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Not a box of nuts and bolts: Distribution channels for specialty drugs?

Liang XU
Singapore Management University, leonxu@smu.edu.sg

Vidya MANI
University of Virginia

Hui ZHAO
The Pennsylvania State University

"Not a Box of Nuts and Bolts": Distribution Channels for Specialty Drugs

Liang Xu
University of Nebraska-Lincoln
Vidya Mani
University of Virginia
Hui Zhao
Penn State University, Smeal College of Business, University Park

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Abstract

One of the most important trends in the pharmaceutical industry is the rapid growth of specialty drugs. Specialty drugs, mostly bio-based, tend to be high-risk, high-priced, and more regulated than traditional drugs, resulting in unprecedented challenges in distribution. Such challenges lead to the emergence of specialty distributors (SDs), which, compared with traditional wholesalers (WSs), manage more controlled networks and carry a smaller variety of drugs. Using a unique dataset assembled from multiple proprietary and public data sources on transactions, inventory, and chargebacks for 419 specialty drugs across 11 manufacturers (including 8 of the top 15 pharmaceutical manufacturers),161 distributors, and129,911 POCs (point-of-care) in 2012-2015, we investigate unique factors associated with manufacturers' SD usage (vs. WSs). We also develop a nested logit model to examine factors that drive manufacturers' choice of specific SDs if they were to use an SD channel. We find that the restrictive access element of regulations (instead of regulations in general), downstream POC's required drug variety, and distributors' experience in providing critical value-added services for manufacturers (i.e., managing chargebacks) are associated with higher SD usage. Moreover, if a manufacturer were to use an SD channel, it is more likely to choose one if it has used this SD or the SD-affiliated WS before, or if this SD has better performance. WSs and SDs represent distinct approaches to balance channel accessibility and channel control. Our results provide important insights and guidance to manufacturers, regulators, and downstream POCs, while contributing to the limited empirical research on B2B distribution decisions.

Keywords: Distribution channel decision, pharmaceutical industry, specialty drugs, regulations

1. Introduction

One of the most important trends in the pharmaceutical (pharma) industry is the rapid growth of specialty drugs (Conti and Berndt 2016, GAO 2013). Although there is no universally accepted definition of specialty drugs provided by either the Food and Drug Administration (FDA) or the pharma industry, specialty drugs, in general, possess the following common characteristics: (1) They are usually biologic-based and require special handling due to sensitivity to light and/or temperature; (2) They target complex and typically chronic diseases; and (3) They tend to be higher-priced, riskier, more complex to distribute and administer, hence more regulated than traditional drugs. For example, *Humira*, a specialty drug listed by CVS Caremark (a top Pharmacy Benefit Manager) as a treatment for rheumatoid arthritis, must be refrigerated at 2-8°C (36-46°F) and cannot be frozen; it also costs over $1,900 per syringe. In contrast, *Motrin*, a traditional nonsteroidal anti-inflammatory drug (NSAID) for rheumatoid arthritis, can be stored at room temperature and costs only about $10 for 90 tablets.

In 2012, for the first time, the number of specialty drugs approved by FDA exceeded the number of traditional drugs (AHIP 2015) and the robust R&D pipelines for specialty drugs are fueling their continuous growth. As of December 2011, about 5,408 bio-medicines were in various stages of R&D, with 833 in Phase III, the last stage of clinic trials (PhRMA 2013). Although accounting for only about 1% of total prescriptions (IMS Health 2012), specialty drugs accounted for 45% of all pharmacy spending in 2018 and the total spending on specialty drugs reached $218 billion in 2018 (CVS 2018). Many believe that specialty drugs may save the "empty pipeline" issue faced by the pharma industry (Moeller 2013).

While pharma manufacturers continue to make strides in developing and producing specialty drugs, they must contend with the complexity in distributing these drugs. This complexity is primarily due to the need to protect drug integrity and security during transit (e.g., keeping drugs under required conditions all the time) and assure safe use in different provider settings (e.g., clinics, hospitals, and pharmacies). The growing regulatory scrutiny of the pharma supply chain has further raised the stakes. The serious risk associated with specialty drugs is closely monitored in accordance with the Risk Evaluation and Mitigation Strategy (REMS), a regulation enforced by FDA to hold manufacturers accountable for the integrity and safe use of drugs during the distribution, prescription, and dispensing process (FDA 2007). At the same time, under the growing practice of purchasing and reimbursing based on drugs' therapeutic effectiveness (Xu, et al. 2019), patients, as well as payers, urge manufacturers to improve the supply chain for specialty drugs because research has shown that the safety and efficacy of specialty drugs are highly dependent on how the drugs are handled (Frokjaer and Otzen 2005). Patients typically hold manufacturers accountable for any issues surrounding the efficacy or safety of drugs, even if these issues occur due to improper handling by their distributors. As a pharma manufacturer cold-chain director said, "…what they [the

distributors] are handling is not just a carton of nuts and bolts" (Harrington 2016). Evidently, distribution channel control for safety and traceability is critical.

The above challenges in distributing specialty drugs have compelled pharma manufacturers to rethink their conventional distribution strategy with traditional wholesalers (WSs) and to look into whether they should adopt "specialty distributors" (SDs), which have emerged as a specialized channel focused on distributing specialty drugs. In addition to being better equipped for special handling, SDs carry a more focused assortment of specialty drugs and are marketed as being able to provide expertise in the distribution of specialty drugs, such as regulatory compliance, extended tracking and data services, as well as potential provider/patient support (HDMA 2015). Further, most SDs provide a controlled distribution network, which restrict resales of manufacturers' products to secondary distributors, hence potentially reducing the risk of diversion and counterfeit, to which high-priced specialty drugs are particularly vulnerable (Fein 2011).

Despite the potential advantages of SDs, many manufacturers continue to choose WSs for distributing their specialty drugs (Fein 2011). Investigation into and interactions with the industry indicate that manufacturers might consider many unique factors/features in pharma before making their decisions to use SDs, whether exclusively or partially. For example, manufacturers depend on their distributors for REMS regulation compliance, which is very important. It remains unclear how such regulations affect manufacturers' distribution decisions. Further, manufacturers choose their distribution channels to reach their downstream POCs (point-of-care), e.g., hospitals, clinics and pharmacies, to provide access to their drugs. While SDs typically carry a focused variety of specialty drugs, some POCs (e.g., general hospitals) need a large variety of pharmaceuticals. Would they prefer WSs which usually carry larger assortment of drugs? In addition, manufacturers rely on distributors to provide critical value-added services, such as managing chargebacks, in the pharma industry. Managing chargebacks is a complex process and subject to error, which may lead to massive revenue losses for manufacturers if not managed well. The experiences of emerging SDs in providing such critical services which WSs have provided them for decades in the pharma industry could be an important factor.

Our study seeks to understand the above factors that influence the manufacturer's use of SD. This can help SDs and WSs better serve the manufacturers in their distribution of specialty drugs and inform the policy makers in regulating the distribution of specialty drugs. Specifically, considering the above unique features of the pharma industry and building on previous literature, we hypothesize the impact of three factors, namely, regulations, downstream's required product variety, and distributor's experience in providing critical value-added services, on the manufacturer's use of SDs (i.e., the proportion of the drug distributed through SDs). This is Study I. We then look at if a manufacturer were to use an SD channel, what are the additional factors that would determine a particular SD to be chosen. We do so by developing

a nested logit model which captures a manufacturer's two-stage decision-making process, where it first decides whether a manufacturer uses an SD channel and if yes, which specific SD to use. This is Study II. In addition to the factors considered in our hypotheses in Study I, Study II also considers the impact of prior relationships and distributors' performance on a manufacturer's choice of specific SDs.

We conduct our study using a novel and large dataset we assembled from multiple proprietary and public data sources for the period of 2012 through 2015, including data from 11 manufacturers (8 of which are among the top 15 pharma manufacturers ranked by global revenue, Pharma Executive (2013)), 419 unique specialty drug NDCs (National Drug Codes, a unique identifier at which level a drug is priced, ordered and distributed), 119 WSs, and 42 SDs (including the top 3 industry players—AmerisourceBergen (ABC), Cardinal, and McKesson). A brand drug may correspond to multiple NDCs, depending on, e.g., dosage, form (tablet vs. gel), etc.

Our results show that: (1) It is not the distribution regulation (REMS) in general but one specific element (i.e., the restrictive access element) that drives usage of the SDs. (2) The manufacturers rely on their downstream POCs to reach patients and hence choose the distribution channel that is able to meet their downstream POCs' product variety requirement. Specifically, for downstream POCs that require high variety of drugs (e.g., general hospitals), manufacturers tend to continue to use WSs that carry a large assortment of drugs. On the other hand, for POCs that require a focused assortment of drugs (e.g., clinics), manufacturers are more likely to use SDs, which are characterized by narrow and focused assortment, to reach them. (3) The SDs' experiences to provide critical value-added services (i.e., managing chargebacks in the pharma setting) that have been long provided by WSs for the manufacturers, is positively associated with manufacturer's usage of the SDs. (4) When it comes to the decision of which specific SD to choose if the manufacturer were to choose an SD channel, a manufacturer's prior relationship with the SD or the SD-affiliated WS and the SD's prior performance play important roles in the manufacturer's choice.

Our research makes a few important contributions. First, our study adds to the literature on supply chain safety and security for risky products by examining the manufacturers' distribution channel decisions for such products. Second, with the unique dataset, we are able to contribute to the very limited empirical research on distribution channel decisions in B2B setting (Mithas and Jones 2007, Langer et al. 2012). We do so by drawing from literature on channel decisions in B2C setting and supplier selection in B2B setting. Third, our study enriches and extends the literature on the impact of regulations on firms' supply chain decisions by going one layer deeper and considering different elements of the regulation introduced by specialty drugs in the pharma industry. We find that it is a specific element (i.e., the restrictive access element) of the regulatory requirement that would lead to higher usage of a specialized channel (i.e., SDs). Finally, in a practical sense, our study presents a deeper understanding of the important factors associated with pharma manufacturers' SD usage. It provides insights to the manufacturers, downstream POCs,

distributors, as well as regulators on both traditional WSs and emerging SDs as they compete in this ever-growing market of specialty drugs (see conclusions for a summary of these). While the pharmaceutical supply chain is less transparent than other industries, our study provides a look into many unique aspects in pharmaceutical distribution.

The rest of the paper is organized as follows. After reviewing related literature in Section 2, we conduct study I by developing and testing three hypotheses regarding the important factors associated with manufacturers' SD usage in Section 3. In Section 4, we conduct study II by presenting our nested logit model with results about manufacturers' choices of specific SD. We present robustness tests in Section 5 and conclude with discussion of the managerial insights and future research in Section 6. All tables and figures can be found at the end of the paper.

2. Literature Review

Certain types of products, such as agriculture products, foods, and pharmaceuticals are perceived as risky products as they relate to human health and have a high risk for spoilage in distribution. In pharmaceuticals, specialty drugs are particularly risky due to their biologic nature. Distribution of these drugs has a huge impact on their efficacy (Frokjaer and Otzen 2005). Prior literature has looked at the design of supply chain for risky products with a focus on supply chain safety and security (Speier et al. 2011, Ho et al. 2015). Different strategies have been proposed to improve the supply chain safety and security for risky products, such as total quality management (Lee and Whang 2005), improving security practice at supply chain partners and service providers (Sarathy 2006), and reducing supply chain complexity (Speier et al. 2011). Our study adds to this literature by examining the manufacturers' distribution channel decision for risky products, in particular, specialty drugs.

The vulnerability of the supply chain for risky products typically results in government regulations. In our context, the distribution of pharmaceuticals is regulated through REMS imposed by FDA. Most regulations in other industries have similar requirements across different firms, e.g., air pollution prevention (Gray and Deily 1996), oil spill prevention (Gawande and Bohara 2005), restriction of hazardous substances (Kraft et al. 2013) and the Sarbanes–Oxley Act on the disclosure of conflict minerals (Swift et al. 2019). However, REMS are not imposed on all drugs and for drugs that are imposed with REMS, different elements (action requirements) can be mandated for different drugs, depending on each drug's specific risk profile. Hence, we must look beyond the impact of whether REMS is imposed on a drug and investigate one layer deeper to see which element(s) of REMS imposed on the drug impacts the manufacturers' distribution channel decision on these drugs. This enriches and extends the literature on the impact of regulations on firms' supply chain decisions.

One element of REMS for some specialty drugs is the restrictive access, which requires that only POCs with specific training and certifications can sell the drugs. Similar restrictive access requirement is observed

in the distribution of wine and medical devices as well. For example, almost all states in US require wineries to sell their products to state-licensed wholesalers who then are required to distribute the products to licensed retailers for resale to end consumers. Santiago and Sykuta (2016) suggest that such a requirement compels wineries to leverage more formal contracts to govern their distributors to enhance compliance. In the pharma industry, the restrictive access element of the regulation does not specifically restrict the type of channel used to reach the POCs. Hence, we add to the above literature by exploring whether the manufactures choose to use a specialized channel to assure a controlled distribution network even when it is not directly mandated in the regulation.

Our paper touches the channel access vs. channel control issue, on which there has been very limited literature. Frazier and Lassar (1996) focuses on access and control of the channel for consumer products: either to use every available retailer or to have exclusivity of distribution through only a small number of retailers. These considerations are mostly based on brand strategy and brand image. We add to this limited literature by studying risky products (drugs) for which the considerations of access and control are from very different perspectives, i.e., the accessibility to patients and product safety.

Although prior research has emphasized the importance of distribution channels (Bowersox 1969), there has been very limited empirical research on distribution channel decisions in the B2B setting, possibly due to a lack of data (Mithas and Jones 2007, Langer et al. 2012). Thus, we draw some of our factors from the literature on channel decisions in B2C setting and literature on supplier selection in B2B setting.

In the B2C setting, sellers choose their channels to best reach their customers based on the customers' preferences (Lee et al. 2013). With the growing popularity of e-commerce, most of these studies investigate factors that influence customers' preference between purchasing from online vs. offline channels. Such factors may include price (Brynjolfsson and Smith 2000), convenience (Forman et al. 2009), assortment breadth offered (Brynjolfsson et al. 2009), as well as consumer characteristics such as age, income, and education level (Xue et al. 2007). Similar to this line of inquiry, we study the emergence of a specialized distribution channel (the SD channel) in pharma industry and the factors that would influence the manufacturers' decisions to use this channel. In our setting, different from the B2C setting, downstream POCs decide what products (drugs) to purchase based on their needs rather than their preferences for the channel, and the manufacturers must choose the right channel to reach these POCs for the highest accessibility of their drugs. Since POCs differ in their required product variety (the number of different drugs they need to buy), manufacturers may choose the distribution channel accordingly, i.e., they may choose WSs (which carry large number of drugs) for hospitals (that typically require large variety of drugs) and choose SDs (which typically carry more focused assortments) when reaching downstream clinics (which typically require a small variety of drugs).

While there is limited empirical research on distribution channel decisions in the B2B setting, one related stream in the B2B literature focuses on how buyers select suppliers or service providers. Dickson (1966) suggested factors buyers generally consider when choosing a supplier and indicated that they should depend on the context and products/services involved. Many studies used survey data to assess the relative importance among these factors. Aside from cost, quality, delivery, relationship, and flexibility, many of these studies have highlighted the value-added services provided by the supplier as one important consideration (Choi and Hartley 1996, Brewer et al., 2001, Van der Rhee et. al 2009). To some extent, one could view the drug manufacturers in our context as the buyers of the services provided by the distributors. Our study empirically investigates the impact of the distributors' experiences in providing critical value-added services (i.e., managing chargeback in our context) on the manufacturers' distribution channel decision.

Our study is also related to literature in the supply chain and operations field that has mainly focused on distribution channel management. This includes literature from the perspective of network design (Rangan et al. 1986), contracts and information sharing (Schwarz and Zhao 2011, Zhao et al. 2012), and pricing and channel coordination (Tsay and Agrawal 2004, Hu and Schwarz 2011). Some of these studies are specific to the pharma industry. For example, Zhao et al. (2012) model how fee-for-service contracts between pharma manufacturers and distributors change supply chain players' decisions and the impact of information sharing on supply chain performance. Hu and Schwarz (2011) examine the controversies surrounding group purchasing organizations' (GPOs') role in the distribution channels. However, the function of distribution channel in linking pharma manufacturers and downstream POCs remains mostly underexplored. Our study contributes to the literature by exploring the distribution channel choice to ensure the product integrity in distribution supply chain.

3. Study I: Manufacturers' Distribution Channel Decisions

In this section, we propose to study three factors that influence manufacturers' distribution channel decisions (i.e. their usage of the emerging SD channel) in distributing specialty drugs. These three factors are explored in three hypotheses, respectively. In the following, we build our hypotheses based on previous literature and the unique features of the pharma industry.

3.1. Hypotheses

Given that the pharma industry is subject to extensive regulation and the fact that we are dealing with risky products, our first hypothesis focuses on the impact of regulations on the manufacturer's distribution channel decision for a specialty drug. We then examine the impact of two firm-level factors: In Hypothesis 2, we explore the impact of the downstream POCs' requirement of drug variety on a manufacturer's channel decision and in Hypothesis 3, we explore the impact of distributors' experiences in providing critical value-added services (i.e., managing chargeback) on the manufacturer's channel decision.

3.1.1. Regulations

The pharma industry has regulations covering almost every part of the industry, starting from drug discovery and clinical trials, to manufacturing, distribution, and reimbursement. Based on the complexity and risk of each drug, FDA may impose Risk Evaluation and Mitigation Strategy (REMS) on some drugs to hold manufacturers accountable for the integrity and safe use of these drugs during the distribution, prescription, and dispensing process (FDA 2007). REMS is typically required for a drug shown to be effective but also found to be associated with serious adverse effects. In this case, the drug cannot be approved or will be withdrawn from the market if it lacks REMS to mitigate the risk.

In general, regulations have significant influence on firms' corresponding behavior in various contexts such as air pollution prevention (Gray and Deily 1996), oil spill prevention (Gawande and Bohara 2005), restriction of hazardous substances (Kraft et al. 2013), and the Sarbanes–Oxley Act on the disclosure of conflict minerals (Swift et al. 2019). In the distribution area, in particular, Santiago and Sykuta (2016) suggest that regulation restricting alcohol sale within licensed distributors and retailers compels wineries to adopt more formal contracts to govern their distributors to enhance compliance. Similarly, Mercier et al. (2017) suggest that the FDA-issued requirement in 2016 regarding the sanitary transportation practices in food industry compels the industry to adopt more consistent record-keeping techniques to satisfy the temperature requirements for perishable products. In general, the introduction of regulations on supply chain security fosters mindfulness for potential problems, improves security practices at supply chain partners and service providers (Sarathy 2006), and reduces supply chain complexity (Speier et. al 2011). Thus, we expect that the REMS regulation on managing the integrity and safe use of drugs in distribution, prescription, and dispensing process would also shape manufacturers' distribution channel decisions.

However, a deeper look into REMS reveals that, unlike most of the regulations in other industries, not only is REMS not imposed on all drugs, REMS consists of several different elements and not all elements are required for those drugs monitored under REMS. Hence, different drugs monitored under REMS may contain different REMS elements and each element requires different actions in distributing the drugs. Indeed, no two REMS are alike (Morel and Murphy 2009). In this situation we must look beyond just the impact of whether REMS is imposed on a drug but also need to investigate the impact of the detailed elements of REMS on manufacturers' distribution channel decisions.

We find that the most common REMS elements are the requirements of a medication guide, a communication plan, and an implementation plan. The medication guide and communication plan provide patients and POCs educational materials to help them understand the safe use of the drugs and the risks involved if the drugs are not handled appropriately. The implementation plan requires manufacturers to propose detailed plans to ensure compliance; it also mandates manufacturers provide FDA regular assessments of a plan's implementation. As can be seen, these most common elements of REMS are not

restrictive in terms of distribution channels because these materials and plans usually come from the manufacturers. Hence, they do not typically impose special requirements on the distributors that help implement them, indicating that most distributors, whether WSs or SDs, are likely able to accomplish them.

On the other hand, for drugs that pose serious risks, in addition to the above elements, REMS usually contains an element of restrictive access that imposes more restrictions on the way these drugs reach POCs and patients (Morel and Murphy 2009). Such an element of restrictive access typically requires that only POCs with specific training and certifications can sell the drug. Additionally, patients who are prescribed these drugs and parties prescribing and handling these drugs may need to enroll in a program so that their information can be collected and monitored regularly. For example, REMS for Rosiglitazone (a treatment for type 2 diabetes) was enforced by FDA in December 2008, and specified that prescribers and dispensers of Rosiglitazone need to be specifically trained and certificated to assure the safe use of the drug due to the potentially increased risk of heart attacks among patients. In response, GlaxoSmithKline (GSK), the manufacturer of Rosiglitazone, stated that:

> *GSK will monitor distribution data and prescription data to ensure that only enrolled distributors are distributing, enrolled pharmacies are dispensing, and enrolled physicians are prescribing Rosiglitazone…*

Obviously, REMS with the restrictive access element has much stricter requirements for the distributors involved. Prior literature has found that regulation restricting sale within licensed distributors and retailers has compels manufacturers to adopt more formal contracts to govern their distributors to enhance compliance (Santiago and Sykuta. 2016). Hence, we expect that manufacturers will likely choose distributors that are specifically equipped for designing and implementing such REMS element. Indeed, as suggested by Sharma and Mehrotra (2007), manufacturers must make a tradeoff between access and control when deciding upon a distribution channel. While WSs typically have widely-accessible networks to a large number of partners along the supply chain, it may be more challenging to oversee and maintain restrictive access, which is required by REMS with the element of restrictive access.

Compared with WSs, SDs are generally marketed and perceived as a more dedicated and secure channel that could provide manufacturers more control over their distribution channels. First, SDs provide controlled distribution arrangements that limit resales to secondary distributors, thus reducing the number of intermediaries and alleviating the risk of diversion to unintended agents (Fein 2011). As a result, manufacturers can track and trace distribution of their products more easily and have better control over who has access to their drugs. Second, SDs are generally better equipped for ongoing patient data collection; they also provide services for patient, physician, pharmacy and hospital enrollments, which are essential for the implementation and assessment of the REMS restrictive access element. For example, by maintaining a registry with POCs, patient enrollment, a patient call center, compliance monitoring, and

auditing, the McKesson SD can provide a drug-specific solution to designing, implementing, and managing all the requirements of REMS.

In summary, while the common elements of REMS (e.g., the requirements of a medication guide, a communication plan, and an implementation plan) may not pose special requirements to the distributors, the restrictive access element of REMS does, and hence likely affects a manufacturer's distribution channel decision. Therefore, we expect to see a higher proportion of a drug monitored by REMS with the restrictive access element to be distributed through the SDs. We thus postulate:

HYPOTHESIS 1: *The presence of REMS with the restrictive access element on a specialty drug is positively associated with the SD usage for this drug (i.e., the proportion of this drug distributed through SDs).*

3.1.2. Downstream POCs' Requirement of Drug Variety

The B2C literature suggests that customers seek specific channels that best fulfill their needs, such as price, convenience, and assortment breadth (or product variety). In particular, Brynjolfsson et al. (2009) shows that basket shoppers prefer to purchase from channels with wide assortment breadth. In our B2B context, the customers are not patients but POCs. Manufacturers rely on the downstream POCs to reach patients. One important difference among POCs is the variety of drugs they carry and purchase. For instance, a general hospital typically provides medical services in multiple disease categories such as oncology, urinary health, and cardiovascular diseases, hence would purchase a large variety of drugs. In contrast, a clinic may be more focused on a particular disease category (e.g., cardiovascular disease), and hence may only need to carry and purchase a much smaller variety of drugs. In our setting, downstream POCs decide what products to purchase based on their needs rather than channels and the manufacturers decide the distribution channels to reach the POCs. Therefore, manufacturers may tailor their distribution channel in accordance with the required assortment breadth of their targeted customers (i.e., POCs) to better serve their customers (Wallace et al. 2004, Sharma and Mehrotra 2007).

Specifically, WSs and SDs have distinct strategies for managing assortment breadth. As indicated in Fein (2011), WSs strive to distribute a full spectrum of different drugs. By maintaining presence in all drug categories, especially carrying complementary product categories, WSs stay competitive in providing POCs with a large variety of drugs and the convenience of a one-stop shopping experience (Thilmany and Grannis 1998, Cachon and Kök 2007). On the other hand, SDs offer a narrow assortment of drugs focused mainly on specialty drugs and thus may obtain an expertise and efficiency advantage over WSs in managing these products (Dukes et al. 2009). Therefore, manufacturers may be more inclined to leverage the benefits of WSs' wide spectrum of drugs to reach POCs that require a large variety of drugs, while reaching POCs which purchase a small variety of drugs through SDs. Hence, we expect to see a lower proportion of drugs

distributed through SDs to a POC which purchases a larger variety of drugs. We therefore postulate the following:

HYPOTHESIS 2: *The required drug variety by a downstream POC is negatively associated with the SD usage to that POC (i.e., the proportion of specialty drugs distributed through SDs to that POC).*

3.1.3. Providing Critical Value-Added Services to Manufacturers

As mentioned, while there is limited literature on selecting distribution channels in B2B setting, there is plenty of literature on supplier selection in the B2B setting. According to this literature, the critical value-added services provided by the suppliers to the buyers is one of the important considerations (Choi and Hartley 1996, Brewer et al., 2001, Van der Rhee et. al 2009). In a similar vein, in our context, the distributor's provision of critical value-added services may also be important in manufacturers' distribution channel decisions.

Indeed, aside from distributing products to downstream POCs, pharma distributors have also been in charge of a critical value-added service, i.e., managing chargebacks, for the manufacturers that impacts the manufacturers' bottom line (Fein 2011). Specifically, given that manufacturers typically negotiate different price contracts with thousands of its downstream POCs, tracking and managing these contracts require a significant amount of effort. Such a job has been performed by WSs for decades. In particular, distributors purchase drugs from the manufacturer at the wholesale prices and also keep track of price contracts between manufacturers and different POCs. Depending on the different contracts, these prices are usually lower than the wholesale prices. The distributors then sell the drugs to the POCs at the contract-specific prices and claim the differences between the contract prices and the wholesale prices from manufacturers as chargebacks.

Managing chargebacks is complex, tedious, and subject to errors, leading to potentially massive revenue losses for manufacturers. There are two common errors when processing chargebacks: (1) chargebacks may be claimed for drugs never shipped or shipped to non-contracted POCs and hence are ineligible for chargebacks; and (2) returned products may be resold and a duplicate chargeback may be improperly requested, an activity known as "double dipping". According to a survey by the International Data Corporation (IDC), among the 12% of chargebacks that are flagged, 33.3% of them cannot be reconciled and have to be written off, resulting in manufacturers' loss of 4-5% of the industry's annual revenue, or $11 billion annually (Basta 2010).

Thus, the SDs' experiences in accurately and efficiently managing chargebacks for the POC to which the manufacturer sells would be an important consideration in the manufacturer's distribution channel decision. Unfortunately, data regarding accuracy in handling chargebacks is unavailable; in fact, many such errors are never found. Hence, we expect the emerging SDs' experiences in handling chargebacks would affect manufacturers' SD usage. We thus postulate the following:

HYPOTHESIS 3: *The SDs' experiences in providing critical value-added services (i.e., managing chargebacks) for a POC is positively associated with the SD usage to the POC (i.e., proportion of specialty drugs distributed through the SDs to the POC).*

3.2. Research Setting

The Electronic Data Interchange (EDI) has been widely used by the pharma industry to streamline ordering and purchasing processes throughout the supply chain. In particular, the EDI 867 data records all transactions between distributors and downstream POCs, such as clinics, hospitals, and retail pharmacies. The EDI 852 data records the inventory status of NDCs held by different distributors. The EDI 844 data records chargeback claims from distributors to manufacturers. Distributors allow manufacturers to access the EDI data for monitoring inventory in the supply chain (Schwarz and Zhao 2011, Zhao et al. 2012). We obtained the EDI 867/852/844 data from a cloud data service company. One of key services provided by this company is helping manufacturers select the right distribution channel for their products.

The EDI 867 dataset includes transactions between distributors (WSs or SDs) and downstream POCs. Transactions are collated annually for each NDC and include information on the quantity sold, the distributor used, and the POC destination, as well as the POC class of trade (to be detailed in Section 3.2.1). The quantity sold in each transaction is measured in the so-called *extended unit* at the NDC level. The extended unit helps to normalize different package sizes (e.g., 10/25 vial tray), and the detailed transactions at the NDC level allow us to account for different handling requirements of NDCs that have different dosage forms (e.g., capsule or vial) of the same brand of drug. For example, Temodar, a drug for treating brain cancer, needs to be stored at 15-30°C when supplied in capsule forms, but must be refrigerated at 2-8°C when supplied in vial (injectable) forms.

We use the EDI 852 dataset to measure the performance of distributors. This dataset contains information on inventory on hand at distributors, inventory returned to morgue (that is, inventory returned to distributors that cannot be resold and has to be destroyed), and quantity sold from distributors to downstream POCs. To measure distributors' experiences in managing chargebacks, we use the EDI 844 dataset which records all chargeback claims made by distributors to manufacturers. Each chargeback claim includes information such as the contract price at which the distributor sells to the POC and chargeback amount the manufacturer needs to pay the distributor. However, for 84.4% of the transactions in our dataset, the POCs' contract prices (prices negotiated between POCs and a manufacturer) and chargeback amounts (payments claimed by distributors to a manufacturer) are blanked out. Hence, we collect information on the number of drugs whose chargeback is handled by a distributor to measure this distributor's experience in managing chargebacks.

Aside from the aforementioned main datasets, we also independently collected additional information for each drug in our data. This includes information about drug characteristics (e.g., ATC code, method of

administration, orphan drug designation, etc.), associated regulation (e.g., whether monitored under REMS), and historical information (e.g. time since approval). Specifically, we used the National Drug Code Directory to obtain information such as administration method and new drug application (NDA) or biologic license application (BLA) number, which indicates whether a drug is a traditional chemical molecule or a biologic. We used the Drugs@FDA database to obtain the approval date of each drug. We obtained information on whether a drug is monitored under REMS, as well as the individual elements of REMS, from the REMS@FDA website. We obtained information on whether a drug is an orphan drug from the FDA Orphan Drug database. An orphan drug targets a disease that affects a patient population of less than 20,000 in the U.S. and its manufacturer is granted a seven-year exclusivity to sell the drug. From the World Health Organization (WHO) website, we collected information on each drug's Anatomical Therapeutic Chemical (ATC) code. This is a five-level code that indicates the therapeutic class of a drug, with ATC1 being the broadest category and ATC5 being the most granular category. We collated information across all these sources to create a comprehensive master dataset for each drug in our sample.

One of the challenges of our study is the lack of a universally accepted definition for specialty drugs. We observe that pharma manufacturers, insurance companies, and pharmacy benefit managers (PBMs) each have their own definitions of specialty drugs depending on their business purpose. For example, PBMs need to identify specialty drugs for designing a formulary, which specifies the lists of drugs and their corresponding coverage and copayments for reimbursement for insurance companies. Since there is no universally accepted definition of a specialty drug, we combined the specialty drug lists from two of the largest PBMs, Express Scripts and CVS Caremark, as well as from the insurance company BlueCross BlueShield. We also incorporated biologic designations by FDA into our definition of specialty drugs. If a drug appears in any one of these lists, we consider it a specialty drug. As part of our robustness tests (in Section 5), we use only FDA's biologic designations as an alternative definition for specialty drugs.

3.2.1. Sample Description

Since the goal of this study is to understand manufacturers' distribution channel decisions for specialty drugs, we focus exclusively on specialty drugs. We eliminated transactions in Puerto Rico, Hawaii, Alaska, and other islands and concentrated on the 48 contiguous states in the U.S. The main POC classes of trade in our data are clinics, hospitals, and retail pharmacies. The POC class of trade is historically instituted by the pharma industry to recognize the differences between POCs in dispensing venue, patient population served, nature of business, and professional capabilities. All POC classes of trade are indicated in our data. In total, we have 71,687 clinics, 6,660 hospitals, and 51,564 retail pharmacies in our data. The other POC classes of trade, such as federal facilities, long-term care, and miscellaneous, account for less than 1.5% of the transactions. We excluded these POCs because they may have different distribution protocols than those of the mainstream commercial healthcare providers. For instance, in April 2012, the Department of

Veterans Affairs (VA) directly selected McKesson as the primary pharma supplier to the VA Healthcare System. To mitigate the impact of outliers, we dropped transactions at the top and bottom 1 percentiles.

The original data is organized at the Firm-NDC-Distributor-POC-Year level. The data includes 11 firms (including 8 of the top 15 pharma manufacturers according to the global sales in 2013, accounting for 39.1% of total sales among the top 50 pharma manufacturers in 2013); 419 specialty drugs (i.e., NDCs that are specialty drugs); 119 WSs; 42 SDs; and 129,911 POCs, in the time period from 2012-2015. We use the first two-digit zip code (referred to as the zip2 code henceforth) of each POC to define the market in which these drugs are distributed. To test Hypothesis 1, which calls for a drug-level analysis, we create an estimation sample by aggregating our data at the Firm-NDC-POC-Year level. Each observation corresponds to a firm's SD usage in distributing a particular NDC to a particular POC in a particular year, i.e., the proportion of the NDC volume distributed through SDs to a particular POC. The final sample has 1,302,134 panel values, and each panel is observed on average for 1.9 years from 2012-2015. To test Hypotheses 2 and 3, which call for a firm-level analysis, we obtained an estimation sample by aggregating our data at the Firm-POC-Year level. Each observation corresponds to a firm's SD usage in distributing all its NDCs to a particular POC in a particular year.

3.2.2. Definition of Variables

We use subscripts f, i , m, p, and t to indicate firm, NDC, market, POC, and year, respectively. Below, we describe the variables for testing our hypotheses and the additional controls used in our analysis.

Dependent Variable:

We define $PctSD_{fimp,t}$ as the percentage of the volume of drug i that firm f distributes through SDs to POC p in market m in year t, and $PctSD_{fmp,t}$ as the percentage of all drug volume of firm f distributed through SDs to POC p in market m in year t. These two dependent variables correspond to the drug and firm level analyses, respectively. Note that since the REMS regulation is drug specific, we test Hypothesis 1 at the drug level. The required drug variety and the experiences for managing chargebacks for each POC are across drugs, hence we test Hypotheses 2 and 3 at the firm level. The independent variables for testing each of the hypotheses are described as follows.

Independent Variables:

Hypothesis 1 - Regulation: To examine the impact of regulation and its critical element on manufacturers' distribution channel decision (i.e., the SD usage), we obtained information on whether REMS is imposed on a drug and, if so, the elements included in each REMS from FDA website. As mentioned, the element particularly relevant to the distribution channel is restrictive access. Specifically, REMS is considered to have an element of restrictive access if only certified POCs are authorized to sell the drug, that is, if prescriber or dispenser certifications are required. Thus, we classify drugs into three groups: those monitored under REMS with restrictive access, those monitored under REMS without restrictive access

and those not monitored under REMS. Correspondingly, we define three binary variables, i.e., $REMSRestrict_{i,t}$, $REMSNoRestrict_{i,t}$ and $NoREMS_{i,t}$, to indicate the REMS status of each drug. Notably, $REMSRestrict_{i,t}$ and $REMSNoRestrict_{i,t}$ are not opposites of one another because some drugs do not have REMS at all. We include $REMSRestrict_{i,t}$ and $REMSNoRestrict_{i,t}$ in the regression model and set $NoREMS_{i,t}$ as the default case.

Hypothesis 2 – Drug variety at POCs: To examine the impact of a downstream POC's required drug variety on a manufacturer's distribution channel decision, we introduce the variable $Variety_{p,t}$ as a measure of the number of different NDCs purchased by POC p. We construct the variable at the NDC level to account for the distinct handling requirements that distributors have to accommodate for different NDCs.

Hypothesis 3 – Distributors' Experiences in Managing Chargebacks: To examine the impact of the distributors' experiences and measure the average experiences of WSs and SDs in managing chargebacks, we construct the variables $ChargebackWS_{p,t-1}$ and $ChargebackSD_{p,t-1}$. Given that distribution decisions are made by a firm for each NDC, we define these two variables as the number of NDCs that a POC p purchases with chargeback contracts and are distributed through WSs or SDs at period $t-1$, respectively. In constructing $ChargebackWS_{p,t-1}$ and $ChargebackSD_{p,t-1}$, we exclude the focal drug i itself to avoid the false correlation with the dependent variable. Similar to the variable $Variety_{p,t}$, $ChargebackWS_{p,t-1}$ and $ChargebackSD_{p,t-1}$ are at the firm level.

Controls:

To control for additional factors that may influence a manufacturer's distribution channel decision, we include variables that have been considered in previous literature (Rangan et al. 1992, Lee et al., 2013). We classify these variables as drug, firm, market, competition, and POC characteristics based on Lee et al. (2013). The definitions of the control variables can be found in Table 1.

Furthermore, we use $Firm_f$, $ATC1_i$, Mkt_m and $Year_t$ to represent the firm, ATC1, market, and year fixed effects, respectively. We include the firm fixed effects to capture firms' time-invariant preferences in distribution channels such as differences in firm types (e.g., biotech versus traditional pharma manufacturer), long-term contracts with distributors etc. The market fixed effects help us to control for systematic differences in SD usage across markets, which could arise from differences in location, demand for specialty drugs, and the presence of WSs and SDs, among other factors. The ATC1 fixed effects allow us to control for systematic differences in SD usage across therapeutic classes due to differences in targeted diseases and handling requirements. For instance, drugs that belong to the ATC1 of "L" or "V" in our data are mostly oncology drugs and thus may be more likely distributed through SDs due to their special handling requirements. The year fixed effects are included to capture the aggregate change in a given distribution channel over time. We also include POC classes of trade indicators such as $Clinic_p$ and

$Hospital_p$ to account for potential differences in distribution channels to reach different POC classes of trade.

Descriptive statistics for all variables are shown in Table 2.

3.2.3. Model and Estimation

In this section, we explain the empirical model used for testing our hypotheses. As mentioned in Introduction, REMS is drug-specific. Thus, to test Hypotheses 1, we perform a drug level analysis according to the following regression model:

$$PctSD_{fimp,t} = \beta_1 REMSRestrict_{i,t} + \beta_2 REMSNoRestrict_{i,t} + \beta_3 Variety_{p,t} + \beta_4 ChargebackWS_{p,t-1} + \beta_5 ChargebackSD_{p,t-1} + Controls + \mu_{fimp} + \varepsilon_{fimp,t}, \quad (1)$$

where $Controls = \theta_1 Clinic_p + \theta_2 Hospital_p + \theta_3 CumPctWS_{fm,t-1} + \theta_4 VolNDC_{i,t-1} + \theta_5 Wac_{i,t} + \theta_6 Injectable_i + \theta_7 Rare_i + \theta_8 Age_{i,t} + \theta_9 CntATC2_{i,t} + \theta_{10} MktSize_{m,t} + \theta_{11} FirmSize_{f,t} + Firm_f + ATC1_i + Mkt_m + Year_t$

In the above model, μ_{fimp} represents the unobserved panel heterogeneity after controlling for the firm, market, ATC1, and year fixed effects. Note that it is possible that a firm with low average SD or WS usage may distribute certain drugs to particular markets through SDs or WSs due to some unobserved factors in these markets. For example, a traditional pharma manufacturer that distributes most of its products through WSs may use SDs for distributing a high-risk oncology drug in California, where the state e-Pedigree law requires the tracking and tracing of each transaction involving drugs with serious risks along the supply chain. To account for potential unobserved panel heterogeneity, we choose a random-effects model, which is more appealing than a fixed-effects model for the following two reasons. First, a fixed-effects model can produce biased estimates for a large number of panels observed over short time periods (Greene 2008). Since our data consists of 1,302,134 panels observed on average over two periods, a fixed-effects model may not be appropriate. Second, most variables of interest in our study do not change or vary only slightly over time (e.g., $REMSRestrict_{i,t}$, $REMSNoRestrict_{i,t}$). Hence, a fixed-effects model would provide poor estimates of these variables. Additionally, we use cluster standard errors at the firm level, which allows us to account for heteroscedastic and auto-correlated errors within a cluster (Greene 2008, Arora et al. 2009).

Since variables such as $Variety_{p,t}$, $ChargebackWS_{p,t-1}$ and $ChargebackSD_{p,t-1}$ are at the firm level, for Hypotheses 2 and 3, Model (1) would estimate an average effect of these variables, which may be potentially biased in favor of the low volume drugs. Therefore, we develop a firm-level analysis according to the regression model below to further test Hypotheses 2 and 3:

$$PctSD_{fmp,t} = \alpha_1 Variety_{p,t} + \alpha_2 ChargebackWS_{p,t-1} + \alpha_3 ChargebackSD_{p,t-1} + Controls + \mu_{fmp} + \varepsilon_{fmp,t} \quad (2)$$

where $Controls = \kappa_1 Clinic_p + \kappa_2 Hospital_p + \kappa_3 CumPctWS_{fm,t-1} + \kappa_4 MktSize_{m,t} + \kappa_5 FirmSize_{f,t} + Firm_f + Mkt_m + Year_t$

Note that we do not include the drug-specific variables in Model (2) because this analysis is at firm level.

We now address some potential endogeneity issues associated with Model (1). Specifically, the regulatory decision related to REMS may depend on some unobserved drug characteristics, such as whether the drug is lethal or the first drug in a disease class. This may influence the manufacturer's distribution channel decision and thus cause an omitted variable bias in our estimates. To mitigate this, we first include an extensive set of drug-related variables, such as $Injectable_i$, $ATC1_i$, $Wac_{i,t}$, $Age_{i,t}$, and $Rare_i$, as controls. Next, following a similar approach by Cachon and Olivares (2004), for each drug in our data, we construct a variable $REMSRestrictIV_{i,t}$ which equals the average value of $REMSRestrict_{i,t}$ for all other brands of drugs within the same ATC2 code from the same firm as an instrument for $REMSRestrict_{i,t}$. We adopt this approach for two reasons. First, we believe this instrument meets the exclusion restriction criteria because the REMS status of other drugs, which is separately determined by FDA, should be unrelated to the manufacturer's distribution channel decision of the focal drug. Second, we believe that $REMSRestrictIV_{i,t}$ is relevant because drugs within the same ATC2 code tend to treat similar diseases and have similar risk profiles. We find $REMSRestrict_{i,t}$ is strongly correlated with the instrumental variable (Spearman's rank correlation is 0.89 ($p<0.001$)). Further, we conduct a first-stage regression analysis to examine how $REMSRestrictIV_{i,t}$ predicts $REMSRestrict_{i,t}$ as follow:

$$
\begin{aligned}
REMSRestrict_{i,t} &= \phi_1 REMSRestrictIV_{i,t} + \phi_2 REMSNoRestrict_{i,t} + \phi_3 Variety_{p,t} \\
&+ \phi_4 ChargebackWS_{p,t-1} + \phi_5 ChargebackSD_{p,t-1} + \phi_6 Clinic_p + \phi_7 Hospital_p \\
&+ \phi_8 CumPctWS_{fm,t-1} + \phi_9 VolNDC_{i,t-1} + \phi_{10} Wac_{i,t} + \phi_{11} Injectable_i + \phi_{12} Rare_i \\
&+ \phi_{13} Age_{i,t} + \phi_{14} CntATC2_{i,t} + \phi_{15} MktSize_{m,t} + \phi_{16} FirmSize_{f,t} + Firm_f + ATC1_i \\
&+ Mkt_m + Year_t + \varepsilon_{fimp,t} \qquad (3)
\end{aligned}
$$

The result of the first-stage regression is shown in Table 3. The F-statistics of the excluded instrument in the first stage regression is F(1,8)=273.01. This is over the recommended threshold (F-statistic of 10), indicating that the instrument is not "weak" and the IV (instrument variable) estimator is asymptotic unbiased (Staiger and Stock 1997).

3.3. Results

We now present our estimation results from Model (1) and Model (2). Our analysis of Model (1) is run with the instrumental variable for $REMSRestrict_{i,t}$. As Table 4 shows, we added variables sequentially in Model (1) to see the incremental change with each additional independent variable predictor. Column (3) of Table 4 describes the estimates of the full Model (1) and Column (4) describes the estimates of Model

(2). We refer to Column (3) of Table 4 for assessing Hypothesis 1 and Column (4) for assessing Hypotheses 2 and 3, respectively.

H1: The Impact of Regulation and Its Critical Elements

Column (3) in Table 4 shows that the coefficient of $REMSRestrict_{i,t}$ is positive and significant (0.3394; $p<0.05$), suggesting that a drug monitored under REMS with the restrictive access element is associated with a higher SD usage. Hence, Hypothesis 1 is supported. Specifically, compared with drugs without REMS, drugs monitored under REMS with restrictive access are associated with a 33.94 percentage point increase in SD usage. On the other hand, the coefficient of $REMSNoRestrict_{i,t}$ is not significant (-0.0048; $p=0.934$), suggesting that the mere imposition/presence of REMS on a drug, but without the restrictive access element, is not associated with a manufacturer's SD usage. Furthermore, the comparison between the coefficients of $REMSRestrict_{i,t}$ and $REMSNoRestrict_{i,t}$ is significant ($p<0.1$), supporting the hypothesis that the manufacturer responds differently to REMS with/without restrictive access. Hence, it is not the presence of REMS but the presence of the specific element of restrictive access in REMS on the drug to be distributed that drives the SD usage.

This result implies that when a drug is monitored under REMS with restrictive access, i.e., limiting the accessibility of a drug within a controlled network, the manufacturer may react by distributing a greater proportion of the drug through SDs. Indeed, as suggested by Sharma and Mehrotra (2007), manufacturers must make a tradeoff between access and control when deciding upon a distribution channel. Although manufacturers intrinsically prefer a broad and accessible channel (like the one offered by WS) in order to reach as many customers as possible, the advantages of such a channel are offset by the diluted control within the channel, especially with the presence of the restrictive access element of REMS. The restrictive access element of REMS requires manufacturers to oversee their distribution channels to ensure that these drugs are appropriately prescribed, distributed, and used. Hence, this is likely to influence manufacturers' assessment of the tradeoff between access and control and ultimately, their distribution channel decisions. Anecdotal evidence suggests that, due to their tightly controlled networks, SDs are better at preventing drugs from being diverted to uncertified POCs or illegal secondary distributors, thus ensuring regulatory compliance (Fein 2011, Shelley 2009). As indicated by our data, Table 5 shows that SDs sell to fewer secondary distributors than WSs, suggesting that drugs distributed through the SD channel are handled by fewer intermediaries and thus are less likely to be diverted into the hands of unintended agents. Hence, REMS with the restrictive access element may also help to prevent counterfeits from entering the supply chain. For example, Epogen (a drug used for anemia treatment) faced a severe counterfeit problem in 2004 (estimated financial impact of $48 million (Jaret 2004)). Subsequently, FDA mandated REMS with restrictive access for Epogen in 2008 (which might be related to the earlier counterfeit case).

When REMS requires no restrictive access, the scope of REMS is usually limited to providing POCs and patients with education about the safe use of the drug. Such REMS does not require a controlled network and may be easily satisfied by any distributor. Therefore, as the result on $REMSNoRestrict_{i,t}$ suggests, manufacturers does not have particular preference to distribute the drug through an SD channel under REMS without the restrictive access element.

H2: The Impact of Downstream POC's Required Drug Variety

Column (4) in Table 4 describes the estimates of Model (2), which represents our firm-level analysis. Column (4) shows that the coefficient for $Variety_{p,t}$ is negative and significant (-8.56e-4; $p<0.05$), suggesting that a higher variety of drugs purchased by a downstream POC is associated with a lower SD usage by a manufacturer in distributing drugs to that POC. Specifically, a one standard-deviation increase in $Variety_{p,t}$ for a POC is associated with a 2.15 percentage point decrease in manufacturers' SD usage in reaching that POC. Therefore, Hypothesis 2 is supported. This also implies that manufacturers can leverage WSs' large assortment of drugs to meet the needs of downstream POCs that need a large variety of drugs (e.g., general hospitals), thus providing such POCs with one-stop-shopping convenience.

We also note that POC class of trade is associated with manufacturers' SD usage. Note that the POC class of trade base case is pharmacy. The comparison between the coefficients of $Hospital_p$ and $Clinic_p$ indicates the manufacturer tends to have a higher SD usage when reaching clinics than hospitals (b=0.403, $p<0.005$). Hospitals are generally larger in scale than clinics and could be more equipped and sophisticated in assuring security of the supply chain (e.g., protecting product integrity and preventing counterfeits entering the supply chain) (McCain 2012). This may be one of the reasons to explain the difference in SD usage when manufacturers distribute to hospitals and clinics respectively.

H3: The Impact of the Distributors' Experience to Manage Chargebacks

Column (4) in Table 4 shows that the coefficient for $ChargebackSD_{p,t-1}$ is positive and significant (0.0115; $p<0.05$), suggesting that the SDs' increased experience in managing chargebacks is associated with a greater proportion of a drug distributed through the SDs. Specifically, a one standard-deviation increase in $ChargebackSD_{p,t-1}$ is associated with a 3.29 percentage point increase in manufacturers' SD usage. Given the large number of drugs distributed, such change of SD usage would have a considerable impact on the operations of WSs and SDs. Therefore, Hypothesis 3 is supported, implying that manufacturers distribute a higher proportion of their drugs through SDs to reach a POC if the SDs have more experience in managing chargebacks with this POC. On the other hand, we do not find much evidence on the impact of $ChargebackWS_{p,t-1}$ on manufacturers' SD usage. This is consistent with our conjecture that WSs have a long history of handling chargebacks and therefore their experience in managing chargebacks is of less concern to manufacturers.

4. Study II: Which Specialty Distributor to Choose?

In the previous section, we focus on factors impacting a manufacturer's SD usage in distributing its specialty drugs. In this section, we further study factors affecting a manufacturer's choice of a specific SD, should it decide to use an SD channel. To do so, we first provide additional background of the pharma distribution industry in Section 4.1, based on which we develop the nested logit model for our analysis in Section 4.2. We will then describe our sample in Section 4.3 and discuss detail estimation results in Section 4.4.

4.1. Background of Pharma Distribution

Many large SDs have emerged in recent years following the rapid growth of specialty drugs on the market. In general, there are four categories of SDs: ABC SD, Cardinal SD, McKesson SD, and the non-big3 SDs (such as Besse Medical Supply, and CuraScript). The first three are affiliated to the corresponding big3 WSs (ABC, Cardinal and McKesson) and we refer to them as WS-affiliated SDs. To maintain their competitive positions in the distribution of specialty drugs, the big3 WSs have started their own branches of specialty distribution channel by either building their own specialty divisions or acquiring other SDs. For example, ABC developed Oncology Supply and ASD Healthcare in house, McKesson acquired Oncology Therapeutics Network in 2007, and Cardinal acquired Metro Medical Supply (the largest non-big3 SD then) in 2015. Although these WS-affiliated SDs are operated independently from their respective WSs, we expect these SDs may still be connected to their WSs in the following two aspects. First, since the SD and the WS are under the ownership of the same parent company, a manufacturer's relationship with the WS, as measured by the manufacturer's prior usage of the WS, may affect the manufacturer's selection of the affiliated SD. This is because prior research has shown that buyers are more likely to purchase from a familiar and trusted channel (Langer et al. 2012, Kim and Krishnan 2015) and such familiarity and trust developed by a channel party (the WS in our context) may spillover to its affiliated party (the SD in our context) (Rosenbloom 2007). Second, a WS-affiliated SD may inherit from its WS the knowledge and procedures that the WS has accrued when dealing with the manufacturer, and such knowledge has shown to be important for streamlining operations and reducing human errors (Bharadwaj and Matsuno 2006). Thus, we expect that a manufacturer that has previously used a WS is more likely to use the corresponding WS-affiliated SD when it comes to choosing a specific SD. At the same time, if a manufacturer is already working with a WS or an SD, it would be more likely to continue working with that WS or SD. Hence, we will investigate the impact of prior usage of a specific SD or WS on a manufacturer's choice of a specific SD.

In addition, most manufacturers select their supply chain partners based on certain performance criteria. For example, manufacturers select third-party logistics providers based on measures such as efficiency, loss, and damage (Menon et al. 1998). Therefore, in this study, we also explore how distributors' performance

affect a manufacturer's choice of specific SD. In the pharma industry, two distributor performance measures are especially important. First, it is important for a manufacturer to know how efficiently distributors are able to manage their inventories. This is because the industry overall requires a high service level but the maximum inventory a distributor can hold is limited through fee-for-service (FFS) contracts, which are the premium contracts for drug distribution between manufacturers and distributors. Such limits are set to reduce investment buying, i.e., holding excessive inventory in anticipation of drug price increases (see Schwarz and Zhao (2011) and Zhao et al. (2012) for details on the origin and development of FFS contracts in the pharma industry). Following Schwarz and Zhao (2011), we use distributors' inventory turnover rates to measure distributors' efficiency in providing distribution services. Second, given the limited shelf lives and the high prices for specialty drugs, the distributors' ability to manage their inventory to reduce waste or spoilage is another important indicator of the distributors' performance.

4.2. Nested Logit Model

Based on the background of the pharma distribution industry discussed above, we classify all distributors (WSs and SDs) into eight alternatives (categories) that cover the different options in the current market: ABC WS, Cardinal WS, McKesson WS, non-big3 WS, ABC SD, Cardinal SD, McKesson SD, and non-big3 SD. Note that although the non-big3 WS and the non-big3 SD could refer to many different distributors, for brevity, we call the above eight alternative distributors. For Study II, we restrict our sample to drugs approved after 2013 to directly examine a manufacturer's choice of a specific SD following the initial introduction of its drugs. In this subsample, we find that in 94.8% of the instances, manufacturers chose only one SD or WS among the above eight alternative distributors to distribute a drug to a POC. This observation supports the use of a discrete choice model (e.g., McFadden 1981) to capture manufacturers' choice of distributors.

Each of the eight distributors is either a WS or SD, with distributors in the same channel (WS or SD) being more similar than across channels. Correspondingly, we employ a nested logit model to account for a manufacturer's two-stage nested decision among the eight alternative distributors, as illustrated in Figure 1. In the first stage, manufacturers decide whether to choose a WS or SD channel. In the second stage, manufacturers decide which specific WS or SD to choose. To formulate manufacturers' decisions, we assume that each NDC-POC pair (i, p) at year t associates some utility, U_{ipjt}, with distributor j=ABC WS, Cardinal WS, McKesson WS, non-big3 WS, ABC SD, Cardinal SD, McKesson SD, and non-big3 SD. Formally, U_{ipjt} is specified by the following random utility model,

$$U_{ipjt} = V_{ipkt} + W_{ipjt} + \epsilon_{ipjt} \quad (4)$$

where $k =$ WS or SD, indicates a manufacturer's choice between WS or SD channel. V_{ipkt} represents the utility component from choosing distribution channel k, and W_{ipjt} represents the utility component from choosing specific distributor j. Following the literature on nested logit models (e.g., McFadden 1981), we

assume the residual term, ϵ_{ipjt}, follows a generalized extreme value distribution. The joint probability of choosing distributor j is $P_{ipjt} = P_{ipjt|k}P_{ipkt}$, where P_{ipkt} is the probability of choosing channel k for pair (i,p) at year t, and $P_{ipjt|k}$ is the conditional probability of adopting distributor j if choosing channel k. Formally, we have:

$$P_{ipkt} = \frac{\exp(V_{ipkt}+\lambda_k I_{ipkt})}{\sum_{l\in\{WS,SD\}}\exp(V_{iplt}+\lambda_k I_{iplt})} \text{ and } P_{ipjt|k} = \frac{\exp(W_{ipjt})}{\sum_{h\in S_k}\exp(W_{ipht})}$$

where $I_{ipkt} = \ln\sum_{h\in S_k}\exp(W_{ipht})$ is the expected utility of choosing distribution channel k, λ_k measures the dis-similarity of distributors within distribution channel k, and S_k denotes the set of distributors under distribution channel k.

4.3. Sample Description and Variables

As mentioned, we restrict our sample to drugs approved after 2013. This allows us to isolate the impact of a manufacturer's relationship with distributors on the manufacturer's choice of a specific distributor for its new drugs. We have 58 NDCs in our restricted sample. The 2012 data is used for constructing the explanatory variables.

In addition to all the variables studied in Study I, we construct the following new variables, namely, manufacturers' prior usage of a distributor and distributor performance. Specifically, we define $PriorUsage_{fipj}$ as the percentage of firm f's drug volume distributed through distributor j in reaching POC p among all distributors prior to the approval of drug i, i.e.,

$$PriorUsage_{fipj} = \frac{firm\ f's\ total\ drug\ volume\ distributed\ through\ j\ to\ POC\ p\ prior\ to\ the\ approval\ of\ i}{firm\ f's\ total\ drug\ volume\ distributed\ to\ POC\ p\ prior\ to\ the\ approval\ of\ drug\ i}.$$

For example, for a drug approved in 2014, $PriorUsage_{fipj}$ measures firm f's usage of distributor j in reaching POC p from 2012-2013. Similarly, we define $PriorBranchUsage_{fipj}$ as the percentage of firm f's drug volume distributed through distributor j^- in reaching POC p among all distributors prior to the approval of drug i, where j^- represents the distributor different from j but belonging to the same parent company. For example, for $j =$ ABC SD, $PriorUsage_{fipj}$ measures firm f's prior usage of ABC SD among all distributors in reaching POC p, while $PriorBranchUsage_{fipj}$ measures firm f's prior usage of ABC WS among all distributors in reaching POC p. If $j =$ non-big3 SD, then j^- represents the non-big3 WS. As mentioned, the WS-affiliated SDs, though operated independently, may benefit from the business relationships accrued by their respective WSs. Thus, we expect that a manufacturer to more likely to choose an SD to reach a POC if it used the SD or the affiliated WS to do so previously.

We also include variables on distributors' performance measures, such as inventory turnover rates and spoilage rates. Since distributors' performance in distributing a new drug i is not revealed until its approval and introduction to the market, we approximate a distributor's performance in managing drug i by the distributor's average performance in distributing other drugs within the same ATC1 that were approved

prior to drug i. Specifically, we define $Turnover_{fij}$ as the average inventory turnover of distributor j for drugs within the same ATC1 as drug i prior to the approval of drug i. Here, we refer to the inventory turnover as the ratio of the annual volume of a drug distributed through a distributor and the average inventory the distributor holds for the drug. Similarly, we define $Spoilage_{fij}$ as the average spoilage rates at distributor j for drugs within the same ATC1 as drug i prior to the approval of drug i. Here, we refer to the spoilage rate as the ratio of the total volume of a drug's returned-to-morgue (i.e., inventory returned to distributors that cannot be resold and has to be destroyed) and the total volume of the drug distributed through the distributor. Furthermore, we define $ChargebackDistributor_{fipj}$ as the number of NDCs of firm f having chargeback contracts with POC p and managed by distributor j prior to the approval of drug i. This variable represents distributor j's experience in managing chargeback between firm f and POC p. Finally, we define $Big3_j$ as a binary variable to indicate whether distributor j is a big3 distributor (including both big3 WS and big3 SD) or not.

With the above variables, our model is as follows:

$$V_{ipkt} = \gamma_{1k} REMSRestrict_{i,t} + \gamma_{2k} REMSNoRestrict_{i,t} + \gamma_{3k} Variety_{p,t} + Controls \quad (5)$$

$$W_{ipjt} = \delta_1 PriorUsage_{fipj} + \delta_2 PriorBranchUsage_{fipj} + \delta_3 ChargebackDistributor_{fipj} + \delta_4 Turnover_{fij} + \delta_5 Spoilage_{fij} + \delta_6 Big3_j \quad (6)$$

Eq (5) captures a manufacturer's utility from choosing a WS or SD channel. Although the explanatory variables in Eq (5) are the same across channels, the coefficients in Eq (5) are channel-specific, thus capturing the different utility of choosing a WS or SD channel. The control variables in Eq (5) are the same as those in Model (1). Eq (6) captures a manufacturer's utility from choosing a specific distributor within either the WS or SD channel. The explanatory variables in Eq (6) are distributor-specific, thus capturing the different utilities manufacturers obtain from choosing different distributors. We estimate the model through Maximum Likelihood Estimation (MLEs) using the Stata command *nlogit*.

4.4. Results for the Nested Logit Model

Table 6 provides the estimation results of the nested logit model (Eq (5) and Eq (6)). As Table 6 shows, the coefficient of $PriorUsage_{fipj}$ is positive and significant (7.8555; $p<0.005$), suggesting that a manufacturer's prior usage of an SD is associated with an increased likelihood of the manufacturer's choice of this SD for its new drugs. Interestingly, we find that the coefficient of $PriorBranchUsage_{fipj}$ is also positive and significant (3.6333; $p<0.005$). This suggests that a manufacturer's prior usage of a WS is also associated with an increased likelihood of manufacturer's choice of the corresponding WS-affiliated SD for distributing its new drugs, although the magnitude of the impact is lower than that of the prior usage of the focal SD itself.

Similar to Forman (2005), to ease interpretation of these coefficients, we analyze the marginal effects of a change from 0 to 1 in $PriorUsage_{fipj}$ and $PriorBranchUsage_{fipj}$. Specifically, we evaluate the impact on a manufacturer's likelihood of choosing a distributor if $PriorUsage_{fipj}$ or $PriorBranchUsage_{fipj}$ change from 0 to 1, where 0 corresponds to not using the distributor previously and 1 corresponds to using the distributor exclusively to distribute a drug to a POC. As Table 7 shows, an increase in $PriorUsage_{fipj}$ of an SD from 0 to 1 is associated with a 14.08% increase in the likelihood of choosing this SD. An increase in $PriorBranchUsage_{fipj}$ (i.e., an increase in the prior usage of the WS belonging to the same parent company) from 0 to 1 is associated with a 6.61% increase in the likelihood of choosing the SD under the same parent company with the WS. As expected, the impact of $PriorBranchUsage_{fipj}$ (indirect impact) is smaller than that of $PriorUsage_{fipj}$ (direct impact). These results imply that the prior relationships with a distributor, or a distributor's related branch, have substantial impact on a manufacturer's choice of a specific distributor. By creating their own SDs, even if these SDs are operated independently, WSs can leverage their existing relationships with manufacturers to influence manufacturers' choices of their affiliated SDs.

In terms of the impact of the distributors' performance, we find that the coefficient of $Turnover_{fij}$ is weakly significant (-0.0561, p=0.082). We also find that the coefficient of $Spoilage_{fij}$ is negative and significant (-7.7709; p<0.005), suggesting the performance of a distributor in reducing spoilage is positively associated with the likelihood that a manufacturer chooses the distributor to distribute its drugs. However, as observed in our data, distributors in general have very low spoilage rates; therefore, the impact of spoilage is limited. Specifically, a 3.01% increase in the spoilage rate of an SD (i.e., the average spoilage rate across all SDs) is associated with a mere 0.42% increase in the likelihood of a manufacturer choosing the SD. Consistent with the results of Hypothesis 3 in Section 3.4, we also find that the coefficient of $ChargebackDistributor_{fipj}$ is positive and significant (0.0913; p<0.05), suggesting that an increase in the experience of a distributor in managing chargebacks is associated with a higher likelihood of a manufacturer choosing the distributor. Specifically, as Table 7 shows, a one-unit increase in $ChargebackDistributor_{fipj}$ (i.e., handling one more NDC's chargeback to POC p) is associated with a 0.16% increase in the likelihood of a manufacturer choosing this distributor to reach a particular POC p.

We show the marginal effects of factors such as $REMSRestrict_{i,t}$ and $Variety_{p,t}$ on manufacturers' choices between WS and SD channels in Table 7. We see that compared to a drug without REMS, a drug monitored under REMS with the restrictive access element is associated with a 52.83% increase in the likelihood of distributing the drug through an SD channel. This demonstrates the substantial impact of REMS with the restrictive access element on manufacturers' choice between WS and SD channels. Finally, we observe that a one-unit increase in $Variety_{p,t}$ (i.e., one more NDC purchased by POC p) is associated

with a 0.0274% decrease in the likelihood of a manufacturer choosing an SD channel. These results are also consistent with our findings in Section 3.4.

5. Robustness Tests

In this section, we perform several robustness tests on our main results. First, we use an alternative definition of specialty drugs to show that our results are not driven by the specific definition of specialty drugs. In Study I (Section 3), we define specialty drugs as the set of drugs obtained by combining the specialty drug lists from the top two PBMs, a large insurance company and the FDA biologic designation. In this robustness test, we define specialty drugs as biologics because the unique nature of biologics in terms of handling and safe use requirements may have direct implications on manufacturers' distribution channel decisions. Note that all biologics are classified as specialty drugs in Study I (Section 3), hence this alternative definition only considers a subset of drugs as specialty drugs. Together, we have 154 NDCs that are biologics and thus considered as specialty drug for this analysis. The estimation results of Hypotheses 1-3 based on this alternative definition of specialty drugs are shown in Columns (1) of Table 7A. The post-estimation comparison between the coefficients of *REMSRestrict* and *REMSNoRestrict* is also significant ($p<0.1$). Thus, our results with this alternate definition are consistent with our main results from section 3.

Second, it is possible that a manufacturer's distribution channel decision is dictated by special handling requirements of its drugs. In Study I, we use the variable $Injectable_i$ as a proxy for the handling complexity for a drug. In this robustness test, we use an alternative measure to account for a more precise requirement on how drugs need to be handled. Specifically, we manually compile the handling and storage requirements for the specialty drugs in our data from the *dailymed* website. In brief, special handling requirements are of the following kind: "Store at 2~8°C (36~46°F); do not freeze or shake; protect from light". We define a binary variable $SpecialHandle_i = 1$ if drug i is required to be stored at 2-8°C, the typical cold chain requirement; otherwise, we set $SpecialHandle_i = 0$. Based on this definition, 185 of the total 419 specialty drug NDCs in our data have $SpecialHandle_i = 1$. We find that $SpecialHandle_i$ is highly correlated with $Injectable_i$ ($\rho = 0.85$; $p<0.001$). Therefore, we include only $SpecialHandle_i$, but not $Injectable_i$ in the regression; and our main results continue to hold. In addition, as Column (2) of Table 7A shows, the coefficient of $SpecialHandle_i$ is not significant, indicating that the special handling requirement is not associated with manufacturers' SD usage. This implies that specialty drugs without special handling requirement may also be distributed through SDs, possibly due to other considerations such as channel control and data management. In fact, in our data, 82.1% of the specialty drugs that do not require special handling are also handled by SDs. Therefore, it appears that special handling capability, especially the cold chain capability, may have become a standard requirement in the pharma distribution industry (Healthcare Distribution Alliance 2015) and thus is no longer a differentiating factor between WSs and SDs.

Third, in constructing the instrument $REMSRestrictIV_{i,t}$ for $REMSRestrict_{i,t}$, we computed the average value of $REMSRestrict_{i,t}$ for all other brands of drugs within the same ATC2 code from the same firm. Alternatively, we use the average value of $REMSRestrict_{i,t}$ for all other brands of drugs within the same ATC1 code from the same firm as an instrument for $REMSRestrict_{i,t}$. Since ATC1 code is broader than ATC2 code, more other drugs are included in constructing the instrument for a focal drug. The estimation results using this new instrument are shown in Column (3) of Table 7A, and the result is consistent with our main results.

Next, we show that our results from the nested logit model are robust against alternative specifications of distributor's performance measures. Specifically, in Study II, we construct the prior performance of distributors, i.e., $Turnover_{fij}$ and $Spoilage_{fij}$ by aggregating the performance of distributor j in distributing other drugs that are within the same ATC1 as drug i and approved prior to drug i. In this robustness test, we define $Turnover_{fij}$ and $Spoilage_{fij}$ by aggregating the performance of distributor j in distributing other drugs that are within the same ATC2 as drug i and approved prior to drug i. As Table 7B shows, our main findings continue to hold with these alternative specifications.

6. Discussion and Conclusion

Pharma manufacturers have used a conventional "pick-pack-ship" distribution model through wholesalers (WS) for decades. However, the sharp increase of specialty drugs in the industry has forced manufacturers to possibly consider other alternatives due to the many unique challenges in distributing the specialty drugs. As pointed out by the director at Navigant Consulting Inc, "Specialty drug distribution is a new concept; it's foreign territory" (MHA Business Summit 2016). As the first study on the distribution of specialty drugs, this paper investigates two questions about manufacturers' distribution channel decisions: (1) With the emerging specialty distributors (SD) in the distribution industry that has been dominated by traditional wholesalers, what are the major factors affecting a manufacturer's usage of an SD channel? (2) If a manufacturer were to use an SD channel, which SD would they choose?

We tackle the above two questions using a novel and extensive panel dataset assembled from a number of data sources, including large proprietary EDI 867/852/844 datasets from 11 big pharma manufacturers (8 of which are among the top 15 pharma manufacturers ranked by global sales according to Pharma Executive (2013)), National Drug Code Directory, drug characteristics database Drugs@FDA and drug regulation database REMS@FDA. Our results show that: (1) While imposing REMS regulation on a drug is not associated with the manufacturers' SD usage on this drug, imposing REMS *with the restrictive access element* on a drug seems a key driver for the manufacturers' usage of an SD channel for the drug. This is because SD typically provides a tighter-controlled network. (2) Manufacturers distribute a smaller proportion of their drugs through SDs to reach POCs that need to purchase a larger variety of drugs because WSs can better serve these POCs by providing one-stop-shopping services with their large variety of drugs.

(3) SDs' experiences in managing chargebacks, a critical value-added service provided by WSs for pharma manufacturers for decades, is important: Manufacturers distribute a greater proportion of their drugs through SDs with more experience in managing chargebacks. (4) When it comes to deciding which SD to choose, manufacturers' prior relationships with an SD or even its affiliated WS play a very important role in the manufacturer's choice of this SD for distributing its new drugs. Given that the big3 WSs all have developed their own SDs, these SDs can leverage the relationships developed by their affiliated WSs with the manufacturers to maintain competitive positions, especially when compared with non-big3 SDs.

Our findings offer important insights and practical guidance to different stakeholders involved in specialty drug distribution, as we discuss below:

For regulators: REMS regulation is implemented to protect drug integrity and ensure safe use through various measures such as medication guides, communication plans, implementation plans, and restrictive access. However, the pharma industry increasingly recognizes that these programs may erect barriers for accessing these drugs. As our results show, if REMS has the restrictive access element for a drug, a manufacturer tends to use the SD channel to ensure a controlled network, which is only accessible to certified POCs, and requires patient/provider registries and ongoing patient data collection. POCs outside the controlled network thus have no effective ways to obtain access to the drug. As one long-term care (LTC) provider said, it is "terrible" that LTC facilities often do not have access to such networks. Such controlled networks may contribute to further fragmentation, as well as the complexity in coordination of care (MHA Business Summit 2016). While FDA on average only approves 38 drugs per year from 2012-2015, there are 70 drugs currently under REMS, and 60% of these REMS programs have the restrictive access element (Brill 2017). As regulators consider REMS's role in protecting patient safety, they should realize the tradeoff between the benefits of REMS and its impact on patients' access to such drugs. Regulators, manufacturers, and distributors should work together to create pathways for qualified POCs outside the controlled networks to obtain access to these drugs. For drugs with less severe risks, regulators may consider applying REMS *without the restrictive access element* to increase access to these drugs.

For manufacturers: Our results bring two important insights for pharma manufacturers. First, WSs and SDs adopt distinct strategies in balancing access to and control of drugs. Compared with WSs, which typically have extended networks and carry a large variety of drugs, SDs tend to manage controlled distribution networks and typically carry a small number of drugs. Therefore, SDs seek to provide manufacturers with more dedicated and controlled channel for drugs that may require restrictive access to comply with REMS regulation, while WSs strive to carry a full spectrum of drugs to meet the needs of basket buyers such as large hospitals. Understanding the distinction between WSs and SDs helps manufacturers to tailor their distribution channel based on their needs: whether to have a widely accessible or more controlled distribution network. In addition, the ability of WSs and SDs to meet downstream POCs'

need for drug variety makes a difference. When reaching POCs such as large hospitals that require a large variety of drugs, manufacturers can leverage the full spectrum of drugs carried by the WS to offer these POCs the one-stop-shopping convenience. Second, manufacturers value distributors' experiences to perform two essential functions in their decision channel decisions: distribution and critical value-added services such as managing chargebacks and REMS compliance. In distribution, our results show that distributors' efficiency in managing inventory (i.e. inventory turnover) seems to be of less concern to manufacturers, possibly because such logistics services have developed to become a core competency of the businesses and the industry as a whole (WSs and SDs) is doing well. Distributors' ability to manage waste (i.e., spoilage), on the other hand, is more important. In addition, manufacturers value prior relationships with the SD, or even its affiliated WS, when choosing a specific SD.

For distributors: Since the emergence of specialty drugs and SDs, there has been an unresolved question in the industry: "Who [WSs or SDs] will win the battle for control of specialty drugs?" (McCain 2012). Our study sheds some light on the answer to this question. As mentioned, WSs and SDs adopt distinct strategies in balancing access to and control of drugs. WSs and SDs should continue to strengthen their respective competitive advantages while finding creative ways to make up for the less competitive aspects. For example, if WSs want to strengthen their competitive position in distributing specialty drugs, developing controlled networks within WSs may be a straddling strategy that could weaken their advantage in accessibility. Instead, WSs could build SD branches or independently-operated-but-affiliated SDs. According to our Study II results, such WS-affiliated SDs could leverage the relationship inherited from the WS while offering a controlled network for REMS compliance. Further, emerging non-big3 SDs should work harder to develop relationships with manufacturers in order to be competitive. Finally, all distributors, SDs or WSs, should ensure their abilities to perform distribution services (including managing inventory and spoilage) and critical value-added services such as managing chargebacks, because they are valued by the manufacturers.

For downstream POCs: If a regulator mandates REMS with the restrictive access element for a particular drug, the distribution of that drug must be limited to a controlled network and only certified POCs within the reach of authorized distributors can have access to the drug. For POCs excluded from the controlled network, they have to understand that the purpose of such REMS is to protect patients by ensuring the safe use of the drug. Thus, if POCs outside the controlled network want to have access to the drug, they have to prove their capability in prescribing, dispensing, and administering to be included in these controlled networks. Purchasing from an unauthorized secondary distributor is risky.

As the first work to systematically studying distribution channels for specialty drugs, our work has several limitations. First, we do not observe the complete history of manufacturers' distribution channel decisions since the approval of their drugs; hence, we are unable to capture the evolution of drugs'

distribution channels over time. However, when studying a manufacturer's choice of a specific SD, we analyze a limited sample of new drugs approved from 2013-2015. Our main results continue to hold for the new approved drugs. Second, due to data availability, we compare the performances of WSs and SDs at the distributor level in managing inventory turnover and spoilage rate, which is already difficult to obtain. It would be interesting to compare the ultimate patient outcomes, such as the time span from receiving a prescription to filling the script, as a drug is distributed through WS and SD channels. This data is however, very difficult to obtain. Third, in this study, we are not able to obtain data on transportation cost, loss of integrity and counterfeits associated with the WS and SD channels. Measuring the cost and supply chain security of WS and SD channel in terms of these aspects will be worthwhile for future study. Finally, it will be interesting to empirically examine the tradeoff of REMS with restrictive access on loss of accessibility on the one hand and benefits of safe use on the other hand. Given the growing importance of specialty drugs to the pharma industry and to the healthcare sector as a whole, we hope our work will stimulate further studies on the distribution channels of specialty drugs in particular and in the B2B setting in general.

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Tables and Figures

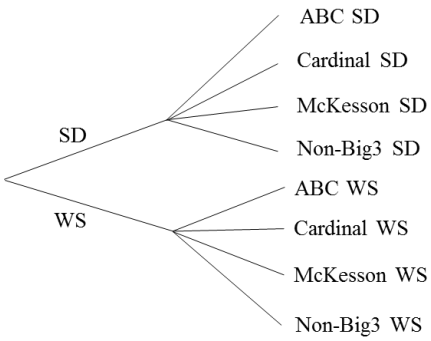

Figure 1: The two-stage nested decision for choosing a distributor

Table 1: Definitions of the control variables

Category	Variables	Descriptions
Drug	$Injectable_i$	A drug is "injectable" if the administration method is subcutaneous, intramuscular, or intravenous, while "oral" otherwise (Conti and Berndt 2016).
	Wac_{it}	The average wholesaler acquisition cost (WAC) of drug i. This is the most typical price measure used in the pharma industry to indicate how expensive a drug is (Ellison and Snyder 2010).
	$Rare_i$	A binary variable to indicate whether a drug is classified as orphan drug. $Rare_i$ accounts for the market size and competition faced by a drug.
	$Age_{i,t}$	The number of years since drug i's approval.
	$VolNDC_{i,t-1}$	The demand of drug i, measured by total volume sold by firm f in period $t-1$.
Firm	$CumPctWS_{fm,t-1}$	The relationship between a manufacturer and WSs, defined as the cumulative percentage of volume sold through WSs up to period $t-1$ in market m divided by the corresponding total cumulative volume sold (similar to Langer et al. 2012).
	$FirmSize_{f,t}$	The firm size, measured by the total volume of drugs sold by firm f.
Market	$MktSize_{m,t}$	The market size, measured by the total volume of drugs sold to market m.
Competition	$CntATC2_{i,t}$	The number of drugs within the same ATC2 code, which captures the competition faced by a drug since drugs within the same ATC2 code usually target similar diseases (Arora et al. 2009).
POC	$Clinic_p$	A binary variable to indicate whether a POC is a clinic.
	$Hospital_p$	A binary variable to indicate whether a POC is a hospital.
	$Pharmacy_p$	A binary variable to indicate whether a POC is a retail pharmacy.

Notes: The variables $VolNDC_{i,t-1}$, $FirmSize_{f,t}$, and $MktSize_{m,t}$ are log transformed when included in the regression models while the other variables are not.

Table 2: Descriptive statistics of all variables

Variable	Obs	Mean	Std. Dev.	Min	Max
PctSD	2,720,953	0.140	0.346	0	1
REMSRestrict	2,720,953	0.078	0.269	0	1
REMSNoRestrict	2,720,953	0.054	0.225	0	1
NoREMS	2,720,953	0.868	0.338	0	1
Clinic	2,720,953	0.265	0.442	0	1
Hospital	2,720,953	0.208	0.406	0	1
Pharmcy	2,720,953	0.526	0.499	0	1
Variety	2,720,953	23.785	25.178	1	244
ChargebackWS	1,237,137	4.401	10.201	0	153
ChargebackSD	1,237,137	0.749	2.857	0	54
CumPctWS	2,136,594	0.809	0.203	0	1
VolNDC	2,720,953	13.930	1.944	1.10	17.94
Wac	2,720,953	456.282	994.969	0	29061
Injectable	2,720,953	0.600	0.490	0	1
Rare	2,720,953	0.113	0.317	0	1
Age	2,720,953	8.920	6.415	0	47.67
CntATC2	2,720,953	76.202	42.003	2	123
MktSize	2,720,953	15.477	0.973	2.30	16.91
FirmSize	2,720,953	17.937	0.753	10.62	18.63
ATC1	A-0.85%; B-13.26%; C-0.06%; G-0.01%; H-5.4%; J-38.81%; L-22.95%; M-4.02%; N-14.29%; V-0.35%				

Table 3: The first stage regression results of the instrument

	Estimates
REMSRestrictIV	1.0528*** (0.0637)
REMSNoRestrict	-0.0017 (0.0068)
Clinic	-6.645e-4 (0.0013)
Hospital	0.0039 (0.0029)
Variety	-4.07e-5 (4.54e-5)
ChargebackWS	8.81e-5 (9.07e-5)
ChargebackSD	-1.803e-4 (2.852e-4)
Firm, Market, ATC1, Year Fixed Effects	Yes
Other Controls	Yes
# of Observations (n)	970,879
Adj R2	0.9834

Note: Values reported are coefficient estimates with standard errors in parentheses. * p<0.05, ** p<0.01, *** p<0.005.

Table 4: IV estimates on factors affecting manufacturers' SD usage

	Model (1)			Model (2)
	(1)	(2)	(3)	(4)
REMSRestrict	0.5966***	0.4282*	0.3394*	-
	(0.1996)	(0.1874)	(0.1633)	-
REMSNoRestrict	-0.0039	-0.0048	0.0149	-
	(0.0623)	(0.058)	(0.0421)	-
Clinic		0.2816 ǂ	0.3375**	0.4381***
		(0.1498)	(0.1217)	(0.1124)
Hospital		-0.0516*	-0.0392*	0.0351
		(0.0254)	(0.0163)	(0.0265)
Variety		-8.09e-4***	-7.08e-4***	-8.56e-4*
		(1.28e-4)	(1.73e-4)	(3.89e-4)
ChargebackWS			-5.56e-4***	-2.72e-4
			(9.0e-5)	(3.95e-4)
ChargebackSD			0.0108***	0.0115*
			(0.0039)	(0.0048)
Firm, Market, ATC1, Year Fixed Effects	Yes	Yes	Yes	Yes
Other Controls	Yes	Yes	Yes	Yes
# of Observations (n)	1,691,411	1,691,411	970,879	540,690
Number of panels	981,119	981,119	534,406	264,097
R2 for overall model	0.2200	0.3775	0.5045	0.4335

Notes: Values reported are coefficient estimates with cluster standard errors (cluster on firm) in parentheses; ǂ p<0.1, * p<0.05, ** p<0.01, *** p<0.005.

Table 5: Number of secondary distributors reached by WS/SD channel

Num. of Secondary Distributors	WS	SD
Medical Supply Distributor	188	33
Wholesaler	127	21
Repackager	26	4
Specialty Distributor	11	2
Export Company	7	2
Reverse Distributor	5	4

Table 6: Nested Logit estimates on factors affecting manufacturers' choices of specific SD

	Nested Logit	(1)
Distributor specific variables	PriorUsage	7.8555***
		(1.1086)
	PriorBranchUsage	3.6333***
		(1.1375)
	ChargebackDistributor	0.0913*
		(0.0446)
	Turnover	-0.0561
		(0.0323)
	Spoilage	-7.7709***
		(0.9336)
	Big3	0.4040
		(0.4613)
Channel specific variables	REMSRestrict	21.6729***
		(1.2777)
	REMSNoRestrict	-29.9943
		(30.3496)
	Clinic	0.8140*
		(0.3415)
	Hospital	-0.4126
		(1.1087)
	Variety	-0.0112***
		(0.0022)
	Firm, Market, ATC1, Year Fixed Effects	Yes
	Other Controls	Yes
	Log pseudolikelihood	-38031.425
	# of Observations (n)	773,400

Notes: The default channel is WS. Values reported are coefficient estimates with cluster standard errors (cluster on firm) in parentheses; * p<0.05, ** p<0.01, *** p<0.005.

Table 7: Marginal effects of selected variables on the likelihood of choosing a specific SD

	SD	ABC SD	McKesson SD	Cardinal SD	Big3	Non-big3 SD
PriorUsage	0.1408	0.2163	0.1276	0.1444	0.1628	0.0750
PriorBranchUsage	0.0661	0.1020	0.0597	0.0676	0.0765	0.0351
Spoilage	-0.1393	-0.2139	-0.1262	-0.1429	-0.1610	-0.0742
ChargebackDistributor	0.0016	0.0025	0.0015	0.0017	0.0019	0.0009
REMSRestrict	0.5283	-	-	-	-	-
Variety	-2.74E-04	-	-	-	-	-

Notes: The table shows the change in the likelihood of a manufacturer's choice of SD channel or specific SD by changing the independent variable by 1. Since *REMSRestrict* and *Variety* are channel-specific, they cannot impact a manufacturer's choice of specific SD. Thus, we can only conduct marginal analysis of *REMSRestrict* and *Variety* on a manufacturer's choice of SD channel but not its choice of specific SD.