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Green Drug Supply Chain Investigation by Time-Market Balance and Risk

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Abstract

The quality of pharmaceutical products plays a crucial role in healthcare systems such as hospitals for better patient services. Drug Supply Chain Management requires approaches to uncertainty and risk consideration. This study is a comprehensive multi-objective mathematical model considering the uncertainties and potential reserves in supply and medicine. The proposed model includes three general objective functions that minimize total production costs, including the costs of transportation, maintenance, breakdown, collection, and disposal of waste. The model also maximizes the quality of potential storage. The results show the proposed method has a high quality to solve the model and leads to the optimization of the results to provide the drug supply chain for the proposed example. We have identified three important risks and uncertainties in addressing drug supply planning: the indefinite duration of the licensing process, the risk of a forced brand change, and indefinite repayment levels that lead to varied demand diversification. The results of comparison with other multi-objective optimization methods in existing articles also show better performance of the proposed model. A significant cost reduction results from implementing our model instead of using the over-storage role to estimate the volume of active drug elements, as seen in today's industry.

Keywords

Market Supply Planning, New Product Introduction, Two-Stage Variable Planning, Regulation Affairs

1. Introduction

Unlike many industries, there are fundamental differences between the Supply Chain Management (SCM) of consumer products and pharmaceuticals. Drugs

are manufactured and distributed under strict regulatory requirements. One of the most challenging parts of the product is before it goes to the market, where there is an important balance between minimizing healthcare costs and saving patients' lives. Therefore, Healthcare SCM requires special attention compared to conventional products. For the past four decades, a great deal of work has been done in Drug SCM (DSCM) by combining different techniques to improve effectiveness, efficiency, and patient satisfaction. DSCM can be defined as the costly and complex steps involved in a fuzzy environment with uncertain demands that include human, material, information, and financial flows. Pharmaceutical SCM (PSCM) includes suppliers, hospital departments, logistics services, and medical services that apply limited resources (time, materials, capital) and coordinates their actions with an integrated logistics process to ensure their collective performance (patient satisfaction). Secondly, PSCM improves their performance as well. DSCM is significant for health services providers, insurance companies, and governments constantly striving to be as effective as possible in providing the services. This is due to the lack of resources, reduced delivery time, increased customer expectations (in quantity and quality), cost growth (demand and investment in new health-related technologies), and reduced delivery time. For this reason, the present study addresses the essential issue of DSCM with uncertainty and the possible storage through the fuzzy method to solve the limitation problem. The present paper is organized as follows. First, the authors provide an introduction and Research Background. Next, we discuss the Methodology and Mathematical model for SC, followed by Results in the third section. Finally, we present the Conclusion.

Research Background

Supply Chain Decisions (SCDs) are a strategic issue for any company. The issue of equipment placement and customer allocation is the core of a production system. Manufacturing companies need to efficiently locate their production/assembly plants, warehouses, and distribution centers to maintain their maximum profit margins in today's competitive market and provide the best possible level of service at the lowest cost to maintain their competitive position against other companies. In addition to decisions about the location of equipment in the available space, these points are also important: specifying how such equipment interacts, how to transfer raw materials and finished or unfinished products between the source and destination equipment, and decisions about the location of equipment.

Also, since the primary and secondary factories are often located in scattered locations around the world; and they are often located in different regions, providing a coordinated program for the various categories of the supply network is of paramount importance to achieve better performance for the entire network through the integration of supply, production and distribution categories [1]. This field of research is generally rich in literature, but despite the specific dif-

ferences mentioned, little work has been done on PSCs. The most common limiting assumptions used in models in the literature are the supply of unlimited raw materials, the forecast of known demand and prices for new and existing products, and the limited time horizon. On the other hand, decisions are influenced by data uncertainty, which usually stems from the uncertain nature of clinical trials and the demand side. Reference [2] proposes a multi-stage, multi-period, and multi-scenario randomized mixed integer optimization model for several vaccines in which demand was considered an indeterminate parameter, and the method was based on the scenario used to control this type of uncertainty. Also, the results of different expected clinical trials were identified with the probabilities of their occurrence, while the details of processing times, investment costs, and production scale were also considered in the proposed model. The expected net profit value was also used as a target function to evaluate decisions.

In product portfolio selection, if a company wants to maintain its competitive position in the market, it must constantly introduce new products to the market. Thus, a significant challenge is which products should be included in the R&D portfolio [3] and how to allocate resources [4] to maximize return on investment in a fast and reliable way. Such decisions must be made under significant uncertainties in PSCs (such as demand uncertainties, selling prices, clinical trial results, risk of failure or prolongation of R&D success, the emergence of an alternative product, etc.) [5] [6] [7]. R&D costs related to new product development and product business features, such as production costs, selling prices, and marketing costs, are some important product features that can be considered for decision-making [8] [9]. Also, constraints on capital budgeting, resources, and technical and regulatory constraints are often imposed on this problem. Among the various methods for controlling uncertainty, random programming is the most common method to approach portfolio selection uncertainty. For example, reference [9] developed a continuous decision-making approach to address the problem of developing a new product. From a set of continuation or release options at each stage of the testing process, they considered four outcomes: 1) high success, 2) goal success, 3) low success, and 4) failure, each with probabilities predetermined for clinical trials. Then, a multi-stage random programming method called MILP formulation was developed. The mentioned challenges demonstrate the need for proper management of inventory issues such as order quantities, purchase dates, and inventory levels while considering customer satisfaction without adversely affecting public health, patient safety, or relationships with PSC members [10] [11]. Despite these facts, this field has been out of focus in the past and has recently received more attention from researchers in operational research. Among the inventory policies developed in the inventory management literature, some policies, such as periodic reviews for industries related to public health (due to the risk of scarcity), are not acceptable. Therefore, the usual method adopted for PSC is a continuous review. Due to the special nature

of pharmaceutical products (e.g., high prices and shortage costs, sensitive molecular inputs that decompose over time, etc.), compared to other perishable products, they do not follow the common models in the articles.

In short, these issues place severe constraints on inventory management and other risks imposed on the company. Therefore, inventory management in PSCs requires special models that are created while considering all specific aspects. The summary of the research conducted in the last few years is presented in Table 1.

Table 1. A summary of the research conducted in the last few years.

Results	Research Methods	Year	Reference
The benefits of vendor-managed inventory in the pharmaceutical industry	Random model	2010	[13]
Pharmaceutical supply chain	Dimethyl	2012	[14]
Production planning in the pharmaceutical industry	Exploratory algorithm	2012	[15]
Dynamic allocation of resources in the pharmaceutical industry with delivery costs and different tax rates to maximize the company's net profit	Linear and Dynamic Planning	2012	[16]
Lost sales due to delays in the market supply	Multi-objective fuzzy	2012	[17]
Planning and scheduling in drug supply and supply	Ideal planning	2012	[18]
Existing studies on the drug supply chain	Review study	2012	[19]
Identify the amount of economic production under the minimum volume restrictions on the production of perishable products such as drugs	Mathematical model	2013	[20]
The structural decision for market supply functions in the pharmaceutical industry	Grand Theory	2015	[21]
Creating an optimal supplier price strategy	Game theory and Nash equilibrium	2015	[22]
The literature on green supply chain management	Library review	2015	[23]
Supply Chain Management towards firm performance	Fuzzy	2017	[24]
Inventory policy, transportation, and pricing in a two-tier multi-stage supply chain	Nonlinear model	2017	[25]
Green supply chain management	Fuzzy	2019	[26]
Multi-product and multi-level closed-loop pharmaceutical supply chain with quality concepts in mind	NSGA II	2020	[27]
Supply chain management practices	Integration	2021	[28]

2. Research Method and Mathematical Model of SC

The SC network design and planning refers to determining the optimal network structure (*i.e.*, locations of facilities and allocations) as well as determining how to optimally use the resources of production, distribution, and storage throughout the chain to respond quickly and appropriately to customer orders and requests [12]. This section presents the mathematical model of SC in this article. The proposed model is a multi-objective, multi-stage, multi-period (dynamic) SC with potential reserves and various transportation equipments that will be examined in uncertain conditions. Decisions about opening and closing equipment at each stage and increasing capacity along the planning horizon are considered according to the different incremental demands of drug distribution centers and returned products and the transport time required to transfer products between different stages of the chain. The schematic diagram below shows the overview of the supply chain, which consists of several factories, distribution centers, and other pharmacies. The forward arrows indicate the direct flow of products for delivery to the customer. The dotted arrows point backward to show the reverse flow of products needing return and rotten drugs. The collections, parameters, and variables of the model are shown in **Appendix 1** (Figure 1).

2.1. Limitations

By applying constraints, we first ensure that customer demand is met at all costs. The second limitation is related to the amount of inventory stored in distribution centers (*Inv*). This constraint states that the input and output of a node must be the same. Thus, the amount of inventory at the end of each period is calculated.

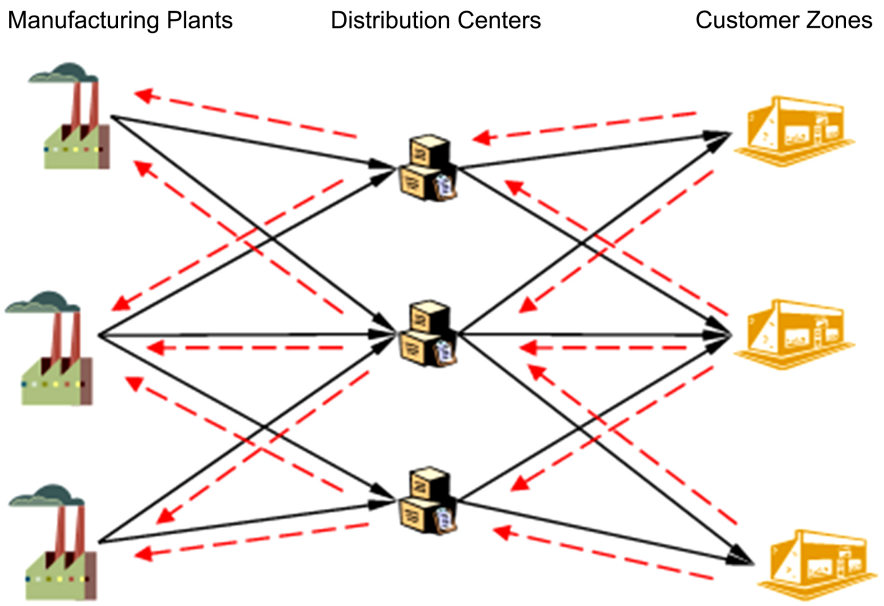

Figure 1. Proposed method in the uncertain green supply chain with possible drug storage.

$$\sum_{w}\sum_{v} x^{t}_{w,c,p,v} \geq \tilde{D}^{t}_{c,p},\ \forall c,p,t \tag{1}$$

$$\sum_{m}\sum_{v} x^{t}_{m,w,p,v} + Inv^{t-1}_{w,p} = \sum_{c}\sum_{v} x^{t}_{w,c,p,v} + Inv^{t}_{w,p},\ \forall w,p,t \tag{2}$$

Constraints (3) to (6) are the capacity constraints of the problem. The third limitation states that it is not possible to use the production capacity and possible factory storage beyond the installed capacity until the relevant period. The fourth limitation is the same as the previous one, but it is set for distribution centers, which means that no more than the storage capacity of the products can be transferred from one period to the next. Limit (5) shows the maximum amount of transportation by v equipment in each period between factories and distribution centers. Restriction (6) is similar to the previous case only between distribution centers and sales centers (second stage of the supply chain). Note that how to add capacity options in constraints (3) and (4) is significantly different from constraints (5) and (6). It is assumed that if a capacity option is used in one period to increase the capacity of factories or warehouses, this excess capacity will remain open in all remaining periods and cannot be eliminated. This assumption is made because it does not make sense to shut down equipment that has received excess capacity over time and spend it in vain. Since it is easy to rent excess capacity from any type of transportation equipment for transportation-related restrictions, it is possible to rent excess capacity only in periods when extra capacity is required; and the remaining courses with the capacity of transportation equipment owned by the company can be transferred.

$$\sum_{w}\sum_{p}\sum_{v}\left(\tilde{a}_{p}\cdot x^{t}_{m,w,p,v} + \tilde{a}'_{p}\cdot z^{t}_{m,w,p,v}\right) \leq \widetilde{Cap}_{m}\cdot\delta^{t}_{m} + \sum_{om}\sum_{t}\widetilde{Mcap}_{om}\cdot\sigma^{t}_{m,om},\ \forall m,t \tag{3}$$

$$\sum_{p}\tilde{\gamma}_{p}\cdot Inv^{t}_{w,p} \leq \widetilde{Cap}_{w}\cdot\delta^{t}_{w} + \sum_{ow}\widetilde{Wcap}_{ow}\cdot\sigma^{t}_{w,ow},\ \forall w,t \tag{4}$$

$$\sum_{w}\sum_{c}\sum_{p}\tilde{\gamma}_{p}\left(x^{t}_{m,w,p,v} + z^{t}_{m,w,p,v} + y^{t}_{w,m,p,v}\right) \leq \widetilde{Tcap}1^{t}_{v} + \sum_{ov}\widetilde{Vcap}_{v,ow}\cdot\sigma 1^{t}_{v,ov},\ \forall v,t \tag{5}$$

$$\sum_{w}\sum_{c}\sum_{p}\tilde{\gamma}_{p}\left(x^{t}_{w,c,p,v} + z^{t}_{w,c,p,v} + y^{t}_{c,w,p,v}\right) \leq \widetilde{Tcap}2^{t}_{v} + \sum_{ov}\widetilde{Vcap}_{v,ow}\cdot\sigma 2^{t}_{v,ov},\ \forall v,t \tag{6}$$

Restrictions (7) to (11) are associated with the reference products and the flow of these materials in the supply chain. Constraint (7) states that the amount of products returned from sales centers equals the percentage of products transferred to that point. The buyer inspects these products in the same period they are sent to the sales centers, and some of them are referred for repairs if needed. The potential storage of these drugs may be due to the materials used in manufacturing, manufacturing process, or shipping conditions. Constraint (8) is related to the balance of the flow of reference materials from sales centers to distribution centers and from distribution centers to factories. Restriction (9) stipulates the need to send potential reserves after arriving at the factory. Limit (10) shows the balance of the flow of repaired products from the factory to the distribution centers and from the distribution centers to the sales centers. Restriction (11) stipulates that each customer will receive as many products as they

referred in the next period.

$$\sum_{w}\sum_{v} y^{t}_{c,w,p,v} \geq \sum_{w}\sum_{v} \widetilde{Def}_{p} \cdot x^{t}_{w,c,p,v},\ \forall c, p, t \tag{7}$$

$$\sum_{m}\sum_{v} y^{t}_{w,m,p,v} = \sum_{c}\sum_{v} y^{t}_{c,w,p,v},\ \forall w, p, t \tag{8}$$

$$\sum_{w}\sum_{v} z^{t}_{m,w,p,v} = \sum_{w}\sum_{v} y^{t-1}_{w,m,p,v},\ \forall m, p, t \tag{9}$$

$$\sum_{c}\sum_{v} z^{t}_{w,c,p,v} = \sum_{m}\sum_{v} z^{t}_{m,w,p,v},\ \forall w, p, t \tag{10}$$

$$\sum_{w}\sum_{v} y^{t-1}_{c,w,p,v} = \sum_{w}\sum_{v} z^{t}_{w,c,p,v},\ \forall c, p, t \tag{11}$$

It is assumed that the transport capacity of any equipment is independent of each other between factories and distribution centers and between distribution centers and sales centers. Constraints (12) to (20) are logical constraints of the problem. Restriction (12) requires that returned medicines be returned only to open warehouses. In this constraint, M is a huge number. Restrictions (13) and (14) prohibit potential reserves from changing status (from having to not having and vice versa) more than once. Stored drugs can be returned, and stored drugs cannot be returned on the planning horizon. In constraint (15), we can add capacity options to factories and distribution centers, but we cannot remove them. We also state with limitation (16) that a drug to which capacity options have been added cannot be reduced. Constraint (13) to (17) ensures we can only add capacity options to drugs stored in the relevant period. Constraints (18) to (20) relate to the logical relationships of transport capacity options. Constraint (18) requires that we can use a capacity option in only one stage of the supply chain. Restrictions (9) and (20) need that at each step of the supply chain, we can order only one of the available capacity options for one type of drug, and ordering more than one capacity option is prohibited.

$$\sum_{c}\sum_{p}\sum_{v} y_{c,w,p,t,v} \leq \delta^{t}_{w} \cdot M,\ \forall w, t \tag{12}$$

$$\delta^{t}_{i} \geq \delta^{t+1}_{i} \quad \forall i \in Mc \cup Wc \tag{13}$$

$$\delta^{t}_{i} \leq \delta^{t+1}_{i} \quad \forall i \in Mo \cup Wo \tag{14}$$

$$\sigma^{t}_{i,o} \leq \sigma^{t+1}_{i,o} \quad \forall i \in M \cup W, o \tag{15}$$

$$\delta^{t}_{i} \geq \sigma^{t-1}_{i,o} \quad \forall i \in M \cup W, o \tag{16}$$

$$\sigma^{t}_{i,o} \leq \delta^{t}_{i} \quad \forall i \in M \cup W, o \tag{17}$$

$$\sigma 1^{t}_{v,ov} + \sigma 2^{t}_{v,ov} \leq 1 \quad \forall v, ov, t \tag{18}$$

$$\sum_{ov} \sigma 1^{t}_{v,ov} \leq 1 \quad \forall v, t \tag{19}$$

$$\sum_{ov} \sigma 1^{t}_{v,ov} \leq 1 \quad \forall v, t \tag{20}$$

2.2. Objective Functions

We present three objective functions for a multi-period supply chain in this case.

The first objective function is the classical function of minimizing model costs. The second function is to minimize the total transport time and possible storage in the problem. The third objective function is related to transportation costs, which contradicts the second objective function. To reduce service time, we must use more expensive vehicles with higher speeds, which causes an undesirable increase in this objective function. In the following, we will describe the relevant functions in detail. We consider the parameters with the sign Tilda (~) on them to be uncertain. The first line of objective function f_1 deals with the potential storage costs of new drugs and the cost of capacity options for drugs required, both in factories and in distribution centers. The second line deals with operating costs and the operation of capacity options added during their operation. Also, each product type's cost of production and possible storage is considered. The third line of the model is related to the storage costs of materials in the warehouses of distribution centers.

$$\begin{aligned}\min \tilde{f}_1 = & \sum_{i\in Mo\cup Wo}\sum_t \widetilde{CO}_i \cdot \left(\delta_i^{t+1}-\delta_i^t\right)+\sum_{i\in Mc\cup Wc}\sum_t \widetilde{CC}_i\left(\delta_i^t-\delta_i^{t+1}\right)\\ & +\sum_{i\in M\cup W}\sum_o\sum_t \widetilde{CA}_{i,o}\cdot\left(\sigma_{i,o}^{t+1}-\sigma_{i,o}^t\right)\\ & +\sum_{i\in M\cup W}\sum_t\left(\widetilde{COP}_i\cdot\delta_i^t+\sum_o \widetilde{CAOP}_{i,o}\cdot\sigma_{i,o}^t\right)\\ & +\sum_m\sum_w\sum_p\sum_v\sum_t\left(\widetilde{CP}_{p,m}\cdot x_{m,w,p,v}^t+\widetilde{CR}_{p,m}\cdot z_{m,w,p,v}^t\right)\\ & +\sum_p\sum_w\sum_t \widetilde{CS}_{p,w} Inv_{w,p}^t\end{aligned} \tag{21}$$

The second objective function minimizes the total shipping time to increase the level of service. It is necessary to explain that this function is considered independent of the weight of the products and therefore minimizes the total arrival time of all products to the destination. This assumption is made to not depend on the time of arrival of products to their weight, which seems illogical.

$$\begin{aligned}\min \tilde{f}_2 = & \sum_w\sum_p\sum_v\sum_t\left(\sum_m dis_{m,w}\cdot\left(x_{m,w,p,v}^t+z_{m,w,p,v}^t+y_{w,m,p,v}^t\right)\right.\\ & \left.+\sum_c dis_{w,c}\cdot\left(x_{w,c,p,v}^t+z_{w,c,p,v}^t+y_{c,w,p,v}^t\right)\right)\Big/\widetilde{SPT}_v\end{aligned} \tag{22}$$

The third objective function is introduced to minimize shipping costs. These costs include the cost of moving products between source and destination (which depends on the weight of the products) and the cost of adding capacity options at each stage of the supply chain.

$$\begin{aligned}\min \tilde{f}_3 = & \sum_w\sum_p\sum_v\sum_t \tilde{\gamma}_p\cdot\widetilde{CT}_v\cdot\left(\sum_m dis_{m,w}\cdot\left(x_{m,w,p,v}^t+z_{m,w,p,v}^t+y_{w,m,p,v}^t\right)\right.\\ & \left.+\sum_c dis_{w,c}\cdot\left(x_{w,c,p,v}^t+z_{w,c,p,v}^t+y_{c,w,p,v}^t\right)\right)\\ & +\sum_v\sum_{ov}\sum_t\left(\sigma 1_{v,ov}^t+\sigma 2_{v,ov}^t\right)\cdot\widetilde{CA}_{v,ov}\end{aligned} \tag{23}$$

3. Results

The proposed model consists of two conflicting objectives: minimizing total costs (including total opening costs, shipping/inventory costs, and inventory maintenance) and minimizing unsatisfied maximum demand in all periods. In detail, the creation of MSs, MDCs, and LDCs is further enhanced by many strategic decisions, for example, the location of MSs, MDCs, and LDCs, as well as some tactical decisions, such as optimal materials on a horizon. Medium-term planning is ongoing and maintaining the inventory of each family of products in each period; moreover, the production capacity of the MSs and the storage capacity of the MDCs should be done.

3.1. Definition of the Problem and Mathematical Model

This study proposes a multi-objective mathematical model for multiple healthcare products and a multi-level closed-loop green supply chain. This model includes suppliers, manufacturers, interconnectors, hospitals, collection, recycling, and disposal centers. Then, at the producers' request, the raw materials are transferred from the suppliers to the producers. Manufacturers produce pharmaceutical and medical products. For the sensitivity of health products and high quality, we use acceptance sampling for the quality inspection. In this study, the acceptance criteria are $c = 0$. If there are no defective products (such as drug effects and packaging) for each category, this group will accept and be transferred to a cross-docking center. Otherwise, these people will be taken to a collection center to process. At the request of the hospitals, the shipment was transferred from the outpatient center to the hospitals and stores in the pharmacy. In this study, we hypothesize that if pharmaceutical products are transported to hospitals at the earliest opportunity, the hospitals will penalize manufacturers for deteriorating the nature of pharmaceutical products. Also, hospital medicines and medical waste are separated from other waste materials to reduce the environmental impact. Therefore, these waste materials are transported to collection centers for processing. Collection centers then separate the waste elements, and they can be reused. These elements are transferred to recycling centers. The rest of the elements will be transferred to disposal centers. Recyclable elements, after processing, are shipped to suppliers to produce raw materials. In summary, the proposed model includes three objective functions. The first objective minimizes production costs, the next goal maximizes the quality level of the products, and the third one minimizes the environmental impacts. One of the main issues in the green supply chain is considering the amount of carbon dioxide emissions. This study considers the distance traveled by the vehicle, fuel consumption per kilometer (depending on the vehicle load), and carbon dioxide emissions per trip, which should calculate the total emission of CO_2.

Model assumption

1) All costs are known.

2) Demand for cross-connections, suppliers, manufacturers, recycling, collec-

tion, and disposal centers are equal.

3) Raw materials are derived from recycled materials, which are less expensive than conventional materials.

4) Carbon dioxide emissions are negligible for separation, disposal, and inspection activities.

5) Facility locations are definite.

6) Hospitals will process their requests within a specified period. Also, there is no drug transfer between hospitals.

7) Safety rules are provided for all shipments.

8) When demand in supply is short, hospitals make it up by purchasing from other manufacturers.

9) Reverse order costs are not considered.

3.2. Mathematical Model

In this paper, we model the Healthcare SC that considers quality and green concepts. The proposed model includes three objective functions. First, we formulate the problem of minimizing the total cost of production, maximizing the level of production quality, and minimizing the environmental impact of products and transportation as a mathematical program (Table 2, Table 3).

Table 2. Cost function changes with increasing MS facility.

Frequency	Goal function
1	1937.5
2	2137.5
3	2337.5
4	2537.5
5	2737.5
6	2937.5
7	3137.5
8	3337.5
9	3537.5
10	3737.5
11	3937.5
12	4137.5
13	4337.5
14	4537.5
15	4737.5
16	4937.5
17	5137.5
18	5337.5
19	5537.5
20	5737.5

Table 3. Cost function changes with increasing MDC fixed cost.

Frequency	Goal function
1	1937.5
2	2037.5
3	2137.5
4	2237.5
5	2337.5
6	2437.5
7	2537.5
8	2637.5
9	2737.5
10	2837.5
11	2937.5
12	3037.5
13	3137.5
14	3237.5
15	3337.5
16	3437.5
17	3537.5
18	3637.5
19	3737.5
20	3837.5

Figure 2 and Figure 3 show the effect of the initial cost of building the facility on the total cost of the chain. As it can be seen, given the strategic importance of the facility, by increasing this initial cost, the total supply chain cost will also increase significantly. Recently, healthcare supply chains have been discussed by various researchers. The quality of green products and concepts plays an essential role in improving healthcare systems and protecting the environment. This study presents a comprehensive multi-objective mathematical model for healthcare's multi-product and multi-level supply chain. This model includes three objective functions. Firstly, it minimizes overall production costs, including transportation, purchase, burnout, commissioning, recycling, collection, and disposal costs. The latter maximizes the level of production quality. The third minimizes the environmental impact of products and transportation. The innovation of this model examines various aspects of the drug supply chain, including:

- The comprehensive structure of a closed-loop drug supply chain with reverse flow including suppliers, manufacturers, cross-connections, hospitals, collection, recycling, and waste disposal;

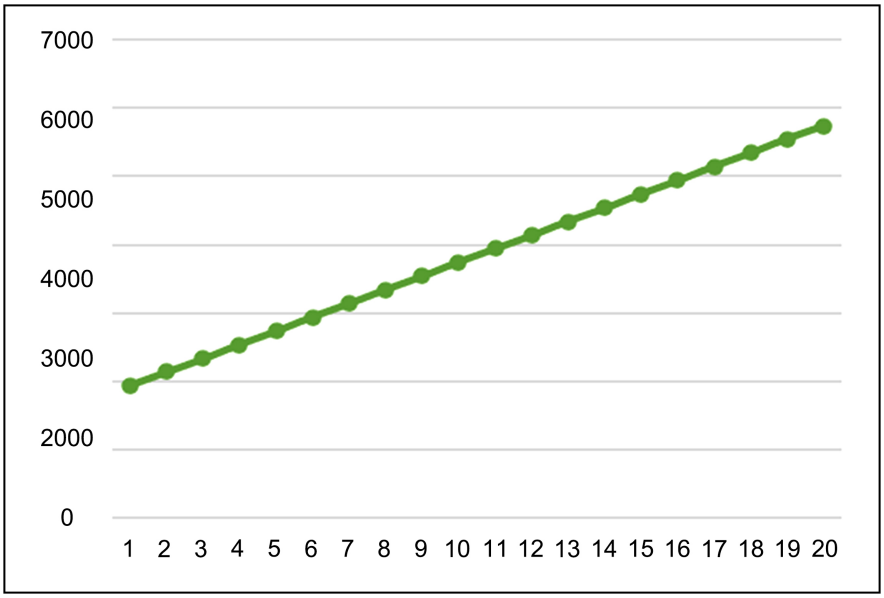

Figure 2. Cost function changes with increasing MS facility.

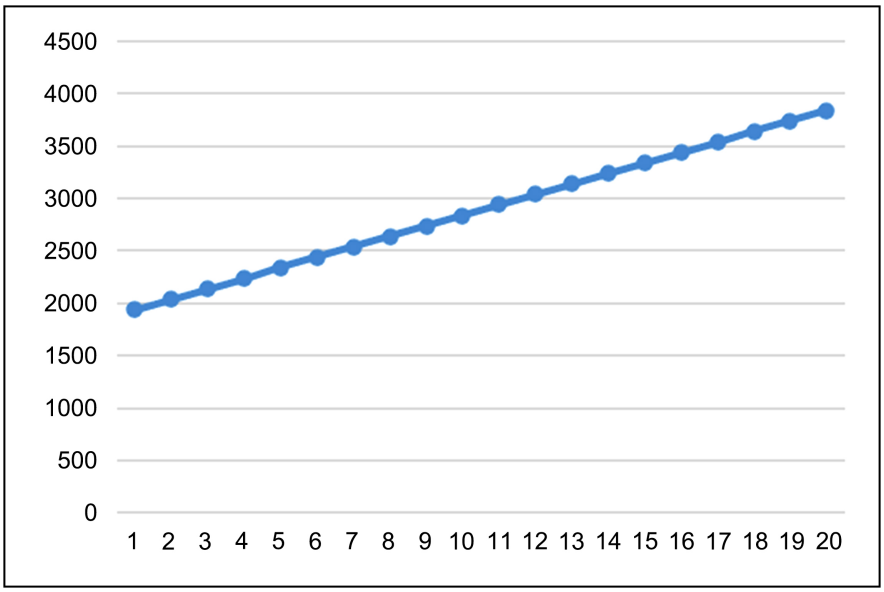

Figure 3. Cost function changes with increasing MDC fixed cost.

- Total production costs (transportation, purchase and maintenance, breakdowns, setting up, recycling, collection and disposal of costs);
- The quality level of production due to the sensitivity of healthcare products;
- Green Concepts of CO_2 emissions, separation of drugs and medical waste, recycling, and disposal.

3.3. Time-Market Balance and Risk Considering Potential Reserves

Initial balance

According to customer demand, an initial inventory covering a small part of

the demand in the first period is considered to be placed in warehouses one to three. These values are in Table 4.

3.4. Optimization Problem-Solving Process in the Proposed Problem

We set the reliability parameter to a constant value of α = 0.95, regardless of which criterion (requirement/possibility/validity) we have used. In this research, we use the fuzzy validity criterion and return from the uncertainty space resulting from fuzzy parameters to the non-fuzzy dependent area on the α parameter. By solving the model directly and with a single goal, we calculate the ideal and anti-ideal values for each goal function according to Tables 4-8 (before solving, we change all the goals to the maximization mode by multiplying by (−1) value).

In calculating the anti-ideal values for all three cases, due to the size of the model, the number of iterations exceeds the allowable limit of 10,000, and the optimization algorithm is stopped. According to the values, the worst values obtained from solving one-objective problems for the other goals in all three of the above optimizations, the lowest possible value was assigned to the anti-ideal values. Since these values are used only as a starting point for scaling the membership function of the objective function, it is not necessary to calculate them

Table 4. Initial inventory values.

$Inv_{w,p}$	P1	P2	P3	P4	P5
W1	14	10	65	12	70
W2	11	9	38	12	90
W3	14	9	14	10	8

Table 5. Ideal and anti-ideal goals.

Goal function	$^{*}\underset{\sim}{z}$	$\tilde{z}$	$Dif = \tilde{z} - \underset{\sim}{z}$
f_1	−6,000,000	−3,804,560	219,540
f_2	−135,000	−98,479	36,521
f_3	−350,000,000	−5,752,450	292,475,000

Table 6. Fuzzy method.

i	Average	μ_i	$-z_i$	$U(i)$	$w = \mu_{and}$
1		0.889	4,048,070		
2	0.901	0.925	101,218	0.904	0.895
3		0.889	89,965,200		

Table 7. Results of the application of the proposed method.

i	1	2	3	4	5	6	7	8	9
m1	0.89	0.891	0.89	0.89	0.89	0.889	0.891	0.89	**0.891**
m2	0.923	0.917	0.918	0.921	0.92	0.935	0.917	0.925	**0.917**
m3	0.889	0.891	0.89	0.89	0.89	0.886	0.891	0.889	**0.891**
average	0.901	0.900	0.899	0.900	0.900	0.903	0.900	0.901	**0.900**
w	0.895	0.895	0.895	0.895	0.895	0.895	0.895	0.895	**0.895**
U	0.904	0.903	0.902	0.904	0.903	0.908	0.903	0.905	**0.903**
−z1	4,044,990	4,044,590	4,045,280	4,046,330	4,046,260	4,048,450	4,046,550	4,045,630	**4,046,610**
−z2	101,303	101,522	101,465	101,377	101,383	100,837	101,516	101,218	**101,521**
−z3	89,926,600	89,501,700	89,593,300	89,733,300	89,723,900	90,745,600	85,110,900	90,076,200	**85,903,300**

Table 8. Results of the application of the method of the studied articles.

i	1	2	3	4	5	6	7	8	9
m1	0.947	0.772	0.82	0.854	0.826	0.946	0.54	0.92	**0.911**
m2	0.756	0.897	0.773	0.898	0.888	0.969	0.845	0.886	**0.68**
m3	0.889	0.922	0.928	0.907	0.915	0.808	0.943	0.880	**0.913**
average	0.864	0.864	0.840	0.886	0.876	0.908	0.776	0.895	**0.835**
w	0.810	0.818	0.807	0.870	0.851	0.858	0.658	0.888	**0.757**
U	0.856	0.853	0.847	0.882	0.872	0.895	0.753	0.898	**0.809**
−z1	3,921,520	4,305,180	4,200,440	4,125,490	4,187,150	3,922,770	4,813,670	3,980,580	**4,000,670**
−z2	107,392	102,252	106,783	102,211	102,570	99,614	104,140	102,644	**110,177**
−z3	90,042,400	80,310,600	78,499,400	84,865,800	82,400,800	113,625,000	74,173,600	92,676,000	**83,055,600**

accurately. Suppose the membership function's value is negative in any optimization problems. In that case, the value is less than the assigned anti-ideal, and the entire calculation must be repeated. Therefore, the careful selection of these values is important. By having the ideal and anti-ideal values of each objective function, we can optimize the model with the criterion of "fuzzy" and the balance factor γ equal to 0.5. The obtained values are as follows:

With the above values in hand, we can solve the proposed model for the problem. For the results of computations not to depend on the opinion of a particular decision maker, we have to define an auxiliary utility function to extract the best options based on it. We consider the decision-maker function as the weighted sum of the mean, minimum, and maximum objectives and use it as a scale for

comparison. To be more precise, we have the following equation:

$$U = \left(\min\left(\mu_i\right) + \text{Average}\left(\mu_i\right) + \max\left(\mu_i\right)\right)/3$$

We solved the program for the same weight vectors to compare this method with the presented methods. In fact, in the proposed method, we have set the value of the compatible space expansion coefficient to zero and the previous method to 100%. The answers to the presented method and the previous method can be seen according to the following tables:

As it can be seen, in all the non-dominant responses generated by our proposed method, which can be seen in Table 9, the value of the parameter "*w*" is minimum; in addition to generating more non-dominant responses, different values are obtained for the desirability function of each response. For this reason, we choose the answer leading to the maximum value of this function as the best answer, which is answer number 6 with the value of 0.908. It is observed that the value of this utility function is also higher than the value obtained for the previous proposed method: 0.905. According to the results, it can be seen that all the answers generated in our proposed method have the condition that the criterion "fuzzy" equals the predetermined value of 0.895. For a more explicit comparison, the best answer obtained from our proposed method (based on the utility function *U*) with other optimization methods can be seen in the table below. Note that *LPi* indicates single-objective optimization to optimize the i^{th} objective function of the problem without regard to other objectives. Our proposed method performs better than all other methods due to the utility function "*u*", the average degree of satisfaction of the goals, and the factor "*w*" which equals the "Werner Method". Table 9 shows the comparison of the proposed method with other proposed methods.

Figure 4 shows the scatter of the obtained answers according to the three studied objective functions. We can observe the expected increasing trend in the value of the first and third objective functions by decreasing the value of the second objective function. The second objective function is related to the total transport time of products.

Table 9. Compare the proposed method with other proposed methods.

	Wang *et al.* paper	Pedro *et al.* paper	Close *et al.* paper	Kim *et al.* paper	Proposed Method
m1	0.889	0.889	0.891	0.250	0.039
m2	0.935	0.925	0.891	0.161	0.136
m3	0.886	0.889	0.891	1.000	1.000
Average	0.903	0.901	0.891	0.470	0.392
w	0.895	0.895	0.891	0.316	0.215
U	0.908	0.905	0.891	0.544	0.477

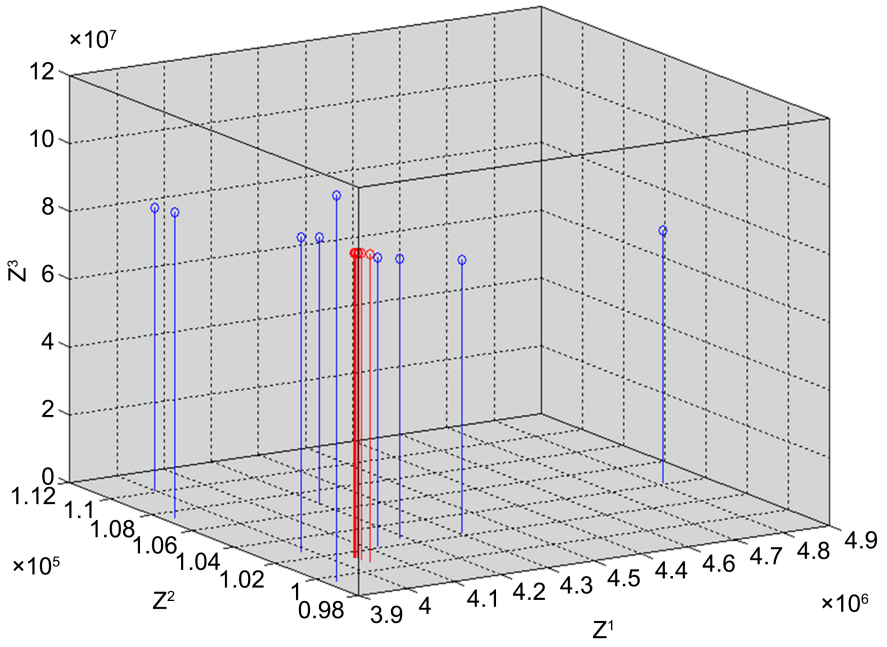

Figure 4. Dispersion of the resulting points in the presented and proposed method.

Three factories and three warehouses are open at the beginning of the first period. Because customers are in fixed locations each period, we do not include them in the figure. The reciprocating flows of the material are not shown in the figure to prevent it from being messy. A significant change in SC status occurs in the second period. Two factories and one warehouse are opened, and one warehouse is closed. The overall structure of the potential storage of drug equipment over time is consistent with the definitive single-objective model. In mathematical modeling, this can be used as a criterion for the validity of the designed model.

4. Conclusions

We have identified three important risks and uncertainties in addressing drug supply planning: the indefinite duration of the licensing process, the risk of a forced brand change, and indefinite repayment levels that lead to varied demand diversification. We created the two-step random MILP model to market the design. Important supply preparation decisions are the formulation required, the sheets' volumes, and the packaging's storage capacity, which must be planned in advance. All possible release dates are based on the other expected variables as they depend on the outcome of the licensing process. Unexpected additional decisions include packaging volumes and the list of laminated goods. Since uncertainties arise due to the unspecified date of licensing at unspecified points on time, other expected restrictions are used to force pre-licensing decisions to be the same. An extensive numerical experiment was performed in the case study that reflects the industry's reality. In the numerical experiment proving the applicability of our modeling approach, our numerical analysis could have led to the following managerial insights:

- Risk packaging results from limited capacity. The focus should be on larger markets to reduce market time.
- The inevitable market supply delays must be transferred to low-interest markets.
- Our modeling approach operates from a rigorous (severe) risk packaging process due to a better evaluation of cost and other opportunities in reducing time to a better market.
- Packaging material suppliers should be selected case-by-case based on efficiency rather than cost.
- A significant cost reduction results from implementing our model instead of using the over-storage role to estimate the volume of active drug elements, as seen in today's industry.
- Excessive stockpiling of active drug elements before market launch carries a high risk of relative decision (larger packaging volumes), resulting in a high disposal cost.
- Finally, since the chemical industry is the backbone of the pharmaceutical industry and also seeks rich literature in this field, compared to the young area of the pharmaceutical industry, many ideas can be inspired by old ideas to advance the younger generation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix 1

Collections

T	Planning horizon
M	Factory Complex
Mc	A set of factories that may close ($Mc \subset M$)
Mo	A set of factories that may open ($Mo \subset M$)
W	Collection of distribution centers
Wc	A set of distribution centers that may be closed ($Wc \subset W$)
Wo	A set of distribution centers that may open ($Wo \subset W$)
C	Collection of drug distribution centers
V	A set of transport equipment
O	A set of capacity options
Om	Collection Center Capacity Options ($Om \subset O$)
Ow	Set of Capacity Options for Distribution Centers ($Ow \subset O$)
Ov	Capacity Options for Transport Equipment ($Ov \subset O$)
P	Collection of produced products
R	Set of raw materials

Parameters

$D_{c,p}^{t}$	Customer "C" demand in the "T" period for "P" product
α_p	Capacity consumption rate to produce "P" product of factory capacity
α_p'	The capacity consumption rate for "P" product repair of factory capacity
Cap_m	Initial production capacity of the "M" factory
Cap_w	Initial storage capacity of "W" distribution center
$Mcap_{om}$	Production capacity of the "om" option for installation in factories
$Wcap_{ow}$	Storage capacity of the "ow" option for installation in distribution centers
$Vcap_{ov}$	Hold capacity "ov" option for installation on distribution centers
γ_p	"P" product weight
Def_p	Percentage of potential storage in p-type products
$Tcap1_v^t$	Maximum displacement capacity by type V equipment in t period between factories and distribution centers
$Tcap2_v^t$	Maximum displacement capacity by type V equipment in t period between distribution centers and shopping centers
CO_i	Cost of opening equipment i $\left(i \in Wo \cup Mo\right)$
CC_i	Cost of closing equipment i $\left(i \in Wc \cup Mc\right)$
$CA_{i,o}$	Cost of installing option o on equipment i
COP_i	Fixed cost of equipment operation i
$CAOP_{i,o}$	Fixed operating cost of option o on equipment i
$CP_{p,m}$	The production cost of the "P" product in the "M" factory
$CR_{p,m}$	The repair cost of the "P" product in the "M" factory
$CS_{p,w}$	Warehouse cost of "P" product at the end of each period in the "W"

warehouse

CT_v The cost of moving each volume unit of the product per unit distance by equipping "v"

SPT_v Transmission speed by equipping "v"

Variables

$x^t_{w,c,p,v}$ The amount of product p moved between warehouse w and shopping center c by equipping v in period t

$x^t_{m,w,p,v}$ The amount of product p produced and transferred between factory m and warehouse w by equipment v in period t

$z^t_{m,w,p,v}$ Product value p probable storage and displacement between factory m and warehouse w by equipping v in period t

$z^t_{w,c,p,v}$ The amount of product p that is potentially stored and moved between warehouse w and customer c by preparing v in period t

$y^t_{c,w,p,v}$ The amount of product p requires potential storage and relocation between pharmacy c and warehouse w by preparing v in period t

$y^t_{w,m,p,v}$ Product value p requires possible storage and displacement between warehouse w and factory m by preparing v in period t

δ^t_m f factory m is open in period t, the value is one; otherwise, it is zero

δ^t_w If the warehouse w is available in period t, it takes the value of one; otherwise, the value of zero

$\sigma^t_{m,o}$ If option "o" is installed on factory m in period t, the value will be one; otherwise, it will be zero

$\sigma^t_{w,o}$ If option "o" is installed on the warehouse w in period t, the value will be one; otherwise, zero

$\sigma 1^t_{v,ov}$ If "ov" is installed on equipment v between factories and distribution centers in period t, it takes one value

$\sigma 2^t_{v,ov}$ If "ov" is installed on the equipment v between distribution centers and customers in period t, it takes one value