Robust Optimization of the Pharmaceutical Supply Chain for Minimizing Expiration and Wastage

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By

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Abstract:

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This thesis addresses the optimization of a three-echelon pharmaceutical supply chain for manufacturing and distributing medication products. The pharmaceutical supply chain (PSC) is of great importance and complexity as it requires efficient medication production, inventory management, and distribution methods to save patients' lives. In addition, it is considered a complex supply chain since it operates under different uncertainties and includes the perishability of medication. Pharmaceuticals accounted for $328 billion out of the $3.24 trillion annual healthcare costs in the United States in 2015 (Plunkett, 2015). The proposed three-echelon robust optimization model considers aspects of product perishability, demand uncertainty, and emission when optimizing the manufacturing and distribution of medication products. Two different models were optimized using the proposed approach to test its effectiveness and size scalability. The sensitivity analyses performed provide managers with a helpful understanding of the parameters that affect the developed (PSC) the most. From the obtained results, it can be concluded that managers can use the proposed robust approach to perform a quick and easy (PSC) optimization while accounting for demand uncertainty, product perishability, and resulting emissions to make well-informed decisions.

Indexing Terms: Pharmaceutical Supply Chain, Manufacturing and Distribution, Wastage and Perishability, Robust Optimization.

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Declaration and Copyright

Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of Khalifa University of Science and Technology. The work is entirely my own except where indicated by special reference in the text. Any views expressed in the thesis are those of the author and in no way represent those of Khalifa University of Science and Technology. No part of the thesis has been presented to any other university for any degree.

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1. Introduction

1.1 Background

The supply chain of pharmaceuticals is a major part of the medical industry, in addition to being one of the most complex supply chains due to its association with patients' health (Schiel, 2018; Urias, 2017). The research in the (PSC) is broad due to the importance of the medication being delivered, the necessary costs of the supply chain, and the effect of medication on patient's lives. The (PSC) can be defined as a "combination of processes, organizations and operations involved in the development, design and manufacturing of useful pharmaceutical drugs" (Singh, Kumar, & Kumar, 2016). The complexity of the pharmaceutical supply chain is derived from the large number of entities each having different objectives, collectively working to manufacture, distribute, transport, and sell medication to patients under different uncertainties and risks (Halabi & Gostin, 2015; Papalexi, Breen, Bramford, & Tipi, 2014).

1.2 Motivation

The importance of medication towards curing people causes the pharmaceutical supply chain to score over $825 billion globally in revenues with an expected annual growth of 4-6% on average (Bravo & Carvalho, 2015). The complexities and uncertainties in the (PSC) can lead to a variety of outcomes such as medication shortages, late deliveries, and surplus which leads to expiration and wastage. These outcomes lead to a range of different problems such as the spread of disease and fatalities in the case of medication shortage and late deliveries, while wastage and financial losses are suffered in case of medication surplus. The causes of medication shortage and late deliveries can be attributed to several inadequate measures involving the distribution strategy(s), the inventory policy(s), and demand forecasting. Therefore, the (PSC) should always aim to satisfy the medication demand fully to avoid disease spread and death.

Regarding medication wastage, lack of supply chain management, the improper analysis of demand forecasts, and/or inefficient inventory management can be the main causes of medication surplus and eventually wastage (Kot, Grondys, & Szopa, 2014). Individual and institutional entities resort to stockpiling a surplus of medication products in times of uncertainty to avoid shortages, which often turns to wastage when the demand does not meet the stocked supply. The handling of medication wastage is paramount as pharmaceuticals generally contain biologically active and often toxic chemicals that can threaten the ecosystem when disposed of improperly. In addition, medication disposal by patients lacks awareness

regarding the environmental impacts, which was demonstrated by several surveys where the garbage or sewage systems were used to dispose of expired medication. This was demonstrated by several surveys indicating that the garbage or sewage systems were frequently used to dispose of expired medication. Several disposal guidelines have been set forth by the (WHO), as well as drug take-back programs being implemented in several countries for proper drug disposal and donation.

However, proper disposal of expired medication requires a reverse supply chain, also known as reverse logistics (RL) or pharmaceutical waste management (PWM), to acquire expired medication and deliver it to specialized facilities that can properly process it. Pharmaceutical waste management is a separate supply chain that requires proper planning and financing to be able to collect and dispose of expired medication effectively, with an expected global market value growth from $1.19 to $1.98 billion between 2018 and 2025 (GlobeNewswire, 2020). Therefore, the aim towards reducing the necessary costs of waste management starts by optimizing the (PSC) to satisfy the medication demand, limit the generation of wastage, and optimize the process to reduce the overall cost.

1.3 Pharmaceutical Supply Chain Entities

There are several entities in the (PSC) such as the primary and secondary medication manufacturers, wholesalers, and providers. The manufacturer procures raw materials required from a supplier to manufacture the medication, package it, and send it to the wholesaler. The wholesaler purchases large amounts of medication from the manufacturer(s) and sells them to hospitals and/or pharmacies, which dispenses them to patients. The transportation provider is another important part of the supply chain as they facilitate the delivery of the shipment between echelons, and handle emergency deliveries in case of shortages. In addition to the complexity of the pharmaceutical supply chain, its managers face several challenges and uncertainties such as limitations in transportation and storage capacities, demand uncertainty, and medication perishability.

1.4 Problem Statement and Gaps

Several studies aimed to optimize different versions of the (PSC) by considering different aspects such as various uncertainty types, inventory policies, single or multiple objectives, and optimization techniques. Most of the reviewed studies considered at least two echelons encompassing a manufacturer and a medication provider and focused on a single objective; to minimize the model’s cost. Fewer studies included multiple echelons, where a raw material

supplier or wholesaler is considered, and some studies considered additional objectives such as minimizing the unmet demand or the emissions. Finally, the reviewed models varied between linear and non-linear mixed-integer programming models; (MILP) and (MINLP). A variety of different optimization methods such as stochastic, robust, or fuzzy optimization were the most used for optimizing the developed models, in the literature, while considering uncertainty. As stated earlier, the reviewed literature lacked a multi-echelon (PSC) model that can be optimized easily, while considering uncertainty, wastage, and emissions.

1.5 Thesis Objective

This work aims to study and optimize a three-echelon pharmaceutical supply chain using a (MILP) model that addresses uncertainty, wastage, and emissions by minimizing the total cost objective function. The three-echelon (PSC) model represents the manufacturer, wholesaler, and hospital/provider aiming to manufacture, distribute, and dispense medication to patients. The developed (MILP) model was solved using the AIMMS and CPLEX solver, along with a robust programming approach to handle the model's uncertainty. From the reviewed literature, every multi-echelon model was complex to formulate and required complex heuristic approaches to be optimized and was often non-robust in nature. Thus, we aim to formulate a three-echelon (PSC) that can be easily optimized and scaled to desire, while handling medication demand uncertainty, medication perishability, and resulting emissions. The proposed model and programming approach will be beneficial for decision-makers in optimizing their (PSC) to make accurate and reliable decisions to satisfy the demand during uncertainty.

1.6 Thesis Outline

The remainder of this paper is organized as follows: Section 2 discusses the pharmaceutical supply chain background literature and the main contribution of our work. Section 3 presents the methodology and formulation of the proposed model. Section 4 presents the results of the formulated model, along with the sensitivity analyses of model parameters. Finally, Section 5 presents the conclusion from the results, as well as draw some useful managerial insights.

2 Literature Review

The literature review begins by outlining the global (PSC) financial trends and the resulting output wastage. Next, literature regarding reverse logistics (RL) of pharmaceutical waste is outlined, and the particular strategies and methodologies used are highlighted. Afterward, the forward logistics (FL) literature regarding the optimization of different versions of the pharmaceutical supply chain, supply chains of other perishable products, and the different approaches to deal with uncertainty. Finally, the gap in the literature of pharmaceutical supply chains is outlined along with the contribution of this paper to the advancement of (PSC) optimization and its real-world applications.

2.1 Pharmaceutical Supply Chain Trends and Wastage Production

The sale of over-the-counter medication in the United States grew from $16.8 billion to $35.2 billion between 2008 and 2018, with expected global growth from $129 billion to $162.9 billion between 2019 and 2025 (CHPA, 2017; marketresearchreportstore, 2020). In addition, pharmaceutical companies in first- and third-world countries are producing chemicals annually at a rate of 100,000 tons for use in making pharmaceutical products (Aus der Beek, 2016). In terms of supply chain and logistics, supply chain management costs account for up to 30% of total hospital expenses, while medication transportation and handling can account for up to 40% of the total logistics costs (Gebicki, Mooney, Chen, & Mazur, 2014; McKone-Sweet, Hamilton, & Willis, 2005). Inaccurate demand forecasting, improper inventory management, product perishability, and over-prescription are some of the leading causes of medication wastage.

A literature review study combined the results found by 48 survey papers in 34 countries with more than 33 thousand participants, regarding the chosen disposal methods of expired and/or unused medication (Alnahas, Yeboah, Fliedel, Abdin, & Alhareth., 2020). The vast majority of the participants mainly choose to dispose of expired and waste medication products via the garbage and sewer. This highlighted the lack of drug take-back options in most countries, as well as the overwhelming lack of awareness regarding the dangers of improper pharmaceutical waste management. Another study in Vienna examined pharmaceutical waste samples regarding their content and market value with 637 out of the collected 1089 items were medication products (Vogler & de Rooij, 2018). Of the medication waste found, 18% were full packs and 36% had not yet expired, and when the price of the wasted medicine was extrapolated for Vienna, the number became € 37.65 million.

Besides the financial losses imposed on the healthcare systems of countries and patients, the disposal of expired medications is environmentally harmful. The general waste management strategies followed in most countries include disposing of unwanted/expired medication in landfills, dumps, recycling, and burning pharmaceutical waste (Alnahas, Yeboah, Fliedel, Abdin, & Alhareth., 2020). In addition, antibiotics disposed of via garbage or sewage systems contain active pharmaceutical ingredients which have been found in the water and soil, hinting at the fact that harmful chemicals have the potential to find their way into the food chain and water table (DM, et al., 2016; Kim & Aga, 2007). The disposal of medication by garbage and sewer is still the most common method in many countries with the absence of the proper disposal of expired medications from the patient side (Tong, Peake, & Braund, 2011). Excess medication and changes to a medication plan can result in an excess amount of medication that will be left unused and result in wastage. A survey study was conducted for 53 pharmacists living in 19 different countries regarding their activities to reduce medication wastage (Bekker, Gardarsdottir, Egberts, Bouvy, & Bemt., 2018).

2.2 Reverse Logistics in the Pharmaceutical Supply Chain

Recent studies on reverse flow in supply chain management can be split into three categories: Sustainable, Green, and Closed Loop supply chain management (Schenkel, Cani€els, Krikkea, & van der Laan, 2015; Gurw, Searcy, & Jaber, 2015; Xin, 2010). Sustainable supply chain management aims to integrate sustainable goals in the supply chain, while Green supply chain management considers environmental aspects and aims to reduce any negative impacts on the environment in any supply chain (Nassir, Genovese, Acquaye, Koh, & Yamoah, 2016; Roy, Schoenherr, & Charan, 2018; Kumar & Kant, 2015; Fang & Zhang, 2018). However, the more realized practices in reverse flow have to do with reverse logistics and circular economy, both of which are associated with the closed-loop supply chain approach (Govindan & Soleimani, 2017; Govindan K. S., 2015).

Reverse logistics (RL) is associated with the recovery and recapture of any remaining value in a product once it is deemed useless by a consumer or lose the necessary traits needed for its appropriate or safe use (Agrawal, Singh, & Murtaza, 2015). In the (PSC), reverse logistics is followed when pharmaceutical wastage is collected and transported for proper disposal, with the vast majority of related studies focusing on the optimization of the collection operation of medication wastage from pharmacies and hospitals (Saravanan & Kumar, 2016; Franco & Alfonso-Lizarazo, 2017). The principle of circular economy aims to achieve a win-win situation in the economic, societal, and environmental aspects, while reverse logistics focus on

environmental and economic aspects only (Genovese, Acquaye, Figueroa, & Koh, 2017; Lai, Wub, & Wong, 2013). In the (PSC), the circular economy could be framed in terms of keeping end-of-use medicine as long as possible in the economic and social cycle of use, which is a more difficult task than the reverse logistics of end-of-life medicine.

A literature review study aimed to research reverse flow methods in the (PSC) and reviewed 127 papers in the areas of medication donation, reverse logistics, and circular economy (Viegas, Bond, Vaz, & Bertolo, 2019; Agrawal S. S., 2015). The literature study found that the pharmaceutical supply chain suffers from a lack of unity regarding theoretical approaches, which obstructed the assessment of any flaws or potential improvement. This gap was found to be caused by several factors, including the forward (PSC) issues such as demand uncertainty, complexity, and lack of supply chain flexibility which affect the reverse flow of medication. For the improvement of any (RL) operation, the forward (PSC) was found to need improvement with factors such as entity coordination, collaboration, pricing, cleaner production, and governmental incentives. The lack of coordination and collaboration in the forward operation was found to be the main hindering aspects of any reverse flow process, whether donation, reverse logistics, or circular economy.

In the (PSC), reverse logistics can be defined as the process of implementing an efficient and cost-effective flow of finished goods, in this case, unwanted or expired medication, from the point of consumption to the point of origin for proper disposal (Rogers & Tibben-Lembke, 1998). For hospitals and pharmacies, the (RL) process can be executed by an entity in the original (SC) through a contractual agreement, or by hiring a third-party logistics company to collect and dispose of the expired medication (Weraikat, Zanjani, & Lehoux, 2016; Hu, Dai, Ma, & Ye, 2016). Concerning patients, an additional step of collecting the expired medication is required, but in any case, proper coordination and negotiation strategies must be performed to increase the efficiency of the process and collect more expired medication (Liu, Wan, Wan, & Gong, 2020).

2.3 Forward Logistics in the Pharmaceutical Supply Chain

Forward Logistics based models deal with making well-informed decisions, to optimize the medication inventory to reduce medication wastage, expiration, and the total operation cost. The reviewed literature collectively aimed to optimize different versions of the (PSC) for different end applications, such as global optimization or the efficient dispensing of medication in case of disasters. However, the reviewed literature aimed to always satisfy the demand while

dealing with its uncertainty using different tools and techniques. The reviewed literature can be found in (Table 1) at the end of the literature review section.

A pharmaceutical supply chain inventory literature viewed the supply chain as a whole, since its echelons are interdependent, which is why single-echelon models were deemed not realistic to adequately define the (PSC) (Sbai & Berrado, 2018). In addition, (Sbai & Berrado, 2018) provided several supply chain network structures, as well as the required aspects such as the medication demand-type, inventory review policy, and the number of products needed to define the pharmaceutical supply chain. Similarly, another study by (Settanni, Harrington, & Srai, 2017) reviewed several inventory models and aimed to redefine many aspects of the pharmaceutical supply chain, such as problem conceptualization and boundary definition.

An inventory optimization study modeled a continuous review policy between a two-echelon (PSC) comprising a manufacturer and a hospital, subject to a space constraint and a customer service level constraint (Uthayakumar & Priyan, 2013). (Uthayakumar & Priyan, 2013) incorporated all the associated costs into the objective function of an (MINLP) model being bound by the two constraints to find the best order quantity that would result in the lowest total cost. Another two-echelon optimization study aimed to find the optimum medication order schedule by following two approaches, a classical supply chain and a vendor managed inventory (VMI) method, for maximizing the profits objective function of a mixed-integer linear programming (MILP) model with several constraints (Candan & Yazgan, 2016). Similarly, (Weraikat D. Z., 2019) underlined the effectiveness of the (VMI) approach when it was used to optimize a two-echelon (MINLP) model between a manufacturer and a hospital to decrease wastage and stockouts.

(Kelle, Woosley, & Schneider, 2012) investigated a decision support system for a hospital with different (s, S) policies and constraints, by presenting a couple of simple models to be optimized iteratively, using Excel, to enable proper managerial decision making. Similarly, another on-site medication distribution study was performed on a two-echelon model involving the main inventory and several medication dispensing machines (Gebicki M. e., 2014). The model optimized the service level and total cost objective functions, using different inventory policies while considering medication criticality, availability, and expiration factors. Likewise, (Zahiri B. J.-M., 2018) aimed to optimize a multi-objective multi-echelon model to minimize the total cost and maximum the unsatisfied demand subject to different constraints. For a global pharmaceutical supply chain, (Susarla & Karimi, 2012) developed a simple (MILP) robust

model for a deterministic global (PSC) network design problem with the ease of implementation.

Following the same formulation done by (Uthayakumar & Priyan, 2013), (Priyan & Mala, 2020) proposed two-game theory approaches in managing product flow and inventory issues for a two-echelon (PSC) model, where the different game theory algorithms were tested using MATLAB and a numerical example. Finally, (Franco C. a.-L., 2020) proposed a simulation-optimization approach based on a sample path method for optimizing tactical and operational decisions in a two-echelon pharmaceutical supply chain subject to parameter uncertainty. Two mixed-integer programming models were designed to deal with the uncertainties, with the first aiming to minimize the total costs, while the second aiming to minimize expiration and inventory levels.

2.3.1 Other Perishability Supply Chain Studies

2.3.1.1 Blood Supply Chain:

Blood and its by-products are very important products that can only produce by human beings, with no alternative substitute, which highlights the importance of the blood supply chain (Cohen & Pierskalla, 1975). The blood supply chain (BSC) encompasses the collection, testing, processing, and distribution of blood, which means that several challenges, such as the satisfaction of the stochastic demand (Beliën & Forcé, 2012). The design of a blood supply chain is very important given the importance of blood, its perishability rate, and the consequences of inventory excess or shortage.

A two-stage stochastic programming hospital inventory optimization model was proposed to obtain optimal periodic (R, S) review policies, to minimize the total cost while keeping blood shortage and wastage to a minimum (Dillon, Oliveira, & Abbasi, 2017). Since the proposed model was a two-stage model, the first stage aimed at defining the (R, S) parameters without considering uncertainty, while the second stage optimized the model based on the uncertainties of each proposed scenario. (Zahiri, Torabi, Mohammadi, & Aghabegloo, 2018) proposed an expanded (BSC) study to optimize a dual-objective (MINLP) stochastic model to minimize the total cost and maximize the remaining life of the blood products. First, a multi-stage stochastic programming approach was used, then a multi-objective meta-heuristic algorithm was employed to obtain the non-dominated solutions.

Another study by (Zahiri B. a., 2017) designed and optimized a robust multi-period bi-objective model (BSC) model for the location-allocation of blood. First, the formulated (MINLP) model

is linearized, then it was converted into two different credibility-based models: a fuzzy-chance constrained model and a robust possibilistic model. A similar study, (Ramezanian & Behboodi, 2017), aimed at designing and optimizing a location-allocation (BSC) model with social aspects, such as donor's distance to the facility, experience, and incentives being considered. First, a deterministic (MILP) model was developed, then reshaped into a robust optimization model to overcome parameter uncertainty and minimize the total cost objective function.

2.3.1.2 Food Supply Chain:

The food supply chain includes a wide range of products with different perishability characteristics that require proper supply chain design to guarantee customer satisfaction while avoiding financial loss and product wastage. (Mohebalizadehgashti, Zolfagharinia, & Amin, 2020) aimed to consider environmental aspects in the design of a location-allocation multi-echelon meat supply chain with several products. A multi-objective (MILP) model was proposed to minimize the total cost and CO_2 emissions and maximize the total capacity utilization. The model was implemented on a real case study, and an augmented ε-constraint approach converted the multi-objective model into a single-objective one and solved it to obtain a set of Pareto-optimal solutions.

2.3.1.3 Dairy Supply Chain:

An important part of the food supply chain is the dairy supply chain (DSC), which encompasses the sourcing and processing of raw milk into dairy products, as well as inventory and logistics management of the product flow from factory inventory to distribution centers or customers. Due to its complexities, such as the fluctuation and uncertainties in supply and demand, the (DSC) production and distribution planning caught the attention in technical literature studies (Sel & Bilgen, 2015).

A study aimed at developing a two-echelon production and distribution supply chain model involving several dairy products to increase the total net profit (Guarnaschelli, Salomone, & Méndez, 2020). The proposed model was a two-stage stochastic approach (MILP) one due to uncertainties such as raw material availability and product demand. The uncertainties are ignored in the first stage, then considered when making decisions in the second stage depending on the scenarios. (Sel C. , Bilgen, Bloemhof-Ruwaard, & van der Vorst, 2015) proposed a planning and scheduling (MILP) model for a dairy supply chain to integrate tactical and operational decisions. The designed multi-echelon model aimed to optimize the total cost objective function and was broken down into planning and scheduling (MILP) sub-models using a decomposition heuristic approach. Another study by (Wari & Zhu, 2016) aimed to

develop a (MILP) multi-period three-stage scheduling model for an ice cream supply chain without heuristics to target the supply chain over a longer period to minimize the makespan.

2.3.2 Pharmaceutical Supply Chain and Data Uncertainty

A certain degree of data uncertainty exists in any (PSC) design study due to the dynamic and imprecise nature of the model parameters and variables. In any model, several parameters can influence the final solution, with some being more critical than others. For that reason, ignoring data uncertainty in a pharmaceutical supply chain model will diminish the validity of the results and lead to an unrealistic model. Three main approaches are often used to deal with data/parameter uncertainty: stochastic, robust, and fuzzy programming approaches.

- *Stochastic programming Studies:*
  A supply chain design study by (Sazvar, Mirzapour Al-e-hashem, Baboli, & Akbari Jokar, 2014) aimed to develop and test a two-echelon dual objective supply chain model that focused on minimizing the total cost and the production of greenhouse gases. A two-stage stochastic programming approach was used to deal with the random uncertainty of the model. The model was initially linearized before assessing each objective, then the model was used to solve a pharmaceutical case study. Another stochastic programming study aimed to optimize a multi-objective two-stage stochastic programming (MINLP) model over 27 scenarios and used conditional value at risk to measure the risk of some of the uncertain parameters (Rahimi, Ghezavati, & Asadi, 2019). Furthermore, the proposed model had three objectives: maximizing the profits, minimizing the environmental impact, and maximizing the social impact.

- *Robust Optimization Studies:*
  (Sabouhi, Pishvaee, & Jabalameli, 2018) aimed to develop a robust supply chain model between raw material suppliers and manufacturers and proposed a two-stage hybrid possibilistic stochastic approach for risk aversion. Their model focused on the importance of proper supplier selection and used a fuzzy data envelopment analysis model to calculate the efficiency of suppliers. The fuzzy model was first linearized then the resulting approach was used to minimize the total cost at different scenarios. Similarly, (Diabat, Jabbarzadeh, & Khosrojerdi, 2019) designed a robust dual-objective scenario-based two-stage optimization model to distribute perishable products in the case of a disaster. The objectives were to minimize product delivery time and total operation cost, with the ε-constraint method used to obtain a single-objective model. Another robust optimization study by (Yavari & Geraeli, 2019) proposed a multi-echelon model which includes

multiple products and is optimized over multiple periods. First, a multi-objective (MILP) model was designed as a deterministic model to minimize the cost and environmental pollution, and then it was converted to a single objective model to be solved by a developed heuristic method.

- *Fuzzy Programming Studies:*
  A (PSC) network design aimed to find the optimum facility location and inventory management strategies while addressing uncertainties in demand and perishability (Savadkoohi, Mousazadeh, & Torabi, 2018). Thus, a 3-echelon distribution (MINLP) model was initially designed to minimize the total cost, before being linearized to be solved. Due to the uncertainties and lack of historical data, a fuzzy/possibilistic programming approach was proposed based on the subjective opinions of decision-makers. Another study focused on designing and optimizing a resilient 3-echelon (MINLP) model to minimize the total cost under fuzzy constraints and parameters (Dai, Aqlan, Zheng, & Gao, 2018). A fuzzy programming approach was applied to deal with the fuzzy uncertainties, and two algorithm approaches were considered to optimize the model: a hybrid genetic algorithm (HGA) approach and a hybrid harmony search (HHS) algorithm approach.

2.4 Gaps and Contribution

Based on the past literature, several models were developed to optimize different versions of the pharmaceutical supply chain. However, their results were non-robust in nature and involved specific cases. In addition, the literature review points to the fact that demand uncertainty, among other parameters, is a very important aspect to consider, with past models using complex approaches to address the uncertainties in their developed models. Therefore, decision-makers require a multi-echelon (PSC) model that addresses parameter uncertainty, while being simple to understand, change, and scale to varying conditions.

In this paper, we try to fill the previously mentioned gaps by proposing a single-objective (MILP) model for the production, storage, and distribution of pharmaceutical products in a three-echelon (PSC). The main contributions of this study include: (1) a single objective robust programming model is developed for optimizing a three-echelon pharmaceutical supply chain, considering medication perishability and demand uncertainty. (2) The developed model provides a framework for optimizing the total cost of the pharmaceutical supply chain, where several aspects of our model, such as the number of facilities, echelons, or even medication products, can be scaled to varying conditions. (3) A robust programming approach is used in

the proposed model to deal with the demand uncertainty and its effect on the total cost of the pharmaceutical supply chain model and the number of products that are produced and distributed. (4) Several numerical experiments are provided to highlight the performance of our model and solutions.

Table 1: The forward supply chain reviewed literature that deal with pharmaceuticals, other perishable products, and data uncertainty.

Author(s) Name	**Study Date**	**Journal Name**	**Model Type**	**Other Features**
Uthayakumar, R. et al.	2013	Operations Research for Health Care	MINLP	Algorithm approach
Candan, G. et al.	2016	DARU Journal for Pharmaceutical Science	MILP	Classical (SC) and VMI
Weraikat, D. et al.	2019	Operations Research for Health Care	MINLP	VMI
Kelle, P. et al.	2012	Operations Research for Health Care	MILP	Simplified
Gebicki, M. et al.	2014	Health Care Management Science	Simulation model	Event Driven Simulation
Zahiri, B. et al.	2018	Information Sciences	MILP	Novel Robust Optimization
Susarla, N. et al.	2012	Computers and Chemical Engineering	MILP	Robust
Priyan, S. et al.	2020	Operations Research for Health Care	MINLP	Game theory algorithms
Franco, C. et al.	2020	Computers and Chemical Engineering	Two different MIPs	Sample path method
Dillon, M. et al.	2017	International Journal of Production Economics	MINLP	Two-stage stochastic programming
Zahiri, B. et al.	2018	Computers & Industrial Engineering	Stochastic MINLP	Meta-heuristic algorithms
Zahiri, B. et al.	2017	International Journal of Production Research	MILP	Fuzzy chance-constrained
Ramezanian, R. et al.	2017	Transportation Research	MILP	Robust optimization
Mohebalizadehgashti, F. et al.	2020	International Journal of Production Economics	MILP	augmented ε-constraint approach
Guarnaschelli, A. et al.	2020	Computers and Chemical Engineering	MILP	Two-stage stochastic programming

Sel, C. et al.	2015	Computers and Chemical Engineering	MILP	Decomposition heuristic + Constraint Programming (CP)
Wari, E. et al.	2016	Computers and Chemical Engineering	MILP	Non-heuristic approach
Sazvar, Z. et al.	2014	International Journal of Production Economics	Linearized MINLP	Two-stage stochastic programming
Rahimi, M. et al.	2019	Computers & Industrial Engineering	Linearized MINLP	Two-stage stochastic programming + CVaR
Sabouhi, F. et al.	2018	Computers & Industrial Engineering	(DEA)	Possibilistic chance constrained programming (PCCP)
Diabat, A. et al.	2019	International Journal of Production Economics	Scenario-based two-stage optimization	ε-constraint method + Lagrange relaxation approach
Yavari, M. et al.	2019	Journal of Cleaner Production	MILP	Heuristic approach
Savadkoohi, E. et al.	2018	Chemical Engineering Research & Design	Linearized MINLP	Fuzzy/Possibilistic programming
Dai, Z. et al.	2018	Computers & Industrial Engineering	MINLP	Fuzzy programming + three different algorithms

3 Methodology and Formulation

3.1 Methodology

A (MILP) model of a three-echelon (PSC) with a manufacturer, wholesaler, and medication provider echelons aiming to manufacture, transport, and distribute several medication products over several time periods.

3.1.1 Sets, Parameter, and Variables

The first step in building the model was to identify the sets involved, which represent different echelons, products, and time periods. With the chosen sets for the proposed (MILP) model being:

- i represents the medication manufacturer echelon, with (i = 1 to I)
- j represents the medication wholesaler echelon, with (j = 1 to J)
- k represents the medication provider echelon, with (k = 1 to K)
- p represents the multiple medication products, with (p = 1 to P)
- t represents the multiple time periods, being in months (t = 1 to T)

(Table 2) shows the notations of the parameters and variables used in the (PSC) model.

Table 2: The description of the notations used in the formulation of the developed (PSC) model

RMCp	Cost of raw materials needed for manufacturing medication (p)	WIj,p,t	Stored inventory amount of medication (p) at wholesaler (j) at time-period (t)
Pi,p,t	Production amount of medication (p) at manufacturer (i) at time-period (t)	WWj,p,t	Wastage amount of medication (p) at wholesaler (j) at time-period (t)
PCi,p	Production cost of medication (p) at manufacturer (i)	EP	Emission production rate caused by vehicle transportation [based on distance]
MICi,p	Inventory storage cost of medication (p) at manufacturer (i)	OCj,p	Ordering cost of medication (p) from wholesaler (j)
MIi,p,t	Stored inventory amount of medication (p) at manufacturer (i) at time-period (t)	Dj,k	Distance between wholesaler (j) and medication provider (k)

WCp	Wastage cost associated with medication (p)	fj,k,t	Frequency of deliveries between wholesaler (j) and medication provider (k) at time-period (t)
MWi,p,t	Wastage amount of medication (p) at manufacturer (i) at time-period (t)	Xj,k,p,t	Transported amount of ordered medication (p) from wholesaler (j) to medication provider (k) at time-period (t)
EC	Emission cost	PICk,p	Inventory cost of storing medication (p) at medication provider (k)
EAp	Emission amount associated with the production of medication (p)	PIk,p,t	Stored inventory amount of medication (p) at medication provider (k) at time-period (t)
OCi,p	Ordering cost of medication (p) from manufacturer (i)	PWk,p,t	Wastage amount of medication (p) at medication provider (k) at time-period (t)
TC	Transportation cost of all the products [based on distance]	MDk,p,t	Medication demand of medication provider (k) of medication (p) at time-period (t)
fi,j,t	Frequency of deliveries between manufacturer (i) and wholesaler (j) at time-period (t)	S	Maximum allowable storage for manufacturer (i), wholesaler (j), and medication provider (k) respectively.
Di,j	Distance between manufacturer (i) and wholesaler (j)	αp	The shelf-life of medication (p)
Xi,j,p,t	Transported amount of ordered medication (p) from manufacturer (i) to wholesaler (j) at time-period (t)	SSp	Safety stock of medication (p)
WICj,p	Inventory cost of storing medication (p) at wholesaler (j)	Cap	Maximum transportation capacity between any two echelons

3.1.2 Objective Function

The proposed (PSC) model has three echelons, multiple products, multiple time-periods, and one objective function: the minimization of the total cost across the entire model. The total cost of the pharmaceutical supply chain model (1) was divided into the costs associated with the three echelons for an easier understanding of each echelon's contribution to the total cost, as well as for the tracing of costs in the (PSC) model.

$$\boldsymbol{Minimize}\ Total\ Cost = Manufacturer + Wholesaler + Provider \quad (1)$$

3.1.2.1 Manufacturer Total Cost:

The total manufacturer cost (2) was associated with the sourcing of raw materials, the manufacturing of different medication products, and the storage of the products. Thus, the total cost at different time periods associated with the manufacturer echelon was the raw material costs, the production costs, the storage/inventory costs, the wastage costs, and the pollution costs. Wastage was considered to occur if medication stored at the manufacturer goes beyond its expiry date, and the pollution cost was considered each time a medication product is manufactured.

$$Manufacturer\ Cost = \sum_{i,p,t} RMC_p * P_{i,p,t} + \sum_{i,p,t} PC_{i,p} * PR_{i,p,t} + \sum_{i,p,t} MIC_{i,p} * MI_{i,p,t} + \sum_{i,p,t} WC_p * MW_{i,p,t} + \sum_{i,p,t} EC * EA_p * P_{i,p,t} \quad (2)$$

3.1.2.2 Wholesaler Total Cost:

The total wholesaler cost (3) was associated with the ordering of medication products from the manufacturer, the transportation of medication products from the manufacturer to the wholesaler, and the storage of the medication products at the wholesaler. Thus, the total cost at different time periods associated with the wholesaler echelon was the ordering costs, the transportation costs, the storage/inventory costs, the wastage costs, and the pollution costs. Wastage was considered to occur if medication stored at the wholesaler goes beyond its expiry date, and the pollution cost was considered each time medication products were transported between the manufacturer and wholesaler.

$$Wholesaler\ Cost = \sum_{i,j,p,t} OC_{i,p} * X_{i,j,p,t} + \sum_{i,j,t} TC * 2f_{i,j,t} * D_{i,j} + \sum_{j,p,t} WIC_{j,p} * WI_{j,p,t} + \sum_{j,p,t} WC_p * WW_{j,p,t} + \sum_{i,j,t} EC * EP * 2f_{i,j,t} * D_{i,j} \quad (3)$$

3.1.2.3 Medication Provider Total Cost:

The total medication provider cost (4) was associated with the ordering of medication products from the wholesaler, the transportation of medication products from the wholesaler to the

medication provider, and the storage of the medication products at the medication provider. Thus, the total cost at different time periods associated with the medication provider echelon was the ordering costs, the transportation costs, the storage/inventory costs, the wastage costs, and the pollution costs. Wastage and pollution costs were considered for the medication provider echelon in the same manner they were considered for the wholesaler echelon.

$$Provider\ Cost = \sum_{j,k,p,t} OC_{j,p} * X_{j,k,p,t} + \sum_{j,k,t} TC * 2f_{j,k,t} * D_{j,k} + \sum_{k,p,t} PIC_{k,p} * PI_{k,p,t} + \sum_{k,p,t} WC_p * PW_{k,p,t} + \sum_{j,k,t} EC * EP * 2f_{j,k,t} * D_{j,k} \quad (4)$$

3.1.3 Constraints

The developed model included many constraints about different cost associated with each echelon, such as production, storage, wastage, and transportation constraints. The most important constraints are the total supply and total demand constraints, which were left till the end of this subsection.

3.1.3.1 Production Constraints:

For the production of medication, many views might be considered, such as a continuous production rate or a controlled production rate. To minimize the total cost, a controlled production ratio based on the demand must be considered, which also addresses the uncertainty in the demand. Thus, the first constraint (5) connects the production ratio with the medication demand, and the second constraint (6) defines the production amount as 50 times the production ratio:

$$\sum_i PR_{i,p,t} - \frac{(\sum_k MD_{k,p,t})}{50} \geq 0 \quad (5)$$

$$P_{i,p,t} = 50 * PR_{i,p,t} \quad (6)$$

The production ratio was introduced in the model since the manufacturer produces batches of medication, and 50 units of medication were chosen to be produced per batch. This constraint, (5), is the only time in the model where the uncertainty in the demand can be expressed. An inequality sign (>=) is used because the deterministic integer variable ($PR_{i,p,t}$) cannot be equally related with the uncertain free variable, which is based on an uncertain parameter. In addition, uncertainty can be added to any of the other variables such as production, transportation, inventory…etc.

3.1.3.2 Shelf-Life and Wastage Constraints:

The medication decay (α_p) of the products of the (PSC) model has to be taken into consideration for finding out the wastage that will be produced, and in this research, each medication product decay is assumed not to change with time (i.e.: constant decrease of shelf-life). Since the shelf life is related to the product and time period only, the time for each product to expire is calculated by inverting the medication decay (7).

$$Exp_p = \frac{1}{\alpha_p} \tag{7}$$

Afterwards, the wastage equation for each echelon (8-10) equals the previous/leftover wastage amount plus the stored inventory turned to waste:

$$MW_{i,p,t} = MW_{i,p,t-1} + MI_{i,p,t-Exp_p} \tag{8}$$

$$WW_{i,p,t} = WW_{i,p,t-1} + WI_{i,p,t-Exp_p} \tag{9}$$

$$PW_{i,p,t} = PW_{i,p,t-1} + PI_{i,p,t-Exp_p} \tag{10}$$

It is assumed that when a certain medication is stocked for a certain expiry time, (Exp_p), then that medication quantity expires and turns into wastage. Despite the next constraint highlighting that leftover inventory from time (t-1) is added to inventory at time (t), leftover inventory from (t-Exp_p) will turn into wastage if it is present. Wastage was registered in the robust counterpart when leftover inventory lasted more than (t-Exp_p) periods.

3.1.3.3 Inventory/Storage Constraints:

The first step for the inventory constraints was to define the inventory equations for each echelon and the respective amount(s) of medication entering and exiting the inventory of that echelon, for each medication at different time periods. The inventory constraints for each echelon (11-13) include the previous leftover inventory, production or income medication, the removal of wastage, and the removal of medication for other echelons or to satisfy the demand.

$$MI_{i,p,t} = MI_{i,p,t-1} + P_{i,p,t} - MW_{i,p,t} - \sum_j X_{i,j,p,t} \tag{11}$$

$$WI_{j,p,t} = WI_{j,p,t-1} + \sum_i X_{i,j,p,t} - PW_{i,p,t} - \sum_k X_{j,k,p,t} \tag{12}$$

$$PI_{k,p,t} = PI_{k,p,t-1} + \sum_j X_{j,k,p,t} - PW_{i,p,t} - MD_{k,p,t} \tag{13}$$

3.1.3.4 Transportation Capacity Constraints:

For the transportation of medication, it is assumed that only one vehicle type exists between the facilities of any two echelons to transport medication. Since only one vehicle type is present, its maximum carrying capacity has to be taken into consideration to calculate the transportation cost between echelons. Thus, the total amount of delivered medication equals the number of trips/frequencies multiplied by the maximum carrying capacity of the vehicle as shown below between the manufacturer and wholesaler (14) and between the wholesaler and medication provider (15).

$$\sum_p X_{i,j,p,t} = f_{i,j,t} * Cap \tag{14}$$

$$\sum_p X_{j,k,p,t} = f_{j,k,t} * Cap \tag{15}$$

The frequency variable is an integer variable used to calculate the transportation cost between echelons during each time period. The total transportation cost will equal the transportation rate of the vehicle, which is based on the distance traveled, multiplied by twice the number of trips done (frequency) since the vehicle is traveling to and from a particular echelon. When performing the sensitivity analysis, the frequency variables were set to be non-negative instead of an integer, where the truck would deliver medication even if the truck is not full.

3.1.3.5 Total Supply and Demand Constraints:

For the total supply constraint equations, the sum of the medication distributed to all the entities of the next echelon should be less than or equal to the sum of the produced/received medication plus the inventory amount of that echelon. The total supply constraint equations of the manufacturer (16) and wholesaler (17) are shown below respectively:

$$\sum_j X_{i,j,p,t} \leq P_{i,p,t} + MI_{i,p,t} \tag{16}$$

$$\sum_k X_{j,k,p,t} \leq \sum_i X_{i,j,p,t} + WI_{j,p,t} \tag{17}$$

For the demand constraint equations, the sum of the received medication from all the previous echelon entities should be greater than or equal to the sum of the distributed/demanded medication and the inventory amount. The total demand constraint equations of the wholesaler (18) and medication provider (19) are shown below respectively:

$$\sum_i X_{i,j,p,t} \geq WI_{j,p,t} + \sum_k X_{j,k,p,t} \tag{18}$$

$$\sum_j X_{j,k,p,t} \geq PI_{k,p,t} + MD_{k,p,t} \tag{19}$$

3.1.3.6 Addition of Lead Time Constraints:

Incorporating the delivery lead time between echelons involves the addition of two variables and two constraints. The added variables are $Y_{i,j,p,t}$, and $Y_{j,k,p,t}$, which correspond to the amount of product transported from the manufacturer and the amount of product transported from the wholesaler, respectively. The lead time constraint equations simply define the number of products leaving one echelon equal to the number of products arriving at the next echelon with the addition of the lead time. Assuming a lead time of one day and the smallest time-period value being one day, the lead time constraint equations of the manufacturer (20) and wholesaler (21) are shown below respectively:

$$Y_{i,j,p,t} = X_{i,j,p,t+1} \tag{20}$$

$$Y_{j,k,p,t} = X_{j,k,p,t+1} \tag{21}$$

In addition, the total supply and demand constraints of the wholesalers are set to start after one day, while the same constraints are set to start after two days for the provider since none of the echelons have any starting inventory.

3.2 Formulation in AIMMS

The formulation discussed in section 3.1 is implemented in the same order in AIMMS to clearly define and optimize the proposed model. The process begins by declaring the sets, followed by the parameters which will contain the given data, followed by the decision variables which will be computed by AIMMS, then the constraints of the model, and finally, the mathematical program desired. Regarding the objective function, it is set as a free variable with its equation defined clearly. After finishing the declaration, the main execution of the model is prepared to solve and optimize the developed model. After solving the model, viewing each variable's data tab reveals the optimized results that AIMMS reached.

3.2.1 Sets

The first step in incorporating the model in AIMMS is the declaration of the sets (Figure 1) included in the model as they are the basis onto which the model is built. The sets presented in the simplified model are the ones associated with the three echelons (i, j, and k), the medication product (p), and the time-period (t) of the model. Therefore, five independent sets are initially entered along with their identifying letter/domain and their limits/data set.

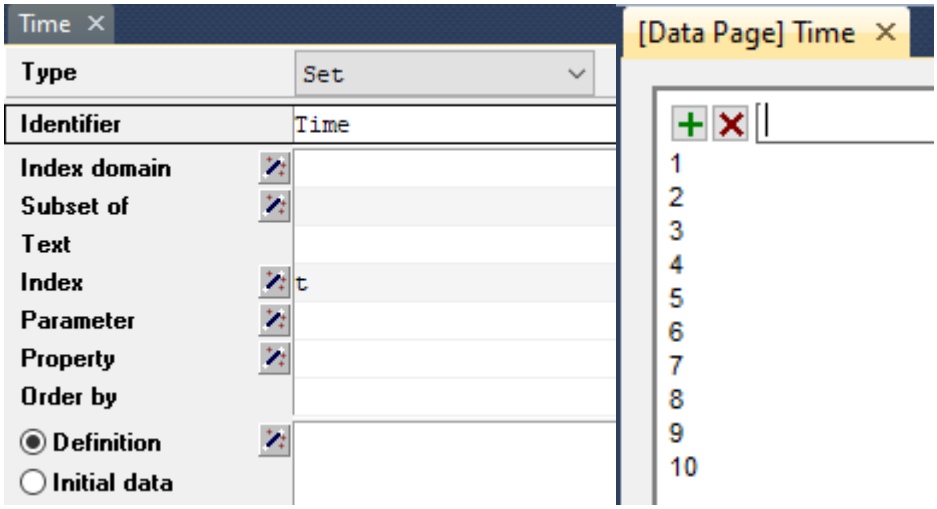

Figure 1: (Left) the window where the set's name and index are identified. (Right) the data page where the set's data is inputted to define its limits.

3.2.2 Parameters

After the assignment of the sets in the model, the next step was to declare the parameter's name, link them to their respective index domain, and assigning their values (Figure 2). This was done by assigning an index domain to the new parameter to determine how many data points are required to be entered, then enter the given/collected data points. Certain parameters had a few data points, such as the raw material cost, which were listed in the definition window directly. Other parameters existed as single data points, such as the transportation cost, and these were integrated directly into the objective function and/or constraint equations.

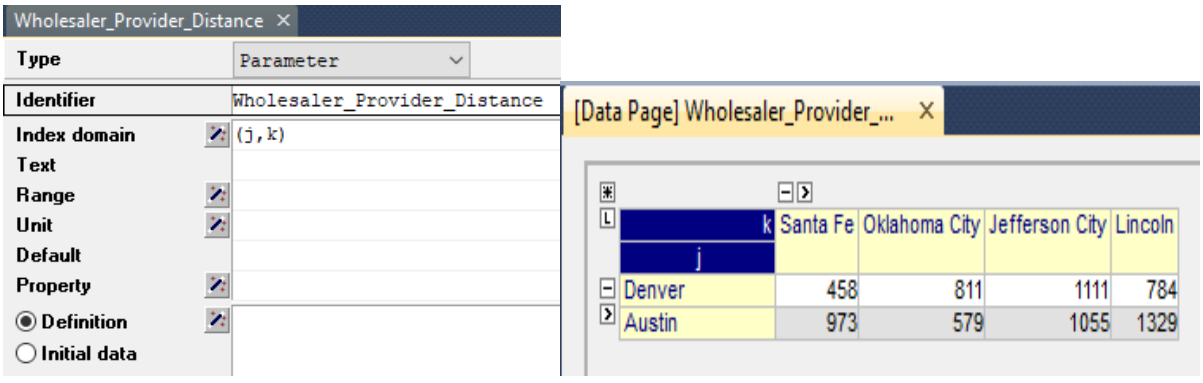

Figure 2:(Left) the window where the parameter's name and index domain are identified. (Right) the data page where the set's data is inputted to define the parameter.

3.2.3 Variables

After defining the parameters and inputting their data points, the decision variables present in the objective function equations were declared and linked to their respective index domain. For example, the amount of medication produced depends on the manufacturer, medication product, and time-period sets (Figure 3). The created decision variables will initially not have any values, and their characteristics can be set as desired, for example, the range of their values could be set to free, nonpositive, nonnegative, integer, or binary. In addition, variables can be set to uncertain via the property tab and linked to an uncertain parameter.

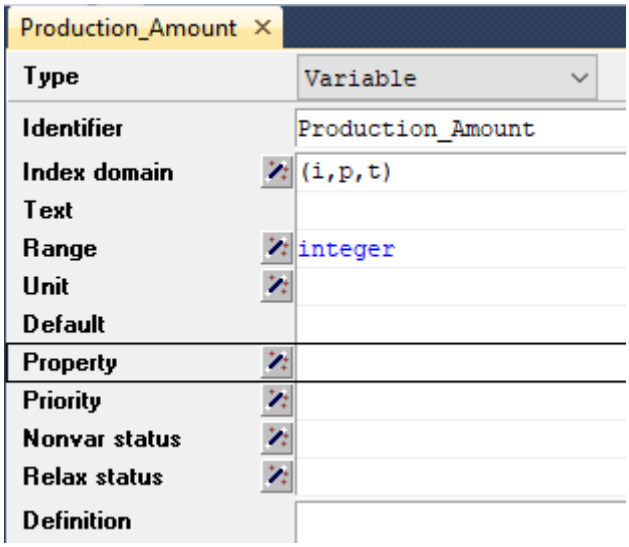

Figure 3: the production amount variable which depends on the manufacturer (i), medication type (p), and time period (t) as shown in the index domain area. In addition, this variable's value range is set to integer only.

The objective function of the model (Figure 4) was also set as a free variable since it is the objective function, and its value is yet to be known. The total cost objective function equation was defined in the definition area and was divided into three free variables, similar to section 3.1.2 of the formulation, to track which echelon is contributing the most towards the total cost. And since the objective function was further divided into three free variables corresponding to each echelon, (Figure 5) shows the equation that defines the total manufacturer cost.

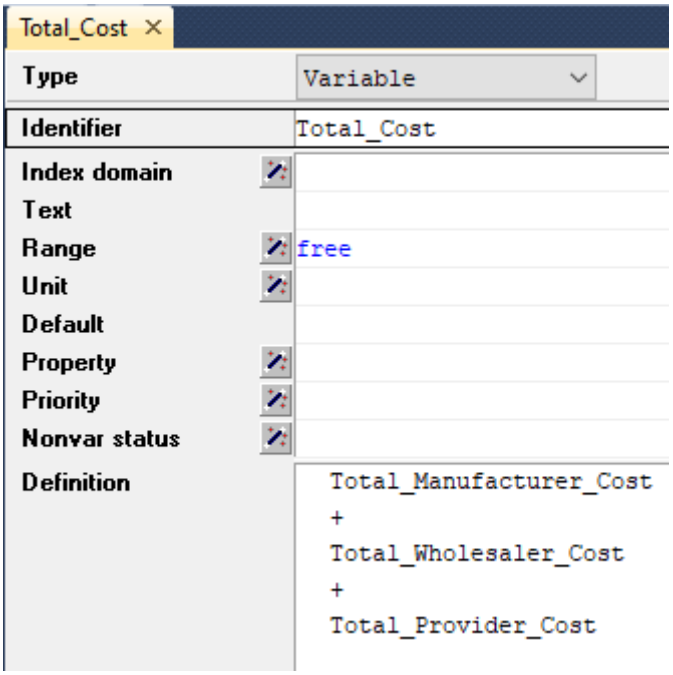

Figure 4: the objective function variable which does not depend on any index domain, has a value range of free since it is the objective function, and has an equation to define it.

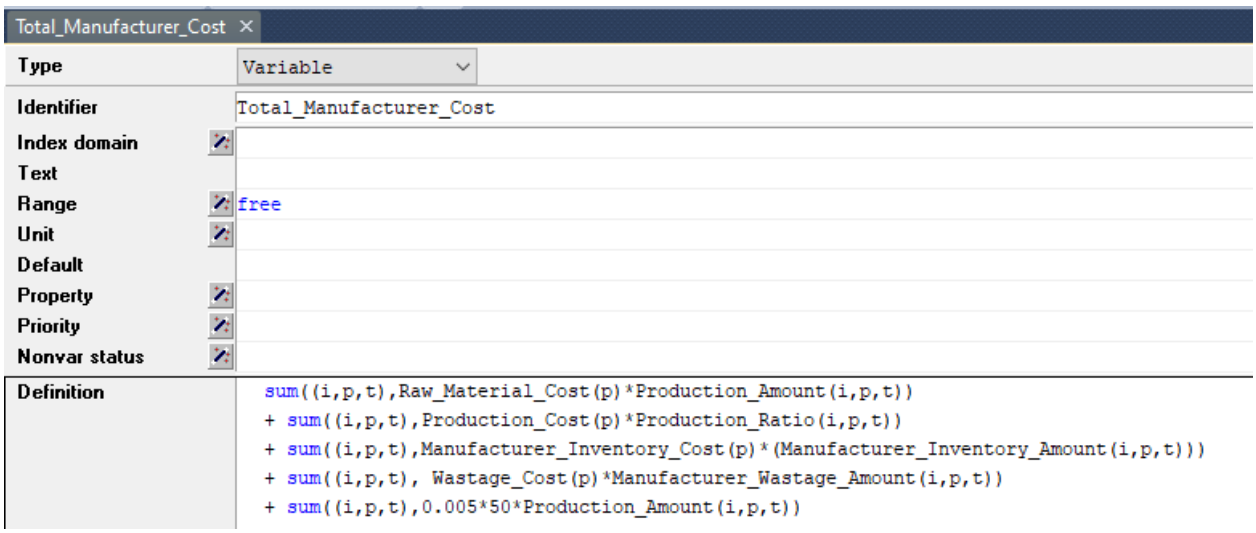

Figure 5: the total manufacturer cost variable which also does not depend on any index domain, similar to the main objective function. It has a value range of free since it is part of the main objective function and has an equation to define it.

3.2.4 Constraints

After defining the parameters and variables, the next step would be to establish the constraints. Similar to the parameters and variables, the constraints must have an index domain of all the included variables and will need to include a complete formula, with right- and left-hand sides, in the definition area to constrain the model (Figure 6).

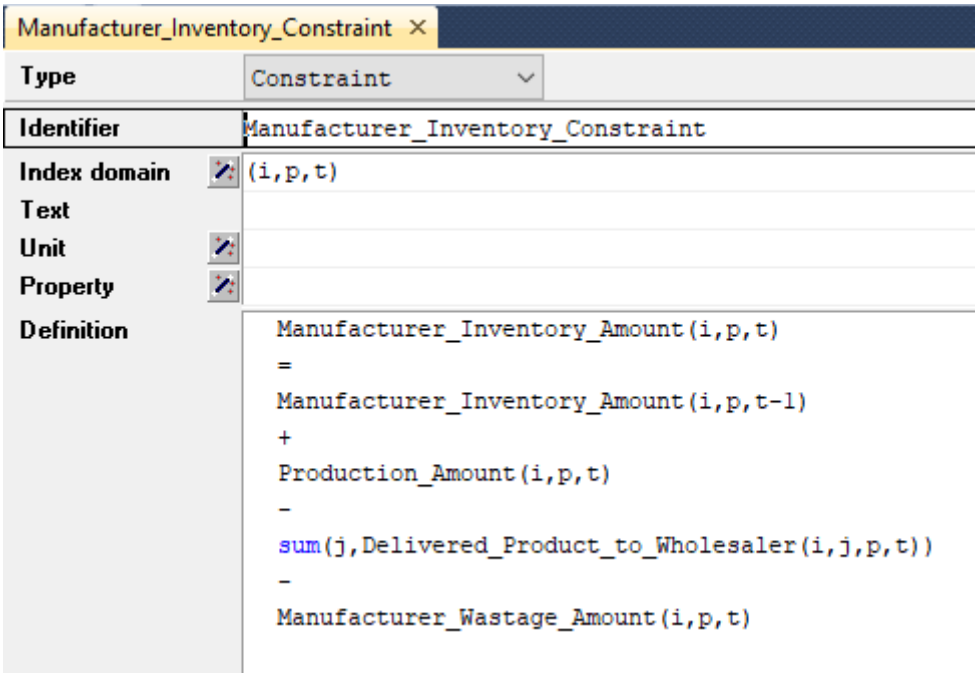

Figure 6: the manufacturer inventory constraint which is indexed to the manufacturer, medication product, and time-period domain sets. It also includes a complete formula of all the variables and/or parameters that defines the constraint.

3.2.5 Mathematical Program

After defining all the sets, parameters, variables, constraints, and the objective function, a mathematical formula is set up in a mathematical program (Figure 7) page to declare which variable is the objective function. In addition, the mathematical program requires the specification of the direction, whether to minimize or maximize the objective function and which variables and constraints should be considered in the optimization of the model. In this research, the total cost variable is chosen as the objective function and set to be minimized subject to all the variables and constraints.

In addition, since a robust counterpart of the model will be considered, a deterministic counterpart must first be clearly defined before being solved. (Figure 8) shows the procedure that defines the deterministic counterpart of the model, using a separate procedure, which essentially does not consider any uncertainty and outputs the individual costs of each echelon as well as the total model cost.

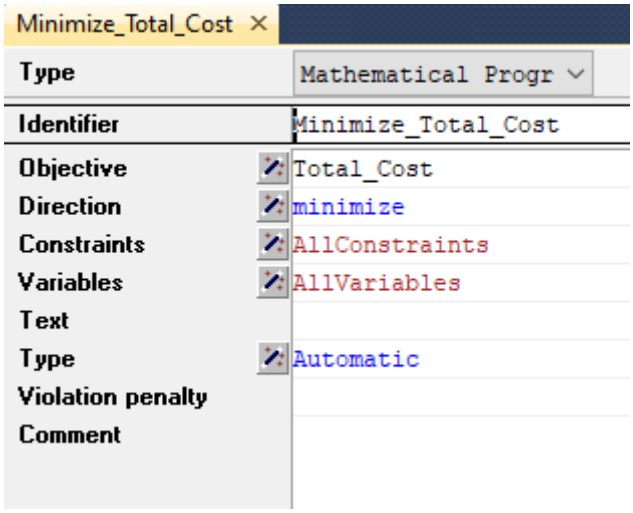

Figure 7: the mathematical program which defines the objective function, whether to minimize or maximize it, and which variables and constraints to consider.

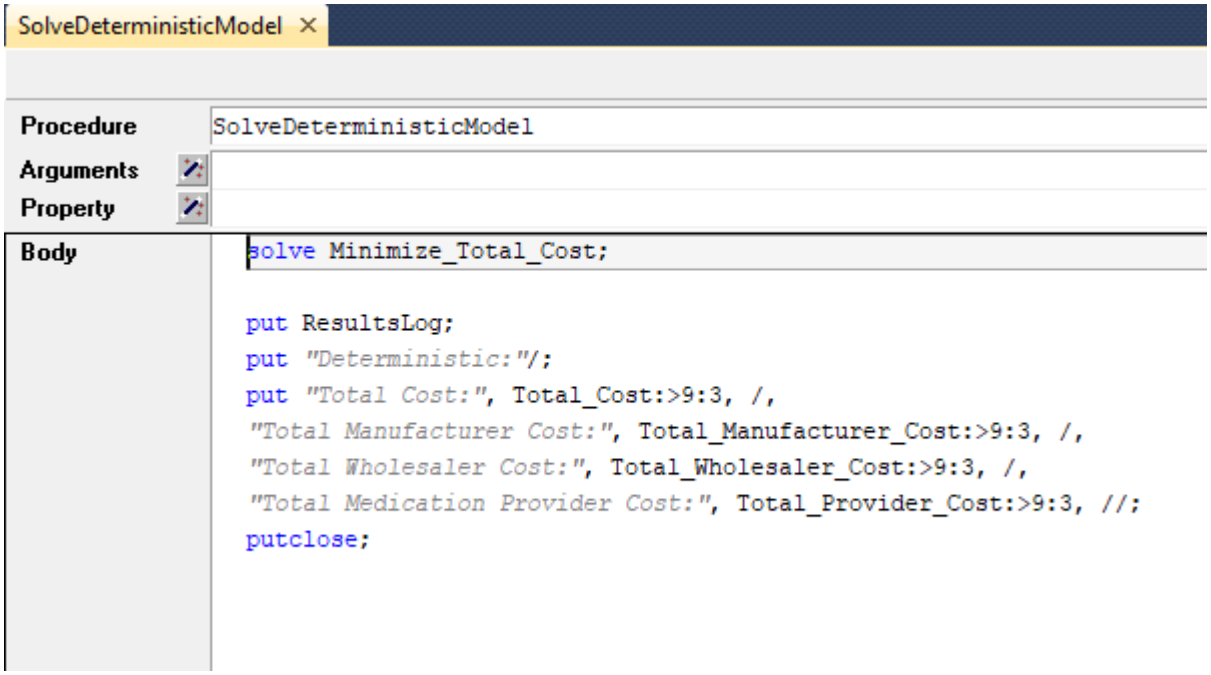

Figure 8: the deterministic counterpart procedure of the model which does not consider any uncertainty, and the necessary commands to solve the model and display the total cost results.

To optimize the model, the main execution procedure is chosen to clear all the variables, show a progress window, and minimize the total cost mathematical program that was just mentioned (Figure 9). The resulting (MILP) model will be solved using AIMMS software developer version 4.71 and CPLEX 12.1 solver, and the results of the model can be seen when checking the data points of the model's variables including the objective function. Before starting the optimization process, the F5 key is pressed to check the model followed by the F6 key to optimize/run the model. AIMMS will the run the model for however much iteration it requires

until it reaches an optimized result, in which case the programs display the number of constraints and variables generated as well as the number of iterations needed to solve/optimize the model.

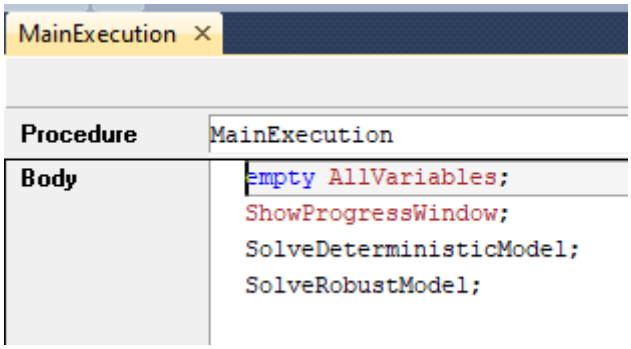

Figure 9: the main execution procedure where the commands are entered to solve the model, for both the deterministic and robust counterparts.

AIMMS also provides a WebUI option to display the results in the form of charts, graphs, and maps. The Map option was used to display the route taken, or network followed, by the program to distribute the medication to the various providers to satisfy the demand. The route displayed in (Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, & Figure 17) is similar to the travelling salesman problem, where the most efficient route is taken to satisfy the demand. The displayed numbers in the mentioned figures are the amounts of medication transported between the echelons.

3.2.6 Uncertainty and Robust Model Counterpart

Uncertainty is one of the many properties that can be added/identified to any parameter or variable and is particularly important when considering the medication demand which is an uncertain parameter in real life. To create a more realistic model, at least the medication demand had to be set as uncertain, and to simulate a parameter whose values varied by a normal distribution, the box command was used. The Box command meant that the parameter's value can take any value between a predefined lower and upper limit as shown in (Figure 10).

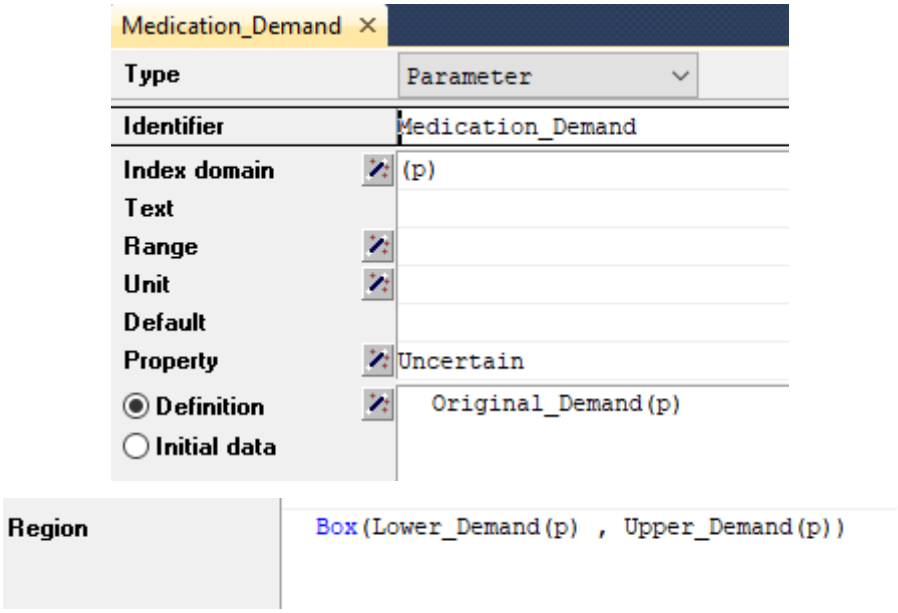

Figure 10: the uncertain medication demand parameter, which essentially depends on specific data points, Original Demand. In addition, its property is set to uncertain and the region of the uncertainty is set between a lower and higher limit.

AIMMS allows the user to keep the deterministic model, for which the demand is known completely, as well as create a robust model counterpart that considers uncertain parameters and variables. For solving the uncertainty version of the model, a separate procedure that turns the model into a robust one will need to be done. A created element parameter, GMP_RC, in a separate declaration, addresses all the generated mathematical programs to be used to solve the robust counterpart of the (PSC) model.

Next, a separate procedure folder, similar to the main execution procedure folder shown in (Figure 8 and Figure 11) is created for both the deterministic and robust versions of the (PSC) model, respectively. For the robust counterpart, a special AIMMS procedure is shown in (Figure 11) to define and generate a robust counterpart of the original deterministic model.

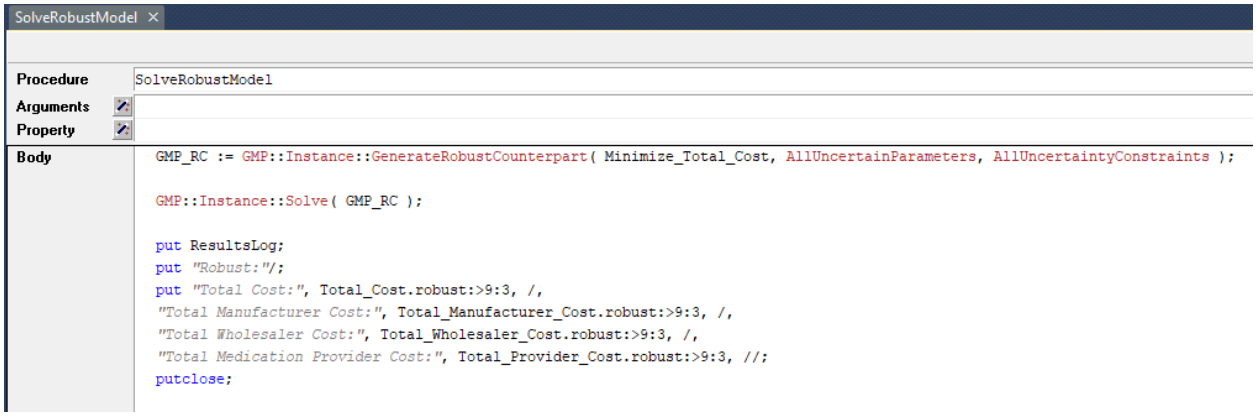

Figure 11: the robust counterpart procedure of the model which considers any uncertainty, and the necessary commands to solve the model and display the robust version of the total cost results.

As shown in (Figure 11), the element parameter created was used to define the robust counterpart of the model, then the command is given to solve the element parameter while considering all the uncertain parameters and constraints. Since two different counterparts were created, two different corresponding procedures had to be created and had to be mentioned in the main execution (Figure 9) procedure to be solved.

4 Results.

4.1 Model I:

To test the developed approach, a simplified model including one manufacturer, two wholesalers, four medication providers, three products, and ten-time periods is used. Due to the lack of pharmaceutical data, data from a similar study was borrowed, (Uthayakumar & Priyan, 2013). A two-echelon (PSC) for the manufacturing and delivery of three medication products was performed by a similar study, (Table 3) presents the values of the parameters used by (Uthayakumar & Priyan, 2013). Since our proposed approach involves a three-echelon (PSC), additional parameters used in the model were obtained by making realistic assumptions.

Table 3: Model parameters adapted from (Uthayakumar & Priyan, 2013).

Parameter	Product #1	Product #2	Product #3
RMC_p	150	200	100
$PC_{i,p}$	1812	2480	2244
$MIC_{i,p}$	7	9	10
WC_p	12	28	22
EC	$50 per ton of CO_2		
EA_p	0.005 CO_2 ton/product		
$OC_{i,p}$	20	25	30
$OC_{j,p}$	20	25	30
TC	$0.49 per km		
$WIC_{j,p}$	2	1.5	3
EP	0.001 CO_2 ton/km		
$PIC_{k,p}$	4	6	3
$MD_{k,p,t}$	600	800	1100
α_p	0.15	0.1	0.2
Cap	500 products		

Since our study includes one more echelon, some of (Uthayakumar & Priyan, 2013) parameters were used exactly as is, while others required realistic assumptions. First, the parameters used directly from the reference study or those that required minimal assumptions are mentioned, followed by parameters that required major assumptions or obtained from different sources.

The raw material cost used in (Table 3), RMCp, was the ordering cost of each raw material. For the ordering cost from the manufacturer and wholesaler, OCi,p and OCj,p respectively, it was assumed to be the same for both echelons. For the medication demand, MDk,p,t, the data used was the average demand of each product per year, which was assumed to be constant during all time periods. For the medication decay rate, αp, the data used was one of the expiry rates, as different expiration rates existed between the manufacturer and the hospital echelon throughout the study.

For the inventory costs of the manufacturer, wholesaler, and medication provider echelon, $MIC_{i,p}$, $WIC_{j,p}$, and $PIC_{k,p}$ respectively, the manufacturer's inventory cost parameter in this model was given the same data as the holding cost of raw material. For the wholesaler inventory cost parameter, it was given the same data as the holding cost of finished products. And finally, for the provider inventory cost, it was chosen as the holding cost of products in the hospital echelon. Regarding the wastage cost, WC_p, the data used was the cost of expiration of each finished product. The inventory costs were assumed to encompass the cost of renting the warehouse(s), worker's salaries, and any specific storage requirements.

The production cost, PCi,p, followed an equation [Di*(δi + δ0i*Qi)] which depends on the order quantity (Qi) and the demand (Di). The same demand data points were chosen, but the order quantity (Qi) was chosen to be 200, based on the average optimal order quantity obtained by the paper, to obtain the above production costs. The production cost was high if single units of each medication were being manufactured, which is why it was assumed that the above-calculated production cost was for batches of 50 products. The production cost was assumed to encompass the cost of running the machinery, insurance, and worker's salaries.

For the emission cost, EC, a rate of $50 per ton of CO_2 was estimated by the environmental defense fund, with the mentioned value being used for all the three echelons (Howard & Sylvan, 2015). For the emission production amount produced during transportation, EP, a rate of 900 grams of CO_2 per kilometer was found for long haul trucks. The emission rate was converted to tons of CO_2 produced per kilometer driven to be approximately 0.001 tons of CO_2 per kilometer (TransportEnvironment, 2015). For the CO_2 emission produced during the manufacturing process, EA_p, it was assumed to be five times the pollution production rate due to transportation, at a rate of 0.005 tons of CO_2 per produced product.

For the transportation cost, $0.49 per km was chosen to encompass the truck operating cost as well as the labor cost, as calculated by a transportation study (Levinson, 2005). For the maximum transportation capacity, Cap, the chosen value for all the vehicles involved was 500 products per trip to be able to calculate the frequency and transportation cost. For the distances between the three echelons, $D_{i,j}$ and $D_{j,k}$, seven cities in the United States were chosen as an illustration of the simple model and the distances between them (in km) were used in the model (Table 4 & Table 5**Error! Reference source not found.**).

Table 4: the chosen random distance values between the single manufacturer (i) and both wholesalers (j).

i\j	Denver	Austin

Phoenix	1390	1622

Table 5: the chosen random distance values between both wholesalers (j), and the four medication providers (k).

j\k	Santa Fe	Oklahoma City	Jefferson City	Lincoln
Denver	458	811	1111	784
Austin	973	579	1055	1329

4.1.1 The Manufacturer Echelon:

For the manufacturer echelon, the main variable to be determined was the medication production amount, and because only one manufacturer was chosen (Table 6) shows the production amount for each period. Since the amount of produced medication was computed by AIMMS software, the sum of the resulting raw material, production, storage, pollution, and wastage costs were calculated to be slightly less than $18.86 million. Since the medication production amount was found, the sum of the total costs of the raw materials, the production, and the pollution cost was approximately $18.86 million as shown in (Table 17).

Table 6: the resulting number of products to be manufactured for each medication product during each time-period.

p\t	1	2	3	4	5	6	7	8	9	10
1	2400	2400	2400	2400	2400	2400	2400	2400	2400	2400
2	3200	3200	3200	3200	3200	3200	3200	3200	3200	3200
3	4400	4400	4400	4400	4400	4400	4400	4400	4400	4400

4.1.2 The Wholesaler Echelon:

For the wholesaler echelon, the main variables to be determined were the amount of medication delivered from the manufacturer to both wholesalers (Table 7 & Table 8), along with a Map displaying which wholesaler supplied which medication provider for each product (Figure 12, Figure 13, and Figure 14). Finally, (Table 9) shows the frequency of transportation between the manufacturer and wholesaler echelons. These variables aid in calculating the various costs of the wholesaler echelon for all the products and periods. Since the amount of delivered medication and the transportation frequency were computed by AIMMS software, they aid in calculating the ordering cost, transportation cost, and pollution cost. The combined value of these three costs for both wholesalers during all periods and all the products was approximately $2.905 million, as can be seen in (Table 17).

Table 7: the amount of product transported from the manufacturer in Phoenix to the wholesaler in Denver for all the three products across all time periods.

p\t	1	2	3	4	5	6	7	8	9	10
1	1800	2400	2400	2400	2400	2000	2000	2000	2000	1900
2	2400	3200	3200	3200	3200	3200	3200	3200	3200	3200
3	3300	4400	4400	4400	4400	3300	3300	3300	3300	4400

Table 8: the amount of product transported from the manufacturer in Phoenix to the wholesaler in Austin for all the three products across all time periods.

p\t	1	6	7	8	9	10
1	600	400	400	400	400	500
2	800	-	-	-	-	-
3	1100	1100	1100	1100	1100	-

Table 9: the frequency of deliveries required to deliver the medication products between the manufacturer and both wholesalers during each time period.

j\t	1	2	3	4	5	6	7	8	9	10
Denver	15	20	20	20	20	17	17	17	17	19
Austin	5	-	-	-	-	3	3	3	3	1

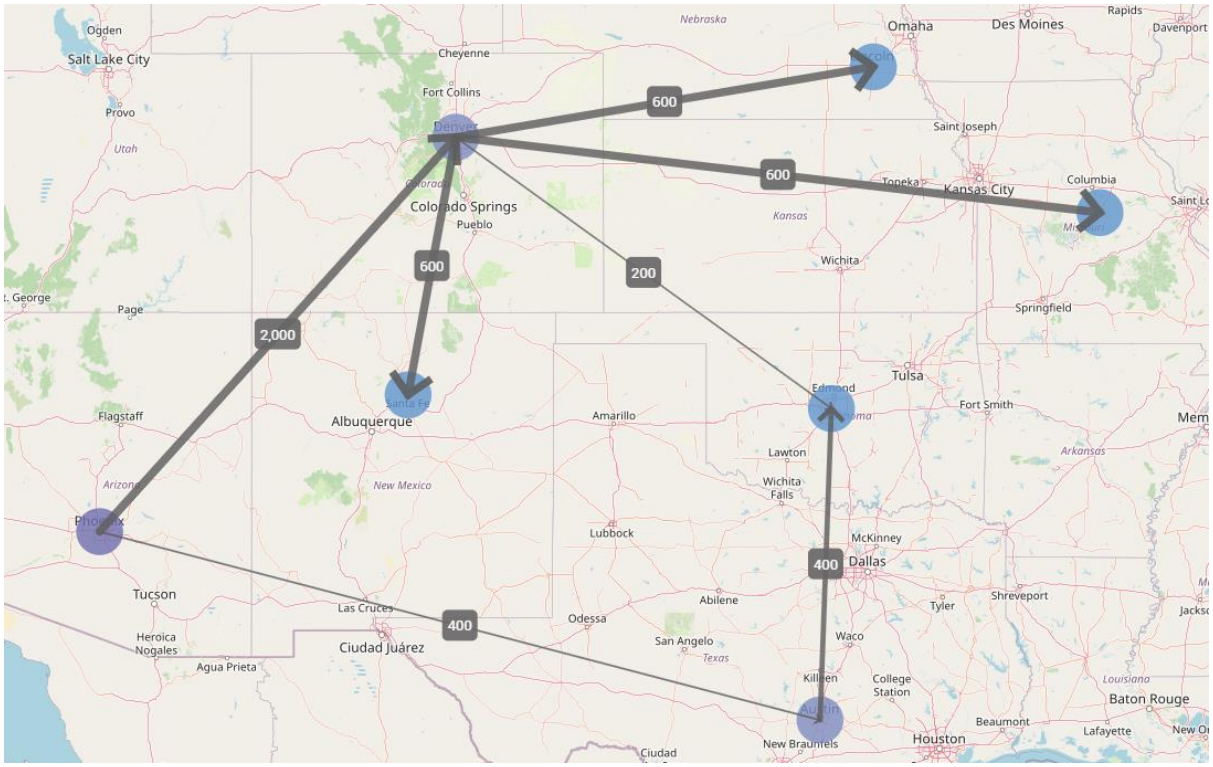

Figure 12: the amount of product one transported between the three echelons at the sixth time-period.

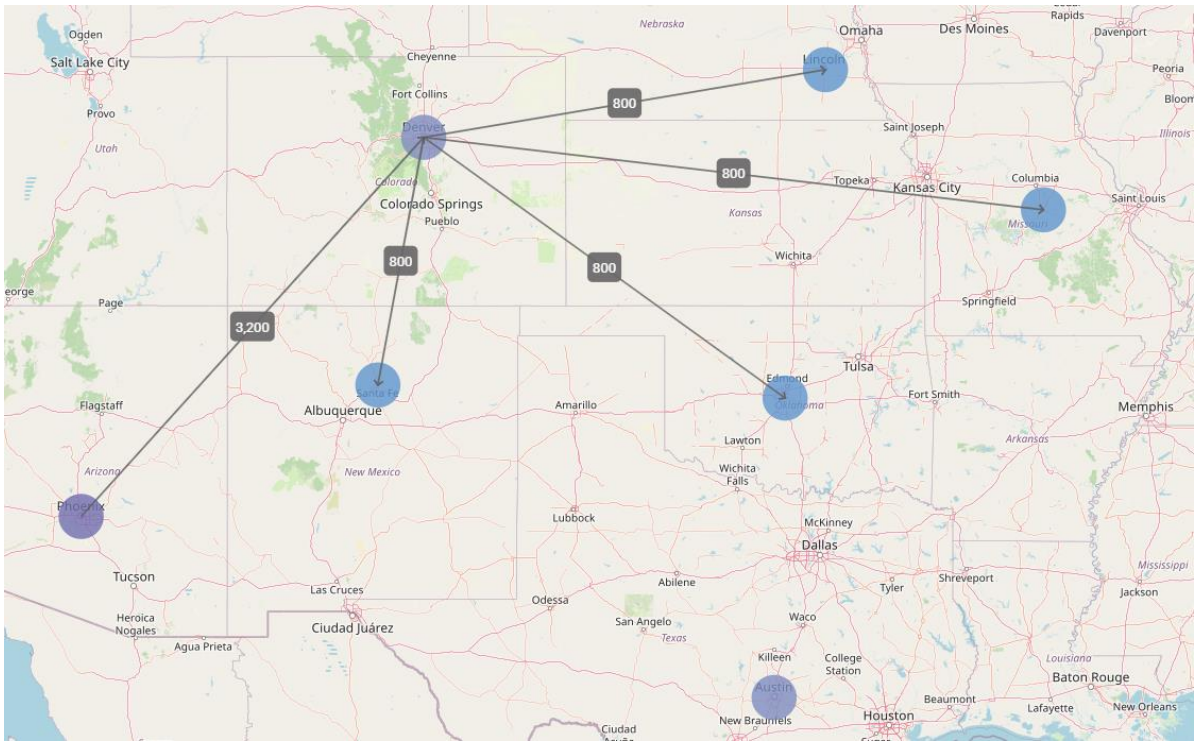

Figure 13: the amount of product two transported between the three echelons at the sixth time-period.

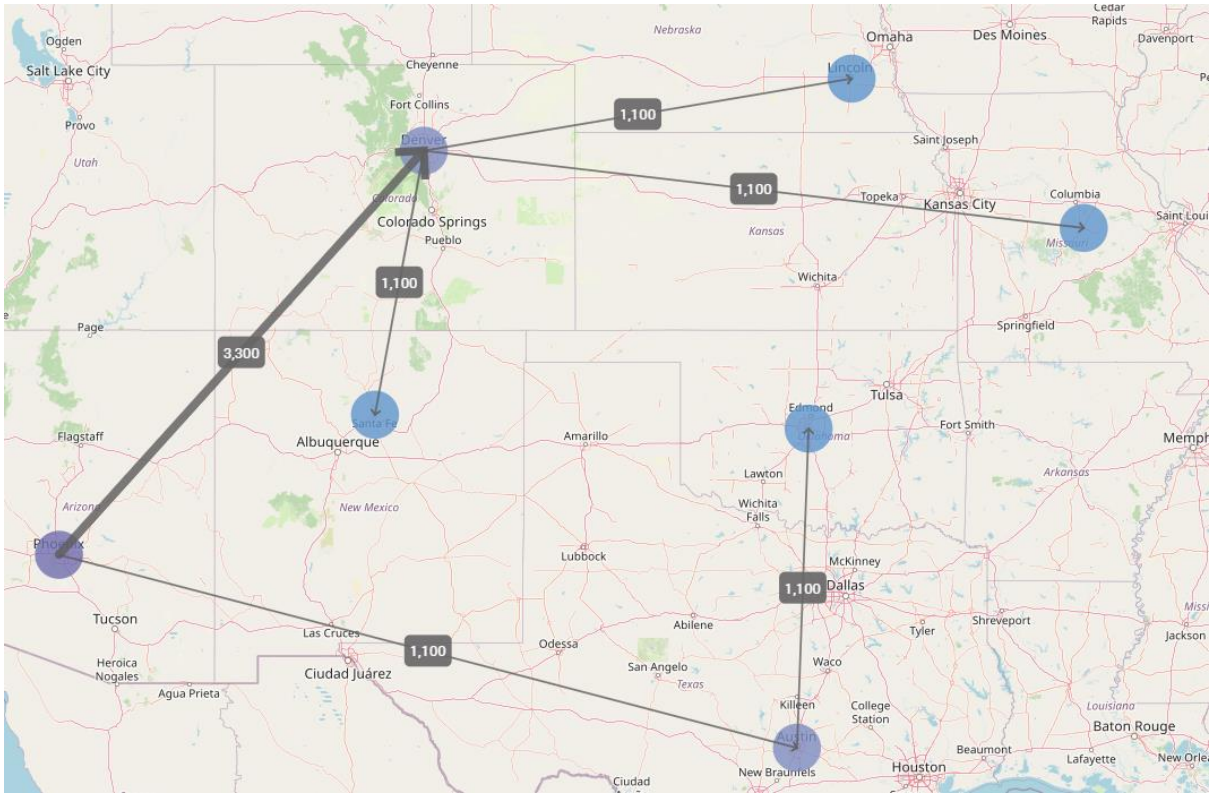

Figure 14: the amount of product three transported between the three echelons at the sixth time-period.

4.1.3 The Medication Provider Echelon:

Similar to the wholesaler echelon, the medication provider echelon required the determination of the same variables; the amount of each product transported from each wholesaler to each provider, which can be seen in (Figure 12, Figure 13, and Figure 14). The amount of product that each wholesaler provided to each medication provider is shown in (Table 10, Table 11, Table 12, Table 13, **Error! Reference source not found.**, and Table 14), in addition, (Table 15 & Table 16) show the frequency of transportation from both wholesalers. These variables aid in calculating the various costs of the medication provider echelon for all the products and periods.

Table 10: the amount of product transported from the wholesaler in Denver to the provider in Santa Fe for all products during all time periods.

p\t	1	2	3	4	5	6	7	8	9	10
1	600	600	600	600	600	600	600	600	600	600
2	800	800	800	800	800	800	800	800	800	800
3	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100

Table 11: the amount of product transported from the wholesaler in Denver to the provider in Oklahoma City for all products during all time periods.

p\t	2	3	4	5	6	7	8	9	10
1	600	600	600	600	200	200	200	200	100
2	800	800	800	800	800	800	800	800	800
3	1100	1100	1100	1100	-	-	-	-	1100

Table 12: the amount of product transported from the wholesaler in Denver to the provider in Jefferson City for all products during all time periods.

p\t	1	2	3	4	5	6	7	8	9	10
1	600	600	600	600	600	600	600	600	600	600
2	800	800	800	800	800	800	800	800	800	800
3	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100

Table 13: the amount of product transported from the wholesaler in Denver to the provider in Lincoln for all products during all time periods.

p\t	1	2	3	4	5	6	7	8	9	10
1	600	600	600	600	600	600	600	600	600	600
2	800	800	800	800	800	800	800	800	800	800
3	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100

Table 14: the amount of product transported from the wholesaler in Austin to the provider in Oklahoma City for all products during all time periods.

p\t	1	6	7	8	9	10
1	600	400	400	400	400	500
2	800	-	-	-	-	-
3	1100	1100	1100	1100	1100	-

Table 15: the frequency of deliveries between Denver and the rest of the medication providers during each time period.

k\t	1	2	3	4	5	6	7	8	9	10
Santa Fe	5	5	5	5	5	5	5	5	5	5
Oklahoma City	-	5	5	5	5	2	2	2	2	4
Jefferson City	5	5	5	5	5	5	5	5	5	5

Lincoln	5	5	5	5	5	5	5	5	5	5

Table 16: the frequency of deliveries between Austin and the rest of the medication providers during each time period.

k\t	1	6	7	8	9	10
Oklahoma City	5	3	3	3	3	1

Since the amount of delivered medication and the transportation frequency were found, they were used to calculate the ordering, transportation, and pollution costs. The combined value of the costs of the medication provider echelon during all periods and for all the products can be seen at the bottom of (Table 17) along with the total cost of the entire model. The total medication provider echelon cost was approximately $2.76 million, and the model's total cost was computed at $24.53 million.

Table 17: the costs of each echelon in the model, as well as the sum of the total costs of the simple (PSC) model.

Cost Description	Amount ($)
Total Manufacturer Cost	18,856,680
Total Wholesaler Cost	2,905,000
Total Provider Cost	2,766,000
Total Model Cost	24,527,776

4.2 Model I with lead time:

To test the effect of lead time, the model was run for 30 days only, with each period being one day. The demand and the transportation capacity were scaled down accordingly to test the functions of the model on a daily routine. In addition, a lead time of one day was introduced between any two echelons, a variable was created to represent the products leaving the first echelon, and another variable to represent the same number of products arriving at the second echelon the following day. Two additional constraints were added for the lead time, and the total supply and demand constraints were set to start when the first delivery arrives at the respective echelon. Finally, the delivery frequency variables were changed from being integers to being nonnegative as it is assumed that a truck will deliver products even when it is not full. This model retains the same number of manufacturers, wholesalers, medication providers, and products as Model I.

(Table 18) shows the daily demand and the number of units produced daily for each product. Since the daily demand is not a multiple of 50, which is the batch size, wastage is accumulated in one of the wholesaler facilities (Table 18). Finally, the costs associated with the echelons of the lead time-adjusted model, which was run for only 30 days, are shown in (Table 19).

Table 18: the daily demand per provider for each product, the daily manufactured number of each product to satisfy the overall demand, and the daily resulting wastage for wholesaler #1.

p	Daily Demand per Provider	Daily Manufactured number of Products	Daily Produced Wastage in Wholesaler #1
1	20	100	20
2	27	150	42
3	37	150	2

Table 19: the costs of each echelon as well as the sum of the total costs of the developed (PSC) model that accounted for lead time.

	Deterministic Counterpart
Total Manufacturer Cost	$ 2,346,454
Total Wholesaler Cost	$ 681,500
Total Provider Cost	$ 394,400
Total Model Cost	$ 3,422,000

4.3 Model II:

The number of facilities in Model I was scaled up to include three manufacturing facilities in Billings, Albuquerque, and Louisville, and five wholesalers in Denver, Austin, Phoenix, Boise, and Boston. In addition, fifty medication provider locations were chosen between the United States, Canada, and Mexico over the same number of periods and products. (Table 20, Table 21, and Table 22) show the number of units of each product produced by each manufacturer.

Table 20: the number of units of each product manufactured by the Billings manufacturer in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
2	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
3	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6

Table 21: the number of units of each product manufactured by the Albuquerque manufacturer in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	18.6	18.6	18.6	18.6	18.6	18.6	18.6	18.6	18.6	18.6
2	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8
3	34.1	34.1	34.1	34.1	34.1	34.1	34.1	34.1	34.1	34.1

Table 22: the number of units of each product manufactured by the third manufacturer in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
2	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4
3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3

In addition, (Table 23, Table 24, Table 25, Table 26, and Table 27) show the delivery amount between the three manufacturers and the five wholesalers. In addition, (Table 28, Table 29, and Table 30) show the frequency of deliveries between each of the manufacturers and wholesalers. (Figure 15, Figure 16, and Figure 17) displays maps of the distribution networks between the facilities of the first two echelons for each of the three products at the first period only to display the scaling of the model.

Table 23: the number of units of each product transported between the manufacturer in Billings to the wholesaler in Boise for each product and time period in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
2	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
3	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6

Table 24: the number of units of each product transported between the manufacturer in Albuquerque to the wholesaler in Denver for each product and time period in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8
2	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4
3	19.8	19.8	19.8	19.8	19.8	19.8	19.8	19.8	19.8	19.8

Table 25: the number of units of each product transported between the manufacturer in Albuquerque to the wholesaler in Austin for each product and time period in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
3	9.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9

Table 26: the number of units of each product transported between the manufacturer in Albuquerque to the wholesaler in Phoenix for each product and time period in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
3	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4

Table 27: the number of units of each product transported between the manufacturer in Louisville to the wholesaler in Boston for each product and time period in thousands of units.

p\t	1	2	3	4	5	6	7	8	9	10
1	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
2	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4
3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3

Table 28: the frequency of deliveries between the manufacturer in Billings to the wholesaler in Boise.

j\t	1	2	3	4	5	6	7	8	9	10
Boise	30	30	30	30	30	30	30	30	30	30

Table 29: the frequency of deliveries between the manufacturer in Albuquerque to the wholesalers in Denver Austin and Phoenix.

j\t	1	2	3	4	5	6	7	8	9	10
Denver	90	90	90	90	90	90	90	90	90	90
Austin	45	45	45	45	45	45	45	45	45	45
Phoenix	20	20	20	20	20	20	20	20	20	20

Table 30: the frequency of deliveries between the manufacturer in Louisville to the wholesaler in Boston.

j\t	1	2	3	4	5	6	7	8	9	10
Boise	65	65	65	65	65	65	65	65	65	65

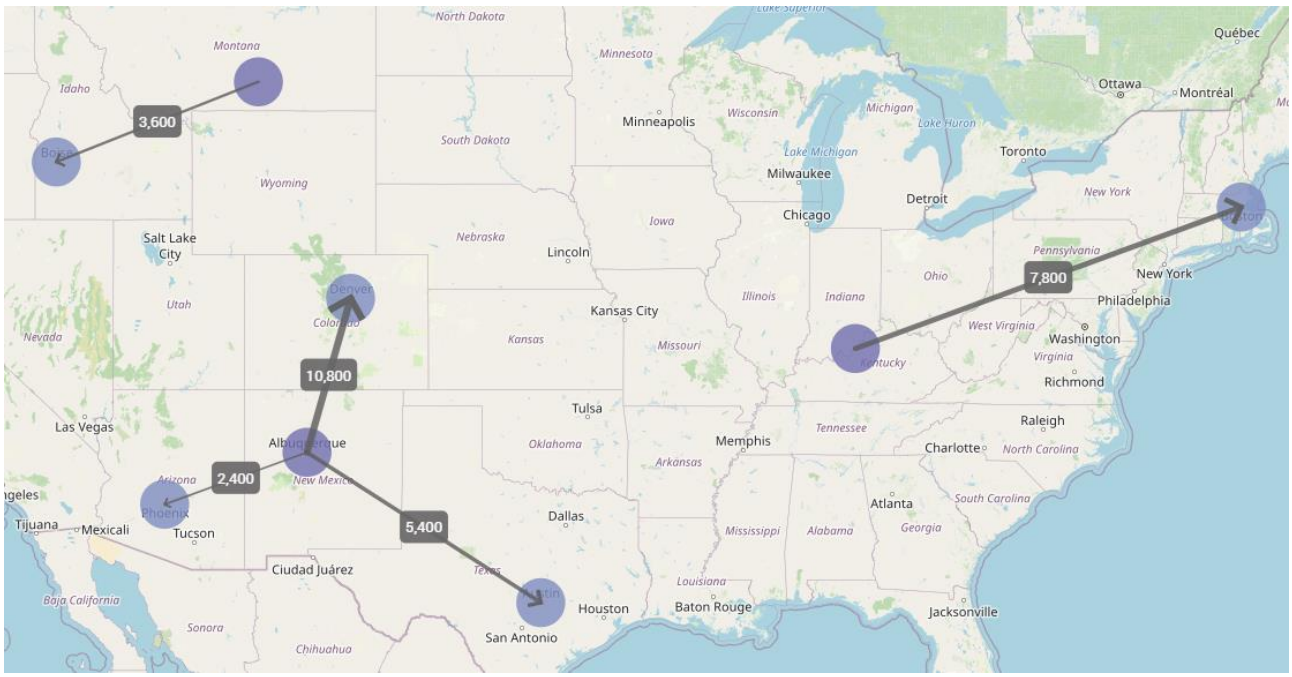

Figure 15: the amount of product one transported between the manufacturer and wholesaler echelons at the first time-period.

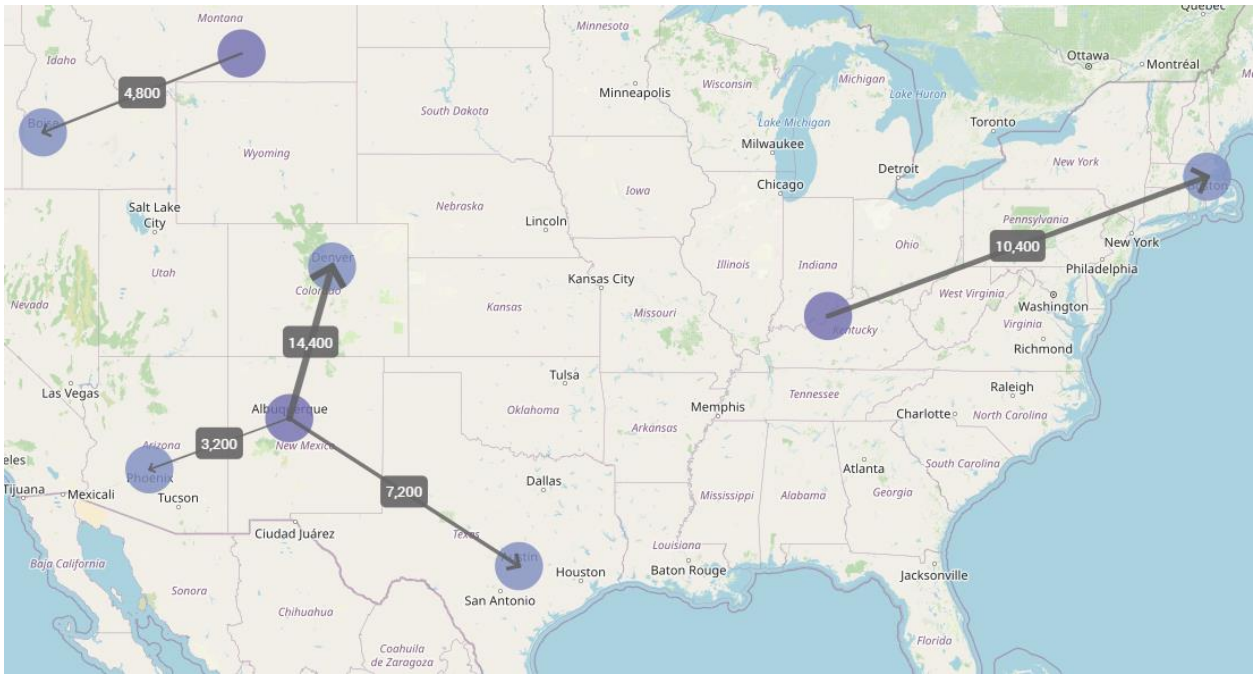

Figure 16: the amount of product two transported between the manufacturer and wholesaler echelons at the first time-period.

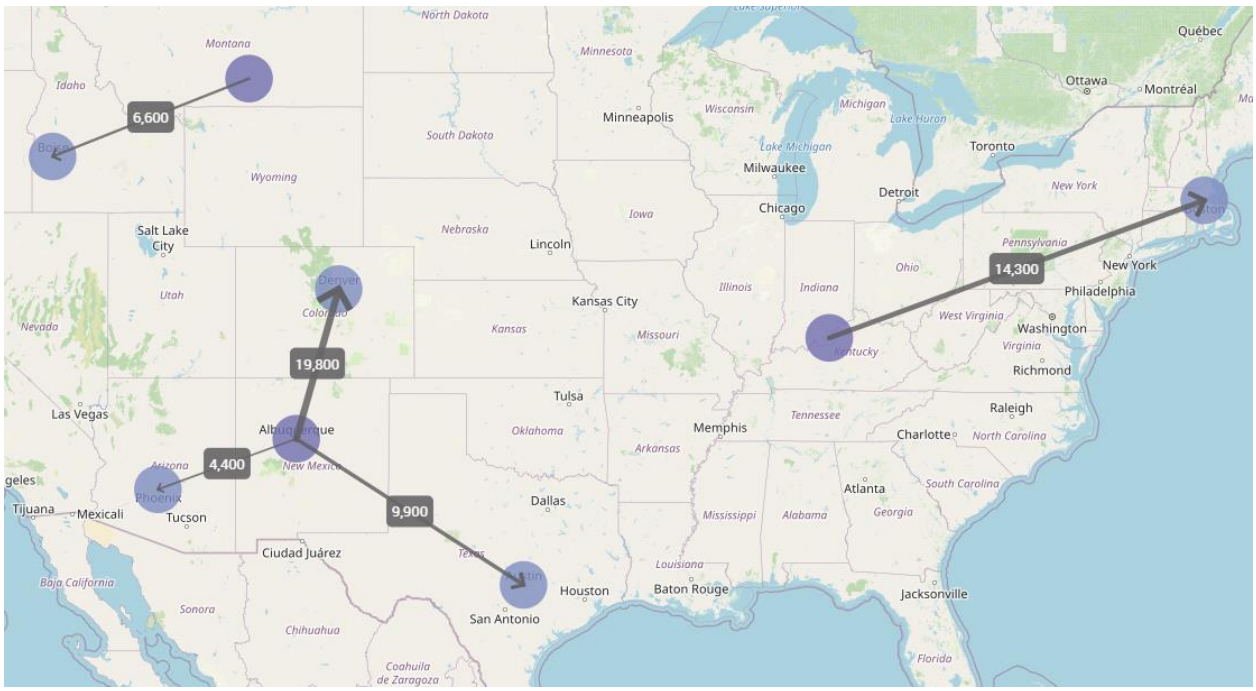

Figure 17: the amount of product three transported between the manufacturer and wholesaler echelons at the first time-period.

Since there were fifty medication providers in the scaled-up model, the number of additional tables would be very large since it needs to factor the number of medication providers, number of medication products, and the number of periods. Thus, the amount of medication products transported between the wholesalers and the medication providers and has not been added. Finally, the costs associated with the scaled-up supply chain are shown in (Table 31).

Table 31: the costs of each echelon in the model, as well as the sum of the total costs of the scaled-up version of the developed (PSC) model.

Cost Description	Amount ($)
Total Manufacturer Cost	235,708,500
Total Wholesaler Cost	35,322,310
Total Provider Cost	34,834,690
Total Model Cost	305,865,500

4.4 Robust Counterpart:

AIMMS was able to generate a robust counterpart for the deterministic results of Model I when the uncertainty of any parameter or variable is introduced. The medication demand was set to uncertain, in the production constraint equation, between a certain plus/minus percentage of its original value and the results from the robust model counterpart were documented to display the effect of that uncertainty on the total cost.

Regarding the production amount, it was set to uncertain by multiplying it by an uncertain coefficient, which is an uncertain parameter with a value of 1 and an uncertainty between a desired high and low values. The production amount is set to uncertain in the manufacturer supply constraint equation only. Thus, for the chosen parameter/variable, different levels of uncertainty from 0% of their original value to plus/minus 50% in increments of plus/minus 10% were set to see the resulting changes in the model's total costs. (Figure 18) show the percentage changes in the costs of the robust counterpart of Model I versus the percentage changes in the demand and the production amount/rate.

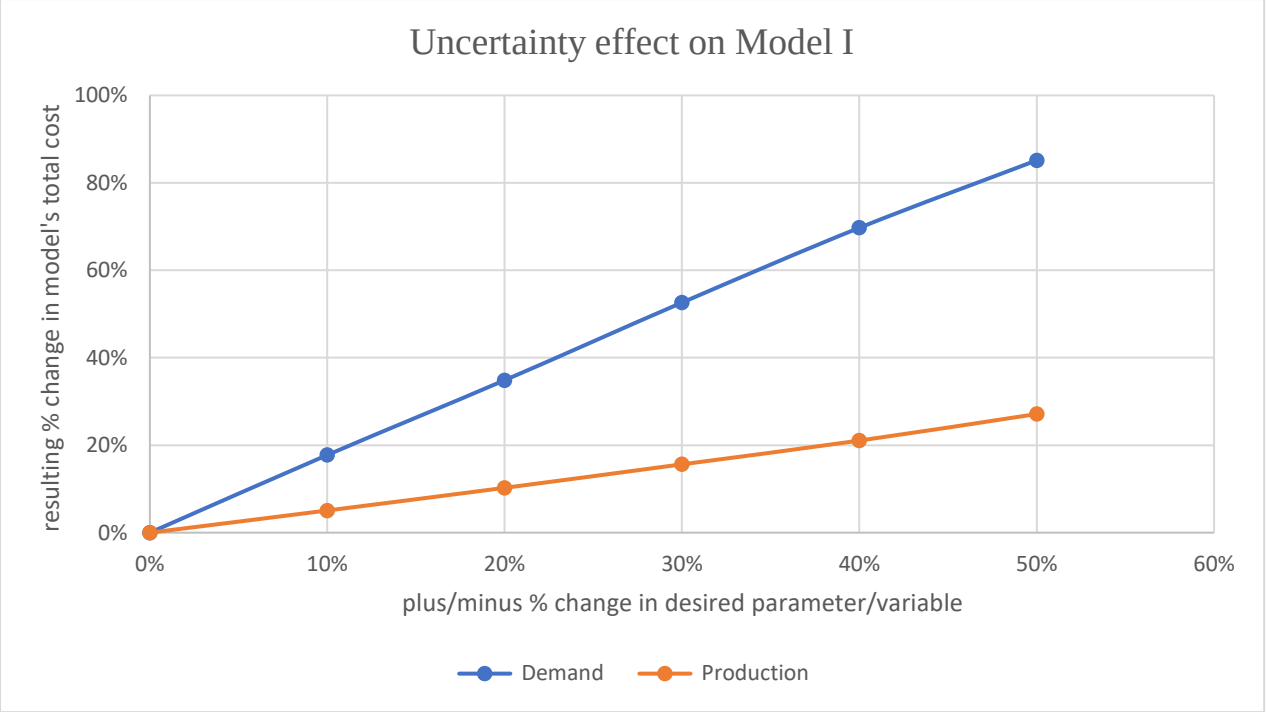

Figure 18: the change in the Model's Total cost as the demand and production rate is changed by a plus/minus 5%.

Regarding the lead-time adjusted model and the scaled-up model, Model II, the results were roughly similar but challenging to obtain. For Model II, the demand uncertainty showed the same results like the ones displayed in (Figure 18), however, AIMMS was unable to generate uncertainty results for the production amount/rate. Regarding the lead-time adjusted model, since the demand was daily, varying it by small percentages resulted in values with decimals, which AIMMS rejected since it was no longer an integer solution.

4.5 Sensitivity Analysis:

The sensitivity analysis determines how the objective function, which in this paper is the model's total cost, is affected based on changes in the parameters. This is done to investigate the change in the outcome of a decision given a certain range change of the affecting parameters. To be able to conduct the sensitivity analysis, every trace of uncertainty is removed as not to conflict with the sensitivity analyses performed on the three models (Figure 19, Figure 20, and Figure 21). Several parameters were tested in the sensitivity analysis, but only four were found to have an impact on the model's total cost. Each parameter was varied between a plus/minus 50% of its original value by increments of 5% for the deterministic counterpart of the model.

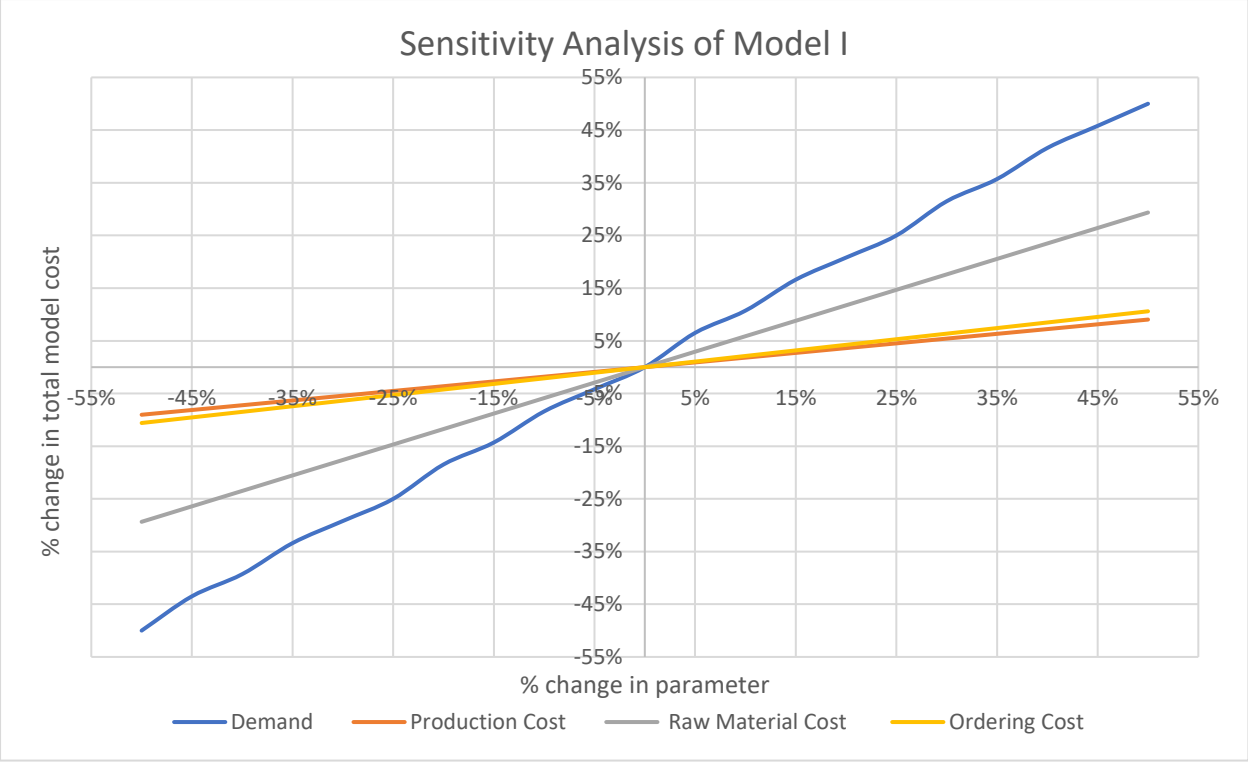

Figure 19: the sensitivity analysis of Model I against the demand, production cost, raw material cost, and ordering cost parameters.

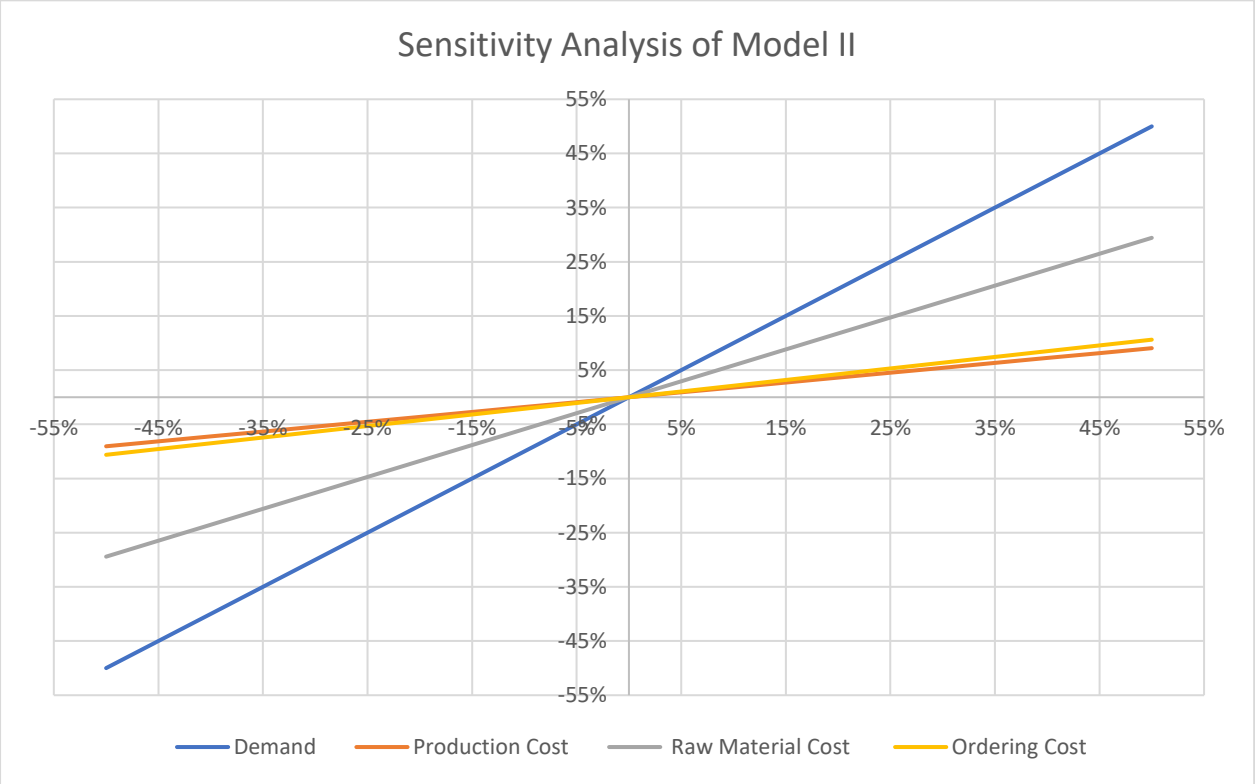

Figure 20: the sensitivity analysis of Model II against the demand, production cost, raw material cost, and ordering cost parameters.

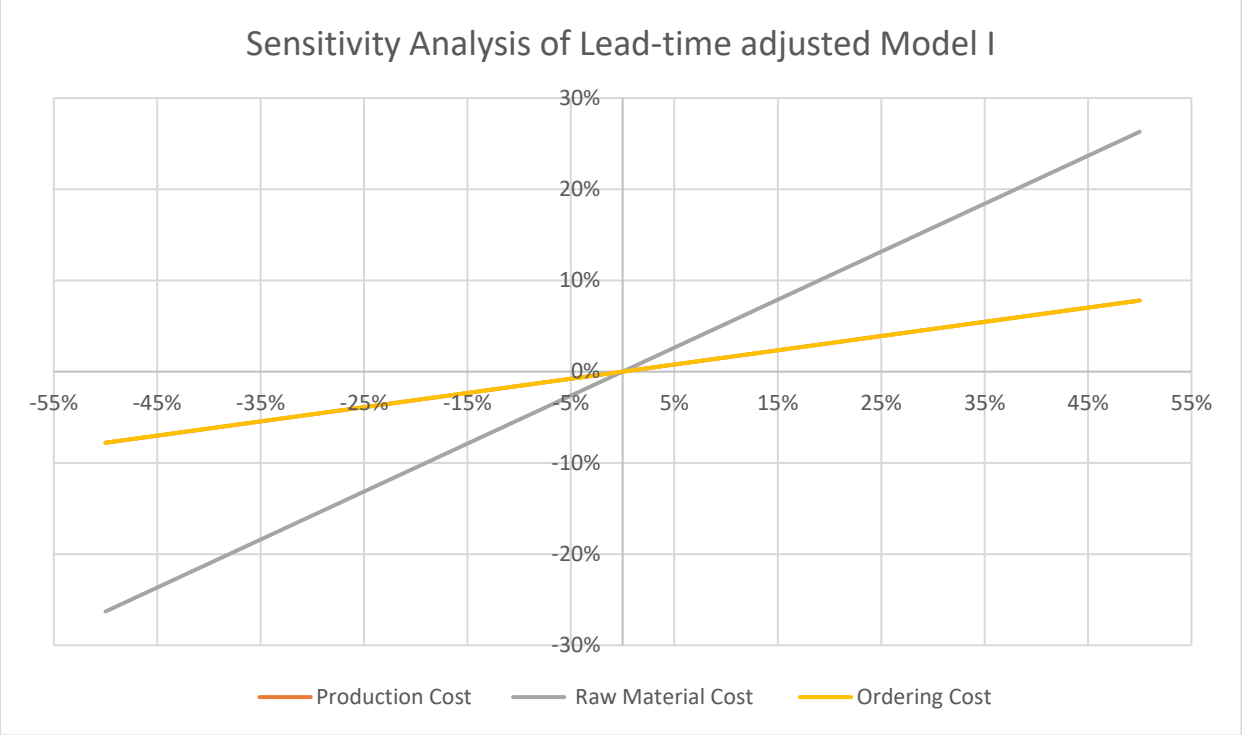

Figure 21: the sensitivity analysis of lead-time adjusted Model I against the demand, production cost, raw material cost, and ordering cost parameters.

In that regard, the medication demand was found to be the most effective parameters over the manufacturer echelon, and by extension the total cost of the model. (Figure 19 & Figure 20) shows the % change in the total model cost to be directly proportional to the % change of the demand as it was varied between plus/minus 50%. Regarding the lead-time adjusted model, the demand was very low that varying by 5% yielded no integer solution as the demand becomes in decimals, which is why no demand data is displayed in (Figure 21).

The next effective parameter was the raw material cost, which affects the manufacturer echelon and has a great effect on the total cost of the model. (Figure 19, Figure 20, and Figure 21) shows the % change in the total model cost for all the three models, where the raw material cost parameter can be seen affecting the model's total cost consistently in a straight line. Following the raw material cost is the ordering cost which affects the wholesaler and medication provider echelons only, and is seen in (Figure 19, Figure 20, and Figure 21) having less effect on the total model's cost than the previously mentioned parameters. Finally, the production cost is seen having a slightly a lower effect on the total model's cost compared to the ordering cost as seen in (Figure 19 & Figure 20) despite affecting the manufacturer echelon. for the lead-time adjusted model, (Figure 21) shows that the ordering cost and production cost parameters have the same effect on the model's total cost.

The rest of the parameters had very minute effects on the total cost of the model, which is why they were not included in this section. Certain parameters were not tested, such as the inventory and wastage costs since the uncertainty was removed and the deterministic model did not produce any wastage and did not require the storage of any medication in any echelon.

5 Conclusions

5.1 Conclusion:

The pharmaceutical supply chain is considered a complex supply chain due to the uncertainties in demand and other parameters, as well as the challenges that it faces. The optimization of the (PSC) becomes a more important field when considering the importance and effect of medication on the well-being of patients. After reviewing many studies that aimed to optimize different pharmaceutical supply chains using different complex techniques, this study aimed to present decision-makers with a simplified, yet realistic, model that aids them in making well-informed decisions. The developed model can be scaled up to include any number of facilities or products in each echelon, as well as account for perishability and demand uncertainty using robust optimization. This was proved with the displayed results of Models I and II as the number of facilities was significantly increased, yet Model II was optimized, nonetheless.

The optimization of the model was done to determine how much should each manufacturer produce and how much should each echelon distribute to the facility in the next echelon to satisfy the medication demand while reducing wastage caused by perishability. The software results highlighted the efficiency of the robust approach used to consider any uncertainty in any variable or parameter, for the applicability of the developed model in practice. In conclusion, the developed approach was simple to formulate and solve using AIMMS software developer version 4.71 and CPLEX 12.1 solver, while being robust against any uncertainties in the parameters. In addition, it provides managers with a quick guide for making decisions on the tactical and operational levels in terms of the manufacturing and distribution of medications to meet demand.

5.2 Managerial Implications:

The results obtained from running the different versions of the developed models provide managers and decision-makers in the pharmaceutical supply chain with insights into their supply chain to minimize the overall costs and wastage while satisfying the demand. Regarding the robust counterpart, the effects of uncertainty in certain parameters and variables are beneficial for managers in determining which parts of the (PSC) should be focused on more. Finally, the results obtained from the sensitivity analyses for each model aim to give managers a clear picture of which parameters, particularly the demand, raw material, production, and ordering costs, should be focused on depending on their effect on the total cost.

5.3 Limitations:

Due to the lack of pharmaceutical data, data from another study and several assumptions were put forth to test the developed model at different scales to prove the scalability feature of the developed model. In addition, the developed model may prove to be non-robust in nature if the data was majorly changed or customized. Furthermore, mixed transportations involving water- and air-based transportation methods and routes were not considered in this study, which could be a limiting factor to the model. Finally, the scalability of the developed model was not tested on a global level, for a global pharmaceutical company, for example, to realize its capabilities for delivering medication globally under demand uncertainty.

5.4 Future Works:

The developed work aimed to optimize a three-echelon pharmaceutical supply chain and the uncertainties associated with it while keeping the model simple and easy to solve. There is a potential for expansion in several different directions. The potential for satisfying any emergency shortages can also be investigated in terms of manufacturers directly transporting the product to providers, or providers collaborating to share their inventory with other providers in cases of emergencies. Furthermore, the investigation into the effect of quantity discounts on the sales of medication is another opportunity to test the developed model, but in this case, the model's objective should be set to increase the profit. Finally, the developed model can be tested to optimize many larger-scale problems such as global supply chains which contain several more constraints and uncertainties.

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