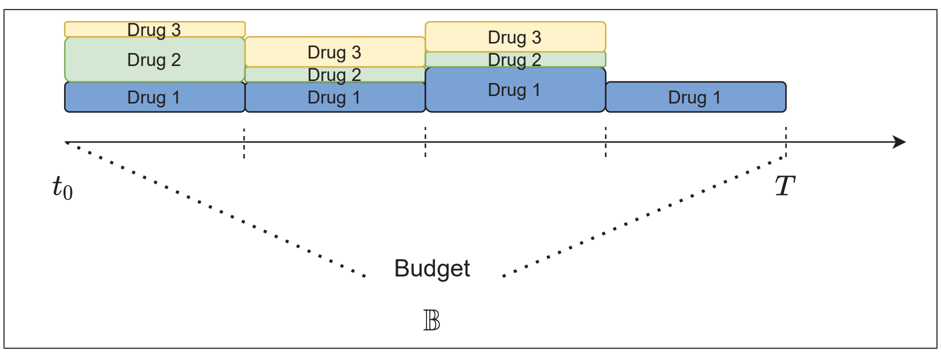


Figure 5.2 An example of the offline DR2O

Let us simplify the system by considering an offline model of DR2O, as using DR2O with an online form is always more complicated due to uncertain demands. This means that we can know exactly the amount of drugs used in time slot t. Hence, as shown in Fig. 5.2, to refill drugs in period T, we need to find a subset of the blocks presented for the amount of drugs in each time slot t in which the total is bounded by the budget $\mathbb{B}$. If we consider the revenue of each drug determined from the surplus between the value ϑ_i and the refilling cost, the objective of DR2O can be formed similarly to the knapsack problem by maximizing the total revenue of all the drugs.

$$\max \sum_{t=1}^{T} \sum_{i \in \mathcal{I}} \vartheta_i(v_i(t-1) + \lambda_i(t)) - [\alpha_i p_i(t) x_i(t) + R_i(v_i(t), r_i(t)) + \psi(v_i(t))]. \quad (5.12)$$

Since the first term of (5.12) is constant because $\lambda_i(t)$ is given, this objective function can be maximized by minimizing the second term as we formulated in DR2O. Thus, the offline DR2O constructs an instance of the knapsack problem which is proven NP-Hard Korte & Vygen (2012).

5.4 Reinforcement learning

5.4.1 Markov decision process model

Firstly, we present the Markov decision process (MDP) to formulate our problem. Based on this model, we then propose a deep Q-Network algorithm to find a solution for DR2O. In general, the MDP model is comprised of three concepts: a state, an action corresponding to a state, and a reward for that action.

The system state $\mathcal{S}$. We consider the system state in the at time instant t, including the current volume of drugs, the user demand, and the costs of buying and storing medicine. In addition, due to specific requirements at time t, some other information could be changed, such as the purchasing budget, the storage capacity for drug i, and the minimum and maximum amount of drugs to refill. For the set $\mathcal{I}$ of drugs i, we could make an order to make a decision for the drugs that have higher priority, and then consider the remaining budget for the rest. Therefore, we make a loop with $|\mathcal{I}|$ iterations to make a decision for each drug i in turn. We denote the state $s_i(t) =< p_i(t), r_i(t), \lambda_i(t), B_i(t), e_i(t), \underline{C}_i(t), C(t), \underline{\rho}_i(t), \bar{\rho}_i(t) >$ of drug i at time t.

Action set $\mathcal{A}$. The action set in our model reflects the refilling decision of each drug i. In particular, the action $a(t) = \{a_i(t)\}_{\forall i \in \mathcal{I}}$, where $a_i(t)$ is the decision of drug i at time t that responses to the state $s_i(t)$.

Reward W. As presented in the objective function, our model aims to minimize the refilling cost including the purchasing and storing costs. Therefore, we first model the reward function based on the purchasing cost as follows $\frac{1}{L_i(x_i(t))}$, where $L_i^{(1)}(x_i(t)) = \alpha_i p_i(t) x_i(t) + R_i(v_i(t), r_i(t)) + \psi(v_i(t))$, and k is the considered time slot. This means that the more money the system needs for its purchases, the less reward it has. The function attempts to navigate the system so it selects actions that obtain higher rewards, which is equivalent to minimizing the purchasing cost.

The next term involves the penalty for the shortage situation, as we aim to avoid this problem for all the drugs in storage. The penalty term is defined by $\psi(v_i(t))$ as formulated above.

We combine these terms in the penalty function by:

$$w_i(t) = (1-\theta)\frac{1}{L_i(x_i(t))} + \theta\psi(v_i(t)), \tag{5.13}$$

where $\theta \in (0, 1]$ is the weighted parameter that is designed to set the priority of each term.

Considering duration T, the state of each drug and its reward are stochastic and follow the MDP, where the state $s_i(t)$ changes to $s_i(t+1)$ with a transition probability, and the reward depends on the state and the selection action.

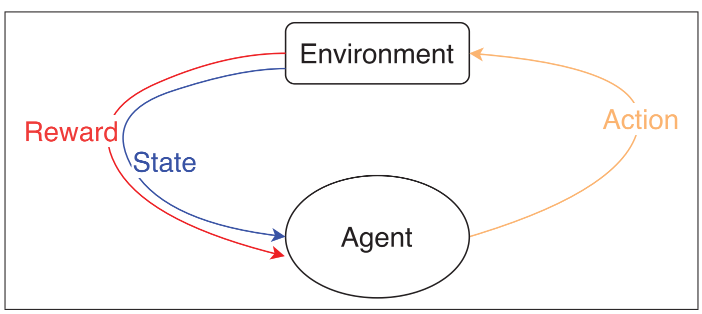


Figure 5.3   Markov decision process

To go from $s_i(t)$ to $s_i(t+1)$ with reward $w_i(t)$, we consider the conditional transition probability, $p(s_i(t+1), w_i(t) | s_i(t), a_i(t))$. It should be noted that the agent can only control its own actions, and has no prior knowledge on the transition probability matrix $P =$

$p(s_i(t+1), w_i(t)|s_i(t), a_i(t))$, which is determined by the environment. The intuition of MDP is presented in Fig. 5.3. Therefore, the main objective of this reinforcement learning is to find a policy to maximize the expected cumulative reward. We have

$$R_i = E\big[\sum_{t=k}^{T} w_i(t)\big] \tag{5.14}$$

5.4.2 Deep Q-Learning

As shown in Fig. 5.3, the agent takes actions depending on the state, called the policy π, which maps the state $s_i(t)$ to the action $a_i(t)$. Mathematically, we express this as $\pi_i : s_i(t) \in \mathcal{S} \rightarrow a_i(t) \in \mathcal{A}$. The Q-learning mechanism is used to maximize the long-term expected accumulated discounted rewards Goodfellow *et al.* (2016). Considering the $Q_i(s_i(t), a_i(t))$ value of π_i for a state $s_i(t)$ and action $a_i(t)$ pair, this value is calculated by the expected accumulated discounted rewards. Therefore, the policy π_i is constructed by taking the action

$$a_i(t) = \arg\max_{a \in A} Q_i(s_i(t), a_i(t)), \forall i \in \mathcal{I}. \tag{5.15}$$

Based on the Q-function from the Bellman equation Goodfellow *et al.* (2016), the optimal policy π_i with value Q_i can be obtained by

$$Q_i(s_i(t), a_i(t)) = E\big[w_i(t+1) + \psi w_i(t+2) + \psi^2 w_i(t+3) + \ldots|s_i(t), a_i(t)\big] \tag{5.16}$$

so that the Q-value for the state, given a particular state, is the expected discounted cumulative reward.

Therefore, in the MDP, we aim to determine an optimal policy expressed as $\pi^* : \mathcal{S}_i \rightarrow \mathcal{A}_i$. Following the stationary distribution in the MDP, the Q-values will converge to the optimal

Algorithm 5.1 Reinforcement learning.

```
1  Input: 𝒮 and 𝒜;
2  Output: Q-matrix;
3  Initialization: Q-matrix;
4  Select a random starting state s_i(t) which has some possible actions from 𝒜;
5  while ||Q − Q′|| ≤ ϵ do
6      Select one of the possible actions, a_i(t) that moves to the next state s′_i(t);
7      Update the Q-value of the state-action pair (s_i(t), a_i(t)) according to (5.17), then set
         to Q′;
8      Set s_i(t) ← s′_i(t);
9      Go to Step 5;
10 end
```

value Q^* with the following equivalent calculation Goodfellow *et al.* (2016)

$$Q_i(s_i(t), a_i(t)) = Q'_i(s_i(t), a_i(t)) + \psi[w_i(t+1) + \delta \max_{s_i \in \mathcal{S}_\rangle} Q'_i(s_i(t), a_i(t)) - Q'_i(s_i(t), a_i(t))], \tag{5.17}$$

where $Q'_i(.)$ is the old value. To obtain the optimal Q-value, the algorithm is executed until the mean changed values of Q-values is less than a threshold, called the training phase.

The details of a training phase can be described as shown in Alg. 5.1. At the beginning, a random Q-matrix is generated (Line 3). A loop is executed (from Lines 5 to 9) to modify this matrix until convergence (i.e., where the change is less than the threshold ϵ). A random state $s_i(t)$ is selected to start the training (Line 4). Line 6 randomly selects a possible state $a_i(t)$ to move to the next state $s'_i(t)$. Line 7 updates the Q-value of the state-action pair $(s_i(t), a_i(t))$ using (5.17). The algorithm continues until it meets the convergence condition.

According to the traditional Q-learning method, it is not difficult to obtain the convergence result with a small state-action space. However, the classic Q-learning model cannot be applied directly to our work because the state-action space is so huge, given that the state in DR2O is comprised of a tuple of parameters that generate a huge combination. Furthermore, the level of refilling drug x_i is set flexibly in a specific range, and so it also increases the size of the state-action space. In this case, there are two problems: i) it is too difficult to build the transition probability for the MDP, and ii) some states that are not visited and that are updated infrequently lead a long convergence in the training phase to obtain the Q^*-value.

To deal with this problem, a Deep neural network (DNN) is used to approximate the Q-function Sutton & Barto (2015). Given the input information of a state $s_i(T)$, the DNN is trained to learn an optimal mapping $s_i(t)$ to $a_i(t)$. Therefore, we design the input of the DNN to present all the features of a state $s_i(t)$, and the output is the Q-values, $Q_i(s_i(t), a_i(t))$. We design this DNN model for the set of drug I; therefore, for a simpler formulation, we remove the i index.

To obtain correct Q-values, the DNN needs a training phase to update the weight parameters in the network. Specifically, given an input-output pair $< s(t), y >$ in the data set $\mathcal{D}$, the DNN aims to minimize the following loss function

$$L = \sum_{(s(t),y)\in\mathcal{D}} (y - Q(s(t), a(t))^2, \tag{5.18}$$

and the given output y is calculated by

$$y = w(t) + \max_{a(t)\in\mathcal{A}} (Q(s(t), a(t)) \,. \tag{5.19}$$

5.4.3 Training and testing phases

We present the training algorithm in Alg. 5.2, which is called the Deep Reinforcement Learning approach for Drug inventory (DRLD). Similar to the standard Q-learning algorithm, an action of DRLD is selected based on the environment and the reward. Instead of using a full history as the Q-learning method to make an action for a current state, we limit a length of history defined by $\gamma(.)$, which is related to the number of input nodes in the DNN. In the training phase, we use ϵ-sampling to generate and collect the data to train the weight parameter of the DNN.

The details of the algorithm are as follows. At the beginning, we initialize the current simulation environment with given sets of $\mathcal{S}$ and $\mathcal{A}$ (Line 1), and initialize for the learning sequence set $\mathcal{D}$ and the DNN model (Lines 3-4). We select a random starting state $s(0)$ from the current $\mathcal{S}$ (Line 6) to execute M training times. An action $a(t)$ is selected with an $\epsilon-$probability, otherwise an action that maximizes $Q(s(t), a(t))$ is selected (Line 8). According to the action $a(t)$, the environment is set by a new state $s(t+1)$ with a reward $r(t)$ (Line 9). If the state $S(t+1)$ does not exist in $\mathcal{S}$, it will be added for training (Line 10). Also, $\mathcal{D}$ is appended by the transition $s(t) \leftarrow s(t+1)$ (Line 11). A training in the DNN is started by sampling a sequence $s(j) \rightarrow s(j+1)$ in $\mathcal{D}$ (Line 12). The training phase is designed to update the weight parameters in DNN with the given state $s(j)$ and the output that is calculated by (5.19) (Lines 13-14). Note that the values of M and T are defined by our experience (e.g., $M = 7$ and $T = 30$). These values are changeable and can be observed depending on each system. However, technically, while setting the values of these parameters higher will increase the accuracy, in fact, it will result in a long convergence since it adds more iterations.

In the testing phase, the trained agent will select an action $a(t)$ with the maximum Q-value given by the training phase. Based on the training Q-matrix, we can operate the refilling drug model, DR2O, as an online mechanism.

5.4.4 Discussion

As presented in Alg. 5.2 and Alg. 5.1, the action of each drug i is chosen independently based on its environment. There is an issue in our system when the actions are executed simultaneously. In this case, the agent will not have the correct information about the environment, which is affected by the other action. To deal with this problem, we suppose that the action updates are executed asynchronously. For example, we rank drugs based on the priority of refilling to perform refilling action in a sequence. Hence, only one or a small subset of drugs will update their environments. This approach allows the environment changes caused by other agents to be observed accurately. In the real system, this modification in our mechanism is needed to coordinate the different drugs in the system.

Algorithm 5.2 DRLD-Training algorithm.

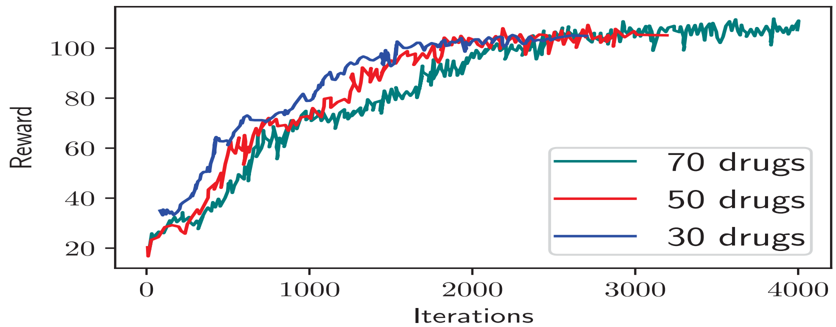
Input: Start the environment $\mathcal{S}$ and $\mathcal{A}$;
Output: Q-matrix;
Initialization: Q-matrix, DNN model;
Set empty for the learning sequence $\mathcal{D}$;
for *j=1:M* **do**
  Select a random starting state $s(0)$;
  for *t=0:T-1* **do**
    Sample an action $a(t)$ with probability ϵ, otherwise select $a(t) = \arg\max Q(s(t), a(t))$;
    Generate a next state $s(t+1)$ and reward $r(t)$;
    Add $\mathcal{S} = \mathcal{S} \cup s(t)$;
    Add the transition $s(t) \rightarrow s(t+1)$ to $\gamma(s(0) \rightarrow s(t+1))$ and save in $\mathcal{D}$;
    Sample a transition $\gamma_j(s(j) \rightarrow s(j'))$ from $\mathcal{D}$;
    Set the output $y(k)$ by (5.19) to train DNN;
    Using a gradient descent to update weights of DNN;
  end
end

5.5 Experiment and Numerical Results

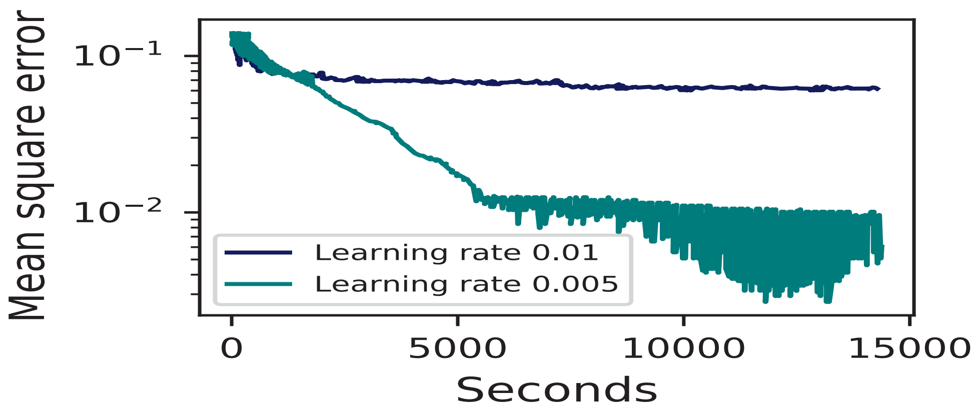
5.5.1 Experiment configuration

In this section, we present our experimental evaluations that mainly focus on the training time required for using reinforcement learning to obtain a near-optimal solution. We use the hardware configuration of the experimental environment with a CPU, 2.4 GHz Intel Core i5, and an 8 GB memory at 1600 MHz DDR3 . Our simulator program was developed in PyTorch framework https://pytorch.org/ and the Ipot optimization library https://coin-or.github.io/Ipopt/. Due to the difficulty of accessing real databases in a hospital, which contain very sensitive information, we refer to the data used in Kelle *et al.* (2012) with a list of 70 drugs. The setting range of parameters in our work is shown in Table 5.2.

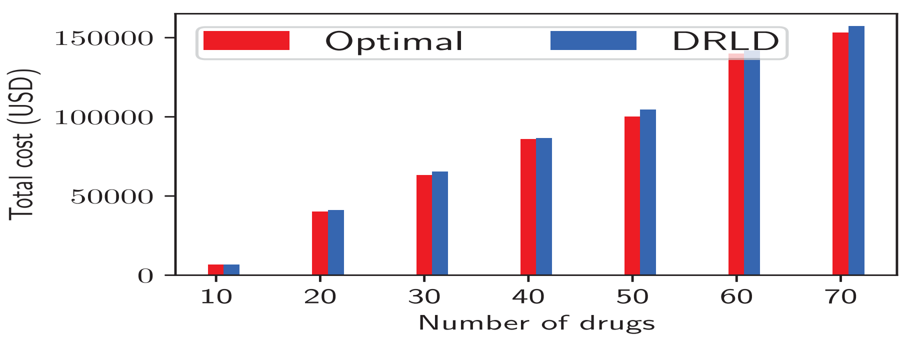
In order to evaluate the system, we compare our work with following baseline approaches:



a) Evaluation of the reward value



b) Evaluation of the DNN



c) Evaluation of the total cost

Figure 5.4 Convergence evaluation

- Optimal: We use Ipopt solver https://coin-or.github.io/Ipopt/ to solve the DR2O problem with an assumption that the demand during T is given. Hence, the optimal result of DR2O, in this case, can be considered as the offline optimal solution to compare with other approaches.

- Overprovisioning: This is a simple strategy that is often carried out in the inventory system. Based on the average utilization (gathered from log files of history), the expired period, and the current remaining volume of drugs, a refilling decision is considered. To prevent the shortage problem, the amount of drugs to be refilled is often provided with an additional volume, which results in a higher cost of operation.

- Ski-rental: As presented in the formulation, DR2O can be an instance of the ski-rental problem. Therefore, to evaluate the performance of the DRLD, we implement an online algorithm with c-competitive value where $c = (2 - 1/T)$.

- Max-min Mjelde (1983): This refilling strategy is one of the most useful mechanisms for inventory management. By using the Min level, a trigger will be active to make a refilling decision to obtain the Maximum target quantity. To prevent the shortage problem, the Min value is often set with a high volume (we use 45 % in our work), therefore, the Max-min baseline also results in a high total cost.

Table 5.2 Simulation settings

Parameters	Settings
Storage demand of drugs	[0.001 - 0.005] ft^3
Total inventory capacity	40 ft^3
Refilling cost of drugs	[5-100] USD/unit
Storing cost	[2-5] USD/ft^3
Drug demand	[5-20] unit

5.5.2 Results

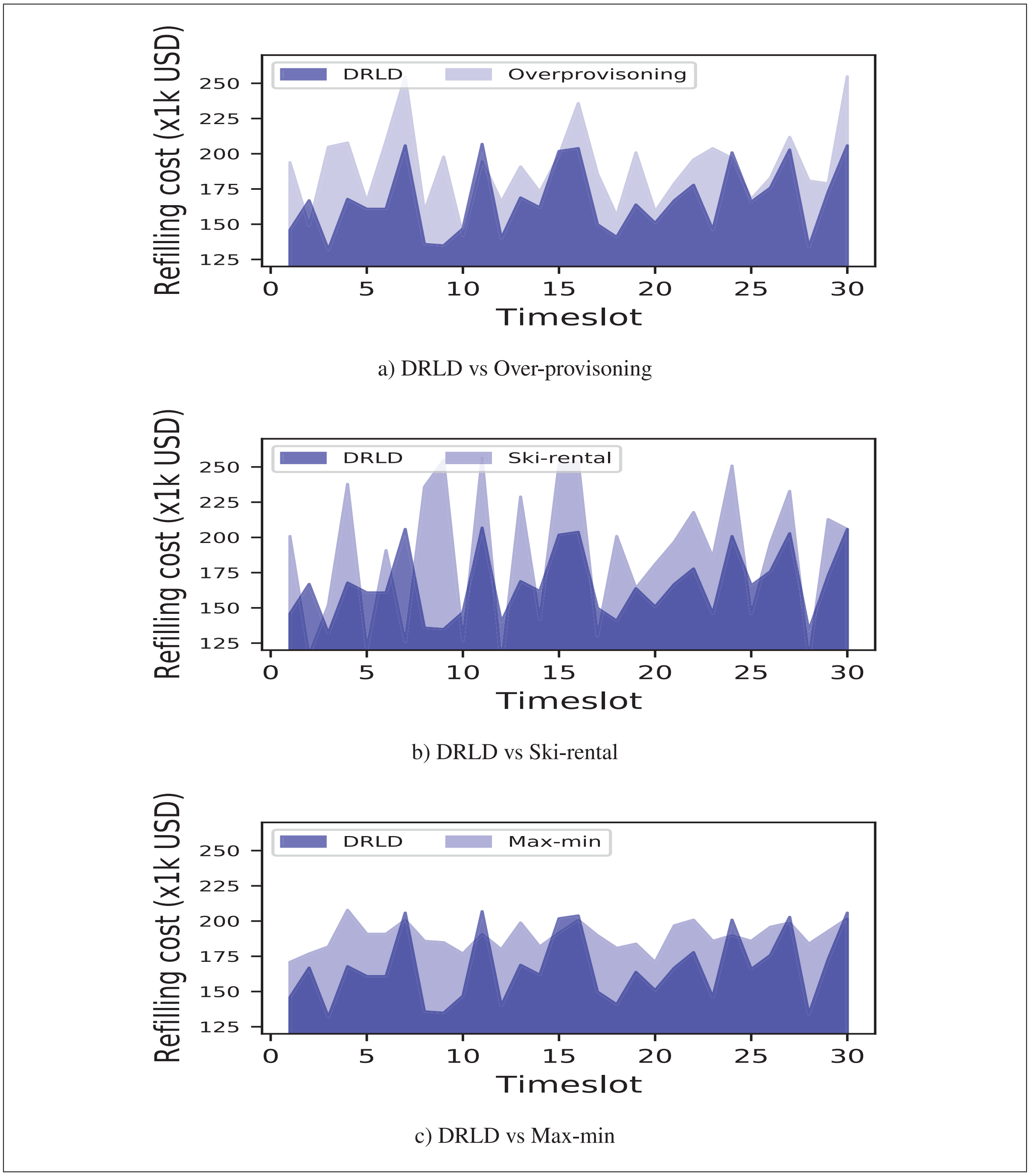
5.5.2.1 Convergence evaluation

We first evaluate the convergence of our proposed method to illustrate its performance. As shown in Fig. 5.4a, we show the reward values, which are significant because they impact the convergence, using different settings (e.g., datasets of 30, 50 and 70 drugs). With the smallest setting, we obtain the fastest convergence, in close to 2800 iterations, because this setting occupies the smallest state space. The system meets the stop condition at around 3200 and 4000 iterations for the larger settings of 50 and 70 drugs, respectively. This evaluation also illustrates a promising aspect of our proposed method: when we increase the number of drugs in the system, the number of iterations does not exponentially increase.

In the next evaluation, we show the mean error rate of the DNN in Fig. 5.4b. This figure shows how the convergence of the DNN is affected by varying the learning rate. The DNN can reach a fast convergence when the learning rate is 0.01 (less than 5000s), but the error rate is still high. After some experiments, we selected a learning rate 0.005 that resulted in a low error rate where the system reached convergence after 10,000s. Although it requires a long training phase, with this rate, the DNN has a better decision-making performance. The convergence status allows us to demonstrate the total cost in the system compared to the optimal results calculated by the Ipopt solver. In Fig. 5.4c, a small gap is visible between the optimal value and the DRLD result for all settings. However, the optimal gap depends on the training phase and the training data. With our limited data set, we present a simple but promising result in this work. We will investigate this aspect in future work to find a real public dataset with which to obtain a practical training model.

5.5.2.2 Evaluation of the refilling cost

We consider the refilling cost in a time horizon with 30 time slots (we refer to one week for each time slot) as shown in Fig. 5.5. We first make a comparison with a simple, commonly-used



a) DRLD vs Over-provisoning

b) DRLD vs Ski-rental

c) DRLD vs Max-min

Figure 5.5 Refilling cost evaluation

method, Overprovisioning. Since the remaining volumes and the upper bound volumes of drugs are often used as the replenishment policy for each refilling inventory, they lead to a higher cost in most time slots. Fig. 5.5a illustrates the trace of the refilling cost during the considered horizon. The Over-provisioning method has a higher cost than that of the DRLD in most of the time slots. As shown in Algorithm 5.1, the system always explores the action space and exploits the knowledge at any given time step that is able to prevent the volumes of drugs from reaching bounded levels. On average, the DRLD can reduce the refilling cost by 12.31% compared to the Over-provisioning method.

Figure 5.5b illustrates the refilling cost of the DRLD and Ski-rental methods. Ski-rental is an online algorithm that makes decisions based on the current situation. However, the Ski-rental method does not involve the learning phase to deal with changes in the system. Furthermore, the performance of the Ski-rental method is sensitive to the competitive setting. In a complicated system with a large number of drugs and uncertain demands, the Ski-rental algorithm does not present a suitable approach to solve DR2O. On average, the Ski-rental method can obtain a better refilling cost than the use of Over-provisioning. However, it is more unstable and results in costs that are on average 10.4% higher than those of the DRLD.

Finally, we evaluate the refilling cost by applying the Max-min approach. The Max-min inventory model seeks to reduce the gap between the Max and Min values, where the Min value represents the reorder point and the Max value represents the targeted quantity. Although this method is simple and non-optimized, it is able to provide an automation model for inventory management by using some triggers. Max-min is similar to Over-provisioning, but more flexible if we set the lower and upper bounds with a high volume. The reorder quantity is calculated by the surplus between Max and Min. As shown in Fig. 5.5c, this method flattens the filling cost during the time horizon. Its results indicate that it is a promising approach to control the shortage problem, but its cost is higher than that of the DRLD by 11.8%.

5.5.2.3 Evaluation of the shortage situation

We evaluate the shortage situation in a time horizon by applying four methods within a finite horizon: Over-provisioning, DRLD, Ski-rental, and Max-min. During 30 timeslots, 4.37% of the drugs hit a shortage level if applying Ski-rental, while Over-provisioning is slightly better with 4.09 %. The Max-min method has an even better result with 3.41 % drugs at a shortage level. Our method, the DRLD, obtains the best result in this evaluation with only 2.21 % of the drugs in a shortage situation in the considered timeslots. Figure 5.6 shows the shortage situations and their evolution for all four approaches. In detail, Over-provisioning often hits serious shortage points, for example at timeslots 14, 24, and 27h, as the average value of the previous usage does not react well with the peak demand. The ski-rental method can obtain a better result compared to the Over-provisioning method, but it also often reaches a shortage level. This method can react better to the changes in demand than the Over-provisioning method, but it is too difficult to implement a correct setting of the c-competitive value for all the drugs in the system. The Max-min method does not hit some peak points, but the shortage situation still occurs frequently during the evaluation period, similar to the Over-provisioning method. As mentioned before, the intuition of the Max-min approach is not that different than that of the Over-provisioning method. Compared to all the baselines, the DRLD has the least amount of shortage points in the figure. At the peak shortage point (time slot 27), the DRLD has only 1.7 % of its drugs that reach a shortage, the lowest rate in the evaluation.

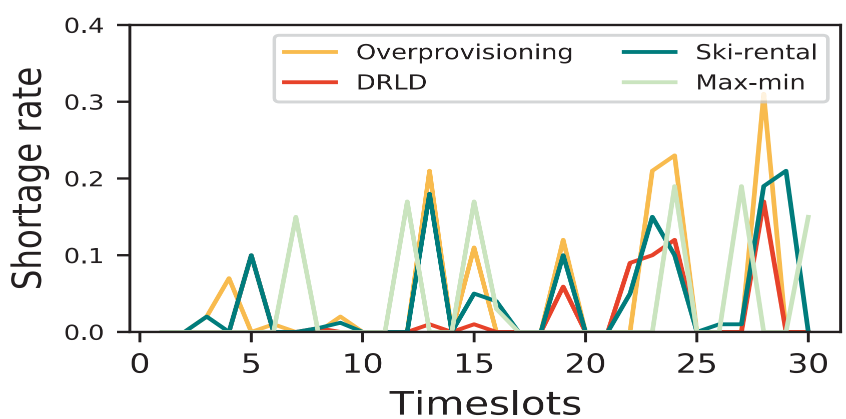


Figure 5.6 Shortage evaluation

5.5.2.4 Evaluation of the unexpected rate

Finally, we evaluated the unexpected rates of refilling drugs during 30 timeslots by using our proposed method and three baselines, as shown in Fig. 5.7. We measured this aspect to

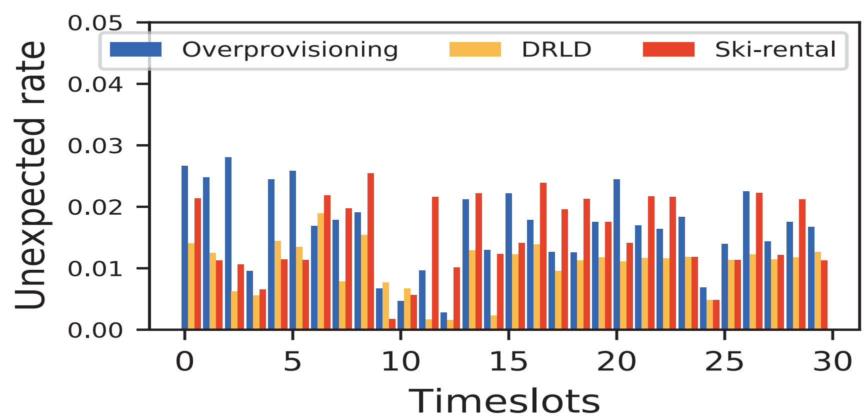


Figure 5.7 Unexpected rate evaluation

illustrate the efficiency of our system for refilling drugs and maintaining the volume of drugs at a stable level during a finite horizon. A high unexpected rate result is often considered as a low performance feature in inventory management. On average, Over-provisioning has the highest rate by 1.675%, and reaches the peak rate by 2.808%. It is unaware of the user demand, and so it is not able to prevent the system from a shortage or an overstock situation. If we increase the amount of the refilling volume, we can reduce the shortage, but it will proportionally increase the refilling cost and the number of redundant drugs. The Ski-rental approach obtains the average rate 1.54% higher than that of the DRLD with 1.03%. This rate can be reduced by adjusting the c-competitive value. In practice, it is impossible to obtain the correct value for all drugs with an unknown usage demand. In Fig. 5.7, the rate of the Ski-rental approach fluctuates, with a large magnitude from the lowest rate of 0.1718% to the highest of 2.54%. With the awareness ability employed in the exploration and exploitation steps of the DRL, DRLD outperforms the other methods in this evaluation. The results illustrated in this figure reveal the efficiency of the DRLD at reducing the number of unexpected drugs in the refilling decision.

5.6 Conclusions

As stated in the literature review, a hospital supply chain is responsible for ensuring that there is an adequate connection between hospital institutions, operations, and the revenue cycle. While inventory management is connected with the procedures of requesting, storing, and utilizing an institution’s inventory, health care institutions across the globe are in search of approaches to improve the efficiency of operations; i.e., effective inventory management that can reduce expenditures while in no way affecting medical care and services. A ineffective hospital supply chain leads to product shortages, product discontinuity, decreased patient safety, poor performance, distribution flaws, and technological mistakes that result in stock shortages in hospitals. Furthermore, our assessment reveals how health centers can effectively mitigate drug shortages in their hospital supply chains by adopting Machine Learning (ML). By promptly processing enormous volumes of data in order to discern patterns and uncover insights that are overly complicated for the human mind, ML can enable health care providers to consistently provide the right quantities, at the right cost, place, and time.

We have proposed a deep learning model to solve the hospital supply chain inventory control, using a mathematical programming model (DR2O) that can capture the requirements for refilling drugs while minimizing the purchasing and storing costs. To solve this optimization problem, we apply a deep reinforcement learning method that can determine how much of the volume of drugs should be refilled at each time slot. Observations and analyses of the stock level changes were conducted based on intensive simulations. Our results outperform the other baselines with a finite horizon, specifically, the Over-provisioning, Ski-rental, and Max-min approaches. Our model has proven to be an efficient and promising mechanism with which to develop a dynamic programming framework for the management of hospital supply chain inventory.

CHAPTER 6

DISCUSSION

It has recently become crucial to develop drug shortage solutions for Canada's hospital pharmacy inventory system in order to deliver high-quality healthcare. Therefore, thorough research and effective medicine shortage solutions are given a lot of attention. Such a driving force directs our attention to addressing the study issues of drug scarcity related to the hospital pharmacy inventory system in Canada. Even though our research thesis has made a substantial contribution, there are still some limitations and research gaps that require further expansion. Therefore, we will review our contributions and talk about potential expansions of our thesis in this chapter.

6.1 Contributions and extension of the research thesis

Our thesis aims at answering three research questions, including i) How can we obtain precisely research work related to the drug shortage topic in the Canada's hospital pharmacy? ii) What are major challenges and current strategies to deal with drug shortage in the Canada's hospital pharmacy? and iii) To design an efficient inventory management model, What and How can AI/ML methods be applied to mitigate or avoid the drug shortage situation?

The described research in this thesis helps to establish an innovation management model for Canada's hospital pharmacy inventory system by providing the answers to these research questions. The first contribution is presented in Chapter 3, which aims to conduct a systematic literature review to accurately obtain research work related to Canada's drug shortages. Based on that, we investigate current factors and challenges in Canada's hospital pharmacy inventory systems, which is presented in Chapter 4. These contributions help us understand current problems and open issues of the Canada's hospital pharmacy inventory system in order to model a pharmacy inventory optimization model and propose an effectively learning inventory management method to be aware of drug shortages based on optimization and machine learning techniques. Specifically, in Chapter 5, we illustrate an optimization model and a promising learning method to automatically manage the pharmacy inventory system in terms of minimizing both the operational and the penalty costs caused by drug shortages. Although this proposed mechanism can only solve a use-case with a limited number of a training data set compared to aforementioned challenges in Chapter 3, to our best knowledge, our study is the first work that models an optimization model for the Canada's hospital pharmacy inventory and solve it based on a deep reinforcement learning method. Our model is designed to accommodate a range of drugs across multiple time periods, providing scalability from 1 to N drugs. However, it's important to note that the complexity of the problem increases with the number of drugs involved, which can pose challenges when solving the problem at a large scale with some optimization solvers such as MATLAB, Gurobi. Therefore, we advocate a machine learning (ML) framework that minimizes the impact of scalability. By leveraging ML techniques, we can optimize the problem-solving process and mitigate the potential complications associated with an increased number of drugs. This approach allows for more efficient and effective management of large-scale scenarios within the pharmaceutical domain. With the three main contributions of this thesis, we present a picture of a Canadian hospital's pharmacy inventory system based on the selected research publications. Although in the limitation scope of our thesis, we cannot give all indications of the nature and complexity of the medication shortage that Canadian pharmacists face, our study can be seen as one of the significant contributions in order to leverage future extensions and research to increase the quality of healthcare services and reduce impacts of drug shortages. We underline impacts of medicine shortages, primarily in terms of health outcomes, but also in terms of convenience. As shown in our survey, the CPhA Drug shortages (Canada) reports that more than a quarter of Canadians have directly encountered or know someone who has suffered a medicine shortage in the recent three years. One-fifth of individuals polled claimed they had personally experienced a medication shortage, ten percent said they knew a family member who had. Such numbers summarized in Chapter 3 show a large number of people in Canada suffering negative impacts from drug shortages. The following were the most commonly reported ways in which health outcomes had suffered:

- patients are agitated, perplexed, furious, and upset, and they have lost faith in drugs and pharmacists;

- alternative drugs have been less effective, especially when used as 3rd or 4th line alternatives;
- antibiotics have been in short supply;
- there have been no alternative medications available;
- alternatives cause side effects, allergies, and/or adverse events;
- phenomenon of skyrocketing prices.

However, as our best knowledge, open-access surveys for Canadian hospital pharmacies are old which more than 5 years ago while new materials are not open or difficult to access. Especially, it is more difficult for those who do not work in the hospital pharmacies.

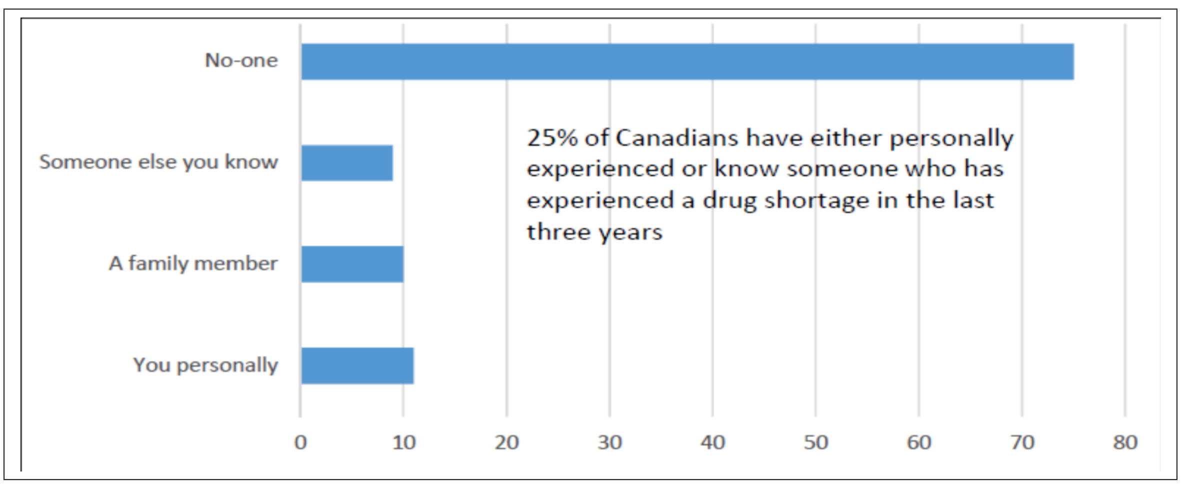


Figure 6.1 Percentage of Canadian who have experience of drug shortages the last 3 years Taken from Association *et al.* (2010)

Meanwhile it's also obvious that the present shortages are more widespread and long-lasting than in the past and affect to several areas that do not belong to health systems. As shown in the report in 2004, 63 percent of respondents said a medicine shortage occurred during one shift, increasing to 81 percent in 2010. In 2004, 80 percent of pharmacists said a shortage had occurred in the previous week, increasing to 94 percent in 2010. Pharmacists reported spending around 17 minutes each shift dealing with shortages in 2004, rising to 30 minutes, or nearly twice as much time, in 2010 related to numerous reasons, such as logistic systems, material supply chains, pandemics, civil wars, etc. With a lot of changes in terms of environmental conditions, society to innovative technologies, we benefit from the research by describing a new situation in the Canadian hospital pharmacy inventory supply chain in which the total supply of regulated drugs fails to meet the projected or current demand at the patient level. Patients who must switch to worse options, according to the survey, are not receiving the same quality of care as they require, or, in the worst-case scenario, cannot be treated by any required drugs at all. Consequently, patients' faith and trust in the healthcare system is eroding time by time. Hence, we aim to illustrate that one of the key priorities of any health care system is to secure the supply of medications. In practice, the alternative is often a common solution for doctors in treatments but it is not always enough and effective if we do not have an efficient solution to make the inventory supply chain sustainable. Therefore, the information acquired from the comprehensive survey (Chapter 3) is scientifically significant to identify the existing challenges and issues that should be taken into account in inventory management. Specifically, our comprehensive survey demonstrates the two critical factors affecting Canada's supply chain including manufacturing problems and transportation, regulation, and management of the supply chain. While manufacturing issues are difficult to address, selected related work presents potential approaches to deal with drug shortages. Modern economic models, optimization algorithms, and AI/ML approaches are very applicable to optimize the inventory supply chains in which multiple agents, brokers, companies, and organizations can be teamed up to participate an intelligent and optimized ecosystem of pharmacies. While our model accounts for various dynamic cost factors such as refilling cost, storage cost, and penalty cost, the inclusion of expiration cost remains a possibility. We can introduce a linear function to represent the expiration cost, which increases proportionally with the quantity of refilled drugs. This is justified by the notion that as the imported drugs increase, the system incurs higher costs associated with expiration.

The demand parameters can be expanded to incorporate trend and seasonality factors. This means that variations in demand, such as higher demand for flu medicines during the winter season, can be accounted for. To achieve this, an additional learning model can be employed to predict drug market demand and provide the necessary parameters for our analysis. By considering trend and seasonality, we can enhance the accuracy and effectiveness of our demand forecasting in the pharmaceutical market.

6.2 Serious consequences from the reactive solutions and calls for immediate actions

Most of the current solutions to cope with drug shortages are reactive solutions such as changing medicines, over-provisioning, obtaining medication from other sources. The survey in Canada drug shortages Canada (2021) demonstrates more than 21% surveyed people who purchased online to look for an alternative medicine. However, substitute drugs often bring side effects which causes deaths or serious impacts while over-provisioning leads a very high cost because of storing, managing and damaging. Billions of dollars could be saved if we have an optimal inventory to reduce the drug waste in the pharmacies.

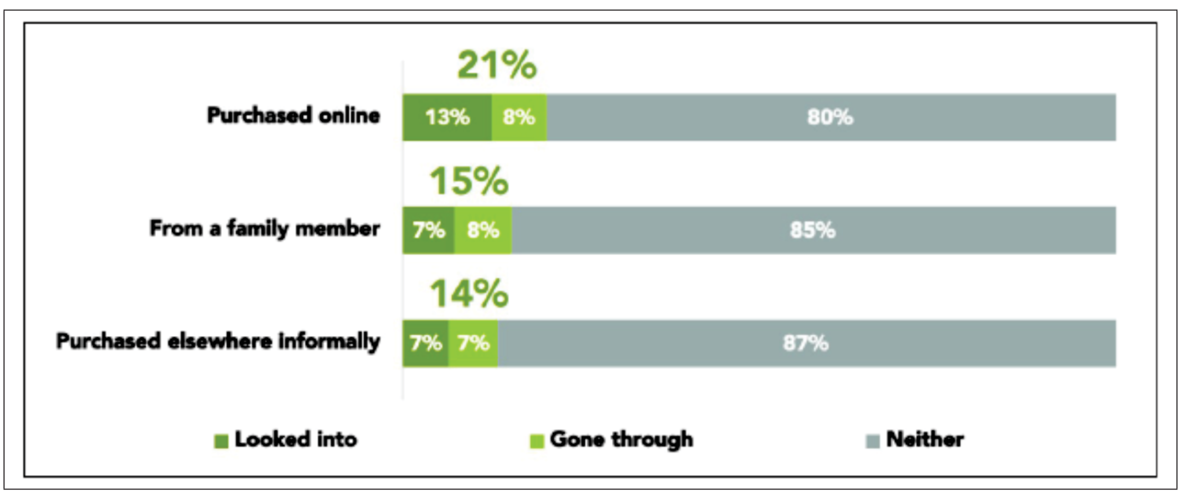


Figure 6.2 Obtaining alternative medication from other sources
Taken from Canada (2021)

Instead of coping with drug shortages by these approaches, proactive solutions will be very potential to predict drug shortage periods and learn and forecast user demand phenomenons to react better to the dynamic environment. For instance, learning history data from patients, and predicting demands based on history and the current environment (such as pandemic) are very attractive in research and practice. In this work, we leverage the use of machine learning to apply to this topic and contribute to research. Although we are excited to bring capabilities of advanced data analysis, AI, and machine learning to help hospital pharmacy leaders, we face difficult questions from pharmacy owners, such as how possible is that? What is the confidence level about the occurrence of an impending shortage? In order to answer these questions and convince managers of pharmacy supply chains, investigations in academic and industry research are key enablers that allow innovative technologies and mechanisms that can be applied to due with drug shortages. These research studies will be a bridge to connect real pharmacy systems and potential research methods in academia.

Despite the potential, they are challenging tasks to work together to employ big data, machine learning, and AI to apply to the health system rather than accepting the status quo to deal with drug shortages. We need to have innovations and higher-level goals for future health care systems. These goals are to understand the deeper infrastructure that every hospital pharmacy in the country uses and relies on and to assist health systems in management so that they can receive what they need for their patients.

From here, we must continue to share, grow, and expand the data we are putting into the system. We believe that optimizing the inventory supply chain and AI and machine learning will be most useful in identifying strategic risks, rather than acute threats that are typically addressed by panic buying or hoarding.

The objective of this thesis is to stabilize hospital pharmacies and the health-care systems. We can provide advanced awareness of supply chain concerns, such as challenges, risk, as well as tools for taking action based on that knowledge.

Taking into account the prospective outcomes of our thesis, we want to assist Canadian hospital pharmacists in proactively identifying measures to address the shortages, such as making good decision to import an amount of drugs. We help pharmacies to see, organize, and put all of that information together, in a way that will enable an optimal solution in the whole inventory system to better manage drug shortages.

6.3 Discussion

We make the following discussion on how to enhance the inventory based on the findings of the research. In actuality, there is not a single, universal approach to addressing the drug shortages. To address and respond to shortages, both in the short and long term strategies need to operate simultaneously from governments, regulatory agencies, manufacturers, distributors, pharmacy corporations, and pharmacists. To reach the global destination of a high quality healthcare service, they must not only cooperate but also exchange resources and personal information. As part of future work, we aim to the real implementation of the proposed model in a pharmacy setting to showcase its practicality and effectiveness. This would involve deploying the model in a live pharmacy environment and evaluating its performance and viability. The implementation process could include several steps. First, it would be necessary to collaborate with a pharmacy or healthcare facility willing to participate in the study. This would involve gaining access to real-time data on drug inventory, demand, and other relevant parameters. Next, the model would be integrated into the pharmacy's existing infrastructure or developed as a standalone system, depending on the specific requirements. This might involve working closely with the pharmacy staff to ensure seamless integration and compatibility with their workflow. Once implemented, the model would be put to the test in a real-world scenario. The performance of the model would be evaluated by comparing its predictions and recommendations with the actual outcomes and decisions made by the pharmacy. This assessment would help assess the accuracy and effectiveness of the proposed approach in managing drug inventory and optimizing supply chain operations. Furthermore, feedback from the pharmacy staff and stakeholders would be collected to identify any challenges or areas for improvement. This iterative process would allow for refinements and adjustments to enhance the model's functionality and address any limitations that may arise.

In summary, we list recommendations to address the drug shortage in Canadian hospital pharmacies:

- long-term consideration in the inventory supply chain should be taken into account, which should put a high priority on the patients instead of benefits;
- to secure enough supply, manufacturers must work together to get more efficiency. The number of drugs in shared inventory systems will be more sustainable;
- manufacturers, distributors, wholesalers, and pharmacists must communicate more effectively. When pharmacists are unaware of the degree of a medicine shortage, it is extremely difficult for them to assist patients in coping with the situation. They must put more effort to be aware of low supply and to predict abnormal phenomena in the inventory supply chain to have efficient alternative solutions;
- arbitration should be limited. Several stakeholders raised the issue of supply arbitrage, or the practice of buying medications in one jurisdiction and selling them in another. Even if prices are varying, market actors must assure enough supply to clients in their own jurisdiction. Price prediction also plays an important role to cope with drug shortages;
- for pharmacists, big data, AI and machine learning will be useful tools to help cope with shortages. Regardless of whether a more concentrated effort is made to address the core causes of shortages, pharmacists must be equipped these tools with the information and skills they need to deal with shortages.

CONCLUSION AND RECOMMENDATIONS

In the past, when inventory systems were simple and there were many manual managements, preventing medicine shortages could be accomplished without the use of a computer since a manager would be aware of exactly which medications were running low and would experience a shortage. The manual method is obviously not scalable. We must start considering inventory systems like elephants when they have to manage a few thousands of medications supplied by various firms through various supply chains. Conducting related work and useful report become very essential to understand current problems and challenges to find answers for drug shortages. Such motivations make us study current problems of Canada's hospital pharmacy inventory in this research thesis. In this chapter, we summarize all our contributions, conclude our thesis and discuss the future work to extend our current research.

7.1 Conclusion

The main contributions of our research thesis are as follows:

- Designing a systematic literature review to precisely obtain research work related to the drug shortage topic in the Canada's hospital pharmacy.
- Studying major challenges and current strategies to deal with drug shortage in the Canada's hospital pharmacy.
- Designing an optimization inventory management model for Canada's hospital pharmacy inventory and proposing a deep learning method to automatically manage the inventory system in terms of minimizing the operational and penalty costs caused by drug shortages.

Going through our thesis, the systematic literature review and the comprehensive survey research gives important elements for us to construct the ML-based architecture. Using the systematic literature review, we can enhance the search procedure to precisely obtain the newest relevant research. Based on this methodology, we acknowledge that the existing research on the hospital pharmacy inventory in Canada is insufficient or antiquated. As a result, our thorough assessment offers a fresh perspective on this supply chain system, including all of its difficulties. We demonstrate that in order to minimize medicine shortages, we must start now by incorporating current technology from inventory to supply chain management. We emphasize the importance of AI and machine learning-based implementation to employ cutting-edge technologies to address the medicine shortage. However, to apply these innovative techniques, understanding clearly and concretely the Canadian hospital pharmacy's inventory supply chain is mandatory. We have offered a systematic literature review to carry out a thorough survey that produced certain and noteworthy findings from high-quality research articles in order to achieve that.

As shown in the results of the research (Chapter 3), it confirmed that many pharmacists in Canada have been saying for months: drug shortages are real and are having a detrimental impact on patients' health and well-being. It also means that the current systems need to be studied and improved to be sustainable and reliable to deal with drug shortages. Reviewing different models and inventory systems, we illustrated that all key players in the drug supply and distribution chain – manufacturers, wholesalers, distributors, pharmacy corporations, governments, and pharmacists – will need to work much more closely together to better plan and inform each other in order to ensure that Canadian drug supply needs are met in the short and long term. Among all aspects, patients should be the highest consideration in the drug shortage period.

In addition, the pharmaceutical industry in Canada has always placed an emphasis on innovation from private companies to the federal government.

The demand for novel pharmaceuticals is greater than ever to address a number of new concerns, prompting us to participate in this thesis.

In order to assist pharmacists in addressing the short-term challenges caused by drug shortages, we have contributed to the research by providing different models and systems of inventory and supply chains. We discuss pros and cons of each to provide practical information, advice, and tips to pharmacists on how to deal with drug shortages.

Furthermore, we followed the evolution of the AI and machine learning technologies to implement a practical automation inventory management to mitigate the drug shortages.

We have contributed to the research by firstly presenting an optimization model for drug shortage in Canadian hospital pharmacy inventory. To deal with the drug shortage, we design a variable to present an amount of drug that should be imported. We considered a time horizontal optimization problem in which the time is slotted and each time slot the system will automatically made inventory decisions. They can also be seen as recommendation to a manager for their inventory actions based on the amount of remaining drugs, demands, prices.

We advocated the deep reinforcement learning framework to be employed in this model as the learning solution. Specifically, the system will be trained based on a sample of data to approximately learning actions of the inventory system. The operational cost is used to construct the reward function in which the system will select an action that can minimize the operational cost in long-term. A deep neural network is used in our model to cope with the complicated environment parameters in the drug inventory system.

Even though our simulation only covers a specific use-case with a small dataset, our result convinces that it is a potential approach which needs to have more investigation.

Through the beginning to the end of thesis, we illustrated that there is a need for more thorough and in-depth investigation into the causes that cause drug shortages in hospital pharmacies. Causes and challenges still exist many hidden aspects that need to be investigated, for example, relationship between pharmacies, stakeholders.

We have surveyed existing models and architectures of inventory managements and supply chains in Canadian hospital's pharmacies. However, there is a scarcity of available data and knowledge about the variables that cause active ingredients, drug prices, user demand, and pharmacy behaviors in response to drug shortages. Therefore, our research thesis still has gaps that need to be fulfilled and enriched. More intensive research in future on these factors which will extend and detail our drug shortage picture of Canadian hospital pharmacies. We aim to collaborate with a hospital in the future to establish a connection between our theoretical study and the actual reality. As a consequence, we will be able to incorporate relevant hospital resources into our complete research, both in terms of data and outcomes. In order to optimize and benefit their systems, we will also try to adapt our solution to a real pharmacy.

7.2 Recommendations

Focusing points in future work in order to better cope with drug shortages

To beyond the future inventory pharmacy system, we will focus on these majors areas: inventory supply chain, and how to organize the workflow and management strategies.

- inventory management. With the first key, we will assist pharmacies in inventory management by providing a real-time inventory view. Intelligent interact to deal with the drug management at each inventory will be considered such as an amount of drugs. These recommendations will allow the manager to better handle internal events. Enabling prediction functions will be promising tools that will be very appealing to persuade pharmacy managers to use it;

- supply chain. In the second section, we will provide a larger and more detailed picture of drug shortage in Canada and in specific provinces. Across several aspects of the supply chain, we will aim to show that all of the prospective possibilities in terms of pharmaceutical alternatives and accessible vendors. This will increase confidence of the pharmacy system, and readily examine all of the possibilities at any moment. New innovation technologies

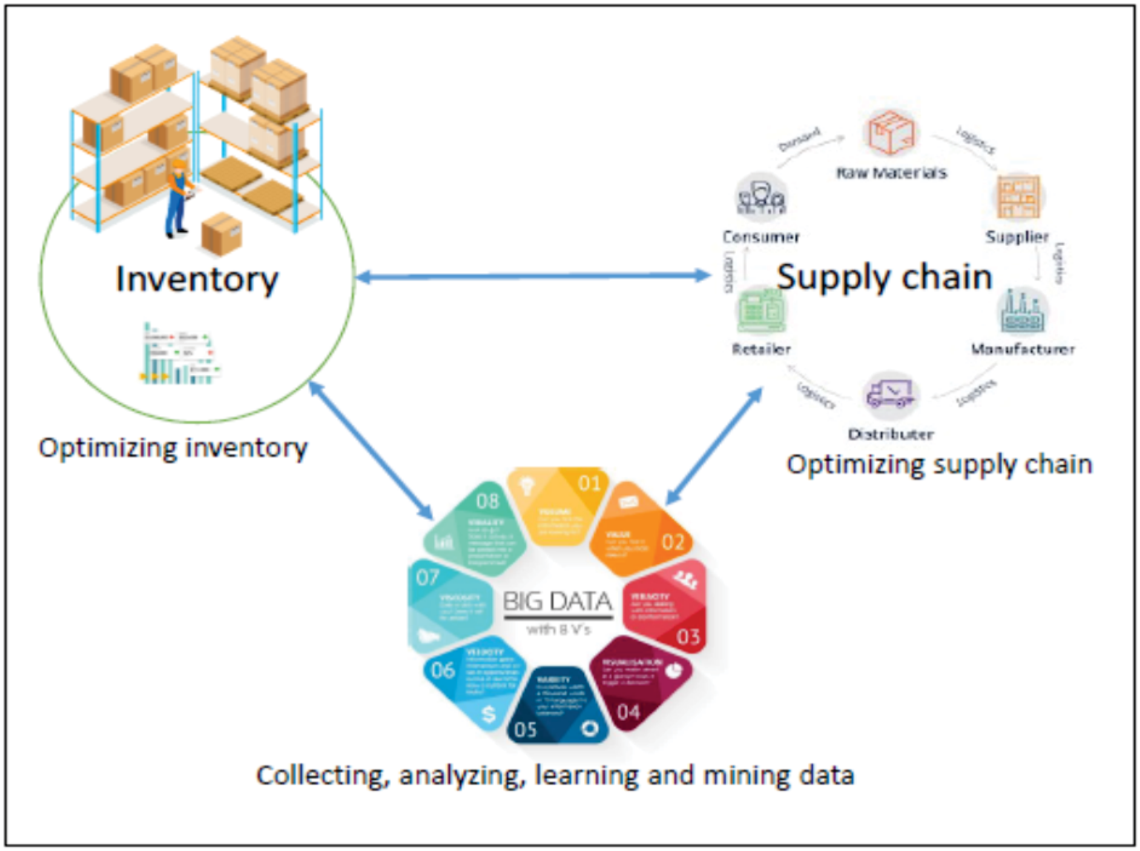


Figure 7.1 Obtaining alternative medication from other sources

in the logistic systems will play important roles in order to enhance the pharmacy supply chains, for example, smart contract, block chain will benefit and significantly contribute to the development of the pharmacy supply chain;

- big data, AI, machine learning. The third category, we will improve the workflow and communication in the Canadian hospital pharmacies to provide tools to organize and automate all the management system. Big data collection will be very potential in future to understand clearly the inventory and supply chain as well as to react better to drug shortages in terms of proactive solutions. Privacy-preserving mechanisms will have many rooms to be utilized to secure the system as well as protect the privacy of patients. These techniques will fill the gaps in our thesis and add more vital contributions in research and practice. Furthermore, considering the Canada’s hospital pharmacies, our practical implementation will have more chances to be used in practice by supporting in several open research projects in Quebec such as Mitacs (MITACS) and NSERC (NSERC) to conduct the results and performance.

APPENDIX I

SUMMARY OF SOME ARTICLES ANALYZED IN THE THESIS

This table summarizes key studies which have examined supply chain parameters which this thesis deemed vital to note. Some of them scrutinized multiple criteria, constraints as well as multi-stage/scale supply chain systems which this research will encompass during its model development and evaluation phase. The table below shows a summary of 30 articles analyzed in the thesis regarding drug shortages.

Table-A I-1 Summary of some Articles Analyzed about Drug Shortages

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Abu Zwaida *et al.* (2021a)	The challenges of drug shortages in the Canadian hospital pharmacy supply chain	Qualitative in-depth, Systematic Literature Review	Highlighting current knowledge gaps that exist about the factors which affect the supply chain, and the inventory management strategies that are utilized by hospital pharmacies in Canada which could lead to drug shortages	Facilitate a patient-focused, thorough assessment of potential consequences of drug unavailability and development of contingency plans that meet a patient's drug related needs	Lack of consistent reporting from reviewed resources	Factors such as raw Materials availability and increases in demand,cause drug shortages

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Abu Zwaida *et al.* (2021b)	Optimization of inventory management to prevent drug shortages in the hospital supply chain	Investigation of a Deep Reinforcement Learning (DRL) model to address this problem.	a general model for drug inventory management in a hospital, supply chain management, optimization to study a drug refilling optimization problem.	a general model for drug inventory management in a hospital, supply chain management, optimization to study a drug refilling optimization problem. Hospital Supply Chain (HSC).To solve optimization problem, deep reinforcement learning method help in determining volume of drugs refilled in each timeslot	Limited scope of analysis, the content evaluated was minimal and could not make generalization	Health centers mitigate drug shortages in their hospital supply chains by adopting Machine Learning (ML). Deep Reinforcement Learning (DRL) model address drug shortage problem under an online solution that can automatically make a drug refilling decision. When the number of drugs is increased in the system, the number of iterations does not exponentially increase.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Aljadeed *et al.* (2021)	The impact of COVID-19 on essential medicines and personal protective equipment availability and prices in Saudi Arabia.	Questionnaire-based cross-sectional study	Analyze impact of the COVID-19 pandemic on the availability of essential medicine and personal protective equipment (PPE) in Saudi Arabia	Effective exchange programs between hospitals. Increase public healthcare spending to ameliorate the negative impact of the pandemic on the healthcare sector	Research did not represent all the employees in the medical and pharmaceutical supply chain reasons behind shortages of drugs and PPE were not explored	COVID-19 pandemic caused a significant disruption in the global pharmaceutical supply chain, its impact was largely manageable in Saudi healthcare institutions
Badreldin & Atallah (2021)	Global drug shortages due to COVID-19: Impact on patient care and mitigation strategies	Systematic Review	Investigate potential impact of DS due to COVID-19 on patient and the role of pharmacists and pharmacy policymakers in alleviating emerging problems	Preserve the drug supply, Improve on communication Implement adjustable policies that govern the preparation plan of any potential drug shortage	Research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	Pharmacists and policymakers should be engaged in alleviating the effects of threat to patient care and outcomes

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Elbeddini *et al.* (2020)	Role of Canadian pharmacists in managing drug shortage concerns amid the COVID-19 pandemic	Review of existing data	To identify and summarize opportunities for improvement in pharmacy as learnt from the pandemic's first wave.	Having patients use their own pMDI Reusing pMDIs after sterilization Using nebulized salbutamol in COVID-19-negative patients	Not applicable	Pharmacists spend a substantial amount of time communicating and connecting with other HCPs, on behalf of their patients, to clarify drug orders and offer recommendations and pharmaceutical opinions to enhance medication management.
Gaudette (2020)	COVID-19's limited impact on drug shortages in Canada	Review and analyze content in Drug Shortages Canada website	Investigate whether the first months of the coronavirus disease 2019 (COVID-19) pandemic were associated with a significant increase in drug shortages in Canada.	Reports cite both supply-side and demand-side causes for shortages.	The study applied observational method and cannot inform about the causal impact of the pandemic on shortages	Drug shortage increased with therapeutic classes associated with COVID-19 care

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Goff *et al.* (2020)	Global contributions of pharmacists during the COVID-19 pandemic.	Interviews of pharmacists	To describe how pharmacists from high and low-middle income countries contributed to crucial patient care and well-being of the public during the COVID-19 pandemic. To find out whether the first months of the (COVID-19) pandemic were associated with a significant increase in drug shortages in Canada.	The process of diagnosing and treating COVID-19 patients in the hospital, after discharge or as an outpatient is complex and therefore requires a multidisciplinary team of experts which includes pharmacists.	The methods used were observational and couldn't inform about the causal impact of the pandemic on shortages. Despite shortage reporting is mandatory in Canada, compliance hasn't yet been assessed, and the real number of shortages may have been greater than reported, both during the pandemic and the comparison period. Shortage reports don't provide direct insight into severity of shortages and their impact on patients.	Pharmacists in Canada focused their efforts largely on keeping patients, families, and health care providers safe during the pandemic. There was an increase of 147 shortages (32 percent) reported by manufacturers during March and April 2020 relative to the same months in previous years.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Hussain *et al.* (2020)	Pharmacy services during COVID-19 pandemic: experience from a tertiary care teaching hospital in Pakistan	Systematic Review	Role played by Pharmacy services in public health in preventing and containing the COVID-19 pandemic	Establishing professional protective and service guidance for pharmacy staff and services, creating and updating drug formularies, addressing the issues of drug shortages, providing public education for prevention and management of infection	limited resources associated with Covid-19 pandemic situation	All over the world, especially in the developed countries pharmacists have responded smartly and speedily for public health
Liu *et al.* (2020)	Providing pharmacy services during the coronavirus pandemic	Commentary reviews	Reviewing the unique needs of pharmacy services in the COVID-19 pandemic	Pharmacists should identify and serve the unique needs of pharmacy services in a pandemic	Chinese pharmacists and pharmacy associations responded forcefully to the COVID-19 epidemic.	Pharmacy community to plan and operate pharmacy services to combat current and future epidemics

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Mallhi *et al.* (2020)	Multilevel engagements of pharmacists during the COVID-19 pandemic	Literature Review	Analyzing the current situation rationally; test, treat, and immunize; policies to guarantee medication safety and rational use of drugs	During the current crisis, innovative and adaptive methods of practicing will be required across all health professions.	Research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.	Governments, public health bodies, and policy makers review existing services and make full use of any unrealized potential among pharmacists working in various sectors
Modisakeng *et al.* (2020)	Medicine shortages and challenges with the procurement process among public sector hospitals in South Africa; findings and implications.	Qualitative in-depth interviews	To highlight challenges in the current pharmaceutical procurement process for public sector hospitals	Effective management of contracts of suppliers by the Provincial Department of Health is crucial to ensure accessibility and availability of essential medicines to all	The study encountered Challenges such as the inaccuracy of the electronic inventory management system used in the hospitals	Computerized inventory management systems is important to reduce medicine shortages

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Martei *et al.* (2020)	Shortages and price variability of essential cytotoxic medicines for treating children with cancers.	A cross-sectional survey	To examine the availability and acquisition costs of essential medicines for treating cancers in children.	Not applicable	Not applicable	Low Middle-income Countries and Low Income Countries facilities used fewer medicines than Upper Middle-income Countries and High Income Countries facilities. Upper Middle-income Countries and Low Middle-income Countries facilities were more likely to report medicines not available or stock-outs.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Raiche *et al.* (2020)	Community pharmacists' evolving role in Canadian primary health care	Investigatory research	Analyzing Integration of community pharmacy in primary health care	pharmacy advocacy groups across the country must coordinate and collaborate on a harmonized vision for innovation in primary care integration, and move toward implementing that vision with ongoing collaboration on primary health care initiatives, strategic plans, and policies	Lack of consistent reporting	Canadians deserve to receive timely, equitable, and safe interdisciplinary care within a coordinated primary health care system, including from their pharmacy team.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Vogler & Fischer (2020)	Drug shortages: The situation in four European countries and their approaches to handle the problem	a primary survey (using a questionnaire)	To survey national measures to manage and combat drug shortages.	There is a need for a multi-country approach in identifying global or at least European answers to the issue of drug shortage.	Not applicable	There was an increasing level of measures to manage and prevent shortages of medicines. Frequent measures include registers to report shortages, facilitated regulatory procedures and stakeholder dialogue.
Zhang *et al.* (2020)	Factors associated with drug shortages in Canada: a retrospective cohort study	A retrospective cohort study	To identify the factors associated with drug shortages in Canada.	Policymakers should try to balance cost-containment with security of drug supply by paying extra attention to markets with comparatively tight profit margins and that are under pressure of price-capping policies, which may result in a market with a single generic supplier	The study evaluated the association between drug price and drug shortage only among DINs listed on formularies due to a lack of price data for all DINs.	13% of the 3470 markets analyzed reported to be in shortage.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Acosta *et al.* (2019)	Medicine shortages: gaps between countries and global perspectives. Frontiers in pharmacology	A scoping study presented as a narrative review of the situation and findings principally based on published articles	To identify and compare, if possible, as well as characterize the current literature concerning medicines shortages between countries, and offer different perspectives including a global context and national approaches	The identification of options and best practices on how to address the most common causes of shortages would be useful. Share of these practices among all countries would be useful in providing future direction. Policy makers require solutions that prevent those cases in which the population's health is affected by episodes of medicine shortages and/or interruption in the supply chain	There were other attributes that may have broaden the study which were not discussed. The study had limited scope of comparison	National strategies for notifying and managing the medicines shortages cases were described and classified by update frequency. The study identified the major differences between market and supply chain management perspectives as well as global and countries' perspectives Generate a glossary that applies logistics management to ensure availability of medicines to overcome shortages.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Ahmadi *et al.* (2019)	Inventory management of surgical supplies and sterile instruments in hospitals: a literature review	Systematic review	To present an up-to-date review of research in the field of inventory management of surgical supplies and instruments.	Cost saving in operating rooms would have a significant financial impact	Not applicable	Operating rooms are the main revenue source, and the major source of waste and cost, among the hospital's departments.
Arbaeen (2019)	Platinum anticancer drug shortages (Master's thesis, University of Sydney)	Content Analysis		Strategies for addressing production disruptions, discontinuation by companies supply, changes in customer demand, supply problems such as transport and storage, and others	Not applicable	Causes of shortages include production disruptions, discontinuation by companies supply, changes in customer demand, supply problems such as transport and storage, and others.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Phuong *et al.* (2019)	The impacts of medication shortages on patient outcomes	A scoping review systematically synthesizing literature	To systematically synthesize the literature to report on the economic, clinical, and humanistic impacts of medication shortages on patient outcomes.	Results of this review provide valuable insights into the impact drug shortages have on patient outcomes. Drug shortages were predominantly reported to have adverse economic, clinical, and humanistic outcomes to patients.	The study reported medication shortages resulted in negative patient clinical, economic, and humanistic outcome.	Drug shortages were predominantly reported to have adverse economic, clinical and humanistic outcomes to patients. Patients have increased out of pocket costs, rates of drug errors, adverse events, mortality, and complaints during times of shortage

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Kritchanchai *et al.* (2018)	Healthcare supply chain management: Macro and Micro perspectives.	Multiple case studies were conducted at 13 hospitals which include secondary hospitals and primary hospitals. Triangulation techniques, including interviews, site visiting and document analysis, were also employed for data collection to enhance reliability and validity of the study.	To explore the operations in the healthcare supply chain materials and information flows across the players at both macro and micro levels.	The concept of supply chain and logistics management should be considered as it contributes to an effective process and patient safety	Not applicable	The healthcare supply chain efficiency could be achieved at 2 levels, namely supply chain level and firm level.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Videau *et al.* (2019b)	Drug shortages in Canada and selected European countries: a cross-sectional, institution-level comparison.	A descriptive cross-sectional study	To identify, describe, and compare drug shortages in health care facilities in Canada and other countries	All stakeholders should work more diligently to prevent and manage drug shortages.	The study was based on data from a single hospital in each country.	From January 8 to February 2, 2018, 84 shortages were reported (average duration was 32 days) there were 62 shortages in the Canadian hospital, (with average duration 9 days) in the French hospital, 46 shortages (average duration 37 days) in the Belgian hospital, 28 shortages (average duration 25 days) in the Spanish hospital, and 98 shortages (average duration 68 days) in the Swiss hospital.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Zwaida *et al.* (2019)	Comprehensive literature review about drug shortages in the canadian hospital's pharmacy supply chain	Literature Review	Covering the drug shortage in the Canadian hospital pharmacy supply chain	By identifying the existing challenges, the patients' quality of life can be improved by resolving the identified issues.	There is limited information regarding the factors causing the active ingredients to be accessed	Highlighting the link between the supply chain challenges and diminished quality of life
Shepherd (2018)	US Drug Importation: Impact on Canadaand# 8217; s Prescription Drug Supply. Health Economics & Outcome Research.	forecasting model	To re-examine and estimate the impact of the U.S. drug importation from Canada on the Canadian prescription drug supply.	The solution for the high drug prices in the United States is not importing another country's pharmaceuticals and threatening their drug supplies.	Not applicable	The model found that if 20% of the U.S. prescriptions were filled using Canadian prescription drug sources, the 2015 Canadian drug supply would be exhausted in 183 days.
Bowles (2019)	Drug shortages: more than just background noise	Systematic review	To compare several aspects of drug shortages among Canada and four other European countries	Not applicable	Not applicable	Drug shortages occurred on every day, primarily affecting injectable products.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Donelle *et al.* (2018)	Assessing Canada's drug shortage problem. CD Howe Institute Commentary.	Systematic review	To examine the size of the drug shortage problem in Canada between 2010 and 2017, scan the stated reasons for shortages internationally	A stable supply solution of a diversity of medicines is required to keep healthcare costs down, avoid costly solutions to sudden emergencies and maintain access to medications for the entire population, including the 10 percent of Canadians who cannot afford their prescription drugs.	Not applicable	Approximately 1,000 shortages have been reported annually, affecting 1,250 products during a recent three-year period.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Beck *et al.* (2017)	Physician approaches to drug shortages: Results of a national survey of pediatric hematologist/oncologists.	A survey	To evaluate personnel who deal with scarce drug prioritization and distribution and the standards used to inform drug distribution during times of shortage among pediatric hematologists	A societal approach to drug shortages is necessary to reconcile disparities in drug distribution during shortage times.	A limited sample size was used, and the voluntary nature of the survey could have resulted in possible selection bias	Most physicians find out about shortages from the pharmacists.
De Weerdt *et al.* (2017b)	Time spent by Belgian hospital pharmacists on supply disruptions and drug shortages: an exploratory study	Filling a template	To quantify in a comprehensive manner the amount of time employees of 17 Belgian hospital pharmacies spends on drug supply problems.	A fully reliable, daily updated list on the federal agency's websites would be a major help to hospital pharmacists.	Five Hospital pharmacies were excluded since they could not fill in the template during several weeks and this could have led to an under estimation.	Hospital pharmacists spent an average of 109 minutes every week on drug supply problems, with a minimum of 40 minutes per week and a maximum of 216 minutes per week.

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	Title	Methodology	Objectives	Solutions	Limitations	Results
Yang *et al.* (2016)	Current situation, determinants, and solutions to drug shortages in Shaanxi Province, China: a qualitative study	A qualitative methodological approach	To analyze, characterize, and assess the drug shortages, and identify possible solutions in Shaanxi Province, western China.	All stakeholders, especially the government, needed to participate in managing the drug shortages.	A small number of interviewees was interviewed.	Five main determinants of drug shortages were identified: too low prices, too low market demands, Good Manufacturing Practice (GMP) issues, materials issues, and approval issues for imported drugs.
Zu'bi & Abdallah (2016)	A quantitative analysis of the causes of drug shortages in Jordan	Quantitative analysis methodology	Investigates the causes of drug shortage in Jordan	Securing the supply of medications and ensuring meeting the needs of end customers in term of accessibility, quality, quantity, and cost of medications	The response rate was relatively low specially from the pharmacists	Factors affecting drug shortage include regulatory and legislative processes, distribution factors, human factors, and supply and demand imbalance

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Table-A I-1 Summary of some Articles Analyzed about Drug Shortages (Continued)

Authors/Year	**Title**	**Methodology**	**Objectives**	**Solutions**	**Limitations**	**Results**
Organization *et al.* (2016)	Medicines shortages Global approaches to addressing shortages of essential medicines in health systems	Experimental research	Technical consultation was hosted by WHO in December 2015 to discuss the bottlenecks and reasons for shortages	Prioritize measures to ensure the continued supply of the medicines that are most needed in public health systems	Reliance of past experiences	Shortages of medicines and technologies are of concern to all countries, end-to-end approach across the health system is needed to mitigate their impact on public health

APPENDIX II

COMPREHENSIVE LITERATURE REVIEW ABOUT DRUG SHORTAGES IN THE CANADIAN HOSPITAL'S PHARMACY SUPPLY CHAIN

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Abstract:

Pharmacies play a central role between the manufacturers and patients because they ensure that patients access their required medications. In health facilities, pharmacies receive drugs from manufacturers and then sell them to patients as per their demand. This paper will cover the drug shortage in the Canadian hospital pharmacy supply chain, which is described as a situation in which the total supply of regulated drugs fails to meet the projected or current demand at the patient level. It can adversely delay or compromise medical procedures, drug therapy and result in medication errors. One of the key priorities of any health care system is to secure the supply of medications; and drug shortages can be linked to a complex combination of factors. These factors include increasing demand, regulatory issues, and inventory issues. The Proposed Methodology is a literature review which is conducted through search engines such as Google Scholar. The search is driven by keywords, phrases, and terms such as drug shortage in Canada, so this research entails a literature review of drug shortage in the Canadian Hospital's Pharmacy Supply Chain.

Keywords: Drug Shortage, Supply Chain, Canadian Hospital's Pharmacy.

1. Introduction

Pharmacies play a central role between the manufacturers and patients because they ensure that patients access their required medications. In health facilities, pharmacies receive drugs from manufacturers and then sell them to patients as per their demand. It is important that patients do not lack the prescribed drugs in pharmacies for the improvement of their health. However, it can be observed that it can be common for patients to not to find their intended prescriptions due to drug shortages. If patients cannot access their desired drugs, then their health risks can be magnified. Instances of drug shortages indicate a break in the pharmacies' supply chain. Majorly, the problem may be with the manufacturers because they represent the beginning of the supply chain. Sometimes, manufacturers may lack the necessary capabilities or resources to manufacture the desired drugs. In such scenarios, there would be no drugs to transport to pharmacies and patients would lack their desired medication. This research entails a literature review of drug shortage in the Canadian Hospital's Pharmacy Supply Chain.

2. Literature review

The literature review will be conducted through search engines such as Google Scholar. The search will be driven by keywords, phrases, and terms such as drug shortage in Canada, Canadian Hospital Pharmacy supply chain, Canada's pharmacy inventory management. Additional information would also be accessed through medical journal databases such as Pub Med, The Canadian Journal of Hospital Pharmacy, Pharmacy and Therapeutics, Journal of Pharmacy Practice, The World Health Organisation website, The International Journal of Logistics Management, House of Commons (Canada) Website, and combine one database for years ranging between 2012 and 2019. The Drug shortage is described as a situation in which the total supply of regulated drugs fails to meet the projected or current demand at the patient level (Boyle, 2012). It can adversely delay or compromise medical procedures, drug therapy and result in medication errors (Lane *et al.*, 2017). The World Health Organization (WHO) had long recognized drug shortages as a complicated global challenge (Saedi *et al.*, 2016). Additionally, the Organization *et al.* (2016) also asserts that the problem affects all countries regardless of their economic development levels such as (low-income, middle-income, and high-income countries). Furthermore, it can be observed that the most common drug shortages globally include cancer medicines, antibiotics, anesthetics, and cardiovascular medicines (Chaar, 2014; Organization *et al.*, 2016).

Drug shortages can be linked to a complex combination of factors. These factors include manufacturing issues such as a shortage of active ingredients, distribution, stochastic demand, and inventory issues among others (Boyle, 2012; Zu'bi & Abdallah, 2016). When manufacturers fail to access active ingredients for the manufacture of drugs, there is a drug shortage. For example, in 2012, it became difficult for manufacturers to get the active ingredient necessary in the making of isoniazid 300 mg tablets, which is used in the treatment of Tuberculosis (TB) (McLaughlin *et al.*, 2017; Jung *et al.*, 2015). The situation also heightens the risk of the health of other people because if the TB is not treated due to lack of access to the appropriate drugs, it can spread to other people (Seaworth *et al.*, 2013).

It can, thus, be challenging to meet the intended health objectives, particularly when the necessary ingredients cannot be accessed, even when other stakeholders in the supply chain have sufficient resources (Fox *et al.*, 2014).

One of the key priorities of any health care system is to secure the supply of medications due to distribution challenges while simultaneously ensuring addressing the needs of end service users in terms of cost, quantity, quality and accessibility (Abdallah, 2013). Growing disruptions within the distributions channel and supply chain place patients and health care systems at greater risk for maintaining a continuous delivery of health quality care services, as pointed out by Sharma *et al.* (2013). Such disruptions have also been noted to be the reason behind increased health care spending and lengthened patient treatment plans (McLaughlin & Skoglund, 2015; Mousazadeh *et al.*, 2015).

Demand is stochastic, which means that it may be unpredictable to determine the type of drugs which would be in high demand in the following phase because the demand may differ from the current one (Bam *et al.*, 2017; Dalton & Byrne, 2017). If demand continue being unpredictable, the issue of drug shortage may continue because pharmaceutical distributors may fail to distribute sufficient drugs for the identified health issues (Canada, 2017).

Pharmaceutical supply is vulnerable to many risks resulting in wastage of valuable resources alongside disrupting the availability of medications leading to the increasing problem of drug shortages (Narayana *et al.*, 2014; Pauwels *et al.*, 2015). Canada faced the worst year in 2012 due to drug shortages when it became apparent that Novartis International AG's production capability would be greatly reduced, thus, affecting the production of drugs at the firm's premises at Sandoz Canada (Barthélémy *et al.*, 2013). The limitation of a firm's production capacity means that patients cannot access the prescribed drugs because the drugs would not be available at the pharmacies (Melchert & Fincham, 2012; Gagnon, 2012). The problem seemed magnified by an increase in the number of manufactured involved in the drug shortages from 41 to 58 in 2010-2011 to 2011-2012 respectively. Between 2006 and 2010, the number of manufacturers involved in the drug shortages totalled 70, which is a significant number based on the understanding that each of these manufacturers has sufficient capacity and resources to manufacture drugs (Barthélémy *et al.*, 2013).

In 2010, the drug shortages issue was also high based on the inability of Canadian pharmacists to locate a medication, whereby in the previous week, 94% of the pharmacists could not locate a medication (Vaillancourt, 2012). It can be observed that the situation is dire when it becomes apparent that about 94% of pharmacists cannot locate a medication. Furthermore, it is also risky when it emerges that hospitals can experience anaesthesia shortages as was the case in Canada, whereby the shortage forced anaesthetics to give unfamiliar medication and inferior anaesthetic medication to patients (Hall *et al.*, 2013).

Drug shortage also jeopardises patients' health because of the ease in which counterfeit drugs can be accessed in the market (Blackstone *et al.*, 2014). However, counterfeit drugs are illegitimate and they can cause further risks to people's lives because they are unsafe (Johnston & Holt, 2014; Iyengar *et al.*, 2016). Being counterfeit drugs, they have not undergone the necessary tests by relevant health organisations to determine their effectiveness and safety levels (Pullirsch *et al.*, 2014; Caulder *et al.*, 2015). Thus, patients are exposed to illegal drugs in the market as they try to seek alternative medication to their situation. Such risks explain the need to have effective supply chains to ensure that quality drugs are available to patients when required.

3. Canadian hospital's pharmacy supply chain

For public health services, private health care providers, clinics and prisons, evaluating the pharmaceutical supply chain enhances patient safety, reduces costs and improves operational efficiency. Fragmentation, the use of multiple distribution channels, various price structures, manual tracking systems, and lack of integrated pharmacy automation are just a few preventable factors that contribute to increasing the costs associated with a chain of custody. Safe pharmaceutical supply. An integrated model, from manufacturer to patient, can improve efficiency and safety. Typical hospital pharmacy supply chain is as illustrated below;

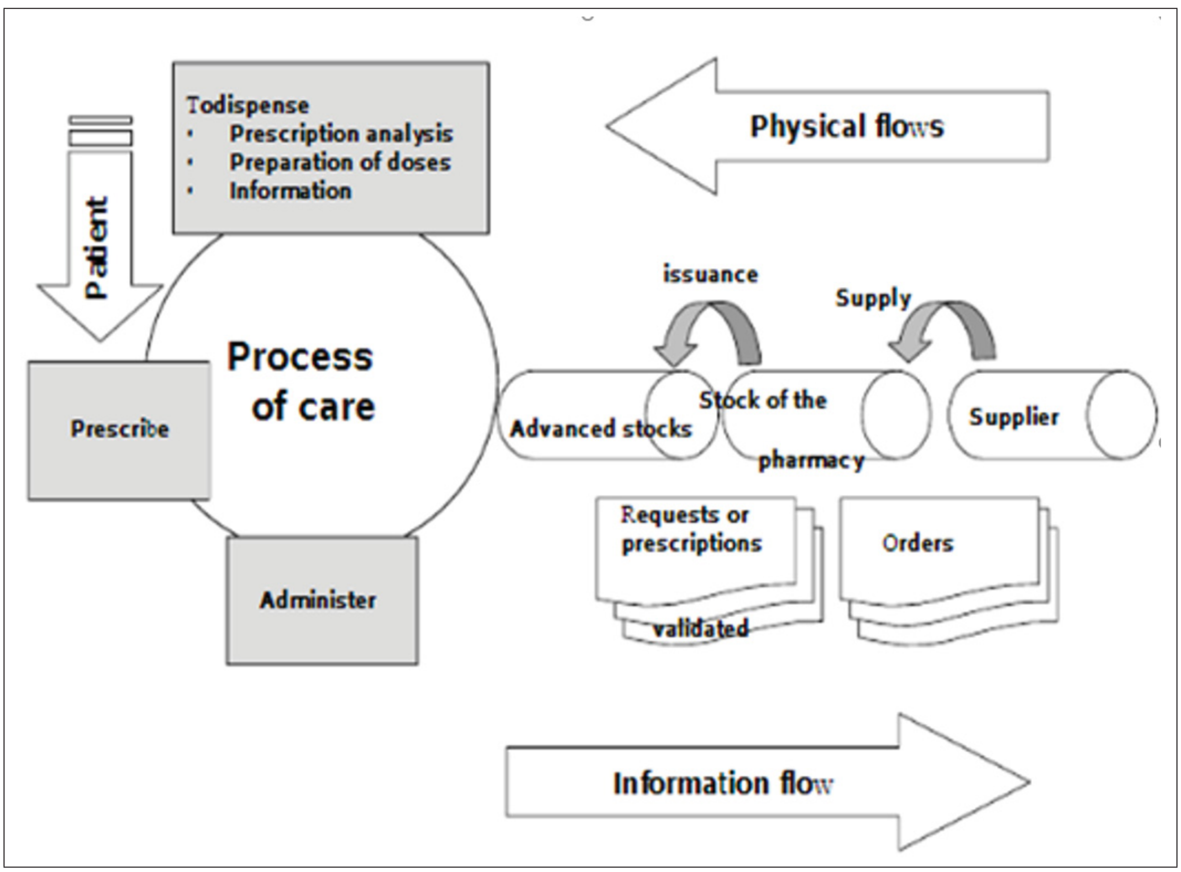

Figure-A II-1 Hospital pharmacy supply chain (derived from literature analysis)

In patient-centered and safety model, three main components are highlighted with respect to hospital supply chains, which are: Pharmaceutical distribution from a single source, automation in hospitals, and pharmacy services with prescription preparation center.

4. The hospital pharmaceutical supply chain

The hospital pharmaceutical supply chain must make it possible to provide patients as efficiently as possible with the hospital pharmaceutical products that will be administered to them, under conditions guaranteeing safety and traceability while respecting the numerous regulations surrounding hospital pharmaceutical products and their dispensation.

4.1 Suppliers

The hospital pharmaceutical market is dominated by a few large groups providing a wide variety of references. The award of contracts for the supply of medicines is regulated by the Public Procurement Code, which restricts the freedom to negotiate with them.

4.2 The pharmacy and its stocks

The activities and responsibilities of the hospital pharmacist are also defined by the law as well as the conditions of delivery and reimbursement of hospital pharmaceutical products. In addition, the inventory management of the pharmacy is made complex by the number of products and the heterogeneity of logistics data, volumes and various packaging, specific storage conditions (fridge, safe places for narcotics, sterile spaces), the management of expiry dates, ...

4.3 Advanced stocks

Each medical unit and medical-technical unit has a stock of hospital pharmaceutical s, managed locally by nurses. The management of these stocks for the same product is different in the care units or in the medical-technical services (filling and billing).

4.4 The care process

Just like inventory management, the process of care is also different depending on the units of care and medical-technical units. For example, the delivery of billable bandage will be done in a care unit on the basis of a prescription and will be invoiced a priori, while in a medico-technical unit, the prescription and billing will be carried out posteriori. In addition, the process of care conditioning the demand for hospital pharmaceutical products is strongly marked by the randomness and preponderance of the human factor. Most importantly for the drugs especially which are in daily basis requested such as on an urgent situations or emergency basis have to be satisfactory or acceptable in quality or quantity and in appropriate supply to eventually reach the patient.

4.5 Information flows

The information flows surrounding the hospital pharmaceutical supply chain are numerous and complex. They must indicate which drug to prescribe to which patient, must ensure the traceability of the administered hospital pharmaceutical products and their invoicing, they must also allow the reimbursement with the insurers, to assure a return of the information for a hospital pharmaceutical assistance on the administration of the drugs.

4.6 The actors

The actors intervening throughout the chain are numerous and must have a double competence (technical and medical), which results in the independent management of hospital pharmaceutical flows compared to other logistical flows of the hospital.

The Canadian Pharmacy Supply Chain incorporates manufacturers, pharmaceutical distributors, and hospitals (house of Commons Canada, 2012).

From the figure above, it can be observed that the supply chain starts with the manufacturers, who deal directly with distributors. The pharmaceutical distributors are bound by the stipulated

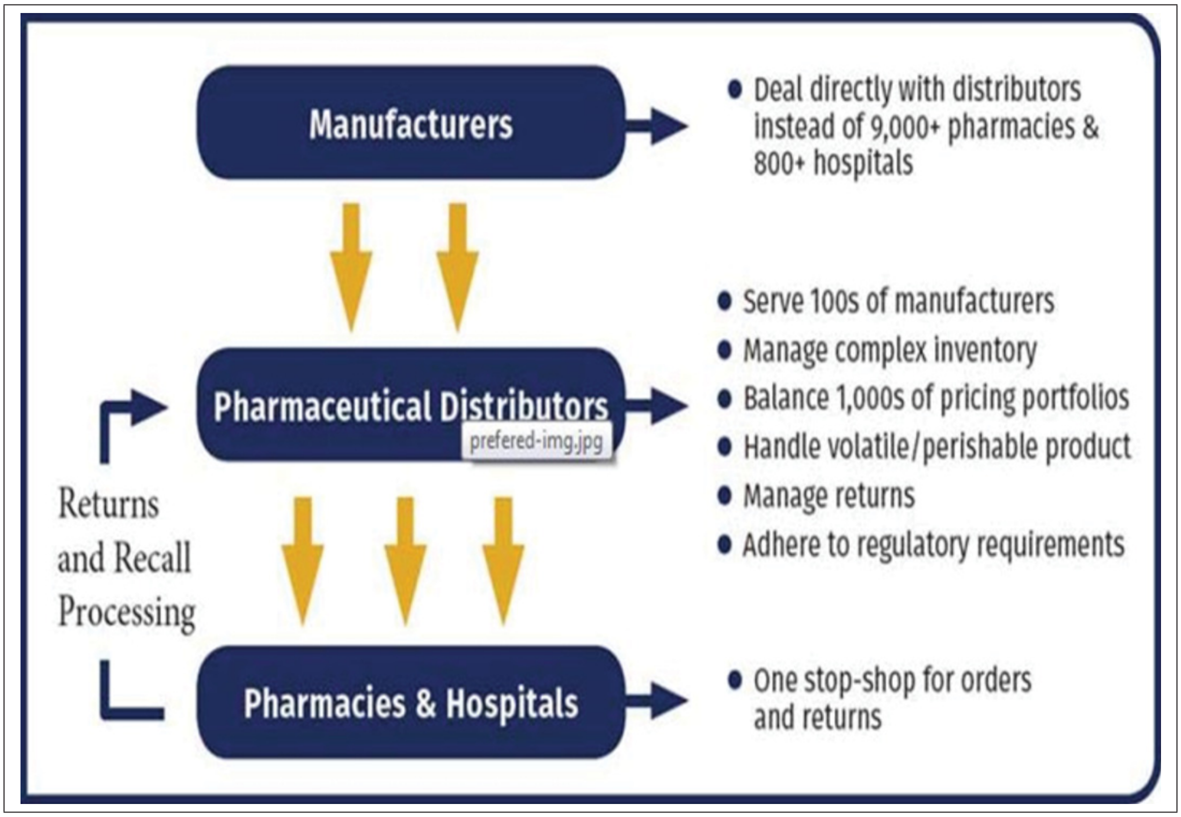

Figure-A II-2 Canada's favored Pharmacy Supply Chain Model
Taken from canadian Association for Pharmacy Distribution Management (2018)

regulatory requirements as they serve hundreds of manufacturers. They ensure that hospitals and pharmacies access the necessary drugs by transporting the drugs to them. The pharmacies and hospitals serve as one-stop shops for orders and returns.

The Canadian Pharmacy Supply Chain Model differs from the Pharmacy Supply Chain Model employed in the European Union.

From the figure above, it can be observed that the manufacturers have a pivotal role as the first in the supply chain. After manufacturing the drugs, the wholesalers assume the responsibility of taking the drugs and distributing to the pharmacies. The wholesalers' operation is founded on enormous volume and slight margin (Kanavos *et al.*, 2011). Furthermore, wholesalers also consider latest variations in the distribution model in several Member States, predominantly concerning elevated cost medicines, as fractional and creaming off a momentous revenue source

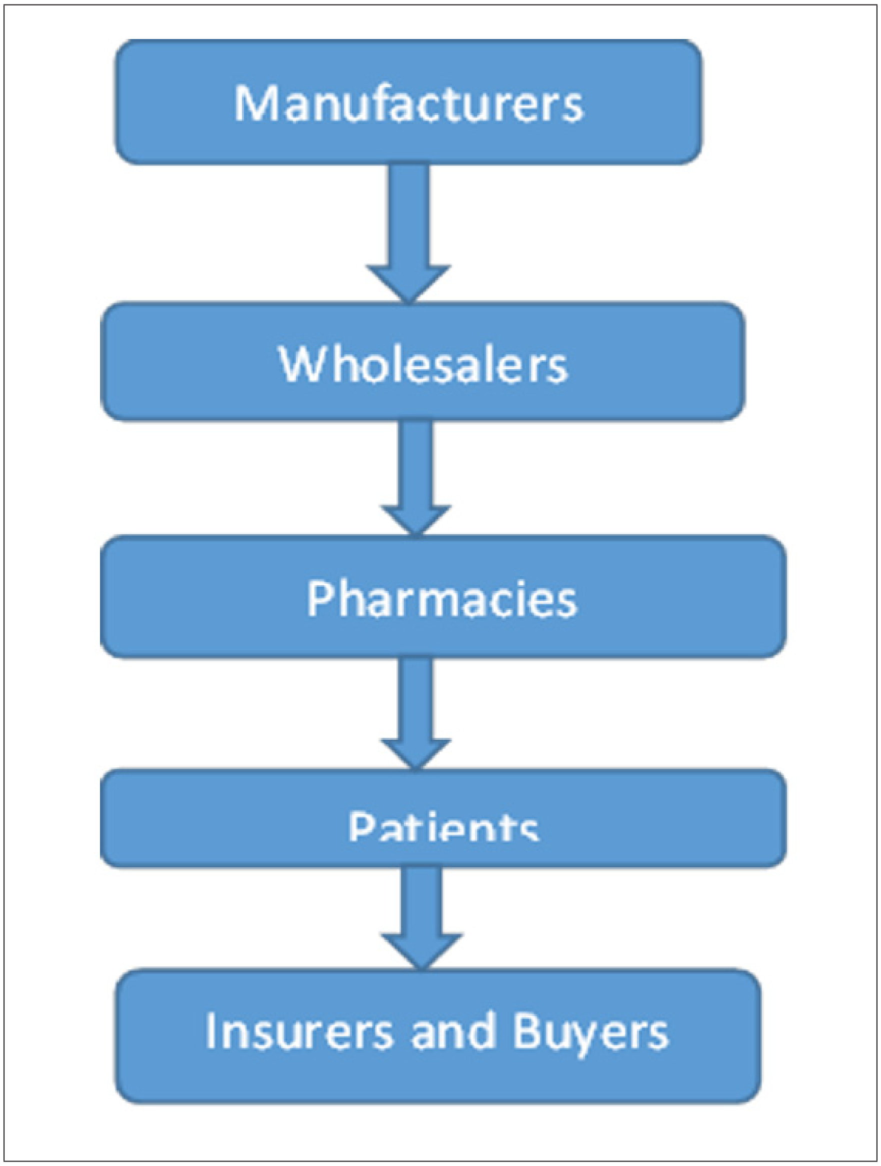

Figure-A II-3 European Union Pharmacy Supply Chain Model
Taken from Kanavos *et al.* (2011)

for their operations. Pharmacists have the capability to negotiate terms of transport and delivery with wholesalers and this is changing the supply environment by forcing the pharmacists to negotiate with manufacturers with the aim of reducing the costs of delivery (Kanavos *et al.*, 2011).Regarding patients, it can be observed that many of them are unaware of the distribution costs. The primary consideration of patients is the affordability and availability of medicines. To manage the costs of accessing drugs, many patients depend on the role of health insurers and payers. The patients use their health insurance to purchase the drugs. Insurers and payers also influence the supply chain because they are subjected to distribution costs and taxation charges. Such costs have forced the insurers and payers to initiate initiatives such as rebate and tendering policies (Kanavos *et al.*, 2011). In Canada's context, the identified stakeholders play significant roles in ensuring that the end user (patient) accesses the necessary drugs whenever required. If a problem occurs in one area, it would affect all the other stakeholders in the supply chain (Ebel *et al.*, 2013). For example, if the manufacturers are unable to produce the required drugs, the pharmaceutical wholesalers and retailers may be unable to provide the drugs (Denton, 2013). Additionally, if the wholesalers are effective but the pharmaceutical wholesalers and retailers lack the necessary capacity to distribute the drugs, the patients would be faced by drug shortage.

The Canadian Association for Pharmacy Distribution Management (CAPDM) plays the role of being the pharmacy supply chain voice in Canada and that the chain is smooth to ensure that drugs reach the patients as anticipated for the improvement of quality of health and life (the House of Common's Standing Committee on Health, 2017). Based on the understanding that the self-distribution pharmacy chains and pharmaceutical wholesalers are responsible for 95% of the drugs distributed to hospital and community pharmacies and even specialized and long-term healthcare facilities, the CAPDM plays a crucial role of managing the supply chain to ensure that manufactured drugs get to the patients (house of Commons Canada, 2012). However, the CAPDM's role can be challenging particularly when the problem seems to be associated with manufacturing bottlenecks. It can be observed that common causes of drug shortages entail problems related to manufacturing such as issues with the Good Management Practices (GMP), unpredicted demand surges or hitches in procuring raw materials (Canada, 2017). When the manufacturers cannot procure raw materials, the pharmacists cannot locate a medication and in turn; patients cannot access drugs (, FDA). Patients' health is put at risk due to compromised or postponed medical procedures, medical blunders and substitutions with different treatments that are ineffective or unsafe (Ventola, 2011; Mazer-Amirshahi *et al.*, 2014; Quadri *et al.*, 2015). As long as the manufacturers continue to experience challenges such as those associated with procuring raw materials, the entire supply chain would remain ineffective. Pharmacies would continue lacking drugs and patients' lives would be jeopardised due to lack of access to the necessary drugs (Ahmadiani & Nikfar, 2016; Rider *et al.*, 2013; Kweder & Dill, 2013).

There is a need to implement measures to ensure that the supply chain runs smoothly through the implementation of effective stock management and inventory.

5. Pharmaceutical stock management and inventory

The pharmaceutical inventory management system involves the amalgamation of technology, processes and procedures to monitor and maintain stocked medications (Shabaninejad *et al.*, 2014). Pharmaceutical departments and companies have a crucial role in ensuring that patients access their desired drugs when they need them after prescription (Kehrer *et al.*, 2013).The ensuing process may require the implementation of an effective stock management program to understand the movement of drugs from the manufacturers and their availability when needed by patients (Shabaninejad *et al.*, 2014; Jaberidoost *et al.*, 2013). Notably, it is possible for pharmaceuticals to struggle to meet patients' needs due to disturbance factors, such as those linked to risk and uncertainty in the industry and the supply chain (Huq *et al.*, 2016). Pharmaceutical departments experience immense challenges in stock management, which are caused by the random nature of the demand in drugs and the multiple constraints that must be considered before each decision is pronounced (Jurado *et al.*, 2016). For example, in a given month, the list of drugs ordered may be different from the list of drugs ordered in the following month due to the variations of ailments at a given time due to the unpredictability of the demand (Azghandi *et al.*, 2018; Mills *et al.*, 2013). Therefore, it may be challenging for pharmacies to prepare adequately with sufficient drugs for all known ailments, but this does not eliminate the need for pharmacies to prepare adequately.

6. Results

From the provided information, it can be observed that the major challenges contributing to the lack of access to medication are related to the various identified factors such as manufacturing issues such as a shortage of active ingredients, distribution, increasing demand, inventory issues and natural disasters. When manufacturers cannot access the required ingredients for the drug manufacturing process, pharmaceuticals would not have drugs to transport and patients would not have drugs to purchase. Furthermore, without sufficient manufactured drugs, the distribution would be affected due to a decrease in the number of drugs transported from the manufacturers to the pharmaceutical wholesalers and retailers. To ensure that pharmaceutical companies are well prepared in the supply chain, it would be necessary to consider such factors as costs of drugs, shipping costs, and costs of storing drugs in the pharmacy (Woo-Miles, 2015). These considerations should be aimed at enhancing the pharmacies to satisfy the identified demand. The major objective of demand satisfaction is to minimize stock out probability due to the observation that demand is stochastic (Bam *et al.*, 2017; Dalton & Byrne, 2017). It can be a challenging task for pharmaceutical companies to meet the demand because demand itself is stochastic; it may vary unexpectedly and rapidly. When patients need their prescriptions, they expect to access drugs from various pharmaceutical outlets. However, these needs are not always met, and patients encounter drug shortages, which jeopardizes their health (De Weerdt *et al.*, 2015b).

The following table is a summary of the information acquired from the literature review regarding the issues affecting the Pharmacy Supply Chain:

7. Discussion

From the literature, it can be observed that there is a need for comprehensive research regarding the factors contributing to the manufacturers' inability to access the necessary ingredients for making drugs. Researchers have indicated about the manufacturers contributing to drug shortage due to their inability to access necessary ingredients. However, there is limited information regarding the factors causing the active ingredients to be accessed. Therefore, there is a gap regarding the factors causing deficiency of active ingredients. More research is required on factors which make manufacturers unable to access active ingredients, such as whether the ingredients are diminishing or otherwise.

Table-A II-1 Summary of the information acquired from the literature review

Factors	**Effect**	**Solution**
A shortage of active ingredients	Leads to drug shortage because drugs cannot be manufactured without active ingredients. Distributors cannot distribute the drugs and patients cannot access their preferred medication	Manufacturers to plan and ensure they have the necessary resources and capability to access the required active ingredients
Distribution	Patients cannot access their preferred drugs. Without sufficient resources to distribute the drugs, patients have no way of accessing the drugs at the pharmacies	Pharmaceutical distributors to liaise with manufacturers to ensure the right drugs are available for distribution. Additionally, pharmaceutical distributors to ensure they have the necessary financial and additional resources to transport drugs to hospital pharmacies
Stochastic demand	An ever changing demand makes it challenging for pharmaceutical firms to stock the necessary drugs. This means that patients would lack the necessary drugs at the pharmacies	Liaising with local hospitals to access quality data regarding changes in demand for specific drugs and disease prevalence. Additionally, the utilization of software to evaluate and assist in predicting changes in demand
Inventory issues	Communication efficiencies within the supply chain lead to inventory reductions at all levels	Proper use of software to ease inventory management

8. Contribution to science

The information acquired from this literature review is scientifically significant because it highlights the link between the supply chain challenges and diminished quality of life. As the challenges in the supply chain continue, people's health would continue being jeopardized due to lack of drugs. Therefore, by identifying the existing challenges, the patients' quality of life can be improved by resolving the identified issues.

9. Recommendation

It is highly recommended that manufacturers need to invest in resources that enhance the acquisition of the necessary ingredients for the production of drugs. Without the necessary ingredients, the manufacturers cannot produce the required drugs. This means that patients would not access the drug even if pharmaceutical companies had the necessary resources and capabilities to purchase and transport the drugs. Based on the stochastic nature of demand, pharmaceuticals need to ensure they are fully stocked at all times to guarantee continuous and effective service delivery to patients. Pharmaceuticals need to keep records and stocks of all necessary drugs required to ensure they understand their demand curves.

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