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ORIGINAL RESEARCH

An integrated framework for modeling pharmaceutical supply chains with disruptions and risk mitigation

Aman Goswami[1] · **Alok Baveja**[2] · **Xin Ding**[1] · **Benjamin Melamed**[2] · **Fred Roberts**[3]

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Abstract
Supply-chain disruptions have numerous causes, including criminal actions, as well as natural disasters and human errors. The complexity of modern supply chains makes it challenging to detect, mitigate, or resolve disruptions. This paper presents an integrated framework for modeling pharmaceutical supply chains (PSCs), incorporating disruptions and mitigations. Based on extensive discussions with supply chain SMEs (subject matter experts) and federal government security officials, this framework unfolds in two steps: (1) a mapping process constructs a supply chain map from a focal firm's perspective, and (2) the supply chain map is overlaid with various types of disruptions that can occur at supply chain locations. To this end, the paper systematically classifies PSC disruptions based on historical data and expert opinion. The paper discusses various pre-disruption and post-disruption mitigations and reports gleaned insights into their efficacy. Finally, the paper discusses the generalizability of this integrated framework to other supply chains, such as medical devices and satellite solar panels.

Keywords Supply chain mapping · Supply chain disruptions · Pharmaceutical supply chains · Disruption mitigation strategies

1 Introduction

The COVID-19 pandemic has exposed vulnerabilities in supply chains worldwide (Choi et al., 2020; Queiroz et al., 2022; Shih, 2020). Challenges experienced by businesses and customers included a lack of supply chain visibility, global shortages, supply delays, port congestion, backlogged deliveries, increased transportation costs, and labor shortages. The

✉ Aman Goswami
ag1814@business.rutgers.edu

1 Department of Supply Chain Management, Rutgers Business School - Newark and New Brunswick, Rutgers University, Newark, NJ 07102, USA

2 Department of Supply Chain Management, Rutgers Business School - Newark and New Brunswick, Rutgers University, Piscataway, NJ 08854, USA

3 Department of Mathematics and CCICADA, Rutgers University, Piscataway, NJ 08854, USA

extent and severity of the crisis were unprecedented, with over 90% of Fortune 1000 companies reportedly facing supply chain disruptions during 2020–23 (Sherman, 2020). To a large extent, disruptions to supply chains can be expected to continue beyond the pandemic unless new insights are gained into understanding disruptions and developing mitigation strategies. Criminal activity picked up during the pandemic, as it usually does during major disruptions, and compounded supply chain challenges, thereby increasing financial and societal costs (Moosavi et al., 2022). An FBI and United States Secret Service (USSS) press release early in the pandemic pointed out that criminals were devising and executing supply-chain attacks of greater severity and frequency (FBI, 2020). Such attacks on supply chains can be expected to continue after the pandemic, and consequently, timely indicators and warnings of such attacks is of paramount importance.

The pharmaceutical industry is a case in point. This industry plays a key role in ensuring the availability of life-saving drugs and healthcare products worldwide. However, complex pharmaceutical supply chains (PSCs) are susceptible to disruptions that impact the availability of essential medications (Marucheck et al., 2011). Some drug shortages have persisted in the post-pandemic period due to ongoing supply disruptions and demand spikes. The American Society of Health-System Pharmacists (ASHP) reported 309 active, ongoing drug shortages in 2023, the highest number in nearly a decade (ASHP, 2023). Despite the Food and Drug Administration's (FDA) efforts to address drug shortages by expediting reviews of new drug production sources (FDA, 2023), shortages have persisted in the US (IQVIA, 2023). Moreover, the incidence of disruptions has increased significantly in the post-pandemic period due to ongoing criminal activities, such as counterfeit drug production and cyberattacks capitalizing on existing PSC vulnerabilities (Stecke & Kumar, 2009) and emerging ones (Ziavrou et al., 2022). The COVID-19 pandemic profoundly impacted the pharmaceutical industry in terms of demand and consumption, R&D, as well as regulatory rules (Velásquez, 2022). Hence, the industry operations management and the research community are faced with the critical challenges of understanding the broad range of disruptions, assessing their impacts on PSCs, and devising mitigations.

Disruptions and their causes may only be observable ex-post (Brenner, 2015). However, disruption-warning tools can help not only in disruption detection, but also in predicting disruption scenarios and their impacts, as well as in developing mitigation strategies. To assist in developing a comprehensive understanding of various disruptions and their impacts, this research provides a classification of disruptions including counterfeit goods and packaging; adulteration of raw materials, active pharmaceutical ingredients (APIs), and excipients (drug additives); transportation thefts; cyberattacks; and campaigns to propagate misinformation about drug products.

During the pandemic, President Biden tasked a Supply Chain Disruptions Task Force with addressing vulnerabilities in critical supply chains, including pharmaceuticals and APIs, by increasing the transparency of sourcing, tracking, and labeling (The White House, 2021). Even before the onset of the pandemic, disruptions to PSCs were already a primary concern of the Department of Homeland Security (DHS). At the beginning of the pandemic, the network of DHS University Centers of Excellence (COEs) launched a 'COVID-19 Supply Chain Initiative' to identify appropriate tools and technologies to proactively address supply chain vulnerabilities (CCICADA, 2020). Multiple COEs collaborated and organized workshops focusing on increased crime during the pandemic, medicine and vaccine shortages, and adulteration, as well as other disruptions to PSCs. At these workshops, specific concerns about disruptions to PSCs were raised by representatives from various DHS agencies and the pharmaceutical industry, including the following: (a) thefts from licit PSCs, (b) counterfeit pharmaceuticals, (c) hoarding and price gouging, (d) the ability of transnational criminal

organizations to transform and adapt rapidly to exploit PSC vulnerabilities, and (e) limited ability of early fraud detection. The representatives described industry-wide efforts to detect counterfeit drugs through tracking financial transactions and called for the development of new tools to help law enforcement identify counterfeit pharmaceuticals. The calls for such PSC disruption-detection tools motivated a DHS-funded study reported in this paper. To this end, a research team was assembled, consisting of DHS COEs, SMEs (subject matter experts), academic and practitioner faculty members, and doctoral students across multiple disciplines, as well as executives from a US-based large pharmaceutical firm.

In order to understand supply-chain disruptions and identify mitigation strategies, extant literature was reviewed. Supply chain disruptions and resilience have been extensively studied by operations researchers (Hosseini & Ivanov, 2022; Ivanov, 2022; Katsaliaki et al., 2021). An important component of such research involves the task of mapping supply chains (MacCarthy et al., 2022; Mubarik et al., 2023). This paper's contribution to the literature is the incorporation of disruptions into the supply chain mapping process, and providing an integrated framework for mapping and modeling such supply chains and disruptions. Specifically, the PSC modeling process of the integrated framework was carried out as follows:

1. A PSC map of operational logistics of facilities, transportation, and information flows was created. Since PSCs are typically complex and dynamic (Marucheck et al., 2011), building a comprehensive map is often a challenging task. To address this issue, the core PSC processes were modeled in some detail while components external to it were simplified by judicious aggregation that preserved the ability to study disruptions. The PSC map was then validated by pharmaceutical executives from the studied firm and two other leading pharmaceutical companies.
2. A general model of disruptions was constructed in terms of the timeline and impact of disruptions. For every disruption, this timeline consists of the distributions of the disruption's inter-arrival time, the time to detect the disruption, and the time to mitigate its impact. Furthermore, the disruption's impact was modeled as a change of an operational parameter.
3. A large volume of data was collected in order to parameterize the baseline (disruption-free) PSC model (with baseline operational parameters). The process of data collection was aided by referring to the PSC map from step 1. The requisite data included distributions of sourcing times, production and testing times at various facilities, transportation times, replenishment lead times, as well as failures and rework probabilities, etc. Sanity checks were applied to the data to ensure the operational stability of the baseline PSC model.
4. A comprehensive classification of supply chain disruptions was compiled, based on historical data, and supplemented with plausible potential disruptions pointed out by industry SMEs.
5. Finally, the individual disruptions were overlaid on the PSC map by location and class. Further, each PSC model parameter, impacted by each disruption class, was identified.

Supply-chain disruptions have been extensively studied in the supply chain management literature (Dong & Tomlin, 2012; Hosseini & Ivanov, 2022; Ivanov, 2022; Katsaliaki et al., 2021; Kleindorfer & Saad, 2005; Penna et al., 2019; Tang, 2006; Tomlin, 2006). However, there is limited research on integrating disruptions with supply chain maps for assessing disruption impacts and developing mitigation strategies. This literature gap motivated the integrated framework of this paper, developed in close collaboration with industry SMEs over a 12-month period. Specifically, the research team conducted extensive interviews with SMEs from a large US-based pharmaceutical company, which served as a focal firm. This

firm provided information for developing a generic PSC model consisting of a supply-chain mapping, parameters, and disruptions. Further, SMEs from additional pharmaceutical companies, outside the focal firm, were asked to vet the model to assess its generalizability and applicability to the pharmaceutical industry at large. These SMEs were senior executives from flagship pharmaceutical companies with extensive experience in managing, planning, and securing supply chains. More specifically, the selected SMEs had experiential knowledge across a broad range of PSC functions, including strategic planning, sourcing, production, operations, quality assurance, regulatory compliance, security, customer relationship management, and financial management. The vetting process with the executives comprised in-depth structured and semi-structured sessions which explored the validity of the integrated framework and its utility to their respective organizations. The SMEs confirmed the validity and generalizability of the integrated framework for modeling PSC disruptions.

This paper describes the integrated framework in terms of PSC modeling, including a detailed PSC map and parameters, and a comprehensive classification of PSC disruptions (see also Domeniconi et al., 2022; Rana et al., 2024). It further discusses mitigation strategies and insights gleaned from the study. Further work using the integrated framework demonstrated its applicability to other industries, such as medical devices (Domeniconi et al., 2023a) and satellite solar panels (Domeniconi et al., 2023b).

The rest of the paper is organized as follows. Section 2 is a literature review of supply chain disruptions, PSC-specific disruptions, and supply chain mapping. Section 3 presents the generic PSC model, including the modeling methodology of the integrated framework, supply chain mapping, disruptions, parameters, and a summary of mitigation strategies. Finally, Sect. 4 concludes with operational and managerial insights, limitations, and directions for future work.

2 Literature review

In this section, we briefly review relevant literature on supply chain disruptions, including those in the pharmaceutical industry, and supply chain mapping.

2.1 Supply chain disruptions

In the literature, supply chain disruptions are "unplanned events or incidents that disrupt the normal flow of goods, services, or information in a supply chain…, which expose firms within the supply chain to operational and financial risks" (Craighead et al., 2007: p.132; Kleindorfer & Saad, 2005). Such disruptions are either due to natural causes (e.g., hurricanes, tsunamis, earthquakes, etc.), accidents (e.g., fires, spillage, unplanned contamination, etc.), or effectuated by criminal agents (e.g., counterfeits, thefts, cyberattacks, etc.). Supply chain disruptions, whether natural, accidental, or criminal, can also significantly impact a firm's financial and brand values (Hendricks & Singhal, 2005; Kleindorfer & Saad, 2005).

The literature on supply chain disruptions has grown in the past two decades. Tang (2006) introduced the notion of operational and disruption risks, where the former are caused by demand and supply mismatches, while the latter are caused by major incidents, man-made or natural. Catastrophic events affecting supply chains, whether natural or man-made, significantly disrupt the flow of products (Kleindorfer & Saad, 2005; Knemeyer et al., 2009).

Disruption management has been of particular interest to researchers, including planning, detecting, responding to, and recovering from such disruptions (Craighead et al., 2007; Snyder

et al., 2016; Tang, 2006). Planning for potential disruptions is part of risk management. As the complexity and frequency of disruptions grows, firms are increasingly focused on developing resilience to mitigate disruption impacts (Ambulkar et al., 2015; Jüttner & Maklan, 2011). Rice and Caniato (2003) introduced the concept of resilience in supply chains. A literature review of supply-chain resilience appears in Kamalahmadi and Parast (2016). Dong et al. (2005) studied supply-chain risk identification, the role of supply chain coordination, and the design of disaster-resilient supply chains. While risk mitigation strategies tend to treat disruptions as homogenous events, DuHadway et al. (2019) proposed that the endogenous or exogenous sources of disruptions should dictate the effective risk management strategies. Speier et al. (2011) presented frameworks for examining potential supply chain disruptions, supply chain design strategies, and associated mitigation strategies. Hosseini and Ivanov (2022) developed a new resilience measure for supply chains that accounted for the ripple effects of disruptions.

Assessing how disruptions affect supply chains is difficult due to the growing complexity and opaqueness of supply chains (Snyder et al., 2016). The ever-growing supply-chain complexity has spurred research on understanding system vulnerabilities, disruption types, and their impacts. For example, Papadakis (2006) compared Make-To-Order (MTO) and Make-To-Forecast (MTF) supply chains and reported that the former are more vulnerable to disruptions. Schmidt and Raman (2012) recognized the importance of how various types of disruptions and organizational factors impact performance outcomes. In addition, Bode and Wagner (2015) studied the upstream complexity characteristics of supply chains and the frequency of supply chain disruptions, and found that they are positively correlated. A systematic review of the COVID-19 pandemic-related supply chain disruptions revealed the need for further research on the causes and impacts of supply chain disruptions (Chowdhury et al., 2021).

2.2 Pharmaceutical supply chain disruptions

PSC disruptions have been examined both empirically and analytically in the literature. Sabouhi et al. (2018) analyzed the impacts of operational and disruption risks to PSCs utilizing Data Envelopment Analysis and mathematical programming methods. Azghandi et al. (2018) leveraged a simulation-based analysis of drug shortages in PSCs to identify the best inventory policies for various disruption types. Mathematical modeling, including the Bayesian network approach, has been used to analyze supplier vulnerabilities and to identify operational strategies for managing PSCs subject to disruptions (Lawrence et al., 2020).

The extant literature on disruptions has focused on understanding/modeling the impact of "on/off" disruption scenarios. While the impact of disruptions has been studied in the operations management research literature, a systematic classification of PSC disruptions is lacking. Accordingly, Sect. 3.3 of this paper addresses this lacuna in the literature by providing a comprehensive classification of supply chain disruptions, based on publicly available information and plausible disruptive scenarios, validated by pharmaceutical industry and security SMEs.

2.3 Supply chain mapping

Extant literature has presented supply chain mapping as a tool for connecting business strategies with supply chain strategies (Gardner & Cooper, 2003). At an operational level, value stream maps have been leveraged to understand planning, management, disruptions, and

resilience of supply chains (Barroso et al., 2011). A recent study presented a hierarchical classification scheme for various types of supply-chain maps (MacCarthy et al., 2022). Furthermore, Mubarik et al. (2023) used exploratory factor analysis to address upstream, midstream, and downstream supply chain mapping.

Generating supply chain maps involves significant time and effort. Gaur et al. (2022) reported on a case study, where teams of over one hundred people took more than a year to map the firm's supply networks. However, supply chain mapping provides a core knowledge asset for understanding material and information flows, internal processes, external entities, and linkages, as well as compliance and testing procedures (Vakil, 2021). Supply chain visibility is a key determinant in managing supply chain risks (Ivanov & Dolgui, 2020). Choi et al. (2020) highlighted the importance of mapping supply chains and described how companies that had invested in mapping their supply chain emerged better prepared during the pandemic. The success of such proactive preparedness was due to the enhanced visibility, gained by supply chain mapping and digital technologies, which facilitated tracking of upstream, downstream, and process value chains (Mubarik et al., 2021).

In a similar vein, supply chain mapping in the agribusiness and automotive industry was used as a tool for understanding supply chain vulnerabilities, risks, resilience, and mitigation strategies (Barroso et al., 2011; Carvalho et al., 2012). In contrast, there is limited literature on pharmaceutical supply chains mapping and disruptions. Yankus (2006) developed an infiltration map of the US pharmaceutical supply chain displaying drug flows to the marketplace. This map advanced the understanding of pathways through which illicit drugs can infiltrate licit PSCs. However, it did not consider the perspective of a pharmaceutical focal firm and its interactions with sources of disruption, and the subsequent exposure of firms to operational and financial risks. Accordingly, the integrated framework of this paper focuses on supply-chain mapping that integrates PSC disruptions with PSC operations. Compared with prior supply chain mapping studies, this paper's PSC modeling approach represents in detail a focal firm's internal processes, while aggregating each class of external entities, such as licit suppliers, illicit suppliers, and customers. The integrated framework produces a comprehensive model of manageable complexity for evaluating the pharmaceutical focal firm's disruption mitigation strategies.

3 The PSC model

This section describes the generic baseline PSC model, including its map (flow diagram) and individual components (Sect. 3.1), the generic disruption model (Sect. 3.2), disruptions classification (Sect. 3.3), and disruption mitigations (Sect. 3.4).

The PSC map bears similarity to value-stream maps (Barroso et al., 2011) which incorporate supply chain actors, (the focal firm and its external entities and linkages), including supply chain processes and inbound/outbound flows of unfinished/finished products (MacCarthy et al., 2022). The baseline PSC model (without disruptions) was developed and parameterized in collaboration with functional and security SMEs in the pharmaceutical industry. The PSC disruption classification is based on a database of historical disruption instances from various publicly available sources, as well as plausible future disruptions identified through discussions with SMEs. Disruption categories were encoded on the generic PSC map.

3.1 The generic PSC baseline model

Like any supply chain, a pharmaceutical supply chain consists of structure (layout of supply-chain components, such as facilities, suppliers, consumers, etc.) and behavior (supply-chain processes, such as demand, production, testing, transportation, etc.) The structural complexity of supply chains combined with the inherent randomness in many of the supply-chain processes render it difficult to analyze how disruptions affect supply chain performance.

The integrated framework utilizes Eisenhardt's approach to building and refining theories from in-depth case studies (Eisenhardt, 1989). Eisenhardt's approach aims to glean theoretical insights through strategic case-study selection and employs diverse data sources including interviews. It constructs a conceptual framework that uncovers relationships among phenomena, and validates findings by replicating in other case studies. This approach has been effectively applied in multiple settings, including large firms seeking innovative expansion to new markets (Dougherty, 1990), investigating the integration-versus-autonomy dilemma in technology firm acquisitions (Graebner et al., 2004), examining definitional perspectives and applications of big data (Wamba et al., 2015), determining the necessary dynamic capabilities for successful circular economy implementations using blockchain technology (Meier et al., 2023), and exploring how firms achieved supply chain agility by building ad hoc supply chains (Müller et al., 2023).

Following Eisenhardt's approach, the research reported here started by selecting a pharmaceutical case-study focal firm. An advisory team of SMEs comprising senior executives was assembled from this firm, with expertise in manufacturing processes, supply chain management, and supply chain security. The advisory team's makeup, in terms of background and expertise, complied with the aforesaid Eisenhardt approach. The model was further vetted and refined by various departments of the focal firm in multiple iterations to obtain comprehensive feedback. Following model development, multiple interviews were conducted with additional pharmaceutical firms, other than the case-study focal firm, for further validation of the model. Finally, consistent with the Eisenhardt approach, the integrated framework was replicated in other supply-chain case studies, beyond the pharmaceutical industry, as described in Sect. 1.

Specifically, for the development of the PSC model, we interviewed SMEs who are both active and retired senior executives from three major pharmaceutical companies, as well as SMEs from various federal agencies, as follows:

1. Company 1: Senior Director of Information Security, Director of Security Architecture, and retired Vice President for Global Supply Chain.
2. Company 2: Executive Director for Product Integrity.
3. Company 3 (the focal firm): Retired Director and Team Lead of Supply Chain Logistics.
4. DHS: Assistant Director, Operational Technology and Cyber Division, Homeland Security Investigations (HSI).
5. DHS: Deputy Director, DHS Joint Task Force – West.
6. DHS: Head of the ICE-HSI National Intellectual Property Rights Coordination Center.
7. US Department of Justice: Deputy Director, Consumer Protection Branch.

The SME from Company 3 was the key information provider on model structure and parameters, as described in the PSC modeling process in Sect. 1. Specifically, this SME was interviewed about the PSC network structure, physical and information flows, manufacturing and testing processes, and inbound and outbound logistics. All SMEs validated the supply chain model, as well as the identified disruptions and their locations. They confirmed that their companies follow a similar supply chain structure and suggested certain disruptions unique

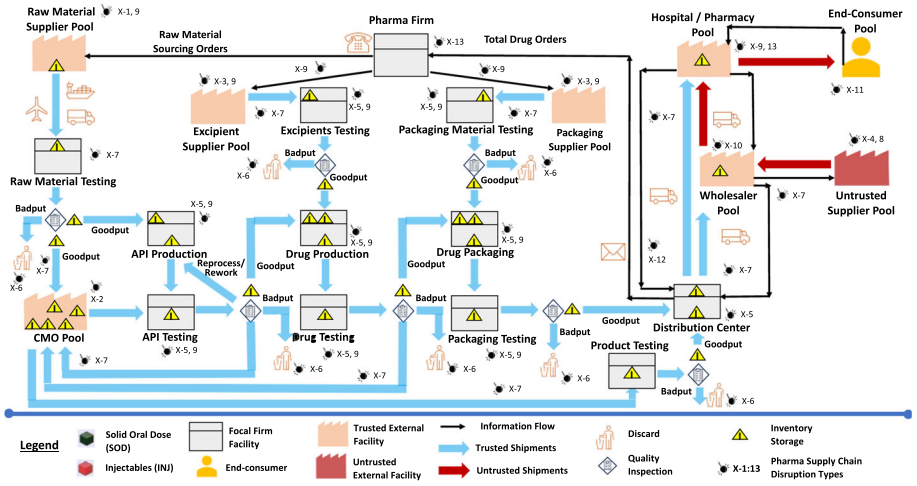

Fig. 1 Generic PSC Map with Disruptions

to their firms, which were incorporated into the supply chain model and the disruption classification presented in Sect. 3.3. Finally, SMEs from federal agencies provided information on the identification of criminal disruptions to supply chains and assisted in gleaning model insights.

PSCs tend to have complex, multi-tiered supply networks, random demand, a large assortment of product types, and an elaborate distribution network. To handle this complexity, this paper's integrated framework modeled the internal operations of a pharmaceutical focal firm with aggregated external entities and linkages. Accordingly, multiple suppliers of the same commodity are modeled as a corresponding supplier pool, drug products are similarly pooled into product categories, and drug consumption is aggregated into end-consumer pools by product category. For example, raw material suppliers are aggregated into a pool, and drugs are aggregated into two categories: solid oral dose (SOD) and injectables (INJ). Figure 1 depicts the structure of the generic PSC model from the viewpoint of a pharmaceutical focal firm.

The map in Fig. 1 consists of color-coded icons representing supplier pools, contract manufacturer organization (CMO) pools, wholesaler pools, hospital/pharmacy pools, and end-consumer pools. Icon labels of nodes indicate their functionality, and the inclusion of the word "Pool" in a label indicates aggregation of corresponding external entities. For example, the *Hospital/Pharmacy Pool* node aggregates hospitals and pharmacies that fulfill demand from the *End-Consumer Pool* node. Suppliers may be trusted or untrusted based on their compliance reliability. Grey icons designate focal-firm facilities, while orange icons and red icons designate, respectively, trusted, and untrusted entities external to the focal firm. For example, counterfeit suppliers, diverters, and third-party wholesalers are all aggregated into the *Untrusted Supplier Pool* node. Generally, suppliers are considered by the focal firm to be "untrusted" because the focal company does not have sufficient evidence to the contrary. Blue and red arrows correspond, respectively, to trusted and untrusted linkages (physical transportation links involving transport times), while black arrows represent instantaneous information flows. Diamond icons that follow testing nodes represent a routing decision of flow units (e.g., batches of raw material, API, drugs, etc.) Specifically, arrows labeled *Goodput*

carry flows of units that passed testing, while arrows labeled *Badput* or *Reprocess/Rework* carry flows of units that failed testing, to be discarded or reworked, respectively. Tested materials include raw material, API, excipients, packaging, and drug end-products. Yellow triangles designate inventories. Finally, a possible disruption at a particular map location is shown on the map as a "hand grenade" icon with an adjacent disruption category code of the form "X-n," where "n" = 1, 2, …, 13, are categories to be described in Sect. 3.3.

Pharmaceutical firms maintain large safety buffers (*safety stocks*) to support production continuity in times of short supplies, with associated carrying costs. To keep adequate supplies on hand, many pharmaceutical facilities use the Make To-Stock (MTS) replenishment policy with a *reorder point and target level.* Whenever the inventory level hits or down-crosses the reorder point, a replenishment order is placed to bring up the inventory level to the target level.

Every material type (raw material, API, excipients, and drugs) has a user-specified expiration period. On production, each material unit (batches, and end-units) is stamped with its production date and expiration date. Each unit is checked for expiration when it is moved, and expired units are discarded. To minimize unit expiration, inventory units are managed in first-in-first-out (FIFO) order. Accordingly, incoming units to an inventory are placed at the tail of the inventory storage, while outgoing units are taken from the head of the inventory storage.

Node parameters consist of user-specified scalars and distributions. For example, the reorder point and the target level of an MTS inventory are scalar parameters, while random delays in manufacturing, testing, and transportation, as well as demand sizes, are modeled by user-specified distributions. Such parameters are based on historical data, as provided by SMEs from the case-study focal firm, and those correspond to a baseline model of PSC operation without disruptions.

The remainder of this section describes the structure of the generic PSC map by functional components of the supply chain (the nodes in Fig. 1).

3.1.1 End-consumer demand

The end-consumer demand for SOD and INJ drugs is modeled in the *End-Consumer Pool* node and drives all PSC operations. This node issues daily orders of SOD and INJ drugs to the *Hospital/Pharmacy Pool* node. The order sizes are drawn from a triangular distribution, with three user-specified parameters: minimum value, maximum value, and mode. If the *Hospital/Pharmacy Pool* node has sufficient stocks on hand in its inventories, it fulfills the orders at the end of the day; otherwise, it fulfills what it can and backorders the shortage.

3.1.2 Hospital/pharmacy pool operations

The *Hospital/Pharmacy Pool* node is replenished by the *Distribution Center* and *Wholesaler Pool* nodes using the MTS policy. More specifically, the *Hospital/Pharmacy Pool* node replenishes all its SOD from the *Wholesaler Pool* node, but an INJ replenishment is split into two orders: one to the *Wholesaler Pool* node and the other to the *Distribution Center* node. The split percentages are user-specified. All replenishment lead times follow a user-specified triangular distribution.

3.1.3 Wholesaler pool operations

The *Wholesaler Pool* node fulfills orders from the *Hospital/Pharmacy Pool* node using the MTS policy. When replenishment is needed, it first sends orders to the *Distribution Center* node. However, if a replenishment order of the *Hospital/Pharmacy Pool* node cannot be completely fulfilled, the *Wholesaler Pool* node orders the balance from the *Untrusted Supplier Pool* node, and when this shipment arrives (possibly containing some non-compliant or illicit end-units), it forwards that shipment to the *Hospital/Pharmacy Pool* node. All replenishment lead times follow a user-specified triangular distribution.

3.1.4 Untrusted supplier pool operations

The *Untrusted Supplier Pool* node is assumed to have an essentially unlimited supply of drug end-units (SOD and INJ), and therefore, it can always replenish the *Wholesaler Pool* node, whenever the *Distribution Center* node cannot completely fulfill supply orders. Every shipment from the *Untrusted Supplier Pool* node has a random fraction of illicit end-units modeled as a user-specified triangular distribution. To keep track of licit and illicit end-items, time-stamped buckets of drug end-units are maintained separately for SOD and INJ replenishments.

3.1.5 Distribution center operations

The *Distribution Center* node fulfills orders from the *Hospital/Pharmacy Pool* node and the *Wholesaler Pool* node. Each month it sends a replenishment order for SOD and INJ end-units to the *Pharma Firm* node. The order sizes are the average total demand (in terms of orders sizes) received by the *Distribution Center* node from the *Hospital/Pharmacy Pool* node and the *Wholesaler Pool* node over the previous four months.

3.1.6 Pharmaceutical Focal-Firm Operations

The *Pharma Firm* node receives monthly orders in SOD and INJ end-units from the *Distribution Center* node. It breaks each order size (in end-units) into batches of user-specified sizes, separately for SOD and INJ drug orders. It then sends messages to all suppliers involved in drug production and packaging to provide the respective supplies. These suppliers are the *Raw Material Supplier Pool* node, *Excipient Supplier Pool* node, and *Packaging Supplier Pool* node. The order sizes to these suppliers are adjusted to account for expected losses due to badput to be discarded at testing nodes.

3.1.7 Raw material supply

The *Raw Material Supplier Pool* node receives monthly orders (in batches) from the *Pharma Firm* node. It processes each batch sequentially and tests each batch at the focal firm's *Raw Material Testing* node. Raw material-related delays of SOD and INJ batches at the production and testing steps follow user-specified distributions, as is the probability of badput after testing. The stream of goodput raw material batches emerging from the *Raw Material Testing* node is split between the focal firm's internal production and the *CMO Pool* node, which is a pool of CMOs, according to user-specified split probabilities. Goodput raw material batches routed to the focal firm enter the *API Production* node with no delay, while those routed to the CMO *Pool* node are shipped with a user-specified transportation delay distribution.

3.1.8 API production

The *API Production* node produces API batches from raw material batches. A flow control mechanism informs the node as to how many API batches to produce per order, following which API production is suspended until the next order arrives. The *API Production* node produces API batches sequentially, each of which is tested at the focal firm's *API Testing* node. API-related delays of SOD and INJ batches at the production and testing steps follow user-specified distributions. Tested batches are designated as goodput, badput (to be discarded), or reprocess/rework (to be routed back to the *API Production* node for reprocessing) with respective user-specified probabilities. The stream of goodput API batches emerging from the *API Testing* node is split between the focal company and the *CMO Pool* node according to user-specified probabilities. Goodput API batches, routed to the focal company, enter the *Drug Production* node with no delay, while those routed to the *CMO Pool* node are shipped following a user-specified transportation delay distribution.

3.1.9 Excipients supply

Excipients are compounds (inactive ingredients) that are mixed with API to produce drugs. The *Excipients Supplier Pool* node receives monthly orders (in batches) from the *Pharma Firm* node. It produces batches sequentially and ships each for testing at the focal firm's *Excipients Testing* node with a user-specified transportation delay distribution. Excipients-related delays of SOD and INJ batches at the production and testing steps follow user-specified distributions, as is the probability of badput after testing. The stream of goodput excipients batches emerging from the *Excipients Testing* node enters the *Drug Production* node.

3.1.10 Drug production

Drug production takes place in the *Drug Production* node, which maintains two inventories for SOD drugs and two inventories for INJ drugs: one for API safety stocks and the other for excipients safety stocks. To produce one batch of drugs, one API batch is combined with one excipients batch. If either inventory is empty, drug production is suspended until both types of batches become available. A flow control mechanism informs the *Drug Production* node how many drug batches to produce per order, following which drug production is suspended until the next order arrives. The *Drug Production* node produces drug batches sequentially and ships each for testing at the focal firm's *Drug Testing* node. Drug-related delays of SOD and INJ batches at the production and testing steps follow user-specified distributions, as is the probability of badput after testing. The stream of goodput drug batches emerging from the *Drug Testing* node is split between the focal company and the *CMO Pool* node according to user-specified probabilities. Goodput Drug batches, routed to the focal company, enter the *Drug Packaging* node with no delay, while those routed to the *CMO Pool* node are shipped with a user-specified transportation delay distribution.

3.1.11 Packaging material supply

Packaging material is used to package individual end-units of SOD and INJ drugs. The *Packaging Supplier Pool* node receives monthly orders (in batches) from the *Pharma Firm* node. It produces each batch sequentially and ships each for testing at the focal firm's *Packaging Testing* node with a transportation delay. Packaging material related delays of SOD and INJ

batches at the production and testing steps follow user-specified distributions, as does the probability of badput after testing. However, only badput packaging-material end-units are discarded rather than the entire packaging batch. The stream of goodput packaging-material batches emerging from the *Packaging Testing* node enters the *Drug Packaging* node.

3.1.12 Drug packaging

Drug packaging takes place in the *Drug Packaging* node, which maintains two inventories for SOD drugs and two inventories for INJ drugs: one for drug safety stocks and the other for packaging-material safety stocks. To produce one unit of packaged drugs, one drug unit is combined with one packaging-material unit. If either inventory is empty, drug packaging is suspended until both types of units become available. A flow control mechanism informs the node as to how many packaged drug units to produce per order, following which drug packaging is suspended until the next order arrives. The *Drug Packaging* node packages drugs in sequential batches and ships each batch for testing at the focal firm's *Packaging Testing* node. Packaged-drug-related delays of SOD and INJ batches at the packaging and testing steps follow user-specified distributions, as does the probability of badput after testing. However, only packaged drug end-units are discarded rather than the entire packaged drug batch. The stream of goodput drug batches emerging from the *Packaging Testing* node is shipped to the *Distribution Center* node.

3.1.13 CMO production

To increase its production capacity (and cost-efficiency), the focal firm outsources all or some of the production operations to a pool of CMOs, represented by the *CMO Pool* node. The outsourced work forms multiple streams as follows:

1. The stream of raw material batches from the focal firm's *Raw Material Testing* node is split into two production sub-streams with user-specified probabilities. The first production sub-stream converts raw material batches to API batches and ships them to the focal firm for testing at the *API Testing* node. The badput probabilities for outsourced API batches at the *API Testing* node are likely higher than for insourced batches because the focal firm cannot directly control outsourced production. The second production sub-stream converts raw material batches to packaged-drug end-units and ships them to the focal firm's *Product Testing* node with user-specified production and transportation delay distributions.
2. The stream of API batches from the focal firm's *API Testing* node is converted into batches of packaged-drug end-units and shipped to the focal firm's *Product Testing* node with user-specified production and transportation transportation delay distributions.
3. The stream of drug batches from the focal firm's *Drug Testing* node is converted into batches of packaged-drug end-units and shipped to the focal firm's *Product Testing* node with user-specified production and transportation delay distributions.

Again, because the focal firm has no control over outsourced production and each stream includes different numbers of production steps, the badput probabilities for the outsourced streams of end-unit batches at the focal firm's *Product Testing* node are correlated with the respective numbers of steps in each stream.

3.2 Disruption model

In the generic PSC model in Fig. 1, all disruptions were incorporated, using a user-parameterized model. Specifically, a given disruption stream consists of multiple disruption instances of the same type, occurring in the same location (node) of the PSC, such that only one disruption in the stream is active at any given time (concurrent multiple streams of distinct disruptions are permissible). A given disruption instance in a disruption stream comprises three consecutive abutting periods and their associated impacts as follows:

1. The *inactive period* is the time interval separating the arrivals of successive disruption instances in the same stream. On arrival, the disruption changes the value of a user-specified parameter at the arrival node. For example, the mean production time of a product batch may be increased, thereby reducing the production capacity of the node.
2. The *detection period* is the time it takes to detect the disruption instance, starting from its arrival time. At detection time (the end-time of this period), any further impact may be null, or the user-specified value of the parameter may change again. For example, the mean production time of a product batch may further increase due to deterioration during the detection period.
3. The *restoration period* is the time it takes to resolve the disruption or at least mitigate it, starting from its detection time. At the restoration time (the end-time of this period), any further impact may be null, or the value of the parameter may change again. For example, the mean production time is typically restored to its original value before the disruption, or there may be only a partial restoration, or the restoration may fail, and the parameter could further deteriorate.

All period durations are user-specified, typically as distributions that model their random nature. All impacts are also specified as distributions of percent changes (negative, positive, or zero) of the associated parameter.

3.3 Disruption classification

To create a disruption classification, a literature review was performed of past pharmaceutical-related supply chain disruptions, and interviews were conducted with SMEs, supply chain researchers, and government agency officials. Further, information was gathered from SMEs on plausible future disruptions, and these were also included in the classification presented in this paper. Typical supply chain disruptions include reduced production capacity, reduced quality, and longer transportation times. The classification presented in this section helps in understanding threats related to pharmaceutical drugs, and subsequently in developing preparedness and mitigation strategies.

PSC disruption categories are classes of disruptions that have similar *impacts* on system performance, regardless of their underlying causes. The PSC disruption classification consists of 13 disruption categories and includes both historical and potential instances of such disruptions, obtained from various publicly available sources. Figure 1 overlays disruption categories on the PSC map at potential occurrence locations, based on empirical findings from the open literature and expert opinion. For example, the Category 1 disruption (raw material adulteration) is denoted X-1 and is located at the *Raw Material Supplier Pool* node. The motivation for this paper's classification approach is twofold. First, modeling supply chain logistics to assess the severity of disruptions only needs to consider the impacts of disruptions rather than their causes. Second, adding causal sources to the classification, such

as weather events, factory closures, labor disputes, etc., would spawn an undesirable proliferation of disruption categories. Accordingly, this paper characterizes disruptions by the functional nature of their impact on a PSC node. A description of each of the disruption categories is presented next.

Disruption Category 1: Raw Material Adulteration. Pharmaceutical drugs can be contaminated by adulterated raw material from poor-quality suppliers or criminal ones. An example of this type of disruption is the infamous Heparin recall of 2008 (Hedlund et al., 2013). Heparin is used as an anticoagulant in the treatment of heart attacks. The majority of its ingredients are sourced from pig intestines processed by farmers in China. Baxter International was responsible for about half of the US's Heparin market. Its contractor, Scientific Protein Labs, used counterfeit precursors (a contaminant, called "over sulfated chondroitin sulfate," OSCS for short) to create the chemicals, which resulted in an adulterated product that killed 81 people and severely injured 785 others (Ramacciotti et al., 2011). The OSCS was supplied by a still-unknown criminal third party, which deliberately selected it precisely because it mimics Heparin and can pass state-of-the-art tests (Bogdanich, 2008). Various strategies have been employed by the pharmaceutical industry to ensure drug quality by improving the processing of raw materials, such as the process of Continuous Production, which has gained traction in recent years. This process manufactures drugs continuously rather than in traditional batches. Analytical methods have been developed to improve the performance of production-inventory systems. For example, Shi (2022) studied continuous production-inventory systems and developed optimal solutions for production systems, particularly for pharmaceutical firms, focusing on their production process validation (FDA, 2020). Similarly, Chang et al. (2019) quantified the stockout risk of production-inventory systems.

Disruption Category 2: API Adulteration. Recall that APIs are the pharmacologic active components of drugs with desired therapeutic benefits. APIs are typically classified into synthetic chemical APIs comprising small molecules that constitute a large part of the commercial pharmaceutical market, or natural chemical APIs comprised of biologics. API adulteration refers to sourcing adulterated synthetic chemical APIs from untrusted suppliers. An example of this type of disruption was the Valsartan recall (Farrukh et al., 2019). Generic versions of angiotension-receptor blockers (ARBs), high blood-pressure/heart-failure medicines, were recalled due to nitrosamine impurities. Such impurities are considered likely carcinogens; they include N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), which are probable human carcinogens (World Health Organization, 2019). In 2018, the FDA learned that a certain API product (manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd., in a factory for some generic Valsartan-containing medicines) contained NDMA. The FDA investigation found that a manufacturing change likely led to this impurity, which had gone undetected by global regulators (FDA, 2021). In order to enhance drug quality through consistent supply of drugs, reduced stockouts, and optimized production processes, Production-Inventory systems with continuous replenishment models can be leveraged. Such models were studied by Shi et al. (2014) and Katehakis et al. (2022). More generally, the quality of API is crucial in ensuring the safety, efficacy, and quality consistency of drugs. Consequently, there has been a concerted effort of reshoring drug production to the US, using continuous production processes (Malhotra, 2015; Shi, 2022), to ensure API quality compliance and cost effectiveness, along with bolstering domestic supply chains. Blockchain technology (see Chang et al., 2022 for a review) can also be leveraged to improve traceability and address quality issues with APIs. A study by Chang et al. (2021) demonstrated how blockchain technology adoption impacts optimal ordering decisions and the associated optimal profit.

Disruption Category 3: Excipients Adulteration. Recall that excipients are inactive but essential drug ingredients that assist with binding and coating during the manufacturing process and stabilize unstable components such as proteins. Most drugs have a higher percentage of excipients, such as lubricants, fillers, binding agents, coatings and disintegrants, as compared to API ingredients. There are almost 500 excipients in the US Pharmacopeia's National Formulary, and the global market for such excipients was about $8.37 billion in 2023 (Precedence Research, 2024). Excipient adulteration refers to the addition of any type of toxic impurity to the manufacturing process. An example of this type of disruption is diethylene glycol (DEG) poisoning, which has been prevalent since the 1937 Elixir sulfanimide incident. The Elixir sulfanimide was an improperly prepared antibiotic that caused mass poisoning and killed over 100 people in the US. The 1938 Federal Food, Drug and Cosmetic Act required drug producers to demonstrate acceptable safety before marketing a product. DEG is commonly used as a solubilizer both in cosmetics and in oral, transdermal, and injectable drugs. The first known case of counterfeiters exploiting the compound was in Panama in 2006, where DEG was substituted for glycerin in a cold medicine, killing over 100 people (Schier et al., 2011). Recently, the FDA has recognized the excipient adulteration risk of ingredients, such as guar gum (a disintegrant used in extended-release tablets; Srivastava et al., 2016), gelatin (used as glue but carrying the risk of adulteration with melamine), and talc (used for anticaking, lubrication, and coating), which was found to include contaminants such as asbestos (Kemsley, 2014). The analysis of excipients requires high performance chromatography to detect adulteration.

Disruption Category 4: Counterfeit. Counterfeit drugs are defined as "products deliberately and fraudulently produced and/or mislabeled as to identity and/or source to make them appear to be a genuine product" (World Health Organization, 2018). For example, a counterfeit drug can contain no API, an incorrect amount of API, an inferior-quality API, incorrect API formulation, toxic contaminants, or completely expired drugs that are re-packaged. The high demands for chemotherapeutic drugs, antibiotics, vaccines, lifestyle drugs, weight loss drugs, antimalarials, antihistamines, and antivirals provides lucrative opportunities for counterfeiters. There are six categories of counterfeit as follows:

1. *Counterfeit product and packaging* occur when both the drug product and its packaging are counterfeited. Counterfeit-packaged drugs may contain the correct API and excipients, in which case illicit imports cause economic harm, or they may contain a wrong composition of API and excipients or no API at all. The latter can introduce harmful or toxic substances into a patient, possibly leading to fatal consequences.
2. *Counterfeit product in genuine or reusable/recyclable packaging material* refers to materials collected via illicit activities such as "trash-diving." Waste material from pharmaceutical facilities can be stolen by criminals for the purpose of using them in counterfeit products.
3. *Counterfeit packaging with repackaged or relabeled genuine product* arises from illicit activities such as counterfeit packaging.
4. *Counterfeit product in relabeled packaging* is carried out by re-packagers in foreign markets to introduce the relabeled product back into local licit pharmaceutical supply chains.
5. *Counterfeit product* refers to tampering with the chemical formulation of the product, via dilution of its component-mix or modifying the dosage form.
6. *Counterfeit with an unapproved/in-development/in-testing product* occurs when drug products, which are yet to be introduced into the market, are counterfeited. Criminal agents are known to steal trade secrets and Intellectual Property information to create counterfeits of this type. An example of this type of disruption was the Viagra and Cialis

counterfeiting of erectile dysfunction drugs. In 2005, 440,000 counterfeit Viagra and Cialis tablets were imported from China and distributed in the US (Nelson et al., 2006). An innovative proposed solution to tackle the counterfeit drug problem is the use of blockchain technology (Chang et al., 2021, 2022), which ensures the traceability and authenticity of drugs, and facilitates regulatory compliance by providing data security. Blockchain technology can aid in detecting counterfeit pharmaceuticals (Haq & Esuka, 2018) and can also be integrated with IoT devices and embedded sensors in packaging to identify tampering (Rastogi et al., 2022).

Disruption Categories 5, 6, and 7: Internal Losses, External Losses, and Transportation Losses. These disruption categories involve, respectively, stealing cargo from a warehouse; "trash-diving" to get waste material, discarded packaging or product ingredients; and cargo thefts during transportation inside and outside facilities. These could also involve losing material or cargo due to natural disasters (earthquakes, tsunamis, hurricanes, etc.), events like fire, traffic accidents, spills, or other ways in which physical inventory is destroyed or lost. The largest known pharmaceutical heist occurred in an Eli Lilly warehouse in 2010, where criminals stole popular supplies of Cymbalta and Prozac. The same criminals had also conducted heists in a GSK warehouse in Virginia worth $13.3 million (Roberts, 2014). Transportation thefts are common at truck stops or parking points where truck drivers take a break. The stolen goods can be further modified and re-introduced into licit supply chains at higher prices.

Disruption Category 8: Diversion. This category involves situations where drug products are diverted out of a licit supply chain. Diversions can occur when a licit wholesaler buys drug products from an untrusted supplier and proceeds to sell or resell them. Diversion of medicines, sold at a discount for use in government sponsored programs, can be counterfeited as well. In addition, such disruptions include consumer-consumer exchanges or business-business unauthorized operations, where sales representatives are hired to call doctors to prescribe these diverted drug products to patients. However, the most prevalent form of drug diversion occurs through fake online pharmacies. An example of this type of disruption was the case of Andrew J. Strempler, a Canadian citizen operating the company Medical Health Consulting Inc., also known as RXNorth.com. He filled prescription orders in The Bahamas with labels stating they were made in Canada (Attaran & Beall, 2014).

Disruption Category 9: Cyberattacks. A cyberattack is an attack of malware, ransomware, or virus of some sort, attacking the information systems of a PSC to gather personal information or create supply-chain disruptions. Cyberattacks are almost always intentional, though accidental disruptions of cyber systems can have similar effects. Importantly, their impact can be more widespread than disruptions that only impact single nodes in the PSC, and their impact can be hard to gauge given the stealthy nature of such attacks. A recent Health-ISAC report directed at pharmaceutical company chief information security officers stressed *increasing concern about bad actors targeting operating technology (OT) systems used to run the manufacturing floor, labs, R&D facilities, warehouses, and distribution centers* (Health-ISAC, 2022). The proliferation of cyberattacks has greatly increased during and since the COVID-19 pandemic. Typically, hackers demand ransom to unlock a computer system they had attacked. For example, this kind of attack impacted United HealthCare services, affecting 400 US and UK hospitals (Landi, 2020). An attack on the UVM Medical Center locked out electronic health records and payroll, among other things. Damages were estimated at $50 million (Diaz, 2022). Attacks on information systems of healthcare providers, which are an integral part of the PSCs, can have a disruptive impact on the operations of multiple PSCs simultaneously.

Disruption Category 10: Wholesaler Price Discrimination. Wholesalers are an integral part of the pharmaceutical industry, engaging in bulk buying and selling of brand-name and generic drugs, in addition to providing a wide variety of services to manufacturers and pharmacies. About 92% of prescription drugs in the US are distributed through wholesalers, who make most of their revenues primarily through selling generic drugs (The Commonwealth Fund, 2022). A significant percentage of generic drugs are handled by only a handful of wholesalers (AmerisourceBergen, Cardinal Health, and McKesson), which act as "price-setters," thereby leading to pricing-based disruption opportunities (e.g., during drug shortages, smaller wholesalers can sell their inventory to larger wholesalers, driving up the prices of drugs.) An example of this type of disruption involved McKesson, which posted inflated pricing data to First Databank (a publisher of drug prices) and proceeded to charge anti-competitive prices for generic drugs. McKesson was implicated in a price-fixing scandal, where company executives engaged in a massive insider-trading scheme and misled investors by falsely attributing higher prices to supply disruptions (Sagonowsky, 2019).

Disruption Category 11: Disinformation Campaigns. These are campaigns by domestic or foreign agencies that spread disinformation about medical products. Disinformation campaigns can create false demand with no scientific backing for certain drugs, thereby impacting the supply and demand of genuine counterparts. An example of this type of disruption involved the drug Ivermectin. The COVID-19 pandemic saw an avalanche of disinformation on Ivermectin and its ability to treat COVID-19. Social media websites such as Facebook, microblogging websites such as Twitter, and various podcasts assisted in spreading inaccurate information about Ivermectin's efficacy. Ivermectin was touted as a miracle-cure for COVID-19 on Florida-based telehealth websites promoting its use (Robins-Early, 2021), though the Centers for Disease Control and Prevention (CDC) and the FDA put advisory warnings against using Ivermectin for treatment of COVID-19.

Disruption Category 12: Illicit Reverse Logistics. Reverse logistics has become a key competency in modern supply chains (Rogers et al., 2013), encompassing returns, refurbishment, repackaging, unsold goods, and end-of-life goods. Criminals steal expired drugs and divert them to secondary markets for resale. Expired drugs still have API of significant potency, making the resale and misuse of the drug product easy to accomplish. These issues are further exacerbated in low-income and middle-income economies where such drugs can find their way into drug donation programs, thereby impacting licit PSCs.

Disruption Category 13: Intellectual Property (IP) Theft. The pharmaceutical industry is built on a complex high-risk and high-cost process of research, development, and commercialization of drugs. These high costs incent companies and employees to engage in IP theft. Theft of IP in the form of research material, data, methods, possibly in collaboration with criminal organizations, can lead to severe economic harm to the affected pharmaceutical firm. Pharmaceutical firms are prime targets for IP theft by insiders, driven by the economic value of IP due to high demand for prescription drugs. An example of this type of disruption was the subject of the Pfizer lawsuit against two of its employees for stealing information and setting up a competitive firm (Sagonowsky, 2021). Another example is the case of GlaxoSmithKline (GSK) employees who tried selling sensitive cancer data to multiple companies in China, backed by the Chinese government (Dunleavy, 2022).

3.4 Mitigation

This research studied both post-disruption mitigation (in reaction to the advent of disruptions) and pre-disruption mitigations (in preparedness for anticipated disruptions).

Starting with post-disruption mitigation, safety stocks are an important case in point. Safety stocks serve as a buffer of inventory available for emergency use in response to supply disruptions. The importance of safety stocks as a primary post-disruption mitigation tool against disruptions is well-documented (Amirjabbari & Bhuiyan, 2014; Graves & Willems, 2000). PSCs typically carry high levels of safety stocks, given the long sourcing and manufacturing times of Key Starting Materials (KSMs) and APIs (Shah, 2004). Thus, safety stocks serve as an important safeguard of continued pharmaceutical supply, especially drugs essential to public health. In the generic PSC model, a receiving node typically contains the safety stocks of materials from one or more incoming nodes. For example, the *Drug Production* node, as a receiving node, carries safety stocks of API incoming from the *API Testing* node and safety stocks of excipients from the incoming *Excipients Testing* node. Recall that all inventories are managed by the MTS replenishment policy, and inventory units are used in FIFO order (the oldest items are used before more recent ones) to ensure that the safety stocks are continually refreshed.

Pre-disruption mitigation strategies primarily aim to increase the efficacy of real-time disruption detection and involve activities that improve the transparency and visibility of the supply chain. Incorporating real-time sensors at key locations of the supply chain is an important pre-disruption mitigation strategy (Lechler et al., 2019). Sensors do not have to be physical devices, but can include actions, such as more thorough and ongoing vetting of suppliers, and other measures to be discussed in Sect. 4. Further, supplier-based diversification is another effective pre-disruption mitigation strategy (Hendricks et al., 2009). In practice, the deployment of sensors and the diversification of the supplier base make the supply chain more resilient to disruptions, thereby increasing supply reliability.

To study the model's behavior and efficacy of mitigation strategies, a baseline PSC simulation was first created (see Sect. 3.1 for model details). Next, disruptions were injected into the baseline simulation model, and it was run without and with mitigations. Specifically, experiments were conducted to understand the impact of disruptions and identify the most effective mitigation strategies. The details of the simulation, experiments, and mitigation strategies are discussed in Domeniconi et al. (2022) and Rana et al. (2024). These details are not included in this paper for the sake of brevity and to keep the primary focus on the integrated framework for modeling complex supply chains with disruptions, along with the insights gleaned in the course of the modeling process.

The ability to understand and quantify resilience is instrumental in emergency planning and response (Zobel & Khansa, 2014). The literature provides various definitions of supply chain resilience (Ponomarov & Holcomb, 2009; Rice & Caniato, 2003; Sheffi & Rice, 2005; Tukamuhabwa et al., 2015), including the important concept of *resilience triangle* which measures the impact of disruptions on supply-chain nodes (Bevilacqua et al., 2017; Tierney & Bruneau, 2007). Bevilacqua et al. (2017) and Sheffi and Rice (2005) provided comprehensive frameworks for applying the resilience triangle concept to supply chains. Figure 2 is a generic depiction of the resilience triangle concept.

Figure 2 shows the generic evolution of a disruption consisting of pre-disruption, disruption, post-disruption phases. Here, the horizontal axis is time, and the vertical axis is the performance metric. The green curve is a graph of the performance metric (e.g., a production quantity over time at the *Distribution Center* node). The dashed vertical red line marks a disruption onset followed by the disruption's impact over the disruption phase (a period of declining drug production followed by recovery). The disruption phase includes the following time markers: start of the disruption (S), point of maximal impact (M), and the time when recovery is complete (R). The resilience triangle is formed by connecting the points S, M, and R, where the resilience triangle's height represents the severity of the disruption,

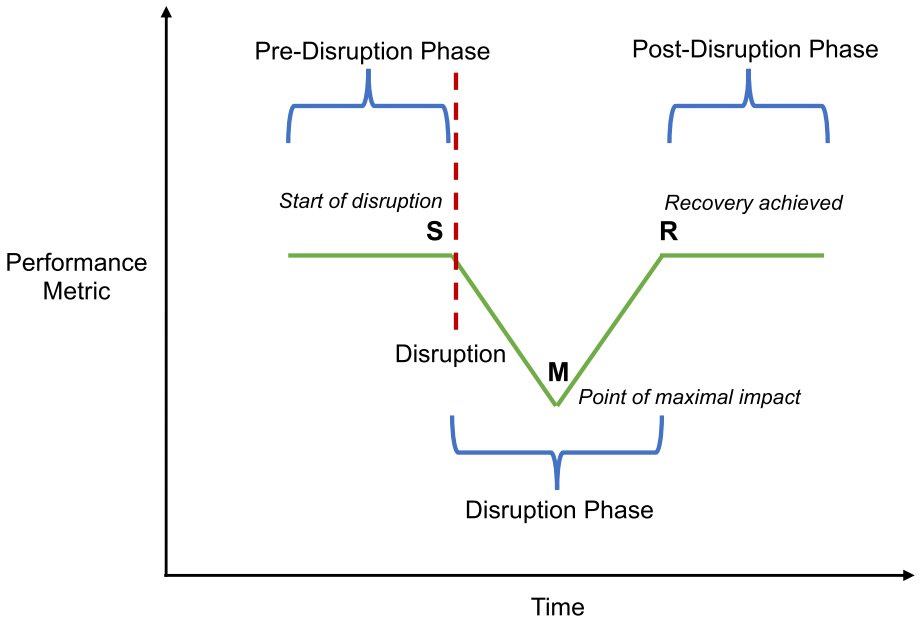

Fig. 2 Generic resilience triangle (Adapted from Bevilacqua et al. (2017), originally from Sheffi and Rice (2005))

its horizontal length represents the recovery time, and its area represents the "magnitude" of the disruption's impact: The smaller the resilience triangle's area, the higher the resilience. Thus, the goal of a firm is to minimize the area of the resilience triangle associated with the disruption.

4 Insights and conclusions

Our interactions with DHS university centers of excellence, pharmaceutical firm executives, security experts, and other practitioners yielded several key operational and managerial insights into PSC functioning, disruptions, and attendant mitigations. These insights are discussed in this section.

First, our work showed that the integrated framework provides a systematic way of compactly mapping out complex supply chains, such as PSCs. To this end, the integrated framework uses detailed modeling of the focal firm's internal processes (production, testing, distribution, etc.) and aggregation of the focal firm's external entities into supplier pools, wholesaler pools, hospital pools, etc. The visualized supply chain map, overlaid with disruption icons, and viewed from a focal firm's vantage point, is conducive to understanding the PSC, while maintaining manageable complexity, thereby facilitating gleaning actionable insights into disruption indicators and warnings and corresponding mitigation strategies. Furthermore, the integrated framework developed in this research can be leveraged to model and analyze other PSCs, as well as supply chains in other industries.

Second, the supply chain map can serve as the basis for developing simulation models to quantify the impact of disruptions on supply chain performance and the efficacy of mitigation strategies that address threats and vulnerabilities. Such a simulation model would be parameterized to represent a baseline model without disruptions, whose performance would be compared to counterparts with deployed mitigation strategies.

Third, since disruptions tend to have a cascading impact on the supply chain (Dolgui et al., 2018), it is important to detect disruptions as soon as possible throughout the supply chain. Consequently, placing capable sensors (e.g., with blockchain technology) at various points in the supply chain can provide early warning of disruption onset indicators.

Fourth, safety stocks are essential in mitigating PSC disruptions (Talluri et al., 2004). The rightsizing of safety stocks depends on factors such as lead times, material costs, and the number of suppliers, and supports business continuity at optimal costs (Grahl et al., 2016; Ivanov & Rozhkov, 2020). For example, early in the COVID-19 pandemic, there was a critical shortage of glass vials (Ganti, 2022). The pharmaceutical industry relies on borosilicate glass which is used for industrial purposes as opposed to the common soda-lime glass which is used in everyday glass objects. Glass vials are also typically managed using the MTS replenishment strategy, subject to the assumption that they are readily available with short lead times, so manufacturers can keep low levels of safety stocks. However, the COVID-19 pandemic uncovered a supply vulnerability in that the borosilicate-glass suppliers could not satisfy the demand spike. Moreover, the problem was further exacerbated by the shortage of raw materials, and specifically the type of sand used to create borosilicate glass. The extensive inter-connectedness of supply chains and combinations of concurrent supply disruptions and demand spikes are often unanticipated. Accordingly, a future research direction is the investigation of multiple concurrent disruptions, extending to higher-tier suppliers. and their supply-chain performance impacts.

Fifth, data accuracy, reliability, and security are critical to PSC management. Disruptions to PSCs that compromise data integrity can severely impact supply chain performance and compliance with regulatory mandates. Modern pharmaceutical firms face data integrity challenges inherent in the ecosystem of disparate suppliers and distributors. Consequently, pharmaceutical firms resort to digitizing data (Chen et al., 2020), and encrypting it has become common practice (Health-ISAC, 2022). One of the pharmaceutical SMEs we interviewed suggested that a disruption that replaces accurate data with false data can be extremely difficult to detect or may even go undetected for an extended period of time. In fact, the SME noted that it suffices to create distrust in data in order to impact PSC performance negatively. The research described here highlights the need to develop processes and procedures to ensure data accuracy, reliability, and security to maintain trust in data.

Sixth, PSC security includes surveillance, vetting of partners, and testing across the supply chain. Surveillance can be carried out by deployment of sensors throughout the supply chain, as mentioned earlier, to provide early warnings of disruptions in progress, which afford the opportunity of early activation of mitigations. During discussions with DHS and SMEs, it was pointed out that PSC security would be improved by enhanced vetting of suppliers and their processes, hiring more inspectors, adding penalties to supply contracts for failure to implement improved security, and judicious use of smart technology (Bocek et al., 2017). Security also includes extensive testing, which is an established practice in PSCs, in part due to the need to comply with regulatory agencies. Accordingly, our PSC model incorporated testing nodes at each production step. Testing nodes, however, are vulnerable to disruptions that make the tests unreliable.

Finally, the integrated framework presented in this paper offers a roadmap to modeling other supply chains, their disruptions, and attendant mitigations by mapping and parameterization, as well as classifying disruptions and overlaying them on the supply-chain map. Once a baseline model is created, one can study the impact of disruptions using simulation.

The PSC map in Fig. 1 facilitated data collection, such as distributions of demand, production times, testing times, transportation times, replenishment lead times, and routing probabilities of work-in-progress. A detailed discussion of the corresponding simulation model, experiments, and mitigation strategies can be found in Domeniconi et al. (2022) and Rana et al. (2024). Furthermore, our subsequent work has demonstrated the extendibility of the integrated framework beyond PSCs to a variety of supply chains, such as medical devices (Domeniconi et al., 2023a), satellite solar panels (Domeniconi et al., 2023b), and food processing (in progress). We believe that this general methodology (further described in Domeniconi et al., 2023c) holds out the promise of furthering empirical and analytical studies of diverse supply chains subject to disruptions. We hope that the collaborative Industry-Government-Academia synergistic model, outlined in this research, can provide a useful three-way stakeholder partnership approach to finding rigorous solutions to emerging operational and societal supply chain challenges.

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Declarations

Conflict of Interest The authors have no competing interests to declare that are relevant to the content of this article.

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