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# Integrated planning for a global pharmaceutical supply chain: an ambidexterity perspective

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## Abstract

Based on the concept of ambidexterity, we develop a multi-objective, multi-product, and multi-period model to integrate planning for research and development (R&D) and production and distribution (P&D) in a global pharmaceutical supply chain (PSC) considering delays in the entire supply chain. We also propose robust possibilistic programming (RPP) approach to deal with the epistemic uncertainty of some critical input parameters. Applying the ambidexterity approach that emphasizes optimizing a balanced framework based on the R&D and P&D planning, our study reconciles the explorative and exploitative supply chain strategies in the context of global PSCs. The proposed integrated model can manage the inherent delays and uncertainties in the R&D processes and P&D systems via a novel, credibility-based, robust possibilistic programming model. We illustrate the application of our model using a real-world case study of one of the largest and most reputable pharmaceutical companies in Iran. The results affirm the credibility and feasibility of the proposed model when juxtaposed with a non-integrated model. Our study suggests the use of ambidexterity approach in resource allocation planning, risk management, and enhancement of performance in sophisticated settings such as global PSCs.

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## 1 Introduction

The unique characteristics of pharmaceutical products in achieving sustainable community health make global pharmaceutical supply chains (PSCs) dynamic and complex. Disruptions at any stage of a global PSC's planning and coordination can significantly impact the supply chain efficiency and directly affect human lives at the global level (Lücker & Seifert, 2017). Therefore, PSCs utilize strategies to minimize the risk of investment failures. Such strategies involve planning for research and development (R&D) processes and optimizing production and distribution (P&D) of pharmaceutical products.

Planning for R&D processes occurs in the early stages of global PSCs when the chains adopt an explorative supply chain approach to produce new pharmaceutical products. This can be seen in the cumulative R&D expenditure of a pharmaceutical company over the long term. According to Austin and Hayford (2021), investments in R&D processes in the pharmaceutical industry have a success rate of only 12% and may take up to a decade to be commercialized. The industry has experienced increased investments in the R&D activities over the past two decades (Marques et al., 2020). Prior studies proposed complex mathematical models like the random capacity planning model for clinical trials, which used a scenario-based approach (Rotstein et al., 1999), realistic risk-assessment models (Colvin & Maravelias, 2011), multi-stage, multi-period stochastic capacity planning models (Gatica et al., 2003), multi-period models for the development of new products (Jahani et al., 2017; Rogers et al., 2002), and multi-site, multi-period, multi-product capacity-planning models (Levis & Papageorgiou, 2004).

In addition, P&D planning allows the pharmaceutical industry to exploit currently developed products, market share, and solutions to responding to unprecedented changes in demand patterns, especially at the times of crisis (Marques et al., 2019; Nasrollahi & Razmi, 2021; Rekabi et al., 2021). Therefore, many companies in the pharmaceutical industry consider the P&D planning as a solution to reducing supply chain costs and risks (Guerrero et al., 2013; Liu et al., 2017). This requires the global PSCs to optimize operating models and speed up the pace of mass production and delivery in a short period of time (Gilani & Sahebi, 2022). Some prior studies, therefore, focused on exploitative strategies that demonstrate allocation-distribution optimization (Laínez et al., 2012; Sousa et al., 2011), multi-product distribution planning (Guerrero et al., 2013; Zandkarimkhani et al., 2020), or multi-period and multi-product production, distribution and capacity planning models (Kabra et al., 2013; Saracoglu et al., 2014). Some other studies applied fuzzy rule-based systems (Shakouhi et al., 2021; Zandkarimkhani et al., 2020) and possibilistic programming (Savadkoohi et al., 2018).

We discerned that many prior studies predominantly focused on one of two areas in global PSCs. They *either* examined planning for R&D processes, encapsulating the explorative approach, *or* they concentrated on P&D planning, representing the exploitative approach. This may render suboptimal solutions and increase the risk of failure across the supply chain, as both planning for R&D processes and P&D planning are interlinked and necessary (Marques et al., 2020). To bridge this research gap, the literature suggests the concept of *ambidexterity*, which refers to an organization's ability to simultaneously pursue both explorative and exploitative approaches (Junni et al., 2013).

The explorative approach is associated with the search, experimentation, and R&D processes. However, it may require vast investment in the early stages of a product's lifecycle (Rojo et al., 2016). It will develop the long-term supply chain's objective to improve profitability (Kristal et al., 2010). In contrast, an exploitative approach is related to continuous improvements, innovative execution, and waste reduction through optimal operational costs that enhance supply chain efficiency (Blome et al., 2013). This study aims to propose an integrated planning model for complex R&D processes and P&D systems that can help optimize explorative and exploitative approaches to profitability across a PSC. Indeed, any delays in the commercialization of pharmaceutical products increase risks of investments in planning for R&D activities and reduce public trust and customer satisfaction. This study develops a multi-objective, multi-product, and multi-period model for integrating R&D and P&D planning decisions in a global PSC, considering delays and operational costs in the chain, and proposes a robust possibilistic programming (RPP) approach to deal with the epistemic uncertainty of some critical input parameters (e.g., those in crisis). Integrating R&D and Production and P&D planning decisions in a global pharmaceutical supply chain requires a multi-objective, multi-product, and multi-period model due to the inherently complex and uncertain nature of this industry.

This model serves two opposing yet interconnected objectives. First, it aims to maximize ENPV of total profit. The maximization of ENPV is a critical element in any business model, but more so in pharmaceuticals, where significant upfront investment is required in the early stages of a product's lifecycle, particularly in R&D. The expected payoff from these investments occurs over an extended period, thus emphasizing the need to focus on long-term profitability. Second, the model strives to minimize the maximum unsatisfied demands. In the pharmaceutical industry, unsatisfied demand can have serious health consequences for patients and can harm a company's reputation. It is essential to minimize such demands, ensuring an adequate and consistent supply of products. The need for such a model is further amplified by the industry's complexity. With multiple products, each with its own lifecycle and demand patterns, the planning process becomes increasingly sophisticated. In addition, the model accounts for different time periods, recognizing that decisions made today have impacts that unfold over many years. In addition, as the success rate of a patent in this industry is low, generic pharmaceutical products will have a higher chance to enter the market, with lower cost than innovative products. Therefore, we define another objective function to maximize the production of innovative pharmaceutical products to better address the profitability of innovative products.

The remainder of this paper is as follows: The next section provides a literature review on the global pharmaceutical supply chain, with an emphasis on planning for R&D processes and planning for P&D. In the following section, we articulate the significant research contributions. We then explore the problem context where we discuss the specific environment and circumstances in which our model was evaluated. The next section describes the formulation of our model and the objective functions, detailing the mathematical representation of the decision-making problem. After the model has been established, the following section discusses the implementation and assessment of the proposed model, including the process of data collection, as well as presenting the results from the Pareto analysis, model validity checks, and sensitivity analysis. The paper culminates with a critical discussion on the results of our study, where we interpret the findings in light of the existing literature and propose the theoretical and practical implications that emerge from our work.

## 2 Literature review

### 2.1 Pharmaceutical industry characteristics

The global pharmaceutical industry includes (1) innovative pharmaceutical products (an exclusive patent of 10–20 years) that require high R&D expenditures at the early stages of production; and (2) generic pharmaceutical products with limited expiration of the original product's copyright or license, maintained by manufacturers involved in the process of production (Lücker & Seifert, 2017; Marques et al., 2020). It is noteworthy that governments often set regulations for generic pharmaceutical products that the pharmaceutical industry must comply with (Abraham et al., 2003). Regardless of the product type, the complexity of pharmaceutical product development has significantly increased over the past two decades (Laínez et al., 2012), requiring regulatory agencies to consider more rigorous procedures to protect public health. For example, the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in Europe are regulatory authorities that develop and establish policies to ensure the safety, efficacy, and security of residents across the production, marketing, and distribution phases in food, cosmetic, and pharmaceutical products (Marques et al., 2020). These regulatory authorities also support the pharmaceutical industry to accelerate innovation in pharmaceutical products and make them more effective, affordable, and secure (Abraham et al., 2003). Although some developing countries like India or China rely on their own regulatory authorities (e.g., the Drug Controller General in India) (Mahajan et al., 2015), due to the rigid framework of the process of new product development in the global pharmaceutical industry, governments in many developing countries pursue the regulations recommended by the FDA in the USA or the European Medicines Agency (EMA) in Europe. The Iran Food and Drug Administration (IFDA) is a regulatory agency that oversees clinical investigations of pharmaceutical products in Iran (Iran Food and Drug Administration, 2021). According to the FDA (2021), the R&D processes of pharmaceutical products consist of five phases (e.g., discovery and development, pre-clinical, clinical, FDA approval, and safety monitoring), followed by the P&D processes (i.e., production, marketing, distribution and delivery in customer zone). These phases are described in Fig. 1.

Indeed, the process of new product development, commercialization and distribution in the pharmaceutical industry imposes substantial challenges for decision-makers. Many scholars considered R&D and P&D processes as the two ends of a typical PSC (e.g., see Lücker & Seifert, 2017; Narayana et al., 2014; Shah, 2004). In other words, R&D processes in a PSC are tailored by the post-market safety monitoring phase (i.e., mass production, inventory, distribution and delivery), making a PSC more complex than a typical supply chain. Therefore, the PSC design has been often a challenging topic in production and operations research (Marques et al., 2018). As a result, Laínez et al., (2012, p. 20) stated that “[the] high cost and low rate in product discovery and clinical development” create a paradoxical tension in commercializing pharmaceutical products; therefore, the industry may be too uncertain about investing in the new products and may look for externally developed products instead.

From the global perspective, strict regulations for new product development in a country can lead to a situation when P&D processes in other countries increase the burden of inventory management, leading to the loss of product values. Furthermore, the complexity of stakeholder engagement in a global PSC (e.g., R&D teams, manufacturers, distributors, customers, service providers, regulatory agencies, and governments) makes investments in new products too risky (e.g. see Bhakoo & Chan, 2011). In this vein, Marques et al. (2019)

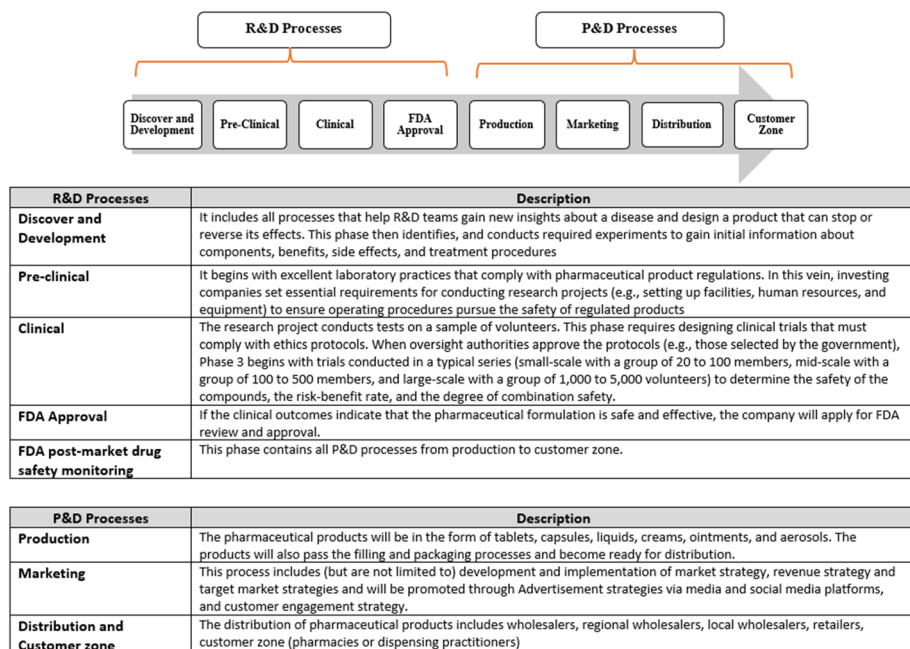


Fig. 1 R&D and P&D processes in a PSC

recommended that future modeling approaches consider key stakeholders' roles in new pharmaceutical development and commercialization to leverage efficiency in the entire PSC. Therefore, pharmaceutical companies prefer to invest less in the early stages of new pharmaceutical product development, and this in turn creates many opportunities for developing countries (e.g., India) to take advantage of the capitalized low-cost production nature of the pharmaceutical industry (Mahajan et al., 2015).

## 2.2 Ambidexterity in the global PSC

The concept of ambidexterity refers to situations in which an organization or a network of organizations explore new knowledge while simultaneously exploiting current opportunities (Junni et al., 2013). Ambidexterity enables organizations to achieve a sustainable competitive advantage by utilizing the existing opportunities and getting ready for future challenges (Ardito et al., 2020). In the context of supply chain management, actors must actively coordinate and integrate organizational resources to achieve these two objectives (Aslam et al., 2018). Early conceptualization of ambidexterity in supply chain management is rooted in studies by Kristal et al. (2010) and Blome et al. (2013), which examined the simultaneous influence of exploitative and explorative supply chain approaches. These studies later inspired a body of research on how ambidextrous supply chain approaches can improve supply chain performance (Aslam et al., 2018). Rojo et al. (2016) and Salvador et al. (2014) suggested that ambidexterity in supply chain management enables the chain to become efficient by focusing on existing opportunities and acquiring external knowledge about market demand. Therefore, Aslam et al. (2018) concluded that in the supply chain ambidexterity, organizations could

quickly respond to short-term market changes and establish long-term strategies to improve profitability.

To better understand the role of ambidexterity in the pharmaceutical industry, we need to articulate the relationships between the explorative and exploitative supply chain approaches and how these two can impact performance. In a meta-analysis on ambidexterity and performance in eight industries (e.g., the pharmaceutical industry), Junni et al. (2013) found that integrating explorative and exploitative approaches can improve organizational profitability. He and Wong (2004) found that organizations may respond differently toward these two approaches (e.g., emphasizing one over the other). Uotila et al. (2009) stated that the balance between the explorative and exploitative supply chain approaches is defined based on the power of internal and external factors. For example, an explorative approach may be appropriate for R&D planning, whereas an exploitative approach may work better in situations where the pharmaceutical products must meet the market demand. Uotila et al. (2009) therefore highlighted that the integration between the two approaches is critical in the R&D-intensive supply chain design (e.g., the pharmaceutical industry).

### 2.2.1 Planning for R&D processes (the explorative approach)

Schmidt and Grossmann (1996) and Jain and Grossmann (1999) proposed optimization models using a mixed-integer linear program (MILP) with resource constraints to reduce the scheduling of testing tasks in phases of discovery and development and preclinical research in R&D planning. Rotstein et al. (1999) presented a random capacity planning model (based on the MILP methodology) for Phase 3 of R&D planning (clinical trials). They also used the model to minimize investments in product development and introduction strategy of pharmaceutical products. Gatica et al. (2003) presented a multi-stage, multi-period stochastic capacity planning model to optimize planning for R&D processes in the clinical trial phase. They proposed the R&D planning as a large-scale, multi-stage, and multi-period stochastic optimization problem that must be resolved through an optimization-based approach. Their methodology reformulated the problem as a multi-scenario MILP model, enabling R&D planning for multiple products to be efficient. This methodological approach was also applied by Maravelias and Grossmann (2001), Rogers et al. (2002) and Levis and Papageorgiou (2004) who proposed a multi-period model for the development of new products, using MILP to maximize the net value of introducing new products to the market. However, these studies applied a heuristic algorithm based on Lagrangean decomposition to propose optimal or near-optimal solutions to the R&D processes.

Some other studies have applied a combination of mathematical modeling approaches to resolving the issues of R&D planning in the pharmaceutical industry. For example, Luna and Martínez (2018, p. 1063) proposed a model-based optimization strategy using a probabilistic tendency approach to efficiently improve operating scenarios in new product development. Their mathematical modeling helped mitigate the risk of failure in the early stages of product development. Colvin and Maravelias (2011) proposed a multi-stage stochastic programming framework to (1) optimize the selection and scheduling of R&D activities using the pass/fail uncertainty conditions; (2) optimize the resource planning decisions (e.g., contracts, outsourcing procedures) for multiple products; and (3) provide a framework for formulating value at risk in pharmaceutical companies. Considering the importance of decisions at the early stages of R&D processes, Marques et al. (2018) presented a multi-objective integer programming model to develop the best design strategy for maximizing the productivity of R&D processes. None of these studies, however, has explicitly considered links of R&D and P&D—a distinct and substantial contribution made by our study.



### 2.2.2 Planning for P&D processes (the exploitative approach)

Planning for P&D is as important as R&D in designing a PSC. Although clinical trials (Phase 3 of R&D activities) help gather important information, the true picture of a product's efficacy and safety evolves over time, especially when it enters the market for consumption (Lücker & Seifert, 2017; Mahajan et al., 2015). Furthermore, after a new pharmaceutical product is prepared for commercialization (Phase 5 of R&D activities), the success of P&D systems is not necessarily guaranteed (FDA, 2021). Accelerating the pharmaceutical product's P&D systems is, therefore, important for two reasons. First, capturing a large portion of the market share for a new product may require years of marketization and commercialization (Marques et al., 2020). Second, to maximize the pace of P&D systems for the pharmaceutical product while minimizing operational costs (e.g., mass production, storage, transportation), it is important not to focus only on one part of the PSC.

Many studies in P&D planning reviewed settings with primary and secondary pharmaceutical production operations (Marques et al., 2020). Primary production (i.e., pharmaceutical substance manufacturing) focuses on transforming primary components into active pharmaceutical ingredients that require a chain of chemical and separation processes. Secondary production (i.e., pharmaceutical product manufacturing) focuses on transforming the active pharmaceutical ingredients into end products that are ready for delivery to customers. This often involves further procedures such as standardizing dosages for different groups, packaging, and developing security against expiration. Therefore, the secondary production must be aligned with distribution networks to ensure the efficiency of the entire PSC (Jahani et al., 2023). Although time and cost are two aligned constraints in the literature of PSC design, some studies focused on these two constraints to provide better strategic decisions for policymakers in both the primary and secondary production operations. According to Rekabi et al. (2021), operating times in the production and delivery of pharmaceutical products in PSCs is vital; therefore, they combined the two multi-objective methods using LP-metric and goal attainment to increase the performance of a real-world production–distribution system. In contrast, Zandkarimkhani et al. (2020) proposed a bi-objective MILP model using fuzzy rule-based systems for perishable pharmaceutical products to minimize the different yet interlinked variables of the network costs and lost demand amount. They note that some lost sales are inevitable; therefore, companies must invest more in distribution facilities to cover a wide variety of hidden demands in the market. The same findings are also observed in the study by Nasrollahi and Razmi (2021), although their model was based on a multi-objective non-dominated ranked genetic algorithm.

Sousa et al. (2011) proposed a mathematical model for optimizing the allocation and distribution structure of a PSC in both primary and secondary production operations. The model was aimed at optimizing the allocation of products to different locations and to customers in various age groups to increase demand satisfaction. However, we found that the study by Uthayakumar and Priyan (2013) is one of the early studies that directly applies operations research and optimization in PSCs to decrease the level of unsatisfied demands. They stated that pharmaceutical product shortages, restrictions in production, and storage and distribution matters require high-level coordination in establishing optimal PSC and inventory management policies; therefore, they proposed a two-echelon mathematical procedure for determining optimal solutions to simultaneously reduce the PSC costs and improve the competitive business environment through minimizing unsatisfied demands. In another study by Akbarpour et al. (2020), an integrated pharmaceutical relief network (min–max robust model) under demand uncertainty and perishability of products in times of crisis was developed and



tested in a developing country. This study showed that P&D modeling in the pharmaceutical industry could substantially improve the efficiency of PSCs. Sousa et al. (2011) then considered the critical roles of production cost, transportation cost, tax, and insurance rates at various locations, utilizing a profit maximization objective function, and proposed a model based on two decomposition algorithms. The same practical approach was taken into consideration in the study by Susarla and Karimi (2012), which proposed an integrated procurement P&D planning model for a multi-product PSC. In their study, the integrated mixed-integer programming model is formulated in terms of holding inventory and raw material costs and tax differences.

According to Sheu and Lin (2012), with the rapid maturity of globalization, global supply chains must utilize operational objectives that help reduce the level of uncertainty and cost and improve coordination in P&D channels. They proposed a multi-objective programming model to systematically minimize network configuration cost and unsatisfied demand and maximize operating profit. Their study later inspired some other PSC studies. For example, Liu et al. (2017) developed two distribution planning models (uncertain demand and service time) for pharmaceutical products using a time–space network approach for daily delivery in a hospital. In addition, Zahiri et al. (2017) proposed a new mathematical model to design a distribution network in a PSC in France in times of crisis. They developed a new approach based on mean-absolute deviation and fuzzy possibilistic-stochastic programming to minimize the total cost of pharmaceutical product delivery while increasing the resilience of the PSC with respect to the social responsibilities of France’s pharmaceutical companies.

### 2.3 Research contributions

As evident in Table 1, we found that studies on PSC planning addressed either R&D planning or P&D planning, even if an integration between these two areas could improve profitability and minimize unsatisfied demand. A lack in this integration may render suboptimal solutions. The integrated planning of R&D processes and P&D operations can help the PSC optimize investments in R&D activities as well as increasing profitability and market share by utilizing effective strategies. Furthermore, delays in R&D phases of production and delivery can jeopardize PSC resilience, both individually and collectively; this is also overlooked in prior studies. Indeed, the timely arrival of pharmaceutical products in the market can increase profitability and reduce unsatisfied demands; this is useful for further investments in R&D processes. To summarize, many prior studies did not consider both the long-term and short-term benefits of integration in supply chain approaches (i.e., ambidexterity in supply chain management) during PSC planning.

This study makes the following contributions to the literature to bridge these research gaps. First, we develop a multi-objective, multi-product, and multi-period model for integrating R&D and P&D planning decisions in a global pharmaceutical supply chain considering delays in R&D and P&D phases. Second, we propose an RPP approach to deal with the epistemic uncertainty of some critical input parameters. Third, applying the ambidextrous approach that emphasizes optimizing a balanced framework based on the R&D planning and P&D planning, our study reconciles the explorative and exploitative supply chain strategies in the context of global PSCs through maximizing ENPV of Total Profit; (ii) minimizing the maximum unsatisfied demands; and (iii) maximizing the production of innovative pharmaceutical products.

The integration of these three objective functions within a multi-objective model acknowledges the interconnectedness and interdependencies among various aspects of the

**Table 1** Previous studies on R&D and P&D planning

Author	Research aim	Methods	Planning for	Model features		
				Single (multi)-product(s)	Single (multi)-period(s)	Uncertainty
Rotstein et al. (1999)	Minimize investments in product development and introduction strategy of pharmaceutical products	Random capacity planning model (based on the MILP methodology)	R&D	Single	Single	Supply uncertainty
Gatica et al. (2003)	Optimize planning for R&D processes in the clinical trial phase	Multi-stage, multi-period stochastic capacity planning model (based on the MILP methodology)	R&D	Single	Multi	Supply uncertainty
Maravelias and Grossmann (2001)	To maximize the net value of introducing new products to the market	Multi-stage, multi-period stochastic capacity planning model (based on the MILP methodology on Lagrangean decomposition)	R&D	Multi	Multi	Supply uncertainty
Rogers et al. (2002)	To maximize the net value of introducing new products to the market	Multi-stage, multi-period stochastic capacity planning model (based on the MILP methodology on Lagrangean decomposition)	R&D	Multi	Multi	Supply uncertainty
Levis and Papageorgiou (2004)	To maximize the net value of introducing new products to the market	Multi-stage, multi-period stochastic capacity planning model (based on the MILP methodology on Lagrangean decomposition)	R&D	Multi	Multi	–

Table 1 (continued)

Author	Research aim	Methods	Planning for	Model features		
				Single (multi)-product(s)	Single (multi)-period(s)	Uncertainty
Colvin and Maravelias (2011)	(1) Optimize the selection and scheduling of R&D activities using the pass/fail uncertainty conditions; (2) optimize the resource planning decisions (e.g., contracts, outsourcing procedures) for multiple products; and (3) provide a framework for formulating value at risk in pharmaceutical companies	Multi-stage stochastic programming framework (based on the MILP methodology)	R&D	Multi	Multi	Supply uncertainty
Susarla and Karimi (2012)	An integrated procurement P&D planning model for a multi-product PSC	An integrated mixed-integer programming model	P&D	Multi	Multi	–

**Table 1** (continued)

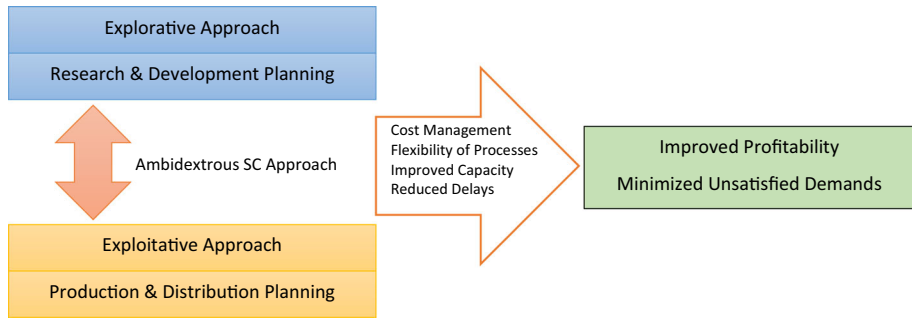
Author	Research aim	Methods	Planning for	Model features		
				Single (multi)-product(s)	Single (multi)-period(s)	Uncertainty
Uthayakumar and Priyan (2013)	To determine optimal solutions to simultaneously reduce the PSC costs and improve the competitive business environment through minimizing unsatisfied demands	A two-echelon mathematical procedure	P&D	Multi	Multi	Demand uncertainty
Liu et al. (2017)	Two distribution planning models (uncertain demand and service time) for pharmaceutical products	A time-space network approach	P&D	Multi	Single	Demand uncertainty
Zahiri et al. (2017)	To minimize the total cost of pharmaceutical product delivery while increasing the resilience of the PSC	Mean-absolute deviation and fuzzy possibilistic-stochastic programming	P&D	Multi	Multi	Demand uncertainty
Luna and Martínez (2018)	To mitigate the risk of failure in the early stages of product development	The probabilistic tendency approach	R&D	Single	Single	–

Table 1 (continued)

Author	Research aim	Methods	Planning for	Model features		
				Single (multi)-product(s)	Single (multi)-period(s)	Uncertainty
Marques et al. (2018)	To develop the best design strategy for maximizing the productivity of R&D processes	A multi-objective integer programming model	R&D	Multi	Multi	Supply uncertainty
Zandkarimkhani et al. (2020)	To minimize the different yet interlinked variables of the network costs and lost demand amount for perishable pharmaceutical products	A bi-objective MILP model using fuzzy rule-based systems	P&D	Multi	Multi	Demand uncertainty
Nasrollahi and Razmi (2021)	To minimize the network costs and lost demand amount for perishable pharmaceutical products	A multi-objective non-dominated ranked genetic algorithm	P&D	Multi	Multi	Demand uncertainty

**Table 1** (continued)

Author	Research aim	Methods	Planning for	Model features		
				Single (multi)-product(s)	Single (multi)-period(s)	Uncertainty
Rekabi et al. (2021)	To increase the performance of a real-world production–distribution system	Two multi-objective methods using LP-metric and goal attainment	P&D	Multi	Multi	Demand uncertainty
Our study	To develop a multi-objective, multi-product, and multi-period model to integrate planning for research and development (R&D) and production and distribution (P&D) in a global PSC	A robust possibilistic programming (RPP) approach to deal with the epistemic uncertainty of some critical input parameters	R&D and P&D	Multi	Multi	Supply uncertainty



**Fig. 2** The supply chain ambidextrous approach proposed in this study

supply chain which is identified as ambidexterity in supply chain management. It helps decision-makers navigate the complexity and uncertainties by considering the trade-offs and contradictions between the explorative approach (R&D planning) and the exploitative approach (P&D planning). The R&D phase of the pharmaceutical supply chain (explorative) focuses on innovation, experimentation, and long-term value creation. It requires flexibility, exploration, and investment in research activities to develop new and innovative pharmaceutical products. On the other hand, the P&D phase emphasizes efficiency, reliability, and meeting current market demands. It focuses on cost optimization, timely delivery, and ensuring customer satisfaction.

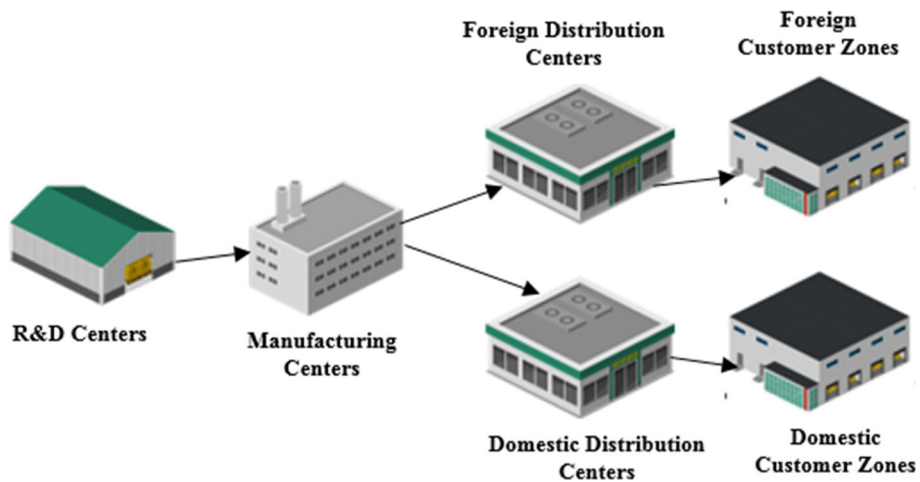
As discussed in the literature, these two conflicting demands are identified in all three objective functions, justifying the need to address the conflicting demands between the R&D and P&D phases. The concept of ambidexterity recognizes the need to balance exploration and exploitation within the pharmaceutical supply chain. This facilitates decision-making that integrates both long-term innovation objectives and short-term operational efficiency, enabling the global PSCs to navigate the complexities and uncertainties while effectively managing conflicting demands.

To achieve these contributions, this study utilizes unique global parameters in advancing supply chain performance such as exchange rates, taxes, import rights, and international transport insurance. The proposed model also considers the inclusion of transfer pricing using an authentic case study. Figure 2 exhibits the role of ambidexterity in developing the integrated model in this study.

### 3 Problem context

Although many pharmaceutical organizations possess a portfolio of generic and innovative pharmaceutical products, this study focuses on the innovative products to better accommodate its objectives. The innovative products are produced based on a set of criteria, including the market situation, government regulations, and social acceptance, the quality of competing products, and financial profitability (Austin & Hayford, 2021; Marques et al., 2020). When a new product from an R&D portfolio is selected for mass production, capacity planning may become complicated due to the limited number of production lines (Gatica et al., 2003); therefore, a cost–benefit analysis must be undertaken to maximize the production capacity for both the innovative and generic products, based on the above criteria (Lücker & Seifert, 2017). As such, it becomes increasingly important to integrate R&D planning for new products and





**Fig. 3** HPC supply chain network

use P&D planning for both the generic and innovative pharmaceutical products to optimize the PSC planning.

To achieve this, we implemented our proposed model in an authentic case study, Hakim Pharmaceutical Company (HPC), one of the largest and most well-known pharmaceutical companies in Iran. HPC can produce a diverse range of medicines such as tablets, coated tablets, hard gelatin capsules, gel capsules, oral drops, syrups, oral suspensions, topical solutions, topical gels, topical creams, and ointments (HPC, 2021). The underlying structure of the HPC supply chain is shown in Fig. 3.

The company has a candidate portfolio of generic and innovative pharmaceutical products that flexibly shape the P&D lines based on the rate of profitability and market share. HPC has also outsourced the production of some generic products to other pharmaceutical companies (HPC, 2021). However, the innovative products that require passing the five phases of R&D planning must be undertaken within HPC itself. Delays in pre-clinical and clinical testing and the IFDA review and approval may also impact benefits resulting from early commercialization (e.g., profitability). Therefore, these delays are also taken into consideration in this study. Although HPC has a large portion of the local market of Iran, its pharmaceutical products are exported to other countries, including Iraq, Afghanistan, Pakistan, United Arab Emirates, Qatar, Turkmenistan, Syria, and Armenia (HPC, 2021). Therefore, the integrated planning for R&D and P&D must comply with international regulations, contracts, and agreements (e.g., Free on Board (FOB) and Cost, Insurance, and Freight (CIF)). This requires us to consider the cost of transportation, insurance, and tax rates between the origin and destination countries.

The multi-objective multi-period optimization model for the HPC case is formulated by defining the problem's parameters, decision variables, objectives, and constraints. The decision variables in this model represent adjustable parameters that have a direct impact on the outcomes.

## 4 Model formulation

The following indices, parameters, and variables are used to formulate the integrated R&D planning and P&D planning problem.

### 4.1 Nomenclature

#### Indices

- $t$  Index of time periods,  $t \in \{1, 2, \dots, T\}$ , unit = year, season, or several months  
 $f$  Index of manufacturing centers,  $f \in \{1, 2, \dots, F\}$ , unit = number  
 $d$  Index of distribution centers,  $d \in \{1, 2, \dots, D\}$ , unit = number  
 $g$  Index of customer zones,  $g \in \{1, 2, \dots, G\}$ , unit = number  
 $i$  Index of pharmaceutical products,  $i \in \{1, 2, \dots, I\}$ , unit = number

#### Parameters (R&D planning)

- $dl_i$  R&D time for product  $i \in n$ , unit = days, months  
 $CDNP^1_i$  Unit R&D cost of product  $i$  in formulation phase, unit = a currency like \$ or Rial  
 $CDNP^2_i$  Unit R&D cost of product  $i \in n$  in IFDA approval phase, unit = a currency like \$ or Rial  
 $cr^1$  Marginal cost of delay time in formulation phase, unit = a currency like \$ or Rial  
 $cr^2$  Marginal cost of delay time in FDA approval phase, unit = a currency like \$ or Rial  
 $lr^1_i$  Delay time for product  $i$  in formulation phase, unit = days, months  
 $lr^2_i$  Delay time for product  $i$  in FDA approval phase, unit = days, months

#### Parameters (P&D planning)

- $P^l_{fi}$  Delay times in production center  $f$  for product  $i$ , unit = days, months  
 $PC_{fi}$  Storage capacity of production center  $f$  for product  $i \in o$ , unit = number  
 $CP_{fi}$  Unit manufacturing cost of product  $i$  in production center  $f$ , unit = a currency like \$ or Rial  
 $CI_{fi}$  Unit storage cost of product  $i$  in production center  $f$ , unit = a currency like \$ or Rial  
 $II_{fit}$  Initial inventory of product  $i$  in production center  $f$  at time period  $t$ , unit = number  
 $DLC_{ft}$  Unit delay time cost in production center  $f$  at time period  $t$ , unit = days, months  
 $\pi_i$  Weight of importance for product  $i$ , unit = percentage  
 $TR^t_f$  Tax rate of income of production center  $f$  at time period  $t$ . If production center is losing out, the tax rate is zero, unit = percentage  
 $CF_{fi}$  Storage capacity of production center  $f$  for product  $i \in n$ , unit = number  
 $D^t_{gi}$  Demand in customer zone  $g$  for product  $i$  at time period  $t$ , unit = number  
 $P_{di}$  Price of product  $i$  in domestic distribution center  $d$ , unit = a currency like \$ or Rial  
 $P'_{di}$  Price of product  $i$  in external distribution center  $d$ , unit = a currency like \$ or Rial  
 $L_{fd}$  Delay times between production center  $f$  and distribution center  $d$ , unit = days, months

$L_{dg}$	Delay times between distribution center $d$ and customer zone $g$ , unit = days, months
$CI_{di}$	Unit storage cost of product $i$ in distribution center $d$ , unit = a currency like \$ or Rial
$C_d$	Storage capacity of distribution center $d$ for product $i \in o$ , unit = number
$II'_{dit}$	Initial inventory of product $i$ in distribution center $d$ at time period $t$ , unit = number
$TC^1_{fd}$	Unit transportation cost between production center $f$ and external distribution center $d \in d^f$ in the country of origin, unit = a currency like \$ or Rial
$TC^2_{fd}$	Unit transportation cost between production center $f$ and distribution center $d \in d^f$ in destination country, unit = a currency like \$ or Rial
$TC^3_{dg}$	Unit transportation cost between distribution center $d \in d^f$ and external customer zone $g$ , unit = a currency like \$ or Rial
$TC_{dg}$	Unit transportation cost between domestic distribution center $d \in d^h$ and domestic customer zone $g$ , unit = a currency like \$ or Rial
$TC'_{fd}$	Unit transportation cost between production center $f$ and domestic distribution center $d \in d^h$ , unit = a currency like \$ or Rial
$IN_d$	Unit insurance cost in domestic distribution center $d \in d^h$ via marine, unit = a currency like \$ or Rial
$IN'_d$	Unit insurance cost in external distribution center $d \in d^f$ via marine, unit = a currency like \$ or Rial
$\mu_i$	Percentage of marketing cost, unit = %
$rf$	Rate of inflation, unit = %
$rt$	Rate of interest, unit = %
$exf_i$	Expiration time of product $i$ , unit = months, years
$TR^t_d$	Tax rate of income of distribution center $d$ at time period $t$ . If distribution center is losing out, the tax rate is zero, unit = %
$DR^t_{di}$	Import duty of product $i$ to the country of distribution center $d$ at time period $t$ , unit = a currency like \$ or Rial
$\overline{TRC^t_{fdi}}$	Upper bound of CIF transfer price of transshipped product $i$ from production center $f$ to external distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial
$TRC^t_{fdi}$	Lower bound of CIF transfer price of transshipped product $i$ from production center $f$ to external distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial
$\overline{TRF^t_{fdi}}$	Upper bound of FOB transfer price of transshipped product $i$ from production center $f$ to external distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial
$TRF^t_{fdi}$	Lower bound of FOB transfer price of transshipped product $i$ from production center $f$ to external distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial
$PI^t_{fdi}$	Domestic sales price of transshipped product $i$ from production center $f$ to distribution center $d$ at time period $t$ , unit = a currency like \$ or Rial
$CD_d$	Storage capacity of distribution center $d$ for product $i \in n$ , unit = number

Other parameters

$It$  Marginal cost of delay, unit = a currency like \$ or Rial

$M$  Large number (using in the model's constraints)

$EX_t$  Exchange rate at time period  $t$ , unit =

Decision variables

$I_{fi}^t$	Inventory level of product $i$ in production center $f$ at the end of time period $i$ , unit = number
$I_{di}^t$	Inventory level of product $i$ in distribution center $d$ at the end of time period $i$ , unit = number
$y_{fd}^t$	A binary variable equal to 1 if relation between production center $f$ and distribution center $d$ in period $t$ is existed, 0 otherwise
$y_{dg}^t$	A binary variable equal to 1 if the relation between distribution center $d$ and customer zone $g$ in period $t$ exists, 0 otherwise
$S_{fdi}^t$	Quantity of product $i$ transshipped from production center $f$ and distribution center $d$ at time period $t$
$S_{dgi}^t$	Quantity of product $i$ transshipped to distribution center $d$ and customer zone $g$ at time period $t$
$Q_{fi}^t$	Quantity of product $i$ manufactured in production center $f$ at time period $t$
$X_{fi}^t$	A binary variable equal to 1 if product $i \in n$ is available for entering the market, 0 otherwise
$X'_{fi}^t$	A binary variable equal to 1 if product $i \in n$ is researched, and developed by the R&D sector, approved by IFDA, manufactured and commercialized by the company for entering the market at time period $t$ , 0 otherwise
$X''_i^t$	A binary variable equal to 1 if product $i \in n$ is transferred from formulation test to IFDA approval at time period $t$ , 0 otherwise
$ref_{fi}^t$	Quantity of deteriorated product $i$ in all production centers at time period $t$
$ref_{di}^t$	Quantity of deteriorated product $i$ in all distribution centers at time period $t$
$yf_{fdi}^t$	1 if FOB transshipment term between production center $f$ and distribution center $d \in d^f$ for product $t$ in period $t$ is selected, 0 otherwise
$yc_{fdi}^t$	1 if CIF transshipment term between production center $f$ and distribution center $d \in d^f$ for product $t$ in period $t$ is selected, 0 otherwise
$z_f^{t+}$	Profit before tax deduction from production center $f$ at time period $t$ , unit = a currency like \$ or Rial
$z_f^{t-}$	Losses before tax deduction from production center $f$ at time period $t$ , unit = a currency like \$ or Rial
$z_d^{t+}$	Profit before tax deduction from distribution center $d$ at time period $t$ , unit = a currency like \$ or Rial
$z_d^{t-}$	Losses before tax deduction from distribution center $d$ at time period $t$ , unit = a currency like \$ or Rial
$trf_{fdi}^t$	FOB transfer price of transshipped product $t$ from production center $f$ to distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial
$trc_{fdi}^t$	CIF transfer price of transshipped product $t$ from production center $f$ to distribution center $d \in d^f$ at time period $t$ , unit = a currency like \$ or Rial

## 4.2 Objective functions

The first objective function maximizes the expected net present value (ENPV) of total profit after tax deduction in Eq. (1). Jahani et al. (2019) stated that the ENPV calculation in the

supply chain network design could help better illustrate how the supply chain performs in different scenarios. To achieve this in the studied global PSC, the objective function can be formulated as follows:

$$Max z_1 = \sum_t \left( \frac{1 + rf}{1 + rt} \right)^{t-1} (z_1^t + z_1'' + z_1''') \quad (1)$$

$$z_1^t = \sum_f \left( 1 - TR_f^t \right) z_f^{t+} - z_f^{t-} \quad \forall t \quad (2)$$

$$z_1'' = \sum_d \left( 1 - TR_d^t \right) z_d^{t+} - z_d^{t-} \quad \forall t \quad (3)$$

$$\begin{aligned} z_1''' = & - \sum_{i \in n} \left( CDN P_i^1 X_i''' + CDN P_i^2 X_{fi}'' \right) - \sum_{f, i \in n} DLC_{ft} \left( X_{fi}'' - X_{fi}^{t+dl_i} \right) \\ & - \sum_i \left( cr^1 lr_i^1 X_i''' + cr^2 lr_i^2 X_{fi}'' \right) \quad \forall t \end{aligned} \quad (4)$$

Equations (2) and (3) calculate the after-tax profit at P&D centers, respectively. Equation (4) reflects the penalty cost of delays in different R&D, production, and market entry stages. In addition,  $z_f^{t+}$  and  $z_d^{t+}$  represent the profit of the production center  $f$  and distribution center  $d$  at time period  $t$ , respectively.  $z_f^{t-}$  and  $z_d^{t-}$  represent the loss of the manufacturing center  $f$  and distribution center  $d$  at time period  $t$ , respectively. Given that the tax belongs to the profit in the proposed objective function, only  $z_f^{t+}$  and  $z_d^{t+}$  are dependent on taxation. Equation (5) represents the profit (or loss) before tax in the production center  $f$  in period  $t$ . Table 2 describes all terms used in this equation accordingly.

$$\begin{aligned} z_f^{t+} - z_f^{t-} = & \sum_{d \in d^f, i} trf_{f,d,i}^t S_{fdi}^t y_{fdi}^t EX_t + \sum_{d \in d^f, i} trc_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t \\ & + \sum_{d \in d^f, i} PI_{fdi}^t S_{fdi}^t - \sum_{d \in d^f, i} TC_{fdi}^1 y_{fdi}^t EX_t \\ & - \sum_{d \in d^f, i} \left( TC_{fd}^1 + TC_{fd}^2 + IN \right) y_{fdi}^t EX_t - \sum_{d \in d^h} \left( TC_{fd}^1 + IN' \right) y_{fd}^t \\ & - \sum_i CI_{fi} I_{fi}^t - \sum_i CP_{fi} Q_{fi}^t - I_t \sum L_{fd} y_{fd}^t EX_t \quad \forall f, t, \quad (5) \\ z_d^{t+} - z_d^{t-} = & \sum_{g, i} P_{di} S_{dgi}'' EX_t - \sum_{f, i} trf_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t - \sum_{f, i} trc_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t \\ & - \sum_f \left( TC_{fd}^2 + IN \right) y_{fd}^t EX_t - \sum_f TC_{dg}^3 y_{fd}^t EX_t - \sum_{f, i} DR_{di}^t trf_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t \\ & - \sum_{f, i} DR_{di}^t \left( TC_{fd}^2 + IN \right) y_{fdi}^t - \sum_{f, i} DR_{di}^t trc_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t \\ & - \sum_{d, i} CI_{di} I_{di}'' EX_t - \sum_{g, i} \mu_i P_{di} S_{dgi}'' EX_t - I_t \sum_g L_{dg} y_{dg}'' EX_t \\ & - \sum_g TC_{dg} y_{dg}^t EX_t \quad \forall d \in d^f, t, \quad (6) \end{aligned}$$

Equation (6) calculates the profit (or loss) before tax in the foreign distribution center  $d^f$  at time period  $t$ , described in Table 3.

It is noteworthy that import duties in many countries are calculated based on the value of CIF goods reported by the importers (Grivani & Pishvaei, 2017). In this study, therefore, the

**Table 2** Explanation of terms used in Eq. (5)

Number	Term	Description
1	$\sum_{d \in d^f, i} tr f_{f, d, i}^t S_{f di}^t y_{f di}^t EX_t$	Revenues at production centers where pharmaceutical organizations sell products directly to external distribution centers through FOB or CIF contracts and domestic distribution centers using inter-organizational agreements
2	$\sum_{d \in d^f, i} tr c_{f di}^t S_{f di}^t y_{f di}^t EX_t$	
3	$\sum_{d \in d^f, i} P I_{f di}^t S_{f di}^t$	
4	$\sum_{d \in d^f, i} TC_{fd}^1 y_{f di}^t EX_t$	The portion of shipping costs when a pharmaceutical product is shipped from a production center to a distribution center that is often paid once when an FOB contract is selected
5	$\sum_{d \in d^f, i} (TC_{fd}^1 + TC_{fd}^2 + IN) y_{f di}^t EX_t$	The shipping and associated insurance costs from a production center to a distribution center when a CIF contract is agreed upon, which would be paid once, as well
6	$\sum_{d \in d^h} (TC_{fd}^1 + IN) y_{fd}^t$	The transportation and associated insurance costs between a production center and a domestic distribution center
7	$\sum_i C I_{fi} I_{fi}^t$	The cost of preserving pharmaceutical products in all production centers
8	$\sum_i C P_{fi} Q_{fi}^t$	The cost of producing generic and innovative pharmaceutical products
9	$It \sum_d L_{fd} y_{fd}^t EX_t$	The delay transition cost of generic and innovative pharmaceutical products from a production center to a distribution center

CIF value is used to calculate the import duties in our model. To convert the value (price) from FOB to CIF, the following formulation is used: *Value (price) of CIF goods = Value (price) of FOB goods + Shipping cost between every two ports of P&D centers + insurance cost between every two ports of P&D centers.*

Equation (7) shows the before-tax profit (or loss) gained from domestic distribution center  $d^h$  in period  $t$ . The expressions used in Eq. (7) are from the sales of pharmaceutical products to consumers, the cost of a purchasing product at an internal price, the cost of storing the product at a distribution center, the cost of transportation from a distribution center to consumers, the marketing cost, and the cost of delays in delivering generic and innovative pharmaceutical products from a distribution center to consumers.

$$\begin{aligned}
 z_d^{t+} - z_d^{t-} = & \sum_{g,i} P'_{di} S_{dgi}^t - \sum_{f,i} P I_{f di}^t S_{f di}^t - \sum_i C I_{di} I_{di}^t - \sum_g TC_{dg} y_{dg}^t \\
 & - \sum_{g,i} \mu_i P_{di} S_{dgi}^t - It \sum_g L_{dg} y_{dg}^t \quad \forall d \in d^h, t
 \end{aligned} \quad (7)$$

**Table 3** Explanation of terms used in Eq. (6)

Number	Expression	Description
1	$\sum_{g,i} P_{di} S_{dgi}^t EX_t$	Revenues gained by external distribution centers from selling pharmaceutical products to customers
2	$\sum_{f,i} trf_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t$	The cost of purchasing pharmaceutical products from manufacturing centers under FOB and CIF contracts
3	$\sum_{f,i} trc_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t$	
4	$\sum_f (TC_{fd}^2 + IN) y_{fd}^t EX_t$	The cost of transportation and insurance between the port of production centers and distribution centers
5	$\sum_f TC_{dg}^3 y_{fd}^t EX_t$	The cost of transportation between two distribution centers
6	$\sum_{f,i} DR_{di}^t trf_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t$	The costs of import duties and taxes when goods are purchased under FOB and CIF contracts, respectively
7	$\sum_{f,i} DR_{di}^t (TC_{fd}^2 + IN) y_{fdi}^t$	
8	$\sum_{f,i} DR_{di}^t trc_{fdi}^t S_{fdi}^t y_{fdi}^t EX_t$	
9	$\sum_{d,i} CI_{di} I_{di}^t EX_t$	The cost of storing pharmaceutical products in warehouses of distribution centers
10	$\sum_{g,i} \mu_i P_{di} S_{dgi}^t EX_t$	The cost of marketing for pharmaceutical products
11	$It \sum_g L_{dg} y_{dg}^t EX_t$	The delay cost related to the shipping of pharmaceutical products from a distribution center to consumers
12	$\sum_g TC_{dg} y_{dg}^t EX_t$	The cost of shipping from a distribution center to consumers

The second objective function in this study intends to minimize the maximum unsatisfied demands. The maximum unsatisfied demands are multiplied by the parameter  $\pi_i$  in Eq. (8) to consider the importance of pharmaceutical products. We consider the maximum possible loss here for a worst-case (maximum loss) scenario.

$$Minz_2 = Max_{g,i} \left( \pi_i \left( D_{gi}^t - \sum_d S_{dgi}^{t-L_{dg}} \right) \right) \quad (8)$$

The coordination of R&D activities and production of innovative pharmaceutical products is critical in the pharmaceutical industry since it ensures the long-term profitability of pharmaceutical companies. In addition, patenting in the pharmaceutical industry is quite dissimilar to other industries, as the patent is the product itself (a new medicine) that has been developed under costly R&D activities and long-term clinical examinations (Masoumi et al., 2012). Therefore, the success rate of a patent in this industry is low, indicating that generic pharmaceutical products will have a higher chance to enter the market, with lower cost than innovative products. This is a threat to the profitability of innovative products. Therefore, we define another objective function formulated in Eq. (9) to maximize the production of innovative pharmaceutical products in our model.

$$Maxz_3 = \sum_{t,i \in n} Q_{fi}^t \quad (9)$$



### 4.3 Flow balance constraints

The flow balance constraints at each facility of the PSC network are formulated at Constraints (10)–(16).

$$I_{fi}^t = II_{fit} + I_{fi}^{t-1} + Q_{fi}^{t-P_{fi}^l} - \sum_d S_{fdi}^t, \quad \forall f, i, t, \quad (10)$$

$$I_{di}^t = II_{dit} + I_{di}^{t-1} + \sum_f S_{fdi}^{t-L_{fd}} - \sum_g S_{dgi}^t, \quad \forall d, i, t, \quad (11)$$

$$\sum_d S_{dgi}^{t-L_{dg}} \leq D_{gi}^t, \quad \forall g, i, t, \quad (12)$$

$$\sum_f S_{fdi}^{t-L_{fd}} + I_{di}^{t-1} \geq \sum_g S_{dgi}^t, \quad \forall d, i, t, \quad (13)$$

$$Q_{fi}^{t-P_{fi}^l} + I_{fi}^{t-1-P_{fi}^l} \geq \sum_d S_{fdi}^t, \quad \forall f, i, t, \quad (14)$$

$$\sum_i S_{fdi}^t \leq My_{fd}^t, \quad \forall f, d, t, \quad (15)$$

$$\sum_i S_{dgi}^t \leq My_{dg}^t, \quad \forall d, g, t, \quad (16)$$

Constraints (10) and (11) indicate the flow and inventory balance at the production center  $f$  and the distribution center  $d$ , respectively, in each period. Constraint (12) ensures that the products shipped to customer zones should be less than or equal to the demand of the corresponding customer zone. However, Constraints (13) and (14) calculate the imbalance in supply and demand of a product between P&D centers and customer zones. Equation (15) demonstrates the flow of pharmaceutical products from a production center to a distribution center if there is a link between the centers. A similar limitation is also considered in Eq. (16) for the flow of pharmaceutical products from a distribution center to a customer zone.

### 4.4 Capacity constraints

Below, the capacity constraints of P&D centers are formulated:

$$Q_{fi}^t \leq PC_{fi}, \quad \forall f, i \in o, t, \quad (17)$$

$$\sum_{f,i \in o} S_{fdi}^t \leq C_d, \quad \forall d, t, \quad (18)$$

$$Q_{fi}^t \leq CF_{fi} X_{fi}^{t-lr_i^2}, \quad \forall f, i \in n, t, \quad (19)$$

$$\sum_{f^*, i^* \in n} S_{f^* di^*}^t \leq CD_d X_{fi}^{t-lr_i^2}, \quad \forall d, i \in n, f, t, \quad (20)$$

Constraints (17) and (18) represent the capacity of generic pharmaceutical products at P&D centers, respectively. Accordingly, Eqs. (19) and (20) indicate the capacity of innovative pharmaceutical products in P&D centers.

#### 4.5 New product allocation

We also develop a set of constraints and equations to rationalize the new product allocation in both explorative and exploitative planning.

$$Q_{fi}^t \leq M X_{fi}^t, \quad \forall f, i \in n, t, \quad (21)$$

$$\sum_{t^* \leq t} X_{fi}^{t^*} \geq X_{fi}^{t+dl_i}, \quad \forall f, t, i \in n, \quad (22)$$

$$\sum_{i \in n} X_{fi}^t = 1, \quad \forall f, t, \quad (23)$$

$$X_{fi}^t \leq X_i^{t''}, \quad \forall f, i \in n, t, \quad (24)$$

Constraint (21) indicates that if an innovative pharmaceutical product is produced, it should have been previously available for market entry at the end of R&D processes. According to Eq. (22), once the innovative pharmaceutical product arrives at time periods less than  $t$ , it should have passed from the R&D process at least for a period of  $t$  to be able to enter the production line. In this vein, Constraint (23) implies that in each production center, only one innovative pharmaceutical product can be researched and developed and then entered the production line. We also develop Constraint (24) to indicate that a pharmaceutical product must earn IFDA approval once it enters the production line.

#### 4.6 Perishability constraints

Perishability may influence supply chain network planning, especially in the exploitative phase. The related restrictions are formulated in Eqs. (25) and (26).

$$\sum_{t''=1}^t Q_{fi}^{t''} - \sum_{t''=1}^{\min(t+exf_i, T)} S_{fdi}^{t''} = ref_{fit}, \quad \forall f, d, i, t \neq T, \quad (25)$$

$$\sum_{t''=1}^t S_{fdi}^{t''} - \sum_{t''=1}^{\min(t+exf_i, T)} S_{dgi}^{t''} = ref_{dit}, \quad \forall f, d, g, i, t \neq T, \quad (26)$$

Equation (25) reflects the number of deteriorated pharmaceutical products in production center  $f$  at each time period. Equation (26) assigns the number of deteriorated pharmaceutical products in distribution center  $d$  at each time period. It is noteworthy that the medicines produced in period  $t$ . Are maximally consumable up to  $t + exf_i$  according to the First In, First Out (FIFO) warehouse management system.

#### 4.7 Shipping contract constraints

FOB and CIF are the most common international shipping agreements in transporting goods between a buyer and a seller, which are formalized in Eqs. (27)–(31).

$$\sum_i y c_{fdi}^t \geq y_{fd}^t, \quad \forall f, d, t, \quad (27)$$

$$\sum_i y f_{fdi}^t \geq y_{fd}^t, \quad \forall f, d, t, \quad (28)$$

$$y f_{fd}^t + y c_{fd}^t \leq S_{fdi}^t \leq (y f_{fdi}^t + y c_{fdi}^t) M, \quad \forall f, d \in d^f, t, i, \quad (29)$$

According to constraints (27) and (28), the FOB and CIF contracts are applied between a production center and a distribution center once these two center connected. Constraint (29) ensures that the shipping contract is only agreed upon once the flow of goods between a production center and a distribution center exists.

$$\overline{TRC}_{f di}^t \leq trc_{f di}^t \leq \overline{TRC}_{f di}^t, \quad \forall f, d \in d^f, t, i, \quad (30)$$

$$\overline{TRF}_{f di}^t \leq trf_{f di}^t \leq \overline{TRF}_{f di}^t, \quad \forall f, d \in d^f, t, i, \quad (31)$$

Equations (30) and (31) introduce the upper and lower bounds of transfer prices under the CIF and FOB contracts, respectively.

#### 4.8 Non-negativity and binary constraints

Equations (32) and (33) are proposed to reinforce the decision variable types.

$$y_{fd}^t, y_{dg}^t, yf_{f di}^t, yc_{f di}^t, X_{fi}^t, X_{fi}^{\prime\prime}, X_i^{\prime\prime\prime} \in \{0, 1\}, \quad \forall f, d, g, i, t, \quad (32)$$

$$I_{fi}^t, I_{di}^{\prime\prime}, S_{f di}^t, S_{dg}^t, Q_{fi}^t, z_f^{t+}, z_f^{t-}, z_d^{t+}, z_d^{t-}, trf_{f di}^t, trc_{f di}^t \geq 0, \quad \forall f, d, g, i, t. \quad (33)$$

### 5 Solution methodology

#### 5.1 Linearization of the proposed model

The proposed model is nonlinear due to several terms of the objective functions. One is the minimum–maximum structure formulated in the second objective function (Eq. (8)). The following linearization method is used to transform this objective function into linear.

$$Min z_2 = \theta \quad (34)$$

$$s.t. \quad \theta \geq \pi_i \left( D_{gi}^t - \sum_d S_{dg}^{t-L_{dg}} \right), \quad \forall g, i, \quad (35)$$

In the first term of Eq. (5), three variables are multiplied, leading to another source of nonlinearity. These three comprise two continuous variables ( $S_{f di}^t, trf_{f di}^t$ ) and one binary variable ( $yf_{f di}^t$ ). To convert this expression to a linear form, we first define the multiplication of the continuous variable  $S_{f di}^t$  and the binary variable  $yf_{f di}^t$  through the development of a new variable  $w_{f di}^t = S_{f di}^t yf_{f di}^t$ . We apply the technique proposed by Chang and Chang (2000) and include Constraints (36), (37) and (38) to the model.

$$w_{f di}^t \leq S_{f di}^t, \quad \forall f, d \in d^f, t, i, \quad (36)$$

$$w_{f di}^t \leq M yf_{f di}^t, \quad \forall f, d \in d^f, t, i, \quad (37)$$

$$w_{f di}^t \geq S_{f di}^t - M yf_{f di}^t, \quad \forall f, d \in d^f, t, i, \quad (38)$$

These three constraints suggest that if  $yf_{f di}^t$  is equal to zero, the auxiliary variable  $w_{f di}^t$  will be zero, as well. Otherwise, if  $yf_{f di}^t$  is equal to one, the variable  $w_{f di}^t$  will be equal to

$S_{fdi}^t$ . We then apply the method proposed by Vidal and Goetschalckx (2001) to convert the multiplication of the three variables to the multiplication of two continuous variables,  $w_{fdi}^t$  and  $trf_{fdi}^t$ . This method helps us linearize and simplify the multiplication. Nobly, at least one of the continuous variables must be characterized by the upper and lower limits to allow the multiplication of two variables. The variable  $trf_{fdi}^t$  has upper and lower limits and can be used for linearization. In this method, the multiplication of these two continuous variables is defined by the development of a new variable  $r_{fdi}^t = w_{fdi}^t trf_{fdi}^t$ . By replacing this variable, Constraint (31) is converted to Eq. (39).

$$\overline{TRF_{fdi}^t} w_{fdi}^t \leq r_{fdi}^t \leq \overline{TRF_{fdi}^t} w_{fdi}^t, \quad \forall f, d \in d^f, t, i, \quad (39)$$

We apply the same approach explained above to convert the second term of Eq. (5) to a linear term. Consequently, the multiplication of the continuous variable  $S_{fdi}^t$  and the binary variable  $yc_{fdi}^t$  are considered by defining the new variable  $w_{fdi}^t = S_{fdi}^t yc_{fdi}^t$ . By replacing the new variable in the corresponding equations, the following Constraints should be added:

$$w_{fdi}^t \leq S_{fdi}^t, \quad \forall f, d \in d^f, t, i, \quad (40)$$

$$w_{fdi}^t \leq M yc_{fdi}^t, \quad \forall f, d \in d^f, t, i, \quad (41)$$

$$w_{fdi}^t \geq S_{fdi}^t - M yc_{fdi}^t, \quad \forall f, d \in d^f, t, i, \quad (42)$$

Using the linearization method, the multiplication of the three binary variables is converted to the multiplication of the two continuous variables  $w_{fdi}^t$  and  $trc_{fdi}^t$ . To correct the multiplication of these two continuous variables in the method, the new variable  $r_{fdi}^t = w_{fdi}^t trc_{fdi}^t$  is defined and replaced by the corresponding equations. By replacing this variable, Constraint (30) is transformed to Eq. (43).

$$\overline{TRC_{fdi}^t} w_{fdi}^t \leq r_{fdi}^t \leq \overline{TRC_{fdi}^t} w_{fdi}^t, \quad \forall f, d \in d^f, t, i, \quad (43)$$

In addition, Constraints (3) and (6) contain non-linear expressions that should be changed to the following linear expressions:

$$\begin{aligned} z_d^{t+} - z_d^{t-} = & \sum_{g,i} P_{di} S_{dgi}^t EX_t - \sum_{f,i} r_{fdi}^t EX_t - \sum_{f,i} r_{fdi}^t EX_t - \sum_f (TC_{fd}^2 + IN) y_{fd}^t EX_t \\ & - \sum_f TC_{dg}^3 y_{fd}^t EX_t - \sum_{f,i} DR_{di}^t r_{fdi}^t EX_t - \sum_{f,i} DR_{di}^t (TC_{fd}^2 + IN) y_{fd}^t EX_t \\ & - \sum_{f,i} DR_{di}^t r_{fdi}^t EX_t - \sum_{d,i} CI_{di} I_{di}^t EX_t - \sum_{g,i} \mu_i P_{di} S_{dgi}^t EX_t - It \sum_g L_{dg} y_{dg}^t EX_t \\ & - \sum_g TC_{dg} y_{dg}^t EX_t \quad \forall d \in d^f, t, \end{aligned} \quad (44)$$

$$\begin{aligned} z_f^{t+} - z_f^{t-} = & \sum_{d \in d^f, i} r_{fdi}^t EX_t + \sum_{d \in d^f, i} r_{fdi}^t EX_t + \sum_{d \in d^f, i} P I_{fdi}^t S_{fdi}^t \\ & - \sum_{d \in d^f, i} TC_{fd}^1 y_{fdi}^t EX_t - \sum_{d \in d^f, i} (TC_{fd}^1 + TC_{fd}^2 + IN) y_{fdi}^t EX_t \\ & - \sum_{d \in d^f} (TC_{fd}' + IN') y_{fd}^t - \sum_i CI_{fi} I_{fi}^t - \sum_i CP_{fi} Q_{fi}^t \\ & - It \sum_d L_{fd} y_{fd}^t \quad \forall f, t, \end{aligned} \quad (45)$$

## 5.2 Robust possibilistic programming approach

Some critical parameters like demand, production cost, delay cost, R&D cost, P&D capacity in production, domestic and external distribution centers, marketing cost, and exchange rates are disrupted by complexities and uncertainties within a supply chain network. Due to the nature of pharmaceutical products and their production (from R&D to trials to P&D) in complex and uncertain environments, historical data is barely ascertainable and accessible in the pharmaceutical industry. Therefore, many studies suggest estimating these critical parameters through experts' opinions and experiences. One reason for this unavailability is that future innovative pharmaceutical products may not necessarily follow the same pattern as other products. The other reason is the high level of data confidentiality, especially in R&D and production phases that prevent an accurate estimation of these critical parameters. Therefore, some of the parameters, like  $\widetilde{D_{gi}^t}$ ,  $\widetilde{CP_{fi}}$ ,  $\widetilde{DLC_{ft}}$ ,  $\widetilde{CDNP_i^1}$ ,  $\widetilde{CDNP_i^2}$ ,  $\widetilde{PC_{fi}}$ ,  $\widetilde{C_d}$ ,  $\widetilde{CF_{fi}}$ ,  $\widetilde{CD_d}$ ,  $\widetilde{\mu_i}$  and  $\widetilde{EX_t}$  in our model, are shown in the form of trapezoidal fuzzy numbers to help us better estimate the role of the parameters.

Fuzzy mathematical programming can be generally classified via two approaches (Alem & Morabito, 2012): (i) objective function targets and constraints with flexibility and variability and (ii) the exact value of input parameters due to the lack of data and knowledge (i.e., epistemic uncertainty). The former approach uses fuzzy rule-based systems to determine a set of alternatives for decision-makers. The latter approach uses a possibilistic programming method to deal with uncertainty due to the lack of prior information and knowledge on the exact value of input variables. It is noteworthy that non-deterministic parameters can be modeled by a set of appropriate functions, like triangular or trapezoidal functions, while the model relies only on the knowledge and experience of domain experts.

In our PSC planning problem, some parameters are disrupted by epistemic uncertainty; a possibilistic programming method would help cope with such imprecise parameters. In the literature of possibilistic programming, several methods are introduced to confront imprecise coefficients in objective functions and constraints (see Jiménez et al., 2007; Pishvaei & Khalaf, 2016). In the solution method presented in this paper, the method proposed by Liu (2004) is used to transform the proposed model using the possibilistic programming method. Instead of the possibility (*Pos*) and necessity (*Nec*) measures, which do not have a self-duality property to build a fuzzy chance-constrained programming (FCCP) model, Liu (2004) proposed the credibility measurement as a self-dual measure. We follow this method and formulate the FCCP model based on the problem described in this study. The compact form of the developed model is presented as follows:

$$\begin{aligned} Maxz_1 &= \widetilde{F}'x - \left( \widetilde{F}x + \widetilde{C}y \right), \\ Minz_2 &= x, \\ Maxz_3 &= Nx, \end{aligned}$$

$$\begin{aligned}
& s.t. \\
& Ax = 0, \\
& Jx \geq 0, \\
& Sy \geq 0, \\
& Rx \leq My, \\
& L'x \geq \tilde{D}, \\
& Lx \leq \tilde{D}, \\
& Ox \leq \widetilde{PC}, \\
& O'x \leq \tilde{C}, \\
& Bx \leq \widetilde{CF}y, \\
& B'x \leq \widetilde{CD}y, \\
& Py = 1, \\
& Dx \geq Qy, \\
& y \in \{0,1\}, \quad x \geq 0
\end{aligned} \tag{46}$$

Vectors of  $C, F, F', D, PC, PD, CF, CD$  represent the cost of the binary variable, the cost of the continuous variable, revenue, demand, and the capacity of manufacturing and distribution centers for generic and innovative pharmaceutical products, respectively. In addition,  $A, J, S, R, L', L, O, O', B, B', P, D, Q, M$  show the coefficient matrices, and  $x$  and  $y$  specify the continuous and binary variables. Finally,  $\tilde{C}, \tilde{F}, \tilde{F}', \tilde{D}, \widetilde{PC}, \widetilde{PD}, \widetilde{CF}, \widetilde{CD}$  represent the uncertain parameters. Assuming that a minimum satisfaction degree of possibilistic chance constraints is controlled by  $\beta', \beta, \alpha, \vartheta, \partial, \aleph, \rho$ , the following crisp equivalent model could be achieved using the credibility measure.

$$\begin{aligned}
Maxz_1 &= \left( \frac{F'_1 + F'_2 + F'_3 + F'_4}{4} \right) x - \left[ \left( \frac{F_1 + F_2 + F_3 + F_4}{4} \right) x + \left( \frac{C_1 + C_2 + C_3 + C_4}{4} \right) y \right] \\
& s.t. \\
& (2 - 2\beta')D_3 + (2\beta' - 1)D_4, \\
& Lx \leq (2 - 2\beta)D_2 + (2\beta - 1)D_1, \\
& Ox \leq (2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1, \\
& O'x \leq (2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1, \\
& Bx \leq ((2 - 2\aleph)CF_2 + (2\aleph - 1)CF_1)y, \\
& B'x \leq ((2 - 2\rho)CD_2 + (2\rho - 1)CD_1)y,
\end{aligned} \tag{47}$$

In a study by Pishvae et al. (2012), the concept and mathematical modeling of the RPP approach were developed and conceptualized to ensure the robustness of the solution. This approach helps find the optimal value of the minimum satisfaction degree of chance constraints, as well as control the worst-case value of objective functions that enables managers to better decide about situations with high complexity and uncertainty. Our study benefits from the RPP method developed by Pishvae et al. (2012). Equation set (47) presents the robust form of our main model:

$$\begin{aligned}
MaxE[z_1] &+ \gamma(E[z_1] - z_{1\min}) + \pi'(D_4 - (2 - 2\beta)D_3 + (2\beta - 1)D_4) + \vartheta((2 - 2\beta)D_2 \\
&+ (2\beta - 1)D_1 - D_1) + \sigma((2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1 - PC_1) \\
&+ \tau((2 - 2\partial)C_2 + (2\partial - 1)C_1 - C_1) + \omega[((2 - 2\aleph)CF_2 + (2\aleph - 1)CF_1 - CF_1)]y \\
&+ \varphi[((2 - 2\rho)CD_2 + (2\rho - 1)CD_1 - CD_1)]y \\
Minz_2 &= x + \pi'(D_4 - (2 - 2\beta)D_3 + (2\beta - 1)D_4) + \vartheta((2 - 2\beta)D_2 + (2\beta - 1)D_1 - D_1) \\
Maxz_3 &= Nx + \pi'(D_4 - (2 - 2\beta)D_3 + (2\beta - 1)D_4) + \vartheta((2 - 2\beta)D_2 + (2\beta - 1)D_1 - D_1)
\end{aligned}$$

$$\begin{aligned}
& + \sigma((2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1 - PC_1) \\
& + \tau((2 - 2\vartheta)C_2 + (2\vartheta - 1)C_1 - C_1) \\
& + \omega[(2 - 2\aleph)CF_2 + (2\aleph - 1)CF_1 - CF_1]y \\
& + \varphi[(2 - 2\rho)CD_2 + (2\rho - 1)CD_1 - CD_1]y \\
& s.t. \\
& L'x \geq (2 - 2\beta')D_3 + (2\beta' - 1)D_4, \\
& Lx \leq (2 - 2\beta)D_2 + (2\beta - 1)D_1, \\
& Ox \leq (2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1, \\
& O'x \leq (2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1, \\
& Bx \leq ((2 - 2\aleph)CF_2 + (2\aleph - 1)CF_1)y \\
& B'x \leq ((2 - 2\rho)CD_2 + (2\rho - 1)CD_1)y \\
& 0.5 < \alpha, \beta, \vartheta, \aleph, \rho \leq 1.
\end{aligned} \tag{48}$$

In which  $z_{1 \min}$  is calculated as follows:

$$z_{1 \min} = (F'_1 - F_1)x + C_1y \tag{49}$$

In the robust model, the worst value of the objective function  $z_{1 \min}$  occurs when the non-deterministic parameters in the objective function are placed in the worst possible values (Homayooni et al., 2023, Gholizadeh et al., 2021). In our study, they occur in their minimum value. The first term of this objective function is associated with the expected value of the original objective function. The second term is related to the over-deviation penalty cost obtained from the expected value. This value proves the optimality robustness. The remainder expressions describe the violation cost of constraints. All these values are presented in Model (48). Model (48) is nonlinear based on the multiplication of  $\aleph.y$  and  $\rho.y$ . To convert this model to a linear model, two continuous variables  $\varphi$  and  $\omega$  are fined and added into the model:

$$\begin{aligned}
\omega' &= \aleph \times y \\
\varphi' &= \rho \times y
\end{aligned}$$

To ensure the correct value for the two newly defined variables, the following constraints are added to the model:

$$\begin{aligned}
Bx &\leq 2(y - \omega')CF_2 + (2y - \omega')CF_1, \\
\omega' &\leq M \times y, \\
\omega' &\geq M \times (y - 1) + \aleph, \\
\omega' &\leq \aleph, \\
B'x &\leq 2(y - \varphi')CD_2 + (2y - \varphi')CD_1, \\
\varphi' &\leq M \times y, \\
\varphi' &\geq M \times (y - 1) + \rho, \\
\varphi' &\leq \rho, \\
\omega', \varphi' &\in [0, 1].
\end{aligned} \tag{50}$$

We then convert the first and third objective functions of the presented model to linear forms using Eq. (51):

$$\begin{aligned}
& MaxE[z_1] + \gamma(E[z_1] - z_{1 \min}) + \pi'(D_4 - (2 - 2\beta)D_3 + (2\beta - 1)D_4) \\
& + \vartheta((2 - 2\beta)D_2 + (2\beta - 1)D_1 - D_1) + \sigma((2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1 - PC_1)
\end{aligned}$$



$$\begin{aligned}
& + \tau((2 - 2\partial)C_2 + (2\partial - 1)C_1 - C_1) + \omega(2(y - \omega')CF_2 + (2y - \omega')CF_1 - CF_1) \\
& + \varphi(2(y - \varphi')CD_2 + (2y - \varphi')CD_1 - CD_1) \\
\text{Max} z_3 = & Nx + \pi'(D_4 - (2 - 2\beta)D_3 + (2\beta - 1)D_4) + \vartheta((2 - 2\beta)D_2 + (2\beta - 1)D_1 - D_1) \\
& + \sigma((2 - 2\alpha)PC_2 + (2\alpha - 1)PC_1 - PC_1) + \tau((2 - 2\partial)C_2 + (2\partial - 1)C_1 - C_1) \\
& + \omega(2(y - \omega')CF_2 + (2y - \omega')CF_1 - CF_1) + \varphi(2(y - \varphi')CD_2 + (2y - \varphi')CD_1 - CD_1) \quad (51)
\end{aligned}$$

We also apply the well-known method of  $\epsilon$ -constraint (Haimes, 1971) to cope with multiple objectives of the presented model. In this method, one objective is chosen to be optimized, and the others are formulated as constraints so that their right-hand-side values (upper bounds),  $\epsilon_i$ , are changed systematically to achieve different Pareto solutions (Chaleshtori et al., 2020). Equation (52) formulates this procedure.

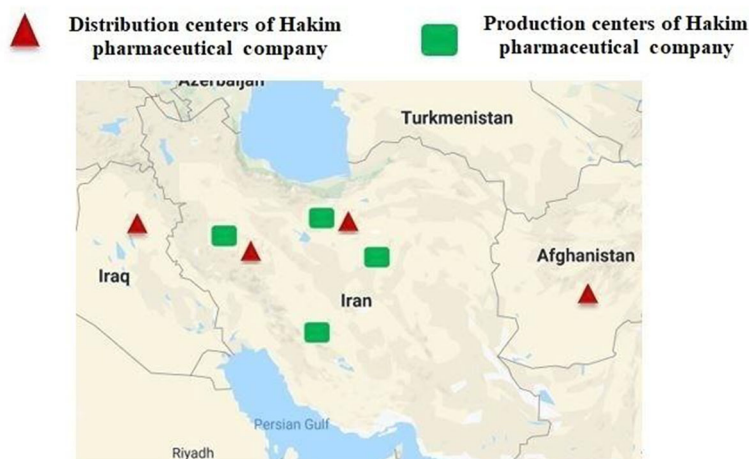
$$\begin{aligned}
& \text{Min} f_j(x) \\
& \text{s.t.} \\
& f_i(x) \leq \epsilon_i \quad \forall i \neq j \\
& x \in \text{feasibleregion} \quad (52)
\end{aligned}$$

## 6 Implementation and evaluation of the model

We implement our model in an authentic case study to examine how the model would perform in varied real scenarios. We collected data from one of the largest pharmaceutical companies in Iran, Hakim pharmaceutical company (HPC), which produces both innovative and generic pharmaceutical products. Other than domestic consumption, the products of HPC are exported to countries like Iraq, Afghanistan, Pakistan, United Arab Emirates, Qatar, Turkmenistan, Syria, and Armenia (HPC, 2021). HPC produces Gemfibrozil, Pregabalin, and Pioglitazone as innovative pharmaceutical products and Acetaminophen, Ibuprofen, and Omeprazole as generic products. The HPC's supply chain includes the R&D sector, production sites, and distribution centers. Due to the high-level confidentiality in data and the low level of R&D activities in the generic products, we only collected and analyzed the data for the innovative pharmaceutical products. We reiterate that the main objective of this study is to integrate R&D planning (explorative approach) and P&D planning (exploitative approach) to determine whether the integrated model can increase the profitability of innovative products in a global PSC. Therefore, the data relating to the innovative products can better examine the applicability of our model.

### 6.1 Case study

We found that the planning horizon for both the R&D and P&D of innovative products in HPC consists of twelve-time windows (each time window equals six months). This process often lasts for six years ( $T = 12$ ). The HPC's supply chain includes four production centers ( $F = 4$ ) and four distribution centers ( $D = 4$ ). The geographical locations of these facilities are illustrated in Fig. 4. As evident in Fig. 4, HPC has two external centers ( $D^f = 2$ ) and two domestic centers ( $D^h = 2$ ). It is noteworthy that in our model, we considered four customer groups and six product families, including three generic ( $I^o = 3$ ) and three innovative ( $I^n = 3$ ) products. This shows that the problem size is equal to  $12 \times 4 \times 4 \times 4 \times 6$ . In other words, the problem described in this study can be categorized as a medium-sized problem.



**Fig. 4** Geographical locations of P&D centers of HPC

To resolve such a problem, we used a personal computer with INTEL core i7 and 8 GB of RAM, helping us find the 20 distinct Pareto optimal solutions within one hour and 13 min.

Table 4 shows the detailed demand values for each pharmaceutical product and customer.<sup>1</sup>

## 6.2 Results

Using the HPC data, the proposed robust possibilistic programming model is coded in GAMS optimization software and solved by the CPLEX solver. Robust optimization is critically important for several reasons, as can be seen in the context of the use of our robust possibilistic programming model. When dealing with complex systems such as the production of pharmaceuticals, several variables need to be considered simultaneously. These variables can range from production rates, time windows, capacity allocation, delays in R&D, and production timelines, all of which are inherently uncertain. In the absence of robust optimization, these uncertainties could lead to suboptimal or even incorrect decision-making, resulting in potentially significant losses in profit and efficiency.

The model that we coded in the GAMS optimization software and solved using the CPLEX solver, demonstrated this clearly. The results (as presented in Table 5) showed the optimal production amount of generic and innovative pharmaceutical products in each time window, providing key insights for production planning. Particularly, the model was able to effectively manage delays in R&D and production of innovative products, suggesting optimal times to introduce these products into the production line to maximize profit.

For instance, our integrated model recommended that production of product (1.4) should commence in production center No.1 at the sixth time window ( $t_7$ ) with a capacity of 3500 units per time window over the remaining six-time windows ( $t_7$ – $t_{12}$ ). This specific allocation and timing strategy is derived from a deep understanding of the ambidextrous nature of integrating R&D and production functions in our model. The optimized strategy proposed by the model demonstrates that a new production capacity can lead to maximizing the total profit. Thus, the robust optimization approach significantly contributes to decision-making

<sup>1</sup> We did not present other parameters due to the high level of confidentiality for the HPC data.

Table 4 Demand for each medication

Customer medication ( $g.i$ )	$D_{gi}^f \times 1000$				Customer medication ( $g.i$ )				$D_{gi}^f \times 1000$			
	$T1 - T12$				$T1 - T12$				$T1 - T12$			
	$D_{gi}^f(1)$	$D_{gi}^f(2)$	$D_{gi}^f(3)$	$D_{gi}^f(4)$	$D_{gi}^f(1)$	$D_{gi}^f(2)$	$D_{gi}^f(3)$	$D_{gi}^f(4)$	$D_{gi}^f(1)$	$D_{gi}^f(2)$	$D_{gi}^f(3)$	$D_{gi}^f(4)$
1.1	285	300	3.1	330	3.1	3.1	3.1	170	161.5	178.5	187	
1.2	190	200	3.2	220	3.2	3.2	3.2	100	95	105	110	
1.3	38	40	3.3	44	3.3	3.3	3.3	4	3.8	4.2	4.4	
1.4	20.9	22	3.4	24.2	3.4	3.4	3.4	22	20.9	23.1	24.2	
1.5	332.5	350	3.5	385	3.5	3.5	3.5	350	332.5	367.5	385	
1.6	2.85	3	3.6	3.3	3.6	3.6	3.6	3	2.85	3.15	3.3	
2.1	142.5	150	157.5	165	4.1	4.1	4.1	250	237.5	262.5	275	
2.2	66.55	70	73.5	77	4.2	4.2	4.2	70	66.5	73.5	77	
2.3	9.5	10	10.5	11	4.3	4.3	4.3	90	85.5	94.5	99	
2.4	28.5	30	31.5	33	4.4	4.4	4.4	130	123.5	136.5	143	
2.5	285	300	315	330	4.5	4.5	4.5	150	142.5	157.5	165	
2.6	28.5	30	31.5	33	4.6	4.6	4.6	50	47.5	52.5	55	

**Table 5** The optimal amount of production in different periods

	Innovative product ( $f_i$ ) $Q'_{fi} \times 1000$											
	$T$											
	$t_1$	$t_2$	$t_3$	$t_4$	$t_5$	$t_6$	$t_7$	$t_8$	$t_9$	$t_{10}$	$t_{11}$	$t_{12}$
1.1	350	350	350	3500	350	350	350	350	350	350	350	350
1.2	350	350	350	3500	350	350	350	350	350	350	350	350
1.3	121.9	0	0	0	47.5	127.3	350	350	350	350	350	350
1.4	0	0	0	0	0	0	3500	3500	3500	3500	3500	3500
1.5	0	0	0	0	0	3500	0	0	0	0	0	0
1.6	0	0	0	0	0	0	0	0	0	0	0	3500
2.1	145	145	145	145	145	145	145	145	145	145	145	145
2.2	145	145	145	145	145	145	145	145	145	145	145	145
2.3	145	83	126.8	127.3	136.8	145	145	145	145	145	145	145
2.4	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	1450	1450	1450	1450	1450	0
2.6	0	0	0	0	0	1450	0	0	0	0	0	1450
3.1	130	130	130	130	130	130	130	130	130	130	130	130
3.2	130	130	130	130	130	130	130	130	130	130	130	130
3.3	0	0	0	0	0	0	0	0	0.38	130	130	130
3.4	0	0	0	0	0	1300	0	0	0	0	0	0
3.5	0	0	0	0	0	1300	1300	1300	1300	1300	1300	0
3.6	0	0	0	0	0	0	0	0	0	0	0	1300
4.1	190	190	190	190	190	190	190	190	190	190	190	190

Table 5 (continued)

Innovative product ( $f.i$ )	$Q'_{fi} \times 1000$											
	$T$											
	$t1$	$t2$	$t3$	$t4$	$t5$	$t6$	$t7$	$t8$	$t9$	$t10$	$t11$	$t12$
4.2	190	190	190	190	190	190	190	190	190	190	190	190
4.3	0	0	0	0	0	0	85.5	190	190	190	190	190
4.4	0	0	0	0	0	0	0	0	0	0	0	1900
4.5	0	0	0	0	0	1900	0	0	0	0	1900	1900
4.6	0	0	0	0	0	0	1900	1900	1900	1900	0	0

in complex and uncertain environments, ensuring optimal results under a variety of possible conditions.

### 6.3 Pareto solutions

The  $\epsilon$ -constraint method as a posteriori (generation) multi-objective solution method is employed in this study to generate various balanced and unbalanced Pareto solutions (Mavrotas, 2007). The main reason to generate the Pareto solutions is to ensure that the main objective functions can be simultaneously improved, although they may even be contradictory in nature (Engau & Sigler, 2020). To ensure that the objective functions proposed in this study contradict each other yet are coexistent and interlinked, we generated the Pareto solutions using the  $\epsilon$ -constraint method. Figure 5 displays the pairwise conflicts of the objective functions. The monetary values are reported in MIRR (million Rial, the Iranian accuracy). The results in Fig. 5 show that the first objective function (profit maximization) varies in a broader range than the other two objective functions (minimizing maximum dissatisfied demand and maximizing the production of innovative pharmaceuticals).

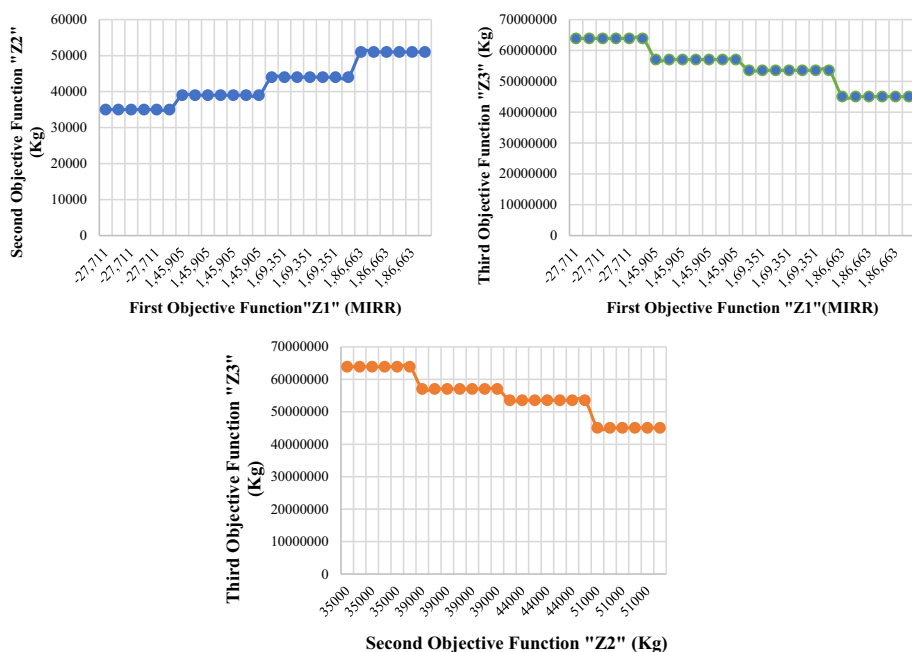


Fig. 5 Pareto solutions generated by the  $\epsilon$ -constraint method

## 6.4 Validation of the proposed model

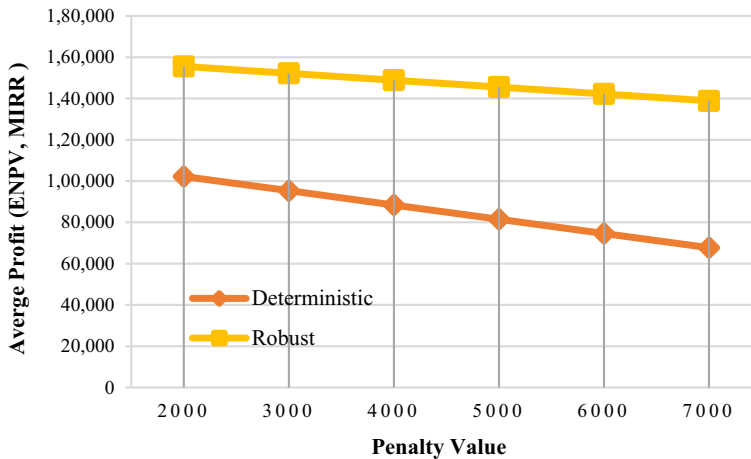
In this section, we develop several simulation tests to analyze the performance of the proposed RPP model. To develop these tests, we apply the validation method presented in Pishvaei et al. (2012). Ten simulation tests are randomly taken on non-deterministic parameters. For each uncertain parameter presented by the trapezoidal membership function (for instance,  $\tilde{d} = (d^1, d^2, d^3, d^4)$ ), a random number must be generated uniformly between the most pessimistic and optimistic values (for example,  $d_{real} = [d^1, d^2]$ ). We then extracted the achieved optimal values of decision variables by solving the RPP model under a nominal value that would later be used in Model (53). The following model is the compact form of the model used to evaluate the solution obtained by the developed robust model.

$$\begin{aligned}
 Max z_1 &= F'x - (Fx + Cy) - \sum_{i,t}^{I,T} pn(\delta_{it}^+ + \delta_{it}^-), \\
 Min z_2 &= x \\
 Max z_3 &= Nx \\
 s.t. \quad & Ax = 0 \\
 & Jx \geq 0 \\
 & Sy \geq 0 \\
 & Rx \leq My \\
 & L'x \geq D^{real} - \delta 1_{it}^+ + \delta 1_{it}^-, \\
 & Lx \leq D^{real} \delta 2_{it}^+ + \delta 2_{it}^-, \\
 & Ox \leq PC^{real} \delta 3_{it}^+ + \delta 3_{it}^-, \\
 & O'x \leq PD^{real} - \delta 4_{it}^+ + \delta 4_{it}^-, \\
 & Bx \leq CF^{real} y - \delta 5_{it}^+ + \delta 5_{it}^-, \\
 & B'x \leq CD^{real} y - \delta 6_{it}^+ + \delta 6_{it}^-, \\
 & Py = 1 \\
 & Dx \geq Qy \\
 & \delta_{it}^+ + \delta_{it}^- = \sum_{n=1}^{n=6} (\delta n_{it}^+ + \delta n_{it}^-) \\
 & \delta n_{it}^+, \delta n_{it}^- \geq 0 \\
 & y \in \{0,1\}, x \geq 0
 \end{aligned} \tag{53}$$

Figure 6 shows the average profit value for the deterministic and robust model solutions under simulation tests and based on varied penalty values (i.e.,  $\delta_{**}^*$ ). Penalty values are used to penalize the violation of constraints under simulation tests. The deterministic stands for the optimization model are developed using Eqs. (1)–(45).

It is noteworthy that when the penalty increases, the use of risk aversion models (i.e., the developed RPP model) is more desirable. Indeed, the RPP model can control the risk of constraint violation and create a reasonable balance between risk and operation costs. Therefore, the proposed robust model results in higher profit for the company than the deterministic model.





**Fig. 6** Average profit with respect to different penalty values for robust and deterministic models

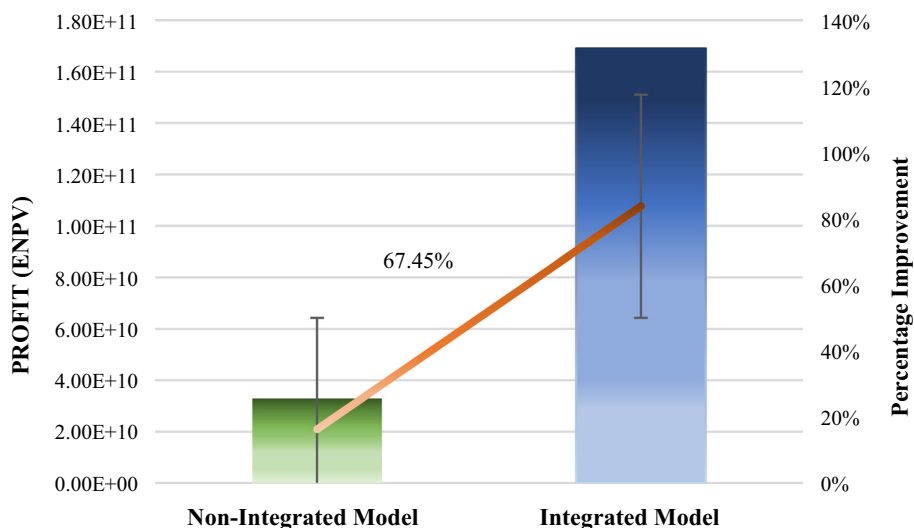
#### 6.4.1 Comparison of the integrated and non-integrated models

We conducted a series of comparative analyses to better understand the performance of the developed model (the integrated model) compared to the non-integrated model. Herein, we name the integrated model by using all formulations provided in Sect. 4. The non-integrated model is implemented by creating two separate models: (1) Manufacturing-distribution model in which the objective functions are optimized by excluding R&D parameters ( $CDNP_i^1 CDNP_i^2$ ) and the related constraints, and (2) R&D model in which the objective functions are optimized by only R&D parameters and the related constraints. We use the results of model (1) for the decision variables as the parameters of this model.

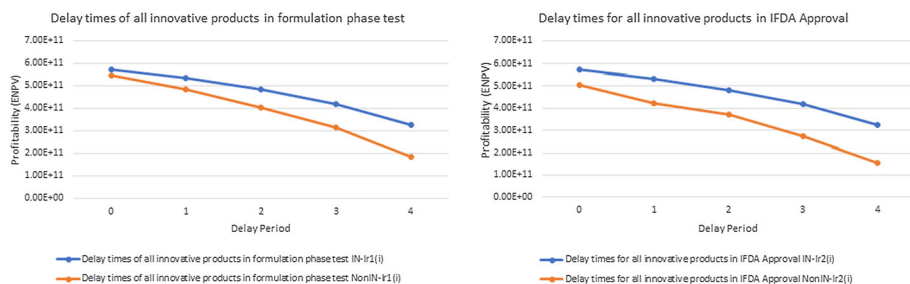
Figure 7 illustrates the performance of both models through the maximization of ENPV in Eq. (1). The results show that the integrated optimization of R&D planning (the explorative approach) and production distribution planning (the exploitative approach) improves the profit up to 67.45%, compared to attempts to optimize planning for these two approaches separately (non-integrated model). Therefore, it can be argued that our model increases the company's profitability in its global supply chain.

Several analyses help us better position the role of the integrated model in the improved profitability of HPC in its supply chain. For example, Fig. 8 exhibits the delay times in producing all innovative products in both the integrated (IN-DLC) and non-integrated (NonIn-DLC) models. The results show the delay times in two stages of the R&D planning (formulation and IFDA approval). Although both the integrated and non-integrated models reduce profitability over the four delay periods (note that zero represents no delay as the first of each stage), the integrated model has less reduced profitability over the four delay periods.

In addition, the integrated model reduced profitability with a lower slope than that of the non-integrated model. Similar trends are reported in Fig. 9, where delays are compared by all product centers (Fig. 9a), between all production centers and distribution centers (Fig. 9b), and between all distribution centers and customer zones (Fig. 9c). While all trends report that delays in both the integrated and non-integrated models declined over time, the integrated model helps the company mitigate the risk of more profit loss than in the non-integrated model. This result may be better explained in Fig. 10, which indicates the accumulated delay



**Fig. 7** The integrated planning model versus the non-integrated model



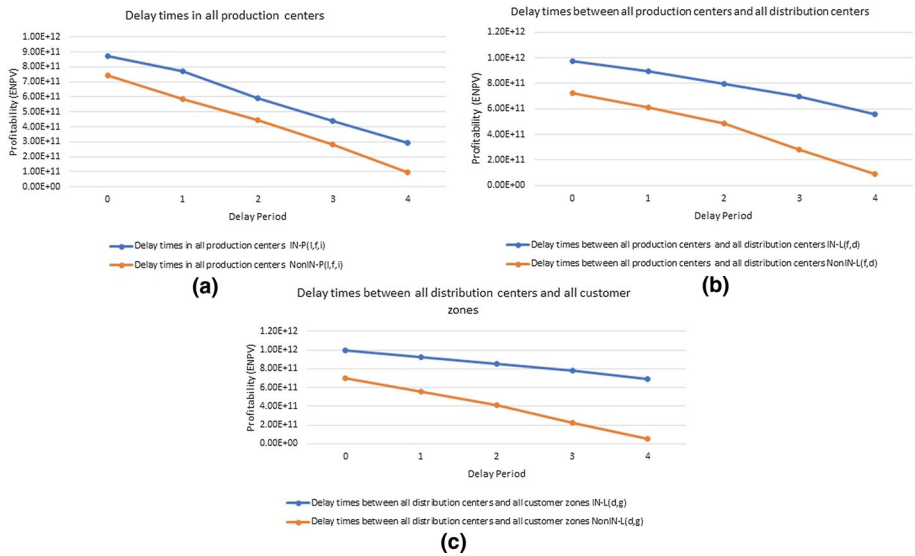
**Fig. 8** Delay times of all innovative products in the R&D phase

times across the supply chain (from R&D to customer zone).

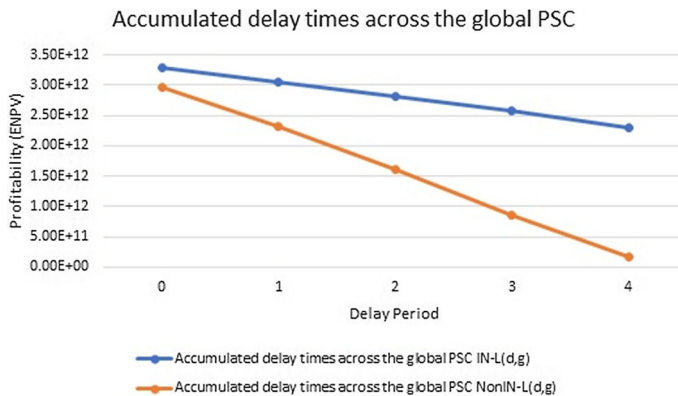
As evident in Fig. 10, delays in the non-integrated model caused a significant decline in the entire global supply chain of innovative products, reducing the profitability to 171,168 MIRR (equivalent to 4,048,930 USD) at delay period 4, based on the exchange rate recorded in December 2021. That is, the profit at delay period 4 in the integrated model has been recorded at 54.290 MIRR, which is equal to only 1,284 USD.

## 6.5 Sensitivity analysis

The most important parameter of our model is the R&D cost. Certainly, a change in the cost of R&D has a significant impact on the selection and production of a new pharmaceutical product. In this regard, the cost impact of the R&D phases, which includes the two phases of formulation test and FDA approval, is evident in Fig. 11. The results show that if the R&D cost increases, the company's profitability will be decreased in both the integrated and non-integrated models. For example, if the R&D cost increases four times, the ENPV of the



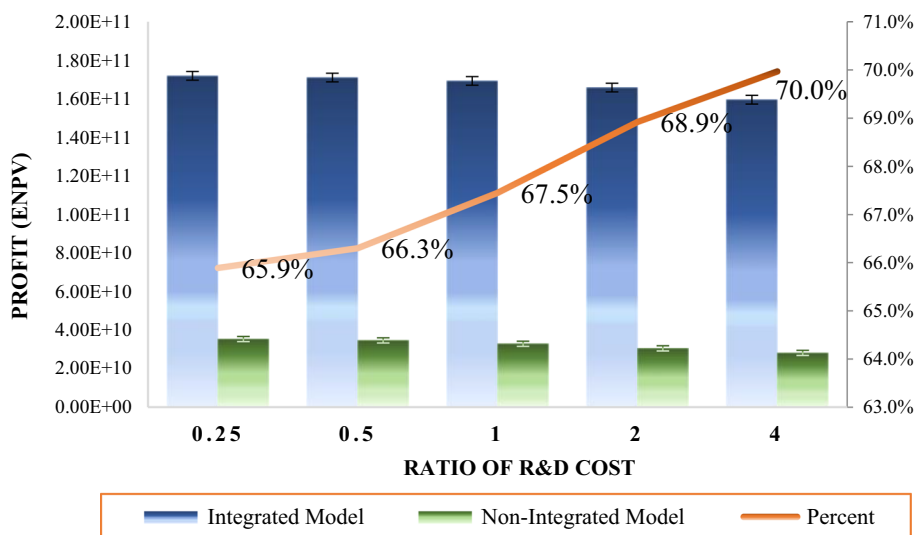
**Fig. 9** Delay times in production centers, distribution centers, and customer zones



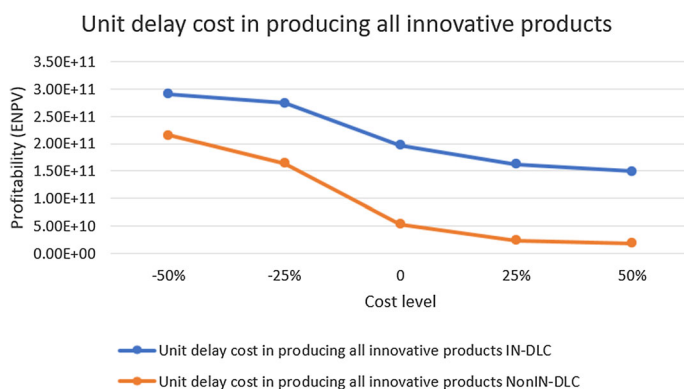
**Fig. 10** Accumulated delay times across the global PSC in both the integrated model (IN) and non-integrated model (NonIN)

integrated and non-integrated models' profits will decrease by 1% and 7.7%, respectively. Therefore, it can be concluded that the integrated model results in more stable solutions than the non-integrated model. If the cost of R&D increases, the superiority of the integrated model over the non-integrated one increases significantly.

Using both models, we also analyzed the unit delay cost in producing all innovative products. As evident in Fig. 12, the results of the integrated model suggest less decline in profitability in all cost levels. However, it is reported that changes in cost level impact both models differently. For example, the profitability differences in both models at the cost levels of + 25% and + 50% are greater than that in - 25% and - 50%. In other words, the more the company increases the production cost of all innovative products, the better the



**Fig. 11** Sensitivity analysis of profit on the integrated and non-integrated models to change the R&D cost parameter

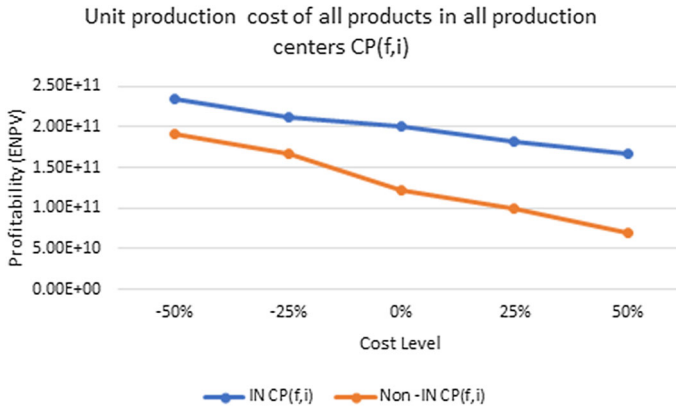


**Fig. 12** Unit delay cost in producing all innovative products

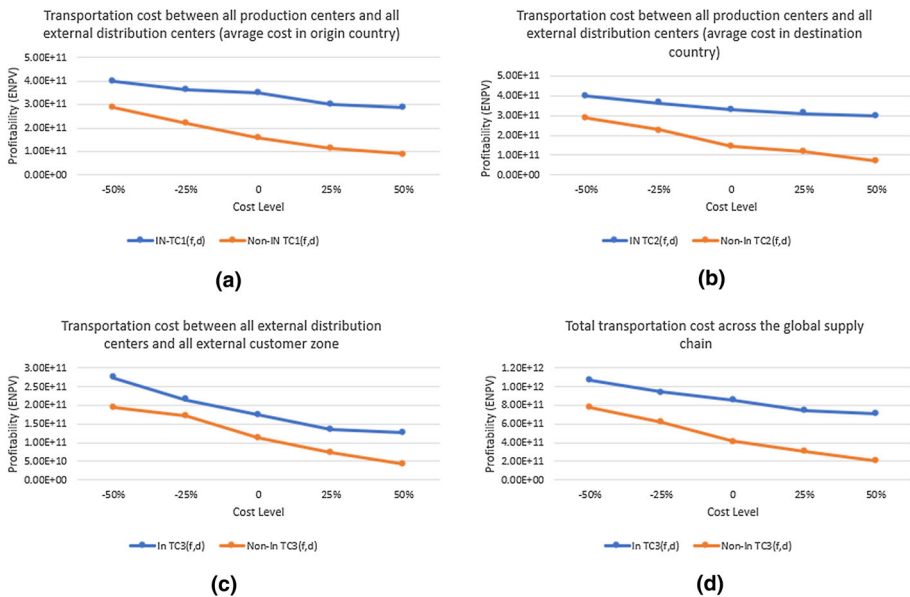
integrated model performs, compared to the non-integrated model. Indeed, the integrated model increases profitability and better manages cost.

Other than the unit delay cost, the unit production cost of all innovative products in all production centers indicates that the integrated model performs better than the non-integrated model (See Fig. 13) in all scenarios (i.e., cost levels of  $-50\%$ ,  $-25\%$ ,  $0\%$ ,  $25\%$ , and  $50\%$ ).

Our analyses indicated that the integrated model could significantly reduce transportation cost in the entire supply chain compared to the non-integrated model. As evident in Fig. 14, we identified four areas in which transportation cost will be significantly impacted: (a) transportation cost between all production centers and all external distribution centers within the origin country; (b) transportation cost between all production centers and all external distribution centers while the products are being shipped toward their destination countries; (c)

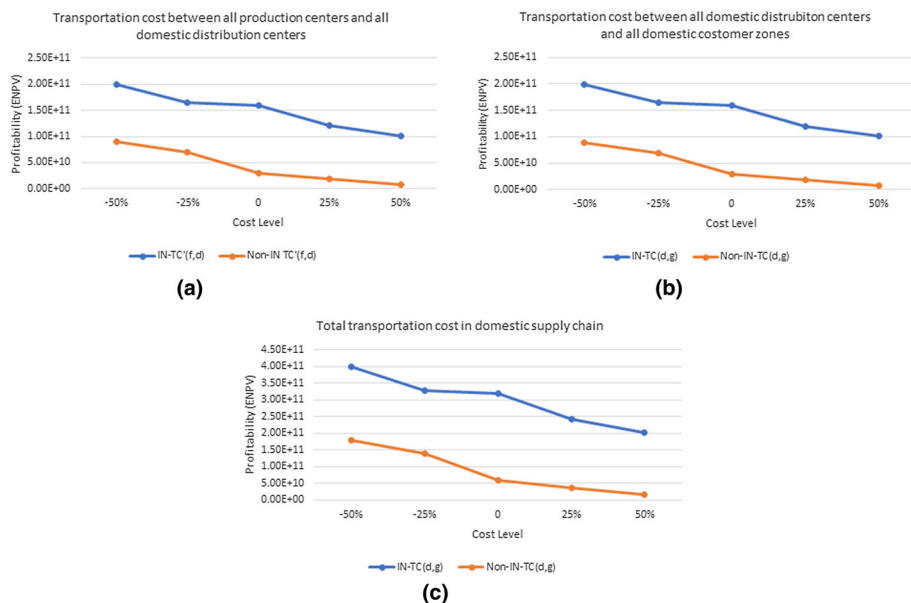


**Fig. 13** Unit production cost of all products in all production centers



**Fig. 14** Transportation cost in different parts of the global supply chain

transportation cost between all external distribution centers and all external customer zones; and (d) total transportation cost across the global supply chain. All sub-figures in Fig. 14 indicate that the integrated model suggests a better performance in varying cost levels. For example, the integrated model suggests a better performance at the cost level of + 25% save USD 4,400,172 in Fig. 14a, USD 4,542,100 in Fig. 14b, USD 1,442,489 in Fig. 14c, and finally USD 10,384,761 in Fig. 14d for the entire supply chain of innovative products. However, cost reduction indices in Fig. 14c appear similar in both integrated and non-integrated models. Thus, although an increase in cost level (from - 50% to + 50%) intensifies the difference in both models to save profitability, Fig. 14c suggests that the change in the cost level does not necessarily

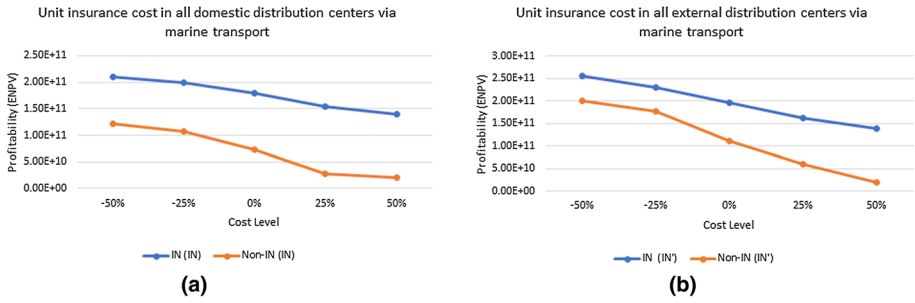


**Fig. 15** Transportation cost in domestic supply chains

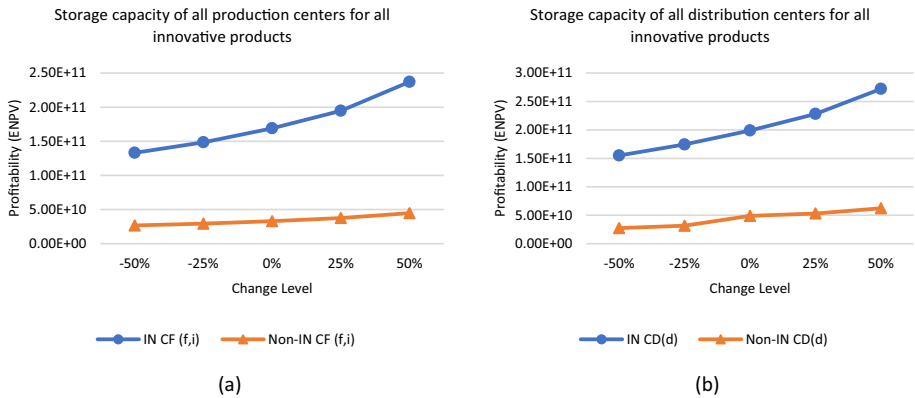
improve profitability. Figure 14d exhibits how the integrated model maintains the total profitability compared to the non-integrated model. According to Fig. 14d, when the company must increase the cost level by 50%, the integrated model will have the best performance compared to the non-integrated model, helping to save up to USD 12,048,099 in the entire supply chain of innovative products.

We found similar patterns for domestic distribution of innovative products, where all transportation costs are calculated within the origin country. Figure 15 exhibits the transportation cost between all production centers (Fig. 15a), between all domestic distribution centers and all domestic customer zones (Fig. 15b), and total transportation cost in the domestic supply chain (Fig. 15c). Figure 15 suggests that the integrated model significantly increases the profit in all five different cost level scenarios. Figure 15a shows that the integrated model generates USD 4,706,105 profit at the cost level of  $-50\%$ , whereas the non-integrated model can only contribute to USD 2,111,546 at the same level. This pattern is also seen in all other cost levels in Fig. 15. However, the most substantial difference in both models can be seen in the cost level of  $0\%$ , where we assume that the company performs as it was when this study was conducted. This means that if the company keeps performing with no change in the transportation cost for domestic purposes, the integrated model will have the maximum difference with the non-integrated model in profit-saving.

One of the most sensitive parameters, especially in global PSCs, is the unit insurance cost. Due to the high level of confidentiality in unit insurance cost in the explorative phase of this study (R&D planning), we only analyze unit insurance cost in distribution centers for all innovative products (exploitative phase). As evident in Fig. 16, unit insurance costs in all domestic distribution centers (Fig. 16a) and all external distribution centers (Fig. 16b) suggest that the integrated model will enable the company to better maintain the level of profitability in all scenarios. The profitability variation of the integrated model in both Fig. 16a and b is less than that in the integrated model, indicating that changes in cost level in the integrated



**Fig. 16** Unit insurance cost in both domestic and external distribution centers



**Fig. 17** Storage capacity of all P&D centers for all innovative products

model have less of an impact than that in the integrated model. In other words, the integrated model is more reliable than the non-integrated model in terms of unit insurance cost.

The other important parameter in this study is associated with storage capacity. Indeed, storage capacity plays a crucial role in maintaining a high level of profitability across the supply chain. As evident in Fig. 17a and b, we analyze the storage capacity of innovative products in all P&D centers, respectively. Other than the better performance of the integrated over the non-integrated model, we found that an increase in capacity level can significantly increase the inventory costs of both P&D centers in the integrated model. For example, the difference in storage capacity of both P&D centers at the change level of 50% is approximately two times greater than that at the change level of – 50%, indicating that the integrated model is more beneficial when the company intends to expand its P&D operations.

## 7 Discussion and conclusion

In this study, we argue that a lack of attention to simultaneous yet mutual understanding of both the explorative and exploitative approaches render suboptimal solutions that may not fully mitigate supply chain risks and significantly improve profitability. However, it may not necessarily be the best possible solution to manage operational costs in the long term.

Drawing from the concept of ambidexterity (Kristal et al., 2010), we argued that the coordination of the explorative and exploitative approaches to supply chain management could improve the system productivity. We, therefore, proposed an integrated planning model for both R&D activities and P&D in the global pharmaceutical supply chain to show how this integration can reduce delays within R&D activities and between R&D activities and P&D of innovative products in the pharmaceutical industry. We developed an RPP model that can manage risks arising from the violation of operational costs and maintain profitability in uncertain and complex environments. Indeed, operational costs in global PSCs rely heavily on changes in regulatory environments (e.g., FDA approval or affordable supply) (Gatica et al., 2003), investments in varying types of products (i.e., innovation versus generic) (Colvin & Maravelias, 2011), and complexity in the process of new product development and commercialization (i.e., innovative business models) (Maravelias & Grossmann, 2001). In this vein, a high level competitiveness in the pharmaceutical industry to capture market share intensifies the importance of operational costs in global PSC success (Kelle et al., 2012). Therefore, it appears impractical to predict operational costs, especially for products that may take a decade to be researched, developed, approved, and commercialized. Our model helps estimate these costs and propose solutions that maintain profitability in different uncertainty scenarios.

In particular, we investigated an integrated decision-making problem context when decisions in R&D planning and P&D planning need to be synchronized. First, we developed a new mathematical model which appropriately integrates the R&D and P&D planning decisions of a global PSC. Our definition generalizes a unique problem setting with inherent delays and uncertainties in R&D activities and other supply chain functions. The deterioration of pharmaceutical products, as well as the delays in R&D phases (formulation test and FDA approval), production, and distribution systems, are incorporated in the proposed model. A novel credibility based RPP model was elaborated upon to adjust the feasibility and optimality robustness of output decisions against uncertainty. With this model, we offered an optimization decision-making support tool that showed how to determine the optimal entrance time of an innovative and urgently needed pharmaceutical product and integrate the R&D and P&D planning systems to ensure more profit for PSCs.

We examined our model using a real-life case-study of a pharmaceutical supply chain that produces both innovative and generic pharmaceuticals. The results showed that the integrated model (the ambidexterity approach) yields significant savings compared to the *either/or* approach to planning for R&D activities and P&D systems. We, therefore, found that the performance of the integrated model is significantly better than that of the non-integrated model.

Concerning the delay times, we found that the integrated model significantly reduced delay times in the entire supply chain (e.g., delays in approval, inventory, quality control, and market entry). According to Shah (2004, p. 933), “the long lead times to make capacity effective mean that decisions often need to be taken at times of high uncertainty. Waiting for the uncertainties to be resolved might delay the time to market by an unacceptable amount.” Our model was able to maintain the efficiency in capacity planning and managing uncertainties to accelerate the process of product commercialization. We also found that with an increase in the number of delays over time, the integrated model can better preserve profitability than the non-integrated model, as the accumulated delay times may jeopardize optimal decision-making in managing the operational costs in the entire supply chain.

We also analyzed the unit production cost of all products in all production centers and found that the integrated model maintains higher profitability than the non-integrated model at all five different scenarios (cost levels of  $-50\%$ ,  $-25\%$ ,  $0$ ,  $25\%$ , and  $50\%$ ). Although some



studies proposed multi-objective models to optimize the clinical trial duration and minimize the operational costs in PSCs, their focus was mainly on the dynamic inventory allocation process (Savadkoobi et al., 2018; Zhao et al., 2019) rather than considering the simultaneous yet interdependent relationships between R&D planning and P&D planning (see Fig. 2). Our results indicate that the integrated model not only preserves higher profits, but also enables the organization to improve efficiency in the most critical parts of the supply chain (e.g., shipping, domestic and international insurance). This result is especially important in light of the building efficient supply chain resilience (Aldrighetti et al., 2021, 2023). All results from the comparison analysis between both non-integrated model and integrated model and sensitivity analysis demonstrated that the integrated model can significantly help to achieve both objective functions.

## 7.1 Theoretical implications and future research directions

This study examined the coexisting yet interlinked approaches to ambidexterity in supply chain management in the context of the global pharmaceutical industry: explorative approach (R&D planning) and exploitative approach (P&D planning). Our study presents a gateway for future studies to consider the concept of ambidexterity in resource allocation planning, risk management, and improved performance in complex environments. It answers the calls of Kristal et al. (2010), Blome et al. (2013), and Aslam et al. (2018) for more research to consider the simultaneous role of exploration and exploitation in supply chain success. The results demonstrate that an integrative approach to both exploration and exploitation could significantly improve the global PSC performance regarding operational costs and unsatisfied demands for innovative products. Our literature review showed that no research has simultaneously targeted these components of a global PSC performance. Therefore, we invite future research to consider our model in other industries focusing on R&D planning and P&D planning for a global supply chain, such as biotechnology, semiconductors, automotive industries, and smart devices.

Our study contributes to the growing literature on supply chain performance and design under disruption and uncertainty (Brusset et al., 2022; Hägele et al., 2023). It emphasizes the vital role of ambidexterity for operational decisions to improve supply chain performance. We, therefore, applied this concept in this study to explain how integration in explorative and exploitative approaches, especially in the global context, can reduce operational costs and maximize unsatisfied demands. This can help achieve supply chain viability (Ivanov, 2022a, 2022b; Ivanov & Keskin, 2023). Indeed, the importance of ambidexterity in supply chain management has been primarily recognized in relation to firm performance and P&D planning. In other words, the research on supply chain performance from the lens of ambidexterity is scarce. In addition, less attention has been paid to the simultaneous and interlinked role of R&D processes and P&D systems across a supply chain, requiring future research to identify and examine factors that generate operational gaps between explorative and exploitative phases in a supply chain. In this study, we considered demand and capacities as uncertain parameters, however, delay parameters as the substantial parameters of the model can also be assumed uncertain. This will enhance the level of complexity for the fuzzy probabilistic model and may a heuristic model be of help for the solution methodology in this case, e.g., using learning approaches (La Torre et al., 2022; Rey et al., 2022; Rolf et al., 2022).

While we did not situate all these decision variables within the problem context for a clearer understanding in this current work, we encourage future studies to incorporate each decision variable within specific problem scenarios. This approach will foster the application

of the model in diverse contexts. Such an exploration can reveal more insights and lead to further fine-tuning of the model. This, we believe, is a worthwhile avenue for future research and development in this field.

## 7.2 Practical and managerial insights

Throughout the development and implementation of our integrated model, we proposed a working decision-making support tool for PSCs and the associated healthcare ecosystems that can accelerate the process of pharmaceutical products' R&D and commercialization while minimizing their operational costs. We believe the model can be applied to all contexts (e.g., the Covid-19 pandemic) that require long-term R&D on innovative products and enormous investments in commercialization. Therefore, this study proposes the following implications for managers in the pharmaceutical supply chains and other supply chains dealing with R&D processes to better make decisions for improving performance. In the case of a pandemic situation, as it needs a quick (not typical) reaction to fight the emergency, we recommend considering tight times and higher monetary values (e.g., unit costs and sales).

First, we encourage managers in pharmaceutical organizations to apply our integrated model for resource allocation, performance improvements, cost management, and risk management across a supply chain. To achieve that, it is recommended to identify delays in operations across organizational processes. For example, R&D processes in many organizations rely strongly on time constraints and the ability to quickly respond to market demands to achieve a competitive advantage over outperforming competitors. These delays may require an in-depth auditing over the working processes and flow of knowledge across the supply chain. It is noteworthy that R&D-based industries requiring high-tech capabilities may be even more fragile to delays than other industries due to uncertainty and competitiveness in the market. Identifying these delays can help managers optimize operational decisions, leading to a significant increase in total profit, as suggested in our integrated model (Ivanov, 2022b). Given the hurdle of delay sensitivity in such organizations, our multi-objective, multi-product, and multi-period model for integrating R&D and production–distribution planning decisions provides solutions within a short period of time, helping managers increase efficiency in operational decisions, especially when dealing with innovative products.

Second, our findings suggested that the integrated model can perform better than the non-integrated model in reducing operational costs (e.g., transportation cost, production cost, insurance, and shipping cost). Indeed, managers can use the insights provided by the results of the authentic case study as input for long-term decisions about continuous improvements in production lines, efficient supply chain networks, and transportation network improvements, with an emphasis on flexibility, resilience, and efficiency in the entire supply chain. Improving the efficiency of production lines and the utilization of global transportation networks enable the global supply chain actors to focus on waste elimination through minimizing waiting times, delays in operations and processes and operational costs, and ultimately encourage managers to develop policies and practices to move organizations more quickly toward global sustainable supply chains. We, therefore, encourage future studies to add constraints and objectives related to environmental concerns into the integrated model (Homayooni et al., 2021). Finally, our proposed model can be extended toward the ripple effect analysis (Dolgui & Ivanov, 2021; Li et al., 2021), correlated stochastic price and demand (Babai et al., 2023), reconfigurable supply chain (Dolgui et al., 2020), contracting in PSCs (Choi et al., 2023), modelling with incomplete information (La Torre & Mendivil, 2022), inclusion of a disease

dynamics (Broekaert et al., 2022; Brusset et al., 2022; Rozhkov et al., 2022), and intertwined supply networks (Ghanei et al., 2023; Ivanov & Dolgui, 2020; Liu et al., 2022).

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