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RESEARCH ARTICLE

Innovative Applications of Unsupervised Learning in Uncertainty-Aware Pharmaceutical Supply Chain Planning

FARID KOCHAKKASHANI[1], (Graduate Student Member, IEEE), VAHID KAYVANFAR[2], AND ROBERTO BALDACCI[2]

[1]Department of Electrical and Computer Engineering, The George Washington University, Washington, DC 20052, USA
[2]Division of Engineering Management and Decision Sciences, College of Science and Engineering, Hamad Bin Khalifa University, Doha, Qatar

Corresponding author: Vahid Kayvanfar (valikayvanfar@hbku.edu.qa)

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ABSTRACT The significance of resiliency, reliability, and equity in the pharmaceutical supply chain is often overlooked but becomes evident in the wake of disastrous events. Disruptive incidents underscore the critical importance of these concepts, necessitating the development of innovative frameworks to effectively address the challenges that emerge in their aftermath. This paper introduces a framework specifically designed to address the issues arising from disruptions within the pharmaceutical supply chain. A novel mixed-integer nonlinear programming (MINLP) model is proposed to formulate the pharmaceutical supply chain that encompasses the distribution of both cold and non-cold pharmaceuticals and vaccines. The abundance of diverse pharmaceuticals and vaccines, each with its distinct characteristics, presents a formidable planning obstacle. A noteworthy contribution of this study lies in innovatively applying AI-driven methodologies to pharmaceutical supply chain, employing five pioneering unsupervised learning algorithms for improved inventory management and control. The model's uncertainty is effectively addressed through an innovative joint chance constraint (JCC) formulation. By employing JCC, the model ensures a high level of reliability in satisfying uncertain patient demands. The MINLP formulation with JCCs presents significant computational complexities and intractability. To alleviate these issues, state-of-the-art reformulation algorithms are provided to transform the model into its equivalent mixed-integer linear programming form. The results indicate the efficiency of the equivalent reformulation techniques and illustrate the capabilities of the model to alleviate the resiliency, reliability, and equity concerns.

INDEX TERMS Pharmaceutical supply chain, equity, resiliency, mathematical optimization, stochastic programming, unsupervised learning.

I. INTRODUCTION

The COVID-19 pandemic has underscored the importance of a resilient and reliable supply chain for vaccines and pharmaceuticals. One of the most significant takeaways from the recent COVID-19 pandemic is that the time required to achieve mass immunization is not determined by the time it takes to develop a vaccine, but rather by the time it takes to scale production and distribute vaccines through the supply chain [1]. The COVID-19 vaccines were developed, tested, and granted emergency use authorization within 11 months, which is a remarkable achievement given that the development of a completely new vaccine traditionally takes an average of approximately 10 years [2]. However, this remarkable scientific achievement can be easily undermined if the supply chain system does not comply with standards related to product conservation, resiliency, reliability, and equity. The pandemic has demonstrated that the supply chain should be capable of withstanding any contingencies, including lockdowns or blockades, ensuring an equitable distribution of vaccines and pharmaceuticals.

With the considerable subsiding of the pandemic, it is now imperative to translate the knowledge gained from this emergency situation into actionable strategies for effective mitigation. These strategies hold immense value in the assessment of risks during the planning stages and feasibility

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studies of the supply chain. Apart from the pandemic itself, there exist various other factors that can potentially disrupt supply chain, such as natural disasters, issues with suppliers or vendors, financial instability, and more. Geopolitical events, stemming primarily from political instability, economic sanctions, border closures, or blockades, also contribute to contingencies in supply chain. Risks associated with these situations are typically classified as high-impact low-probability (HILP) risks and often occupy a high position in Failure Mode and Effects Analysis (FMEA) tables.

During the COVID-19 pandemic, extensive research has been conducted to analyze the effectiveness of large-scale strategies implemented by governments. These studies have focused on various aspects, including the assessment of vaccination facility locations [1], government interventions and their non-pharmaceutical policies [3], [4], [5], as well as forecasting pandemic behavior to ensure the provision of adequate healthcare services [6], [7]. In the realm of supply chain planning, factors such as resiliency and reliability play a pivotal role, particularly in the face of disruption risks [8], [9], [10], [11]. These factors have been emphasized in optimizing supply chain performance during contingencies. Furthermore, the consideration of equity factors has gained significant importance in the analysis of supply chain under disruptive conditions. However, only a limited number of studies have examined this aspect within the context of COVID-19 supply chain [12], [13], [14], [15], [16], [17].

In the majority of the aforementioned studies, there is either a limited consideration of specific types of pharmaceuticals for supply chain planning or a lack of explicit mention of the pharmaceutical types altogether. This represents a limiting assumption prevalent in the majority of articles examining pharmaceutical supply chain. However, [18] takes a different approach by considering various types of pharmaceuticals and incorporating them into the model through the application of ABC analysis for grouping. Furthermore, most articles address the inherent uncertainty in the optimization models by utilizing conventional stochastic programming (SP) [19], [20], robust optimization (RO) [21], [22], or chance constraints [23], [24], [25]. However, there is a paucity of studies that explore the use of joint chance constraints to ensure system reliability in the provision of commodities amidst the risks of disruption. This represents a significant gap in the existing literature. To advance the existing body of research, this paper introduces novel insights into the planning of pharmaceutical supply chain during unpredictable HILP contingencies. The key contributions of this study can be summarized as follows:

1) Comprehensive consideration of various pharmaceutical types, including vaccines, to establish a holistic framework for supply chain planning.
2) Simultaneous utilization of cold and non-cold chain approaches to accommodate pharmaceuticals with conflicting preservation temperatures.
3) Integration of multiple characteristics, such as priority, shelf life, and transportation modes, into the planning model.
4) Utilization of unsupervised learning-based approaches for pharmaceutical grouping, highlighting their advantages over traditional methods like ABC analysis.
5) Emphasis on equity and reliability, ensuring equitable access to pharmaceuticals and studying the framework's resiliency.
6) Introduction of a joint chance-constrained model. Compared to single chance constraints (SCCs) which ensure reliability for each constraint independently, JCCs enforce reliability over the set of defined constraints.
7) Proposal of a state-of-the art equivalent reformulation methodology for efficient solution of the joint chance-constrained model.

The article is structured as follows. Section II presents a comprehensive literature review, highlighting the current research gap in the field. Section III proposes problem description and model formulation. The equivalent reformulation of the model and the AI-driven algorithms are presented in Section IV, while the numerical results are provided in Section V. Finally, Section VI concludes the paper.

II. LITERATURE SURVEY

This section provides a detailed exploration of the existing literature in pharmaceutical supply chain planning. The studies are evaluated and assessed according to their conceptual frameworks and methodologies utilized for modeling and analyzing supply chain systems within the context of disruptions and pharmaceutical procurement. On one hand, an evaluation is conducted regarding the concepts associated with ensuring the resilience of the supply chain amidst disruptions, the reliability of the procurement system, and the equitable distribution of commodities. On the other hand, the methodological aspects of the articles are examined, including the formulation of uncertainty in mathematical models and the inclusion of various pharmaceutical products. Subsequently, the identified research gap is highlighted.

In a broader context of disruptions, scholarly studies delve into the difficult decisions that decision-makers encounter while addressing the disturbances [26], [27]. During the recent pandemic, there has been a notable focus on evaluating the swift decision-making of healthcare policymakers in their response to the COVID-19 outbreak. Numerous articles have specifically examined the policies pertaining to non-pharmaceutical interventions (NPIs). Notably, several articles [4], [5] have highlighted the efficacy of implementing lockdown policies as an effective measure in reducing the fatalities.

Various articles have explored risks and assessed the resiliency of systems under contingencies from different perspectives. For instance, [10] presents a bi-objective robust model that optimizes delivery costs and costs associated

with the supply chain network, specifically focusing on perishable products and disruptions in distribution centers. Their findings underscore the advantages of utilizing mobile warehouses. In [9], a distributionally robust optimization framework is examined to enhance resilience in the healthcare supply chain during the COVID-19 pandemic. The authors propose a model focusing on personal protective equipment (PPE) and worst-case scenarios, highlighting the importance of emergency stockpiles in mitigating contingencies. Similarly, [8] investigates the distribution of non-cold pharmaceuticals during the COVID-19 pandemic, considering resiliency characteristics. The authors illustrate the impact of the infectious virus on hospital service providers and emphasize the efficacy of their model in mitigating disruptions.

Equity is a crucial factor in pharmaceutical supply chain during contingencies, and several studies have focused on addressing this aspect. In [12], a humanitarian supply chain planning framework is proposed to tackle the issue of equitable pharmaceutical procurement. The authors develop a mixed-integer nonlinear programming model considering demand uncertainties and demonstrate promising results in addressing equity concerns in pharmaceutical distribution. In another study [13], the authors address the COVID-19 vaccine procurement problem in Europe using a mixed-integer linear programming (MILP) model. They incorporate deprivation cost into the objective function to ensure unbiased vaccine distribution across the network. The concept of equity is enforced through specific constraints. Sensitivity analysis and managerial insights are provided to emphasize the significance of equity and fairness in the vaccine supply chain. Additionally, [16] highlights the equity characteristics of the vaccine supply chain through patient prioritization. Susceptible patients are categorized based on their healthcare records and clinical information, and the uncertainty in patients' demand is managed using a multi-stage stochastic programming model. The results demonstrate the effectiveness of the prioritization and uncertainty management approaches in achieving equity in vaccine distribution.

The pharmaceutical supply chain encompasses multiple commodities, making it essential to consider this variety in the planning process. Each pharmaceutical product has distinct features, such as specific preservation temperature requirements. In addressing this complexity, [18] introduces an optimization model aimed at minimizing total cost and product shortage in supply chain. The model incorporates the conventional ABC classification of inventory items. Furthermore, it is important to note that there are numerous perishable pharmaceuticals that necessitate temperature control. Examples of temperature-sensitive pharmaceuticals include some eye and ear drops, insulin, vaccines, and HIV test kits. Recent research conducted by [28] highlights the significant impact of product perishability on the emergence and amplification of various risk factors within supply chain networks. Also, [29] explore the optimal operations in managing sustainable warehouse.

In modeling pharmaceutical supply chain during disruptions, it is inevitable to encounter uncertainty in various parameters, particularly in demand. Reference [20] adopts a stochastic programming approach to optimize operations in hospital pharmaceutical supply chain. Although disruptions are not explicitly considered in their problem, the authors acknowledge uncertainty as a key component in their model. The study's results are validated by comparing them to a real case study, highlighting improvements in the supply chain process. In [22], a robust optimization framework is proposed to address uncertainties in demand and cost when designing a vaccine supply network. The results demonstrate the variability in optimal solutions when different levels of uncertainty are taken into account. Another approach to incorporate uncertainty in pharmaceutical supply chain during the COVID-19 pandemic for high-demand commodities is presented in [23]. The article introduces a chance constraint formulation to handle uncertainty in disruptions. Furthermore, the research extends to develop recovery strategies for pharmaceutical supply chain in the face of contingencies.

A. RESEARCH GAP

According to the analyzed studies, several research gaps can be identified in the field of pharmaceutical supply chain. These include:

- The existing body of research on hospital supply chain falls short in adequately capturing the multifaceted challenges encountered by healthcare institutions in procuring essential medical commodities.
- The current literature on pharmaceutical supply chain lacks comprehensive investigations into the implementation of a pharmaceutical supply chain encompassing both cold and non-cold components. Furthermore, there is a noticeable dearth of research on cold chain logistics, particularly in developing countries. Moreover, the integration of diverse pharmaceuticals within hospital supply chain remains an unaddressed aspect, calling for a more holistic approach.
- The utilization of unsupervised learning methods within the domain of pharmaceutical supply chain management is still in its nascent stages, with significant room for further development and exploration. The prevailing literature predominantly relies on conventional and outdated techniques, such as ABC analysis, for categorizing pharmaceutical products, neglecting the potential benefits of more advanced methodologies.
- To the best of the authors' knowledge, the study of joint probabilistic constraints within the pharmaceutical supply chain remains unexplored. This innovative concept allows for the incorporation of a global predetermined reliability level, as opposed to relying solely

TABLE 1. An examination of the pharmaceutical supply chain model put forth in this study in relation to the existing body of literature.

Studies	Characteristics						
	Cold Chain	Vaccine	Uncertainty	Grouping	Equity	Resiliency	Reliability
[20]			Fuzzy	ABC			
[22]	✓	✓	RO				
[30]			SP			✓	
[31]			Fuzzy				✓
[19]			SP				✓
[20]			SP				
[31]	✓						
[12]		✓	SP		✓		
[17]	✓	✓			✓		
[32]			Fuzzy				
[33]		✓	SCC				✓
[13]	✓	✓			✓		
[34]	✓	✓	SP	AI			
This paper	✓	✓	JCC	AI	✓	✓	✓

on per-constraint levels, thereby enhancing the overall conservativeness of the supply chain.

This article endeavors to address the aforementioned gaps in the existing literature by proposing a comprehensive framework that takes into account contingencies within the system. Table 1 illustrates the distinctive features of the proposed framework in comparison to contemporary studies.

III. PROBLEM DESCRIPTION

The issue at hand pertains to the formulation of a comprehensive framework for the pharmaceutical supply chain, which encompasses operational costs and essential considerations pertaining to equity, reliability, and resiliency in the face of HILP disruptions. In order to address this, a systematic approach is taken in developing a distribution plan for groups of pharmaceuticals, referred to as pharmaceutical clusters (PhCs). This approach strives to achieve a desirable balance between equity, resiliency, and reliability, while simultaneously minimizing operational expenses. Furthermore, in order to mitigate the adverse effects of temperature-sensitive pharmaceuticals, the proposed supply chain problem incorporates the cold chain into its framework. As a result, a supply chain is established, encompassing both cold and non-cold items.

The primary focus of this research endeavor is the analysis of a supply chain network composed of four distinct echelons: suppliers, a Demand Hub (DH), hospitals' pharmacies, and hospitals' care units. The underlying network related to this supply chain is depicted in Figure 1. It is important to note that in our case the hospitals are geographically proximate to each other within a city. This idea is prevalent in specific situations, as hospitals frequently cooperate for research endeavors and willingly share resources [35]. To facilitate seamless operations and efficient inventory management, an integrated real-time hospital information system (HIS) is employed, overseen by a third-party logistics provider (3PL). The responsibility for inventory control and management predominantly lies with the 3PL, ensuring a well-defined

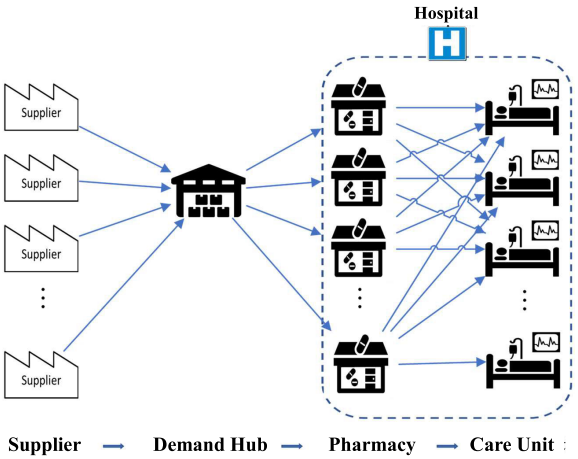

FIGURE 1. Underlying supply chain network.

division of tasks and the involvement of skilled professionals. Consequently, hospitals can devote their undivided attention to delivering high-quality care, thereby maximizing the service level.

The foundation of the network design is rooted in the Supply-Demand Hub in Industrial Clusters (SDHIC) model, as originally proposed by [36] and [37]. The subsequent development in [34] presents a modified network design that refines the previously proposed framework for the pharmaceutical supply chain. The hub adoption displays benefits in other studies as well [38]. The modified framework specifically caters to the unique requirements of the pharmaceutical industry. As depicted in Figure 1, the demand side of the network comprises patients and hospital pharmacies. To accommodate the diverse range of PhCs offered by different suppliers, a Demand Hub (DH) is implemented within the system, strategically located in close proximity to the hospitals, thereby facilitating efficient stockpiling of pharmaceuticals. This supply chain network design, drawn from our case study, is widely applicable, with similar approaches being employed in various regions,

such as South West England [35]. The network design proposed in the aforementioned studies offers numerous advantages, such as reduced capital investments, lower holding costs, decreased labor costs, enhanced efficiency, and risk mitigation. For a comprehensive understanding of the supply chain network, readers are referred to [34].

A. ASSUMPTIONS

The present study operates under a set of underlying assumptions which are presented below.

- The pharmaceutical supply chain is susceptible to HILP disruptions, particularly on the supplier side.
- A global reliability level of 95% is taken into account for the JCCs in terms of fulfilling the patients' demands.
- The model incorporates a deprivation cost to mitigate the risk of pharmaceutical shortages during emergency situations. This cost imposes strict conditions for meeting the affected hospital's demands.
- The proposed approach includes equity considerations to ensure a fair and balanced distribution of PhCs.
- A disruption, lasting from day 1 to day 15, is considered to take place, leading to suspension of some suppliers.
- This study analyzes the supply chain system over a time span of 90 days, corresponding to a season.
- The lead time for all orders in this study is deterministic and fixed at one day, with the exception of emergency orders, which are considered negligible. Due to the close proximity of hospitals, emergency orders have a lead time of zero.
- The patient demand is characterized by uncertainty and is modeled using a Gaussian random variable [39].
- The expiration rate is known for each PhC, and prolonged storage leads to degradation of the products.
- The proposed model incorporates priority considerations, where PhCs with higher priorities are associated with elevated deprivation costs to mitigate the risk of vital pharmaceutical shortages.
- Each supplier has limitations in providing specific pharmaceutical groups, and orders are consolidated and settled on a monthly basis.

B. MODEL FORMULATION

The present study introduces the pharmaceutical supply chain model (PSCM) tailored specifically for PhCs, incorporating joint chance constraints. The formulated model is classified as a mixed-integer nonlinear programming (MINLP) problem. Subsequently, an equivalent reformulation is proposed, leading to the transformation of the model into an MILP formulation in the successive section.

Indices

s	Index of suppliers.
d	Index of pharmacies.
u	Index of care units.
p	Index of PhCs.
m	Index of transportation means (TMs).
t	Index of days.

Parameters

T	The last time period.
ch_p^{DH}	Fixed holding cost of PhC p at DH.
ch_p^{P}	Fixed holding cost of PhC p at pharmacies.
c_p^{dep}	Deprivation cost for PhC p.
c_p^{sup}	PhC p price at suppliers.
c_p^{DH}	PhC p price at DH.
c_p^{P}	PhC p price at pharmacies (emergency purchasing).
$ct_{p,m}^{SD}$	PhC p transportaion cost from suppliers to DH with TM m.
$ct_{p,m}^{DP}$	PhC p transportaion cost from DH to pharmacies with TM m.
$ct_{p,m}^{PU}$	PhC p transportaion cost from pharmacies to care units with TM m.
ce_p^{DH}	PhC p expiration cost at DH.
ce_p^{P}	PhC p expiration cost at pharmacies.
ds_s^{SD}	Distance between supplier s and DH.
ds_d^{DP}	Distance between DH and pharmacy d.
$ds_{d,u}^{PU}$	Distance between pharmacy d and care unit u.
to	Time between DH orders.
to'	Time between pharmacy orders.
$dmd_{p,u,t}$	Demand for PhC p at care unit u at time t.
sc_p^{DH}	DH capacity for PhC p.
$sc_{p,d}^{P}$	Capacity for PhC p at pharmacy d.
v	Volume of PhC p.
te_p	Length of time until initial degradation of PhC p.
ld	Lead time.
vc_m	Capacity of TM m.
ϕ_p	Expiration rate of PhC p.
$bp_{p,s}$	Binary indication related to procurement ability of PhC p at supplier s. Equals 1 if PhC p can be supplied by supplier s; 0 otherwise.
$cap_{p,s,t}$	Supplier s provision capacity for PhC p at time t.
M	A sufficiently large number.
η	Pre-defined reliability level.
ϵ	Equity parameter.
$r(t)$	Deprivation cost coefficient function.

Variables

$I_{p,t}^{DH}$	($\in \mathbb{R}_+$) Stock level of PhC p at DH at time t.
$I_{p,d,t}^{P}$	($\in \mathbb{R}_+$) Stock level of PhC p at pharmacy d at time t.
$X_{p,m,s,t}$	($\in \mathbb{R}_+$) Shipped PhC p from supplier s to DH with TM m at time t.
$Y_{p,m,d,t}$	($\in \mathbb{R}_+$) Shipped PhC p from DH to pharmacy d at time t with TM m.
$Z_{p,m,d,u,t}$	($\in \mathbb{R}_+$) Shipped PhC p from pharmacy d to care untit u with TM m at time t (emergency orders).

$Sh_{p,u,t}$ ($\in \mathbb{R}_+$) Shortage in PhC p at care unit u at time t.

$\rho_{p,s,t}$ ($\in \mathbb{B}$) Order placement indicator. Equals 1 when an order for PhC p is placed by DH from supplier s at time t; 0 otherwise.

$\rho'_{p,d,t}$ ($\in \mathbb{B}$) Order placement indicator. Equals 1 when an order for PhC p is placed by Pharmacy d from DH at time t; 0 otherwise.

$\delta_{p,s,t}$ ($\in \mathbb{B}$) Binary variable indicating procurement of the uth affected care unit. Equals 1 if the affected care unit is supplied with PhC p at time t; 0 otherwise.

$Tr^{SD}_{p,m,s,t}$ ($\in \mathbb{Z}_+$) TMs m required for PhC p delivery from supplier s to DH at time t.

$Tr^{DP}_{p,m,d,t}$ ($\in \mathbb{Z}_+$) TMs m required for PhC p delivery from DH to pharmacy d at time t.

$Tr^{PU}_{p,m,d,u,t}$ ($\in \mathbb{Z}_+$) TMs m required for PhC p delivery from pharmacy d to care unit u at time t.

The objective function of the joint chance constrained pharmaceutical supply chain model (JCC-PSCM) reads as follows.

$$\textbf{JCC-PSCM: } \min \ \mathbf{F}^O(\mathcal{X}) + \mathbf{F}^D(\mathcal{X}). \tag{1a}$$

$$\begin{aligned}\mathbf{F}^O(\mathcal{X}) = &\sum_{p,t} I^{DH}_{p,t}\, ch^{DH}_p + \sum_{p,d,t} I^{P}_{p,d,t} ch^{P}_p + \sum_{p,m,s,t} X_{p,m,s,t} c^{sup}_p \\ &+ \sum_{p,m,d,t} Y_{p,m,d,t} c^{DH}_p + \sum_{p,m,d,u,t} Z_{p,m,d,u,t} c^{P}_p \\ &+ \sum_{p,t:t\geq te_p} \phi_p I^{DH}_{p,t}\, ce^{DH}_p + \sum_{p,d,t:t\geq te_p} \phi_p I^{P}_{p,d,t} ce^{P}_p \\ &+ \sum_{p,m,s,t} Tr^{SD}_{p,m,s,t}\ ct^{SD}_{p,m}\ ds^{SD}_s \\ &+ \sum_{p,m,d,t} Tr^{DP}_{p,m,d,t}\ ct^{DP}_{p,m}\ ds^{DP}_d \\ &+ \sum_{p,m,d,u,t} Tr^{PU}_{p,m,d,u,t}\ ct^{PU}_{p,m}\ ds^{PU}_{d,u}. \end{aligned} \tag{1b}$$

$$\mathbf{F}^D(\mathcal{X}) = \sum_t r(t) \Bigg[\sum_{p,u} dmd_{p,u,t}(1-\delta_{p,u,t}) + \sum_{p,u} \delta_{p,u,t} Sh_{p,u,t} \Bigg]. \tag{1c}$$

The objective function of the model consists of two components: (i) the operational cost of the supply chain, denoted as $\mathbf{F}^O(\mathcal{X})$, and ($ii$) the deprivation cost, denoted as $\mathbf{F}^D(\mathcal{X})$.

The operational cost in (1b) encompasses various factors such as holding costs, expiration costs, purchasing costs, and transportation costs. These costs reflect the expenses associated with managing the supply chain, including inventory maintenance, procurement activities, and transportation of pharmaceuticals. By incorporating these operational costs into the objective function, the model aims to optimize the efficiency and cost-effectiveness of the supply chain operations. On the other hand, the deprivation cost in (1c) represents the cost incurred when the demand for a specific pharmaceutical during a specific timeframe is not fully met. It quantifies the economic impact or penalty resulting from unfulfilled demand. The function $r(t) = 3t$ is defined as a deprivation cost coefficient function [12]. Minimizing the deprivation cost becomes a critical objective as it helps ensure fairness in the distribution of pharmaceuticals and mitigate the negative consequences of unmet demand. By minimizing the deprivation cost, the model strives to improve the overall performance and reliability of the supply chain in meeting the demands of the affected care units.

The model constraints are represented as follows.

$$I^{DH}_{p,t} = (1-\phi_p) I^{DH}_{p,t-1} + \sum_{m,s} X_{p,m,s,t-ld} - \sum_{m,d} Y_{p,m,d,t}, \quad \forall p, t \in \{ld, \ldots, T\} \tag{2}$$

Constraint (2) maintains the balance of the PhC stock level at the DH during period t. This constraint guarantees that stored pharmaceuticals do not exceed their expiration date, and it asserts that the inventory level at the DH is determined by adding the orders received from suppliers to the stock level from the previous period, without including the orders dispatched to the pharmacies.

$$I^{P}_{p,d,t} = (1-\phi_p) I^{P}_{p,d,t-1} + \sum_{m} Y_{p,m,d,t-1} - \sum_{m,u} Z_{p,m,d,u,t}, \quad \forall p, d, t \in \{1, \ldots, T\} \tag{3}$$

Constraint (3) serves as an inventory balance constraint specifically for the pharmacies. Its purpose is to ensure that the stock level at each period is equivalent to that of the previous one. This constraint achieves this balance by incorporating the incoming flows from the DH and excluding the outgoing flows to the care units.

$$\mathbb{P}\Big(\sum_{m,d} Z_{p,m,d,u,t} + Sh_{p,u,t} \geq dmd_{p,u,t}, \quad \forall u \Big) \geq \eta, \ \forall p, t \tag{4}$$

Constraint (4) introduces JCCs for the supply and demand balance. Symbol $\mathbb{P}$ denotes the probability function associated with these constraints. In general, chance constraints enforce the selected constraints to hold with a determined confidence level η. This limitation induces risk-averse formulation and increases reliability. Compared to SCCs that satisfy the confidence level for each constraint, the JCCs impose the prerequisite that a collection of constraints achieves a collective satisfaction of the confidence level. In particular, JCC (4) stipulates that pharmacies fulfill the demand of patients for PhCs during each period. However, it acknowledges that the demand from patients may not

always be fully met, resulting in a shortage. To account for this shortfall, the model incorporates a high cost for shortages. By assigning a significant cost to shortages, the model aims to deter the accumulation of shortages and encourages the effective allocation of pharmaceuticals to meet patient demand as closely as possible. This JCC is formulated to guarantee a global reliability level for the delivery of pharmaceuticals for all affected care units [40], [41], [42].

$$I^{DH}_{p,t} v_p \leq sc^{DH}_p, \quad \forall p, t \tag{5}$$

By imposing constraint (5), the model guarantees that the DH can effectively accommodate the PhCs without exceeding its designated storage size.

$$I^{P}_{p,d,t} v_p \leq sc^{P}_{p,d}, \quad \forall p, d, t \tag{6}$$

Constraint (6) sets a defined threshold for the PhCs stored at the pharmacies. This constraint states that collective quantity of pharmaceuticals retained at each pharmacy should not exceed the pharmacy's maximum capacity pertaining to a specific PhC.

$$\sum_{m,d} Y_{p,m,d,t} \leq I^{DH}_{p,t-1} + \sum_{m,s} X_{p,m,s,t-ld}, \ \forall p, t \in \{ld, \ldots, T\} \tag{7}$$

Constraint (7) enforces a balance at the DH between the outgoing flows to the pharmacies and the available stock of PhCs, including those received from suppliers. Put simply, this constraint ensures that the quantity of pharmaceuticals leaving the DH to the pharmacies does not exceed the available stock including PhCs inside the DH and the ones procured by the suppliers.

$$\sum_{m,u} Z_{p,m,d,u,t} \leq I^{P}_{p,d,t-1} + \sum_{m} Y_{p,m,d,t-ld}, \quad \forall p, d, t \in \{ld, \ldots, T\} \tag{8}$$

Constraint (8) signifies that the maximum pharmaceutical quantities dispatched to the care units is constrained by the available inventory. By considering this constraint alongside the previous one (Constraint (7)), it becomes apparent that a harmonious balance is achieved throughout the entirety of the supply chain.

$$\sum_{m} X_{p,m,s,t} \leq cap_{p,s,t}, \quad \forall p, s, t \tag{9}$$

Constraint (9) ensures that the amount of PhCs received from suppliers does not exceed the maximum capacity of each supplier. This restriction promotes effective supplier management and prevents overloading of the suppliers' capacities.

$$\sum_{m} X_{p,m,s,t} \ v_p \leq sc^{DH}_p \rho_{p,s,t}, \quad \forall p, s, t \tag{10}$$

Constraint (10) governs the delivery process to the DH, ensuring that deliveries from suppliers are accepted based on their capability to provide a specific PhC. Furthermore, this constraint sets a limit on the maximum volume of procurement deliveries from each supplier during period t, ensuring that it does not exceed the volume capacity of the DH for the corresponding PhC.

$$\rho_{p,s,t} \leq bp_{p,s}, \quad \forall p, s, t \tag{11}$$

In essence, Constraint (11) evaluates and determines the feasibility of each supplier to acquire a specific PhC based on the value of the associated parameter. If the parameter is set to 1, it signifies that the supplier possesses the capability to procure a specific PhC at that particular period.

$$\sum_{\tau=t}^{t+to} \rho_{p,s,\tau} \leq 1, \quad \forall p, s, t \tag{12}$$

Constraint (12) outlines the ordering frequency for the DH when procuring from each supplier and for each PhC.

$$\sum_{m} Y_{p,m,d,t} \ v_p \leq sc^{P}_{p,d} \rho'_{p,d,t}, \quad \forall p, s, t \tag{13}$$

Constraint (13) ensures that the volume of PhCs received by each pharmacy remains within the limitations of its storage capacity.

$$\sum_{\tau'=t}^{t+to'} \rho'_{p,s,\tau'} \leq 1, \quad \forall p, s, t \tag{14}$$

Constraint (14) defines a fixed time period for each pharmacy to place orders for a particular PhC, ensuring that orders are made every to' days.

$$Tr^{SD}_{p,m,s,t} \geq \frac{X_{p,m,s,t} \ v_p}{vc_m}, \quad \forall p, s, t \tag{15}$$

Constraint (15) ensures that a sufficient number of vehicles are allocated for transportation based on the volume of PhCs being supplied. It accounts for the capacity constraints of each vehicle type, ensuring that the volume of PhCs does not exceed the capacity of a single vehicle. By adhering to this constraint, the model guarantees the efficient transportation of PhCs from suppliers to the DH, optimizing the utilization of vehicles while respecting their capacity limits.

$$Tr^{DP}_{p,m,d,t} \geq \frac{Y_{p,m,d,t} \ v_p}{vc_m}, \quad \forall p, m, d, t \tag{16}$$

Constraint (16) outlines the necessary quantity of vehicles to transport deliveries from the DH to the pharmacies, similar to Constraint (15).

$$Tr^{PU}_{p,m,d,u,t} \geq \frac{Z_{p,m,d,u,t} \ v_p}{vc_m}, \quad \forall p, m, t, d, u : (d \neq u) \tag{17}$$

Constraint (17) ensures that sufficient TMs are available to facilitate the urgent and time-sensitive transportation of PhCs from pharmacies to care units at other hospitals when emergency situations arise.

$$\sum_{m,d} Z_{p,m,d,u,t} \leq M \ \delta_{p,u,t}, \quad \forall p, u, t \tag{18}$$

By checking the delivery status in Constraint (18), the model ensures that the care units receive the necessary pharmaceutical supplies. This information is essential for calculating the deprivation cost, which reflects the impact or cost associated with the lack of deliveries to the care units.

$$\left| \frac{\sum_{m,d} Z_{p,m,d,u,t}}{dmd_{p,u,t}} - \frac{\sum_{m,d} Z_{p,m,d,u',t}}{dmd_{p,u',t}} \right| \leq \epsilon \quad \forall p, u \neq u', t \tag{19}$$

Constraint (19) imposes the condition that distinct affected care units should strive to achieve the highest possible similarity in terms of rates of demand satisfaction. This constraint enforces horizontal equity and it is designed to ensure a fair and equitable distribution. By employing the equity constraint, it is ensured that the disparity in meeting the demands of different care units remains below or equal to a small predetermined threshold, denoted as ϵ.

IV. SOLUTION APPROACH

This section entails the development of an equivalent reformulation for the suggested MINLP model, followed by the transformation of the model into its MILP counterpart. Additionally, the application of unsupervised learning methodologies for clustering pharmaceutical products is introduced. These procedures are essential to guarantee the achievement of an optimal solution with high accuracy for the pharmaceutical supply chain model. The accuracy is dependent on the number of generated scenarios.

A. EQUIVALENT REFORMULATION

The mathematical model presented in the previous section comprises certain terms that exhibit nonlinearity or nonconvexity, thereby requiring reformulations to transform the problem into a convex optimization framework. Specifically, equation (1c) includes a bilinear term with multiplication of binary and continuous variables, requiring a reformulation to handle its nonlinearity. Moreover, chance constraint (4) is both nonconvex and nonlinear, posing challenges in model tractability. Furthermore, constraint (19) includes an absolute function, which necessitates appropriate reformulation to ensure convexity in the optimization problem. In order to address nonlinearity in equation (1c), a continuous relaxation is provided by introducing a new vector of variables Δ. Accordingly, the formulation is given below [43], [44]:

$$\Delta_{p,u,t} \leq M\ \delta_{p,u,t}, \quad \forall p, u, t \tag{20a}$$
$$\Delta_{p,u,t} \leq Sh_{p,u,t}, \quad \forall p, u, t \tag{20b}$$
$$\Delta_{p,u,t} \geq Sh_{p,u,t} - M(1 - \delta_{p,u,t}). \quad \forall p, u, t \tag{20c}$$
$$\mathbf{F}^D(\mathcal{X}) = \sum_t r(t) \left[\sum_{p,u} dmd_{p,u,t}(1 - \delta_{p,u,t}) + \sum_{p,u} \Delta_{p,u,t} \right]. \tag{20d}$$

Accordingly, an equivalent reformulation of constraint (19) is presented in the following form.

$$-\epsilon \leq \frac{\sum_{m,d} Z_{p,m,d,u,t}}{dmd_{p,u,t}} - \frac{\sum_{m,d} Z_{p,m,d,u',t}}{dmd_{p,u',t}} \leq \epsilon, \quad \forall p, u \neq u', t \tag{21}$$

In order to reformulate the JCC (4), a proposed approach utilizes Boolean programming, as presented by [42], while highlighting its advantages in comparison to the traditional scenario-based reformulation technique [40]. Although the suggested formulation demonstrates satisfactory reliability performance across the entire system, alternative reformulation approaches are necessary due to the inherent difficulty of obtaining numerical solutions using standard optimization solvers. The convexity of the feasible set significantly affects the computational complexity of stochastic problems related to JCCs. Consequently, to solve chance constrained problems, researchers explore three main solution methods:

1) Reference [45] outlines the first approach, which centers on p-efficiency. This approach provides two options for problem-solving: the utilization of an equivalent mixed-integer programming (MIP) problem or the adoption of a decoupled reformulated problem derived from the stochastic model. Various techniques, such as convexification, primal-dual algorithms, or the augmented Lagrangian algorithm, can then be employed to address the reformulated problem.
2) The second approach involves replacing the original high-dimensional stochastic problem with a mixed-integer programming (MIP) problem. This is achieved by assigning a binary variable to each possible realization of the random vector, as outlined in [46].
3) The third approach involves deriving safe convex approximations, acknowledging that the optimal solution may not necessarily be in close proximity to the exact and globally optimal solution, as discussed in [47].

The Boolean reformulation method, as presented in [42], offers an effective solution to overcome the aforementioned challenges and enables a rapid solution to the stochastic optimization model. The general form of a probabilistically-constrained optimization model is shown below:

$$\min\ q^T X \tag{22a}$$
$$\text{s.t. } AX \geq b \tag{22b}$$
$$\mathbb{P}(h_j X \geq \xi_j, \quad \forall j \in \mathcal{J}) \geq \eta \tag{22c}$$
$$X \geq 0 \tag{22d}$$

In the general JCC formulation presented above, X is the vector of decison variables, q is the vector of objective function coefficients, A and h are technology matrices, and b and ξ are the right-hand side values. The assumption is made that the vector of random variables ξ follows a

random distribution of $|\mathcal{J}|$ dimensions with a finite support, while the other parameters are deterministic values. It is worth mentioning that $|\mathcal{J}|$ represents the cardinality of set $\mathcal{J}$. As mentioned before, the symbol $\mathbb{P}$ represents the probability measurement, while η represents the reliability level. Constraint (22c) represents a JCC that is non-convex and poses significant computational intricacy.

1) BOOLEAN PROGRAMMING REFORMULATION

The proposed approach introduces a methodology that involves binarizing the probability distribution function (PDF) of the random variable vector ξ. The Boolean algorithm for JCC reformulation consists of three main steps: constructing the recombination set, binarizing the Probability Density Function (PDF), and representing the feasible region using partially-defined Boolean functions. A summary of the Boolean algorithm can be found in [42], and for a comprehensive understanding of the algorithm, readers are referred to it and the cited references therein. A brief overview of the algorithm is presented accordingly.

Initially, each realization ω_j^k of the random variable ξ_j is checked for being a cut point. This condition is expressed as follows:

$$\{\omega_j^k\} \cup C_i, \quad \text{if } F_j(\omega_j^k) \geq \eta. \tag{23}$$

C_i represents the set of cut points associated with the jth random variable and F_j denotes marginal probability distribution function of ξ_j. The condition examines the univariate quantile of each realization and compares it against the pre-defined reliability level. Subsequently, the set of recombinations ($\tilde{\Omega}$) is constructed utilizing the set of cut points according to the following procedure:

$$\tilde{\Omega} = C_1 \times C_2 \times \ldots \times C_{|\mathcal{I}|}. \tag{24}$$

In the subsequent step, realizations within the set of recombinations are classified according to the concept of p-sufficiency. This concept involves dividing the combination set into two distinct sets: p-sufficient set (Ω^+) and p-insufficient set (Ω^-). Realizations are categorized as follows:

$$\omega_j^k \in \tilde{\Omega} : \begin{cases} \omega_j^k \in \Omega_j^+ (p\text{-sufficinet}), & \text{if } F_j(\omega_j^k) \geq \eta \\ \omega_j^k \in \Omega_j^- (p\text{-insufficinet}), & \text{otherwise} \end{cases} \tag{25}$$

The binarization process of the PDF is undertaken next to construct the feasible region. The binarization is carried out with respect to the cut points. In essence, each realization ω_j^k is mapped to the binary vector $\beta_j^k = [\beta_{i,1}^k, \ldots, \beta_{i,n_j}]$. The binarization condition is proposed as:

$$c_{ij} \in C_i : \begin{cases} \beta_{ij}^k = 1, & \text{if } \omega_j^k \geq c_{ij} \\ \beta_{ij}^k = 0, & \text{otherwise,} \end{cases} \quad i = 1, \ldots, n_j,\ j \in \mathcal{J} \tag{26}$$

Following this procedure, the JCC problem (22a)-(22d) can be transformed into its equivalent MILP formulation, represented as:

$$\min\ q^T X \tag{27a}$$
$$\text{s.t. } A\,X \geq b \tag{27b}$$
$$h_j X \geq \sum_{i=1}^{n_j} c_{i,j} U_{i,j}, \quad \forall j \in \mathcal{J} \tag{27c}$$
$$\sum_{j \in \mathcal{J}} \sum_{i=1}^{n_j} \beta_{i,j}^k U_{i,j} \leq |\mathcal{J}| - 1, \ \forall k \in \Omega_B^- \tag{27d}$$
$$\sum_{i=1}^{n_j} U_{i,j} = 1, \quad \forall j \in \mathcal{J} \tag{27e}$$
$$U \in \{0,1\}^{i \times j}, \ X \geq 0 \tag{27f}$$

where k is the index for scenarios. Thus, the JCC (4) is reformulated as follows:

$$\sum_{m,d} Z_{p,m,d,u,t} + Sh_{p,u,t} \geq \sum_{i=1}^{n_u} c_{i,u} U_{i,u}, \quad \forall u \in \mathcal{U}, p, t \tag{28a}$$
$$\sum_{u \in \mathcal{U}} \sum_{i=1}^{n_u} \beta_{i,u,p,t}^k U_{i,u,p,t} \leq |\mathcal{U}| - 1, \quad \forall k \in \Omega_B^-, p, t \tag{28b}$$
$$\sum_{i=1}^{n_u} U_{i,u,p,t} = 1, \quad \forall u \in \mathcal{U}, p, t \tag{28c}$$
$$U \in \{0,1\}^{i \times u} \tag{28d}$$

where $|\mathcal{U}|$ defines the cardinality of the set of care units. Equations (28a)-(28d) represent an exaxt reformulation for JCC (4) with a convex feasible region. Consequently, the equivalent MILP counterpart of the JCC-PSCM with Boolean reformulation is provided below:

BR-PSCM : min (1b) + (20d).
s.t. (2) − (3); (28a) − (28d);
(5) − (18); (20a) − (20c); (21).

Based on this reformulation one can conclude that the feasible solutions of BR-PSCM are almost indistinguishable from JCC-PSCM for a large number of scenarios.

2) SCENARIO-BASED REFORMULATION

Another method used to reformulate the joint chance constraints is the scenario-based reformulation [46]. This method is used in our study to compare the capabilities of Boolean reformulation with other methods. The main challenge with the conventional scenario approach used to solve chance-constrained problems is that it requires introducing a binary variable for each scenario. This can result in a loose relaxation when dealing with continuous variables. Furthermore, it is evident that the inclusion of a larger number of binary variables significantly increases the runtime of the model and may even lead to intractability. The

scenario-based reformulation of the problem (22a)-(22d) is:

$$\min\ q^T X \tag{29a}$$
$$\text{s.t. } A\,X \geq b \tag{29b}$$
$$h_j X \geq \omega_j^k (1-\theta^k), \quad \forall j \in \mathcal{J},\ \forall k \in \Omega \tag{29c}$$
$$\sum_{k\in\Omega} p^k \theta^k \leq 1-\eta \tag{29d}$$
$$X \geq 0, \theta \in \{0,1\}^k \tag{29e}$$

Here, p^k represents the probability associated with each scenario and Ω defines the set of scenarios. Thus, the scenario-based reformulation of the JCC (4) is given by:

$$\sum_{m,d} Z_{p,m,d,u,t} + Sh_{p,u,t} \geq \omega_u^k (1-\theta^k), \quad \forall p,u,t,k \in \Omega \tag{30a}$$
$$\sum_{k\in\Omega} p_{p,t}^k \theta_{p,t}^k \leq 1-\eta \quad \forall p,t \tag{30b}$$
$$\theta \in \{0,1\}^k \tag{30c}$$

Accordingly, the scenario based reformulation of JCC-PSCM reads as follows.

SR-PSCM : min (1*b*) + (20*d*).
s.t. (2) − (3); (30*a*) − (30*c*);
(5) − (18); (20*a*) − (20*c*); (21).

The scenario generation process is carried out according to a multi-variate Gaussian distribution representing the demand for PhCs [48]. This reformulation also ensures that the SR-PSCM yields almost the same feasible solutions as the original JCC-PSCM for a high number of scenarios.

B. UNSUPERVISED LEARNING ALGORITHMS

This section aims to introduce clustering algorithms that are employed to effectively group pharmaceutical products and establish the PhCs. The grouping is a common practice in pharmaceutical supply chain management which allows handling similar products together. The results obtained from these algorithms are used as an input for the defined mathematical models. The utilization of clustering algorithms is driven by the imperative to address the shortcomings of current methods for commodity grouping. Scholars [49], recognize the inherent diversity within pharmaceutical products, or formulary, and predominantly rely on techniques that are expert driven and usually labor-intensive to devise grouping algorithms.

Among these methods, the ABC analysis has gained significant popularity [18], [50]. This established technique follows the Pareto 80/20 rule and tactically categorizes commodities according to their value and volume. Notably, commodities with higher value but lower volume are given a higher rank in the grouping process, highlighting their significance and priority. Originally developed for inventory control and management studies, this technique has found practical applications beyond their initial scope and can be effectively employed in mathematical modeling as well. However, when dealing with medicines, it is important to acknowledge that it fails to include diverse characteristics, such as size, volume, priority, storage condition, and more. These multiple attributes may present a challenge for decision-makers in comprehensively analyzing medicines, and traditional techniques often fall short in considering and incorporating such complexities.

To address these challenges, it is essential to embrace methodologies that can encompass the diverse features of pharmaceuticals and leverage tools that optimize categorization based on these features. Consequently, this article introduces five unsupervised learning algorithms that possess the capabilities required for pharmaceutical categorization. The selected algorithms are Density-Based Spatial Clustering of Applications with Noise (DBSCAN), Gaussian Mixture Models (GMM), K-means, hierarchical clustering (HC), and spectral clustering (SC). In the interest of conciseness and maintaining focus on the original problem proposed in this article, the detailed explanations of GMM, K-means, and Hierarchical clustering algorithms are deferred to [51], [52], and [53] and the referenced sources. For the purpose of this section, we will provide short explanations for DBSCAN and Spectral clustering algorithms

To the best of the author's knowledge, this article represents a pioneering effort in utilizing various clustering algorithms for the purpose of grouping pharmaceuticals and vaccines. While previous research, such as [34], employed the K-means algorithm for pharmaceutical product classification, this study builds upon that foundation by incorporating four additional methods and conducting a comparative analysis of the results.

1) DBSCAN ALGORITHM

The algorithm, originally proposed in [54], is known as the DBSCAN algorithm. The DBSCAN algorithm starts by selecting an unvisited point and expands a cluster around it by identifying all reachable points within a specified distance threshold, denoted as ϵ. If the number of points within this distance threshold is greater than or equal to a pre-defined minimum points threshold, referred to as MinPts, the algorithm recursively expands the cluster to include these points. This process continues until no more points can be added to the cluster. Subsequently, the algorithm moves on to the next unvisited point and repeats the process until all points have been visited. Points that do not belong to any cluster and do not have a sufficient number of neighboring points within ϵ are considered noise points.

2) SPECTRAL CLUSTERING

Spectral Clustering, introduced in [55], initiates by constructing a similarity matrix that captures the pairwise similarities between data points. Subsequently, the normalized Laplacian matrix is computed to capture the underlying structure of

TABLE 2. Results related to centroids of the clustering algorithms.

Method	Name	Cluster Size	Centroid			
			Demand	Priority	Volume (m^3)	Preservation Temperature ($^\circ C$)
HC	PhC A	97	106.7	2.206	0.31	15-25
	PhC B	17	425.5	2.12	0.0013	15-25
	PhC C	402	8.86	1.65	0.44	15-25
	PhC D	45	21.336	2.267	0.152	2-8
DBSCAN	PhC A	8	17.63	1.75	22.11	15-25
	PhC B	232	32.43	1	0.044	15-25
	PhC C	53	46.47	3	0.06	15-25
	PhC D	192	39.93	2	0.062	15-25
	PhC E	31	108.15	4	0.2	15-25
	PhC F	45	21.336	2.267	0.152	2-8
GMM	PhC A	240	51.46	2.404	0.0046	15-25
	PhC B	53	26.05	2.132	3.87	15-25
	PhC C	223	33.25	1	0.009	15-25
	PhC D	45	21.336	2.267	0.152	2-8
SC	PhC A	44	10.066	2.022	2.83	15-25
	PhC B	268	9.87	1.68	0.193	15-25
	PhC C	204	190.67	1.83	0.158	15-25
	PhC D	45	21.336	2.267	0.152	2-8
K-means	PhC A	425	11.448	1.679	0.4135	15-25
	PhC B	17	425.52	2.118	0.00135	15-25
	PhC C	74	122.421	2.216	0.0362	15-25
	PhC D	45	21.336	2.267	0.152	2-8

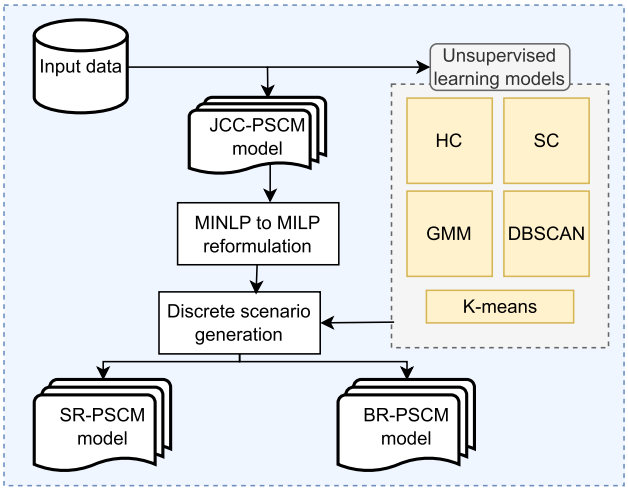

FIGURE 2. The solution approach work flow.

the data. By computing the eigenvectors associated with the smallest eigenvalues of the Laplacian matrix, a low-dimensional representation of the data is obtained. The rows of this matrix are then subjected to clustering using a standard algorithm, such as K-means, to assign data points to clusters.

The obtained clusters using the aforementioned methods are presented in Table 2, and a summary of the solution approach procedure is represented in Figure 2.

V. NUMERICAL RESULTS

To evaluate the efficacy of the proposed approach, a case study was conducted on hospitals in Tehran during the early phases of the COVID-19 outbreak. Data from three hospitals were collected for testing the model, with the specific details and model parameters provided in [34]. The fundamental solution approach unfolds as follows. The results gleaned from unsupervised learning techniques is employed as foundational input for both the deterministic model, and for generating scenarios within the SR-PSCM and BR-PSCM. The deterministic model is established by replacing the random variable by its expected value. Further, the scenarios are generated accordingly, accompanied by the application of necessary reformulation techniques. The models are formulated in mathematical optimization software AMPL, interfaced with a state-of-the-art optimization solver Gurobi 10.0.0. The models are solved on a PC with an Intel i7-7700 processor, 3.6 GHz core speed, and 16 GB of RAM. The results and findings of the analysis are presented in several sections. Section V-A offers an overview of the general outcomes of the model and compares different reformulation approaches. In Section V-B, the model's ability to absorb disruptions and enhance system resiliency is examined. A sensitivity analysis on equity parameters is presented in Section V-C, exploring their impact on the model's outcomes. Finally, Section V-D provides managerial and practical insights derived from the study. By structuring the findings in these sections, a comprehensive evaluation of the proposed approach's effectiveness in the context of Tehran hospitals during the initial stages of the COVID-19 outbreak is presented.

A. GENERAL OUTCOMES

In this section, the results from different clustering methods are tested on the deterministic model. The most suitable

TABLE 3. Optimal objective values pertaining to the objective function (1a) using various clustering algorithms for the deterministic model.

Methods	HC	DBSCAN	GMM	SC	K-means
Objective Value ($)	2,824,960	2,687,411	2,669,220	2,539,893	2,922,420

clustering approach for the pharmaceutical commodities is selected, and the resulting clusters are then utilized as input for the scenario generation in SR-PSCM and BR-PSCM. Subsequently, the stochastic model with JCCs is solved using these clusters. The optimal results obtained after deterministic optimization are presented in Table 3.

The results presented in Table 3 clearly demonstrate that clustering pharmaceuticals based on the SC algorithm yields a superior solution. However, it should be noted that this does not necessarily imply that the SC algorithm outperforms the other methods in all scenarios. Rather, it indicates that for our specific case study, incorporating the SC algorithm for clustering implementation is the most effective approach. This observation can be attributed to the particular structure of the pharmaceutical data utilized in this study and underscores the ability of the SC method to generate more homogeneous clusters. Thus, the results obtained from the SC algorithm are utilized to implement the SR-PSCM and BR-PSCM, leveraging the strengths of this clustering approach in our analysis. It is worth noting that a dedicated cluster is created specifically for cold pharmaceuticals before constructing the remaining clusters. This decision is based on the understanding that the low number of cold pharmaceuticals does not warrant further partitioning or subdivision into additional clusters. By treating cold pharmaceuticals as a distinct cluster, we acknowledge their unique characteristics and ensure that they receive appropriate consideration within the clustering process.

As mentioned earlier, both the Boolean programming and scenario-based reformulation approaches were applied to address the JCCs. The results obtained from the optimization models are presented in Table 4 and Table 5. Upon initial observation, it is evident that Boolean reformulation exhibits a clear advantage over the scenario-based reformulation. The Boolean algorithm outperforms the scenario-based reformulation in terms of runtime, number of constraints, and number of binary variables. These factors play a crucial role in ensuring the tractability of an optimization problem. Moreover, Boolean programming enables the utilization of a significantly larger number of scenarios, thereby allowing for a more comprehensive capture of the model's uncertain characteristics. It is worth mentioning that the scenario-based algorithm failed to converge to the optimal solution even after four hours of runtime for the case of 1000 and 10,000 scenarios. The optimal objective values in Table 5 are adopted from boolean reformulation as both methods provide highly accurate reformulations for a large number of scenarios.

TABLE 4. Results related to BR-PSCM.

Scenarios	Constraints	Binary Variables	Runtime	Objective Value
100	33,056	1,620	656	2,553,493
1000	33,056	1,620	671	2,552,940
10,000	33,059	1,620	674	2,553,862

TABLE 5. Results related to SR-PSCM.

Scenarios	Constraints	Binary Variables	Runtime	Objective Value
100	132,224	2,430	12,657	2,553,493
1000	614,730	10,683	-	2,552,940
10,000	104,234	86,628	-	2,553,862

B. RESILIENCE ANALYSIS

In this section, the resilience of the supply chain against disruptions in the supplier side of the network is assessed. The robust design of the supply chain incorporates backup suppliers to mitigate the impact of perturbations in the supplier side. To analyze the system's response to supplier unavailability, the first supplier in the case of Tehran hospitals is assumed to be subject to a crisis. The objective is to examine the system's ability to maintain the service level under such circumstances. Specifically, the first supplier is responsible for procuring PhC-A and PhC-C. The disruption is assumed to occur from day one to day 15.

The results depicted in Figure 5 illustrate the system's shortage in procuring different PhCs as a metric for the service level. A comparison is made between the shortage levels during normal operation and the disrupted stage to identify the effects of the disruption. Interestingly, Figure 5a demonstrates that PhC-A is not affected by the disruption in the first supplier. Despite the fact that the first supplier is responsible for procuring PhC-A, the combination of other suppliers compensates for the first supplier's inability to accept orders. Consequently, the disruption is mitigated and remains responsive in terms of PhC-A procurement.

The system's ability to cope with disruptions in the other three pharmaceutical commodities (PhCs) differs from its response to PhC-A. While the system collaboratively works to mitigate the incurred contingencies, it struggles to meet patient demands for the remaining PhCs. Despite the first supplier's failure to fulfill its share in PhC-A and PhC-C procurement, its impact extends to lower service levels in acquiring PhC-B and PhC-D, in addition to PhC-C.

The disruption in the first supplier causes a minor disruption in meeting patient demand for PhC-B and PhC-D (see Figures 5b and 5d). The shortage period for supplying PhC-B extends by four days, while for PhC-D it increases by two days compared to the normal condition. However, the supply of PhC-C, shown in Figure 5d, is severely affected, experiencing both an extended shortage period of five days and an increased shortage amount.

C. EQUITY AND SENSITIVITY

To demonstrate the advantages of incorporating equity metrics in the supply chain model, the results are presented in the form of a sensitivity analysis, as depicted in Figures 4 and 3. This analysis aims to highlight the contribution of equity metrics in enhancing fairness throughout the system, while examining their impact on fluctuation. Figure 3 illustrates that as the constraint (19) on equity becomes less stringent (looser), the optimal total cost decreases. However, it is important to note that this reduction in cost comes at a trade-off. Figure 4 demonstrates that by loosening the constraint (19) through increasing ϵ, the level of deprivation increases, resulting in less equity within the system.

According to Figure 3, it can be observed that as the restriction on constraint (19) gradually relaxes, the rate of decrease in the optimal total cost becomes more pronounced. This suggests that loosening the constraint allows for greater cost reduction. In contrast, Figure 4 demonstrates an increasing rate of deprivation cost as the value of ϵ increases. This indicates that as the constraint is relaxed, leading to a higher tolerance for inequity, the level of deprivation and consequently the loss of equity within the system also increases at a faster rate.

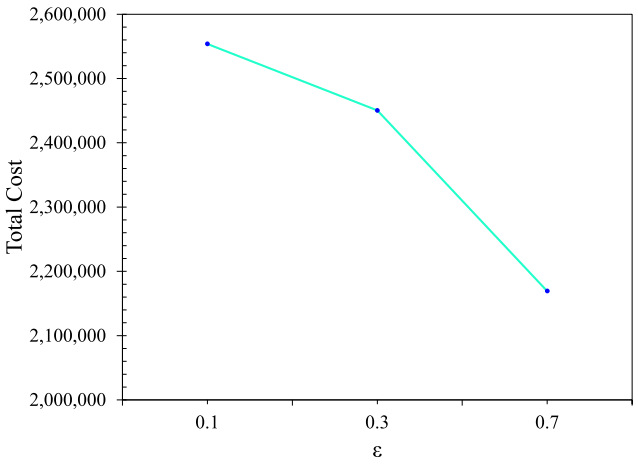

FIGURE 3. Total cost sensitivity to equity parameter ϵ.

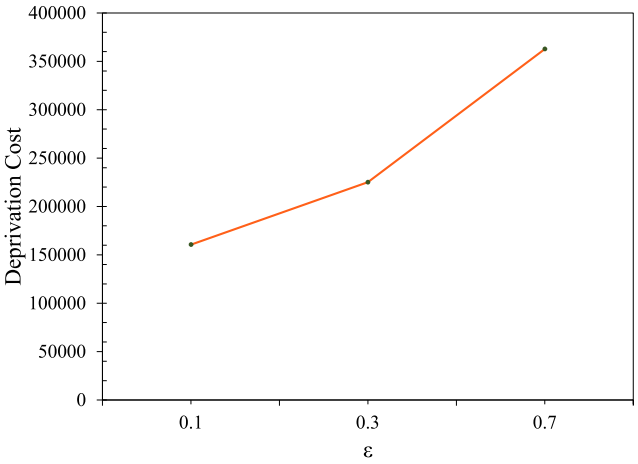

FIGURE 4. The change in deprivation cost with regards to varying equity parameter ϵ.

D. MANAGERIAL AND PRACTICAL INSIGHTS

According to the elicited results four insights are captured:

1) In the context of HILP disasters, it is crucial to give significant attention to the tradeoff between system cost and equity. Achieving higher levels of equity can have a substantial impact on saving lives and ensuring fair resource allocation. The results of the analysis highlight that even with a relatively small increase of approximately 18% in the total cost, the equity level can be significantly improved. Specifically, when transitioning from a lower level of equity ($\epsilon = 0.7$) to a more acceptable level ($\epsilon = 0.1$), a modest increase in cost demonstrates the potential to bring about substantial gains in equity. This emphasizes the importance of considering equity as a vital factor alongside cost considerations in decision-making processes.
2) The selection of the clustering method plays a crucial role in shaping the effectiveness of supply chain operations, particularly in terms of inventory management and control. Decision-makers should go beyond traditional clustering methods and embrace more advanced techniques to fully capture the unique characteristics of pharmaceuticals and vaccines. By doing so, they can better understand the underlying patterns and relationships within the supply chain, leading to more informed decision-making and improved inventory management practices. Expanding the range of clustering tools beyond conventional approaches enables decision-makers to leverage advanced methods that can effectively handle the complexities and specific requirements of pharmaceutical and vaccine supply chain. This strategic approach empowers organizations to optimize their inventory control strategies and enhance overall supply chain performance.
3) In the context of HILP disasters, uncertainty assumes a critical role. Decision-makers are strongly suggested to incorporate uncertain characteristics into their analysis to effectively capture the exogenous risks that pose threats to their systems. It is essential to acknowledge that HILP disasters are characterized by their infrequent occurrence and high impact, making them highly unpredictable and uncertain events. By integrating uncertainty into their analysis, decision-makers can account for the inherent variability and unknown factors associated with these disasters. This enables them to develop robust strategies, contingency plans, and risk mitigation measures to enhance the resilience and adaptability of their systems. Embracing uncertainty as a fundamental component of decision-making allows for a more comprehensive assessment of risks and aids in developing proactive measures to safeguard critical operations in the face of HILP disasters.
4) Decision-makers should be duly advised about the interdependencies that exist within their systems. It is crucial to recognize that a failure in one supplier's ability to provide certain pharmaceuticals can have

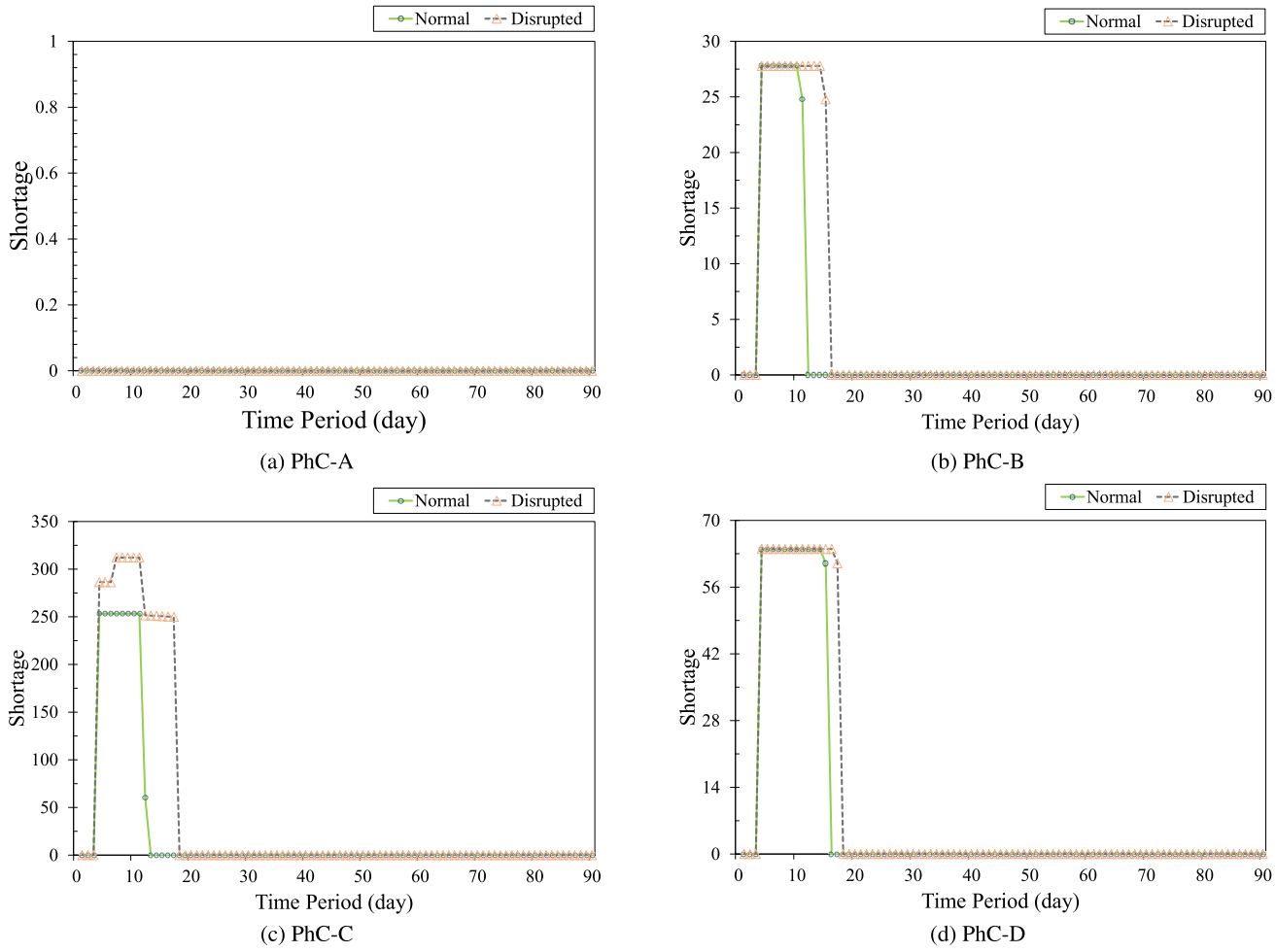

FIGURE 5. The increased deficit observed across various PhCs and time intervals during both normal and disrupted conditions.

ripple effects, causing additional disruptions in the procurement of other pharmaceuticals. These interdependencies within the supply chain network can arise due to various factors such as shared resources, common logistics routes, or dependencies on specific raw materials. Understanding these interdependencies is vital for decision-makers to effectively assess and manage risks.

VI. CONCLUSION

This paper presents a pharmaceutical supply chain planning approach for both cold and non-cold pharmaceuticals during an HILP disruption. An innovative mathematical optimization framework addresses multiple perspectives, such as expenses, service level, reliability, resiliency, and equity. The study begins with an MINLP problem and utilizes clustering methods to group pharmaceuticals and vaccines. Reformulation techniques are then proposed to convert the non-convex MINLP problem into an equivalent MILP formulation. The developed JCC reformulation methods are highlighted for their advantages, and the system's functionality is evaluated in terms of disruption absorption and cost-equity tradeoff.

The utilization of unsupervised learning algorithms in this study provides a valuable advantage in effectively grouping pharmaceuticals and vaccines. Unlike traditional grouping methods that rely on decision-maker discretion, clustering algorithms offer an automated and data-driven approach to forming groups. Through the assessment of five different algorithms, the Spectral Clustering (SC) method emerges as the optimal choice to serve as input for the optimization model. This selection is justified by the lower total cost it achieves for the entire system, thereby enhancing inventory management and control. Once the pharmaceuticals are clustered, they are utilized as input for the stochastic model, and optimal solutions are determined accordingly. In addition, the results demonstrate that the Boolean reformulation approach significantly outperforms the traditional scenario-based approach. The superiority of the Boolean approach is evident in terms of accuracy, runtime, and tractability, offering a more precise and efficient method for solving the optimization problem.

The proposed framework proves to be highly effective in mitigating the effects of HILP disruptions, offering equitable distribution of pharmaceuticals to patients in affected hospitals and penalizing any deprivation of necessary medications. The results highlight the success of the backup suppliers strategy in alleviating the disruption's impact. Additionally, the ripple effect of the disruption on other pharmaceuticals should be considered as another risk. The sensitivity analysis on equity further illuminates the tradeoff between cost and equity levels, providing valuable insights for decision-making.

Future studies can expand on the present research by incorporating additional resiliency strategies into the framework. Moreover, exploring alternative equity metrics beyond horizontal and vertical equity could lead to further analysis and enhancement of the current approach. By building upon these aspects, researchers can advance the understanding and applicability of the framework in pharmaceutical supply chain planning, contributing to more robust and comprehensive solutions in the face of disruptions.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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FARID KOCHAKKASHANI (Graduate Student Member, IEEE) received the M.Sc. degree in industrial engineering from the Sharif University of Technology, Tehran, Iran, in 2022. He is currently pursuing the Ph.D. degree in electrical engineering with the Department of Electrical and Computer Engineering, The George Washington University, Washington, DC, USA. His research interests include mathematical optimization and its applications in healthcare systems, power system planning and operation, power system reliability and resiliency, and energy economics.

VAHID KAYVANFAR having transitioned from a four-year Lecturer with the Sharif University of Technology. He is currently a Postdoctoral Research Fellow with Hamad Bin Khalifa University (Qatar Foundation). He holds editorial positions in some journals and contributes as a reviewer for more than 30 peer-reviewed journals listed in the *Web of Science* database. With a prolific academic record, he has authored more than 40 peer-reviewed journal articles, presented 20 conference proceedings, and authored two books/book chapters. He has received international acclaim, earning esteemed honors, such as acknowledgment from Iran National Elite Foundation, from 2012 to 2016, and the ARAP scholarship from A*STAR in Singapore, in 2016. His primary areas of expertise lie in logistics and supply chains, healthcare optimization, and operations management, with a notable focus on digital supply chains and sustainability.

ROBERTO BALDACCI is currently an Associate Professor of operations research with the College of Science and Engineering, Hamad Bin Khalifa University (HBKU), Doha, Qatar. Prior to joining HBKU, he was a Postdoctoral Research Associate with the Centre for Quantitative Finance, Imperial College, London, U.K., from 2000 to 2001, an Assistant Professor of operations research with the Department of Engineering Sciences and Methods (DISMI), University of Modena and Reggio Emilia, Italy, from 2001 to 2005, and an Associate Professor of operations research with the Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi" (DEI), University of Bologna, Italy, from 2005 to 2022.

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