AN EXPLORATORY ANALYSIS OF THE DUTCH PHARMACEUTICAL SUPPLY CHAIN

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ABSTRACT

The outbreak of the COVID-19 pandemic challenged the Dutch pharmaceutical supply chain (PSC) and required tremendous creativity and effort from PSC partners to guarantee the availability of drugs in the Netherlands and, consequently, Dutch patients’ well-being. At the same time, the COVID-19 pandemic exposed and compounded existing issues and vulnerabilities in the Dutch PSC. This report presents an exploratory analysis of the structure of the Dutch PSC. Insights were gathered from the literature and a series of interviews were conducted with key PSC actors in the Netherlands. We identify the current challenges and solutions provided by different supply chain actors and extract and analyze dependencies and vulnerabilities that could compromise its efficiency and robustness. The main results indicate that the Dutch PSC is part of various international PSCs. Therefore, it is exposed to several demand and supply characteristics and vulnerabilities that also affect other countries. Simultaneously, the regulation and specific organization of the Dutch pharmaceutical sector has a significant impact on national supply and demand dynamics and how the Dutch PSC can be managed. This report wants to shed light on these issues and provide guidelines to further improve the PSC’s performance.

Keywords: Pharmaceutical supply chain, incentives, vulnerability, drug availability and shortages
INTRODUCTION

The COVID-19 pandemic is widely regarded as one of the largest crises the world has faced in the past century. The coronavirus crisis has had many impacts on our society, including causing massive disruptions to global supply chains. These disruptions have affected the supply of our most basic needs, including food and medicine, thereby impacting companies, consumers, and patients.

In the light of the COVID-19 crisis, TKI Dinalog called for exploratory studies on the supply chain structure, supply chain dependencies, and supply chain vulnerabilities of the Dutch food, pharmaceutical, and manufacturing industries. TKI Dinalog expressed an interest in understanding how supply chains have evolved over time and how supply chain structures and operations could be improved. This report answers TKI Dinalog’s call for an exploratory study to identify the structure, dependencies, and vulnerabilities of the Dutch market’s pharmaceutical supply chain (PSC).

The COVID-19 pandemic and associated product shortages in healthcare have brought new attention to the importance of drug availability (Shuman et al., 2020). Drug shortages have been an issue in many countries (EAHP, 2020; AMA, 2020) inspiring several international research initiatives such as COST (2020) and EAHP (2020). Research topics include simulating decision-making in medicine production and trade, highlighting restrictive legal and economic frameworks, disclosing disincentives in the supply chain, and reflecting on best coping practices (COST, 2020).

The Dutch pharmaceutical supply chain faced several medicine availability challenges before the COVID-19 pandemic struck: the Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP) recorded shortages for 750 different drugs in 2018, followed by almost 1500 shortages in 2019 (KNMP, 2019b).

Unsurprisingly, drug shortages, the organizational structure and how to strike a balance between product availability and healthcare affordability have been the subject of social and political debates, including attention from television programs like Zembla (2018, 2020) and BNNVARA (2020). Several dedicated studies were conducted; they will be described in Section 3.

The COVID-19 crisis has both exacerbated and exposed the magnitude of medicine shortages in the Netherlands, increasing the urgency to explore new solutions. The small-scale, exploratory research initiative of TKI Dinalog and Topsector Logistiek has the specific purpose of contributing to exploring new solutions. More specifically, it aims to explore dependencies and vulnerabilities in the networks that supply the Dutch market from a logistics perspective to understand the supply and demand dynamics better and suggest directions for further research.

For this study, the Operations Analytics department of the Vrije Universiteit received the support of TKI Dinalog, Bogin, IQVIA, VIG, and various pharmacists, industry professionals, and other actors in the PSC. Their expertise and help in conducting the research is gratefully acknowledged. Any inaccuracies or mistakes that remain are, of course, the sole responsibility of the authors.

The remainder of this report is structured as follows. Section 2 reviews the literature on network structures, dependencies, risks and shortages in the PSC. Section 3 summarizes the Dutch PSC and the most important parties involved. Section 4 describes the methodology of our study, followed by the results in Section 5. We finish with our conclusions in Section 6 and recommendations in Section 7.
LITERATURE REVIEW

This section surveys the academic and professional literature on the network structures, dependencies, risks and shortages in pharmaceutical supply chains. In particular, we consulted Google Scholar to look for academic literature and EBSCOHost Business Source Elite to search content in trade publications and magazines, using the following search strings: “pharma supply chain”, “pharma supply”, “medicine shortage”, and “drug shortage”. The abstracts of the papers found in the search results were screened to select the studies where insights could be gained about the characteristics of the pharmaceutical supply chain and the main causes of medicine shortages. Papers focusing only on optimizing one aspect of the pharmaceutical supply chain were not included to maintain the focus of the study. Finally, academic papers published in journals that are not indexed in the Journal Citation Reports were also discarded. Only documents written in English were considered.

2.1 SUPPLY CHAIN STRUCTURE, FLOWS AND ACTORS OF THE PSC

A typical PSC is comprised of primary and secondary manufacturers, distributors, wholesalers, and retailers (Cockburn, 2004; Shah, 2004; Amaro and Barbosa-Póvoa, 2008). PSC networks are highly complex, involving hundreds of supply network members (Danese et al., 2006). Specific to the PSC are the primary manufacturers. They produce the active pharmaceutical ingredients (APIs). In contrast, the secondary manufacturers apply further transformations or additions to the APIs to produce the final drugs. Interestingly, Grunow et al. (2003) mentions that the same API might be produced in different plants and can be delivered to different, competing secondary manufacturers. Furthermore, the number of secondary manufacturing sites tends to be larger than the number of primary locations (Shah, 2004).

Pedroso and Nakano (2009) highlight the fact that PSCs have many distribution channels, as manufacturers supply medicines to a wide variety of supply chain actors such as wholesalers, hospitals, clinics, large drugstore chains, governments, regulatory agencies, and NGOs.

The complexity of PSCs has increased significantly since the 1980s, when the pharmaceutical industry moved from a widely integrated industry where large enterprises managed the majority of the value added tasks [drug discovery, clinical development, manufacturing] towards a more complex structure with several agents interacting in all the tasks (Cockburn, 2004). This was not only caused by the emergence of the biotechnology industry (Cockburn, 2004) but also by a shift of the industry towards highly optimized production- and inventory-related assets (Rossetti et al., 2011; Heiskanen et al., 2017), driven by increased pressure from external financial incentives, e.g. stock-shares and dividends (Busfield, 2020).

Shah (2004) and Rossetti et al. (2011) indicate that supply chains in the pharmaceutical industry lack flexibility. The majority of the manufacturing processes require highly-skilled workers that need intensive training. Therefore, changing product variety and volume is challenging. Furthermore, the highly labor-intensive processes in this sector contribute to long lead times (4 to 6 months) (Keskinocak and Ozkaya, 2020). Moreover, PSC manufacturers (primary and secondary) tend to have non-dedicated, capacity-constrained production lines where they manufacture different products (Boulaksil and Fransoo, 2010). This results in complex capacity allocation and scheduling tasks.

According to Shuman et al. (2020), manufacturers in the PSC hold no capacity buffer following the principles of just-in-time production. Therefore, they are unable to meet an unexpected increases in demand. Because of this, market fluctuations in the PSC are addressed with inventory buffers.
In this regard, wholesalers play a very special role in the supply chain of every country. According to Rossetti et al. (2011) and Shah (2004), they are the only members of the PSC that have the capacity to hold additional inventory for a country’s market. Despite the criticality of the inventory carried by the wholesalers, they have received some pressure to decrease their inventory levels through the introduction of a fee-for-service scheme with inventory management agreements in some markets, such as the US (Rossetti et al., 2011; Schwarz and Zhao, 2011). In this scheme, manufacturers only pay wholesalers for the amount of inventory that they distribute while they have a limit on the amount of inventory they can carry (Zhao et al., 2012), and not for the volume of products purchased. This reality limits the PSC’s overall capacity to face unexpected events (Woodcock and Wosinska, 2013) such as a sudden increase in demand, a factory breakdown, or a non-conformance in the quality of an API.

Due to the financialization of the pharmaceutical industry (Busfield, 2020), PSCs have been pushed to reduce costs further and have adopted outsourcing as one of the main strategic decisions for the primary manufacturing stage (see, e.g., Jia, 2007; Olson and Wu, 2011; Subramaniam and Dugar, 2012; Sweeney, 2020). For instance, in 2008, Pfizer reported a plan for an increase in the firm’s outsourced manufacturing from 17 to 30 percent (Van Arnum and Drakulich, 2009). As a result, most APIs are currently produced in China [60%] and India [Shuman et al., 2020; Vinci et al., 2020]. Although this strategy has resulted in a better economic performance, it has reduced the availability of medicines in the EU market [Musazzi et al., 2020; Sweeney, 2020]. This is mainly due to being overly dependent on a few suppliers/countries (Heiskanen et al., 2017; Shuman et al., 2020), a problem that is accentuated by the fact that secondary manufacturing locations tend to be geographically separated from primary manufacturing locations (Shah, 2004).

In addition to the physical flow of goods, Pedroso and Nakano (2009) suggest that PSCs have one additional channel compared to traditional supply chains: a technical information flow. This technical information flow is needed to communicate product characteristics to physicians that prescribe medicines to patients. Thus, Pedroso and Nakano (2009) suggest that information in the PSC has two paths: a demand creating path and a material delivering path (with purchasing, sales, and inventory information). In addition, pharma manufacturers lack information about customer demand as it is shielded by wholesalers (Schwarz and Zhao, 2011), and there is a general lack of visibility and traceability in the supply chain.

To ensure that medicines are available at ‘acceptable’ price levels, authorities regulate prices based on several factors such as an economic evaluation of the drug (the existing alternative drugs, the therapeutic value of the drug, etc.) and income levels (Le Pen, 1997; Martikainen et al., 2005; Paris and Belloni, 2013; Vogler, 2020). Since countries and regions are different with respect to these factors, the outcome of these tools is a price differential across these areas. This market heterogeneity is also distinctively visible amongst European Union (EU) members (Martikainen et al., 2005; Kanavos et al., 2011; Vogler, 2020).

2.2 RISKS AND MEDICINE SHORTAGES
According to van Hoek (2020), there is limited research on how supply chain managers can manage risks proactively. This is particularly true for the PSC due to its specific characteristics and associated risks, which differ from other industries. In this regard, Ward and Hargaden (2019) developed an exploratory risk assessment of the PSC. They suggest that PSCs could be overexposed to vulnerabilities as they lack flexibility in sourcing, flexibility in order fulfillment, visibility, and collaboration.

Jaberidoost et al. (2013) carried out a systematic literature review on PSC risks. They classified the PSC risks into seven risk categories: supply and suppliers, organization and strategies, financial, logistic, market, political, and regulatory. The authors found that the most frequently reported risks were related to supplier issues (failure to supply the API in terms of quantity, quality and time), followed by inventory management issues. Furthermore, by interviewing pharmaceutical industry experts, Moktadir et al. (2018) identified fluctuations in imports arrival and machine or equipment failure as some of the most impactful risks in the PSC of Bangladesh. Jaberidoost et al. (2015), however, found that risks associated with the political/financial instability of their study’s scope, e.g., sanctions, interest rates and currency...
fluctuations, were the most relevant risks in Iran’s PSC.

While many risks have been identified in the PSC, the most relevant ones cause a strong unintended effect on the main value-adding activities provided by the PSC. According to both Uthayakumar and Priyan (2013) and Narayana et al. (2014), PSCs provide consumers with added value by delivering medicine availability, affordability, and safety. This value is created only if all the agents involved in the product value chain (biotechnology, pharmaceutical, and healthcare) have an effective interaction to produce value [Narayana et al., 2014]. However, out of the three factors identified, medicine availability is the added value that can be most affected by supply chain management efforts. Therefore, medicine shortages are one of the most relevant risk effects to study in terms of the operation of PSCs.

The COVID-19 pandemic disrupted many supply chains, including PSCs, and caused high levels of stock-outs. Shortages, however, are not new to PSCs [Shuman et al., 2020]. An emphasis on efficiency rather than responsiveness has been one of the main drivers for companies to use outsourcing as an effective tool to cut their costs [Downey, 2008; Rossetti et al., 2011; Nagurney et al., 2013]. This supply chain elongation coupled with other characteristics (such as little capacity and inventory buffer at different stages across the PSC) of the supply chain has made shortages a characteristic of PSCs. Numerous professionals and academics have reported that shortage levels in the pharmaceutical sector have increased in recent years, see, e.g., Gray and Manasse Jr (2012); Bogaert et al. (2015), and Mijkovic et al. (2020). The literature confirms that this issue is a global challenge that is experienced in different regions such as North America [see, e.g., Eggertson, 2011; Hall et al., 2012; Jia and Zhao, 2017, and Tucker et al., 2020], Europe [see, e.g., Heiskanen et al., 2017; Benhabib et al., 2020; Pharmaceutical Group of European Union, 2020, and Sweeney, 2020], Asia [see, e.g., Kanchanachitra et al., 2011 and Bochenek et al., 2018], and Australia [Quilty et al., 2011].

Despite a general agreement on the increasing shortage levels of medicines, no harmonized definition for the concept of a medicine shortage was introduced until recently. De Weerdt et al. (2015a) and Fox and McLaughlin (2018) identify over 26 definitions for medicine shortages formulated and used by different PSC stakeholders, e.g., regulators, manufacturers, wholesalers, and hospitals. This lack of consensus has created communication problems between different parties involved [Musazzi et al., 2020] and has made it difficult to compare countries and regions in terms of medicines shortage levels [Bogaert et al., 2015]. To address this issue, the European Medicines Agency (EMA) has suggested the following definition [Heads of Medicines Agencies, 2019]: “A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level.” Nevertheless, determining a medicine shortage remains a very challenging task. Fox et al. (2014) and Bogaert et al. (2015) point out that in studies on particular PSCs, researchers and policymakers present a modified definition for shortages depending on the stakeholders’ interest. Costelloe et al. (2015) define medicine shortage as “the inability to purchase a particular drug from wholesalers on a particular day” whereas Heiskanen et al. (2015) adopt the definition suggested by Besançon and Chaar (2013) as “a drug supply issue requiring a change that impacts patient care and requires the use of an alternative agent.” Focusing on European hospital pharmacists, Pauwels et al. (2015) consider drug shortage as “a shortcoming in the supply of a medicinal product that affects the patient’s ability to access the required treatment in due time.”

Several studies investigate and categorize the main causes of medicine shortages, e.g., Besançon and Chaar (2013), Birgli AG (2013), Fox et al. (2014), and Acosta et al. (2019).

Besançon and Chaar (2013) investigate the main causes of drug shortage and divide them into two groups: demand-side and supply-side related causes. On the demand side, the researchers identify demand fluctuation, limited purchasing capability (affordability and capability to pre-finance a purchase), structure of the tendering process and contracts (if a tender policy gives an exclusive contract to a manufacturer, other manufacturers would be out; hence fewer alternatives would be available on the market. If the winning manufacturer faces shortages in capacity, the market would undergo a shortage
period), and non-traditional demand (exporting/parallel trade) as causes of shortages on the demand side. Arfwedson (2004) defines parallel trade as follows: re-importation [or parallel trade as it is known in Europe] occurs when products protected by patent, trademark or copyright are first placed into circulation on one market, then [re-imported into a second market without the authorization of the original owner of the intellectual property rights]. Several researchers identify price differential across countries and regions as a (potential) cause for parallel trading, e.g., Darba and Rovira (1998), Szymanski and Valletti (2005), De Weerdt et al. (2015b), and Vogler (2020).

Exchange rates could also act as a driver for parallel trading (De Weerdt et al., 2015b). For a list of cases of parallel trade in the EU, interested readers are referred to studies performed by Bart (2008) and Pauwels et al. (2015).

On the supply side, Besançon and Chaar (2013) list the following: manufacturing stopped production of a medicine, availability of raw materials, batch recall, market structure (many generics have single or few manufacturers), inventory (given that it is common practice in the PSC to adopt just-in-time principles, hence keeping no or little inventory, the PSC is unable to meet the demand in case of any sudden increase), information management (lack of tools that systematically signal potential shortages along the PSC).

Birgli AG (2013) classifies the causes of shortages into three categories: economic, business, and manufacturing/supply chain. Economic causes are identified as the root causes of the other two categories. Economic causes are said to consist of price reductions and reductions in spending, reference pricing, legislation supporting parallel distribution, delays in payment, and tendering (for generic drugs). Business-related causes involve reduced product introductions/market withdrawals, parallel distribution, quotas/supply chain filters, and tightening of payment terms. Manufacturing/supply chain-related causes encompass fewer manufacturing sites, the just-in-time supply chain, channel strategy including Direct to Pharmacy (DTP), and changes in API legislation. Birgli AG (2013) identifies several causal relations between the causes in the different categories and emphasizes that product shortages can increase the risk of counterfeits due to affordability and accessibility issues.

Fox et al. (2014) investigate causes for shortages for generic injectables, listing mainly quality issues, discontinuation, increased demand, shortages of raw materials, and a loss of manufacturing sites (natural disasters).

Acosta et al. (2019) associate shortages with four principal determinants: market (such as an increase in sales, price-related aspects, voluntary withdrawal, parallel or gray market, etc.), supply chain (structure of the network or supply chain in the country, supply of raw materials and excipients), manufacturing process (quality concerns, changes in the product formulation, industrial development capacities, production problem), and political/ethical issues (regulatory problems, public policy, etc.).

Several characteristics of pharmaceutical products and the markets in which they are sold have received additional attention. The pharmaceutical sector has mainly followed just-in-time principles due to high inventory costs (Ventola, 2011; Birgli AG, 2013; Fox et al., 2014; Bogaert et al., 2015) or high costs associated with recalling items from different markets (Mirtallo et al., 2012). This has resulted in smaller inventories of raw material, semi-finished products, and finished products at different stages of the PSC (see, Fox et al., 2009; Mirtallo et al., 2012; Birgli AG, 2013; Shuman et al., 2020). Furthermore, manufacturers outsource part of the production to subcontractors who receive most of the APIs from only a handful of producers (Heiskanen et al., 2017). Ventola (2011) points out that 80 percent of the raw materials used in pharmaceuticals sold on the US market are imported from Europe, India, or China. Besançon and Chaar (2013) assert that the PSC is structured in such a way that a few manufacturers rely on one source and that the number of these sources is limited. They also identify that these sources are located in few countries, such as India and China, which further increases supply risks due to long distances to the destination markets and cultural differences limiting the consistency of good manufacturing practices at offshore facilities (see, e.g., Gray et al., 2011, comparing quality risks of inshore and offshore plants). Consequently, PSCs are highly dependent on the producers of raw materials (Besançon and Chaar, 2013). If quality issues arise at raw materials producers, a PSC is easily disrupted with shortages occurring at all its stages (Bogaert et al., 2015; Heiskanen et al., 2017).
To maintain the quality of medicines, regulators establish and monitor good manufacturing practices (GMPs) (see, e.g., Kweder and Dill, 2013; De Weerdt et al., 2015b). In case of any non-conformity to GMPs, authorities employ a predefined set of corrective actions, such as recalling all the products from the market or shutting down production lines or plants. If plant closure is part of the enforcement action, then the production line could restart only when the manufacturer fully complies with GMPs (see, e.g., Ventola, 2011; Besançon and Chaar, 2013; Pauwels et al., 2014; Bogaert et al., 2015; Iyengar et al., 2016). Enforcement actions can, therefore, be drastic and may span a long period of time.
3.1 Overview of the Current Situation

First, we list a set of key players in the field. The government is involved in several forms: the medicines evaluation board ("College ter Beoordeling van Geneesmiddelen", CBG [2020]) decides on drug registration, then the Care Institute Netherlands ("Zorginstituut Nederland" Zorginstituut Nederland [2020]) decides on reimbursement. The Ministry of Health, Welfare and Sport (Rijksoverheid, 2020b) is involved in limiting the cost of drugs, see also Rijksoverheid (2020a). The quality and safety of care is supervised by the Health and Youth Care Inspectorate ("Inspectie Gezondheidszorg en Jeugd", IGJ) (Ministry of Health and Sport, 2020), and there is a government research institute called the National Institute for Public Health and the Environment (RIVM, Rijksinstituut voor Volksgezondheid en Milieu [2020]). Moreover, several industry associations are active in the Netherlands. For drug manufacturing, these are ‘Biosimilars en generieke geneesmiddelenindustrie Nederland’ BOGIN (BOGIN, 2020) for biosimilars and generic drugs and ‘Vereniging Innovatieve Geneesmiddelen’ VIG (VIG, 2020) for innovative drugs. Finally, there is a pharmacists’ organization called the ‘Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie’ (KNMP) KNMP (2020) and a wholesalers’ organization called the ‘Bond van Groothandelaren in het Pharmaceutische Bedrijf’ BGPharma (BGPharma, 2020).

The Dutch pharmaceutical sector is bound by many regulations. On a national budgetary level, the so-called budgettair kader zorg (BKZ) limits the total amount spent on health care. On a product level, the wet geneesmiddelenprijzen (WGP) is a law that enables the government to set a maximum price for specific drugs (Farmatec, 2020). This maximum is defined as the average price of such drugs in surrounding countries (currently defined as Belgium, France, Norway, and the United Kingdom, but the selected countries change over time). Reimbursement by basic health insurance is limited to products listed in the Geneesmiddelen vergoedingssysteem GVS (Rijksoverheid, 2020). Generic drugs sold in public pharmacies are tendered by a number of health insurance companies covering the majority of the Dutch population. When a patient needs a certain drug (molecule), they should receive the version their insurance selected, and not any of the other equivalent versions that the pharmacy also stocks. This is called a preference policy (‘preferentiebeleid’) (KNMP, 2020). This tendering process was first introduced in 2008. For a description of the Dutch pharmaceutical sector before that time, see De Wolf et al. (2005). Hospital pharmacies are not bound by the preference policy and have instead united in procurement groups. A total of seven groups cover all 120 hospitals in the country. The points described above lead us to conclude that the market for Dutch pharmaceuticals is highly regulated.

The pharmaceutical sector in the Netherlands differs from that in other countries. In particular, IQVIA (2020) observes that tendering per insurance company is rather unique in Europe (only Germany has a similar system). Pharmaceutical expenses per person in the Netherlands are among the lowest in Europe (Eden McCallum, 2017; OECD, 2020, Figure 5.15) and, perhaps as a consequence, Dutch pharmacies are among the biggest (Eden McCallum, 2017). The low expenses can for a large part be attributed to the insurance companies that have been very successful at lowering drug prices, however, their system has more consequences than merely the price level, as we will see later.

A high-level overview of the Dutch PSC appears in Inspectie Gezondheidszorg en Jeugd (2018) and can be summarized as follows. The API is produced (e.g., in China) and then turned into a tablet (e.g., in India). Subsequently, a European country imports the drug. It needs to be tested in a European laboratory before it can be released. The drug is then stored and distributed within Europe. Eventually it reaches pharmacies, optionally via a wholesaler. Manufacturing APIs in Asia is certainly a financially attractive option, but is from a Dutch perspective also associated with enhanced international corporate responsibility risks (Fransen et al., 2019). Some European manufacturers are still active, especially for drugs with a complex manufacturing process.
While the authors of this report are unaware of the exact numbers for the Netherlands, we can look at our neighbors to get an indication of the share of Asian and EU production. The German interest group of generics and biosimilars reports that 63 percent of the issued API certificates are for Asia, and 33 percent for Europe [Pro Generika, 2020].

### 3.1.1 Drug shortages

In recent years, Dutch PSCs exhibited challenges in terms of medicine availability. In 2018, the Netherlands recorded shortages for 750 different drugs, followed by almost 1500 shortages in 2019 [KNMP, 2019a]. A shortage is defined as being unavailable throughout the Netherlands for at least 14 days. The list, published under the name *Farmanco*, is drawn up and maintained by the pharmacists’ organization KNMP. In contrast, the medicines evaluation board CBG (CBG, 2020) collects reports of shortages and expected shortages from manufacturers. In 2019, it received 3070 such reports about 1965 different drugs [Inspectie Gezondheidszorg en Jeugd, 2020]. When a manufacturer fails to report an anticipated shortage, IGJ can impose a fine (the so-called ‘bestuurlijke boete’). These fines were raised significantly [Weda et al., 2019; Nederlands Juristenblad, 2020] to a maximum of € 860,000 in December 2018. Subsequently, the CBG only publishes unresolved shortages, which amount to only a few per year. Hence, signals for potential drug shortages reported by the CBG differ from signals observed by pharmacies through the KNMP [Postma et al., 2018].

Shortages can occur both in originator drugs and generic drugs. Recent evidence from the Dutch Ministry of Health, Welfare and Sport [2019, 2020] finds that 60 percent of the reported, anticipated delivery problems in 2018 were linked to generic drugs, whereas the remaining 40 percent were linked to originators. IQVIA [2020] studies several other European countries and finds that 80 percent of the shortages occur in generics. It is unclear how this compares to the Dutch numbers mentioned earlier since the quantity of expected Dutch delivery problems that materialized into actual shortages were not specified. European and Dutch ratios may differ in practice. For example, Pauwels et al. [2015] surveyed hospital pharmacists about shortages in anti-infective drugs. In contrast to other European countries, they found that Dutch shortages were exclusively in generic drugs rather than in originator drugs.

Several root causes of shortages have been identified. Inspectie Gezondheidszorg en Jeugd [2020] reported on the situation in 2019. The most frequently mentioned cause was a delay in the production or release of the end product (58%; n=1766). Another reported cause was a surge in demand (21%; n=637); this surge often occurred as a consequence of a shortage of a similar product. The least frequently mentioned cause of shortages were business economic reasons (1%; n=31). The National Institute for Public Health and the Environment (RIVM) finds a cause in supply chain dependencies [Weda et al., 2019]. It also states that causes are often outside of the Netherlands. Carp et al. [2018] analyzed shortages over time and found a stronger increase in shortages for preferential drugs than for drugs in general. IQVIA [2020] notes that separate tenders per insurance company create a situation where multiple products need to be available for the same contract, and that seems to generate more reported shortages. Finally, Carp et al. [2018] suggest that low prices have decreased manufacturers’ interest in the Dutch drug market. International manufacturers would sometimes choose not to sell to the Netherlands to avoid parallel imports from the Netherlands to other countries.

### 3.2 MITIGATING ACTIONS

Several solutions to drug shortages have been mentioned. The Dutch Ministry of Health, Welfare and Sport is planning to impose an ‘iron stock’ requirement, defined as five months worth of stock for all drugs on the Dutch market [Tweede Kamer, 2020]. Four months worth of stock should be kept by manufacturers; one month by wholesalers [Pharmaceutisch Weekblad, 2020]. The expected effect of such an iron stock was studied and claimed to resolve 85 percent of the temporary shortages [Kerstens et al., 2019]. Increasing stocks is also proposed in other government-related documents such as Weda et al. [2019]; Veldman [2020]. However, several PSC partners raised a concern that iron stock is not the solution to several more deeply-rooted problems, and several financial challenges related to keeping iron stock are still open to debate [NPO Radio1, 2020]. Therefore, iron stock remains a controversial topic and does not enjoy support from all industry partners.

Weda et al. [2019] establish that reducing shortages requires international collaboration. A recent government document [Veldman, 2020] discusses the medical industry’s resilience in light of the
corona crisis. It emphasizes how international dependencies in drug production and import made the Netherlands and Europe vulnerable. It claims there is a political consensus about reducing dependence on China and India, and observes an increasing number of calls for reshoring parts of the medical production industry. The document explores the option of having stand-by production capacity, and advises the Netherlands to pursue this for medical equipment and protective equipment, but not for drugs because the current capacity is limited.
METHODOLOGY

4.1 SCOPE

Although this research was inspired by supply chain challenges and specific drug shortages during the corona crisis, the Dutch PSC displayed challenges in terms of medicine availability in previous years (KNMP, 2019a). Therefore, the research consortium decided to focus on the structure, dependencies and vulnerabilities in the Dutch PSC in general. In other words, issues related to COVID-19 may arise to illustrate the variety of issues that the PSC is dealing with, but COVID-19 will not play a leading role in this research.

Due to the large number of drugs in the Dutch PSC, the consortium wanted to narrow down the research scope by classifying and selecting products that could help focus ideas.

Based on an initial literature review and exploratory interviews with different (Dutch) PSC stakeholders, we learned that pharmaceutical products can be classified in various ways. For example, by distinguishing between (1) commercial trade vs. pharmacy preparation, (2) inpatient (hospital) vs. outpatient (e.g., pharmacy, drug store), (3) prescription vs. over-the-counter drugs. Another classification would distinguish between generic or innovative medicines, ‘orphan’, biological medicines, and vaccines. Given our study’s exploratory nature and the focus on supply chain implications, we focus on four different types of products with varying characteristics in terms of market, regulations, and techno- logical processes. This decision is inspired by the fact that generic and patent-protected drugs typically face different market conditions and that production technologies can differ (chemically synthesized vs. biological). By studying different types of products, we aim to understand different PSC structures, vulnerabilities, and dependencies in order to acquire a more comprehensive impression of the industry. For each of these types, we want to examine the current supply chain structures, incentives, and industry dynamics that have resulted in the current structure and the implications they have in terms of product cost and product availability. Moreover, we want to identify potential levers to influence supply chain performance and/or supply chain structure. The four different product types that we will analyze can be classified in a 2 x 2 matrix, see Table 1.

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Table 1. Classification of pharmaceutical products. The middle column contains all products that are currently not under patent. Such a product can either still be produced by the original manufacturer, or by others. These variants from other manufacturers are called generics (for chemically synthesized drugs) or biosimilars (for biological drugs). In the rightmost column, products are called specialty drugs (the chemically synthesized ones) and biologicals.

Note that the distinction between off-patent and patent protected is reminiscent of the distinction between functional and innovative products by Fisher (1997) and Lee (2002). Both Fisher (1997) and Lee (2002) distinguish between functional and innovative products to reflect the demand uncertainty a supply chain faces. Lee (2002) also considers supply uncertainty by taking stable and evolving production processes into account. The resulting 2x2 matrix lead to the traditional overview of four supply chain strategies: efficient supply chains when demand and supply are stable, responsive supply chains when supply is stable but demand is uncertain due to the innovative nature of the product, risk hedging when supply is evolving but demand is fairly stable, and agile supply chains in case both demand and supply are considered uncertain. For each of the supply chain strategies, a variety of supply chain decisions need to be made to ensure that the required level of cost efficiency or demand responsiveness is achieved.

4.2 DATA COLLECTION APPROACH

A qualitative exploratory study seemed most appropriate based on our objective to collect information and perspectives related to the structure and operations within the Dutch PSC. A qualitative exploratory approach allows the researcher to...
gather detailed information about a phenomenon directly from the people confronted with it on a daily basis. This approach is most relevant when the phenomenon is not completely understood due to its specificity or difficulty studying it. Different strategies have been developed for conducting qualitative exploratory research. For this project, we used a multiple case study approach supported by structured interviews [similar to Chaudhry and Hodge (2012)]. Collecting evidence from multiple cases is an established method to make the results robust [see Yin (1994)].

Prior to the interviews several preparatory meetings were held. In addition to interactions with consortium partners VIG and BOGIN, we also benefited from conversations with pharmacists’ organization KNMP, a hospital pharmacist with experience in the generic drug manufacturing industry, a manufacturer of patent-protected drugs, and the wholesaler organization BGPharma. Each of these parties informed us about various aspects of the Dutch PSC; this enabled us to conduct the interviews that followed efficiently.

We interviewed eight pharmacists. In this report, they are referred to as PH1–PH8. We aimed for a varied selection: some work in public pharmacies, others in hospital pharmacies, and university hospital pharmacies. Moreover, we interviewed two leading wholesalers [W1 and W2], and four manufacturers [M1–M4], a mixture of generic and patent-protected manufacturers. All of the interviewees are active in the Netherlands and were considered knowledgeable given their professional experience and current functions within their organizations. Interviewees were informed of the nature of the interview in advance and could invite colleagues with complementary expertise, which several interviewees did. The key information is summarized in Figure 1.

We used a semi-structured interview format with open-ended questions for the interviews with the pharmacists, wholesalers, and manufacturers. This enabled us to follow the same procedure for each interview and gather consistent information throughout [Sekaran and Bougie, 2003; Kvale and Brinkmann, 2009]. This format [as opposed to traditional surveys] allows the interviewees to cover some topics that were not considered initially and to obtain more knowledge from the interviewees.

All interviews were conducted through video-chats online because of COVID-19 restrictions. The interviews were not recorded; this allowed the interviewee to talk freely.

The interviews started with a brief round of introductions of the participants [interviewees and interviewers], an explanation of the purpose of the project and the meeting, and the next steps. At least two interviewers participated in each interview, taking detailed notes that were sent back to the interviewees for validation. The research team processed the feedback, and the information collected in the interviews was studied to identify common topics for each echelon of the PSC. Responses provided by just a single interviewee were marked for further analysis if they suggested a very specific and relevant characteristic of the PSC.

<table>
<thead>
<tr>
<th>Category</th>
<th>Interviewee</th>
<th>Public</th>
<th>Hospital</th>
<th>University hospital</th>
<th>Off patent</th>
<th>Patent protected</th>
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</thead>
<tbody>
<tr>
<td>Pharmacist</td>
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<td>PH8</td>
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<tr>
<td>Wholesalers</td>
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<td>W2</td>
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<tr>
<td>Manufacturers</td>
<td>M1</td>
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<td>M4</td>
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Figure 1. A schematic overview of our interviewees.
In the interviews with pharmacists, we asked them to mention drugs that are important for the Dutch market. This overview of drugs will help us in the following ways:
- To understand the range of products involved.
- To identify relevant manufacturers to interview.
- The overview may trigger wholesalers or manufacturers to elaborate on particular vulnerabilities that occur in the SC of a specific drug.

We consider pharmacists equipped to create such a list since they have an overview of all products on the market and of shortages. They experience the difficulty of switching the patient to an alternative treatment.

We asked each pharmacist to list three drugs that they found important in each quadrant of Table 1. Those three drugs had to display different levels of product availability in recent years: one that was (A) always available, one that had temporary shortages (B, between two and five months)\(^1\), and one that had structural shortages (C, more than a year). When we use the word ‘shortage’, we imply the EMA definition as described in Section 2: that demand exceeds supply on a national level.

Subsequently, we asked the pharmacists’ organization KNMP to verify whether the mentioned drugs were placed in the correct category and availability level. All products for which KNMP was unable to confirm the category, for example because the stated availability did not agree with the Farmanco list, were removed from the list.

4.3 SUPPLY CHAIN MAPPING
In the supply chain management literature, researchers adopted different ways to visualize pharmaceutical supply chains depending on the focus of studies. Focusing on distribution networks that start from a logistics center, Zhuan et al. (2008) use connectors between entities to represent the flow of products in the network. In the diagram, arrows indicate whether a drug can be shipped from a logistics center to a customer, either directly or through a distribution center and/or a transfer center. Susarla and Karimi (2012) provide a generic illustration for a multinational pharmaceutical supply chain that includes the suppliers of raw materials, primary and secondary manufacturers, distribution centers, waste treatment plants, and consumer markets. The diagram, however, gives little information on which entity keeps inventory.

Masoumi et al. (2012) focus on multiple competing PSCs, each of which has a structure similar to what is presented by Susarla and Karimi (2012). Hansen and Grunow (2015) visualize a PSC that starts from API production and delivers to a set of heterogeneous markets, i.e., the blistering stage includes market-specific information. The SC visualization offers a detailed representation of the various production stages (formulation, production, blistering, packaging) and inventories that are held at the different stages of the supply chain.

Our study focuses on examining the pharmaceutical supply chain dependencies, vulnerabilities, and associated shortages in the Dutch market, inventory locations and targets. Therefore, we will use the SC visualization by Hansen and Grunow (2015) as a starting point and enrich it with insights provided by the interviewees and the literature.

4.4 RISK AND VULNERABILITY ASSESSMENT OF PSCS
A map of the PSC enables us to relate potential risk drivers and vulnerability drivers of drug shortages to its structure. Frameworks to identify and assess supply chain vulnerabilities and risks are abundant (see, e.g., Rao and Goldsby, 2009; Ho et al., 2015; Hosseini et al., 2019, for overviews). Most frameworks are generic in the sense that they can address a broad range of different supply chains and products. Such assessment frameworks typically rely on several predefined risk and vulnerability driver categories and subcategories, e.g., demand-side risks, supply-side risks, and catastrophic risks (Wagner and Bode, 2006). This approach of using predefined categories of risks has been used by studies concerned with identifying vulnerabilities and risks in the PSC. For example, Ward and Hargaden (2019) identify, among several pre-selected risks, ‘connectivity’, i.e., the degree of dependence on external organizations, as the greatest vulnerability of the PSC in Western Europe, especially when it concerns the PSC’s inflexibility in sourcing and order fulfillment. Similarly, Enyinda et al. (2010) and Moktadir et al. (2018) use a predefined set of risks to gauge the importance of different risks in the PSC. In contrast, Jaberidoost et al. (2015) use a combination of pre-selected risks and interviews with open-ended questions to identify the most relevant risks in the PSC.

The richness of pre-selectable risk driver categories and the applicability to various supply chains are among the strongest features of generic

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1. Note that manufacturers are obligated to report an anticipated shortage to the Dutch government two months in advance [Meldpunt Geneesmiddelenlentekorten en -defecten, 2020].
vulnerability assessment frameworks, but they can also be regarded as limitations in the light of this study. Firstly, despite several notable attempts to unify and harmonize several risk categorizations (e.g., Pettit et al., 2013; Pournader et al., 2014; Ho et al., 2015; Hosseini et al., 2019), risk drivers and included subfactors still commonly vary from one framework to another. While vulnerability assessment frameworks can address supply chains at multiple, inextricably linked, levels (Peck, 2005, 2006), it is unclear how (and which) risk drivers specifically affect the supply chain structure. Also complicating the lack of consensus in risk driver classifications is the differences in perspective about their usage. While some frameworks adopt approaches that exploit the selected risk drivers as a starting point for subsequent data collection (e.g., Pettit et al., 2013; Moktadir et al., 2018), others merely use risk categories as a means to structure data collected in earlier stages (e.g., Hallikas et al., 2004; Manuj and Mentzer, 2008; Chowdhury and Quaddus, 2017). Although the latter approach is arguably less restrictive with respect to the (a priori) scope of the data collection phase, its downside is that only few standardized data collection formats (questionnaires, surveys, field studies) exist to extract risk drivers directly from stakeholders in specific supply chains. Developing methodologies to overcome these limitations are beyond the scope of our research.

As we aim to explore the vulnerabilities associated with the overall PSC structure for four different drug categories (rather than targeting general vulnerabilities for specific products), we do not attempt to apply a generic vulnerability assessment framework directly. Nonetheless, we recognize the potential of risk driver categorizations for exposing vulnerabilities in the PSC. Therefore, in the first phase, we pursued a set-up where interviewees could freely discuss their concerns with respect to structural dependencies and vulnerabilities in the PSC in a series of semi-structured interviews (cf. Jaberidoost et al., 2015). In the second phase, we structured and related the results of these interviews back to the relevant stakeholder dependency categories and risk driver categories defined within the risk and vulnerability frameworks of Pettit et al. (2013), Ho et al. (2015), Moktadir et al. (2018), and Hosseini et al. (2019) whenever possible. Moreover, based on the interviewees’ inputs, we reflected on the impact of the supply chain network structure and how it is operated.
RESULTS

To visualize the pharmaceutical supply chain network and structure the inputs received from the different SC partners on dependencies, vulnerabilities, and associated shortages in the Dutch market, we have adjusted the SC visualization of Hansen and Grunow (2015). Based on the interviews with different Dutch PSC actors, we decided to add raw material suppliers, excipient manufacturers, pre-wholesalers, and particular, distinct ‘markets’ such as hospitals, (public) pharmacies, patients, and other markets. Note that we have reduced the level of detail for the secondary production stage by removing packaging and blistering from the Hansen and Grunow (2015) framework.

Figure 2 gives a general overview of the PSC structure that supplies the Dutch market. The structure, dependencies, and vulnerabilities in the PSC will be explained in more detail in the following subsections.

5.1 PHARMACIST STAGE

As described in Section 4, we asked the pharmacists to nominate several drugs that they found important for the Dutch market. The mentioned drugs were classified according to the four quadrants in Table 1 and their availability level. We only kept the products that KNMP could verify were placed in the correct category, resulting in a number of items per category shown in Table 2 (note that several drugs were mentioned more than once).

We further narrowed down the list by selecting one item per category in consultation with our consortium partners. This resulted in the products mentioned in the first column of Figure 3. Note that the patented drugs are found in the bottom half of this table (the ones for which just one manufacturer is listed).
Then we give a short description of each of the selected drugs, starting with the generics. Omeprazole, listed by PH2, is used to reduce stomach acid and was selected because of its frequent use. PH7 mentioned Microgynon 30 and the corresponding generic versions: the most popular oral contraceptive pill. A worldwide shortage of this product in 2018 resulted in a lot of media attention.

PH8 listed Valsartan: an oral medication used to treat high blood pressure. Recent shortages are attributed to a product recall due to an impurity found in the API. The impurity is called N-nitrosodimethylamine (NDMA, nitrosamine). Infliximab is a so-called monoclonal antibody used to treat a number of autoimmune diseases (PH6). Only a few biologicals with shortages were mentioned. Our selected product for this category is Somatropin: an often-used growth hormone that has few alternatives, according to PH6. Note that after cross-checking the pharmacists’ list with KNMP and our consortium, there were no biologicals left in category C (unavailable for more than a year).

We also selected patented drugs, although this was more complicated than selecting generics. It is not always possible to concisely state when a drug loses its patent: one drug can have multiple patents for different medical conditions, and patents expire at different dates in different countries. Tafinlar is an oral cancer treatment typically provided through hospital pharmacies. It is expensive and always available, even during the corona crisis (PH6).

Finding patent-protected drugs with availability issues turned out to be challenging for the interviewed pharmacists. Innovative products are generally known to have higher margins and are typically supported by responsive or agile supply chains (Lee, 2002). Our consortium partner VIG recommended that we list Floxapen: an antibiotic that is off-patent but for which the original manufacturer still holds a reasonable share of the market. VIG was also able to identify one patented drug that faced a shortage of more than a year: Thyrax, used to treat thyroid hormone deficiency. The shortage occurred when the manufacturer was moving their production facility, and the issue attracted attention because thyroid patients are very sensitive to changes in their medication. Keytruda was mentioned as a biological that is always available and was considered important because it is one of the most expensive drugs in the Netherlands (PH6). Finally, along the lines of a suggestion from PH7, the VIG recommended the inclusion of Novorapid: a type of manufactured insulin (‘insulin aspart’), an injectable treatment for diabetes.

To prepare for our interviews with other supply chain partners, we aimed to better understand the selected drugs’ position in the Dutch market. To that end, we investigated manufacturers’ market shares for the selected drugs by analyzing Dutch sales data provided by IQVIA. This information is found in Figure 3.
Due to the high impact of COVID-19 on the PSC’s daily operations, we also asked pharmacists to highlight notable additional (i.e., previously non-existent) changes in the availability of drugs during the first wave of COVID-19. We compiled the responses from the pharmacists in Table 3 using the classification from Table 1. Pharmacists indicated that additional changes in availability at the time exclusively related to temporary (category B) shortages of off-patent, chemically synthesized products.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Availability</th>
<th>Off-patent</th>
<th>Patent protected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical synthesized</td>
<td>A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Propofol [5]</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>Midazolam [5]</td>
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<td></td>
<td></td>
<td>Hydroxychloroquine [2]</td>
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<tr>
<td></td>
<td></td>
<td>Remifentanil [2]</td>
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<tr>
<td></td>
<td></td>
<td>Paracetamol</td>
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<tr>
<td></td>
<td>C</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Biological</td>
<td>A</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>B</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>C</td>
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<td>0</td>
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</table>

Table 3. Notable changes in the availability of drugs during the first wave of COVID-19 (in parenthesis: number of pharmacists that mentioned the products).
Pharmacists listed the following reasons for the drug shortages reported in Table 3 during the first COVID-19 wave. Propofol is used to sedate patients in operating rooms. It is also frequently used for intubating patients (PH1, PH3) and was mentioned in the treatment protocols of virtually all Dutch hospitals [PH1]. It faced shortages because of the sudden increase in patients that needed intubation following COVID-19 complications. PH1 mentions that the shortage was further exacerbated because patients with comorbidities [e.g., obesity] were hospitalized relatively frequently and needed higher doses of Propofol for intubation.

As a result of the Propofol shortages, Midazolam was used as an alternative for sedation [PH1, PH7]. PH2 mentioned that, during the COVID-19 crisis, Midazolam was also used in homes for the elderly to relieve the pain of COVID-19 patients who could not be hospitalized. Interestingly, PH7 commented that when hospital pharmacists also faced Midazolam shortages, pharmacies were allowed to produce batches of Midazolam for their own use. This reduced the pressure on the supply of Midazolam at public pharmacies.

Remifentanil, a painkiller, also experienced increased demand during the first wave of COVID-19 (PH5), thereby causing shortages of this product. Hydroxychloroquine faced increased demand and shortages because of its alleged ability to combat COVID-19 (PH8). Lastly, public pharmacists PH7 highlighted that they faced shortages of Paracetamol due to hoarding and panic buying during the first wave of COVID-19.

PH8, also a public pharmacist, commented that they have observed a 15 percent decrease in overall sales volumes since the eruption of COVID-19. PH8 suggested that this could be explained by the lower number of patients who started new treatments due to the reduced number of visits to general practitioners.

Please note that pharmacists indicated that sudden, unexpected increases in demand exclusively triggered the changes in the availability of drugs during the first COVID-19 wave. Pharmacists did not previously mention this reason for the general drug availabilities in Table 2. Furthermore, the most notable changes in availability during the first COVID-19 wave occurred in the off-patent, chemically synthesized quadrant. This seems to be largely in line with the drug shortages generally reflected in Table 2. However, none of the pharmacists specifically reported additional drug shortages for patent-protected drugs, nor increases in availability [category A] of specific drugs. Instead, pharmacists exclusively indicated temporary availability issues [category B] with off-patent, chemically synthesized drugs.

5.1.1 Network structure and practices according to pharmacists

Figure 2 illustrates how patients can receive drugs from a public pharmacy or the hospital pharmacy as a part of their treatment. Section 3 explained how generic drugs sold in public pharmacies are subject to tenders organized by insurance companies (the so-called preference policy). Recall that hospital pharmacies are not bound by these tenders and have created procurement groups to organize their own tenders.

Drugs administered in a hospital are not reimbursed per item but as part of a larger treatment package (‘Diagnose Behandel Combinatie’, DBC). The government decides how much is reimbursed for the majority of those treatments. In contrast to the preference policy, the insurance company does not know exactly what brand is provided. Given these predetermined reimbursements, hospital procurement groups have an incentive to negotiate similarly low prices with manufacturers to avoid losing money on every patient that needs a specific treatment [PH4].

PH4 compares procurement groups to the preference policy. When a procurement group chooses a generic drug producer, they agree on a price and commit to that manufacturer for a relatively long time (1 to 2 years). Moreover, procurement groups often purchase biologicals that are (very) expensive. PH2 confirms that hospital pharmacies dispense the vast majority of biologicals; public pharmacies can only dispense insulin in this category. PH4 adds that for off-patent biologicals, the alternatives (biosimilars) are not exactly the same. Although the hospital’s target is to administer the preferred drug (the one negotiated by the procurement group) to 80 percent of patients, PH4 explains that meeting that target is not strictly enforced. Sometimes, for medical reasons, patients are better off with an alternative drug. According to PH4, allowing alternative drugs to be administered to patients maintains a market for the alternatives. As a result, they remain approved/licensed for sale in the Netherlands. If the preferred manufacturer
faces a shortage, then others can meet the demand. PH4 speculates that this might explain why hospitals do not face shortages for biologicals. In contrast to the preference policy for chemically synthesized drugs, PH4 observes that the Dutch market is not very interesting for manufacturers whose drugs are not preferred.

Public pharmacies are either independent or belong to a chain. In both cases, they place their orders with a single distributor (wholesaler). Note that some wholesalers have their own pharmacy chains. In the event of a shortage, PH2 indicates that wholesalers distribute the drugs evenly between pharmacies, regardless of whether a pharmacy is independent or part of their chain. PH2 also indicates that in the event of a shortage at the pharmacy, they ask other pharmacies to deliver the drug or send the patient directly to other pharmacies. These lateral shipments or transfers of patients are not common and therefore are not added to Figure 2.

During the interviews, all the interviewees confirmed the structure and logic of the 2 x 2 matrix. Several of them reflected on the striking differences in product availability they observed in the different quadrants. The interviewees indicated that most shortages occur in the upper left quadrant of Table 1 (chemically synthesized, off-patent) (PH3, PH5) and that they face few shortages for patent-protected drugs (PH5). In fact, several interviewees indicated having difficulties in identifying patent-protected drugs with shortages (e.g., PH1, PH6).

Pharmacists listed several chemically synthesized, off-patent drugs for which they experienced shortages, reflecting on the impact and possible causes. If drug shortages occur, they are usually acute and cause severe problems that last for a relatively short period of time (PH8). Mentioned causes include problems with a specific API (PH8), the introduction of new regulations or systems (e.g. a track-and-trace system introduced in 2019) requiring adjustments to the packaging of drugs (PH7), and hoarding behavior for specific drugs. Examples of the latter include Hydroxychloroquine – it was hoarded because it was suspected to be effective against COVID-19; this created significant problems for rheumatism patients who had no alternatives (PH8) - and Paracetamol (PH7). Other mentioned causes of shortages are the complexity of the production process of some drugs, which makes it difficult to scale up production (PH2), long lead times between placing orders and delivery for some medicines (e.g. for influenza vaccines where they expect an increased demand due to COVID-19 as patients want to avoid having pneumococci and COVID-19 infections at the same time) (PH8), raw materials being unavailable because a manufacturer has gone bankrupt or has seized production (PH8), and quality issues in batches (PH4).

Pharmacists observed that generic drugs in the Dutch PSC are manufactured by just a few manufacturers abroad - typically in India and China. When shortages occur, increased demand cannot be met (PH5). Biologicals are more commonly produced in Western countries. According to PH1, this could make the supply chain for biologicals shorter and may explain why there are fewer shortages in this category.

Some respondents were unaware of shortages in the biologicals category (PH1), had no delivery issues for expensive biologicals (PH3), and were never confronted with delivery issues for patent-protected drugs in oncology or immunology (PH3).

Aside from the fact that hospital procurement groups allow non-preferred drugs to be used, the high margins in patent-protected drugs are also mentioned as one reason why shortages typically do not occur in this category (PH4). Sometimes hospitals experience a problem with patent-protected drug availability, but the problem lies with the wholesaler. If they call the manufacturer, they hear that it is available (PH4). The availability of specific drugs at wholesalers and manufacturers will be discussed in Sections 5.2 and 5.3.

Some pharmacists have the impression that the supply to some countries (in casu: the Netherlands) is reduced in favor of others as drugs that are not available in the Netherlands are often still available abroad (PH6). They observe that the Netherlands is not the best market because of price-control (and low prices) and the limited size of the market (PH5). Interviewee PH3 puts this in perspective: when a biosimilar was put on the market and sales prices were reduced by 80 percent, originator Abbvie stayed on the market, possibly because the overall market size is sufficiently large to deliver the product to the market (also at much lower prices) (PH 3).

Other interviewees, such as PH8, indicate that there is too much focus on cost-efficiency in the Dutch PSC. Dutch pharmacies hardly make any profit from selling a box of medicine. To make
living, pharmacies need larger volumes. According to PH8, this explains why Dutch pharmacies are on average larger than those in other countries. PH2 also indicated that the size of Dutch pharmacies is becoming larger and that very small pharmacies are closing. PH8 claims that the supply chain from wholesaler to pharmacy has to be incredibly efficient, otherwise it would not be financially feasible. The interviewee is convinced that the Dutch PSC is approaching a breaking point [PH8].

The production process and origin of tablets’ raw materials are kept secret, even if the patent on the product has expired. This makes contaminations difficult to predict and next to impossible to trace [PH2].

5.1.2 Issues and mitigation
Although most commonly-used drugs are always available [PH8], drug shortages are a challenge to public and hospital pharmacists. Some hospital pharmacists indicated facing hundreds of delivery issues/product shortages per year [PH3]. Depending on the hospital size, one person is required one day a week [PH3]; up to four or five pharmacists are in charge of monitoring drug shortages and finding alternatives [PH5]. It is hard to find alternatives for some drugs [e.g., Questran and Plaquenil] [PH8]. In other cases, an alternative product may exist but patients suffer when switching between products [e.g., Thyra for thyroid patients (BOGIN) or drugs for psychiatric patients] [PH3].

When no alternatives are available on a national level, it may be possible to acquire the product from abroad². The inspectorate can give a waiver so that drugs can be imported [PH4, PH5]. When a drug has been out of stock for a long time, the drug is listed in the Staatscourant and pharmacies are allowed to import the drug, e.g. via the international pharmacy in Venlo. Those imported boxes can only be sold for a limited period, so it does not make sense for a pharmacy to stock up on the product from abroad. Ordering drugs via the international pharmacy costs more, including additional shipping costs, and it is not always clear who will pay for the extra costs (insurance company, patient, or pharmacist) [PH2].

PH3 explains that imports can bring up many additional issues, such as different packaging, use instructions in a foreign language, and dosages that differ from what is required for the Dutch market. Pharmacists then have to solve this; PH3 writes an addendum to the foreign leaflet themselves. An alternative solution for patients that live close to the border is to buy their drugs in a German or Belgian pharmacy, which PH2 sometimes recommends.

Some hospital pharmacies have suppliers that could produce some drugs themselves in the face of stockouts. PH5 indicated having a manufacturer in Gorinchem that can produce alternatives, but raw materials are not always available. While it is a solution that could be used, it is neither cheap nor quick [PH5].

5.1.3 Explanations provided for the current situation
Pharmacists gave a multitude of explanations for the shortages. For example, PH4 indicated that the PSC lacks flexibility in the sense that when there is a change in demand (forecast), the supply chain [manufacturers] cannot react accordingly or change their plan. Another cause cited by several pharmacists was that price levels and associated margins on products have an impact on product availability [PH6, PH8].

The high margins on patent-protected drugs are mentioned as one reason why shortages typically do not occur in this category [PH3, PH4]. When hospital pharmacist PH4 experiences a problem with patent-protected drug availability, the problem lies with the wholesaler. If PH4 calls the manufacturer, the drugs are always available.

International price differences are also suggested as the cause of larger product unavailability in the Netherlands. PH8, familiar with the Dutch and Belgian situation, indicates that prices are typically lower in the Netherlands and uses this to explain why drug shortages are much larger in the Netherlands than Belgium. If drug shortages occur, PH8 believes pharmacists in the Netherlands import most frequently from France, followed by Germany.

Temporary shortages are observed, particularly when a drug goes off-patent (in the transition phase). PH1 has experienced two months of shortage in such cases. If patents expire, generics or biosimilars are immediately available and prices can drop by 90 to 95 percent, making margins very small [PH6]. PH1 speculates that, in anticipation of this moment, production of the original product is reduced in advance, resulting in a shortage briefly before patent expiration.
Expected price drops are believed to have significant impacts on product availability in the Dutch supply chain. These price drops are not only caused by expiring patents but also by changes in legislation or the preference policy. An example is provided by PH8, who points out how the adjustment of the WGP law announced for April 2020 (eventually postponed to October 2020) would imply that pharmaceutical companies would face lower prices for their drugs in the Netherlands. The moment the law was to change, any existing stock would have to be devalued. PH8 noticed how the anticipated price drop caused stock in Novorapid to run low at the wholesalers in March 2020. The preference policy causes shortages according to several pharmacists (PH3, PH4). PH3 clarifies this by observing that the demand for a product (drug) is fairly stable, but that the short contracts that are being offered to suppliers disturb the market and make it difficult for companies to maintain a large amount of stock as they face the risk that they will be left with unsold stock once a new drug is selected (PH3).

5.1.4 Pharmacist recommendations
Pharmacists indicated that price levels contribute to product unavailability issues, and some also think that pricing can improve the PSC. PH6 thinks that ‘in the Netherlands, the expensive drugs are too expensive and the cheap ones are too cheap.’ The pharmacist is puzzled by the fact that some drugs cost less than a Mentos even though they are subject to much more stringent quality requirements. At the same time, PH6 wonders why certain costly drugs are offered when the difference in life quality or expected life duration is small compared to other drugs.

PH2 thinks that increased international collaboration and a quicker response of inspection services to contaminations could improve the PSC.

5.2 WHOLESALER STAGE
This subsection describes the results from our interviews with two wholesalers active in the Netherlands, labeled W1 and W2.

5.2.1 Network structure and practices
Wholesale operations are based in every country; they receive supplies of medicines from manufacturers, keep an inventory of drugs, and meet the demand that arises in the country. Four leading wholesalers on the Dutch market carry almost the same medicine portfolio. According to W2, they stock 12,000 to 13,000 SKUs. If we include over-the-counter (OTC) drugs sold at supermarkets and drugstores (‘drogisterijen’) then the product range in the Netherlands is thought to be much larger, perhaps more than 20,000 (W2). The exact numbers appear inconclusive. W1 indicates that the total assortment that can be ordered is probably larger than 75,000 SKUs.

W1 and W2 elaborated on the different market segments that they supply. According to Figure 2, they can supply pharmacies (either their own or independent pharmacies), hospitals or hospital pharmacies, self-dispensing doctors, and other markets. Examples of ‘other markets’ that were mentioned include pharmacies in the Caribbean (within the kingdom of the Netherlands), and other exceptional customers most likely exist. In addition, W2 stated that a wholesaler cannot supply directly to a patient; all drugs have to go through a pharmacy (a claim confirmed by PH2).

Generally speaking, all wholesalers carry a complete medicine portfolio. A notable exception relates to drugs used in hospitals. Only three Dutch wholesalers choose to serve this segment of the market as it requires significant investments in terms of expanding the assortment and supporting ward services (W2).

Although Dutch wholesalers are in direct competition with one another, W1 indicates that there is also collaboration. Since they are all committed to helping patients, they have occasionally supplied each other’s pharmacists if a problem occurred at one of the wholesalers (e.g., a change in IT systems resulting in disrupted deliveries). Moreover, shipments between wholesalers are also possible to resolve specific product shortages at a given wholesaler.

Wholesalers receive supplies either from a pre-wholesaler or from a manufacturer’s warehouse in the Netherlands or elsewhere in Europe. A pre-wholesaler can be affiliated with another wholesaler or a manufacturer. In both cases, it can be operated by 3PL (W2). The pre-wholesaler is not the owner of the product (manufacturers are the owners; consignment stock) but it keeps safety stock and supplies wholesalers (W1) and potentially other parties with the manufacturer’s product, as depicted in Figure 2.

Some Dutch wholesalers have pre-wholesale activities within the group; others do not (W2). W1
explains that a pre-wholesaler is always a separate legal entity from the wholesaler and that they cannot share data.

According to W2, they do not receive drugs from outside of Europe, but the marketing authorization holder they buy from can purchase products outside of Europe.

Their visibility upstream in the supply chain ends at the distribution point in Europe. W1 reports that a lot of generic drugs come from Asia. There are still manufacturers in Europe, but capacity is limited in the Netherlands. Only a few production sites remain, such as Apotex [currently: InnoGenerics] (W1).

W2 explained how parallel trade - importing from and exporting to other EU countries - has played a role for the last 40 years and how it is related to price levels and volumes. According to W2, there is not much export, and around 10 percent of the Dutch market is import. This estimate is confirmed by a figure of 12.1 percent import in 2018 found in Stichting Farmaceutische Kengetallen (2019).

To narrow the focus, we showed the interviewees the selected drugs in Figure 3. W2 emphasized that the supply chain situation of chemically synthesized drugs is completely different from biologicals. Firstly, the complexity of the production process of biologicals is not to be underestimated. The active ingredient sometimes has to go through as many as 17 different production sites. Secondly, production of biologicals involves living organisms for which one cannot speed up production; this can sometimes be done for chemically synthesized drugs (W2).

5.2.2 Issues and mitigation
Reflecting on the current issues with product availability in the Dutch PSC, wholesalers observe that out-of-stocks usually become available again within 3 to 4 months. Wholesalers say that the real root cause of supply chain problems can only be answered by the manufacturers (W1).

Sometimes shortages are related to parallel trade. Import and export relationships may change suddenly, and the impact on the supply chain can be profound. W2 illustrated this with two examples. Firstly, during the first COVID-19 wave, several countries (including Portugal) blocked drug exports to retain stock for their own citizens. Because marketing authorization holders are obliged to supply the market ‘sufficiently’ to meet the ‘needs of patients’ (Geneesmiddelenwet, 2020, Art 49 part 9), regardless of the manufacturer’s market share, the manufacturers of registered drugs had to react quickly to cover the demand that could no longer be covered by imports (W2). Secondly, changes in the WGP law can have a significant impact on import and export relationships. When Norway was added to the Dutch list of reference countries instead of Germany, it implied a complete rearrangement of the portfolio at W2. All of a sudden, import was no longer interesting. Again, the manufacturer has to step up to meet the demand. W2 explains that the manufacturer will only discover this issue a few weeks before, or possibly a week after, the moment it happens. A notable discrepancy is that manufacturers are obliged to signal changes in product availability, but other supply chain partners (e.g., parallel traders) are not obliged to do so. The situation is challenging for manufacturers, but W2 points out that manufacturers decided to introduce a price difference among European countries. When this results in imports and exports, regulation forces them to adapt to changes in demand quickly.

Another reason for shortages is quotas (W1). To reduce import and export flows, manufacturers can decide only to sell a limited amount to each wholesaler. Recall that in Section 5.1.1, pharmacist PH4 indicated that wholesalers are sometimes out of stock while manufacturers still have products available. This might be due to quotas. W2 indicates that shortages due to quotas only rarely affect the patient. When it does, it tends to be for patent-protected (single source) products because there are only a few alternatives available (W2). W1 explains that manufacturers can determine the height of their quotas based on Farminform (2020) data on the drugs delivered to patients each month. By totaling the SKUS for one product or molecule, total sales are known, and a fraction can be assigned to each wholesaler. According to W1, the data lags two months behind and if a wholesaler has additional demand - for example because they acquired new pharmacies - then they contact the manufacturer to obtain more product, but this can take a few months (W1).

If shortages occur, W1 allocates the same percentage of products to each of its customers, spreading product availability across all parties involved. If W1 runs out of stock, there are two possibilities to acquire drugs: import the regular way, or get permission from Dutch government to import without paperwork.
W1 observes that the supply chain of generics witnessed a major change in 2008 after the introduction of the preference policy. Changes in the preference policy make it very difficult for supply chain partners to forecast demand (W1). Manufacturers already start decreasing the stock of a product that may lose preference in the future (W2). The new preferred party also has little time to ramp up production in time to have sufficient inventory available (W1, W2), so one can face a temporary stockout for both products; this can last six to eight weeks (W2). This results in a domino effect where manufacturer 3 or 4 gets involved, even though they were not initially involved in the preference policy at all. These manufacturers typically have limited stock, and suddenly they need to supply the whole market. As a result, their stocks are also quickly drained. W2 states that bouncing back and forth between labels can take as long as 12-24 months for some products before the situation stabilizes. By then, the next pricing round is already coming up. According to W1, an additional challenge for manufacturers is that they need to plan the production of the end product, and they require the excipients and the APIs before production can start. In fact, sourcing for drugs starts years in advance (W1).

W1 points out that the current practice of tendering per insurance company implies that for a common drug like Omeprazole, three to four different labels have to be kept in pharmacies and wholesaler warehouses even though the active ingredient in each label is the same.

Although tendering has reduced prices, W2 wonders whether patients are better off. There are other, non-financial ‘costs’ related to switching generics frequently: (1) compliance (‘therapietrouw’) and (2) losing the placebo effect since drugs ‘become Smarties’ (are perceived as Smarties) when they are changed frequently (W2).

W2 observes that the generic supply chain is operating at maximum capacity, and hence any hiccup will lead to problems. Leading manufacturers sometimes operate at 103 percent capacity utilization to be able to produce at say 22 cents a box, which they can deliver to the Dutch market for 25 cents. To illustrate the difficult situation generic manufacturers are in, W2 contrasts this with the 60-70 percent capacity utilization that originators employ to be able to meet demand.

5.2.3 Wholesaler recommendations

- Reconsider testing strategies [W1]: When the preference policy was first introduced, the first 3-4 weeks of supply came in by plane and the rest by boat. The products that arrived by plane were tested in a lab - which could take two weeks - before the product could be released to the market. Those lab results were also applicable to the product that later arrived by boat [W1]. Nowadays, drugs need to be sampled from both shipments, even if they are from the same production batch. W1 wonders if this is necessary if temperature and other conditions during transport are met. W1 also wonders why it is not possible to do independent EU testing in the country where it is manufactured since this could reduce lead times.

- Reconsider the frequency of adjusting the WGP law and the preference policy [W2]. The current approach of adjusting the WGP twice a year and having insurance companies changing their preferred suppliers once a year (at different moments in time) leads to many moments when one needs to make important decisions. This creates uncertainty or insecurity in the supply chain according to W2. According to the same interviewee, the Netherlands already has very competitive prices for generics and it is unclear why contracts for more mature drugs have to be tendered so frequently. As a solution, W2 suggests fixing some longer-term contracts for these products and focusing efforts elsewhere, for example, aiming for better prices for other drugs.

- Predict shortages or recalls for specific products using data on increased Internet searches for specific drugs [W1].

- Keep the following outlook in mind: Amazon is already selling pharmaceutical products in the US and W1 speculates it is only a matter of time before they do so in Europe. Our laws currently do not allow that, but laws can be changed or challenged [W1].

5.3 MANUFACTURER STAGE

This subsection describes the results from our interviews with four drug manufacturers labeled M1–M4, as detailed in Figure 1.

5.3.1 Network structure and practices

The interviewees confirmed the PSC’s overall structure depicted in Figure 2, indicating that the
simplified model is basically correct (M3) and that it probably covers 99 percent of the volume in the Dutch market (M1). M2 specializes in biological drugs. Each of their manufacturing plants make dedicated product groups or a specific molecule using only raw materials as inputs (APIs as such are produced within the plant). Moreover, the company consolidates finished products produced across the globe in Europe, from where consolidated shipments are sent to national wholesalers. Almost their entire supply chain, from plant to patient, is a cold-chain. This puts specific demands on storage and distribution. M4 produces chemically synthesized and biological drugs and confirmed the overall structure of the supply chain.

**Procurement** As Figure 2 illustrates, the PSC typically starts with the production of raw materials. Although China and India are important manufacturing countries of raw materials for the PSC, M1 points out that raw material production is a chemical process that occurs in plants all over the world, including the Netherlands and Belgium. Although several raw material manufacturers are typically available, the raw materials used in the PSC can also be used in other industries. This can cause shortages in the PSC (M3). According to M1, the same applies to API manufacturers, so-called primary manufacturers, since they produce chemicals for different industries, e.g., food and pharmaceutical supply chain. API manufacturers do not produce for the PSC exclusively so there is competition between different supply chains for their capacity. Even for producing excipients (such as sugar), the pharma product will have higher standards, so the barriers to entry are very high (M3). M1 confirms that excipients have become more and more important over the last few years, and they are being monitored closely to safeguard product quality.

Unlike raw materials, which can be processed by several chemical manufacturers, the number of API manufacturers is limited. M1, M2, and M3 (page 1) all state that there are only a few (sometimes only 1 or 2) manufacturers available worldwide for some APIs.

According to M1 and M2, this makes generics supply chains quite vulnerable to any disruption, e.g., contamination or natural disaster. To illustrate this, M1 gives the example of a drug for tuberculosis. There used to be only a single API manufacturer in Fukushima. After the tsunami hit the region in 2011, the API disappeared from the market and caused shortages for two years.

M1 points out that pharmaceutical (secondary) manufacturers cannot easily exchange API and excipient manufacturers for their registered drugs since they receive a registration for a specific drug, using specific APIs and excipients. If a manufacturer wants to change these, they must go through the entire product registration procedure once again, which requires a lot of time and effort (M1).

The origin of the drugs supplied to the Dutch market varies amongst the interviewees. M1 produces drugs globally; 60 to 70 percent of the drugs are produced in Europe. For the Dutch market, 70 percent is produced in their own plants, and third-party manufacturers produce the rest. For M2, 95 percent of the shipments for the Netherlands originate from the European consolidation center (which sources products from own production facilities across the globe). The remaining 5 percent is imported from the Far East and is sent directly to the pre-wholesaler (M2). M3 estimates that the drugs they supply to the Netherlands originate for 50 percent from Europe and 50 percent from India. Only a few specific products come from the USA, and they are more expensive (M3). Within Europe, a lot comes from France and Eastern Europe. Quite a lot of pharmaceutical production occurs in France because French insurance companies only reimburse what was produced in France. Hungary and Poland have invested a lot in manufacturing sites and the consolidation of manufacturing started in Eastern Europe, but production later moved to India. API production has consolidated even more than the manufacturing of final products. A lot of M3’s APIs currently come from China for cost reasons. For M4, all finished products for the Netherlands are produced in Europe or at least receive a final production step (not only packaging) at their own or third party plants in Europe (M4).
Lead times and production planning Estimates of lead times for the Dutch PSC vary significantly amongst the interviewees, depending on the materials’ origin and the specific product concerned. Manufacturers that are located in the EU and receive APIs from outside the EU face long lead times between placing an order and receiving it. M1 reports a lead time of six to seven months for APIs manufactured in India, clarifying that these lead times are usually not an issue since demand is fairly stable and ordering and replenishment processes are typically well organized. As a result, M1 keeps little to no safety stock for APIs. M1 also indicates that product replenishments are a ‘continuous’ process. Only if one needs to make changes in the leaflet or the box of a drug does one notice that it takes approximately six months to receive new batches.

M2 indicates that if one had to start production for one of their products from scratch, it would take three months to get a final product. As production is regular and replenishments are continuous, one does notice the 3-month lead time. M2 faces a stable demand for its products, has stable output and uses a 3-year production plan for its products.

M3 explains that sourcing from India makes planning harder. Because everything is produced in bulk, production runs are larger. Ceteris paribus, the time between production runs, increases and lead times become longer. M3 explains that an order for the Dutch market now has an average lead time of six to nine months whereas it used to be three to four months. Products are shipped by sea, and sourcing outside of the EU (e.g., from India) means you need to do EU testing, which takes at least a month, sometimes even longer according to M3.

M4 has an imprecise long-term planning over four to five years, but 6-18 months is the real planning horizon; one to six months of production are more or less fixed. M4 states that lead times can vary per product, for some products it is a matter of weeks and for others months. The company distinguishes between lifesaving drugs and those which are not, and examines whether competitors have alternatives. Critical products are given priority in terms of production and delivery.

Storage and distribution All interviewed manufacturers maintain stocks of finished products, which they store at pre-wholesalers. M4 clarifies how their production sites keep safety stock as neutral packs, packed products. These are not finished products as they are only finished when prepared for a certain country in their language [M4]. Since the way inventory levels are set and monitored is closely related to mitigating the supply chain challenges of the PSC, they are discussed in detail the next subsection.

The interviewees confirm the downstream supply chain’s overall structure in Figure 2, and the depicted product flows via pre-wholesalers and wholesalers to make their products available to patients.

When asked if manufacturers ever deliver directly to hospitals, M1 states that this only happens for very specific products. M2 mentions direct deliveries to pharmacies, but such direct deliveries to pharmacies are typically invoiced to the associated hospital. M2 also delivers very expensive drugs directly to Dutch hospitals within two hours’ notice since the product can be life-saving for patients, and hospitals cannot keep such expensive products in stock. M4 ships high-volume, low-value products to hospitals, hospital pharmacies, and local pharmacies via wholesalers. Low-volume, high-value products are shipped directly to hospital pharmacies and local pharmacies (M4).

M2 observes a market development: it sees increased “direct to patient” deliveries, which they operate in several countries, mentioning websites like onemed.nl and thuisapotheek.nl.

According to M3, national data shows that the demand for drugs consumed by the Dutch market is almost stable and that variation in demand is caused by supply chain actors and practices in the downstream supply chain.

5.3.2 Issues and mitigation Production M3 emphasizes that margins for generics have fallen to almost unsustainable levels. As a result, generic companies are pruning many products from their assortment. Many years ago, they were aware of five to seven producers for a given drug; now only four, three or two remain. Having fewer manufacturers on the market operating at high utilization rates increases vulnerability and lowers the resilience of the supply chain. M3 illustrates this via one of its European factories that had to close due to COVID-19. According to M3, recovering and producing the...
entire backlog took a long time, especially because the plant was already operating above 90 percent utilization.

Large production batches are common. Manufacturers try to reduce changeovers because they need to clean production facilities for every change of product. According to M3, it is still common to package products at the same location where they are produced. M3 also uses postponement, whereby products are bulk produced at the plant, shipped to a different packaging location, preferably in Europe, where the product is quarantined and testing can be done for the entire bulk shipment at once. Since many products can only be tested at one lab in Europe, these labs are often too busy to test immediately and testing can take four to six weeks [M3]. M1 confirms that testing is done at the level of a shipment batch (rather than a production batch) and that testing can sometimes take a long time, but it generally takes two weeks.

Based on what experienced by M1, most of the drugs pass the quality tests, but there are rejections due to packaging mistakes, e.g., missing information or issues with leaflets. If a batch is rejected then it can take six months to receive a resupply. In most cases, competitors will be able to absorb the backlog. When reflecting on reshoring the production of raw materials and APIs, M1 argues that many facilities and much of the knowledge and expertise in this matter are no longer in Europe. This makes it almost impossible to regenerate production in Europe. If India and China were to adopt the same safety and environmental measures, then it would become financially less attractive to produce there [M1]. M3 confirms that Indian plants are huge and modern compared to most European plants, that the people are well educated, yet labor is cheap.

Inventory M1 keeps four months of sales in stock on average at the pre-wholesaler for the Dutch market. The stock level varies across different products and ranges from four weeks up to two to three years [M1]. M2 indicates that for high-risk products (of which they deliver 30 percent of the market), they have at least one month’s worth of the total market demand in stock for the Netherlands. M3 specifies that their normal safety stock equals three months of their own sales volume. For more difficult products with a good shelf life, they keep six months of stock [W3].

As a manufacturer of both generics and patent-protected drugs, M1 points out the financial challenges in maintaining the current stock levels. Assuming sales of 80 million boxes of generic drugs per year in the Netherlands, at an average price of €2.60 per box, keeping six months’ worth in stock amounts to €40 million. If one wants to keep more inventory in stock, say for €80 million, then it becomes clear that this cannot be done at an average price of €2.60 per box [M1].

Most of M1’s products are also supplied by other pharmaceutical companies. If M1 faces a backlog, other producers can often provide the required products. M3 explains that if competitors run out of stock and when they do not notice that they are covering the demand of other suppliers, their own safety stock will decrease rapidly. As this happens a lot and can lead to shortages, M3 closely monitors safety stock levels.

When demand suddenly increases strongly, manufacturers of generics have little flexibility left with which to respond. M1 uses the demand and supply dynamics of a functional product during the first corona wave to illustrate this point. In the spring of 2020, many people thought that if we needed more gloves, we should just order them and they would be delivered quickly as stocks were available. There was stock available for months of demand under normal circumstances but not to handle the strong increase in demand. In fact, production capacity had to be adjusted to meet the new demand!

M1 clarifies how they thought about backup API production and backup drug production facilities in the past. Given the costs to maintain such backup capacity and the current market conditions [price levels], it is clear that manufacturers (of generics) can no longer maintain such backup capacity and that they have to base their capacity utilization on regular demand [M1].

According to M1, patented drugs are priced much higher so manufacturers can afford extra stock. In fact, they must have extra stock. Since doctors prescribe a specific patented drug to the patient, they need to be able to supply their product, otherwise they lose that patient [M1].

Parallel trade and quotas Manufacturers M2, M3 and M4 confirmed that parallel trade complicates their production planning. M2 emphasizes that they
allocate quotas very carefully to ensure product availability on the Dutch market. When problems occur with import flows (that they do not control and can amount to 80 percent of the total demand for some drugs in the Netherlands), they face difficulties when they must suddenly supply the entire market demand. M2 also indicated how the corona crisis affected parallel trade. During the first wave, Norway and England suddenly closed their borders for certain drugs, affecting the availability for the Dutch market (given the share of imports at the time).

M3 confirms that parallel trade leads to oversupply or undersupply. As a result, you need more safety stock, which is expensive to maintain.

**Shelf life** M3 brings up shelf life problems, and observes that shelf lives decreased over time based on regulations (now 24 months at most from the time it is produced). Moreover, M3 observes a tendency to prescribe for 12 months instead of 3, to have fewer dispensing fees. This produces waste and requires all products to have at least a 12-month shelf life (M3). In contrast, M4 claims that it does not have waste due to expiring products, not even for biologicals with a short shelf life.

**Preference policy** Manufacturers made statements regarding the preference policy that confirmed what we saw in previous sections. M3 lists frequent tender changes and changes that are not known soon enough as factors that complicate production planning. M1 states that some generic drug manufacturers choose not to participate; in other words, they do not make price offers to insurance companies. They accept losing part of the market due to that decision. Nonetheless, they can still have a significant market share in the Netherlands in other ways. M3 adds that insurance companies tender 80 percent of the market; the remaining free volume is tendered by wholesalers.

**Contaminations** M1 is very worried about supply chain disruptions due to contaminations such as nitrosamine. Nitrosamine is known to be an issue for Omeprazole and Valsartan, but M1 is convinced that if we can identify more toxic products in end products, then we will discover more contaminations.

5.3.3 Manufacturer recommendations

- M1 is convinced that the pharma supply chain’s complexity is related to quality and safety reasons and the world we live in. M1 would, however, like all countries to recognize EMA for product registrations and sees great potential in increased cooperation and synergy between EU countries.

- M4 suggests so-called ‘shared pack’ medicine boxes that can be given to multiple countries. This would increase flexibility when the minimum order quantity is large compared to national demand. According to M2, the downside is that parallel trade could be stimulated, and increased parallel trade increases volatility in the supply chain. According to M4, shared packs were more prevalent in the past than nowadays. Along these lines, M2 is currently exploring whether a central hub can deliver boxes for the whole Benelux with leaflets in two languages. M3 observes that the situation is already similar for medicines with a EU registration text since that text is the same in every language.

- M3 thinks we can reduce our dependency on Asia by creating incentives for local production, for example, by offering a higher reimbursement for drugs that are produced in Europe. M3 emphasizes that only increasing prices would probably be insufficient and that production in Europe would have to be properly defined.

- M1 adds that if better prices were offered for generics, then a budget could be created to add an extra API in the dossier, have a second source, or increase the safety stock. All of these would reduce risks.

- M1 sees an additional area for improvement concerning pharmaceutical vigilance [studying and reporting side-effects of drugs]. Right now every company has to file the side effects of their drugs individually, even if they are all producing the same drug, e.g., paracetamol. National or European platforms for pharmaceutical vigilance would make sense to M1.

This concludes the description of our results from manufacturer interviews. The following section gathers and categorizes the main risks and vulnerabilities according to all interviewees - pharmacists, wholesalers and manufacturers.

5.4 RISK AND VULNERABILITY EXTRACTION

The concerns that were expressed by the interviewees regarding vulnerability in the PSC are
The vulnerabilities are categorized into several operating environments: (i) lean supply chain and manufacturing practices; (ii) the competitive environment; (iii) the exchange of information; (iv) the legal environment (including policies, regulations, and bureaucracy); and (v) the product or operations environment. The concerns that were expressed most frequently, i.e., by at least 50 percent of the interviewees regardless of the stakeholder group, relate to the limited number of suppliers of raw materials (1), the lack of transparency in the PSC (13), the Dutch tendering scheme (20), and the inflexibility in demand (37). Be aware that the (perceived) vulnerabilities in Table 4 should not be interpreted or treated independently. The values between parentheses refer to specific risks identified in Table 4.

<table>
<thead>
<tr>
<th>#</th>
<th>Operating environment</th>
<th>Vulnerability or risk</th>
<th>Manufactures</th>
<th>Whole-</th>
<th>Hospital Pharmacies</th>
<th>Public Pharmacies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lean manufacturing</td>
<td>Single sourcing of raw materials [including ‘molecules’] and/or lack of alternative raw material suppliers</td>
<td>75.0%</td>
<td>50.0%</td>
<td>60.0%</td>
<td>33.3%</td>
<td>57.1%</td>
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<tr>
<td>2</td>
<td>Lean manufacturing</td>
<td>Consolidation of manufacturers and/or lack of alternative suppliers</td>
<td>50.0%</td>
<td>50.0%</td>
<td>40.0%</td>
<td>33.3%</td>
<td>42.9%</td>
</tr>
<tr>
<td>3</td>
<td>Lean manufacturing</td>
<td>Panic buying or stockpiling by patients or pharmacies</td>
<td>75.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>35.7%</td>
</tr>
<tr>
<td>4</td>
<td>Lean manufacturing</td>
<td>Lack of redundancy in production capacity</td>
<td>75.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>28.6%</td>
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<td>5</td>
<td>Lean manufacturing</td>
<td>Geographic concentration of suppliers</td>
<td>25.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>33.3%</td>
<td>21.4%</td>
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<td>Lean manufacturing</td>
<td>Long lead times</td>
<td>25.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>33.3%</td>
<td>21.4%</td>
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<td>7</td>
<td>Lean manufacturing</td>
<td>Inability of manufacturers to react swiftly to changes in demand and demand forecasts</td>
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<td>0.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>7.1%</td>
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<tr>
<td>8</td>
<td>Lean manufacturing</td>
<td>Inability of parallel traders to react quickly to shortages</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
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<tr>
<td>9</td>
<td>Lean manufacturing</td>
<td>Unavailability of raw materials at local backup production facilities and inflexibility of backup production</td>
<td>0.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>10</td>
<td>Competitive environment</td>
<td>Competition for raw materials with other industries, especially the food industry</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
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<tr>
<td>11</td>
<td>Competitive environment</td>
<td>Consolidation of procurement</td>
<td>0.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>12</td>
<td>Competitive environment</td>
<td>Lack of facilities, knowledge, and expertise to reshore raw material production</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>13</td>
<td>Information exchange</td>
<td>Lack of transparency about inventory levels and import/export volumes among manufacturers and between manufacturers and wholesalers</td>
<td>75.0%</td>
<td>100.0%</td>
<td>20.0%</td>
<td>33.3%</td>
<td>50.0%</td>
</tr>
<tr>
<td>14</td>
<td>Information exchange</td>
<td>Lack of transparency and control of [conditions at] raw material supplier</td>
<td>50.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>66.7%</td>
<td>35.7%</td>
</tr>
<tr>
<td>15</td>
<td>Information exchange</td>
<td>Lack of transparency and control of supply and demand volumes due to parallel trade</td>
<td>50.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td>16</td>
<td>Information exchange</td>
<td>Lack of information transparency about orders between raw material supplier and manufacturer</td>
<td>25.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>21.4%</td>
</tr>
<tr>
<td>17</td>
<td>Information exchange</td>
<td>Lack of automated ordering processes between manufacturer and wholesaler</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>18</td>
<td>Information exchange</td>
<td>Lack of good systems to monitor drug availabilities</td>
<td>0.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>19</td>
<td>Information exchange</td>
<td>Lack of information transparency between pharmacy and manufacturer/wholesaler about prices, volumes, and source of raw materials</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>#</td>
<td>Operating environment</td>
<td>Vulnerability or risk</td>
<td>Manufactures</td>
<td>Wholesalers</td>
<td>Hospital pharmacies</td>
<td>Public pharmacies</td>
<td>Total</td>
</tr>
<tr>
<td>----</td>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>20</td>
<td>Legal environment</td>
<td>Frequent tendering processes</td>
<td>75.0%</td>
<td>100.0%</td>
<td>60.0%</td>
<td>0.0%</td>
<td>57.1%</td>
</tr>
<tr>
<td>21</td>
<td>Legal environment</td>
<td>Complex and expensive procedures regarding the use of 'shared pack' boxes and multilingual boxes/leaflets</td>
<td>75.0%</td>
<td>50.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>35.7%</td>
</tr>
<tr>
<td>22</td>
<td>Legal environment</td>
<td>Frequent WGP recalibrations</td>
<td>25.0%</td>
<td>100.0%</td>
<td>20.0%</td>
<td>33.3%</td>
<td>35.7%</td>
</tr>
<tr>
<td>23</td>
<td>Legal environment</td>
<td>Complex, unharmonised, and expensive registration processes among EU member states for new and existing drugs</td>
<td>25.0%</td>
<td>0.0%</td>
<td>40.0%</td>
<td>0.0%</td>
<td>21.4%</td>
</tr>
<tr>
<td>24</td>
<td>Legal environment</td>
<td>Legal restrictions prohibiting or complicating the import/export of drugs by unlicensed SC partners</td>
<td>25.0%</td>
<td>0.0%</td>
<td>40.0%</td>
<td>0.0%</td>
<td>21.4%</td>
</tr>
<tr>
<td>25</td>
<td>Legal environment</td>
<td>Differences in legal (quality) requirements for the same ingredients by the OTC board, EMA board, and food industry</td>
<td>25.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>26</td>
<td>Legal environment</td>
<td>High costs of (complying with) complex legal policies</td>
<td>25.0%</td>
<td>0.0%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>27</td>
<td>Legal environment</td>
<td>Long external quality and safety testing procedures</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>28</td>
<td>Legal environment</td>
<td>Changing government regulations on approved APIs</td>
<td>0.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>29</td>
<td>Legal environment</td>
<td>Counterfeit products</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>30</td>
<td>Legal environment</td>
<td>Lack of clear regulations for (safety) stockkeeping critical products at wholesaler and manufacturer level</td>
<td>0.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>31</td>
<td>Legal environment</td>
<td>Legal barriers prohibiting export in case of shortages</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>32</td>
<td>Legal environment</td>
<td>Legal barriers requiring multiple quality tests of the same batch for every shipment</td>
<td>0.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>33</td>
<td>Legal environment</td>
<td>Legal requirements requiring redundancy in pharmacy inventory</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>34</td>
<td>Legal environment</td>
<td>Long reimbursement procedures at the EMA following production in special circumstances</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>35</td>
<td>Legal environment</td>
<td>Penalty mechanisms regarding differences between tender prices and market prices</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>36</td>
<td>Legal environment</td>
<td>Tendering processes requiring pharmacies to hold a large variety of labels containing the same active ingredient</td>
<td>0.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>37</td>
<td>Product environment</td>
<td>Inflexibility in demand due to medical reasons and bureaucracy</td>
<td>25.0%</td>
<td>100.0%</td>
<td>40.0%</td>
<td>66.7%</td>
<td>50.0%</td>
</tr>
<tr>
<td>38</td>
<td>Product environment</td>
<td>Contamination and quality risks</td>
<td>50.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>100.0%</td>
<td>42.9%</td>
</tr>
<tr>
<td>39</td>
<td>Product environment</td>
<td>Operational complexity of the drug production process</td>
<td>25.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>21.4%</td>
</tr>
<tr>
<td>40</td>
<td>Product environment</td>
<td>Media exposure of (presumed) contaminations</td>
<td>0.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>33.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>41</td>
<td>Product environment</td>
<td>Increases in drug prescription period (by doctor)</td>
<td>25.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

Table 4. Reported vulnerabilities (in percentage of the stakeholder group that expressed concern).
In downstream order, interviewees indicate that price pressures stimulating an increasingly cost-efficient PSC induced a consolidation of API producers of generic drugs [1], along with low-cost country sourcing of APIs and excipients. Accordingly, the upstream tiers of the PSC are more prone to disturbances. Among the sources mentioned for such disturbances at raw material suppliers, interviewees identified turbulence factors (Pettit et al., 2013) such as natural disasters, pandemics (including COVID-19), (geo)political disturbances and interventions, and supplier/customer disruptions (Pettit et al., 2010) such as product recalls and rejected batches including contaminations [38], plant shutdowns and general seizure of production, and decreased production levels. One interviewee described how a supply disruption at one API supplier created ‘domino effects’ of stock outages at the few remaining suppliers. Interviewees also expressed concerns regarding the prolonged time needed to recuperate from disturbances occurring at consolidated suppliers of raw materials. The consolidation and low-cost country sourcing of raw materials are also presumed to be the reason for a geographic concentration of raw material suppliers [5], mainly in India and China, thereby complicating risk diversification. One interviewee recalled irregular shutdowns and decreased production by local authorities following smog pollution policies as an example of a disturbance exacerbated by the geographic concentration of raw material suppliers.

The geographic remoteness of raw material suppliers for most generics [5], combined with price pressures, has caused the PSC’s upstream tiers to rely almost exclusively on waterborne transportation modes. As a result, lead times tend to be long [6], making these tiers inflexible with respect to unexpected changes in demand or unforeseen setbacks in supply [3, 7, 39]. This corresponds to earlier findings regarding causes for drug shortages observed by Weda et al. [2019] and Inspectie Gezondheidszorg en Jeugd [2020]; see also section 3. Several interviewees also criticized the lack of information transparency and control of API operations [14] regarding local working conditions, means of sustainable production, and (potential sources of) contaminations, in line with similar findings by Fransen et al. [2019]. Similarly, interviewees also criticized the lack of information transparency regarding order cancellations (including order recalls), and order delays. Some interviewees raised the concern that such intransparencies make it more difficult to anticipate, alert, react, and prevent disturbances in the supply of raw materials.

Interviewees argue that price-pressures have not only encouraged consolidation of raw material suppliers but also of manufacturers [2]. Moreover, these price-pressures are also presumed to be the reason for high utilizations of manufacturers’ production capacity and lean inventory management strategies. As a consequence, the inability to scale-up production beyond the base level of capacity, and the high expenses of keeping additional volumes of (safety) stock, are named among the top reasons for making generic drug manufacturers prone to disturbances in either supply or demand. Because raw material suppliers in the prior PSC tier suffer from similar vulnerabilities, disruptions impacting either stage of production may intensify the negative consequences for supply.

For production facilities operating at tight production capacities, accurate production planning is essential (Chopra and Sodhi, 2004). Interviewed manufacturers indicate their dependence on a combination of internal demand forecasts and demand forecasts supplied by third parties. The majority of our interviewees characterize the demand for drugs at the molecule level, safe for exceptional demand disruptions such as panic buying [3] and unforeseen events (including COVID-19) as relatively stable and predictable. However, interviewees report a lack of information transparency [13] about intermediary (i.e., wholesale) supply and demand levels, as well as inventory levels at other manufacturers, thereby complicating production planning and stock management. Similarly, frequent tendering procedures [20] are named among the top sources of unwarranted disturbances in demand across the majority of the interviewed stakeholder groups. This observation reflects earlier findings of VIG (2020) regarding the Dutch preference policy (see section 3). More specifically, interviewees signal a deterioration of inventory levels prior to a tender date, instigated by ramped down production levels in anticipation of potential changes in preferential suppliers. Interviewees also indicate that low inventory levels often persevere for a prolonged period beyond the tender date since the new preferential supplier needs time to ramp up production. Interviewees assert that the inflexibility of lean manufacturing practices, spurred by price-
pressures, are not suitable for coping with frequent and abrupt changes in demand. The interviewees also observe that whenever a stockout occurs at a preferential supplier following a tendering process, stocks at the remaining suppliers – who typically keep low inventory levels as they were not designated as preferential suppliers – are drained relatively quickly.

In addition to frequent tendering processes, frequent WGP recalibrations (22) are also mentioned as a source of price (and therefore demand) disturbance, especially when recalibrations involve a change of countries on the reference list. National and international differences in price, supply, and demand are believed to trigger wholesalers to rebalance stocks through parallel import and export. Some interviewees criticize the lack of information transparency surrounding the imported and exported volumes (15), which are believed to exacerbate the existing intransparency (13), and further complicate stock and production planning. Interviewed manufacturers also express their concerns about complying with government policies regarding their obligation to duly report shortages. Some interviewees argue that the penalties associated with not keeping sufficient stock, regardless of preferential supplier status, as well as the penalties associated with not duly reporting shortages, which can be suddenly caused by reasons beyond their control, in a relatively small sales market may be a reason for manufacturers to withdraw from the Dutch market.

Initiatives by manufacturers and pharmacists to prevent stockouts, such as their own import/export (24), the use of multilingual packs (21), switching resale channels (25), or the switch to another API supplier (23), are often costly, long, and hindered by legal barriers, according to several interviewees. Interviewees also expressed the desire for harmonized legal frameworks concerning drug registration systems at the EU level.

Since lean manufacturing practices, a lack of information transparency, and legal regulations and policies arguably contribute to the PSC’s inflexibility in supply, the overall PSC’s inflexibility is further complicated by an inflexibility in demand. Several interviewees describe the inability or undesirability of patients to switch to different labels, both due to therapy compliance (“therapietrouw”) and a potential loss of placebo effects.

Note that the majority of the frequently mentioned vulnerabilities regarding the upstream part of the PSC concern lean manufacturing practices of chemically synthesized products (see also Table 1).

Biological products seem to observe fewer vulnerabilities in the upstream PSC; most vulnerabilities in the upstream part of the PSC for biologicals are linked to the complexity of their manufacturing process (39) – see also section 5.2. The vulnerabilities in the downstream part of the PSC, on the other hand, mostly concern EU and country-specific challenges. In contrast to the upstream part of the PSC, these vulnerabilities are shared among all types of pharmaceutical products, regardless of their type. The number of different products suggested by pharmacists (Table 2) seems to support the notion that shortages of chemically synthesized products are observed more often than shortages of biological products (not corrected for differences in demand).

5.5 RISK AND VULNERABILITY MAPPING

In an attempt to map the results of Table 4 to vulnerability factors in the literature, every unique vulnerability concern expressed by an interviewee was linked to one or more vulnerability factors and risk drivers identified in the vulnerability assessment frameworks of [a] Pettit et al. (2013), [b] Ho et al. (2015), [c] Hosseini et al. (2019), and [d] Moktadir et al. (2018). Because the vulnerabilities extracted in Table 4 specifically target the PSC’s structure, the resulting mapping encompasses a broad combination of relevant subsets of vulnerability factors from the literature. Table 5 shows the average number of uniquely articulated vulnerability concerns related to each vulnerability subfactor mentioned by an interviewee; this is expressed as the aggregate number of concerns by the stakeholders in a group divided by its corresponding number of interviewees. The last column in Table 5 shows the total percentage of interviewees that articulated one or more concern that could be linked to a particular vulnerability subfactor.

For example, if an interviewed manufacturer expressed a vulnerability concern (8), viz. the Inability of parallel traders to react quickly to shortages, it was mapped to the vulnerability subfactors Flexibility in supply, external and integration capabilities and Import/export channels (parallel trade). On average, an interviewee manufacturer expressed 2.0 unique concerns that were mapped this way.
to the latter vulnerability subfactor, *Import/export channels (parallel trade)*. In total, 64 percent of the interviewees expressed at least one concern that was mapped to the vulnerability factor *Import/export channels (parallel trade)*.

Table 5 ought to expose the top vulnerabilities in the PSC’s structure as perceived by the interviewed PSC partners. According to the results, the top five vulnerabilities of the PSC structure relate to (i) its inflexibility in supply, (ii) the impact of government policy and regulation, (iii) the lack of additional stock and redundancy in inventory, (iv) price pressures, and (v) challenges related to production-ordering policy. More than 75 percent of the interviewees expressed at least one concern that could be related to any one of the factors mentioned above. There also seems to be a consensus among the interviewed groups about most of the five vulnerability factors that pose the biggest potential threat to the robustness of the PSC.

Furthermore, hospital pharmacists emphasized the challenges associated with raw material replacements, raw material availability, and the lack of backup suppliers and single sourcing, while public pharmacists often named potential safety hazards, reputation damage and brand image (i.e., the symbolic profile of the brand), and geographic segregation as potential vulnerabilities.

A word of caution is in order here. First, observe that Table 5 does not account for the beliefs that PSC partners may hold about the relative importance or impact of particular vulnerabilities. Furthermore, Table 5 does not distinguish between causes and effects. Consequently, some subfactors might arguably overlap somewhat. For example, certain *Government policy and regulations* are also believed to enhance *Price pressures*. These *Price pressures* may, in turn, be a potential source of lean stock management practices that exacerbate the lack of *Additional stock and redundancy in inventory*. Coming full circle, the lack of *Additional stock and redundancy in inventory* may have inspired certain *Government policy and regulations*. Therefore, Table 5 should not, by any means, be used to pinpoint a root cause of PSC’s vulnerabilities.

Nonetheless, the overview in Table 5 provides a first impression of the primary focus points and priorities that may initiate a discussion on ways to improve the management of the Dutch PSC. It could also serve as an input for a future, more extensive vulnerability assessment: From descriptive research to prescriptive research.

<table>
<thead>
<tr>
<th>Vulnerability factor [b]</th>
<th>Risk driver</th>
<th>Vulnerability subfactor</th>
<th>Man.</th>
<th>Whol.</th>
<th>HPh.</th>
<th>PPh.</th>
<th>Total [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource Limits</td>
<td>Supply-related / manufacturing</td>
<td>Flexibility in supply, external and integration capabilities [c]</td>
<td>7.0</td>
<td>6.5</td>
<td>4.0</td>
<td>2.7</td>
<td>20.2</td>
</tr>
<tr>
<td>External Pressures</td>
<td>Policy/regulatory, legal, and bureaucratic</td>
<td>Government policy and regulations [a]</td>
<td>4.5</td>
<td>6.0</td>
<td>2.4</td>
<td>1.3</td>
<td>14.2</td>
</tr>
<tr>
<td>Resource Limits</td>
<td>Supply-related / manufacturing</td>
<td>Additional stock and redundancy in inventory [c]</td>
<td>4.5</td>
<td>4.5</td>
<td>1.0</td>
<td>1.3</td>
<td>11.3</td>
</tr>
<tr>
<td>External Pressures</td>
<td>Financial</td>
<td>Price pressures [a]</td>
<td>2.8</td>
<td>3.5</td>
<td>1.6</td>
<td>1.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Resource Limits</td>
<td>Supply-related</td>
<td>Production-ordering policy [c]</td>
<td>2.8</td>
<td>3.5</td>
<td>1.2</td>
<td>1.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Manufacturing / operational</td>
<td>Potential safety hazards [a, b]</td>
<td>1.3</td>
<td>2.5</td>
<td>0.4</td>
<td>2.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Resource Limits</td>
<td>Supply-related</td>
<td>Raw material replacement [c]</td>
<td>2.0</td>
<td>1.5</td>
<td>1.6</td>
<td>1.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Supplier/Customer Disruptions</td>
<td>Manufacturing / operational</td>
<td>Plant shutdown [c]</td>
<td>1.8</td>
<td>1.5</td>
<td>1.0</td>
<td>1.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Supplier/Customer Disruptions</td>
<td>Supply-related</td>
<td>Backup supplier and single sourcing [b]</td>
<td>1.5</td>
<td>1.5</td>
<td>1.4</td>
<td>1.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Resource Limits</td>
<td>Supply-related</td>
<td>Raw material availability [a]</td>
<td>1.8</td>
<td>1.0</td>
<td>1.4</td>
<td>1.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>
### Table 5: Number of (uniquely) articulated concerns related to risk driver categories, adjusted for number of interviewees.

<table>
<thead>
<tr>
<th>Vulnerability factor</th>
<th>Risk driver</th>
<th>Vulnerability subfactor</th>
<th>Man.</th>
<th>Whol.</th>
<th>HPh.</th>
<th>PPh.</th>
<th>Total [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turbulence</td>
<td>Demand-related</td>
<td>Unexpected or drastic changes in client demands [a]</td>
<td>1.5</td>
<td>2.0</td>
<td>0.6</td>
<td>0.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Demand-related</td>
<td>Symbolic profile of brand [a]</td>
<td>1.3</td>
<td>1.5</td>
<td>0.0</td>
<td>2.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Connectivity</td>
<td>Supply-related</td>
<td>Import/export channels (parallel trade) [a]</td>
<td>2.0</td>
<td>1.5</td>
<td>0.6</td>
<td>0.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Connectivity</td>
<td>Infrastructure</td>
<td>Geographic segregation / supplier separation / facility dispersion [c]</td>
<td>1.3</td>
<td>1.0</td>
<td>0.4</td>
<td>1.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Turbulence</td>
<td>Demand-related</td>
<td>Unpredictability in customer demand [a]</td>
<td>1.0</td>
<td>2.0</td>
<td>0.6</td>
<td>0.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Supplier/Customer Disruptions</td>
<td>Manufacturing / operational</td>
<td>Production restoration [c]</td>
<td>1.5</td>
<td>1.0</td>
<td>1.0</td>
<td>0.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Connectivity</td>
<td>Infrastructure</td>
<td>Lack of information transparency [b, d]</td>
<td>1.0</td>
<td>1.5</td>
<td>0.4</td>
<td>1.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Manufacturing / operational</td>
<td>Importance of product purity / contamination risk / quality risk [a, b, d]</td>
<td>1.0</td>
<td>1.5</td>
<td>0.0</td>
<td>1.3</td>
<td>3.8</td>
</tr>
<tr>
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<td>Demand-related</td>
<td>Flexibility in demand [c]</td>
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<td>0.4</td>
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<td>Infrastructure</td>
<td>Reshoring production facilities [b]</td>
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<td>0.5</td>
<td>0.2</td>
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<td>Complexity of process operations [a]</td>
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<td>Restructuring existing transport / flexibility in transportation [c]</td>
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<tr>
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Table 5. Number of (uniquely) articulated concerns related to risk driver categories, adjusted for number of interviewees. Last column: percentage of interviewees expressing concerns related to risk category. Man.: Manufacturers; Whol.: Wholesalers; HPh.: Hospital pharmacies; PPh.: Public pharmacies. [a] Petit et al. (2013); [b] Ho et al. (2015); [c] Hosseini et al. (2019); [d] Moktadir et al. (2018).
CONCLUDING REMARKS

Triggered by the initial logistics impact of the COVID-19 pandemic on a variety of industries, TKI Dinalog called for exploratory studies on the supply chain structure, supply chain dependencies, and supply chain vulnerabilities of the Dutch food, pharmaceutical and manufacturing industries. This report attempts to answer this call for the Dutch pharmaceutical supply chain (PSC).

The COVID19 pandemic challenged the Dutch healthcare system to offer dedicated care for large numbers of patients. Thanks to the creativity and efforts of Dutch PSC actors, the availability of key drugs (e.g. propofol and midazolam) and, therefore, the well-being of patients could be ensured. At the same time, the COVID19 pandemic and associated product shortages brought new attention to the importance of drug availability. As the Netherlands has faced growing drug shortages in the past (for 750 different drugs in 2018 and almost 1500 in 2019, KNMP (2019b)), this report aims to understand the more structural supply and demand dynamics, dependencies and vulnerabilities in the Dutch PSC to contribute to improved reliability and resilience during regular and crisis situations.

Although the dedicated academic literature on pharmaceutical supply chains does not pay much attention to the fact that there is no single pharmaceutical supply chain as such, interviews with pharmacists, wholesalers and manufacturers indicated that the supply and demand dynamics differ structurally for off-patent and patent-protected drugs and that important differences exist at the level of an individual drug. Moreover, interviewees referred to differences in manufacturing and distribution processes for chemically synthesized and biological drugs. It is therefore difficult to draw conclusions about the PSC in general.

Similar to the finding that there is not a single PSC, an exclusively Dutch PSC likewise does not exist. In other words, the Dutch PSC is, to a large extent, part of a more extensive, international PSC. As such, its vulnerabilities often stretch beyond our country’s borders, and the Dutch PSC competes for available products and production capacity. Consequently, interviewees expressed vulnerability concerns that relate both to international challenges as well as challenges closer to home. While most upstream PSC challenges concern practices that occur both inside and outside the EU, most downstream PSC challenges relate to phenomena that occur in the EU and mainly in the Netherlands.

Vulnerability concerns in the upstream PSC are primarily related to off-patent, chemically synthesized (generic) drug supply chains that often involve production steps outside the EU. Here, interviewees most frequently referred to the limited number of API suppliers and a decline in the number of manufacturers for some drugs (see also Table 4). Lower prices have contributed to these developments. For the remaining supply chain actors, lower prices have further increased the focus on cost efficiency, resulting, for example, in larger production batches and difficulties in maintaining additional inventory (see Table 5) or spare production capacity (Table 4). This limits the potential to recover quickly in the event of supply chain disruption.

Many EU countries experience the above-mentioned supply chain vulnerabilities in the international upstream PSC, yet both interviewees and industry reports, such as NOS (2021); KNMP (2021), suggest that the Netherlands suffers more from drug shortages than many other countries. This entails both the number of products facing shortages and the time it takes for shortages to be resolved.

Interviewees at different stages of the Dutch PSC indicated that Dutch regulations and organization of the Dutch pharmaceutical sector influence the supply and demand dynamics in the downstream PSC. A variety of strategies succeeded in lowering prices (e.g. preference policy, package price model, etc.), but interviewees indicated that they also impacted demand variability and product shortages.

The six-monthly WGP price adjustments and frequent drug tenders by different actors (health insurance companies, hospital purchasing groups, wholesalers) create many moments for major SC decisions. This complicates demand forecasting,
stock management and influences import and export flows. The subsequent required changes in the product assortment may lead to temporary overstocking and understocking of the affected products in the period surrounding WGP and tender changes. Interviewees indicated that they can result in domino effects where shortages of one product can induce shortages in several other related drugs. Interviewed pharmacists and manufacturers indicated that, although the demand for a given drug (at molecule level) can be quite stable in the Netherlands, demand variability is created in the downstream PSC at the level of an individual product (e.g. due to changing preferences and changes in import/export flows).

Although inventory targets and fines could force PSC actors to maintain more inventory in the supply chain (see section 3.2), they do not solve the root causes. Moreover, maintaining additional inventory is only one approach to lowering the risk of supply chain breakdowns. For example, Chopra and Sodhi (2004) indicate that having redundant suppliers is known to have a larger impact on mitigating supply risk.

Interviewees indicated that higher product margins enable manufacturers of innovative (patent-protected) drugs to maintain more inventory and redundant production capacity, which allows them to better respond to changes in demand. Although the interviewed pharmacists had difficulty identifying innovative drugs with shortages, this does not imply that no shortages can occur in a more responsive, flexible PSC. If shortages for one particular product occur, significant efforts are often needed to identify medical alternatives since they may not be suitable or accessible for all patients (for medical reasons including therapy compliance and policy reasons including health insurance contracts). However, it is well known that a cost-efficient supply chain operating at full production capacity with low margins is unable to take sufficient mitigating actions to handle supply and demand variability and the disruptions they can cause.
Interviews with pharmacists, wholesalers, and manufacturers resulted in a variety of observations on the current PSC network structure, practices, and perceived dependencies and vulnerabilities. As the scope of the project did not allow for an in-depth analysis of these findings, the authors think it is worthwhile examining the issues raised and suggestions made to improve the performance of the Dutch PSC.

Industry and government efforts could be directed at improving the upstream, international part of the PSC by e.g. increasing the availability of API manufacturers, increasing (flexible) production capacity in the EU, etc. However, the findings from this report indicate that the supply and demand dynamics of drugs can also be improved by taking measures closer to home.

Since regulation has a strong impact on how a supply chain can be organized, the authors want to emphasize that cost-efficient supply chains can work well if both supply and demand are relatively stable. From a logistics point of view, it makes sense to reduce variability in demand for the Dutch PSC as much as possible. Reconsidering the frequency, timing, and number of tenders and improving demand transparency in the supply chain could be two ways of achieving this goal. The COVID-19 pandemic illustrated that supply chain disruptions and steep increases in demand cannot be entirely avoided. Sufficient margins and financial incentives are needed to implement a variety of mitigation strategies. Such strategies should not be limited to maintaining more inventory in the PSC; they could also include efforts to encourage raw material and API suppliers to be added to drug dossiers, and making it more attractive for manufacturers to remain active on the Dutch market.

We hope that the concise conclusions and recommendations in this report will encourage readers to examine the issues and suggestions raised by the interviewed pharmacists, wholesalers, and manufacturers [see Sections 5.1.4, 5.2.3 and 5.3.3]. In our view, the contributions from the Dutch PSC actors are worth examining in more detail as they seem to hold promising potential for further improving the performance of the Dutch PSC.
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Kanavos, P., S. Vandoros, R. Irwin, E. Nicod, M. Casson. 2011. Differences in costs of and access to pharmaceutical products in the EU.


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