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Two-stage stochastic programming approach for the medical drug inventory routing problem under uncertainty

Abstract

Medical drug shortages are an important issue in health care, since they can significantly affect patient health. Thus, selecting the appropriate distribution and inventory policies plays an important role in decreasing drug shortages. In this context, inventory routing models can be used to determine optimal policies in the context of medical drug distribution. However, in real-world conditions, some parameters in these models are subject to uncertainty. This paper examines the effects of uncertainty in the demand by relying on a two-stage stochastic programming approach to incorporate it into the optimization model. A two-stage model is then proposed and two different approaches based on chance constraints are used to assess the validity of the proposed model. In the first model, a scenario-based two-stage stochastic programming model without probabilistic constraint is proposed, while in the other two models, proposed for validation of the first model, probabilistic constraints are considered. A mathematical-programming based algorithm (a matheuristic) is proposed for solving the models. Moreover, the Latin hypercube sampling method is employed to generate scenarios for the scenario-based models. Numerical examples show the necessity of considering the stochastic nature of the problem and the accuracy of the proposed models and solution method.

Keywords: Two-stage stochastic programming, Stochastic inventory routing problem, Medical drug distribution, Latin hypercube sampling method, Chance constraints, Matheuristics.

1. Introduction

The inventory routing problem (IRP) is defined as an extension of the vehicle routing problem in which decisions related to routing and inventory management are made simultaneously [1]. The inventory routing problem is used for different types of products, such as those related to health care (see, for instance [2] and [3]). Typically, the demands in IRP are assumed to be deterministic input parameters. However, in real-world conditions, the actual values of some parameters are unknown during planning phases [4]. Therefore, tools that allow decision-making under uncertainty must be used to consider real situations in order to make practically meaningful decisions. In the IRP, several parameters can be considered as uncertain, which leads to stochastic inventory routing problem (SIRP) models.

Drug shortages are a major problem in health care. Fortunately, operations research can be used to effectively reduce their effects [3]. The University of Utah Drug Information Service has reported that the frequency of drug shortages has been increasing rapidly in the decade from 2001 to 2011. The effects of drug shortages on patient care is an important issue, and has been studied extensively (see for instance, [5], and [6]). The U.S. Department of Health and Human Services (2012) reported that 13% of drug shortages occurs because of inappropriate distribution and inventory policies. Therefore, using the IRP can help in the definition of optimal distribution and inventory policies.

Stochastic programming is a technique to devise mathematical programming models in which some parameters are considered uncertain. Stochastic programming helps decision-makers to make decisions more accurately in contexts where the effect of uncertain parameters cannot be neglected. The results obtained from stochastic programming cannot satisfy all conditions in the future, but they help in achieving better-than-average performance when dealing with uncertainty. Two well-known classes of stochastic programming are two-stage stochastic programming and chance constraints. Two-stage stochastic programming was originally proposed by [7, 8], while the chance constraints approach was introduced by [9]. In this study, two-stage stochastic programming and chance constraints are used to make decisions under uncertainty in the context of the IRP.

In real-world situations, the exact value of future demands cannot be predicted accurately, but they can be described by density (or mass) distribution functions or a discrete numbers of scenarios. Therefore, considering uncertainty made decision makers more capable to have better planning for the future. Considering uncertainty helps managers to determine distribution and inventory policies more accurately and consequently decrease drug shortages.

This study is conducted as follows. First, a two-stage stochastic programming model is proposed for the case of medical drug distribution when the demand is uncertain. In this model, violations of inventory capacity and shortages are considered as second-stage variables, which contrast to other studies related to SIRP. Considering amount of inventory in the first stage helps decision maker to have more information about the size requirements for inventories, while representing more realistically the process of forming drug inventory before the realization of the demand. Second, two chance constraint stochastic models are proposed, and we show that they can be used interchangeably instead of two-stage stochastic programming model that is proposed in this paper, provided that the correct parametrization is employed. Then a matheuristic method is proposed for solving the proposed model and its efficiency is subsequently improved by using valid inequalities. Finally, Latin hypercube sampling method is used for scenario generation method in this paper.

The structure of the paper is as follows: The literature reviews in Section 2. The problem is described in Section 3, then the mathematical models are outlined in Section 3. The matheuristic method for solving proposed model and scenario generation method are discussed in Section 4. The experimental results and analysis are presented in Section 5, followed by the conclusion in Section 6.

2. Literature Review

In most studies related to IRP, a single type of product is distributed by homogeneous fleets. Azadeh et al. [10] and Coelho et al. [11] approached the IRP using metaheuristic algorithms with a single type of product and homogeneous vehicles. On the other hand, multiple products and heterogeneous fleets have also been considered. Coelho et al. [12] proposed an IRP model by considering heterogeneous fleets and developed a matheuristic approach to solve the problem. Coelho et al. [13] used branch-and-cut algorithm for solving IRP with multiple product and homogeneous vehicles. Cheng et al. [14] proposed a mixed integer model for IRP by considering environmental impacts and heterogeneous fleets and solved it by branch-and-cut. Shaabani and Kamalabadi [15] proposed a model for IRP considering multiple perishable products and heterogeneous vehicles. They used the simulated annealing algorithm to solve the problem. In this paper, an MIP model is proposed for IRP by considering multiple products and heterogeneous vehicles.

Roldán et al. [16] reviewed studies related to IRP in which demands and lead times were defined as stochastic parameters. Coelho et al. [17] categorized studies in the context of inventory routing problems in the decades from 1983 to 2013. The studies were classified based on structural variants and time of disclosure of information on demands. Inventory routing problems were classified into three categories based on time of disclosure and type of information on demands. These categories consisted of static, stochastic and dynamic problems. Deterministic values and probability distributions of demands are known in advance in static and stochastic problems. Dynamic problems are those in which demands are unknown at the beginning and the information is revealed over the time.

Stochastic inventory routing problems can be classified based on the methods used to represent the uncertainty. In the first category, the expected values of the recourse function are minimized. The studies related to this class of SIRP are categorized based on the planning horizon, including finite and infinite horizons. Federgruen and Zipkin [18], Federgruen et al. [19] and Jaillet et al. [4] proposed heuristic algorithms to solve the SIRP in a finite horizon. Also, Mirzapour Al-e-Hashem et al.[20] used a hybrid L-shaped decomposition algorithm for solving SIRP. In infinite horizon problems, demands are defined as a Markov process and dynamic programming methods are employed to solve the problems. Some studies that have proposed algorithms to solve this type of SIRP are [21, 22, 1, 23, 24, 25].

Probabilistic or chance constraint programming is another category of SIRP in which solutions are obtained under considering violations in the constraints. Yu et al. [26] and Rahimi et al. [27] proposed chance constraint programming models for IRP and used Lagrangian relaxation/ decomposition to solve the proposed models. Soysal et al. [28] and Soysal et al. [29] considered service level constraints. In these papers, it's assumed that demands follow normal distributions. To the best of our knowledge, this paper is the first study that consider a discrete chance constraint in the context of inventory routing problems.

Table 1 shows studies in the context of IRP with considering uncertainty in demands classified based on different aspects and comparisons of those studies and the models proposed in the present paper. In the proposed models, demands are considered as stochastic parameters. Based on the results shown in Table 1, demand can be considered as a discrete (defined by number of scenarios) or continuous parameter; in this paper, both cases are considered.

In stochastic programming, scenario generation is an important part of the modeling process. The method that is used to generate the scenarios and determine the optimal number of scenarios affects the results of the model. Therefore, selecting an appropriate method for scenario generation and determining the optimal number of scenarios are important issues in stochastic programming. Löhdorf and Nils [30] examined the popular methods for scenario generation in the context of stochastic programming, including the quasi-Monte Carlo method, moment matching, methods based on probability metrics, and the Voronoi cell sampling method. The methods that are used for scenario generation in the SIRP are shown in Table 1.

The Monte Carlo method has been used in several studies of the SIRP for scenario generation. On the other hand, the use of Latin hypercube sampling (LHS) method has not been widely investigated as a method for scenario generation in the context of the SIRP. Despite being the most popular method for scenario generation, the Monte Carlo method might require large numbers of samples to ensure accurate approximation of probability distributions of uncertain variables, a flaw that can be mitigated by the use of LHS. Therefore, the LHS method is used in this paper to generate scenarios according to a predefined distribution function. This method was described by [31] and has been used in several studies (see for instance [32, 33, 34]). The performance effect of the LHS method is compared in this study. Also, the optimal number of scenarios are determined based on standard deviation of the in-sample and out-of-sample objective function evaluations.

This paper provides three main contributions, based on the existing literature. First, as shown in Table 1, inventories and shortages have been considered as second stage-variables in most studies related to SIRP. Using these second-stage decision variables increases the number of decision variables (in specific integer variables) and constraints that depend on the uncertain parameters. Alternatively, the proposed model considers second-stage decision variables that focus on deviations in the material balance constraints, which ultimately leads to a similar behaviour of the solution obtained in terms of uncertainty protection. Naturally, setting greater values of violation costs leads to increase the robustness in the model. Numerical examples illustrate the benefits of considering these second-stage decision variables as such in terms of decreasing the number of integer decision variables.

Second, two additional models are proposed for discussing the applicability of different modeling frameworks and, in turn, to validate the first model. The demand uncertainty in these models are considered by using probabilistic constraints. In the second model, it is assumed that the demand follows a normal distribution and, thus, a deterministic equivalent with continuous chance constraint can be posed to incorporate with uncertainty. We show that the second model can be used interchangeably instead of the first one, when demands follow a normal distribution, provided that adequate parametrization is performed. In the third model, chance constraint considering discrete scenarios are proposed. We show that this model is the most general, in the sense that it can accommodate the two previous models, while also being able to consider a much more general setting in terms of demand uncertainty.

Third, a matheuristic method is proposed for solving the proposed models. This method is developed based on a four phases method proposed by Solyalı and Süral [37] for production routing problem. Moreover, the efficiency of the proposed method is enhanced by adding some valid inequalities. The proposed method plays an important role in dealing with the computationally challenging characteristics of the proposed models, as it can be seen in the numerical experiments conducted.

3. Mathematical formulation

In this problem, a supplier distributes different types of drugs among identical medical centers. Each medical center makes decisions about ordering times and quantities for each drug. It is assumed that there is uncertainty in the demand for drugs. The proposed mixed-integer programming models for the medical drug distribution problem are introduced in this section. The main assumptions are as follows:

- (1) One supplier distributes drugs among the medical centers

Table 1: Classification of the studies in IRP under uncertain demands

	Problem type	Fleet	Distribution of parameter		Expected value of objective function	Chance constraint	Solving method		case	Scenario generation	Second stage decision variables
			Dis	Con	S		Exact	H/MH/MTH			
[18]	SF	Homo		N	*			H	-		I and Sh
[19]	SF	Homo		N	*			H	PP		I and Sh
[4]	SF	Si		TN	*			H	LP	MC	Sh
[21]	SIF	Si	*			*		H	-		
[22]	SIF	Homo	*			*		H	-		
[35]	SIF	Homo	*			*		H	-		
[24]	SIF	Si	*			*		MH	-	MC	
[36]	SIF	Si	*			*		MH	-	MC	
[2]	F	Si	*			*		MH	Hc		
[29]	SF	Homo		N			*		PP		
[28]	SF	Homo		N			*		PP		
[20]	SF	Het	*		*		*		-	MC	I, SH and Q
The first proposed model in current study	SF	Het	*		*			MTH	Hc	LHS	Auxiliary variables
The second proposed model in current study	SF	Het		N	*	*		MTH	Hc	LHS	Auxiliary variables
The third proposed model in current study	SF	Het	*		*	*		MTH	Hc	LHS	Auxiliary variables
SF: Stochastic inventory routing problem with finite horizon, SIF: Stochastic inventory routing problem with infinite horizon, SD: Stochastic and dynamic problem, H:Heuristic, MH: Meta-heuristic, P:Product, PP:Perishable Product, LP:Liquid product, GP:Gas product, Dis:Discrete, Con:Continuous,S:Static,Dy:Dynamic, MC:Monte Carlo, I:Inventory, Sh:Shortage, Hc:Health care, Het: Heterogeneous vehicle, Homo: Homogeneous vehicle, Si: single vehicle, Q: quantity of transported product											

- (2) The drugs are fresh when received by the medical centers.
- 130 (3) Each medical center is served by one vehicle in each period.
- (4) The planning horizon is finite.
- (5) A heterogeneous fleets are considered, and thus capacities and transportation costs of vehicles are different.
- (6) The monitoring of inventory levels and replenishment are done periodically.

135 The notation, parameters and decision variables that are used in the proposed models are shown below.
Sets and indices:

C : Set of medical centers

CS : Set of medical centers and supplier, where 0 corresponds to the supplier, $CS = C \cup \{0\}$

ξ : Set of demand scenarios $\xi \in \Xi$

r : Index of drug type $DT = (1, \dots, R)$

k : Index of vehicle type $VT = (1, \dots, K)$

t : Index of time period $P = (1, \dots, T)$

i, j : Indices of medical centers or supplier, where 0 corresponds to the supplier

140 Parameters:

h_{ir} Inventory holding cost in medical center i per unit for drug type r

I_{ir0} Initial inventory of drug type r in medical center i

ν_k Transportation cost per unit distance for vehicle type k

$\emptyset_{ir}$ Shortage cost per unit of drug type r in medical center i

IC_{ir} Maximum inventory level of drug type r in medical center i

d_{ij}	Distance between medical centers i and j
$Dem_{irt}(\xi)$	Demand for drug type r in medical center i in time period t under scenario $\xi \in \Xi$ with corresponding probability $p(\xi)$
M	An arbitrary large number
Cap_k	Capacity of the vehicle type k
μ_{irt}	The mean value of demand for drug type r in medical center i in time period t
S_{irt}	The standard deviation value of demand for drug type r in medical center i in time period t
$VC1$	Positive violation cost in the constraint related to stochastic demand
$VC2$	Negative violation cost in the constraint related to stochastic demand
B_{irt}	Maximum allowable probability to have a positive shortage for drug type r in medical center i in period t
N_{irt}	Number of scenarios that having positive value of shortage for drug type r in medical center i in period t

Decision variables:

I_{irt}	Inventory level of drug type r in medical center i in period t
Sh_{irt}	Amount of shortage for drug type r in medical center i in period t
q_{irkt}	Amount received of drug type r in medical center i in period t by vehicle type k
$x_{ijk t}$	1 if medical center j is visited exactly after medical center i by vehicle type k in period time t . 0 otherwise.
z_{ikt}	1 if medical center i is visited by vehicle type k in period time t . 0 otherwise.

Auxiliary variables:

w_{ikt}	A dummy variable to eliminate sub-tours
F_{irt}	A dummy variable to linearize the constraint that calculate the product of the decision variables I_{irt} and Sh_{irt}
$V1_{irt}(\xi)$	A dummy variable to capture a positive violation in the constraint related to stochastic demand under scenario $\xi \in \Xi$
$V2_{irt}(\xi)$	A dummy variable to capture a negative violation in the constraint related to stochastic demand under scenario $\xi \in \Xi$
$G_{irt}(\xi)$	1 if shortage is positive under scenario $\xi \in \Xi$. 0 otherwise.

3.1. The first model: two-stage stochastic programming model

In this section, a two-stage stochastic programming model is proposed, considering the uncertain parameter (demand). In the first stage, decisions are made about amounts of drugs received and routing plans. The violations in the stochastic constraints are considered as second-stage variables. The uncertain demands are defined by a number of scenarios $\{1, 2, \dots, |\Xi|\}$. Since it is assumed that a sampling process is used to generate scenarios, the probability corresponding to each scenario is equal to $1/|\Xi|$. The first-stage model can be formulated as follows:

$$\begin{aligned} \min f_1 = & \sum_{i \in CS} \sum_{\substack{j \in CS \\ i \neq j}} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} Sh_{irt} \\ & + E(Q(x_{ijkt}, q_{irkt}, \xi)) \end{aligned} \quad (1)$$

$$\text{s.t.: } \sum_{j \in CS} x_{ijkt} = z_{ikt} \quad \forall i \in CS, i \neq j, k \in VT, t \in P \quad (2)$$

$$\sum_{j \in CS} x_{jikt} = z_{ikt} \quad \forall i \in CS, i \neq j, k \in VT, t \in P \quad (3)$$

$$\sum_{j \in CS} x_{ijkt} = \sum_{j \in CS} x_{jikt} \quad \forall i \in CS, i \neq j, k \in VT, t \in P \quad (4)$$

$$Sh_{irt} \leq M \times F_{irt} \quad \forall i \in C, r \in DT, t \in P \quad (5)$$

$$I_{irt} \leq M \times (1 - F_{irt}) \quad \forall i \in C, r \in DT, t \in P \quad (6)$$

$$\sum_{k \in VT} q_{irkt} \leq IC_{ir} - I_{ir(t-1)} \quad \forall i \in C, r \in DT, t \in P \quad (7)$$

$$\sum_{i \in C} \sum_{r \in DT} q_{irkt} \leq Cap_k z_{0kt} \quad \forall k \in VT, t \in P \quad (8)$$

$$\sum_k \sum_{j \in CS} x_{ijkt} \leq 1 \quad \forall i \in C, t \in P \quad (9)$$

$$w_{jkt} - w_{ikt} + (|C| + 1) x_{ijkt} \leq |C| \quad \forall i \in CS, j \in C, i \neq j, k \in VT, t \in P \quad (10)$$

$$q_{irkt} \leq M \sum_{j \in CS} x_{ijkt} \quad \forall i \in C, k \in VT, r \in DT, t \in P \quad (11)$$

$$q_{irkt} \geq 0, I_{irt} \geq 0, Sh_{irt} \geq 0, w_{ikt} \geq 0, x_{ijkt} \in \{0, 1\} F_{irt} \in \{0, 1\} \quad (12)$$

Objective function (1) consists of three deterministic terms that calculate total cost, including inventory holding, transportation and shortages costs. Also, this objective function contains the expected value of the second-stage objective function. Equations (2) and (3) guarantee that a vehicle can leave from or enter a medical center in case of assigning mentioned medical center to the vehicle. Constraints (4) are vehicle balance equations and ensure that if the i -th medical center is visited by k -th vehicle in time period t , the vehicle must then visit another medical center or return to the supplier. Constraints (5) and (6) show that decision variables I_{irt} and Sh_{irt} are not positive in the same period. Constraints (5) and (6) are the linear equivalents of nonlinear constraint (13). In these constraints, auxiliary binary variables are added to the mathematical model to transform nonlinear constraint (13) into linear constraints (5) and (6).

$$Sh_{irt} \times I_{irt} = 0 \quad \forall i \in C, r \in DT, t \in P \quad (13)$$

Constraint (7) ensures that the inventory level of drug type r in medical center i in each period is not more than the maximum inventory capacity. Constraint (8) ensures that the quantities of the received drugs are not more than the vehicle capacities. Constraint (9) ensures that all customers can be visited at most once in each time period. Constraint (10) enforces sub-tour elimination. Constraint (11) guarantees the relation between q_{irkt} and x_{ijkt} . Constraint (12) defines the variable domains. The objective function and constraints in the second-stage model are as follows:

$$\min E(Q(x_{ijkt}, q_{irkt}, \xi)) = \min_{\xi \in \Xi} p(\xi) \left[\sum_i \sum_r \sum_t VC1 \times V1_{irt}(\xi) + VC2 \times V2_{irt}(\xi) \right] \quad (14)$$

s.t.:

$$I_{irt} - Sh_{irt} = I_{ir(t-1)} - Dem_{irt}(\xi) + q_{irkt} - Sh_{ir(t-1)} + V1_{irt}(\xi) - V2_{irt}(\xi) \\ \forall i \in C, r \in DT, t \in P, \xi \in \Xi \quad (15)$$

$$V1_{irt}(\xi) \geq 0, V2_{irt}(\xi) \geq 0. \quad (16)$$

Constraint (14) calculates the expectation of the cost related to the violation of constraint (15). Constraint (15) represents the relation between the inventory levels in period t and $t-1$. Constraint (16) defines the domain of the decision variables.

All medical drugs must be held in a cool place, dry and away from sunlight and moisture. Some medical drugs require special holding conditions and facilities such as refrigerator, or even the freezer. Medical drugs for multiple sclerosis (MS), diabetes type 1 and biological diseases can be expired quickly or become less effective if they are held in unsuitable conditions such as room temperature. Therefore, an extension of the proposed model is given in Appendix A for considering cases in which the proportion of unusable drugs might play a significant role. This extension considers the amount of drugs that are expired due to unsuitable holding (hence becoming unusable) and focus also on decreasing the amount of unusable drugs. The reported results in Appendix confirms that both models behave similarly for usual drugs (the main case under study, for which the total of unusable drugs are significantly small) and the difference is negligible in this case.

3.2. The second model: stochastic programming with continuous probabilistic constraints

This model is proposed mainly to serve as a mean of validating the first model. In this section, it is assumed that demands follow a normal distribution, which allows the derivation of a deterministic equivalent model without the use of scenarios. The mean and standard deviation of demand for drug type r in medical center i in time period t are μ_{irt} and S_{irt} , respectively. In this model, chance constraint formulations are employed to minimize the amounts of shortages when demands follow a continuous distribution. The objective function and constraints of the second model are as follows:

$$\min f_2 = \sum_{i \in CS} \sum_{\substack{j \in CS \\ i \neq j}} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} Sh_{irt} \quad (17)$$

s.t.: (2) – (12)

$$Prob(Sh_{irt} > 0) \leq \beta_{irt}^1 \quad \forall i \in C, r \in DT, t \in P \quad (18)$$

The objective function (17) consists of three deterministic terms that calculate total cost including inventory holding, transportation, and shortage costs. In this model, the continuous probabilistic constraint is used to incorporate the uncertainty related to demands, while the uncertainty related to demands is considered in the objective function of the second stage in the first model. Equation (18) guarantees that the probability of positive values for shortages is less than a predefined allowable value. This constraint is transformed into a linear constraint by using equation (19), which is possible when the uncertain phenomenon follows a normal distribution.

probability of positive values for shortages is less than a predefined allowable value. This constraint is transformed into a linear constraint by using equation (19), which is possible when the uncertain phenomenon follows a normal distribution.

$$\frac{I_{ir(t-1)} + q_{irkt} - Exs_{irt} - Sh_{ir(t-1)} - \mu_{irt}}{S_{irt}} \geq z^{-1}(1 - B_{irt}) \quad \forall i \in C, r \in DT, t \in P \quad (19)$$

where $z^{-1}(\cdot)$ is the inverse of the cumulative distribution function of a standard normal distribution.

3.3. The third model: stochastic programming with discrete probabilistic constraint

This model is proposed as a generalization of the second model, since it can be used as an approximation when uncertain parameters not necessarily follow normal distributions. In this case, discrete scenarios are generated from the original distribution and the continuous probabilistic constraints are replaced by discrete equivalents. In this case, the probabilistic constraint determines a threshold value for the number of scenarios with positive shortages. The objective function and constraints in the first-stage model are as follows:

$$\begin{aligned} \min f_3 = & \sum_{i \in CS} \sum_{\substack{j \in CS \\ i \neq j}} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijk} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} Sh_{irt} \\ \text{s.t.: } & (2) - (12) \end{aligned} \quad (20)$$

$$I_{irt} - Sh_{ir(t-1)} - V1_{irt}(\xi) + V2_{irt}(\xi) \leq M(1 - G_{irt}(\xi)) \quad \forall i \in C, r \in DT, t \in P, \xi \in \Xi \quad (21)$$

$$-(I_{irt} - Sh_{ir(t-1)} - V1_{irt}(\xi) + V2_{irt}(\xi)) \leq M(G_{irt}(\xi)) \quad \forall i \in C, r \in DT, t \in P, \xi \in \Xi \quad (22)$$

$$\sum_{\xi \in \Xi} G_{irt}(\xi) \leq N_{irt} \quad \forall i \in C, r \in DT, t \in P \quad (23)$$

$$V1_{irt}(\xi) \geq 0, V2_{irt}(\xi) \geq 0 \quad (24)$$

Objective function (20) is similar to objective function of the second model. Constraints(21) and (22) calculate the amount of inventory and shortage of drugs associated with each scenario. Constraint (23) ensures that the number of scenarios for which shortages have a positive value is smaller than N_{irt} . Therefore, the number of scenarios for which inventories have positive values is greater than $|\Xi| - N_{irt}$.

4. Scenario generation and solution methods

The two-phase matheuristic method for solving IRP employed in this paper is based on a multi-phase heuristic proposed by Solyalı and Süral [37] for production routing problem (PRP). The proposed solution method as well as the LHS scenario generation scheme are discussed in this section.

4.1. The matheuristic method

In this method, the problem is decomposed in two phases. The pseudocode of the proposed matheuristic is given and the phases are discussed in following subsections.

Algorithm 1 Proposed matheuristic algorithm

Input: Parameters of the model($h_{ir}, I_{ir0}, \nu_k, IC_{ir}, d_{ij}, Cap_k, Dem_{irt}(\xi), VC1, VC2$)

Phase 1:

Solve a TSP to define a preliminary reasonable medical centers visiting sequence.

The sets α_i and β_i are defined as predecessor and successor sets for i th medical centers.

Phase 2:

According the sets of α_i and β_i a restricted IRP model is constructed by using equations (5)-(8) and (26)-(32)

Phase 3:

Add valid inequalities using equations (34)-(36) and (38)

Solve restricted IRP with valid inequalities and determine the outputs.

return $I_{irt}, Sh_{irt}, q_{irkt}, x_{irkt}, z_{ikt}$

Table 2: Tour precedence structure obtained by a TSP

i	α_i	β_i
0	[1 2 3 4 5]	[1 2 3 4 5]
1	[0 3]	[0 2 4 5]
2	[0 1 3 4 5]	[0]
3	[0]	[0 1 2 4 5]
4	[0 1 3 5]	[0 2]
5	[0 1 3]	[0 2 4]

4.1.1. Phase 1: solving a TSP

In the this phase a TSP model is solved over all medical centers by considering the supplier as start and end points of the tour. The solution of this model determines a sequence for visiting the medical centers in a period to minimize the transportation cost. The sets of α_i and β_i are defined for each medical center and supplier based on the obtained tour. α_i and β_i are defined as sets of nodes (medical centers or supplier) that are visited after and before i -th node in the obtained tour, respectively. For an example with 5 medical centers and one supplier, α_i and β_i sets are shown in Table 2. In this example, it is assumed that the obtained tour by solving a TSP is 0-2-4-5-1-3-0.

4.1.2. Phase 2: constructing a restricted IRP model

In this section, a restricted IRP model is constructed by relaxing integrality constraints of x_{ijkt} and fixing the visiting sequence of medical centers based on the tour obtained in the previous phase. The subtour elimination constraints are omitted in the restricted IRP because the visiting sequence of the medical centers is fixed. It is well known that the subtour elimination constraints increase exponentially in number and thus significantly increases the problem size. Therefore, removing these constraints in the restricted model decreases the solution time of the model considerably. The first-stage model of restricted IRP is as follows:

$$\min f_4 = \sum_{i \in CS} \sum_{j \in \alpha_i} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} Sh_{irt} + E(Q(x_{ijkt}, q_{irkt}, \xi)) \quad (25)$$

$$(26)$$

s.t.: (5)-(8)

$$\sum_{j \in \alpha_i} x_{ijkt} = z_{ikt} \quad \forall i \in CS, k \in VT, t \in P \quad (27)$$

$$\sum_{j \in \beta_i} x_{jikt} = z_{ikt} \quad \forall i \in CS, k \in VT, t \in P \quad (28)$$

$$\sum_{j \in \alpha_i} x_{ijkt} = \sum_{j \in \beta_i} x_{jikt} \quad \forall i \in CS, k \in VT, t \in P \quad (29)$$

$$\sum_k \sum_{j \in \alpha_i} x_{ijkt} \leq 1 \quad \forall i \in C, t \in P \quad (30)$$

$$q_{irkt} \leq M \sum_{j \in \alpha_i} x_{ijkt} \quad \forall i \in C, k \in VT, r \in DT, t \in P \quad (31)$$

$$q_{irkt} \geq 0, I_{irt} \geq 0, Sh_{irt} \geq 0, w_{ikt} \geq 0, 0 \leq x_{ijkt} \leq 1, F_{irt} \in \{0, 1\} \quad (32)$$

Note that the values that are obtained for x_{ijkt} are integer because of the structure of the problem. The second-stage model is defined as follows:

$$\begin{aligned} \min E(Q(x_{ijkt}, q_{irkt}, \xi)) &= \min \sum_{\xi_1 \in \Xi_1} p(\xi) \left[\sum_i \sum_r \sum_t VC1 \times V1_{irt}(\xi_1) + VC2 \times V2_{irt}(\xi) \right] \\ \text{s.t.:} & (15) - (16) \end{aligned} \quad (33)$$

4.1.3. Phase 3: adding valid inequalities in the restricted IRP

Valid inequalities are used to reduce the search space of the MIP and, as a result, decreasing of the running time. Coelho et al.[12] extended the valid inequalities proposed by Archetti et al.[38] and also proposed new valid inequalities for IRP with multiple vehicles for the case of homogeneous vehicles. We formulate these valid inequalities considered in our approach as follows:

$$x_{ijkt} \leq z_{ikt} \quad \forall i \in CS, j \in CS, k \in VT, t \in P \quad (34)$$

$$z_{ikt} \leq z_{0kt} \quad \forall i \in C, k \in VT, t \in P \quad (35)$$

$$z_{0kt} \leq z_{0k-1t} \quad \forall k \in VT \setminus \{1\}, t \in P \quad (36)$$

$$\sum_{k \in VT} \sum_{t'=t_1}^{t_2} z_{ikt'} \geq \left\lceil \frac{\sum_{t'=t_1}^{t_2} Dem_{it'} - IC_i}{\min\{Cap, IC_i\}} \right\rceil \quad \forall i \in C, t_1, t_2 \in P, t_2 \geq t_1 \quad (37)$$

Constraint (34) is the logical inequality that ensures that if j -th medical center is the successor of i -th medical center in the route of vehicle k , it should be allocated to the same vehicle as the vehicle visits i -th medical center. Constraint (35) guarantees that a medical center can be allocated to a vehicle if this vehicle has started from the supplier. Constraint (36) ensures that vehicle type k cannot leave the supplier if the vehicle type $k - 1$ has not been used yet. Despite the fact that this valid inequality has been proposed considering homogeneous vehicles, it can be employed in this context as well, since the vehicles can be trivially ordered according to their marginal capacity cost. Constraint (37) calculates minimum number of vehicles must visit medical center i between time periods t_1 and t_2 . This inequality was originally proposed under the assumption of homogeneous vehicles, single type of product and deterministic value of demand. Therefore, the extension of this valid inequality for the proposed model can be posed as:

$$\sum_{k \in VT} \sum_{t'=t_1}^{t_2} z_{ikt'} \geq \left\lceil \frac{\sum_{r \in DT} \left(\sum_{t'=t_1}^{t_2} \min_{\xi \in \Xi} \{Dem_{irt'}(\xi)\} \right) - IC_{ir}}{\min\{\min\{Cap_k\}, \sum_{r \in DT} IC_{ir}\}} \right\rceil \quad \forall i \in C, t_1, t_2 \in P, t_2 \geq t_1 \quad (38)$$

4.2. Latin hypercube sampling method

As previously mentioned, scenario generation methods can significantly affect the efficiency of two-stage stochastic programming. Monte Carlo sampling method is widely used in the studies related to stochastic programming. Requiring larger number of scenarios for accurate estimation is the important disadvantage of this method. Therefore, other methods of sampling like LHS method are proposed to reduce the required number of scenarios. In LHS method, the cumulative distribution function is divided in N separate regions. The number of regions (N) is equal or smaller than number of scenarios. Then, an equal number of samples are selected from each region. In order to clarify sampling method, an example considering 10 separate regions for generating scenarios from a normal distribution are shown in Figure 1. It is assumed that the mean value and standard deviation of the normal distribution are 50 and 10, respectively. This sampling method guarantees that at least one sample to be selected from different regions in the cumulative distribution function (CDF). Therefore, using this method for scenario generation leads to more accurate estimation with a small number of scenarios.

Insert Figure 1 about here

5. Numerical Examples

In this section, numerical examples are used to examine the validity and efficiency of the proposed models and solving method. In addition, the necessity of considering stochastic demands is examined by analyzing the expected value of perfect information (EVPI) and the value of a stochastic solution (VSS). Also, stability indicators are used for comparing the LHS and Monte Carlo methods and determining the optimal number of scenarios. We conducted our numerical analyses based on the data generated by Coelho and Laporte [13] for IRP with deterministic demands and homogeneous vehicles. Some changes have been done in their test bed because we considered heterogeneous vehicles and uncertainty. Therefore, the modified test bed is shown in Table 3.

Table 3: Distributions to generate parameters

Parameter	Corresponding random distribution
#Customers	10, 20, 30, 40, 50
#Products	2
#Vehicles	3
#Time periods	3, 5
h_{ir}	Uniform (0.02, 0.2) $\times 100$
I_{ir0}	Discrete uniform [50, 100]
$\nu_1(\text{small})$	1
$\nu_2(\text{medium})$	2
$\nu_3(\text{large})$	3
ϕ_{ir}	Uniform (20, 30)
IC_{ir}	Discrete uniform [150,200] $\times$ Discrete uniform[2,4]
$Dem_{irt}(\xi)$	Normal (50, 10)
$x_i(\xi)$	Discrete uniform [0, 500]
$y_i(\xi)$	Discrete uniform [0, 500]

The distances between nodes are calculated by $d_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2} + 0.5$ where (x_i, y_i) are the coordinates of node i . Also, the capacity of different types of vehicles are obtained by $Cap_k =$

$$2 \left\lceil \frac{\sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \sum_{\xi \in \Xi} Dem_{irt}(\xi)}{KT|\Xi|} \right\rceil - 400(2 - k).$$

5.1. Validation and efficiency of the proposed method

In this section, the efficiency of the proposed matheuristic method is examined for different instances. The results obtained for different combinations of $\{|C|, |\Xi|\}$ when number of time periods is 3 are shown in Table 4. It is assumed that violation costs are equal to 60. The optimal value of objective function that is obtained by matheuristic (f_1^*) and required time to obtain optimal value (CPU) are also shown in this table. Also, the lower bound (LB) and MIP gap (Gap_E) that were reported by CPLEX at 3600 seconds are provided. The gap between the best objective value of the first model that is obtained by matheuristic method in 3600 seconds (Bestobj) and the lower bound is calculated by $Gap_M = [(Bestobj - LB)/LB] \times 100$. The results show that matheuristic method finds better solution in 3600 seconds in comparison with CPLEX. Also, the results obtained for different values of $|C|$ are shown in Table 5 when number of time periods and scenarios are 5 and 30, respectively. In this table best values of objective function obtained by the matheuristic method in 3600 seconds are reported. The results show the efficiency of the proposed matheuristic method especially for large size instances.

Table 4: Results obtained for different combination of $\{|C|, |\Xi|\}$

$ C $	$ \Xi $	f_1^*	LB	CPU(s)	$Gap_M(\%)$	$Gap_E(\%)$
10	5	30450.86	30450.86*	0.69	0.00	0.00
10	10	32495.56	32495.56*	0.51	0.00	0.00
10	20	34406.10	34406.10*	0.65	0.00	0.00
10	30	35093.06	35093.06*	1.07	0.00	0.00
10	40	34682.97	34682.97*	1.23	0.00	0.00
10	50	34984.28	34984.28*	1.16	0.00	0.00
20	5	60178.74	60138.74*	3.57	0.07	0.00
20	10	64823.80	64783.79*	9.81	0.06	0.00
20	20	67020.32	66980.31*	11.32	0.06	0.00
20	30	67738.49	67698.5*	10.49	0.06	0.00
20	40	67344.73	67304.73*	12.33	0.06	0.00
20	50	67890.23	67863.23*	18.29	0.06	0.00
30	5	90993.17	90462.10	39.37	0.59	0.78
30	10	98477.61	98273.39*	40.47	0.21	0.00
30	20	101313.60	100842.83	75.78	0.47	0.44
30	30	102650.84	102059.22	119.22	0.58	1.04
30	40	102276.69	101683.45	98.57	0.58	1.00
30	50	102767.90	102169.452	140.46	0.58	0.93
40	5	120258.81	119649.34	89.88	0.51	0.72
40	10	131776.70	131145.17	108.65	0.48	0.85
40	20	136280.97	135664.45	119.09	0.45	0.82
40	30	137693.49	137040.14	184.15	0.48	0.82
40	40	137321.03	136673.20	218.14	0.47	0.48
40	50	137968.63	137296.30	539.66	0.49	1.08
50	5	151943.66	150869.33	16255.53	0.71	0.99
50	10	166086.48	165016.97	11561.09	0.65	1.97
50	20	170924.03	169891.49	6902.43	0.61	1.09
50	30	172652.27	171653.51	3299.408	0.58	1.41
50	40	172526.39	171526.03	5495.68	0.58	3.01
50	50	173169.55	172179.58	4278.91	0.57	1.29

* The optimal value of MIP model was found in 3600 seconds. On the other hand LB is equal to optimal value of objective function.

Table 5: results obtained for different values of $|C|$ when number of scenarios is 30

$ C $	$Bestobj$	LB	Gap _M (%)	Gap _E (%)
10	56130.14	56130.14*	0.00	0.00
20	110107.43	109503.99	0.55	0.50
30	166506.65	165052.76	0.88	1.94
40	221950.29	220399.86	0.70	1.99
50	280522.53	276701.830	1.4	6.19

* The optimal value of MIP model was found in 3600 seconds. On the other hand LB is equal to optimal value of objective function.

5.2. Validation and comparison of the proposed models

As mentioned previously, different approaches were used to deal with uncertainty in this paper. This section shows that the first model is equivalent with the second and third models when the method parameters are determined properly. On the other hand, the first model can be used interchangeably with the second and third models, based on distribution of demands. The interchangeability and validity of the proposed models are examined by studying the effects of their own parameters on the transportation, holding and shortage costs. It's shown that by considering proper values of cost violations, N_{irt} and maximum allowable probability, models will behave equivalently. It should be noted that (C_1) , (C_2) and (C_3) are the values of similar terms in the first, second and third models objectives, respectively.

Table 6: Comparison of three models using proper respective parameters

μ_{irt}	S_{irt}	Violation costs		C_1	β_{irt}^1	C_2	N_{irt}	C_3
		$VC1$	$VC2$					
50	10	19	14.5	3869.33	0.035	3865.91	1	3864
50	10	18	12.3	3684.50	0.045	3682.60	2	3682.08
50	10	17.2	9.7	3337.813	0.093	3335.63	3	3337.32
50	10	15	9.05	3034.99	0.128	3036.31	6	3039.76
50	10	15	9	2955.66	0.15	2952.62	7	2953.54
50	10	4.5	2	2358	0.5	2358	25	2358
50	5	6	7.5	2763	0.2	2760	10	2760
50	5	6	7	2742.28	0.6	2745	15	2745
50	5	4.5	2	2358	0.5	2358	25	2358

5.3. Necessity of considering demand as a stochastic parameter

The importance of considering stochastic demands is shown by the indices for VSS and EVPI in the proposed model. The EVPI index shows how much the decision-maker is willing to pay to obtain perfect information about the future. The great value of EVPI index shows the importance of information. The VSS index calculates the amount of cost saving when the decision-maker uses expected values of uncertain parameters instead of uncertain parameters in the model (see [39] and [40] for more information about these indices). In this section, the effects of violation cost and number of medical centers on EVPI and VSS indices are examined. This indices are calculated by using equation (39) and (40), respectively.

$$EVPI = Z_{HN} - Z_{WS} \quad (39)$$

$$VSS = Z_{EEV} - Z_{HN} \quad (40)$$

where Z_{HN} is the optimal value of two-stage objective function and Z_{WS} and Z_{EEV} are calculated as follows:

$$\begin{aligned}
Z_{WS} = & E_{\xi \in \Xi} [\min \sum_{i \in CS} \sum_{j \in CS} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} S h_{irt} \\
& + Q(x_{ijkt}, q_{irkt}, \xi)] \\
\text{s.t.: } & (2) - (12), (14) - (16)
\end{aligned} \tag{41}$$

$$\begin{aligned}
Z_{EEV} = & E_{\xi \in \Xi} [\min \sum_{i \in CS} \sum_{j \in CS} \sum_{k \in VT} \sum_{t \in P} \nu_k \bar{x}_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} \bar{I}_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} \bar{S} h_{irt} \\
& + Q(\bar{x}_{ijkt}, \bar{q}_{irkt}, \xi)] \\
\text{s.t.: } & (2) - (12), (14) - (16)
\end{aligned} \tag{42}$$

$$\begin{aligned}
[\bar{x}_{ijkt}, \bar{q}_{irkt}, \bar{I}_{irt}, \bar{S} h_{irt}] = & \arg \min [\sum_{i \in CS} \sum_{j \in CS} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijkt} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} S h_{irt} \\
& + Q(x_{ijkt}, q_{irkt}, \xi)] \\
\text{s.t.: } & (2) - (12), (14) - (16)
\end{aligned} \tag{43}$$

The gaps of indices for different value of violation cost are shown in Figures 3 and 2, respectively. These gaps for VSS and EVPI indices are calculated by $(Z_{EEV} - Z_{HN})/Z_{HN}$ and $(Z_{HN} - Z_{WS})/Z_{WS}$, respectively. The number of medical centers and scenarios are considered equal to 30 and 50, respectively. The results illustrate that the VSS decreases when the violation costs increases, which is expected since the higher those costs, the less the model exploits the flexibility offered by the possibility of violations. Meanwhile, EVPI index increases by increasing the violation cost values and consequently, the decision-maker is willing to pay more to obtain perfect information.

Insert Figures 3 and 2 about here

As mentioned before, different scenario generation methods are proposed in the context of stochastic programming. Selecting suitable methods and optimal numbers of scenarios are important issues in stochastic programming. We used stability indices to determine the optimal number of scenarios and to compare the Monte Carlo and LHS methods. The stability indices were proposed by [41] to examine the effects of scenario generation methods on the quality of solutions. The in-sample stability index guarantees that the optimal objective functions for different sets of scenarios are approximately equal.

Out-of-sample stability shows that the optimal objective functions that are obtained based on different sets of scenarios are approximately equal to optimal objective function that are is obtained based on a large set of scenarios. The standard deviations between the in-sample objective functions for 20 different sets of scenarios for demand when scenarios are generated by the LHS and Monte Carlo methods are shown in Figure 4. Also, the standard deviation between out-of-sample objective functions are shown for different scenario generation methods in Figure 5. The total of medical centers are equal to 20 in this case.

Insert Figures 4 and 5 about here

Figure 4 shows that variation among the optimal values of objective functions for different sets of scenarios in the LHS method is smaller than that for the Monte Carlo method. Also, variation among the optimal values of objective functions decreases when the number of scenarios increases. Figure 5 shows that the results that are obtained based on the LHS method are closer to solutions obtained based on large samples. Figures 4 and 5 show that the LHS method obtains more accurate approximations than the Monte Carlo method in the same number of scenarios.

5.4. Comparison of the first proposed model and classic two-stage models

Using the first proposed model decreases the number of constraints and decision variables related to scenarios compared with classical two-stage models. If inventories and shortages are used as second-stage decision variables, they depend on uncertain parameters. Therefore, the number of decision variables and constraints that depend on uncertain parameters increases. On the other hand, using auxiliary variables as second-stage variables decreases the number of constraints and decision variables. The Differences between the number of constraints and decision variables in classical two-stage models and the proposed models for different numbers of scenarios and medical centers are shown in figures 6 and 7, respectively. These figures show that the differences between the number of stochastic constraints and decision variables in the models are increased for large size problem with large number of scenarios.

Insert Figures 6 and 7 about here

6. Conclusions

In this paper, we deal with people's health and, therefore, managerial implications in this kind of study are very important. Delayed and/or cancelled care are the results of drug shortages. In some kinds of diseases like hemophilia, MS and Diabetes Mellitus, delays in care has significantly negative effects on the patients' health. Based on the studies, it can be concluded that 60% of the time drug shortages create unsafe conditions for patients. Because of uncertainty in demands, violations in amount of inventories and shortages are inevitable. Therefore, the proposed model can be used for strategic and scare drugs to reduce the amount of shortages by considering great value of violation cost for this types of drugs.

In this paper, a two-stage stochastic programming model with new second-stage decision variables is proposed for the medical drug inventory routing problem. In this model, alternative auxiliary variables as second-stage variables reduces the number of variables and constraints. Therefore, the computational time decreases. Also, considering these second-stage variables can help decision makers to consider robustness in the model. Moreover, a two-phase matheuristic method was proposed. Numerical examples illustrated the efficiency of this algorithm, especially for large size problems.

Also, two models that considered probabilistic constraints were proposed to deal with uncertain parameters. The first model was shown to be interchangeable with the second and third models. The validation of the first model was examined by comparing it with the second and third models. The effects of the parameters in each method on objective functions were studied. The necessity of considering uncertainty was confirmed by considering the EVPI and VSS indices. The effects of violation costs on these indices are calculated. The results show that EVPI index increases by increasing in the violation costs values. While, VSS index decreases by increasing in the violation costs values.

In this paper, two sampling schemes were considered by stability indices and it was shown that the LHS method can obtain more accurate approximations than the Monte Carlo method. Also, the optimal number of scenarios was determined based on examining in-sample and out-of-sample indices under different numbers of scenarios. One direction for future studies could be using robust stochastic methods in medical drug distribution. Another possible approach is consideration of stochastic demands with dynamic distribution functions. Also, considering scenario reduction method to determine the optimal number of scenarios is proposed as future research.

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Appendix A Proposed a new two-stage stochastic model with considering proportion of unusable rugs

As mentioned before, Some medical drugs require special holding conditions such as in the refrigerator, or even the freezer. In this paper, a new model is proposed in this section that considers the proportion of expired or less effective medical drugs in medical centers as a uncertain parameter. It is considered that the required equipment for holding the medical drugs can have a breakdown in the planing horizon. Therefore, a numbers of drugs can be expired because of unsuitable holding conditions, to which we refer to as unusable drugs. Since the information about the breakdown of holding equipment is not available in advance, proportion of unusable drugs is considered as uncertain parameter. A new two-stage programming model is proposed by considering proportion of unusable drugs and demand as uncertain parameters. Also numbers of maintenance strategies are considered in this study that the decision makers can reduce amount of proportion of unusable drugs by using them. The notation, parameters and decision variables that are used in the proposed models are shown below.

Sets and indices:

S : Set of maintenance strategies

Parameters:

$pu_{irt}(\xi)$	proportion of unusable drugs in medical center i per unit for drug type r in time period t under scenario ξ
l_{is}	Amount of reduction in the proportion of unusable drugs when strategy s is used in medical center i
cr_{is}	Cost of using strategy s in medical center i
cu_r	Cost for each unit of unusable drugs type r

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Decision variables:

$In_{irt}(\xi)$	Inventory level of drug type r in medical center i in period t under scenario ξ
$Ex_{irts}(\xi)$	Amount of unusable drug type r in medical center i in period t under scenario ξ
ms_{ist}	1 if medical center i using strategy s in period time t . 0 otherwise.

505 The proposed two-stage stochastic model by considering uncertain demand and proportion of unusable drugs are as follows:

$$\begin{aligned}
\min f_4 = & \sum_{i \in C} \sum_{j \in CS} \sum_{k \in VT} \sum_{t \in P} \nu_k x_{ijk} d_{ij} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} h_{ir} I_{irt} + \sum_{i \in C} \sum_{r \in DT} \sum_{t \in P} \phi_{ir} Sh_{irt} \\
& + \sum_{s \in S} \sum_{i \in C} \sum_{t \in P} cr_{is} \times ms_{ist} + \sum_{\xi \in \Xi} p(\xi) \left[\sum_i \sum_r \sum_t VC1 \times V1_{irt}(\xi) + VC2 \times V2_{irt}(\xi) \right] \\
& + \sum_{\xi \in \Xi} \sum_{r \in DT} \sum_{s \in S} \sum_{i \in C} \sum_{t \in P} p(\xi) \times cu_r \times Ex_{irts}(\xi)
\end{aligned} \tag{44}$$

s.t.: (2)-(12)

$$In_{irt}(\xi) \geq I_{irt} - V1_{irt}(\xi) + V2_{irt}(\xi) \quad \forall i \in C, r \in DT, t \in P, \xi \in \Xi \tag{45}$$

$$Ex_{irts}(\xi) \geq In_{irt-1}(\xi) \times pu_{irt} - ms_{ist} \times M \quad \forall i \in C, r \in DT, t \in P, t \geq 2, s \in S, \xi \in \Xi \tag{46}$$

$$Ex_{irts}(\xi) \geq In_{irt-1}(\xi) \times pu_{irt} \times l_{is} - (1 - ms_{ist}) \times M \quad \forall i \in C, r \in DT, t \in P, t \geq 2, s \in S, \xi \in \Xi \tag{47}$$

$$\begin{aligned}
I_{irt} - Sh_{irt} = & I_{ir(t-1)} - Ex_{irts}(\xi) - Dem_{irt}(\xi_1) + q_{irkt} - Sh_{ir(t-1)} + V1_{irt}(\xi_1) - V2_{irt}(\xi) \\
& \forall i \in C, r \in DT, t \in P, \xi \in \Xi
\end{aligned} \tag{48}$$

$$\sum_{s \in S} ms_{ist} \leq 1 \forall i \in C, t \in P \tag{49}$$

$$Ex_{irts}(\xi) \geq 0, In_{irt}(\xi) \geq 0, ms_{ist} \in \{0, 1\} \tag{50}$$

510 Objective function (44) consists of four deterministic terms that calculate total cost, including inventory holding, transportation, shortages and maintenance costs. Also, this objective function contains the expected value of the second-stage objective function. The second stage decision variables in this models are violations in the amount of inventory and shortage and the amount of unusable drugs. Constraints (45) calculate the amount of inventory for drug type r in medical center i at time period t under scenario ξ . Constraints (47) and (48) calculate the amount of unusable drugs of type r in medical center i at time period t under scenario

515 ξ when sth strategy is determined for maintenance. Constraints 49 ensures that each medical centers can use one maintenance strategy at most. Constraints 50 determine the domain of decision variables.

The effects of considering proportion of unusable drugs are shown in Figure 8. It is concluded that when the cost for per unit of unusable drugs is small, the total amount of received drugs that is obtained from this model are almost equal to the total amount of received drugs that is obtained from the first model.
 520 However, by increasing the cost for per unit of unusable drugs the differences between the obtained values of the total amount of received drugs from this model and the first model increase. Therefore, it is clear that this model can be used when the medical drugs are expensive.

Insert Figures 8 about here

Figure 1: Regions for selecting scenario in LHS method

Figure 2: VSS index for different value of violation costs

Figure 3: EVPI index for different value of violation costs

Figure 4: Standard deviation between optimal objective function for different scenario generation method under different number of scenarios

Figure 5: Standard deviation between out-of-sample objective functions for different scenario generation method under different number of scenarios

Figure 6: Number of stochastic constraints under different numbers of scenarios

Figure 7: Number of stochastic decision variables under different numbers of scenarios

Figure 8: The effects of considering proportion of unusable drugs