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A two-stage fuzzy optimization model for scarce drugs supply and ration planning under uncertainty: A case study

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HIGHLIGHTS

- A two-stage fuzzy optimization model for the scarce drug rationing problem is proposed.
- The model uses a rolling horizon mechanism and an iterative procedure for supplying and rationing the scarce drugs.
- Two need-based indicators including DALYs and population are utilized to enhance the model performance.
- A robust possibilistic programming method is used to deal with imprecise parameters.

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ABSTRACT

The scarce drugs rationing is a serious challenge in the public health system. This study proposes a two-stage linear programming model for the scarce drug rationing problem which reflects the conflicts of interest between supply chain members. The proposed model uses a rolling horizon planning mechanism along with an iterative procedure for supplying and rationing the scarce drugs. The maximization of minimum suppliers' profit and the minimization of maximum shortage are considered as the first and second stage models' objective functions, respectively. Furthermore, two need-based indicators including disability-adjusted life years (DALYs) and population are utilized to enhance the performance of the proposed model. Besides, human capital method is applied for calculating the shortage costs of demand zones. Due to the inherent epistemic uncertainty in some critical input parameters such as the exchange rate and demand, a credibility-based robust possibilistic programming approach is used to deal with imprecise parameters. Finally, the applicability and usefulness of the proposed approach are investigated by a real case study from Iranian food and drug administration. The computational results demonstrate the superiority of robust programming model against deterministic one.

1. Introduction

Medications as an intermediate input along with the other inputs are used to diagnose, treat and prevent the diseases and eventually to achieve better health [1]. Since the major sector of healthcare expenditures belong to the pharmaceutical sector, the use of pharmaceutical products should be handled efficiently so that the value gained from total healthcare costs could be maximized. In spite of all extensive attempts of the Food and Drug Administration (FDA), medicine shortages still occur because of the challenges in the pharmaceutical industry [2,3]. Drug shortage is defined as the situation in which the total supply of all substitutable versions of a given drug are not able to satisfy the current or projected demand at the patient level [4]. Shortages lead to delay and even in some cases deny needed care for patients. In the US, although there has been a declining trend in the number of drug shortages, for example, from 305 in 2012 reduced to 170 in 2017, they are still considered as a serious crisis [5].

According to survey of FDA in 2012 [2], shortages can be triggered by some potential factors such as production disruptions (80%) (which is included the failures in product or facility quality (66%) and discontinuance in manufacturing (14%)), raw material (API) shortage (8%) and increased demand (6%). Shortages significantly threaten the public health and pose adverse impacts on both patients and health system in terms of clinical (i.e., delay or even deny needed care of patients, the risks of using the second-line alternatives, etc.) and economic aspects (i.e., increase in purchasing costs about 11%, costs for shortages management approximately 216$ million annually, etc.) [6,7]. In order to cope with this challenge, i.e., the imbalance between supply and demand, policymakers ration or prioritize the allocation of scarce drugs [8]. Various definitions are given for the term "rationing" in

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the relevant literature. Policies used for the controlled allocation of scarce goods and/or services [9] or limited access to beneficial health care services [10] are some instances of such definitions. For more information about the rationing, interested readers may refer to Keliddar et al. [11]. In general, rationing is a technique to response the physical shortages of valuable scarce products [8]. The main objective of rationing is to allocate the scarce products to demand zones in order to enhance the equity among them [8, 12]. In this regard, widespread researches have accomplished about ethical frameworks and principles of scarce drugs allocation [13–15]. Furthermore, some researchers highlight the use of the need-based indicators to allocate limited resources which can be an excellent representative for estimating real public needs in different geographic regions [16]. For example, McIntrye [17] identified four key indicators to estimate the relative need of different geographic regions including population size, demographic composition, health and socio-economic status.

According to above-mentioned descriptions, it can be concluded that the optimal and need-based allocation is a substantial point which should be paid attention to rationing problem of scarce drugs. To deal with this issue, a variety of operations research methods can be applied to achieve the optimal strategy. In this context, Angelis et al. [18] suggested applying the Multi-Criteria Decision Analysis (MCDA) techniques as a methodological approach to prioritize the scarce resources in healthcare. Moreover, some works used multi-objective linear programming and goal programming approach for limited health resources allocation and scarce drugs (e.g., [19–21]). Koyuncu et al. [22] presented a model for resource allocation associated with pandemic influenza (i.e., vaccination and antivirals) during restricted supply which aimed to minimize the number of deaths, number of cases and total morbidity days. Schniederjans et al. [23] developed an integer linear programming (ILP) model for rationing antiviral drugs associated with Influenza-A. The model aims to mitigate inequity among different regions based on population characteristics. In another paper, Anparasan [24] proposed an ILP model for resource-limited allocation epidemics in a natural disaster which determines the number, sizes, and locations of treatment facilities and the transportation of patients to treatment centers. Sung [25] presented an ambulance scheduling problem to prioritize patients for receiving emergency medical resources in a mass casualty incident. Swaminathan [26] proposed a bi-objective mixed integer linear programming model and along with a heuristic algorithm for scarce multi-period drugs rationing problem.

Another challenging issue in scarce drug rationing is the shortage continuing in the future periods. According to a survey by Jarosławski et al. [27], the shortage duration of orphan drugs is estimated at 15 months in the US. Among several works which have been performed in this field, Swaminathan [26], Gaivoronski et al. [28] and Sung [25] were the ones which incorporated this assumption in their proposed models while this substantial assumption is incorporated in this study (see Table 1). In addition, during a supply-limited period, the complete fulfillment of the demand is an illogical assumption, and unfulfilled demand would be considered either completely lost or backlogged. However, the relevant literature suffers from a lack of such an important assumption. To this aim, Karuppasamy [29] developed a pharmaceutical inventory model with backlogged demand. Also, several research works addressed the backlogged demand in a supply-constraint situation (see Pervin et al. [30], Wang et al. [31]). Therefore, one of the other contributions of this paper is considering the demand as backlogged.

On the other hand, the perturbation of demand in the pharmaceutical sector is a frequent phenomenon and consequently addressing demand uncertainty in the rationing planning models seems to be necessary [32]. However, in most of the aforementioned approaches, all the input parameters are assumed to be deterministic. Hence, Feng et al. [33] presented a multi-objective stochastic mathematical model for limited medical resource allocation in which the patient arrival and service times of each medical were premised as uncertain parameters. Gaivoronski et al. [28] proposed a multi-stage stochastic optimization model for the scarce resources allocation problem in which the demand and supply are considered as the uncertain parameters. In most of the real-life problems due to unavailability or lack of sufficient reliable historical data, the use of stochastic programming is tough and even impossible. Here, to cope with the imprecision of parameters fuzzy mathematical programming is applied. Fuzzy mathematical programming is a flexible tool to deal with epistemic uncertainty of the parameters which can be classified into two distinct categories: (1) flexible programming and (2) possibilistic programming. The first one results from uncertainty in the target values of goals and constraints and the second one arises from uncertainty in input data of problem because of unavailability of historical data and lack of knowledge about the exact value of the parameters. Notably, several recent studies (see [34–36]) in the field of healthcare management have addressed the epistemic uncertainty of input parameters such as demand. There are a wide variety of methods for dealing with the objective functions and constraints involving imprecise parameters such as Jimenez et al. [37] , Dubois et al. [38] and Inuiguchi et al. [39]. Among them, chance constrained programming is an adjustable approach whereby by the aid of the possibility, necessity and credibility measures besides the expected value of the fuzzy number, the decision maker can control the confidence level of satisfaction of possibilistic chance constraints [40–42].

It should be noted that some medicines or their ingredients could be supplied from the global marketplace due to the lack of sufficient production capacity or production equipment [34]. For example, in the US, 80% of the raw materials used in pharmaceuticals are supplied from outside of the United States [43]. The global purchasing environment exposes considerable risks for suppliers and buyers that one of these significant risks is the currency exchange rate fluctuations [44]. Thus, a little perturbation on the exchange rate influences the decisions associated with purchasing and production quantities. Hence the exchange rate's fluctuations affect the quantity of purchased from foreign suppliers. Some papers considered the exchange rate as an input parameter while ignored the impact of its fluctuations on their models (e.g., [45]) and most of the relevant literature applied stochastic programming approaches to cope with this problem (see [46–48]). As mentioned previously, the use of stochastic programming encounters significant drawbacks in the real-life situation according to unavailability of reliable historical data. Furthermore, some sources of uncertainty such as unstable economic and political situations consistently vary the exchange rate value. Thus, due to the dynamic fluctuating nature of this parameter, even with historical data, the exchange rate value does not necessarily follow its historical pattern. Therefore, in this paper, a suitable possibility distribution is used to confront this challenge, which is obtained from experts' opinions and available insufficient data. According to the classification of Table 1, this paper is the only paper that employs the credibility-based fuzzy chance-constrained programming method for the first time to handle the epistemic uncertainty of parameters in the domain of scarce drug supply and rationing problem.

It should be pointed out that the significant conflicts of interest between members of the pharmaceutical supply chain (i.e., suppliers and policymakers) are accounted as the main issue in the rationing process [49]. As Table 1 shows all the related papers in this context have investigated rationing problem from the viewpoint of the government (i.e., single perspective view) and they have ignored the importance of suppliers' decisions as the influential and effective participants on the scarce resources rationing process. Thus, this paper studies the rationing problem from both the government and suppliers point of view and strives to consider the benefits of both decision makers. For this purpose, a two-stage model which can consider the interests of suppliers at the first stage and the government's interests at the second stage is employed. The proposed two-stage linear programming model uses a rolling planning horizon approach along with an iterative algorithm which can appropriately update the allocation decisions according to actual and nominal data. Besides that, the proposed model is under assumptions of multi-period planning horizon and backlogged demand.

Last but not least, in order to boost the effectiveness of the proposed model and estimating actual needs of demand zones, despite other related papers in Table 1, we applied the combination of two need-based criteria, including population and DALY. In addition, for the first time, the shortage cost of demand zones is calculated based on human capital approach which converts the years of life lost into its equivalent cost.

The rest of the paper is organized as follows. Section 2 is assigned to the problem statement. In Section 3, the mathematical formulation of the proposed model and the linearization method are provided. Section 4 is dedicated to the credibility-based robust possibilistic programming model. The depiction of the case study and numerical results derived from the proposed model are discussed in Section 5. In the end, Section 6 presents the concluding remarks and suggestions for future studies.

2. Problem statement

Food and Drug Administration of the Islamic Republic of Iran (IFDA) (http://www.fda.gov.ir) is considered as a case study of this research. IFDA is established with the aim of determining and adjusting the criteria and regulations associated with the import, export, procurement, production, storage, transportation and distribution of pharmaceutical products and equipment. It should be noted that, with respect to the vital role of the drug on social health, it is responsible for adopting and implementing necessary policies in order to enhance the public accessibility to appropriate high-quality medicines.

The majority of the drug shortages' sources in Iran can be classified into two groups: (1) systemic, and (2) environmental factors [2]. The shortage resulting from the system is due to the IFDA's lack of knowledge about problems in the supply and procurement of medicines via suppliers such as manufacturer and importers companies. Suspension in production process caused by increasing manufacturing cost, increasing purchasing cost from international suppliers, increasing exchange rate, uselessness and low quality of available medicines, are some of the main reasons for disruption in the supply stream. One of the most important environmental reasons which can result in drug shortage is the changing consumption pattern; for example, increasing the demand rate of some drugs related to the prevalence of a specific disease.

To avoid the long-term and severe shortages, IFDA forces the medical science universities of each province to report about scarce drugs, frequently. After that, if the information obtained from medical science universities is confirmed by IFDA, information about the total drug shortages of the overall provinces are transferred to suppliers including manufacturer and importer companies. Then the suppliers start to satisfy the required demands. Accordingly, the manufacturers can produce the required drugs based on the production capacity limitation, and also importer centers are allowed to import the drugs based on the amount of available budget and their import quota. It should be noted that for the medicines which can be produced by domestic manufacturers, the pharmaceutical importer companies are only allowed to import a specific amount of drugs which is determined in their quota by IFDA. In the next step, the pharmaceutical products are rationed and allocated by IFDA concerning suppliers' optimal decisions. In other words, the flow quantity from customs and manufacturing centers to cross-docking centers (for aggregating medicines) and therefrom to regional distribution centers are determined by IFDA.

Currently, the rationing process of scarce drugs for each province is done based on the obtained formula at 1986, and a predetermined percent has been dedicated to each province according to the amount of population and number of prescriptions of that province [50]. As a result, due to the lack of utilization of a need-based allocation model, the current rationing model is devoid of efficiency and violates "goodness "and "fairness" which are the main goals of the national health system [51]. Based on the World Health Organization (WHO) report [52], regarding the importance of rationing as a prerequisite for the universal health coverage, it can be concluded that the management and rationing of scarce drugs are crucial and a systematic method should be applied for this problem. To the best our knowledge, this paper is the first one in the literature that considers the rationing problem at the national level and proposes mathematical modeling considering need-based criteria including demographic and burden of disease for the optimal allocation. Fig. 1 displays the schematic procedure of supply and rationing processes of scarce drugs under consideration.

For this purpose, a two-stage, multi-product and multi-period model using a rolling planning horizon approach is proposed. The proposed two-stage approach is illustrated in Fig. 2. As it can be seen from Fig. 2, there are two stages in each iteration, so that at the outset of each period, based on the demand foreseen (nominal demand), the supply and allocation decisions from the current period to final period is planned. Hence, in the first stage, the decisions associated with the number of drugs provided by manufacturer and importer companies are determined based on the total required nominal demands of provinces where suffer from drug shortages. In the second stage, the decisions related to rationing and optimal allocation of drugs are adopted based on the required demand of each province. In other words, the output variables in the first stage are addressed as the input parameters for the second stage. It should be noted that the first stage decisions are determined according to the suppliers' viewpoint aiming to maximize their profits and the second stage decisions are determined based on the IFDA's viewpoint to minimize the shortage.

After obtaining the optimal values of the decision variables of the first stage, two states are possible to occur. In the first case, the total quantities provided is lower than the nominal demands of the provinces, in which case provinces should be quoted on the basis on their cost of deficiency. In the second case, the total supply is higher than the nominal demand of the provinces. In this case, first, the total demand of the provinces is met, then the surplus is divided by the ratio of the population among the provinces. It should also be noted that in this work, the human capital approach is used to calculate the shortage cost in each province. This method is explained in detail in the next section.

At the end of each iteration, according to the new information obtained about the actual demand value of the last period, updating the optimal value of the inventory level in provinces and also planning for future periods become essential. In this way, we have employed the rolling planning horizon approach. Also, after obtaining the revised optimal value of inventory level in the second stage, the model saves the revised inventory level information of all provinces so that shortage may be resolved

Table 1
Classification of reviewed papers in the domain of scarce resources allocation.

Author	Perspective status	Objective function	Decision variables	Criterion	Uncertainty	Time period
Chae et al. (1989)	Single	Improving health status, maximizing equity , equalizing health expenditure	Budget allocation	Population, mortality and morbidity rate	–	Single-period
Esmeria (2001)	Single	Satisfying the cure rate at least 85% of patients	Allocation of anti-TB drugs to health centers	Health status	–	Single-period
Khodaparasti et al. (2016)	Single	Maximizing equity, local accessibility, and efficiency	Medical Facility location	–	–	Single-period
Koyuncu (2010)	Single	Minimizing the number of deaths, number of cases and total morbidity days	Allocation of budget for vaccinations, ICU beds and non-ICU beds	Population, mortality and morbidity rate	–	Single-period
Schniederjans et al. (2017)	Single	Minimizing inequity	Allocation of antiviral drugs to regional medical departments	Population	–	Single-period
Anparasan (2017)	Single	Maximizing the number of patients transported to medical facilities	Number, size, and location of medical facilities, allocation of patients to facilities	Mortality rate	–	Single-period
Swaminathan (2003)	Single	Minimizing leftover budget, minimizing shortage	Allocation of drugs to clinics	Scio-economic	–	Multi-period
Sung (2016)	Single	Maximizing the number of expected survivals from a mass casualty incident	Allocation of patients to the hospitals	–	–	Multi-period
Gaivoronski et al. (2012)	Single	Minimizing cost and risk	Allocating scarce water resources	–	Stochastic programming	Multi-period
Feng et al. (2017)	Single	Minimizing average patients waiting time, minimizing average medical wasted cost	Number of medical resources and staff	–	Stochastic programming	Single-period
This paper	Bi	Minimizing shortage cost	Quota of each demand zone	Population and DALY	Possibilistic programming	Multi-period
		Maximizing suppliers' profit	Production and purchasing quantities			

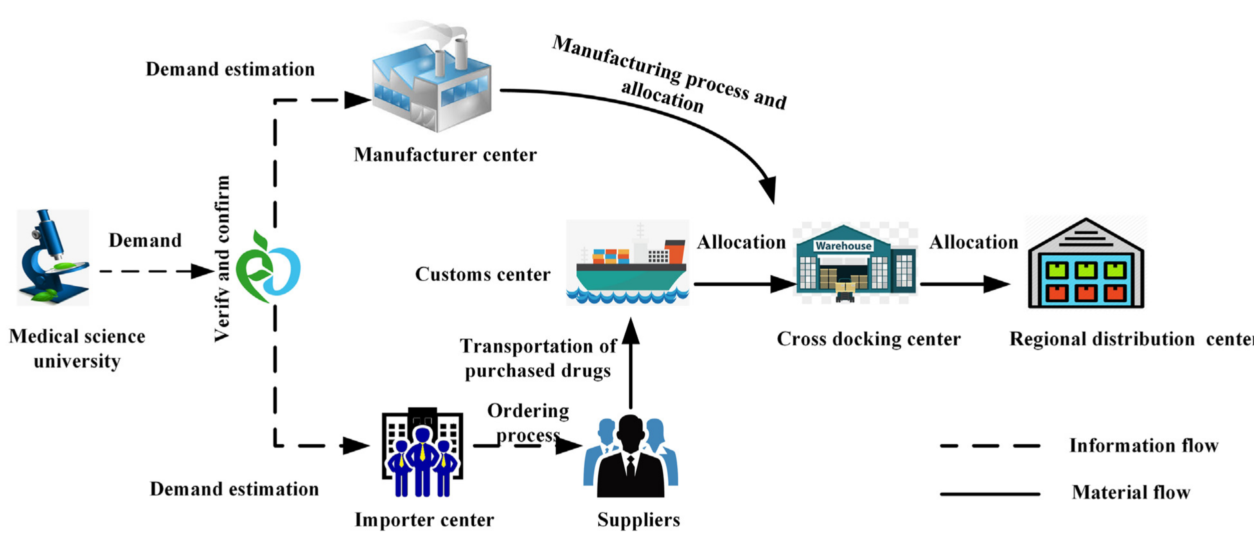

Fig. 1. The depiction of the studied problem.

in some provinces. It means that the inventory level of a given province in the current period is sufficient for the fulfillment of the next period nominal demand. In the words, subtraction of next period nominal demand and inventory level of the current period is greater than its safety stock. In this situation, supply and allocation planning will not be accounted for them for the next

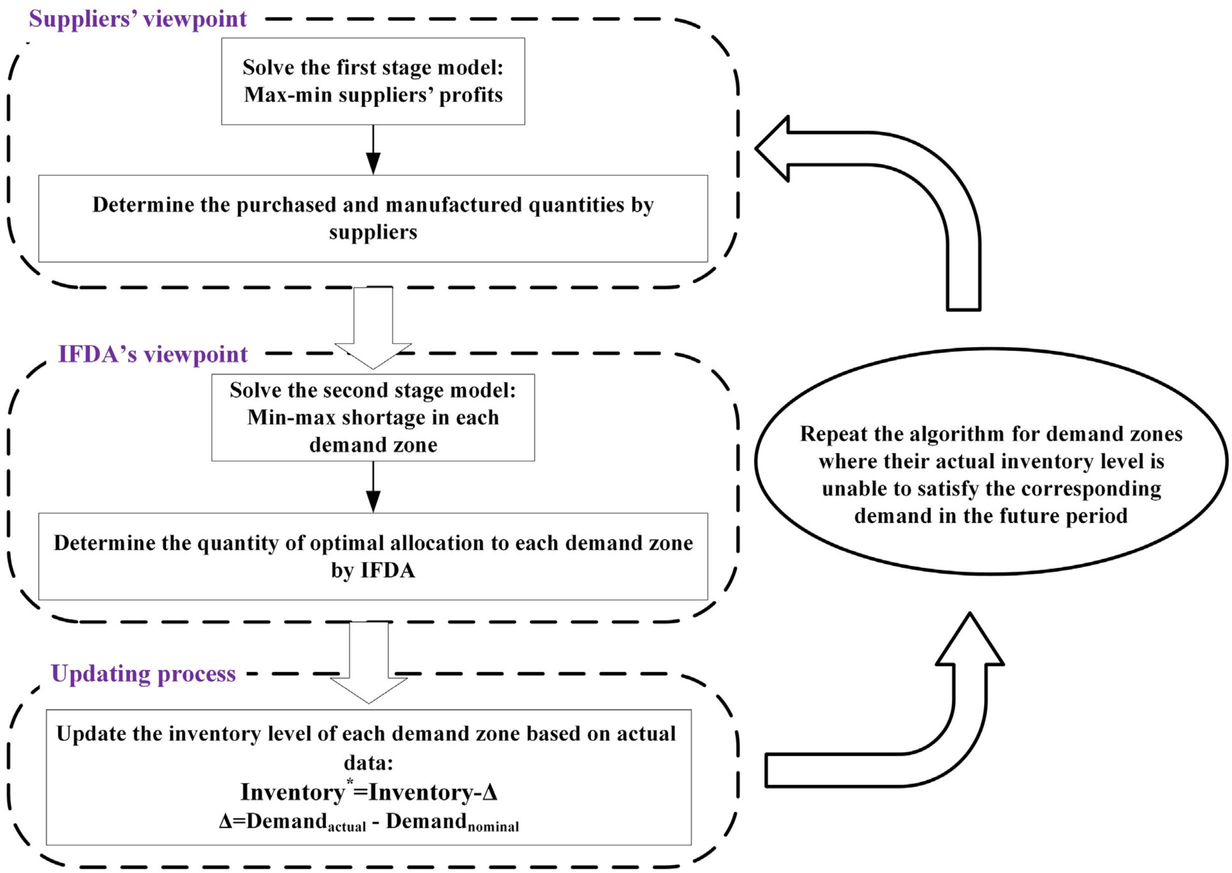

Fig. 2. The proposed iterative algorithm of concerned problem.

period; otherwise, this process is repeated until the shortage is resolved in all provinces.

The main problem to be considered in this research is determining the number of production and the items purchased by suppliers as well as the number of assigned drugs to each province by IFDA to minimize shortage between them. As mentioned before, the proposed model addresses the global logistics factors such as exchange rates of supplier currency and the customs duties because there are some international suppliers in the studied problem. It is noteworthy that the amount supplied from manufacturer and importer companies may not meet the demand of the provinces, in this case, part of the unmet demands are considered as backlogs. The other relevant assumptions could be explained as follows:

- The locations of the facilities are fixed and predetermined, and only tactical decisions are taken into account for the concerned problem.
- Among the model's parameters, the demand and exchange rate are tainted by epistemic uncertainty, and both of them are expressed as fuzzy numbers.
- The demographic and burden of disease indicators are addressed as need-based criteria to allocate scarce drugs effectively.
- Due to support of the domestic industry, manufacturers receive higher priority to the supply of required demands.

3. Model formulation

Sets, indices, parameters and decision variables used to formulate the proposed two-stage linear programming model, are given below.

Nomenclature

Sets

I	Set of manufacturers, indexed by i
J	Set of importers, indexed by j
K	Set of foreign suppliers, indexed by k
L	Set of cross-docking centers, indexed by l
A_m	Set of province distribution centers, indexed v
M	Set of the province in which province distribution centers are located, indexed by m
P	Set of scarce drugs, indexed by p
R	Set of customs centers, indexed by r
T	Set of time periods, indexed by t

Parameters

a_{pit}	Unit production cost of drug p by manufacturer i in period t
$\tilde{d}_{pmt}$	Demand of province m for drug p in period t
c_{pjkt}	Unit Procurement cost of drug p in the currency of supplier k by importer j at period t
tc_{pkrt}	Unit transportation cost of drug p between supplier k and custom center r in period t
v_{pit}	Unit selling price of drug p by manufacturer i in period t
v'_{pjt}	Unit selling price of drug p by importer j in period t
ω_{pi}^{max}	Maximum quantity of drug p produced by manufacturer i which can be economic
ω_{pi}^{min}	Minimum quantity of drug p produced by manufacturer i which can be economic
β_{pj}	Maximum budget of importer j for supplying of drug p
ρ_{pt}	Customs duty rate of drug p in period t

$\widetilde{ex}_{kt}$ Exchange rate from the currency of supplier k to the standard currency
φ_{pj} Upper limit of quota for supplying drug p by importer j
δ_{pj} Lower limit of quantity purchased of drug p by importer j
μ_{pm} Unit cost of unmet demand of drug p at province m
$\bar{y}_{pjkrt}$ Upper limit on the quantity of drug p purchased by importer j from supplier k and shipped to the customs center r in period t
$\bar{q}_{pit}$ Upper limit on the quantity of drug p produced by manufacture i in period t
h_{pm} Unit cost of extra drug p in province m
ϑ Priority weight coefficient

Decision variables

q_{pit} Quantity of drug p produced by manufacturer i in period t
y_{pjkrt} Quantity of drug p purchased from supplier k by importer j and shipped to customs r in period t
x_{pilt} Quantity of drug p transferred from manufacturer i to cross-docking center l in period t
z_{prlt} Quantity of drug p transported from customs center r to cross-docking center l in period t
u_{plvt} Quantity of drug p transported from cross-docking center l to province distribution center m in period t
I_{pmt} Inventory level of drug p at province distribution center m in period t

Using the above notation, the concerned problem can be formulated as follows.

3.1. First stage model

The decisions related to suppliers are determined in this stage. Quantities imported and manufactured by suppliers are output variables of this stage.

3.1.1. Objective function: maximizing the minimum profit of suppliers.

$$\begin{aligned} maxf_1 = \vartheta * min_{p,i,t}\left((v_{pit} - a_{pit})q_{pit}\right) + (1-\vartheta) \\ *min_{p,j,t}\Bigg(\sum_{k,r} v'_{pjt} y_{pjkrt} \\ - \sum_k \widetilde{ex}_{kt} \sum_r (c_{pjkt} + tc_{pkrt}) y_{pjkrt} \\ - \rho_{pt} \sum_{k,r} \widetilde{ex}_{kt} (c_{pjkt} + tc_{pkrt}) y_{pjkrt}\Bigg) \end{aligned} \quad (1)$$

The first stage objective function maximizes the minimum manufacturers and importer profits for all drugs in all periods which implies a lower bound for supplier's profits to ensure equity between them. Since manufacturers have higher priority than importers for the supply of required demands, we incorporate coefficient $\vartheta > (1-\vartheta)$ in the above objective function. The first term displays the manufacturers' profit (the difference between sale price and production cost) and the second term expresses the importer revenues. The third and fourth terms illustrate the transportation and procurement costs of international suppliers and customs duties costs. It should be noted that the customs duty rate is reduced in drug shortages duration by the government.

3.1.2. Constraints

$$\omega_{pi}^{min} \le q_{pit} \le \omega_{pi}^{max} \quad \forall p.i.t \quad (2)$$

$$\sum_{k,r} \widetilde{ex}_{kt}\, c_{pjkt}\, y_{pjkrt} \le \beta_{pj} \quad \forall p.j.t \quad (3)$$

$$\delta_{pj} \le \sum_{r,k} y_{pjkrt} \le \varphi_{pj} \quad \forall p.j.t \quad (4)$$

$$\sum_i q_{pit} + \sum_{j,k,r} y_{pjkrt} \le \sum_{m,t=t'}^{T} \tilde{d}_{pmt} - \left(I^*_{pm,t-1} + ss_m\right) \quad \forall p.t \quad (5)$$

$$y_{pjkrt}.q_{pit} \ge 0 \quad \forall p.i.j.k.r.t \quad (6)$$

Constraint (2) ensures that the quantity of produced items in each manufacturer center at each period should be limited between the lower and upper bounds of production capacity. Constraint (3) expresses that the purchase quantity from foreign suppliers by each importer center in each period should be equal to or less than the maximum budget dedicated to that drug. Constraint (4) ensures that the total purchase quantity from all international suppliers should be less than the importer quota and greater than the determined lower bound. Constraint (5) guarantees that the total products obtained by providers should be less than the entire province's need; i.e., the difference between the aggregate nominal demand of all provinces from the current period until final period and the total safety stock and the previous period inventory of provinces. Finally, Constraint (6) displays the non-negativity of decision variables.

3.2. Second stage model

The second stage begins based on the result obtained from the first stage. The decisions related to drug rationing is adopted in this stage by IFDA. Accordingly, *the second stage model can be formulated as follows.*

3.2.1. Objective function

$$min\, f_2 = \sum_{p,m} \gamma_{pmt} \quad (7)$$

$$\gamma_{pmt} = \max(h_{pm} I_{pmt}, -\mu_{pm} I_{pmt})$$

The second stage objective function seeks to minimize the maximum shortage cost in drugs rationing and allocation between demand zones in all period. In other words, the above objective function assists the policy makers to allocate resources, effectively.

3.2.2. Constraints

In the following, Constraints (8)–(14) correspond to customs and manufacturer centers, flow balance in the cross-docking center, inventory balance and auxiliary equations of the objective function, respectively.

$$\sum_l z_{prlt} \le \sum_{j,k} \bar{y}_{pjkrt} \quad \forall p, r, t \quad (8)$$

$$\sum_l x_{pilt} \le \bar{q}_{pit} \quad \forall p, i, t \quad (9)$$

$$\sum_i x_{pilt} + \sum_r z_{prlt} = \sum_v u_{plvt} \quad \forall p, l, t \quad (10)$$

$$I_{pmt} = I_{pm,t-1} + \sum_{l,v} u_{plvt} - \tilde{d}_{pmt} \quad \forall p, m, t \quad (11)$$

$$\gamma_{pmt} \geq h_{pm} I_{pmt} \quad \forall p, m, t \quad (12)$$

$$\gamma_{pmt} \geq -\mu_{pm} I_{pmt} \quad \forall p, m, t \quad (13)$$

$$z_{prlt}, x_{pilt}, u_{plvt}, \gamma_{pmt} \geq 0 \quad \forall p, i, r, l, v, m, t \quad (14)$$

Constraint (8) ensures that the total drugs transferred from customs center to each cross docking center, should not exceed the total medicines provided by importer centers. Similarly, Constraint (19) is doing the same for each manufacturer center. Constraint (10) states that the total drugs entering into each cross docking center is equal to the total drugs entering regional distribution centers. Constraint (11) ensures the inventory balance equation at each province. Constraints (12) and (13) are auxiliary constraints related to objective function (7). It has been assumed that $\mu_{pm} > h_{pm}$ and both of them are nonnegative. Accordingly, for positive values of I'_{pmt}, amount of positive variable γ_{pmt} in the objective function would be equal to $h_{pm} I'_{pmt}$. In the case of negative values of I'_{pmt}, γ_{pmt} would be equal to $-\mu_{pm} I'_{pmt}$. In either case, the positive value of γ_{pmt} remains in the objective function. It should also be noted that μ_{pm} represents the loss imposes on each province because of drug shortages or unmet demand which are calculated based on human capital approach. It is discussed further in Section 3.3. Also, h_{pm} is the cost associated with excess inventory in a given province. Constraint (14) corresponds to non-negativity decision variables.

3.3. Disability-adjusted life years (DALYs) and human capital method

All the health resources are scarce [53]; hence, the optimal allocation of these resources among people should be based on their actual needs. To understand this need, a method for quantifying the health status of people is used that provides an understandable picture of the people's needs in different regions. To achieve this, the disability-adjusted life years (DALYs) method is applied which is a time-based metric for measuring the health loss in a given population. This measure was developed to evaluate the global burden of disease (GBD) in the 1990s for the first time [54,55]. Indeed, DALY is a societal metric which calculates the years of healthy life lost due to premature mortality and impairment. As a result, one unit of DALY is equal to one year of healthy life lost [54].

DALYs for a disease are composed of two main components: The Years of Life Lost (YLL) due to early death in the population and the Years Lost due to Disability (YLD) (http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/), as follows:

$$DALY = YLL + YLD$$

According to the global burden of disease (GBD) survey in 2017, ischemic heart disease, road injuries and low back and neck pain were the three leading causes of DALYs in Iran (http://www.healthdata.org/iran). For further information about DALYs, interested readers can refer to [56].

From the societal perspective, the hours lost due to the unemployment caused by illness and disability lead to productivity loss. There are various methods to calculate this loss [57]. In this study, the human capital approach is used to convert the years of life lost into its equivalent productivity cost. Accordingly, an individual's contribution in society is estimated by a person's income, hence productivity loss is obtained by multiplying the total lost hours by its corresponding income. [58]. Dahl et al. [59] estimated the productivity loss attributable to breast cancer in Norway by using of HC method around 58,200 €per case annually. As mentioned before, parameter μ_{pm} is computed based on the HC approach. The detailed calculation of μ_{pm} is provided in Section 5.

3.4. Linearization

The Objective function (1) consists of two max–min functions. Hence, the Model (1) to (6) is non-linear.

It is impossible to directly solve the problem through optimization solvers. In order to convert the model into an exact equivalent linear form, we define two free variables $\lambda_1$andλ_2 for the first and second terms of Objective function (1), respectively:

$$max\, f_1 = \vartheta\lambda_1 + (1-\vartheta)\lambda_2 \quad (15)$$

Subject to:

$$\lambda_1 \leq (v_{pit} - a_{pit})q_{pit} \quad \forall p, i, t \quad (16)$$

$$\lambda_2 \leq \sum_{k,r} v'_{pjt} y_{pjkrt} - (1+\rho_{pt}) \sum_{k,r} \widetilde{ex}_{kt}(c_{pjkt} + tc_{pkrt})y_{pjkrt} \quad \forall p, j, t \quad (17)$$

Plus Constraints (2)–(6).

4. Proposed credibility-based robust possibilistic programming model

As mentioned before, since the rationing process is done at the national level, the access to sufficient and reliable historical data of provinces' demands is very limited and in some cases impossible. Therefore, it is not possible to extract the appropriate probability distribution for the uncertain parameters and stochastic programming approaches cannot be used to handle the uncertainty in the proposed model. Also, because of the dynamic nature of exchange rate parameter and various factors affecting the amount of exchange rate over the planning horizon, the use of prediction based on historical data is not applicable. In such cases the estimation of imprecise parameters usually carried out based on experts' experiences and judgments. Fuzzy mathematical programming is the most well-known approach used, to model this kind of uncertainty, i.e., epistemic uncertainty.

Generally, flexible programming and possibilistic programming are considered as two subsets of fuzzy mathematical programming. Flexible mathematical programming models are used to cope with ambiguity in decision maker (DM) preferences under the flexibility in target value of goals and constraints. The second one is due to the existence of ill-known parameters in objective function and constraints that are usually modeled as corresponding possibility distribution based on available data and expert's knowledge [60].

Therefore, due to the lack of knowledge about the exact value of demand and exchange rate, these parameters are formulated as possibilistic data in the form of triangular fuzzy numbers as follows:

$$\tilde{d}_{pmt} = \left(d_{pmt(1)}, d_{pmt(2)}, d_{pmt(3)}\right)$$
$$\widetilde{ex}_t = \left(ex_{t(1)}, ex_{t(2)}, ex_{t(3)}\right)$$

To cope with the uncertain parameters in the constraints and objective functions of the proposed models, a credibility-based chance constrained programming (CCP) method is applied in this research. Credibility-based CCP is a plausible approach of possibilistic programming that was first introduced by Liu [61] and benefits from both the unique features of the credibility measure and chance constrained programming (CCP) approach. Compared to other possibilistic programming approaches (see [37,38,62]), CCP enables the decision maker to adjust the confidence level of chance constraints and can support different types of fuzzy numbers such as triangular and trapezoidal forms. Besides, it relies on valid mathematical concepts, i.e., the expected value of a fuzzy number and well-known fuzzy measures [42,63]. Notably, this approach is formed based on the credibility measure which despite the necessity and possibility measures is a self-dual measure. It means that, if the credibility value of a fuzzy occurrence is 1, that event will certainly take place and the fuzzy event will fail if its credibility value achieves 0. Furthermore, unlike the possibility and necessity measures that are extremely optimistic and pessimistic attitudes, the credibility measure possesses compromise attitude [64]. In other words, credibility measure is formed by the linear combination of the possibility and necessity measures as follows.

$$\begin{aligned} \mathrm{Cr}\left\{\tilde{\xi} \le r\right\} &= \frac{1}{2}\left(\sup_{x\le r}\mu(x) + 1 - \sup_{x>r}\mu(x)\right) \\ &= \frac{1}{2}\left(pos\left\{\tilde{\xi} \le r\right\} + Nec\left\{\tilde{\xi} \le r\right\}\right) \end{aligned} \tag{18}$$

where $\tilde{\xi}$ is a fuzzy variable with membership function $\mu(x)$ and r is a deterministic number. We assume $\tilde{\xi}$ is a triangular fuzzy number in the form of $\tilde{\xi} = (\xi_{(1)}, \xi_{(2)}, \xi_{(3)})$. Based on Zhu and Zhang [60], Eqs. (19) and (20) can be used to convert the fuzzy chance constraints into their equivalent crisp ones as follows.

$$\mathrm{Cr}\left\{\tilde{\xi} \le r\right\} \ge \alpha \Longleftrightarrow r \ge (2-2\alpha)\,\xi_{(2)} + (2\alpha-1)\,\xi_{(3)} \tag{19}$$

$$\mathrm{Cr}\left\{\tilde{\xi} \ge r\right\} \ge \alpha \Longleftrightarrow r \le (2\alpha-1)\,\xi_{(1)} + (2-2\alpha)\,\xi_{(2)} \tag{20}$$

where α is the minimum satisfaction degree of fuzzy chance constraints which is determined by the DM and is reasonable to be greater than 0.5 (i.e., $\alpha > 0.5$). Also, to cope with equality constraints with credibility measure, following definition can be used [65]**:**

$$\mathrm{Cr}\left\{\tilde{\xi} = r\right\} \ge \alpha \Longleftrightarrow \begin{cases} r \ge \left(\frac{\alpha}{4}\right)\left(\xi^2+\xi^3\right) + 0.5(\xi^1+\xi^2)\left(1-\left(\frac{\alpha}{2}\right)\right) \\ r \le \left(\frac{\alpha}{4}\right)(\xi^1+\xi^2) + 0.5\left(\xi^2+\xi^3\right)\left(1-\left(\frac{\alpha}{2}\right)\right) \end{cases} \tag{21}$$

Among several credibility-based fuzzy mathematical programming models, i.e., the expected value, the CCP, and the dependent CCP, we have used the expected value for the objective function, and chance constrained programming (CCP) approach to model the constraints containing imprecise parameters [41]. Despite the credibility-based CCP methods proposed by Hung [66] and Yang and Liu [67], this hybrid approach does not increase the complexity of the original problem and does not need additional information related to confidence level or ideal value of objective function. In this model, since the first and second stage's objective functions have been formulated as the max–min and min–max forms, respectively, they are transferred to their corresponding constraints after linearization. As a result, both of them are bereft of uncertain parameters, the expected values of objective functions equivalent to themselves. To this aim, at first consider the compact form of the proposed models as follows:

$$\begin{aligned} &\max f_1 = X \\ &s.t.\ AX \le \tilde{B} \\ &\qquad \tilde{C}x \le D \\ &\qquad F \le EX \le G \\ &\qquad X \ge 0 \end{aligned} \tag{22}$$

$$\begin{aligned} &\min f_2 = Y \\ &s.t.\ IY \le K \\ &\qquad LY = \tilde{B} \\ &\qquad MY \ge S \\ &\qquad Y \ge 0 \end{aligned} \tag{23}$$

where formulation (22) and (23) display the compact forms of the first stage and second stage models, respectively. Also, A, C, and E are coefficient matrices of constraints (2)–(5) and (16)–(17), I, L and M are coefficient matrices of constraints (8)–(13). $\tilde{B}$ and $\tilde{C}$ are uncertain parameters related to demand and exchange rate which are presented as fuzzy numbers. Vector X and Y denote the continues variables of the first and second stage, respectively. Now, based on above-mentioned descriptions, consider the following compact forms as credibility-based chance constrained programming models:

$$\begin{aligned} &\max E[f_1] = X \\ &s.t.\ Cr\{AX \le \tilde{B}\} \ge \alpha \\ &\qquad Cr\{\tilde{C}x \le D\} \ge \beta \\ &\qquad F \le EX \le G \\ &\qquad X \ge 0 \end{aligned} \tag{24}$$

$$\begin{aligned} &\min E[f_2] = Y \\ &s.t.\ IY \le K \\ &\qquad Cr\{LY = \tilde{B}\} \ge \delta \\ &\qquad MY \ge S \\ &\qquad Y \ge 0 \end{aligned} \tag{25}$$

where α, β and δ are minimum confidence levels of chance constraints which are determined based on DM opinions. According to Eqs. (19)–(21) the crisp equivalents of the above models are formulated as follows:

$$\begin{aligned} &\max E[f_1] = X \\ &s.t.\ AX \le (2\alpha-1)\,B_{(1)} + (2-2\alpha)\,B_{(2)} \\ &\qquad \left((2-2\beta)\,C_{(2)} + (2\beta-1)\,C_{(3)}\right)X \le D \\ &\qquad F \le EX \le G \\ &\qquad X \ge 0 \end{aligned} \tag{26}$$

$$\begin{aligned} &\min E[f_2] = Y \\ &s.t.\ IY \le K \\ &\qquad Y \ge \left(\tfrac{\alpha}{4}\right)\left(B_{(2)}+B_{(3)}\right) + 0.5(B_{(1)}+B_{(2)})\left(1-\left(\tfrac{\alpha}{2}\right)\right) \\ &\qquad Y \le \left(\tfrac{\alpha}{4}\right)(B_{(1)}+B_{(2)}) + 0.5\left(B_{(2)}+B_{(3)}\right)\left(1-\left(\tfrac{\alpha}{2}\right)\right) \\ &\qquad MY \ge S \\ &\qquad Y \ge 0 \end{aligned} \tag{27}$$

It should be noted that, in possibilistic programming the confidence levels of chance constraints are determined by DM in a reactive or interactive process which cannot guarantee the optimality of confidence level values. Also, with increase in the number of chance constraints, the problem complexity increased considerably [35]. As could be seen, possibilistic chance constrained programming model behaves as a conservative manner and violation of chance constraints is ignored [68].

To overcome the above-mentioned drawbacks in the CCP approach, the robust possibilistic programming (RPP) approach proposed by Pishvaee et al. [40] is applied in this research. However, here, despite the RPP approach introduced by Pishvaee et al. [40] credibility measure is used to form the RPP model. Among the different robust possibilistic models proposed by Pishvaee et al. [40], RPP II model possesses more realistic logic than others. Accordingly, the proposed credibility-based robust possibilistic programming model can be formulated as follows:

$$\begin{aligned} &\max f_1 - \varphi_1\left((2\alpha-1)\,B_{(1)} + (2-2\alpha)\,B_{(2)} - B_{(1)}\right) \\ &\qquad -\varphi_2 X\left(C_{(3)} - (2-2\beta)\,C_{(2)} - (2\beta-1)\,C_{(3)}\right) \\ &s.t.\ AX \le (2\alpha-1)\,B_{(1)} + (2-2\alpha)\,B_{(2)} \\ &\qquad \left((2-2\beta)\,C_{(2)} + (2\beta-1)\,C_{(3)}\right)X \le D \\ &\qquad F \le EX \le G \\ &\qquad X \ge 0 \end{aligned} \tag{28}$$

$$\begin{aligned}
&\min f_2+\omega_1\left(\left(\frac{B_{(1)}+2B_{(2)}+B_{(3)}}{4}\right)-\left(\frac{\alpha}{4}\right)\left(B_{(2)}+B_{(3)}\right)\right.\\
&\quad\left.-\ 0.5(B_{(1)}+B_{(2)})\left(1-\left(\frac{\alpha}{2}\right)\right)\right)+\\
&\quad\omega_2\left(\left(\frac{\alpha}{4}\right)\left(B_{(1)}+B_{(2)}\right)+0.5\left(B_{(2)}+B_{(3)}\right)\left(1-\left(\frac{\alpha}{2}\right)\right)\right.\\
&\quad\left.-\left(\frac{B_{(1)}+2B_{(2)}+B_{(3)}}{4}\right)\right)\\
&s.t.\ IY\le K\\
&\quad Y\ge\left(\frac{\alpha}{4}\right)\left(B_{(2)}+B_{(3)}\right)+0.5\left(B_{(1)}+B_{(2)}\right)\left(1-\left(\frac{\alpha}{2}\right)\right)\\
&\quad Y\le\left(\frac{\alpha}{4}\right)\left(B_{(1)}+B_{(2)}\right)+0.5\left(B_{(2)}+B_{(3)}\right)\left(1-\left(\frac{\alpha}{2}\right)\right)\\
&\quad MY\ge S\\
&\quad Y\ge 0
\end{aligned}\tag{29}$$

where the second and third terms in the formulation (28) and (29) denote the total violation penalties of chance constraints. In other words, these terms are used to control the feasibility robustness of the obtained solution. Also, φ_1, φ_2, ω_1 and ω_2 indicate the unit penalty costs of violation of the chance constraints and their values should be determined according to the problem context. It should be noted that despite the traditional CCP approach, in the above formulation the minimum confidence levels (i.e., α,β) are determined endogenously and optimized according to the problem constraints and objective function.

4.1. Linearization of the proposed model

Due to the product of two continues variables in the objective function and second constraint set, the credibility-based RPP model of the first stage (i.e., Formulation (28)) is nonlinear. Also, since the Hessian matrix of the objective function and solution space is not negative semi definite (NSD) and positive semi definite (PSD), respectively, the model is not a convex problem. Hence, it is impossible to use the MINLP solvers for finding globally optimal solution. Thus, the McCormick Envelopes are used to relax the non-convex problem into a convex problem in which a lower bound and upper bound are determined for both continuous variables [69]. This convex relaxation causes to find close optimal solutions. In other words, the optimal solution in the relaxed problem will not always be the optimal solution to the objective problem. To do so, if we assume X and β to be continuous variables and that there are a lower and an upper bound for β (LB=0.5, UB=1), variable ρ instead of using the product of these two variables is used and equation of $(0.5X\le\rho\le X)$ is added to the model. Accordingly, by substituting in the formulation (30), we rewrite the RPP II credibility-based model of the first stage as follows:

$$\begin{aligned}
&\max E\left[f_1\right]-\varphi_1\left((2\alpha-1)\,B_{(1)}+(2-2\alpha)\,B_{(2)}-B_{(1)}\right)\\
&\quad-\varphi_2\left(2X\left(C_{(3)}-C_{(2)}\right)+2\rho(C_{(2)}-C_{(3)})\right)\\
&s.t.\ AX\le(2\alpha-1)\,B_{(1)}+(2-2\alpha)\,B_{(2)}\\
&\quad D\ge X\left(2C_{(2)}-C_{(3)}\right)+2\rho(C_{(3)}-C_{(2)})\\
&\quad 0.5X\le\rho\le X\\
&\quad F\le EX\le G\\
&\quad X\ge 0
\end{aligned}\tag{30}$$

5. Implementation and evaluation

In this section, the performance and desirability of the proposed model are evaluated via two real case studies which are used for treating neurological disorders. The first one is for epilepsy which this disease one of the most prevail chronic neurological disorders throughout the globe (around 2.4 million people per year). Most of the epilepsy patients are diagnosed in developing countries (nearly 80%). Epilepsy is considered as an untreatable disease but can be controlled by the medications about 70% of times [http://www.who.int/en/news-room/fact-sheets/detail/epilepsy]. In Iran, the epilepsy prevalence rate is higher than the global standard rate [70]. According to the latest statistics reported by Iranian Epilepsy Association (IEA), approximately 1200,000 of Iranian people suffer from the epilepsy. Moreover, the scientific investigations have demonstrated that the total number of the Iranian epilepsy patients is more than 2.5 times greater than that of European patients (http://www.iranepi.org). Sodium valproate is considered as one of most effective and primarily medicines for the treatment of epilepsy. It has been also employed to treat bipolar disorders and prevent from the migraine headaches (https://en.wikipedia.org/wiki/Valproate). The second one is used for Parkinson which this disease is the most common neurodegenerativedisorder causing a person to lose control over some body functions. Based on the survey conducted by the National Institutes of Health (NIH), about half a million people are diagnosed with PD in the US (https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=109). The prevalence rate of PD has been reported about 285 per 100,000 population in Iran [71]. Levodopa is the main therapy for Parkinson's patients. Due to increasing epilepsy and Parkinson prevalence in Iran and also the importance of these drugs for neurological disorder patients, sodium valproate and levodopa-b were selected as the studied scarce drugs to evaluate the performance of the proposed model. Here, without loss of generality, we perused the results of the sodium valproate in detail, while the results of evaluation of the levodopa-b were summarized in Appendix.

Sodium valproate was supplied by five production companies and three importer companies in Iran while Levodopa-b was produced by one manufacturer and purchased by one importer company. It should be noted that importer companies purchased the drug from two provider countries under the full supervision of IFDA, in compliance with the principles, requirements and drug standards. Moreover, three distribution centers are in charge of distributing the drugs to all the provinces. These centers have branches across the country so that each local distribution center receives products of its main distribution center.

It was assumed that production capacities of two major sodium valproate's manufacturers and the only levodopa-b's manufacturer are diminished (up to 40%) because of insufficient raw materials however they will improve in subsequent periods. This will lead to the shortage of these two medications in 12 provinces of the country. Also, for both cases, the planning horizon was 8 months and the duration of time periods was considered 2 months. To estimate the nominal demand of each period, yearly nominal demands of provinces and consumption average of each region at each period were extracted using the linear trend of historical data. Due to imprecise and uncertain nature of demand parameter, the prominent points of the triangular fuzzy numbers were prognosticated. Tables 2 and 8 represent the estimated demand and population data corresponding sodium valproate and levodopa-b, respectively, used to implement the proposed decision making approach.

Notably, the data related to real demand of provinces were generated under a uniform distribution function varying in the range of $[d_1,d_3]$. Additionally, it was presumed that there is no initial inventory at neither of the local distribution centers; so that the shortage at the first period is equal to nominal demand. Furthermore, the data associated with exchange rate were adopted from the central bank of Iran (https://www.cbi.ir/). All monetary calculations of the problem were performed with Iranian currency (Rial) and Euro was considered as the foreign supplier currency. Finally, all mathematical models were solved by GAMS 24 optimization software with CPLEX solver using a core i7 computer with 4 GB RAM.

As explained at Section 3.2.2, one of the main contributions of the proposed model is applying the DALYs measure to compute the disease burden of the provinces, followed by conversion to its equivalent cost unit using human capital method. Indeed, in the

Table 2
Data related to each province at each period.

No	Provinces	Population	Nominal demand (*1000)	Real demand (*1000)
1	Tehran	13,267,637	(1000,1500,2000)	∼Uniform (1000,2000)
2	Esfahan	5,120,850	(850,900,950)	∼Uniform (850, 950)
3	Fars	4,851,274	(650,700,750)	∼Uniform (650 ,750)
4	Khorasan-e Razavi	6,434,501	(700,750,800)	∼Uniform (700, 800)
5	Azerbaijan-e Sharghi	3,909,652	(700,750,800)	∼Uniform (700, 800)
6	Khuzestan	4,710,509	(500,550,600)	∼Uniform (500, 600)
7	Mazandaran	3,283,582	(450,500,550)	∼Uniform (450, 550)
8	Guilan	2,530,696	(350,400,450)	∼Uniform (350, 450)
9	Azerbaijan-e Gharbi	3,265,219	(250,300,350)	∼Uniform (250 ,350)
10	Kerman	3,164,718	(300,350,400)	∼Uniform (300, 400)
11	Khorasan Shomali	863,092	(300,350,400)	∼Uniform (300,400)
12	Sistan va Baluchistan	2,775,014	(100,200,300)	∼Uniform (100,300)

presented model, shortage cost imposed on the provinces can be calculated by using human capital method as follows:

Step 1: Since sodium valproate is used to treat three different diseases including epilepsy, migraine and bipolar disorders, we calculated the total population affected with these diseases based on the prevalence ratio of each disease at each region [70–73].

Step 2: Since epilepsy, migraine are neurological disorder while the bipolar disorder is classified as mental disease, their corresponding DALYs values were assigned to each one [74]. For this purpose, the lost years due to disability or premature mortality (burden of disease for each province) were achieved for each region.

Step 3: The DALYs average for each province was calculated.

Step 4: Applying the human capital approach, the productivity loss imposed to each region was determined. Based on this method, the lost earning of each person was equivalent to losses imposed on the society. Then income average of each region was calculated by multiplying the extracted value with the population (income average of each person was considered around 120 million Rails per year in Iran).

Step 5: Now, the shortage cost average of each province in each period can be achieved by multiplying income average to DALY value of each region.

The estimated DALY values and shortage costs imposed to each province are listed in Table 3. Based on this Table, the proposed model had more emphasis on provinces suffering more from the shortage, as they received higher priorities compared to the others. Also, to avoid the potential deficiencies in further periods, a safety stock level was defined as a fraction of yearly demand for each province. These steps were also computed for levodopa-b. It is only employed for Parkinson disease, hence, by considering the prevalence ratio about .002 for each region, the population affected and DALY value were included in Table 8. Other steps were similar to previous case.

5.1. Computational results

Table 4 summarizes the results of the model along with the optimal inventory levels at each region. Accordingly, some provinces including Tehran, Esfahan, Khorasan-e Razavi, Azerbaijan-e Sharghi and Khuzestan, exhibited to have higher priorities for receiving medications as they possessed higher shortage cost and higher demands. Hence, the unmet demands of the remaining provinces were postponed to the next periods. In the second iteration, the inventory levels of the demand zones are updated by realizing the new unfolded data of the previous period. Therefore, allocation process of the second period is performed based on the actual inventory levels of the first period. Considering backlogged demand assumption, the demand zones which did not receive their required medicines in the current period, will take the highest priority in the next periods. In other words, this way assists the government to equitably ration the medications among the provinces. As it can be seen, shortages still remained up to the third period; since the inventories were not sufficient, the proposed algorithm was repeated for another period. In the fourth period, the amounts supplied by the manufacturers and importer companies were sufficient, so the additional supply was dispensed in proportion of the population among the demand zones. Finally, the algorithm was ceased in the fourth iteration as the shortage was resolved, and inventory levels approached to their safety stock. This allocation policy makes our approach more effective and applicable in practice.

Furthermore, Table 5 represents the computational results of solving the deterministic and robust models based on the data extracted from the first case study. As it could be seen, deterministic model outperformed the robust model in terms of the objective functions' values for both stages. That is reasonable since this extra cost in the robust model is related to the robustness cost considered to protect the system against uncertainty and it is ignored in deterministic model. For instance, the second objective function's average value (for total periods) in deterministic model, robust model and also robustness cost were 7020,204, 10,468,337 and 3448,133, respectively. Moreover, due to the problems in drug supply system in the first and second periods, aggregated shortage costs were significantly higher than the other time periods. However, the manufacturer capacity levels increased by passing of time which improved both objective functions.

It is noteworthy that, the results derived from solving the proposed model via the second case study, put emphasis on this conclusion (see Table 9).

5.2. Performance assessment of credibility-based RPP approach

The deterministic and robust models could not be compared due to differences in their objective functions terms. In this regard, the performance of the proposed robust approach was assessed through substituting the optimal solution obtained by both of models under nominal data (i.e., X^*, Y^*) in two realization models:

$$\begin{aligned} &\max f_1 = X^* - \tau_1 v_1 - \tau_2 v_2 \\ &s.t.\ AX^* + v_1 \le B_{real} \\ &\quad C_{real}X^* + v_2 \le D \\ &\quad F \le EX^* \le G \\ &\quad X^* \ge 0 \end{aligned} \tag{31}$$

$$\begin{aligned} &\min f_2 = Y^* + \sigma_1^+ u_1^+ + \sigma_2^- u_2^- \\ &s.t.\ IY^* \le K \\ &\quad LY^* - \tilde{B} = u_1^+ - u_2^- \\ &\quad MY^* \ge S \\ &\quad Y^* \ge 0 \end{aligned} \tag{32}$$

Table 3
the summary of computational results of DALYs value and shortage cost for each province at each period.

Provinces	Neurological disorders DALYs=294.9		Mental disorders DALYs=1336.3		Average DALYs(1000)	Shortage cost ratio (per period)
	Affected Population	DALYs (1000)	Affected Population	DALYs (1000)		
(1) Tehran	4,776,349	115.61	39,803	411.65	263.6	1.41E+01
(2) Esfahan	1,894,715	49.58	15,363	158.88	104.2	2.38E+00
(3) Fars	679,178	16.44	12,128	125.43	70.9	5.44E−01
(4) Khorasan-e Razavi	1,029,520	24.92	12,869	133.10	79.0	9.13E−01
(5) Azerbaijan-e Sharghi	1,211,992	29.34	13,684	141.52	85.4	1.16E+00
(6) Khuzestan	518,156	12.54	9,421	97.44	55.0	3.22E−01
(7) Mazandaran	361,194	8.74	9,851	101.88	55.3	2.28E−01
(8) Guilan	328,990	7.96	7,592	78.52	43.2	1.61E−01
(9) Azerbaijan-e Gharbi	326,522	7.90	1,633	16.88	12.4	4.51E−02
(10) Kerman	344,954	8.35	3,165	32.73	20.5	7.93E−02
(11) Khorasan Shomali	336,606	8.15	2,589	26.78	17.5	6.57E−02
(12) Sistan va Baluchistan	222,001	5.37	1,110	11.48	8.4	2.08E−02

Table 4
Summary of final results.

No	Provinces (m)	First iteration		Second iteration		Third iteration		Fourth iteration	
		Shortage quantity D_t	Inventory level after allocation I_t	Shortage quantity D_t	Inventory level after allocation I_t	Shortage quantity D_t	Inventory level after allocation I_t	Shortage quantity D_t	Inventory level after allocation I_t
1	Tehran	1,500,000	0	1,359,700	0	1,351,441	0	1,131,492	89,026
2	Esfahan	900,000	0	908,911	0	933,089	0	873,082	34,520
3	Fars	700,000	0	727,586	0	680-,336	0	661,049	32,703
4	Khorasan-e Razavi	750,000	0	716,017	0	787,246	0	726,511	43,241
5	Azerbaijan-e Sharghi	750,000	0	759,396	0	772,272	0	762,825	26,162
6	Khuzestan	550,000	0	541,331	0	511,770	0	531,421	31,613
7	Mazandaran	500,000	−463,370	947,225	0	712,347	0	514,573	22,165
8	Guilan	400,000	−400000	826,996	−232,566	612,346	0	416,111	17,078
9	Azerbaijan-e Gharbi	300,000	−300000	612,745	−612,745	891,131	−891,131	1,149,773	21,802
10	Kerman	350,000	−350000	714,125	−714,125	1,068,656	0	303,152	21,075
11	Khorasan Shomali	350,000	−350000	607,225	−607,225	947,843	−236,232	588,795	5,813
12	Sistan va Baluchistan	200,000	−200000	335,625	−335,625	442,453	−442,453	659,479	18,532

$D_t = D_t^{nominal} - I_{t-1}^{actual}$.

$I_{t-1}^{actual} = I_{t-1} - D_{t-1}^{actual}$.

It should be noted that in the realized model, the uncertain parameters values were randomly generated by a uniform distribution. Since it is possible to confront the infeasibility of this model, a violation variable was defined for each chance constraint (i.e., υ_1, υ_2). In addition, parameters of $\tau_1, \tau_2, \sigma_1^+, and\, \sigma_2^-$ are the corresponding penalty values determined according to the DM preferences. The results obtained from solving the realization model under 10 random realizations are provided in Table 6. As it can be seen, the robust approach outweighed both the deterministic and credibility-based CCP models under confidence level of 0.9 in both stages regarding two measures of average and standard deviation of objective functions.

Additionally, the results achieved by the second case study which included in Table 10, confirm the superiority of the proposed model over others. These results justified the application of the proposed model in practice. Moreover, Fig. 3 depicts the superiority of credibility-based RPPII over other presented models in terms of the objective function of the first stage.

5.3. Sensitivity analyses

In this section, sensitivity analyses are discussed in detail to examine the effect of some critical parameters (including demand, exchange rate and confidence level of satisfaction of constraints (α, β)) on the objective functions values (such as importers profit, total profits and shortage cost). Table 7 summarizes the sensitivity analyses results of the demand and exchange rate for the first case.

Regarding the first stage equations, the exchange rate value directly influenced the importers' profit. As the results shows, by increase of the exchange rate up to 30%, the objective functions values remained constant, while further increase to 34% (up to 4%) had a drastic effect on importer profit and it led to dramatic decrease of their profit. The reason could be searched in diminishing the feasible region due to increase of the exchange rate value and decrease of the quantity provided by the importers of foreign suppliers. It should be mentioned that, since more contribution of total profit belongs to the manufacturers, it is less affected by these variations. On the other hand, under the constant value of demand, the increase of exchange rate value deteriorated the second objective function value. The growth of exchange rate caused a reduction in total supply quantity, and increased the shortage in the provinces. Furthermore, results indicated that a slight increase up to 35% intensified the reduction in the importer profit; by more increase up to 36%, the profit approached to 0 and second objective function value became doubled. These severe variations indicated the significant sensitivity of the first objective function to the changes in the exchange rate values. Fig. 4. shows the effect of variations in the exchange rate on the importer profit and shortage cost values.

Moreover, the behavior of the demand parameter was investigated by sensitivity analysis. The corresponding results indicated that the first objective function was not sensitive to the demand value. This could be due to two factors; (1) in the first model, demand parameter was applied in Formulation (2) and the production capacity of manufacturers and importers' budget could

Table 5
The objective functions' values of the presented models under different iterations.

Iteration	First		Second		Third		Fourth	
Objective functions	OF1	OF2	OF1	OF2	OF1	OF2	OF1	OF2
Deterministic model	383,135,804	12,935,391	384,135,804	11,029,730	391,953,993	4,115,334	403,619,857	363
Robust model	381,835,537	20,552,443	382,835,537	14,316,964	390,518,212	5,447,422	402,219,336	1,556,520

Table 6
Performance of deterministic, credibility-based CCP and robust models under different realizations.

Realization no	Deterministic Model Solution		Credibility-Based CCP model solution 0.9		Credibility-Based RPPII model solution	
	OF1	OF2	OF1	OF2	OF1	OF2
1	400,557,885	18,232,553	401,235,340	18,176,522	401,972,646	18,168,140
2	402,166,730	17,634,899	402,219,356	17,583,661	403,101,552	17,570,486
3	402,166,730	17,848,384	402,214,340	17,801,792	403,081,001	17,783,971
4	401,228,323	17,864,566	402,219,340	17,823,379	402,279,653	17,800,153
5	400,346,401	17,873,656	401,329,340	17,838,805	401,896,309	17,809,243
6	401,677,017	17,952,726	402,212,150	17,901,113	402,661,339	17,881,313
7	398,934,974	17,559,506	400,756,128	17,501,435	401,386,842	17,495,093
8	398,893,597	17,579,152	400,756,128	17,523,844	401,371,906	17,514,739
9	399,523,452	17,319,972	400,925,453	17,281,522	401,599,258	17,255,559
10	400,557,885	18,232,553	401,219,340	18,198,661	401,972,646	18,164,140
Average	400,605,299	17,809,797	401,508,691	17,763,073	402132315	17,744,284
Standard deviation	1,219,048	293,030	638,256	294,461	638,208	292,018

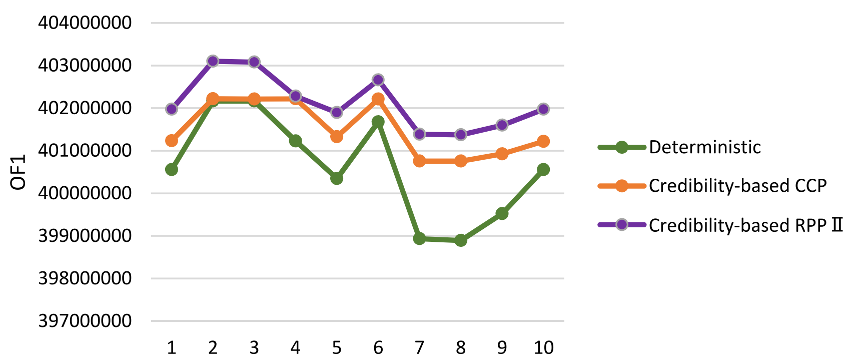

Fig. 3. Comparison between the presented models under different realizations.

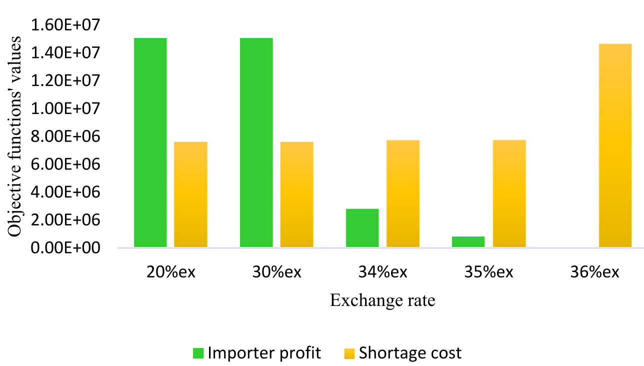

Fig. 4. Objective functions' values vs exchange rate alteration.

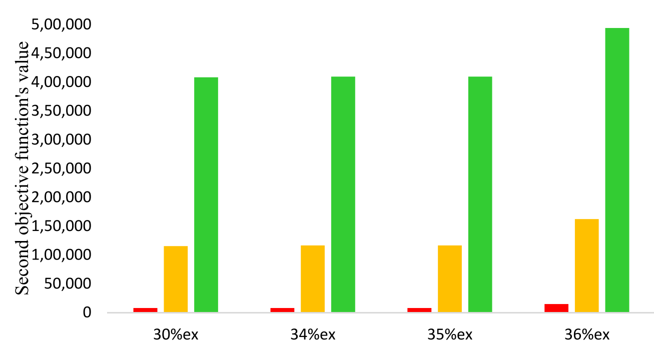

Fig. 5. Second objective function's value vs. alterations of the exchange rate and demand.

not respond the current demand, hence the greater demand could not be satisfied. (2) The first stage objective function did not include shortage cost for suppliers. As a result, no shortage cost was imposed on the suppliers due to the unfulfilling demands. Accordingly, increase in the demand will not change the results of the first model. On the other hand, by assuming consistency of exchange rate value, the increase in demand led to significant deterioration of the second objective function value. This could be attributed to enhanced gap between supply and demand and the more unfulfilled shortage. Fig. 5. shows the impact of demand variations on the objective functions under different exchange rates. In other words, the second objective function was under direct effect of the demand and also indirect influence of the exchange rate.

The same sensitivity analyses were also performed for the second case study and its results were provided in Table 11. It stands to reason that its numerical outcomes were not equal to the first ones but it was acceptable as the model was tested via different data. Hence, its sensitivity range of parameters were dissimilar to the first case. Nevertheless, the results achieved were not in contrast with the conclusions drawn.

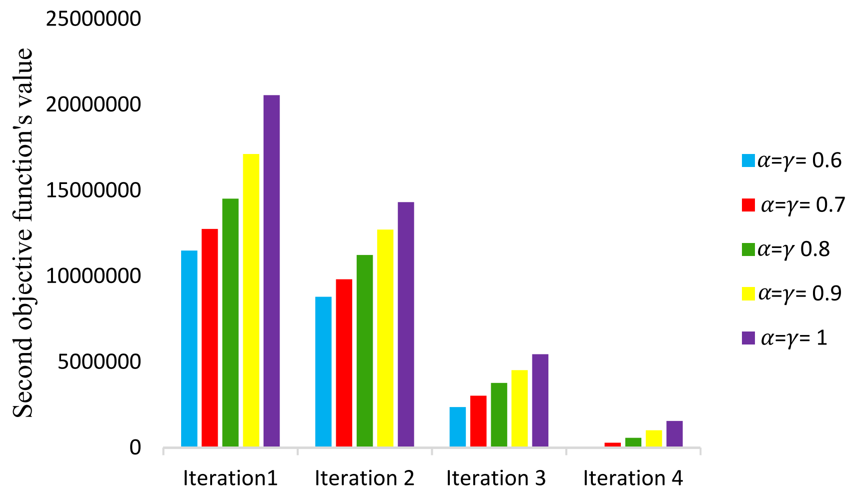

Fig. 6. Values of second stage objective function under variations of confidence level values.

Table 7
The summary of sensitivity analyses on parameters.

Parameters		Objective functions' values		
Exchange rate	Demand	Importer profit	Total profit	Second model
30%ex	d(t)1.5d(t)2d(t)	1.5069E+71.5069E+71.5069E+7	3.9675E+83.9675E+83.9675E+8	7,622115,238408,239
34%ex	d(t)1.5d(t)2d(t)	2.8045E+62.8045E+62.8045E+6	3.84E+083.84E+083.84E+08	7,740116,400409,317
35%ex	d(t)1.5d(t)2d(t)	8.2192E+58.2192E+58.2192E+5	3.83E+083.83E+083.83E+08	7,749116,450409,382
36%ex	d(t)1.5d(t)2d(t)	000	3.81E+083.81E+083.81E+08	14,638162,147493,790

Table 8
the summary of information related to each province.

Provinces	Population	Nominal demand (*1000)	Actual demand (*1000)	Neurological disordersDALYs=294.9		Shortage cost (Rial) (per period)
				Affected Population	DALYs (1000)	
(1) Tehran	13,267,637	(200,300,400)	∼Uniform (200,400)	26,535	72.25	1,734,010
(2) Esfahan	5,120,850	(100,150,200)	∼Uniform (100, 200)	10,242	28.02	672,370
(3) Fars	4,851,274	(100,150,200)	∼Uniform (100 ,200)	9,703	26.54	636,980
(4) Khorasan-e Razavi	6,434,501	(120,,160,200)	∼Uniform (120, 200)	12,869	35.09	842,230
(5) Azerbaijan-e Sharghi	3,909,652	(50,100,150)	∼Uniform (50, 150)	7,819	21.23	509,590
(6) Khuzestan	4,710,509	(100,150,200)	∼Uniform (100, 200)	9,421	25.66	615,750
(7) Mazandaran	3,283,582	(40,70,100)	∼Uniform (40, 100)	6,567	17.99	431,730
(8) Guilan	2,530,696	(40,60,80)	∼Uniform (40, 80)	5,061	13.86	332,650
(9) Azerbaijan-e Gharbi	3,265,219	(40,70,100)	∼Uniform (40 ,100)	6,530	17.69	424,660
(10) Kerman	3,164,718	(40,70,100)	∼Uniform (40, 100)	6,329	17.10	410,500
(11) Khorasan Shomali	863,092	(100,200,300)	∼Uniform (100,300)	1,726	4.72	113,240
(12) Sistan va Baluchistan	2,775,014	(40,70,100)	∼Uniform (40,100)	5,550	15.04	360,960

Table 9
the objective functions' values of the presented models under different iterations.

Iteration	First		Second		Third		Fourth	
Objective functions	OF1	OF2	OF1	OF2	OF1	OF2	OF1	OF2
Deterministic model	4,114,731,166	188,951	32,532,251,750	329,817	37,774,352,100	289,926	43,234,753,838	162,444
Robust model	4,011,082,987	32,8576	31,365,231,752	342,611	36,489,099,419	293,435	41,836,991,697	162,444

Fig. 6 indicates the performance of the second stage objective function value under variations of confidence levels in the credibility-based CCP model. As it be seen from this figure, for the value of $\gamma = \alpha = 1$, the objective function is at its worst value in four iterations while for the value of $\gamma = \alpha = 0.6$, the value of the objective function is the least. Thus, as the confidence levels values increase, feasible region of problem reduces and eventually, values of second stage objective function is also exacerbated in all iterations.

6. Conclusions and future research

In the situations where the demand outpaces supply, resource rationing becomes an inevitable process. However, the serious challenge in this process is fair allocation of the medication among the patients. Besides, the conflicts of interests and preferences between members, government and providers (who involved in this supply chain) may intensify the problem complexity. It is due to the fact that providers' (such as suppliers and manufacturers) decisions affect the policy makers' decisions; hence, their decisions and goals should be taken into account in the rationing of the scarce resources. In this study, this concern was addressed by a two-stage mathematical programming model in a multi period planning horizon in which the demand was assumed as backlogged. The proposed model was solved by an iterative algorithm in which the impact of new information on each iteration was accounted by rolling planning horizon approach. This mechanism enables the decision makers to make

Table 10
Performance of deterministic, credibility-based CCP and robust models under different realizations.

Realization No	Deterministic Model Solution		Credibility-Based CCP Model Solution 0.9		Credibility-Based RPPII Model Solution	
	OF1	OF2	OF1	OF2	OF1	OF2
1	41,186,464,864	689,261	43,509,215,456	676,175	43,818,638,967	675,312
2	41,214,690,001	612,437	43,574,001,937	595,904	43,842,700,148	583,172
3	41,224,838,365	716,589	43,541,760,859	712,616	43,827,569,482	665,020
4	41,234,691,200	721,829	43,550,002,682	697,843	43,842,700,148	671,730
5	41,234,691,200	450,932	43,550,002,682	540,932	43,842,700,148	550,932
6	41,234,691,200	611,730	43,550,002,682	618,115	43,842,700,148	621,829
7	41,197,828,918	565,020	43,551,079,914	549,957	43,838,645,920	526,589
8	41,234,691,200	633,172	43,552,295,723	620,183	43,834,484,127	612,437
9	41,206,550,168	705,312	43,523,008,238	593,423	43,822,909,141	542,766
10	41,176,052,220	542,766	43,544,411,095	530,813	43,831,146,023	519,261
Average	41,214,518,934	624,905	43,544,578,127	620,666	43,834,419,425	596,905
Standard Deviation	21,967,091	87,816	17,574,021	67,094	9,014,157	60,969

Table 11
The summary of sensitivity analyses on parameters.

Parameters		Objective functions' values		
Exchange rate	Demand	Importer profit	Total profit	Second model
100%ex	d(t)1.5d(t)2d(t)	9.6774E+99.6774E+99.6774E+9	2.323E+102.323E+102.323E+10	186114162,147493,790
150%ex	d(t)1.5d(t)2d(t)	9.1216E+79.1216E+79.1216E+7	4.0537E+94.0537E+94.0537E+9	192427431966676353
200%ex	d(t)1.5d(t)2d(t)	5.6016E+75.6016E+75.6016E+7	3.9833E+9 3.9833E+93.9833E+9	195787432076676580
250%ex	d(t)1.5d(t)2d(t)	4.5959E+74.5959E+74.5959E+7	3.9632E+93.9632E+93.9632E+9	213218432108676645

informed and updated decisions on the processes of supplying and rationing the scarce medication. The first stage model was formulated from the suppliers' perspective aiming to maximize their minimum profit. The decisions associated with production and purchasing were determined in this stage. The second stage model was based on policymakers' perspective aiming to minimize the maximum shortage cost. In this stage the decisions related to rationing and allocation of scarce drugs were also adopted. To eliminate discriminative allocation, two need-based metrics involving population and disability-adjusted life years (DALYs) were employed. Also, a human capital approach was used for the first time to compute the shortage cost in different regions.

Other important challenge of rationing process is the uncertainty of input parameters, which has not been considered before. This challenge was also addressed in this paper. For this purpose, a credibility-based robust possibilistic programming model was applied to deal with the uncertain parameters. The proposed model was verified and validated by two real case studies of food and drug administration of the Islamic Republic of Iran and the computational results were comprehensively analyzed. The results showed that in spite of the conventional rationing process (which assigns a predefined value as quota for each province), the flexibility and adjustability of proposed model enables the governments to allocate the medications among the demand zones based on their corresponding shortage cost and demand. By this way, policymakers could equitably allocate scarce resources. Also, the results of deterministic and credibility-based robust models revealed that deterministic approach could not be an appropriate tool for optimizing the corresponding supply chain suffering from deficient knowledge about input data. Finally, the results of sensitivity analyses illustrated that fluctuations in the exchange rate could directly influence the amount of shortages in demand zones. To resolve this problem, the government could assign a fixed exchange rate to the providers to pave the way for timely supply of the medications. The proposition of a multi-objective programming rationing model capable of considering three performance measures including the efficiency, equity and effectiveness can be considered as an attractive topic for future researches. Moreover, bi-level programming structure can present a better real-life decision making process for the scarce drug rationing problem, since it can illustrate the behavior of the policymaker and suppliers more appropriately.

Declaration of competing interest

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to https://doi.org/10.1016/j.asoc.2019.105514.

Appendix. The second case study results

See Tables 8–11.

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