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Optimal Policies on Managing Drug Supply and Patient Access to Drugs

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Abstract

Health care decision-makers face several uncertainties regarding pharmaceutical products. For new and expensive drugs, the performance outside of clinical trials could be uncertain. For old and low-profit pharmaceutical products, the supply could be uncertain, causing drug shortages. In three essays, I study mitigating strategies to deal with different types of uncertainties associated with pharmaceutical products.

In the first essay, I compare two types of pharmaceutical reimbursement contracts to mitigate the uncertainties associated with new and expensive drugs. I construct a game-theoretic model to analyze the interactions between a pharmaceutical manufacturer and a payer. The payer's reimbursement of a drug is either related to the cost-effectiveness or the sales volume of the drug in the two contracts, respectively. I find key factors that determine the two parties' preferences for the two contracts. I also find conditions under which each type is preferred by both parties and can achieve a Pareto improvement.

In the second essay, I study mitigating strategies for drug shortage, which has become a serious problem in many countries in recent years. I construct a multi-period supply chain model to analyze the interactions between a representative hospital and an unreliable pharmaceutical manufacturer. The hospital owns an in-house manufacturer and can procure the drug from the two manufacturing facilities. I also assume that the hospital can make emergency production. I study the two parties' procurement and production decisions and examine the impacts of the hospital's optimal decisions on the external manufacturer's profit.

In the third essay, I study mitigating strategies for drug shortages from the governments' perspective. I construct a game-theoretic model consisting of a pharmaceutical manufacturer, a wholesaler, and a government. I compare two types of mitigating strategies that the government can implement: providing subsidies to the wholesaler, or using a government-owned manufacturer. I identify key factors for the

government's preference over the two strategies and examine the impact on the private sector.

The three essays have theoretical contributions to game theory and supply chain risk management literature and have policy implications for policymakers to manage drug supply and patient access to drugs.

Keywords

Healthcare Policies, Pharmaceutical, Uncertainties, Game Theory, Supply Chain Management, Pharmaceutical Reimbursement Contracts, Risk-Sharing Agreements, Drug Shortages, Dual-Sourcing, Contingent Sourcing, Subsidy

Summary for Lay Audience

Health care decision-makers face several uncertainties regarding pharmaceutical products when making decisions. For new and expensive drugs, their performance in the real-world could be uncertain. For old and low-price drugs, there could be manufacturing problems, which may cause drug shortages. In this thesis, I study strategies to deal with different types of uncertainties associated with pharmaceutical products.

In the first essay, I compare two types of drug reimbursement contracts. I assume a drug company is selling a new and expensive drug to treat patients with a disease. A payer (e.g., government drug benefit programs or insurance companies) is considering covering the drug so that patients do not need to pay from their own pockets. However, the payer may have two concerns: 1) the health benefit that the drug can provide to the general patients may be lower than that in the clinical trials; and 2) more drugs may be sold than originally estimated, causing a higher expenditure to the payer. Therefore, the payer is considering two reimbursement contracts in which the payment to the manufacturer is linked to either the health benefit or the sales volume of the drug. We identify circumstances in which both the manufacturer and the payer prefer the same type of contract, which can achieve a win-win situation.

In the second essay, I study mitigating strategies for drug shortages, which has become a serious problem in many countries in recent years. Due to the prevalence of drug shortages of many common drugs, several US hospitals allied and established a manufacturer to produce certain generic drugs to make the drugs more available for patients. Motivated by this initiative, I analyze when the hospitals would benefit from owning a drug manufacturer, and what are the impacts on the external manufacturers.

In the third essay, I study government interventions on mitigating drug shortages. I compare two types of government interventions: providing subsidies or using a public manufacturer. I find that the government should provide subsidies to inexpensive but critical generic drugs without alternatives, and it should use a public manufacturing facility to produce expensive lifesaving drugs.

Co-Authorship Statement

I hereby declare that this thesis incorporates material that is a result of joint research. Essay 1 is co-authored with Dr. Hubert Pun and Dr. Gregory S. Zaric. Essay 2 is co-authored with Dr. Gregory S. Zaric and Dr. Hubert Pun. Essay 3 is co-authored with Dr. Gregory S. Zaric and Dr. Hubert Pun. I am the first author of all three essays. I was in charge of all aspects of the projects, including formulating the research questions, conducting the literature review, research design, model formulation and analysis, and preparing the manuscripts. I certify that this dissertation and the research to which it refers is fully a product of my own work.

Overall, this dissertation includes three original papers, and the first essay is published in an academic conference proceeding.

Essay 1) H. Sun, H. Pun and G.S. Zaric, Value or Volume? A Comparison of Two Risk-sharing Approaches, *Proceedings of the Decision Sciences Institute Annual Meeting 2018* (pp. 2101-2114).

Essay 2) H. Sun, G.S. Zaric and H Pun, Mitigating Drug Shortages: Should Hospitals Use Their Own Drug Manufacturer?

Essay 3) H. Sun, G.S. Zaric and H Pun, Mitigating Drug Shortages: should Governments Use Subsidies or Establish A Public Drug Manufacturer?

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Chapter 1

1 Introduction

Health care decision-makers face several uncertainties regarding pharmaceutical products. For new and expensive drugs, the performance outside of clinical trials could be uncertain. For example, in real clinical practice, the effectiveness of new drugs could be lower than the efficacy observed in clinical trials. This is because clinical tries usually have targeted patients with higher adherence levels (Adamski et al., 2010). Sales volume could be larger than originally anticipated due to factors such as poor forecasts, off-label usage, expansion of indication, and marketing effort by the manufacturers (Zhang et al., 2011). Many payers use a formulary (a list of drugs that will be reimbursed by the payer) to manage and control pharmaceutical spending. However, the uncertainties add significant risks to the payers when making formulary decisions.

To better control pharmaceutical expenditure and manage patient access to drugs in the presence of various uncertainties, there emerged "risk-sharing agreements" between payers and pharmaceutical companies in recent years (Adamski et al., 2010). Under a risk-sharing agreement, the reimbursement price of a drug is related to its performance in the real world. For example, Price-Volume Agreements (PVAs) are widely used in many European counties to deal with sales uncertainties and control financial expenditure. Under a PVA, the manufacturer receives partial or no payment for sales that exceed a pre-agreed volume threshold (Zhang and Zaric, 2015; Zhang et al., 2011). To deal with uncertainty in the effectiveness of new drugs, outcome-based schemes are adopted by payers and health systems. For example, in 2002, the National Institute for Health and Care Excellence (NICE) in UK established an outcome-based contract with pharmaceutical manufacturers for beta interferon to treat multiple sclerosis. According to the agreement, drug manufacturers have to pay refunds to NICE if the cost-effectiveness of the drugs exceeds a threshold value of £35,000/ quality-adjusted life year (QALY) gained (Adamski et al., 2010).

In addition, many old and low-profit drugs, such as generic drugs, are vulnerable

to to supply uncertainties caused by manufacturing problems (e.g., quality problems, production technology malfunction, and production delays) due to low profit margins, complex production processes, and high market concentration (Jia and Zhao, 2017; Malacos, 2019; Woodcock and Wosinska, 2013). For example, saline, the most widely used fluid in medical facilities and hospitals, has experienced several shortages in the US since 2014. Due to the low profit margin, manufacturers' pursuit of economies of scale, and market consolidation, there are only three major saline manufacturers in the US. Most shortages are caused by manufacturing problems such as recalls due to quality issues, and manufacturing delays due to natural disasters at the overseas facilities (Mazer-Amirshahi and Fox 2018). Shortages not only have clinical consequences such as inferior outcomes, increased morbidity and mortality, but also add significant costs to health care systems due to replacement cost and staff time (Alevizakos et al., 2016; Fox et al., 2014; Hedman, 2016). In order to reduce shortages, government agencies, such as the Food and Drug Administration (FDA) in the US, are taking actions to collaborate with the pharmaceutical industry by sharing information, searching for alternative manufacturers, or importing critical drugs in shortage directly from other overseas manufacturers (Food and Drug Administration, 2018). However, drug shortages are still prevalent. For example, in June 2018, the US experienced shortages for 182 drugs and pharmaceutical supplies, affecting all common drug classes (Hoffman, 2018).

To mitigate supply uncertainties, several US hospitals allied and established a not-for-profit pharmaceutical company named "Civica Rx" in 2018 to produce certain drugs (Kodjak, 2018; Tirrell, 2018). By July 2020, more than 50 health systems are members of Civica RX, representing more than 1,200 US hospitals and over 30 percent of all licensed US hospital beds (Civica Rx, 2020). Governments are also important stakeholders in managing drug supply and patient access to drugs. Policymakers proposed various government interventions to mitigate drug shortages such as maintaining public lists of essential drugs with limited supply or expected supply shortages, providing subsidies to those drugs, and producing those drugs at public manufacturers. (MacLeod, 2020; McGinley, 2019; Milne et al., 2017).

In this thesis, I study the optimal policies on managing drug supply and patient access to drugs in the presence of various uncertainties. Using a game-theoretic approach, I study the dynamics of key stakeholders' optimal decisions, and the impacts of the interactions on their welfare. I analyze the efficiency of different drug reimbursement schemes between payers and pharmaceutical companies when the performance of the drug in the real-world is uncertain. I study the efficiency of strategies to mitigate drug shortages from hospitals and governments' perspective, respectively, when the manufacturing process is subject to supply uncertainties. In three essays, I analyze policymakers' optimal policy decisions under different circumstances and the impact of each policy on the benefit of other parties such as the pharmaceutical manufacturers and wholesalers.

Overview of Three Essays

In the first essay, I compare two types of risk-sharing agreement to mitigate uncertainties in new and expensive drugs. Previous studies have investigated the performance of financial-based risk-sharing agreements (Zaric and O'Brien, 2005; Zhang and Zaric, 2015; Zhang et al., 2011) and outcome-based risk-sharing agreements (Antonanzas et al., 2011; Barros, 2011; Mahjoub et al., 2014). There are limited studies that compared different types of risk-sharing agreements. For example, Zaric and Xie (2009) compared two outcome-based agreements, and Levaggi (2014) compared the welfare of a listing process through uncertain bargaining and a value-based pricing agreement with risk-sharing. However, none of these studies compared a financial-based risk-sharing agreement with an outcome-based risk-sharing agreement.

To fill this gap, I construct a game-theoretic model consisting of a payer and a pharmaceutical company to compare a volume-based risk-sharing agreement (PVA) with a value-based risk-sharing agreement (based on the cost-effectiveness of the drug). There are two sequential decisions in the model. First, the payer selects from the two risk-sharing agreements to determine how a new drug will be reimbursed. Next, the pharmaceutical company decides its level of marketing effort that can affect both sales volume and cost-effectiveness of the drug. This study captures two types of uncertainties

that may affect the performance of a new drug: 1) uncertainties in patients' health benefits from the drug, which reflects patients' heterogeneity in response to the same drug; and 2) heterogeneity in physicians' prescribing behavior that can be caused by differences in interpreting clinical guidelines for patient treatment eligibility.

I find that each risk-sharing agreement may or may not be able to align the incentives of the two parties, depending on different circumstances. Under some circumstances, none of the two agreements can be mutually preferred by payers and manufacturers, which may explain the resistance from one party during the implementation, as observed in reality. For example, if the drug price is either low or high, then neither of the risk-sharing agreements could be mutually preferred by the two parties. Under some other circumstances, a properly selected risk-sharing agreement can be mutually preferred by the two parties, which creates a "win-win situation and leads to a smooth implementation. For example, if the drug price is intermediate, then the two parties may prefer the same agreement depending on patient treatment eligibility for the drug (specified in clinical guidelines). Specifically, if a relatively large proportion of patients are eligible for the drug, then both parties may prefer a volume-based policy. If a relatively small portion of patients are eligible for the drug, then a volume-based policy may be mutually preferred by the two parties. Therefore, neither risk-sharing agreement is a universal solution that can be applied in all situations, and payers should not always stick to one type of agreement. For example, some payers prefer to use a volume-based agreement for ease of negotiation and implementation, and this study indicates that payers may be better off by applying a value-based risk-sharing agreement in some cases.

In the second essay, I study the hospital's sourcing strategy and inventory management policies to mitigate drug shortage. Several previous studies investigated sourcing strategies to mitigate supply uncertainties from a single firm's perspective (Tomlin, 2006; Xanthopoulos et al., 2012), and some studies analyzed the interactions between buyer(s) and supplier(s) under supply uncertainty with a single-period setting (He and Zhang, 2008; Keren, 2009; Li et al., 2010; Wang et al., 2010). In this study, I construct a multi-period supply chain model to analyze the interactions between a representative hospital and an unreliable pharmaceutical manufacturer (the external

manufacturer). The hospital owns an in-house manufacturer and can procure the drug from the two manufacturing facilities. I assume the hospital also has a second chance to make emergency production at the in-house producer. I assume the manufacturing process has a random yield rate to capture the main cause of drug shortages, which is manufacturing problems. I analyze the hospital's ordering and production decisions, and the external manufacturer's production decision. First, I analytically characterize the optimal solutions in a single-period setting and generate insights into the structures of the long-term procurement decisions for each party. Next, I propose two long-term inventory management policies and evaluate the performance of the two policies in the multi-period setting with a heuristic.

There are several findings. I find that the expected shortage amount can be reduced if the hospital operates an in-house producer as its regular source or contingent source, indicating the importance of the establishment of additional drug suppliers such as Civica Rx. The hospital would benefit from using the in-house manufacturer to make regular production if the in-house production cost is low, the external manufacturer's yield rate is low, or the external manufacturer's yield is highly uncertain. The hospital should make use of emergency production at the in-house producer if the emergency production cost is relatively low compared with the revenue of the drug and the shortage cost.

The analysis also shows that the two long-term inventory management policies have comparable and relatively high performance for the hospital, indicating that the hospital can use either policy for its long-term inventory management practice. However, the manufacturer's yield rate has a large impact on its performance if one of these inventory management policies is used, indicating that it is beneficial for the manufacturer to make investments on improving its reliability.

In the third essay, I study mitigating strategies for drug shortages from the governments' perspective. I construct a game-theoretic model consisting of a private manufacturer, a wholesaler, and a government. The wholesaler procures the drug from the manufacturing facilities and sells it to the downstream demand, such as hospitals and

pharmacies. I consider two types of government interventions to mitigate drug shortages: establishing a public manufacturer, or providing subsidies to the wholesaler. I construct three models corresponding to three strategies that can be implemented by the government: 1) a basic model (the status quo), in which the government does not intervene; 2) a dual sourcing model, in which the government operates public manufacturer, and the wholesaler can procure the drug from the two manufacturing facilities; and 3) a subsidy model, in which the government provides subsidies based on the wholesaler's unit procurement cost or its unit selling price. I analytically characterize the optimal decision for the three parties and compare their welfare under different strategies.

I show the advantages and disadvantages of each strategy. An advantage of both mitigating strategies is that the shortage amount can be reduced by either strategy compared with the status quo, indicating the positive effect of the two strategies on mitigating shortages. An advantage of a subsidy strategy is that it can align the incentives of all three parties and achieve an "all-win" situation. However, a disadvantage is that the supply chain remains a sole sourcing situation under a subsidy strategy, and is thus more vulnerable to supply uncertainties compared to supply chains with multiple suppliers. In contrast, an advantage of a dual sourcing strategy is that it adds a supplier of the drug, which eases the market concentration and makes the supply chain more reliable and resilient to supply uncertainties. A disadvantage is that a dual sourcing strategy cannot be mutually preferred by all three parties, because the private manufacturer is no better off compared with the status quo. In some circumstances, the wholesaler may prefer to procure everything from the public manufacturer, and the private manufacturer is not making any profit. In this situation, the private manufacturer may exit the market, leaving the public manufacturer the sole supplier of the drug. Therefore, the government and/or the wholesaler may need to provide incentives to the private manufacturer to keep it in the market and maintain the dual-sourcing situation in the long term. I also provide analysis regarding governments' optimal policies to mitigate drug shortages under different circumstances, which has implications for policymakers.

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Chapter 2

2 Essay 1: Value or Volume? A Comparison of Two Risk Sharing Approaches

2.1 Introduction

The large proportion of pharmaceutical spending in both health expenditures and gross domestic product is a big concern in many countries. For example, 20% of health expenditures were spent on pharmaceuticals in Organization for Economic Co-operation and Development (OECD) countries in 2013 (Organization for Economic Co-operation and Development, 2015). Many payers use a formulary (a list of drugs that will be reimbursed by the payer) to manage and contain pharmaceutical spending (Zaric and Xie, 2009).

However, when making formulary listing and reimbursement decisions, there are several uncertainties such as the sales volume or the effectiveness of new drugs. Sales volumes could be larger than originally anticipated due to factors such as poor forecasts, off-label usage, expansion of indication, and marketing effort by the manufacturers (Zhang et al., 2011). The effectiveness of new drugs in real clinical practice could be lower than the efficacy in clinical trials, which usually have targeted patients with higher adherence levels (Antonanzas et al., 2011). To deal with these uncertainties, many payers have adopted risk-sharing agreements under which the reimbursement for a pharmaceutical product is related to its performance in real-world settings (Adamski et al., 2010).

Although the uncertainties in both sales volume and health outcome co-exist in many situations, we are not aware of any direct theoretical comparisons between sales volume-based and health outcome-based contracts. Our study intends to fill an important gap by comparing the performance of a sales volume-based agreement and a cost-effectiveness-based agreement to provide theoretical foundations for selection and decision making in the future. We focus on the comparison between a sales volume-based agreement and a value-based cost-effectiveness rebate.

To control financial expenditure, a price-volume agreement (PVA) uses a sales threshold, and manufacturers must pay a partial or full rebate to payers for excessive sales over the threshold. These contracts are widely used in Australia and many European countries (Adamski et al., 2010). To manage the uncertainties in health outcomes, a value-based cost-effectiveness rebate (CER) specifies a cost-effectiveness threshold and manufacturers pay rebates to payers if the drug fails to meet the benchmark (Adamski et al., 2010). A well-known example of this type of plan was in the listing for Multiple Sclerosis drugs in the UK (Palace et al., 2015). These risk-sharing agreements are expected to help payers control pharmaceutical spendings, increase "value for money", and also facilitate earlier patient access to breakthrough drugs and treatments.

Several studies have investigated the performance of a PVA (Zaric and O'Brien, 2005; Zhang and Zaric, 2011, 2015; Zhang et al., 2011) and some examined the efficiency of a CER (Antonanzas et al., 2011; Barros, 2011). Limited studies compared different types of risk-sharing agreements. For example, Zaric and Xie (2009) compared two cost-effectiveness-based agreements and showed that the optimal agreements for the two parties depend on several factors and neither of them is always preferred by either party. (Levaggi, 2014) compared the welfare of a listing through an uncertain bargaining process and a value-based pricing agreement with risk sharing, and showed that the total welfare is always better under a value-based pricing scheme but the distribution of the benefits between consumers and the manufacturer depends on the rebate rate.

We are not aware of any direct comparisons between a sales volume-based and a health outcome-based agreement. In this study, we construct a game-theoretical model consisting of a manufacturer and third-party payer to compare the desirability of a PVA and a CER by the two parties. It should be noted that the two contracts under comparison are not always applicable in reality. For example, a CER is not an option when outcome is not measurable. However, our study intends to provide insights into situations where both contracts are available options and need to be compared. We model the manufacturer's marketing efforts explicitly as it can significantly affect both the cost-

effectiveness and the sales volume of a new drug. To our knowledge, our study is the first modelling paper on the theoretical comparison of the two risk-sharing approaches.

2.2 Literature Review

We first survey theoretical studies on health-outcome based risk-sharing agreements. Zaric and Xie (2009) compared two risk-sharing agreements (a delisting scheme and a rebate scheme) based on the effectiveness of a new drug by modelling a manufacturer's optimal decisions on the drug price and marketing effort. The authors reported that the performance of the two schemes depends on several factors and none of them is always preferred by the manufacturer or the payer. Two studies (Antonanzas et al., 2011; Barros, 2011) analyzed the performance of health-outcome based risk-sharing agreements based on patient level effectiveness. Barros (2011) modeled the interaction between a manufacturer and a payer with and without a risk-sharing agreement. the manufacturer decides the drug price whereas the payer decides patient eligiblity for a new drug through a cutoff threshold on the effectiveness of the drug. The author found that too many patients may be treated under a risk-sharing agreement, and social welfare may decrease if the manufacturer anticipates a future risk-sharing agreement while deciding the drug price. Antonanzas et al. (2011) constructed a Nash-bargaining game with risk-sharing agreement in which the price of a new drug is negociated between a manufacturer and a payer depending on their bargaining power. The authors found that fewer patients are treated under a risk-sharing agreement, which is in contrast to the results in Barros (2011). The authors also concluded that the optimal contract depends on factors such as monitoring costs, the marginal production cost, etc. However, none of the above studies on health-outcome based risk-sharing agreements considered comparison with financial-based risk-sharing agreements, leaving an important theoretical gap.

Next, we investigate non-modeling literature on success factors, challenges, barriers, and other aspects of risk-sharing agreements. Several studies constructed taxonomy to categorize existing risk-sharing agreements (Adamski et al., 2010; Carlson et al., 2010; Garrison et al., 2013; Towse and Garrison, 2010). Some studies summarized challenges of risk-sharing agreements such as high administration cost, low transparency, lack of data collecting infrastructure, the additional burden to the existing health care

systems, and conflict of interests (Adamski et al., 2010; McCabe et al., 2010; Stafinski et al., 2010; Towse and Garrison, 2010).

Our study extends the literature by comparing the performance of two different types of risk-sharing agreements while taking into account the manufacturer's decision on marketing effort after a reimbursement scheme is signed. To our knowledge, our study is the first theoretical comparison between a financial-based risk-sharing agreement with a health-outcome based risk-sharing agreement, which fills an important gap in the existing literature.

2.3 Model

We construct a game-theoretic model to analyze the interactions between a payer and a pharmaceutical manufacturer (referred to as the manufacturer). We assume that the manufacturer received regulatory approval to sell a new drug, and the payer is considering listing the drug on its formulary. To manage the uncertainties in the sales volume and cost-effectiveness of the new drug, the payer is considering choosing from two risk-sharing agreements: a price-volume agreement (referred to as PVA, and a value-based cost-effectiveness rebate (referred to as CER). Let i be the index for the two risk-sharing agreements, $i \in \{PVA, CER\}$. All model notation is summarized in Table 2.1.

We normalize the size of the patient population to one. Let $\beta \geq 0$ be the incremental health benefit for a patient using the new drug compared with the current standard of treatment. The units of β could be quality-adjusted life years (QALYs), life years (LYs) or any other units that the payer cares about. We assume that β is a random variable distributed on the interval $\left[\underline{\beta},\ \overline{\beta}\right]$, according to a probability density function (PDF) $f(\cdot)$ and a cumulative distribution function (CDF) $F(\cdot)$. The randomness of β captures patients' heterogeneity in the incremental health benefit that may be attributed to patient characteristics (e.g., age, gender, health condition) or other factors. Let λ be the payer's willingness to pay for each unit of the incremental health benefit.

We assume that the payer applies a threshold policy to determine the treatment eligibility (i.e., the prescribing criteria) for the new drug: there is a threshold of the

Table 2.1: Summary of notation

Decisions	
m	The manufacturer's marketing effort
i	The payer's choice of the risk-sharing agreement, $i \in \{PVA, CER\}$
Random Variable	
β	Incremental health benefit per patient under the new drug compared with the current standard treatment
ϵ	Heterogeneity in doctors' prescribing behavior
Parameters	
$\underline{\beta}, \overline{\beta}$	Lower bound and upper bound of β
$f(\cdot), F(\cdot)$	PDF and CDF of β
λ	Payer's willingness to pay threshold
y	Treatment eligibility threshold of the new drug, i.e., the lower bound of incremental health benefit for patients who are eligible for the new drug
$\underline{\epsilon}, \overline{\epsilon}$	Lower bound and upper bound of ϵ
$g(\cdot), G(\cdot)$	PDF and CDF of ϵ
k	Parameter of the efficiency of the marketing effort in the cost function
p	List price of the new drug
c_M	Manufacturer's marginal production cost per unit of drug
c_P	Payer's non-drug related cost per unit of drug
a_P^i	Payer' implementation cost of contract i per unit of drug
x	Volume threshold for rebate in a PVA
Calculated Quantities	
Q	Expected total sales of the new drug.
B	Expected total health benefit of the new drug
S^i	Expected total rebate in contract i
π_M^i	Manufacturer's expected profit
π_P^i	Payer's expected payoff
Other notation	
$*$	Superscript for optimal value

incremental health benefit (referred to as the treatment eligibility threshold), y, such that all patients with $\beta \geq y$ will be treated with the new drug, and patients with $\beta < y$ will be treated with the current standard of treatment. We assume that the treatment eligibility threshold is specified in a clinical guideline that has been determined by a third-party organization, which is exogenous to our model and does not depend on other parameters. For example, in the risk-sharing agreement for four Multiple Sclerosis (MS) drugs in the UK established in 2002, the government agreed to fund the drugs to treat MS patients according to the guideline set by the Association of British Neurologists (ABN) in 2001 (Adamski et al., 2010). According to the ABN guideline, up to 30% of the MS patients could be eligible for the drugs (Sudlow and Counsell, 2003), i.e., not all patients with a

positive incremental health benefit are eligible for the new drugs. According to the appraisal by National Institute for Health and Care Excellence (NICE), the drugs are not cost-effective based on the ABN guideline, i.e., the ABN guideline is focused on clinical benefits instead of the cost-effectiveness or the price of the drugs.

We assume that physicians can observe the incremental health benefit for each patient (i.e., the realization of β) prior to the prescribing decision through diagnostic tests or observations. However, two factors may affect the actual patient eligibility, i.e., whether a patient will be treated with the new drug or not. The first factor is heterogeneity in physicians' prescribing decisions, which can be caused by differences in physicians' interpretations of clinical guidelines, situations that are not adequately captured by clinical guidelines, and physicians' attitudes to risks and benefits (Lugtenberg et al., 2009; Multiple Sclerosis Trust, 2019; Riggs and Ubel, 2015). Therefore, some physicians may prescribe the new drug to patients who are not eligible according to the clinical guideline, whereas others may prescribe the new drug more strictly. Let a random variable ϵ capture the heterogeneity in physicians' prescribing behavior, which is distributed on the interval $[\underline{\epsilon}, \overline{\epsilon}]$, $\overline{\epsilon} \geq 0$, according to a PDF $g(\cdot)$ and a CDF $G(\cdot)$.

The second factor that may affect the actual patient eligibility is the manufacturer's marketing effort, $m > 0$. Typical marketing effort includes physician detailing, direct-to-consumer advertising, and professional meetings (Hébert and Stanbrook, 2007; Mizik and Jacobson, 2004). The marketing effort incurs a cost km^2, where k is the efficiency parameter of the marketing effort. Similar to some other studies (Tirole, 1990; Zhang and Zaric, 2015), the cost function in our study has the following properties: 1) the marketing effort can only increase sales; 2) there are diminishing marginal returns in the marketing effort; and 3) no cost will occur without any marketing effort.

Without any marketing effort, patient treatment eligibility, $y + \epsilon$, is a random variable subject to heterogeneity in physicians' prescribing behavior. The manufacturer's marketing effort shifts the patient treatment eligibility from $y + \epsilon$ down to $y - m + \epsilon$,

causing physicians to prescribe the new drug to some patients who are not eligible according to the original clinical guideline. In other words, the marketing effort only affects the mean of the physicians' prescribing behavior, but it does not change the variance of the physicians' prescribing behavior. Let $\theta = \min\left\{\max\left\{y - m + \epsilon, \underline{\beta}\right\}, \overline{\beta}\right\}$. Let q and b be the total sales and total health benefit of the drug subject to the random ϵ, respectively, where $q = \int_{\theta}^{\overline{\beta}} f(\beta)d\beta$ and $b = \int_{\theta}^{\overline{\beta}} \beta f(\beta)d\beta$. Let E_ϵ denote the expected value over ϵ. The expected total sales volume $Q = E_\epsilon[q]$ and the expected total health benefit of the drug is $B = E_\epsilon[b]$. We assume that each patient consumes one unit of the new drug if prescribed.

Let p and c_M, $p > c_M > 0$, be the price and the manufacturer's marginal production cost per unit of the drug, respectively. Let c_P be the payer's non-drug-related incremental cost per unit of the drug, which could be positive or negative. A negative c_P indicates that the new drug causes a reduction in non-drug healthcare expenditures. For example, the drug may prevent or delay expensive surgeries or prevent infections that are expensive to treat. A positive c_P indicates that the new drug causes an increase in non-drug healthcare expenditures. For example, it may be necessary to administer the drug in a hospital or spend time in a hospital to treat a drug reaction. Let a_P^i be the administration cost for implementing contract i, which is assumed to be fully borne by the payer. The payer's monetary benefit is $MB = \lambda b - (p + c_P + a_P^i)q$. The first term λb denotes the monetary value that the payer attached to the total incremental health benefit of the new drug. The second term $(p + c_P + a_P^i)q$ is the total costs incurred to the payer.

Let s^i be the rebate from the manufacturer to the payer under contract i. In a PVA, a sales volume threshold x is predetermined in the contract, and we assume that the manufacturer must pay a full rebate to the payer for the excess of sales, i.e. $S^{PVA} = \max\{0, p(q - x)\}$. In a CER, there is no rebate when $MB \geq 0$, and the manufacturer must fully compensate the payer's loss if $MB < 0$, i.e. $s^{CER} = \max\{0, (p + c_P + a_P^{CER})q - \lambda b\}$. Let S^i be the expected value of s^i over ϵ, i.e., $S^i = E_\epsilon[s_i]$.

Let π_P^i and π_M^i be the payer's and the manufacturer's expected payoff under contract i, which are calculated as follows.

$$\pi_P^i = \lambda B - (p + c_P + a_P^i)Q + S^i \quad (2.1)$$

$$\pi_M^i = (p - c_M)Q - km^2 - S^i \quad (2.2)$$

We assume that the payer first chooses the risk-sharing agreement i to maximize her expected payoff, and then the manufacturer chooses the marketing effort, m, to maximize his expected payoff. The payer will choose a PVA if her expected payoff in a PVA is greater than the payoff in a CER, i.e. $i_P^* = PVA$ if $\pi_P^{PVA*} \geq \pi_P^{CER*}$, and vice versa. Similarly, the manufacturer prefers a PVA if the expected payoff in a PVA is greater than the payoff in a CER, i.e. $i_M^* = PVA$ if $\pi_M^{PVA*} > \pi_M^{CER*}$, and vice versa. We do not consider any participation constraint for the payer as her payoff is always non-negative in a CER according to the setup of the rebate, and therefore π_P^{CER} could be considered as the reservation payoff for the payer.

2.4 Analysis

In this section, we analytically characterize the optimal decision and payoff for each party. We assume that β is uniformly distributed on the interval $[0,1]$ and ϵ is uniformly distributed on the interval $[-\bar{\epsilon}, \bar{\epsilon}]$, $\bar{\epsilon} > 0$. We also verify that the main results hold with other distributions such as normal distributions and beta distributions. We assume that the rebate threshold in a PVA is exogenously set equal to the expected sales (i.e. $x = Q$) because many PVAs in reality set the volume limit based on anticipated expenditure (sales) (Adamski et al., 2010).

We first derive the closed-form solutions of the manufacturer's optimal marketing effort and the optimal payoff for the two parties under each risk-sharing agreement. Next, we examine the optimal risk-sharing agreement with respect to some key parameters. We also show the manufacturer's preference for the risk-sharing agreement, which may impact the implementation of the scheme in reality. Due to the complex expression of the optimal payoffs, we show the preferred risk-sharing agreement for the two parties using numerical examples.

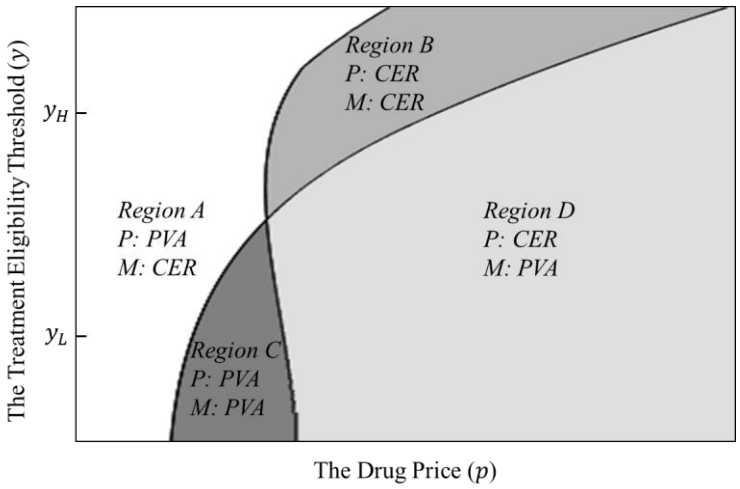

Figure 2.1: Policy graph of the risk-sharing agreement preferred by the payer and the manufacturer. In each region, the first row is the payer's preferred risk-sharing agreement, and the second row is the manufacturer's preferred risk-sharing agreement. y_L and y_H represent a board treatment eligibility and a targeted treatment eligibility, respectively, which are used in Figure 2.2 and Figure 2.3.

Let superscript $*$ denote the optimal solutions. The closed-form solutions for the manufacturer's optimal marketing effort (m^*) and the optimal payoff for the two parties under agreement $i \in \{PVA, CER\}$ (i.e., π_P^{i*} and π_M^{i*}) are summarized in Table A.1 and Table A.2 in the appendix.

Next, we show the preferred risk-sharing agreement for the two parties numerically using parameter values $\lambda = 50000, \overline{\epsilon} = 0.1, c_M = 5000, c_P = 500, a_P^{PVA} = 200, a_P^{CER} = 1000$ and $k = 10000$. We also perform robustness checks using different values of the administration costs, which are one of the major concerns of implementing a risk-sharing agreement (Adamski et al., 2010), and our results are qualitatively robust over a wide range of values.

Preliminary analysis demonstrates that the optimal solutions are sensitive to the drug price (p) and the treatment eligibility threshold (y). Therefore, we shows a two-way policy graph of the risk-sharing agreement preferred by the two parties with respect to p and y in Figure 2.1. Figure 2.1 indicates that with a sufficiently low drug price, the payer prefers a PVA, but the manufacturer prefers a CER (Region A). When drug price is

sufficiently high, the payer prefers a CER, but the manufacturer prefers a PVA (Region D). When drug price is intermediate, the two parties may prefer the same risk-sharing agreement. For example, both parties prefer a PVA when treatment eligibility is broad (i.e., y is low; Region C); and both parties prefer a CER when treatment eligibility is targeted (i.e., y is high; Region B).

To explain the logic behind Figure 2.1, we present additional details in Figure 2.2 and Figure 2.3 with different values of y (i.e., y_L and y_H in Figure 2.1). Figure 2.2 shows the optimal values for the manufacturer's marketing effort (m^*) and several calculated quantities (Q^{i*}, B^{i*} and S^{i*}, $i \in \{PVA, CER\}$) with respect to the drug price (p). Figure 2.2.a and b show that with both broad (y is small) and targeted (y is large) treatment eligibilities, the optimal marketing effort in a PVA is greater than that in a CER ($m^{PVA*} > m^{CER*}$), the optimal marketing effort in a PVA is increasing in the drug price, and the optimal marketing effort in a CER is non-monotonic (increasing then decreasing) in the drug price. Figure 2.2.c to f show that the optimal total sales (Q^{i*}) and health benefit (B^{i*}) of the new drug have the same trend as the optimal marketing effort.

Figure 2.2.g and h show that the optimal rebate in a PVA is always positive ($S^{PVA*} > 0$). This is because the manufacturer pays a rebate to the payer when there are excessive sales, but it does not receive any reward from the payer if the total sales is below the volume threshold. The optimal rebate in a CER is zero ($S^{CER*} = 0$) when drug price is sufficiently low, and it is positive ($S^{CER*} > 0$) and increasing rapidly in drug price when drug price is sufficiently high. This is because when drug price is low, there is a higher chance that the monetary value of the total health benefit exceeds the payer's costs ($\lambda b > (p - c_P - a_P^{CER})q$) so that the manufacturer does not pay a rebate. In other words, the optimal rebate in a PVA is less than that in a CER ($S^{PVA*} < S^{CER*}$) when drug price is low, and the optimal rebate in a PVA is greater than that in a CER ($S^{PVA*} > S^{CER*}$) when drug price is high. Because the rebate can be considered as the payer's revenue and the manufacturer's cost, the payer prefers a PVA and the manufacturer prefers a CER when drug price is low, and the payer prefers a CER and the manufacturer prefers a PVA when drug price is high (this can be seen from Figure 2.1 and Figure 2.3).

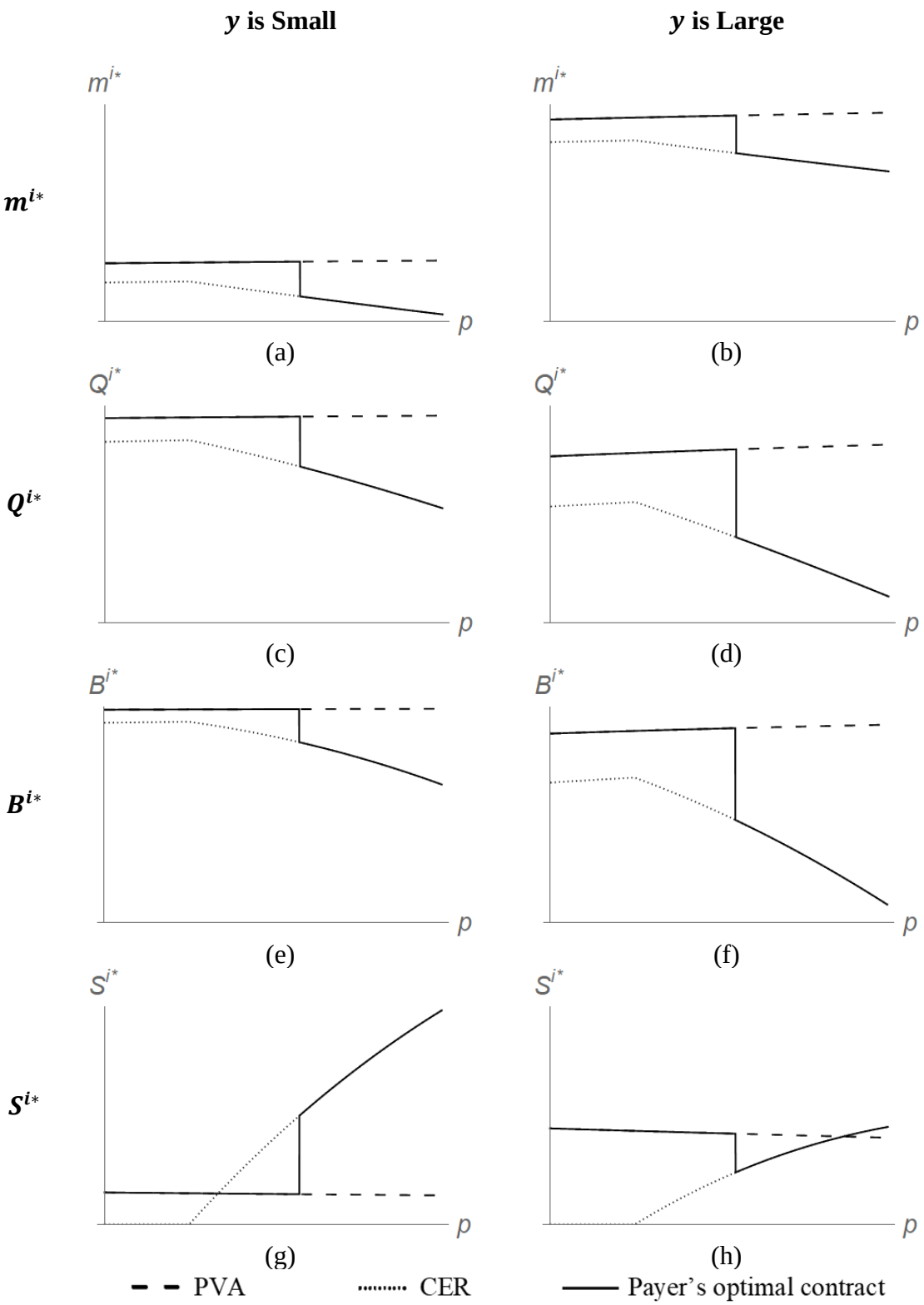

Figure 2.2: Optimal values with respect to the drug price (p). (a), (c), (e) and (g): the treatment eligibility (y) is small, i.e., $y = y_L$ in Figure 2.1; (b), (d), (f) and (h): y is large, i.e., $y = y_H$ in Figure 2.1.

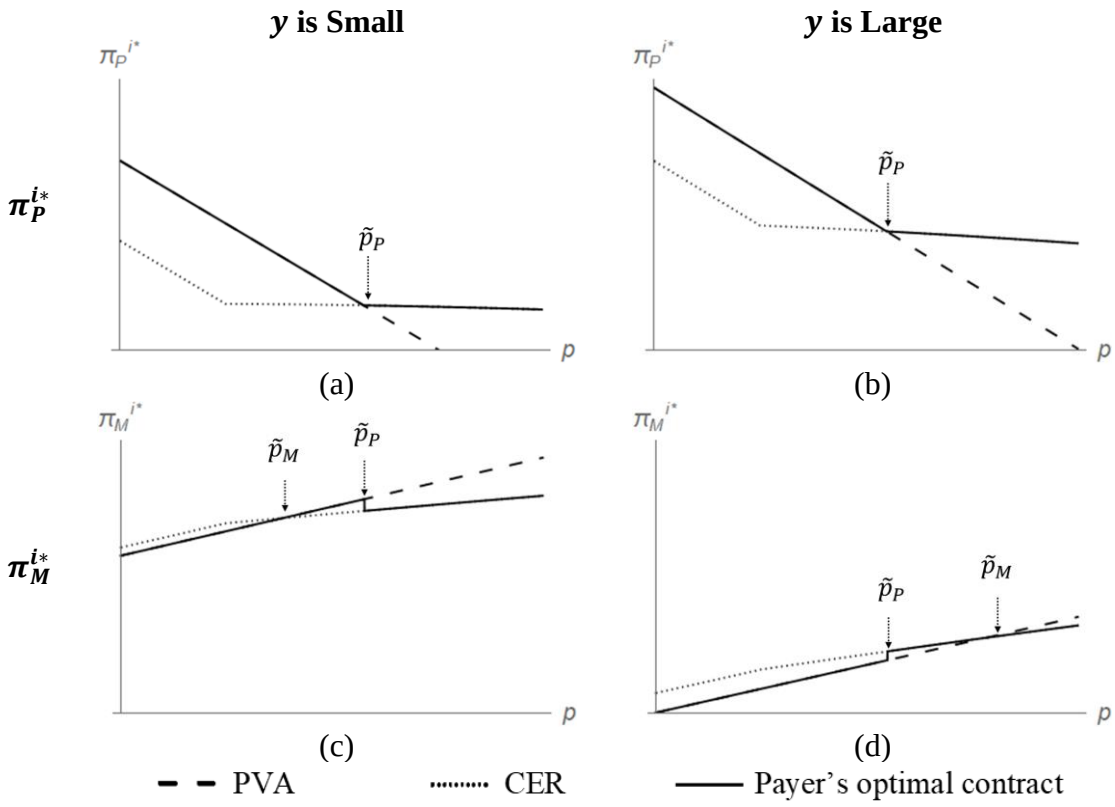

Figure 2.3: The optimal profits for the two parties (π_P^{i*} and π_M^{i*}, $i \in \{PVA, CER\}$) with respect to the drug price p. (a) and (c): the treatment eligibility (y) is small, i.e., $y = y_L$ in Figure 2.1; (b) and (d): y is large, i.e., $y = y_H$ in Figure 2.1.

Figure 2.3 shows the optimal payoff for the two parties (π_P^{i*} and π_M^{i*}) with respect to the drug price. Let $\tilde{p}_P$ be the payer's switching price where the payer's preferred contract switches from a PVA to a CER. Let $\tilde{p}_M$ be the manufacturer's switching price where the manufacturer's preferred contract switches from a CER to a PVA. Define switching patients as patients who are not eligible for the new drug according to the clinical guideline but are treated with the new drug due to marketing effort, i.e., patients with an incremental health benefit $\beta \in [y - m, y)$. With a broad treatment eligibility, the total incremental health benefit from the switching patients is small, which reduces the manufacturer's switching price and creates a range for a PVA to be preferred by the two parties. With a targeted treatment eligibility, the total incremental health benefit from the switching patients is large. This allows a health outcome-based contract to be preferred

by the manufacturer up to a higher switching price, which creates a range for a CER to be preferred by the two parties.

We perform robustness checks on the assumptions made for model tractability. When relaxing the assumption on a bounded uniform distribution and assuming a normal distribution for β and ϵ, the general insights are the same as presented here. If the administration cost is sufficiently high, then there is no region where both parties prefer a PVA, and the general insights for the other three regions remain the same.

2.5 Discussion

In this article, we compare the performance of a sales volume-based agreement and a cost-effectiveness-based contract between a payer and a manufacturer as uncertainties in sales volume and cost-effectiveness co-exist in many situations. We find the conditions under which the two parties agree or disagree on the preferred contract. Our study suggests that neither of the two risk-sharing agreements is always preferred by both parties. In general, the payer prefers a PVA but the manufacturer prefers a CER when price is much lower than the payer's willingness to pay. With a sufficiently high drug price, the payer prefers a CER but the manufacturer prefers a PVA. When price is intermediate, the two parties may prefer the same contract depending on the combinations of parameters. For example, both parties may prefer a CER with a broad treatment eligibility and prefer a PVA with a targeted treatment eligibility.

As observed, the two parties may prefer the same contract under certain circumstances. When choosing properly under these circumstances, a risk-sharing agreement can re-distribute risks between the two parties and create an all-win situation: for the payer, both the total health benefit and the cost to the health care system are taken into consideration and maximized; for the manufacturer, market access is accelerated, profit and the resulting incentives for future investment in new drug development are protected; for the patients, as some payer may only list a drug on the formulary with a risk-sharing agreement (Morgan, Thomson, Daw, & Friesen, 2013) due to unforeseeable risks and health budget constraints, such a contract also accelerates patients' access to new drugs and improve patients' welfare.

An important policy implication is that neither risk-sharing agreement is a universal solution that can be applied in all situations, and payers should not always stick to one type of agreement. For example, some payers prefer to use a volume-based agreement for ease of negotiation and implementation, and this study indicates that payers may be better off by applying a value-based risk-sharing agreement in some cases.

There are some limitations to this study. We compare a value-based risk-sharing agreement (a CER) and a volume-based risk-sharing agreement (a PVA). Future studies may consider other types of risk-sharing agreements to increase options for the two parties. We assume the price is set exogenously, but it could be negotiated between the two parties or a decision variable of either party depending on their power. We assume all parameters are publicly known and did not consider any information asymmetry. However, some key parameters of the health benefit could be one party's private information. For example, the manufacturer may have a better knowledge of the type of distribution of health benefit through clinical trials, or the payer may have a better knowledge of the information through investigation or research. We assume the sales limit in a PVA is set equal to the expected sales. Future studies may consider other forms or treat it as either party's decision. We assume that the treatment eligibility is set in clinical guidelines by a third-party organization and it is an exogenous parameter that does not depend on other parameters. One possible extension is to assume that the treatment eligibility threshold depends on the drug price or to endogenize the treatment eligibility threshold as the payer's decision.

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Chapter 3

3 Essay 2: Mitigating Drug Shortages: Should Hospitals Use Their Own Drug Manufacturer?

3.1 Introduction

Drug shortages are a significant problem in many countries in recent years (Hall et al., 2013). In 2018, the FDA in the US stated that there is an increase in drug shortage occurrences as well as a spike in the intensity and duration of each shortage (Brennan, 2018), and the American Medical Association (AMA) declared that drug shortages pose an urgent public health crisis (American Medical Association, 2018). According to the American Society of Health-System Pharmacists, the US experienced shortages for 182 drugs and pharmaceutical supplies in June 2018, including IV bags, injectable painkillers, anesthetics, and cancer drugs. Drug shortages not only have clinical consequences such as inferior outcomes, increased morbidity and mortality, but can also add significant costs to health care systems due to replacement cost and staff time (Alevizakos et al., 2016; Fox et al., 2014; Hedman, 2016).

Shortages are caused by a variety of factors, such as manufacturing problems (e.g., quality problems, production delays), natural disasters, difficulties in acquiring raw materials, sudden increases in demand, and discontinuation by a manufacturer (De Weerdt et al., 2015; Fox et al., 2014; Malacos, 2019). According to the University of Utah Drug Information Service, among all the drug shortages in the United States in 2018, 51% of the causes are unknown, 30% of shortages are caused by manufacturing reasons, and other direct causes account for smaller proportions ranging from 1% to 10% (Malacos, 2019). Shortages may also be caused by underlying factors such as low-price and low-profit margin (e.g., generic drugs), production difficulties, regulatory issues, and high market concentration (Blank, 2018; Chabner, 2011; Jia and Zhao, 2017; Woodcock and Wosinska, 2013).

To mitigate drug shortages, government agencies, such as the FDA in the US, are

taking actions to collaborate with the pharmaceutical industry by sharing information, searching for alternative manufacturers, or importing critical drugs in shortage directly from other overseas manufacturers (Food and Drug Administration, 2018). However, drug shortages are still prevalent, even for some commonplace generic drugs and lifesaving drugs. Several US health organizations have formed an alliance and established a not-for-profit generic drug company named "Civica Rx" (https://civicarx.org/) in 2018, to manufacture certain generic medicines (Kodjak, 2018; Tirrell, 2018). In December 2019, 18 Civica Rx medications are in production, and more than 45 health systems are members of Civica Rx, representing more than 1,200 US hospitals and over 30 percent of all licensed US hospital beds (Civica Rx, 2019, 2020). This might be a potential way to ease the market concentration on the generic drug market and serve as an additional source or redundancy for drug supply.

Motivated by this initiative, our research investigates circumstances under which hospitals would benefit from owning an in-house pharmaceutical manufacturer, and the impacts on the external manufacturers. We formulate the problem using a supply chain management framework. We assume that drug shortages are a result of supply uncertainty at manufacturing facilities, since manufacturing problems are a major cause of drug shortages. We focus on hospital' sourcing strategies to mitigate drug shortages.

There has been substantial research on mitigating supply disruptions with different sourcing strategies in both pharmaceutical and non-pharmaceutical supply chains. However, the majority of studies have focused on buyers' decisions, and ignore the interactions between suppliers and buyers. In the setting of the establishment of Civica Rx, due to the large number of hospitals in the alliance and their potential influential power in the supply chain, we decide to construct a model to analyze the interactions between the hospitals and the external pharmaceutical manufacturers. In our model, we assume that a hospital, representing the alliance of all hospitals who established Civica Rx, could procure a drug through two sources (dual-sourcing): an external pharmaceutical manufacturer, and a hospital-owned manufacturer (referred to as the in-house producer). We also assume that the hospital has a second chance to make emergency production (contingent sourcing) if needed. Our assumption on a single

external pharmaceutical manufacturer is due to the high market concentration on the generic drug market, and often there are very few or even a single manufacturer producing a particular generic drug in the US market (Blank, 2018).

We analyze the hospital's ordering and production decisions and the external manufacturer's production decision with the presence of supply uncertainty. We first solve a single-period model analytically. We then propose two long-term inventory management policies (a Target Inventory Policy and a Scale Factor Policy), and we evaluate the performance of the two policies in the multi-period setting with a heuristic.

Our study reveals several findings. First, the hospital would benefit from using an in-house manufacturer to make regular production if the in-house production cost is low, the external manufacturer's yield rate is low, or the external manufacturer's yield is highly uncertain. Second, the hospital should make use of emergency production at the in-house producer, if the emergency production cost is relatively low compared with the revenue of the drug and the shortage cost. Third, we show that the expected shortage quantity can be reduced if the hospital operates an in-house producer as her regular source and/or contingent source.

In addition, the analysis shows that the two inventory management policies (the Target Inventory Policy and the Scale Factor Policy) have a comparable performance for the hospital. Both policies perform well under different parameters of the yield rate, indicating that the hospital can use either policy as the long-term inventory management policy. In contrast, the manufacturer's yield uncertainty has a larger impact on its own profit than that on the hospital's profit in the long term. If the yield rate decreases (i.e., the mean of yield rate decreases) or the yield uncertainty increases (the variance of yield rate increases), then the manufacturer's long-term profit under each inventory management policy decreases more rapidly than the hospital's profit does. This means that it is beneficial for the manufacturer to make investments in improving his yield rate and reliability.

Our study has important implications for hospitals' drug procurement practices. Our analysis indicates that hospitals should trade-off between the procurement cost and

other factors (e.g., shortage cost of the drug, and reliability of different suppliers), instead of focusing only on procurement costs to choose the cheapest supplier, as observed in drug procurement practices in reality. Considering the long-term impact on the external manufacturers and the drug supply chain, hospitals should also procure drugs from both the internal and external manufacturers to avoid driving out the external manufacturers from the market.

3.2 Literature Review

Many early studies (e.g., Gerchak et al. (1988) and Henig and Gerchak (1990)) showed that the optimal periodic review policy in the presence of yield uncertainty is non-order-up-to type, which requires different analysis from the models in which only demand is uncertain. Therefore, we investigate studies explicitly dealt with supply uncertainties. We survey three streams of literature: (1) mitigating supply uncertainty with lot sizing and sourcing strategies; (2) supply uncertainty with multiple decision-makers; (3) drug shortages from a pharmaceutical supply chain perspective. Literature that falls in two or more categories will be included in the most relevant category.

3.2.1. Mitigating supply uncertainty with lot sizing and sourcing strategies

Yano and Lee (1995) provided a comprehensive review of lot-sizing problems with yield uncertainty, including different types for yield randomness (binomial, stochastically proportional, and interrupted geometric, etc.) and different time horizons (single-period, multi-periods). Khouja (1999) summarized extensions for single period newsvendor problem (random demand) in 11 categories, including extensions to random yields. Agrawal and Nahmias (1997) studied the optimal order size and the optimal number of suppliers under deterministic demand and yield uncertainty. Their model addressed a key trade-off: small order from many suppliers can reduce yield uncertainty, but fixed costs associated with each supplier provides a penalty for having a large number of suppliers.

Inderfurth (2004) studied a single-period inventory problem with random yield and random demand, and the author derived analytical solutions with uniform

distributions. The study found that depending on the parameter combinations, the optimal policy can be a non-linear type. Rekik et al. (2007) extended Inderfurth (2004) by considering two types of errors: additive errors and multiplicative errors. The authors stated that results in earlier literature are only valid for a certain range of parameters, and they derived closed-form solutions for all values of parameters with the uniform distribution. Tomlin (2006) studied a firm's optimal sourcing strategy for mitigating supply disruption, which is similar to our study and will be elaborated in section 3.2.4.

Li et al. (2010) studied a single period supply chain with a single retailer and two suppliers with supply disruption. This study is also similar to our study and will be elaborated on in section 3.2.4. Xanthopoulos et al. (2012) studied a single-period newsvendor-type (stochastic demand) model with dual-sourcing supply chain with or without service level constraints. The authors studied a retailer's optimal sourcing strategy from two suppliers both of whom are susceptible to supply disruption risk and examined both risk neutral and risk-averse decision-makers. Hou et al. (2017) studied a single period model consists of a buyer, a main supplier and a backup supplier. The main supplier is prone to supply disruption, and the buyer could sign a capacity reservation contract with the backup supplier to mitigate supply risk. This study also has the feature of multiple decision-makers.

3.2.2. Supply uncertainty with multiple decision-makers

Many studies on supply uncertainty focus on the optimal decision(s) by a single decision-maker. Since we study the interaction between a hospital and an external manufacturer in our model, we also survey supply uncertainty with multiple decision-makers. He and Zhang (2008) studied supply chain with one supplier and one retailer under random yield and random demand. The authors proposed several risk-sharing contracts and found that under certain conditions, random yield may enhance the supply chain performance and decrease the double marginalization effect. Keren (2009) studied a two-tier supply chain with one retailer and one supplier with supply uncertainty, which will be discussed and compared with our study in section 3.2.4.

Güler and Keskin (2013) analyzed supply chain coordination under random yield and random demand. They found that the randomness in the yield does not change the coordination ability of the contracts, including wholesale price, buy-back, revenue share, quantity discount, and quantity flexibility, but affects the values of the contract parameters. Chen and Yang (2014) studied a supply chain in which a buyer procures from a supplier with a random yield and has an opportunity to source from an emergency backup supplier. The authors developed two Stackelberg games: a buyer-Stackelberg model (the buyer moves first) and a supplier-Stackelberg model (the supplier moves first).

Cai et al. (2017) studied contracts to coordinate a vendor-managed inventory (VMI) supply chain with one retailer and one unreliable supplier. The authors compared two contracts: an option contract, and a subsidy contract. Cai et al. (2019) studied supply chain coordination with yield uncertainty and downside risk aversion. The authors examined a supplier led supply chain, and a buyer led supply chain and shown that a revenue-sharing contract can coordinate both supply chains.

3.2.3 Drug shortages from a supply chain perspective

Chick et al. (2008) studied an influenza vaccination supply chain with a government and a manufacturer under random yield. The authors constructed a joint epidemic and supply chain model and proposed a variant of the cost-sharing contract, which could coordinate the supply chain and hence improve the supply of vaccines. Two studies investigated inventory management strategies for an integrated pharmaceutical supply chain consisting of a hospital and a pharmaceutical company, both assuming that the pharmaceutical company and the hospital cooperate and jointly derive a coordinated supply chain decision system (Priyan and Uthayakumar, 2014; Uthayakumar and Priyan, 2013).

Taylor and Xiao (2014) investigated a donor’s optimal subsidy decision to improve the availability and affordability of recommended malaria drugs provided by the private-sector in some developing countries. The authors found that the donor should

only subsidize the purchases of retailers for malaria drugs and should not subsidize their sales. Saedi et al. (2016) presented a stochastic optimization model (a continuous time Markov chain model) to find a hospital's optimal stock levels and order quantity levels that minimize the impact of drug shortages in the presence of supply disruptions and stochastic demand. The authors analyzed the balance point among substitutable drugs, considering important factors (e.g., the space occupied by an item, disruption rates, and recovery rate), and shown that the proposed scheme outperforms the current policies in many key aspects.

Jia and Zhao (2017) developed a model to capture the objectives of key supply chain parties, and investigated Pareto-improving contracts through price increases paired with strengthened failure-to-supply clauses. The authors verified the model results using real data of several drugs undergoing shortages. Tucker et al. (2019) constructed a multi-stage stochastic program model to study a pharmaceutical company's optimal decision on vulnerable or resilient supply chains under supply disruption and studied the impacts of proposed drug shortage mitigating policies on the supply chain decisions. The authors found that it may be optimal for pharmaceutical companies to keep vulnerable supply chains for certain types of low profit margin drugs, and redundancy regulations would be at least as efficient as market-based solutions.

3.2.4. The Contribution of this Research

Our research is most similar to three previous studies, but with important differences. Table 3.1 categorizes the three similar studies and our study along two important dimensions: the number of decision-makers and the number of sources. Tomlin (2006) studied a firm's optimal sourcing strategy for mitigating supply disruption. The author considered an infinite-horizon, periodic-review inventory system with stochastic demand,

Table 3.1: Comparison of our study with similar literature discussed in section 3.2.4

	Single sourcing	**Multiple sourcing**
Single decision-maker		Tomlin (2006)
Multiple decision-makers	Keren (2009)	Li et al. (2010); Our study

and studied a dual-sourcing strategy in which a firm could source from two suppliers: an unreliable but cheaper supplier, and a reliable but more expensive supplier. Their study and our study are similar in terms of the number of suppliers. However, the firm is the only decision-maker in Tomlin (2006), whereas we construct a game-theoretic model consisting of two interactive decision-makers.

Keren (2009) studied a two-tier supply chain with one supplier and one retailer, using a single-period model with deterministic demand and random supply. Keren (2009) and our study are similar in terms of the multi-decision-maker setting (game-theoretic model). However, the main difference is that Keren (2009) considered a single source of supply, whereas our study considers a dual sourcing strategy. Another difference is that Keren (2009) only considered a single-period model, whereas our study analyzes both a single-period setting and a multi-period setting.

Li et al. (2010) constructed a supply chain consisting of one retailer, two suppliers unreliable supply, and one spot market for emergency replenishment. The multi decision-maker setting in their study is similar to our model. However, a major difference is that Li et al. (2010) focused on the pricing strategies of suppliers, whereas our study focuses on the production decisions of the suppliers (manufacturing facilities) and we assume that all prices are exogenous. Another difference is that Li et al. (2010) constructed a single-period model, whereas our study analyzes both a single-period setting and a multi-period setting.

In summary, our study differs from existing literature by analyzing a hospital's dual sourcing strategy and contingent sourcing strategy on mitigating drug shortages, while taking into consideration the interactions between the hospital and the manufacturer and capturing the multi-period feature of many drug supply chains.

3.3 Model

We develop a multi-period model to analyze the interaction between a hospital (H, she) and an external pharmaceutical manufacturer (M, he). Let i be the index for the two decision-makers, $i = H, M$. We adopt the convention that the notation $A^+ = \max\{0, A\}$,

Table 3.2: Summary of notation

Symbol	Description
Decisions	
q_{Mt}	The hospital's order quantity from the manufacturer M in period t
q_{Rt}	The hospital's in-house production quantity in the regular procurement phase in period t
q_{Et}	The hospital's in-house production quantity in the emergency procurement phase-in period t
x_{Mt}	The manufacturer's planned production quantity in period t
Random Variable	
u_t	The manufacturer's random yield rate in period t
Parameters	
i	Index for the players and systems: $i = M$ for the manufacturer; $i = H$ for the hospital; $i = C$ for the centralized system; $i = T$ for the total system in a decentralized setting
t	Index for the time periods, $t = 1, \dots, T$
T	Total number of time periods
a, b	The lower and upper bounds of u_t
$f(\cdot), F(\cdot)$	PDF and CDF of u_t
μ	The mean of u_t
σ^2	The variance of u_t
D	The hospital's deterministic and static demand for the drug
z_{it}	The initial inventory level of player i at the beginning of period t
r	The hospital's unit revenue
c_R	The hospital's unit regular in-house production cost
c_E	The hospital's unit emergency in-house production cost
c_M	The manufacturer's unit production cost
w	The manufacturer's unit wholesale price
h_i	The unit holding cost of player i
s_i	The unit shortage cost of player i
Calculated Quantities	
y_t	Quantity delivered from M to H in period t, $y_t = \min\{q_{Mt}, z_{Mt} + u_t x_{Mt}\}$
Π_{it}	The expected profit of player i in period t
Γ_{it}	The optimal expected total profit of player i from period t onward

and $E[\cdot]$ denotes the expected value. The terms "increasing" and "decreasing" are used in a weak sense, i.e., "increasing" indicates "non-decreasing" and "decreasing" indicates "non-increasing". All model notation is summarized in Table 3.2.

Let T be the total number of periods, and $t = 1, \dots, T$ be the index for each period. We assume the hospital has a deterministic and static demand in each period (i.e., the same constant demand in each period), D. This is because for many pharmaceutical

products, the demand generally remains stable over time, and changes in demand have not been identified as a major contributing factor for drug shortages (Fox et al., 2014). We assume the hospital uses a dual-sourcing strategy, making use of an in-house producer who is reliable, and the external manufacturer (the manufacturer hereafter) who is subject to a random yield.

We assume the manufacturer faces stochastically proportional yield in each period with rates $u_1, \dots, u_T$, which are continuous random variables independent and identically distributed (i.i.d.) between a and b, $0 \leq a < b \leq 1$, with a probability density function (PDF) $f(\cdot)$ and a cumulative distribution function (CDF) $F(\cdot)$. This assumption is commonly used in studies involving manufacturing yields such as Inderfurth (2004) and Keren (2009).

Since one important reason why the hospital owns an in-house producer is to produce the drug in a more reliable way, we assume the in-house producer has a perfect yield rate in the basic model. For example, some manufacturers produce drugs using equipment that is more than 50 years old, which are vulnerable to manufacturing problems (Woodcock and Wosinska, 2013), and the hospital's newly established in-house producer may have a better yield rate than the manufacturer because of the advanced technology, better maintenance, or newer equipment. We also solve two extensions in which the in-house producer has a constant yield loss and a random yield rate, respectively. We assume the wholesale price of the drug is exogenous and fixed. Although drug prices may increase after a drug shortage (Alevizakos et al., 2016), our model applies to the situation where drug price is regulated and is not likely to be a decision or change in the short run, which is the case in many countries (Hou et al., 2017).

Let z_{it} be the initial inventory of player i at the beginning of period t, which equals the leftover stock at the end of the previous period, with $z_{i1} = 0, i = H, M$. In each period, the hospital has two procurement phases: a regular procurement phase followed by an emergency procurement phase. We define three decision making stages from stage 1 to stage 3 in each period. At the beginning of stage 1 in period t, the

hospital makes two decisions: the in-house production quantity, q_{Rt}, and the order quantity from the manufacturer, q_{Mt}. At the beginning of stage 2, for a given q_{Mt}, the manufacturer chooses his planned production quantity x_{Mt}. The two manufacturing facilities then produce, and the manufacturer's yield rate is realized. Let c_R and c_M be the unit production cost for the planned production quantity in the regular procurement phase for the hospital and the manufacturer, respectively. At the end of stage 2, the hospital receives regular replenishment from the two manufacturing facilities: the in-house producer delivers q_{Rt} units; the manufacturer delivers y_t units,$y_t = \min\{q_{Mt}, z_{Mt} + u_t x_{Mt}\}$, and charges a fixed wholesale price $w > c_M$. For any unfulfilled order quantity $(q_{Mt} - z_{Mt} - u_t x_{Mt})^+$, the manufacturer incurs a unit shortage cost, $s_M \geq 0$. The shortage cost may include penalty costs, loss of reputation, or loss of future sales to the hospital (Keren, 2009). For any leftover quantity $(z_{Mt} + u_t x_{Mt} - q_{Mt})^+$, the manufacturer incurs a unit holding cost, $h_M > 0$ ($h_M < 0$ may present a unit salvage value, if there exists a secondary market). To avoid infinite profit, we assume that $c_M > -h_M$ (the salvage value is less than the production cost).

At the end of the regular procurement phase, the hospital may still be in short supply of the drug. We assume that the in-house producer can make emergency production for the hospital if needed because the hospital's main motivation to own the in-house producer is to mitigate drug shortages and the in-house producer may be more willing to allocate emergency capacity for the hospital. At the beginning of the emergency production phase, the hospital chooses the emergency production quantity q_{Et} (stage 3). Emergency production occurs at a unit production cost c_E, and the hospital receives emergency replenishment from the in-house producer. Finally, demand occurs, which will be satisfied with the hospital available inventory, and all revenue and costs are realized.

We assume $c_E > c_R$ since emergency production may require overtime working hours and/or expedited delivery of raw materials. Note that we do not impose any assumptions on the relationship between w and the hospital's in-house production costs (c_R and c_E) since the hospital may or may not have advantages in the production cost depending on the specific drug. For drugs with a low price and low profit margin for the

manufacturer, the hospital's in-house production cost may be higher than the manufacturer's wholesale price. For drugs with a high price and high profit margin for the manufacturer, the hospital may have an advantage in the in-house production cost.

At the end of the emergency procurement phase, the hospital incurs a unit shortage cost $s_H \geq 0$ for unfulfilled demand. The shortage cost s_H should include all costs caused by the unavailability of the drug that the hospital cares about. For example, if an alternative drug is available, then the difference in drug price and related service fees between the alternative drug and the original drug should be included in s_H. If there is no alternative drug and a shortage of the drug leads to canceled surgeries, then s_H should include the fees for the surgery and subsequent hospital stay. s_H should also include staff time on searching for alternative drugs, communicating with patients, and other activities for managing shortages. Therefore, s_H can be very high, even significantly higher than the hospital's unit revenue for the drug, r. The unit revenue is the amount that patients are billed for receiving the drug in the hospital. The hospital incurs a unit holding cost $h_H > 0$ for leftover stocks ($h_H < 0$ may present a unit salvage value if there is a secondary market). To avoid infinite profit, we assume w and c_R are each greater than $-h_H$. To avoid a trivial solution, we assume that at least one of w and c_R are less than $r + s_H$, otherwise, the hospital would never procure or produce the drug.

We assume that all parameters are known by all parties. The sequence of events is illustrated in Figure 3.1. Let Π_{it} be the expected profit of player i in period t, which is calculated as follows.

$$\begin{aligned}\Pi_{Ht}(q_{Mt}, q_{Rt}, q_{Et}) \\ &= E[r\min\{D, z_{Ht} + q_{Rt} + y_t + q_{Et}\} - wy_t - c_R q_{Rt} - c_E q_{Et} \\ &\quad - h_H(z_{Ht} + q_{Rt} + y_t + q_{Et} - D)^+ \\ &\quad - s_H(D - z_{Ht} - q_{Rt} - y_t - q_{Et})^+]\end{aligned} \tag{3.1}$$

$$\begin{aligned}\Pi_{Mt}(x_{Mt}) = E[&wy_t - c_M x_{Mt} - h_M(z_{Mt} + u_t x_{Mt} - y_t) \\ &- s_M(q_{Mt} - y_t)]\end{aligned} \tag{3.2}$$

The hospital's expected profit (Equation 3.1) includes the revenue from the drug,

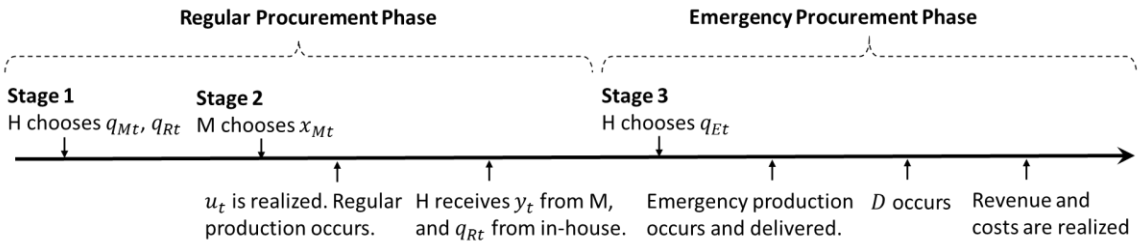

Figure 3.1: The sequence of events in period t

the procurement cost paid to the manufacturer, the in-house regular production cost, the emergency production costs, the shortage cost, and the holding cost. The manufacturer's profit function (Equation 3.2) includes the revenue, the production cost, the holding cost, and the shortage cost.

Let $\Gamma_{it}(z_{it})$ be the optimal total expected profit of player i from period t onward (i.e., the value function) for any initial inventory z_{it}, which is formulated as follows.

$$\Gamma_{Ht}(z_{Ht}) = \max_{q_{Rt},q_{Mt},q_{Et}\geq 0} \Pi_{Ht}(z_{Ht}, q_{Rt}, q_{Mt}, q_{Et}) + \delta E\big(\Gamma_{Ht+1}(z_{Ht+1})\big) \tag{3.3}$$

$$\Gamma_{Mt}(z_{Mt}) = \max_{x_{Mt}\geq 0} \Pi_{Mt}(z_{Mt}, x_{Mt}) + \delta E(\Gamma_{Mt+1}(z_{Mt+1})) \tag{3.4}$$

Where δ is a discount factor for the value of time. The initial inventory of player i in period $t+1$ is the leftover inventory in period t, i.e., $z_{Ht+1} = (q_{Rt} + y_t + q_{Et} - D)^+$, and $z_{Mt+1} = (z_{Mt} + u_t x_{Mt} - q_{Mt})^+$.

Our model is a multi-stage stochastic programming, with the two parties' sequential and iterative decision-making process in each period. Although this model setting captures the important features of a pharmaceutical supply chain, we are not able to solve it analytically in the original multi-period setting. Therefore, we first solve a single-period model and obtain closed-form solutions to generate insights into the structure of the two player's optimal production plans. We then propose two long-term inventory management policies and evaluate the performance of the two policies using a heuristic in the multi-period setting.

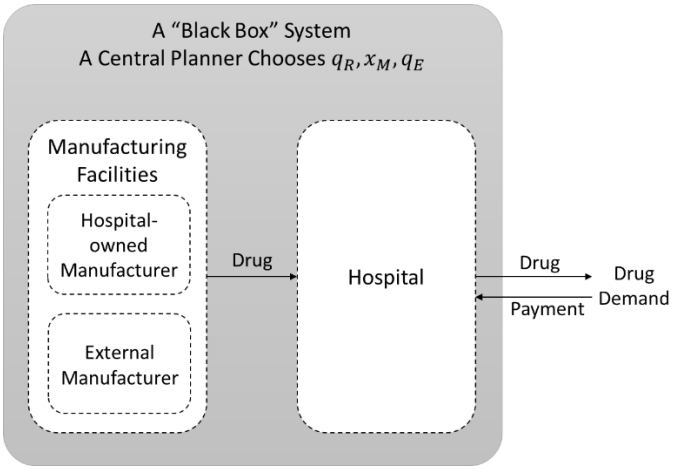

Figure 3.2: A schematic illustration of the centralized system

3.4 Single-Period Analysis

We first solve a single-period model. We drop the subscript for the time period, t, in this section. Similar to other studies (Keren, 2009; Li et al., 2012), we assume that the manufacturer's yield rate u is uniformly distributed between a and b. This assumption allows us to derive close-form solutions and examine some main properties of the hospital's optimal procurement plan. We also verified that the main results hold under other distributions, such as beta distributions and truncated normal distributions. Therefore, our main results are robust and not distribution specific. We first solve a centralized system with dual sourcing as the benchmark for the best case. Next, we solve a decentralized system with dual sourcing.

3.4.1 Centralized System with Dual Sourcing

In a centralized system with dual sourcing (Model C, the centralized system), we envision a single integrated system (Figure 3.2) consisting of the hospital and the two manufacturing facilities. We continue to refer to the two manufacturing facilities as the manufacturer and the in-house producer in this section, even though they are part of an integrated system. A central planner makes decisions to maximize the total profit in this system.

The centralized system differs from the decentralized system in several aspects.

The first difference is the decision variables in each system. The decision variables in the centralized system are q_R, x_M and q_E. q_M is no longer a decision because it is used to determine the transfer payment between players within the system. The second difference is the sequence of decisions. Under a centralized system, the order of decision sequence does not matter because the decisions are made by the same decision-maker. Therefore, the central planner chooses q_R and x_M simultaneously in the regular procurement phase, and he chooses the emergency production quantity q_E in the emergency procurement phase.

Several parameters are also different in the two systems. Let $z_C = z_H + z_M$ be the total initial inventory in the centralized system, which can be accessed by the central planner at the beginning of the period. Let $s_C = s_H$ be the unit shortage cost for the centralized system for unfulfilled demand. This is because s_M can be interpreted as the manufacturer's loss of reputation and future sales to the hospital, which is within the integrated system. Let $h_C = \min\{h_H, h_M\}$ be the holding cost in the centralized system, i.e., the leftover stocks will be stored in the less expensive facility. All other parameters and sequence of events are the same as the decentralized system.

Let Π_C be the expected profit for the centralized system. Unlike the centralized system in much of the supply chain literature, the profit in our integrated system is not simply the sum of the two parties' profit functions. This is because the central planner's production quantities at the two manufacturing facilities are embedded in the min and max functions in Π_C, which cannot be obtained by summing up the hospital and the manufacturer's profit functions together. Π_C is given by:

$$\begin{aligned}\Pi_C(q_R, x_M, q_E) = E[&r\min\{D, z_C + q_R + u\,x_M + q_E\} - c_M x_M - c_R q_R - c_E q_E \\ &- h_C\,(z_C + q_R + u\,x_M + q_E - D)^+ \\ &- s_H(D - z_C - q_R - u\,x_M - q_E)^+]\end{aligned} \tag{3.5}$$

The expected profit in the centralized system includes the revenue, the regular production costs at the two manufacturing facilities, the emergency production cost, the holding cost, and the shortage cost. The central planner's problem can be formulated as

follows.

$$\max_{q_R, x_M} \Pi_C \tag{3.6}$$

$$\text{s.t.} \quad q_E = \arg\max \Pi_C \,|q_R, x_M \tag{3.7}$$

$$q_R, x_M, q_E \geq 0 \tag{3.8}$$

Let $L_C = z_C + q_R + ux_M$ be the central planner's inventory level at the beginning of the emergency procurement phase. Let $\tilde{q}_E^C$ be the best response function for Equation (5), which is summarized in Lemma 3.1.

Lemma 3.1: *In Model C, the best response function for the emergency production quantity for any given q_R and x_M is as follows.*

$$\tilde{q}_E^C = \begin{cases} 0, \ if \ c_E \geq r + s_H \\ (D - L_C)^+, if \ c_E < \ r + s_H \end{cases}$$

Lemma 3.1 indicates that if c_E is sufficiently high ($c_E \geq r + s_H$), then the central planner will not make any emergency production, even if there is a shortage. If c_E is sufficiently low ($c_E < r + s_H$), then the central planner will set the emergency production quantity equal to the shortage quantity at the beginning of the emergency replenishment phase. In Lemma 3.1, the threshold for c_E is $r + s_H$, indicating that the hospital should consider both the revenue and the shortage cost of the drug when determining whether to make emergency production or not.

Let superscript C denote the optimal solutions in the centralized system. Let $Q_E^C = E[q_E^C]$ be the optimal expected emergency production quantity. Proposition 3.1 summarizes the central planner's optimal decisions about q_R^C and x_M^C, as well as the resulting expected emergency production quantity, Q_E^C.

Proposition 3.1: *The optimal production plan in the centralized system is one of the following:*

a. If $z_T \geq D$, then $q_R^C = 0$, $x_M^C = 0$ and $Q_E^C = 0$

b. If $z_T < D$*:*

I. $q_R^C = D - z_C > 0, x_M^C = 0$ *and* $Q_E^C = 0$ *if and only if (iff)* $c_R \leq \overline{c}_R^C$

II. $q_R^C = 0$ *and* $x_M^C = A_C(D - z_C)$*, iff* $c_R > \overline{c}_R^C$

i. $Q_E^C > 0$ *iff* $c_E < r + s_H$

ii. $Q_E^C = 0$ *iff* $c_E \geq r + s_H$

where $\overline{c}_R^C = \left(\frac{\sqrt{h_C+\phi}\sqrt{-2ac_M+b(2c_M+bh_C)+a^2\phi}-bh_C-a\phi}{b-a}\right)^+$, $\phi = \min\{c_E, r + s_H\}$, *and* $A_C = \frac{\sqrt{h_C+\phi}(D-z_C)}{\sqrt{-2ac_M+b(2c_M+bh_C)+a^2\phi}}$.

Proposition 3.1 indicates that the central planner will not produce anything if the demand can be satisfied by the initial inventory. Otherwise, the central planner's optimal production plan is depending on the production costs at the manufacturing facilities. If the hospital's regular production cost is sufficiently low ($c_R \leq \overline{c}_R^C$), then the central planner prefers to produce at the hospital's in-house producer in the regular procurement phase, and the production quantity is the difference between the demand and the initial inventory. If the hospital's regular production cost is sufficiently high ($c_R > \overline{c}_R^C$), then the central planner will produce at the manufacturer during the regular procurement phase, and the production quantity is the product of the adjustment factor A_C and the quantity still in short ($D - z_C$). If the emergency production cost is sufficiently low, then the central planner will make emergency production. Otherwise, he will not produce anything during the emergency procurement phase, regardless of shortages. The optimal solutions in the centralized system provide a benchmark for the best case, and we compare it with the decentralized system in section 3.4.3.

3.4.2 Decentralized System with Dual Sourcing

In this section, we solve the decentralized system with dual sourcing (Model D, the decentralized system). The problem is formally formulated as follows.

$$\max_{q_R, q_M} \Pi_H \tag{3.9}$$

s.t. $x_M = \arg\max \Pi_M \,|q_M$ (3.10)

$$q_E = \arg\max \Pi_H \,|q_R, q_M, x_M \tag{3.11}$$

$$q_R, q_M, x_M, q_E \geq 0 \tag{3.12}$$

Equation 3.9 is the hospital's problem of choosing q_R, and q_M in stage 1. Equation 3.10 is the manufacturer's optimal decision of x_M in stage 2, for any given q_M. Equation 3.11 is the hospital's optimal decision of q_E in stage 3, for any given q_M, q_R, and x_M. Inequality 3.12 is the non-negativity constraint for all decision variables.

Let superscript $*$ denote the optimal solutions in Model D. Define L as the hospital's inventory level at the beginning of stage 3, where $L = z_H + y + q_R$. Let $\tilde{q}_E$ be the hospital's best response function for her emergency production quantity. Lemma 3.2 shows the expression of $\tilde{q}_E$.

Lemma 3.2: *In Model D, the hospital's best response function for the emergency production quantity for any given q_R and x_M is as follows.*

$$\tilde{q}_E = \begin{cases} 0, \ if \ c_E \geq r + s_H \\ (D - L)^+, if \ c_E < \ r + s_H \end{cases}$$

$\tilde{q}_E$ has a similar expression and intuition with $\tilde{q}_E^C$ in Model C. $\tilde{q}_E$ can be obtained by replacing L_C in $\tilde{q}_E^C$ with L.

Let $\tilde{x}_M$ be the manufacturer's best response function for Equation 8. Before discussing $\tilde{x}_M$, we present a condition under which the manufacturer will not produce anything, regardless of the value of q_M.

Lemma 3.3: *If $c_M > \left(\frac{a+b}{2}\right)(w + s_M)$, then $x_M^* = 0 \ \forall \ q_M$.*

The manufacturer's production decision is based on the trade-off between the cost

and benefit of production. In Lemma 3.3, the left-hand side of the inequality is the manufacturer's production cost if he plans to produce one unit of drug. The right-hand side is the manufacturer's expected benefit if he plans to produce one unit of the drug, which is the product of his expected yield rate ($\frac{a+b}{2}$), and the benefit of selling one unit of drug. $\frac{a+b}{2}$ is the mean of the uniformly distributed yield rate based on our assumption, and we numerically verified that it can be replaced by the mean of the yield rate with other distributions. The benefit of selling one unit of drug includes the unit revenue from selling the drug and the unit shortage cost that he can avoid ($w + s_M$). If the production cost outweighs the expected benefit, then the manufacturer will not produce anything, regardless of the order quantity from the hospital. In other words, there is no interaction between the two parties in this situation. To guarantee the manufacturer's participation, we assume the following assumption holds throughout the rest of the analysis.

Assumption 3.1: $\left(\frac{a+b}{2}\right)(w + s_M) > c_M$.

Define $A_M = \frac{\sqrt{w+h_M+s_M}}{\sqrt{2(b-a)c_M+(s_M+w)a^2+h_M b^2}}$ as an "adjustment factor" that determines how the manufacturer's production level varies with respect to the hospital's order quantity. Lemma 3.4 summarizes the manufacturer's best response function $\tilde{x}_M$, i.e., how the manufacturing uses the adjustment factor A_M to determine his production quantity. Lemma 3.5 states a property of A_M.

Lemma 3.4: *The manufacturer's best response function is given by:*

$$\tilde{x}_M = A_M(q_M - z_M)^+.$$

Lemma 3.5: $A_M \geq 1$.

The manufacturer will not produce anything if his initial inventory can fully satisfy the hospital's order quantity (i.e., $q_M < z_M$). Otherwise, he will use the adjustment factor A_M to determine his planned production quantity for any quantity that needs to be produced ($q_M - z_M$). The coefficient A_M is similar to Equation (6) in Keren (2009), but with a difference in the denominator.

Lemma 3.5 states that if the manufacturer needs to make production, then he will plan to produce no less than the quantity needed. This is intuitive due to the existence of his yield uncertainty.

Proposition 3.2 summarizes the hospital's optimal production plan.

Proposition 3.2: *The optimal production plan for the hospital in the decentralized system with dual sourcing is one of the following.*

a. *If* $D \le z_H$, *then* $q_R^* = 0$, $q_M^* = 0$ *and* $Q_E^* = 0$

b. *If* $z_H < D \le z_M + z_H$:

   I. $q_R^* = D - z_H$, $q_M^* = 0$, *and* $Q_E^* = 0$ *iff* $c_R \le w$

   II. $q_R^* = 0$, $q_M^* = D - z_H$, *and* $Q_E^* = 0$ *iff* $c_R > w$

c. *If* $D > z_M + z_H$:

   I. $q_R^* = D - z_H, q_M^* = 0$, *and* $Q_E^* = 0$, *iff* $c_R \le \underline{c}_R$

   II. $q_R^* = D - z_H - z_M, q_M^* = z_M$, *and* $Q_E^* = 0$, *iff* $\underline{c}_R < c_R \le \overline{c}_R$

   III. $q_R^* = 0$ *and* $q_M^* = z_M + A_H(D - z_H - z_M)$, *iff* $c_R > \overline{c}_R$

      i. $Q_E^* = 0$ *iff* $c_E \ge r + s_H$

      ii. $Q_E^* = \hat{Q}_E > 0$ *iff* $c_E < r + s_H$

where $\underline{c}_R = w$, $\overline{c}_R = \left(\frac{\sqrt{(h_H+\phi)((2Ab-1)(h_H+w)+a^2A^2(\phi-w)}-A(bh_H+a\phi)}{A(b-a)}\right)^+$, $A_H = \max\left\{1, \frac{\sqrt{(\phi+h_H)}}{\sqrt{A^2a^2(\phi-w)+(2Ab-1)(h_H+w)}}\right\}$, *and* $\hat{Q}_E = \frac{(z_H+z_M+aA(q_M^*-z_M)-D)^2}{2A(b-a)(q_M^*-z_M)}$.

Proposition 3.2.a and b state that the hospital first tries to satisfy the demand using the existing inventories. If the existing inventories at the two manufacturing facilities are not sufficient, Proposition 3.2.c indicates that the hospital's production plan

depends on the costs of the in-house production and outsourcing. If c_R is sufficiently low (Proposition 3.2.c.I), i.e., the hospital's in-house production is cheaper and more reliable, then the hospital will produce all quantity needed at the in-house producer in the regular production phase. If c_R is intermediate (Proposition 3.2.c.II), then the hospital's in-house production cost is reasonably high which can be justified by the higher reliability than the manufacturer. In this case, the hospital will purchase the manufacturer's initial inventory, which does not involve yield risk and is cheaper than the in-house production. The hospital will produce the rest of the quantity needed at the in-house producer during the regular procurement phase. If c_R is sufficiently high (Proposition 3.2.c.III), then the hospital will only order from the manufacturer in the regular procurement phase. This is because c_R is too high to be justified by the higher reliability. The order quantity includes two parts. The first part is the manufacturer's initial inventory, z_M which is risk-free and does not need any adjustment. The second part involves yield risks and the hospital uses a coefficient A_H to make adjustment. Due to the existence of yield uncertainty, A_H is no less than 1. The hospital's expected emergency production plan is a direct result of the best response function of $\tilde{q}_E$. For the rest of the analysis, we focus on the non-trivial cases in which the demand cannot be satisfied by the existing inventories (Proposition 3.2.c), and production has to take place.

$\bar{c}_R$ is an important threshold value that determines whether the hospital will use the in-house producer in the regular phase or not. Therefore, we show some properties of $\bar{c}_R$ in Proposition 3.3.

Proposition 3.3:

$$\frac{\partial \bar{c}_R}{\partial s_H} \geq 0; \frac{\partial \bar{c}_R}{\partial r} \geq 0; \frac{\partial \bar{c}_R}{\partial c_E} \geq 0.$$

If s_H or r increases, the hospital will be more willing to mitigate drug shortages to either avoid a high shortage cost or pursue a high revenue. Therefore, she is more likely to use a reliable source, i.e., $\bar{c}_R$ is increasing in s_H and r. If c_E increases, the hospital will be more reluctant to make emergency production. Therefore, she is more likely to switch from a reliable source to an unreliable source at a higher threshold of c_R,

i.e., $\bar{c}_R$ is increasing in c_E.

Let Ω denote the expected shortage amount, i.e., $\Omega = E[(D - z_{Ht} - q_{Rt} - y_t - q_{Et})^+]$. Lemma 3.6 summarizes the expression of the expected shortage amount under the optimal production plan, Ω^*.

Lemma 3.6: *The expected shortage amount under the optimal production plan in Model D is as follows:*

a. $\Omega^* = \frac{(q_R^* + z_H + z_M - D + aA(q_M^* - z_M))^2}{2A(b-a)(q_M^* - z_M)}$, *if* $c_R > \overline{c}_R$ *and* $c_E > r + s_H$

b. $\Omega^* = 0$, *otherwise.*

Lemma 3.6 states that the establishment of the hospital's in-house producer can mitigate drug shortages, unless both c_R and c_E are sufficiently high. If c_R is low ($c_R \leq \overline{c}_R$), then shortages can be mitigated in the regular procurement phase. If c_E is low ($c_E \leq r + s_H$), then shortages can be mitigated in the emergency procurement phase. If both c_R and c_E are high, then the hospital will not produce anything at the in-house producer, which is a sole-sourcing situation. Note that, if the emergency production is not possible (e.g., for drugs that need a long lead time or emergency production capacity is not available), then we can set $c_E = \infty$, and $c_E > c_R + s_H$ is always satisfied so that the hospital never make emergency production.

3.4.3 Numerical Analysis

In this section, we conduct numerical analysis to analyze and illustrate some results and observations. We first analyze Model D. Next, we compare Model D with Model C.

Table 3.3. Parameter values for numerical analysis

Parameter	D	a	b	z_M	z_H	w	c_M	h_M
Value	10000	0	1	1000	1000	500	200	50
Parameter	s_M	r	h_H	s_H	c_R	**Low** c_E	**High** c_E	
Value	100	1500	100	1800	750	1500	3500	

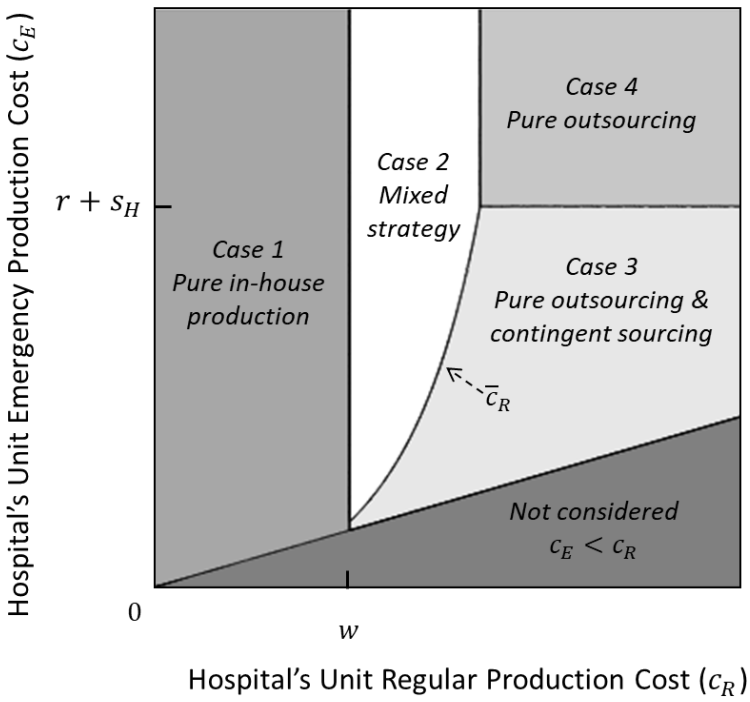

Figure 3.3: Policy graph of the hospital's optimal procurement strategy in Model D with respect to the hospital's unit regular production cost (c_R) and unit emergency production cost (c_E). In the regular procurement phase, the hospital's optimal strategy is one of the following: pure in-house production (only make in-house production), a mixed strategy (procure from both manufacturing facilities), and pure outsourcing (only procures from the external manufacturer). Contingent sourcing: the hospital prefers to make emergency production at the in-house producer.

Model D

Depending on the hospital's optimal ordering decision in the regular procurement phase, we refer to the procurement plans in Proposition 3.2.c.I, II, and III as a pure in-house production strategy, a mixed procurement strategy, and a pure outsourcing strategy, respectively. Depending on the hospital's emergency production decisions, we refer to the procurement plans in Proposition 3.2.c.I.ii as a contingent sourcing strategy in which the hospital will make emergency production if needed.

Figure 3.3 provides a graphical illustration of the hospital's optimal procurement strategy as a function of c_R and c_E in the Model D when $z_H < D - z_M$ (i.e., Proposition 3.2.c). In Case 1, c_R is low ($c_R \leq w$), and the hospital prefers a pure in-house production strategy. In Case 2, c_R is intermediate ($w < c_R \leq \overline{c}_R$), and the hospital prefers a mixed

procurement strategy and she will procure the drug from both manufacturing facilities. This is because the hospital will purchase the manufacturer's initial inventory, which does not involve yield uncertainties and is cheaper than the hospital's in-house production. The hospital will produce the rest amount that is needed in the in-house producer. In Case 3, c_R is high ($c_R > \bar{c}_R$) and c_E is low ($c_E < r + s_H$), and the hospital prefers a pure outsourcing strategy in the regular phase and a contingent sourcing strategy in the emergency procurement phase. In Case 4, both c_R and c_E are high ($c_R > \bar{c}_R$, and $c_E > r + s_H$), and the hospital prefers a pure outsourcing strategy in the regular phase, and will not use a contingent sourcing strategy. Note that, in Figure 3.3, the hospital does not use a contingent sourcing strategy when $c_R < \bar{c}_R$. This is because we assume that the hospital's in-house producer has a perfect yield rate. If the in-house producer also has yield uncertainties, which is highly likely in the real world, then the hospital will use a contingent sourcing strategy in Case 1 and Case 2 if $c_E < r + s_H$.

Next, we examine some properties of $\bar{c}_R$. Let Δc be the difference between the hospital's in-house regular production cost and the outsourcing cost, $\Delta c = c_R - w$. Δc can be interpreted as the hospital's cost disadvantage if she produces at the in-house producer instead of procuring from the manufacturer in the regular phase. Let μ and σ^2 be the mean and variance of u, respectively. Figure 3.4 shows $\bar{c}_R$ as a function of Δc with different means and variances of u. The graphs in Figure 3.4.a and b have a fixed mean of u with different variances (a and b move symmetrically with respect to the mean). The graphs in Figure 3.4.c and d have a fixed variance of u with different means (a and b move simultaneously to the same direction). In all four graphs, $\bar{c}_R$ is decreasing in Δc, indicating that the hospital is more willing to procure from the manufacturer if c_R is higher than w.

We then analyze the impact of the parameters of the yield rate on $\bar{c}_R$. Figure 3.4 a and b show that $\bar{c}_R$ is sensitive to the variance of the yield rate (σ^2), regardless of the value of c_E. The impact of μ on $\bar{c}_R$ depends on whether the hospital uses a contingent sourcing strategy or not. If the hospital has a second chance to make emergency production for any shortfall quantity (i.e., c_E is low), then $\bar{c}_R$ is not affected by μ very much (Figure 3.4 c). If the hospital does not take advantage of a second chance to make

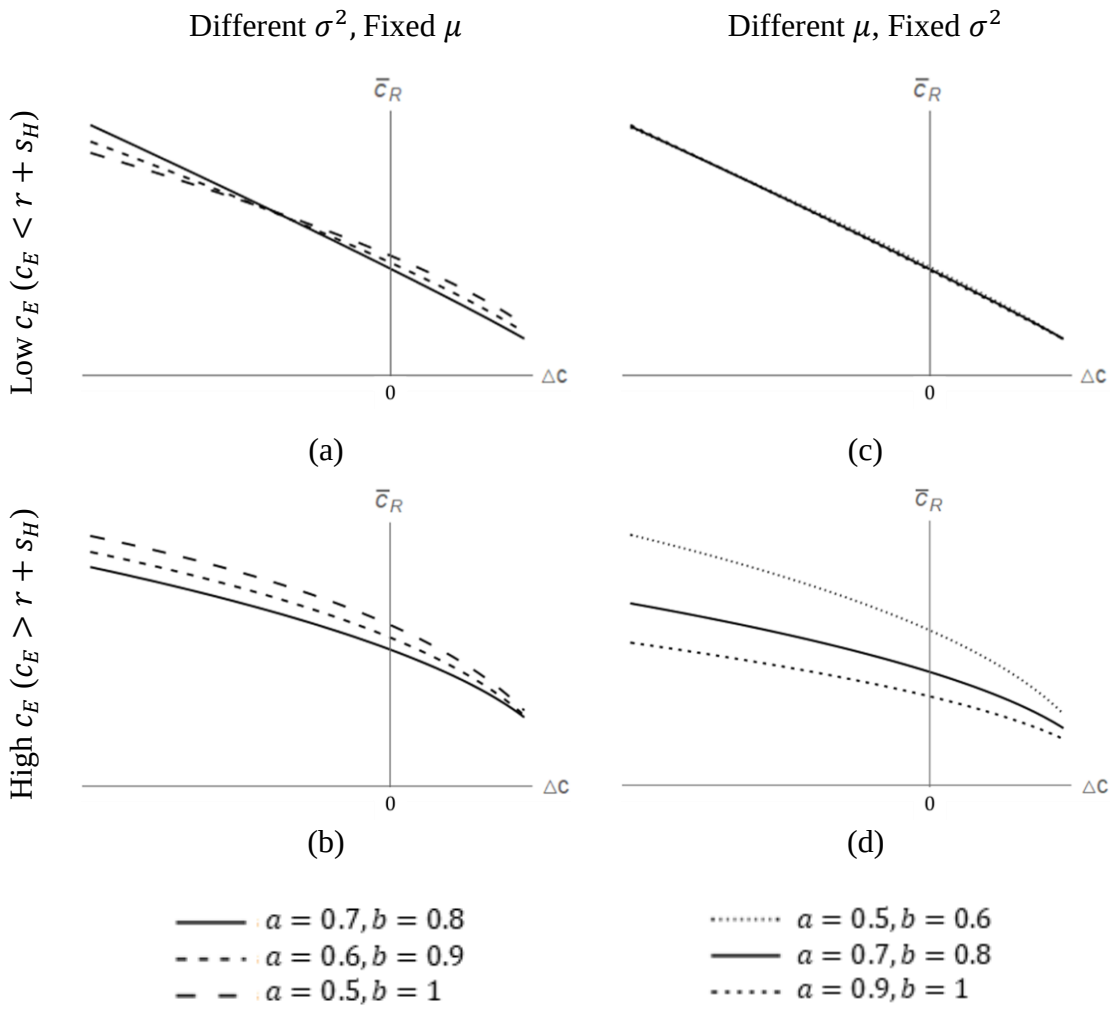

Figure 3.4: $\bar{c}_R$ as a function of $\Delta c = c_R - w$ with different μ and σ^2. (a) with different σ^2 and fixed μ, when c_E is low; (b) with different σ^2 and fixed μ, when c_E is high; (c) with different μ and fixed σ^2, when c_E is low; (d) with different μ and fixed σ^2, when c_E is high.

emergency production (i.e., c_E is high), then the hospital is very cautious when choosing the optimal production plan in the regular procurement phase. In this case, even a small change in μ will have a large impact on $\bar{c}_R$ (Figure 3.4 d).

In summary, several factors have a large impact on the threshold value $\bar{c}_R$, such as the hospital's cost disadvantage (Δc), the emergency production cost c_E, and the variance of the manufacturer's yield rate (σ^2). $\bar{c}_R$is sensitive to the mean of the manufacturer's yield rate (μ) only if the hospital does not use a contingent sourcing strategy.

Model D vs. Model C

In this section, we compare the performance of Model D and Model C. Recall that we assume $s_C = s_H$ in Model C, therefore, we let $s_M = 0$ for this section for a fair comparison between the two systems. Let Π_T^* be the total optimal profit of the hospital and the manufacturer Model D, $\Pi_T^* = \Pi_H^* + \Pi_M^*$. Let Π_C^C be the optimal profit for the integrated system in Model C.

Figure 3.5 shows the efficiency of Model D compared with Model C (Π_T^*/Π_C^C) as a function of c_R when c_E is low. This scenario corresponds to a horizontal line in Figure 3.3 across Case 1, 2 and 3. Figure 3.5 indicates that Model D has some inefficiencies when c_R is low ($c_R \leq \underline{c}_R$) and c_R is high ($c_R \geq \overline{c}_R^C$). In Model C, the central planner will always deplete the existing inventories at both manufacturing facilities (z_T), before producing anything. However, when c_R is low ($c_R \leq \underline{c}_R$), the hospital uses a pure in-house production strategy in Model D, and she does not purchase anything from the manufacturer. Therefore, when c_R is low, the inefficiencies in Model D are mainly due to the waste of the manufacturer's initial inventory and his holding cost. When $c_R \in [\overline{c}_R^C, \overline{c}_R]$, the hospital uses a mixed procurement strategy, and the inefficiencies of Model D are due to the decentralized decision-making process. When $c_R > \overline{c}_R$, the hospital uses a

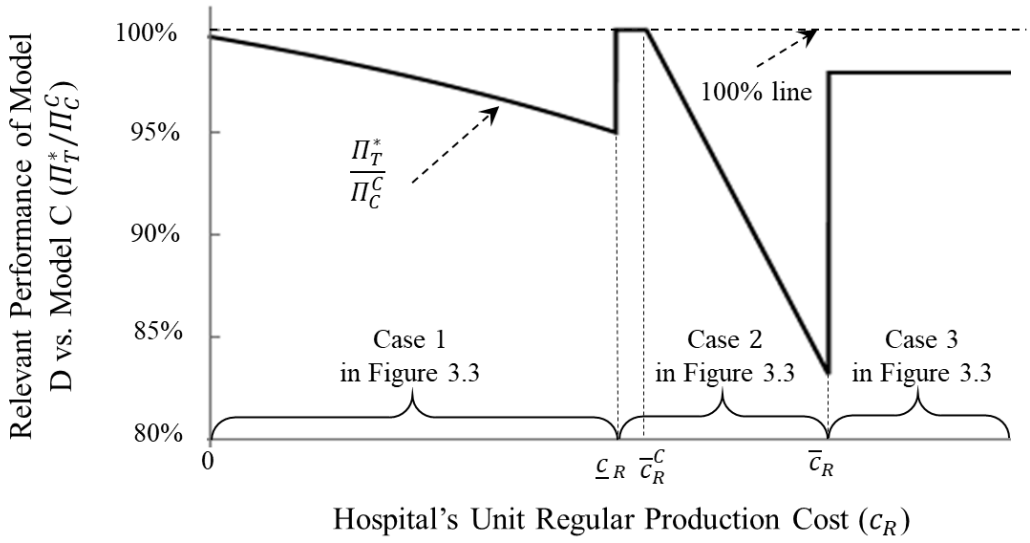

Figure 3.5: Relevant performance of Model D vs. Model C (Π_T^*/Π_C^C) with respect to the hospital's unit regular production cost (c_R) when c_E is low ($c_E < r + s_H$).

pure outsourcing strategy, and the inefficiencies are mainly due to the holding cost. This is because the central planner can store the leftover stocks in the cheaper warehouse, whereas the two parties in Model D do not have this flexibility.

When c_R is between $\underline{c}_R$ and $\overline{c}_R^C$, the optimal production plans in the two systems are the same. The initial inventories at both manufacturer facilities will be used, and the shortfall quantity will be produced at the hospital's in-house producer. Therefore, when the hospital's in-house regular production cost is either low or high, a decentralized system with dual sourcing has inefficiencies compared with a centralized system, and other types of coordinating mechanisms could be designed to improve the total supply chain performance.

3.4.4 Extensions

In this section, we relax the assumption that the hospital's in-house producer has a perfect yield rate. We consider two scenarios. In the first scenario, we assume that the in-house producer has a constant yield loss. In the second scenario, we assume that the in-house producer has a random yield rate.

Extension 1- The In-House Producer Has a Fixed Yield Loss

Let u_H be the yield rate at the hospital's in-house producer. In this extension, we assume that u_H is a constant and $u_H \in (0,1)$, i.e., the in-house producer has a constant yield loss. We analytically characterized the equilibrium solutions in this extension for the case $D > z_M + z_H$, which are summarized in Proposition 3.4.

Proposition 3.4: *If the hospital's in-house producer has a constant yield rate ,*$u_H \in (0,1)$*, then the optimal production plan for the hospital when* $D > z_M + z_H$ *is one of the following.*

I. $q_R^* = \frac{D - z_H}{u_H}, q_M^* = 0,$ *and* $Q_E^* = 0,$ *iff* $c_R \le u_H \underline{c}_R$

II. $q_R^* = \frac{D - z_H - z_M}{u_H}, q_M^* = z_M,$ *and* $Q_E^* = 0,$ *iff* $u_H \underline{c}_R < c_R \le u_H \overline{c}_R$

III. $q_R^* = 0$ *and* $q_M^* = z_M + A_H(D - z_H - z_M)$*, iff* $c_R > u_H \overline{c}_R$

i. $Q_E^* = 0$ *iff* $c_E \geq u_H(r + s_H)$

ii. $Q_E^* > 0$ *iff* $c_E < u_H(r + s_H)$

where $\underline{c}_R$, $\overline{c}_R$, and A_H *are the same as defined in Proposition 3.2.*

Proposition 3.4 indicates that the equilibrium solutions in this extension have a similar structure with the basic model as indicated in Proposition 3.2 – the threshold values for c_R and c_E in this extension can be obtained by multiplying the threshold values in the basic model by the in-house producer's yield loss, u_H, and the optimal in-house production quantities can be obtained by dividing the corresponding quantities in the basic model by u_H. In other words, when the in-house producer is deterministically reliable, the constant yield rate only has an scaling effect of boosting up the production costs and the production quantities at the in-house producer, but the main structure and qualitative properties of the policy graph in Figure 3.3 remain the same.

Extension 2 – The In-House Producer Has a Random Yield Rate

In this extension, we assume that the in-house producer's yield rate (u_R) is a random variable with a PDF $f_H(\cdot)$ and CDF $F_H(\cdot)$. Due to the complexity of the profit functions, we are not able to analytically characterize the optimal solutions. Therefore, we analyze this extension numerically using the same numerical values in Table 3.3. We follow the same assumption that the external manufacturer's yield rate is uniformly distributed on the interval [0,1]. We assume the emergency production has a perfect yield rate. We consider the case that the in-house producer's yield rate in the regular procurement phase is stochastically dominated by the external manufacturer's yield rate. Let u_H be uniformly distributed on the interval [0, 0.8].

Figure 3.6 presents a policy graph of the hospital's optimal procurement plan with respect to the unit regular in-house production cost (c_R) and the unit emergency production cost (c_E) in this extension, which is a counterpart of Figure 3.3 in the basic model. One major difference between Figure 3.6 and Figure 3.3 is that when c_R is

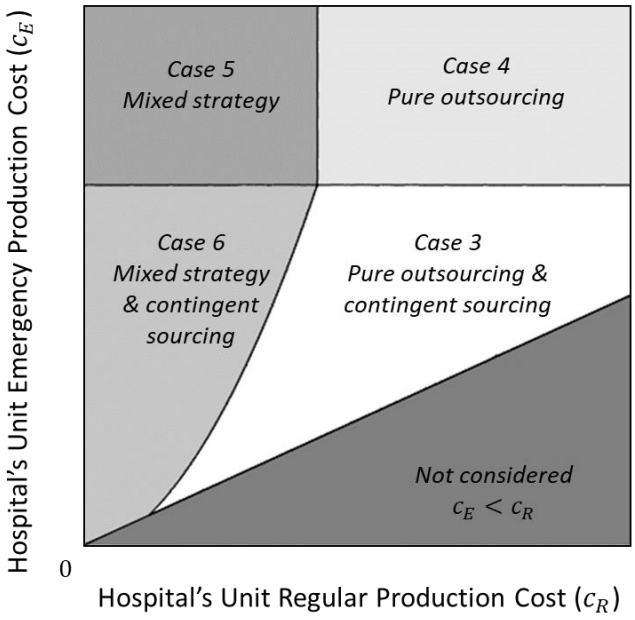

Figure 3.6: Policy graph of the hospital's optimal procurement strategy with respect to the hospital's unit regular production cost (c_R) and unit emergency production cost (c_E) when the in-house producer has a random yield rate (u_H). In the regular procurement phase, the hospital's optimal strategy is one of the following: pure in-house production (only make in-house production), a mixed strategy (procure from both manufacturing facilities), and pure outsourcing (only procures from the external manufacturer). Contingent sourcing: the hospital prefers to make emergency production at the in-house producer.

sufficiently low in this extension, the hospital prefers to procure from both manufacturing facilities in the regular procurement phase. In Case 5 and Case 6 in Figure 3.6, the hospital's order quantity from the manufacturer is greater than its initial inventory ($q_M^* > z_M$), i.e., the hospital will order from the manufacturer even if it does not have any initial inventory. The hospital does not prefer a pure in-house production strategy in this extension due to the low yield rate at the in-house producer. However, the hospital still makes in-house production in the regular phase, which is mainly for risk-pooling purposes. In other words, due to the existence of the random yield rates at both manufacturing facilities, the hospital prefers to procure from both sources to mitigate supply uncertainties if c_R is sufficiently low.

3.5 Multi-Period Analysis

We are not able to derive closed-form solutions for the multi-period case. Thus, we solve

and analyze the multi-period model using a heuristic. Inventory management policies (e.g., order-up-to policy) are widely studied in supply chain management literature (Chao and Zipkin, 2008; Chen et al., 2012; Henig and Gerchak, 1990), and they are easy to implement by inventory managers. We consider three inventory management policies for the hospital in the regular procurement phase: a Target Inventory Policy, a Scale Factor Policy, and a Myopic Scale Factor Policy. The inventory management policies are inspired by the structures of the single period solutions.

We make some assumptions in this section to focus our attention on the hospital's optimal procurement decision in the regular procurement phase. First, we assume that $c_R > w$, i.e., the hospital's regular in-house production is more expensive than procuring from the manufacturer. Otherwise, the hospital will always make in-house production in the regular phase, and there is no interaction between the hospital and the manufacturer in the multi-period model. Second, we assume that the manufacturer uses the structure of his best response function in the single-period setting (as specified in Lemma 3.4) as his production policy in the multi-period setting: in each period, for any given order quantity from the hospital, the manufacturer uses the scale factor A_M to determine the production quantity, $x_{Mt} = A_M(q_{Mt} - z_{Mt})^+$. In addition, we assume that the hospital's emergency production quantity in each period follows her best response function in the single-period setting as specified in Lemma 3.2.

The sequence of events under each inventory management policy is as follows. At the beginning of the time horizon, the hospital decides the policy parameters (will be discussed in section 3.5.1), which will be fixed for the rest of the time horizon. In period $t \in \{1, \dots, T\}$, the hospital and the manufacturer start period t with an initial inventory z_{Rt} and z_{Mt}, respectively. Let $z_{M1} = 0$ and $z_{R1} = 0$. The sequence of events in each period is the same as illustrated in Figure 3.1, where the decision variables are determined according to the following rules: in stage 1, the hospital's order quantities from the two manufacturing facilities, q_{Rt} and q_{Mt} are determined by z_{Ht} and the policy parameters as described in section 3.5.1; in stage 2, the manufacturing's order quantity x_{Mt} is determined according to Lemma 3.2; and in stage 3, the hospital's emergency production quantity q_{Et} is determined according to Lemma 3.4. Figure 3.7 illustrates the

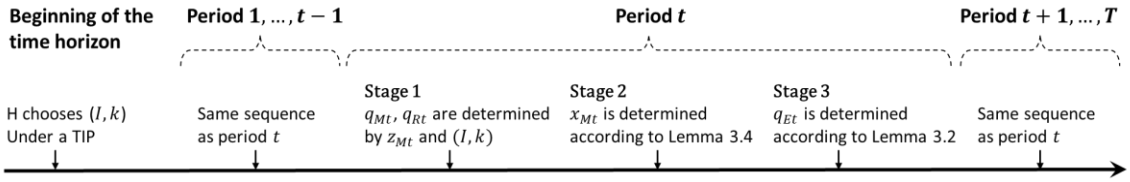

Figure 3.7 Sequence of Events in the Multi-Period Setting under a TIP.

sequence of events in the multi-period setting under a TIP as an example. Under a SFP or a MSFP, only the policy parameters need to be replaced accordingly at the beginning of the time horizon.

We discuss the detail of the three inventory management policies in section 3.5.1. In section 3.5.2, we discuss the solution and evaluation algorithm using the Sample Average Approximation (SAA) algorithm (Kleywegt et al., 2002). We then evaluate the performance of the three inventory management policies in a multi-period setting in section 3.5.3.

3.5.1 Three Inventory Management Policies

A Target Inventory Policy

Under *a Target Inventory Policy (TIP)*, at the beginning of the entire time horizon, the hospital chooses two parameters: a target inventory level I, and an allocation factor k. The target inventory level I incorporates the procurement from both the manufacturer and the in-house producer, and the hospital uses k to allocate the order quantities to the two manufacturing facilities. At the beginning of period t, if the hospital's initial inventory is below I, then an initial shortfall quantity $(I - z_{Ht})$ needs to be procured in the regular procurement phase. The hospital's most preferred source for the initial shortfall amount is the manufacturer's initial inventory because it is cheaper than the hospital's in-house production (recall that we assumed $c_R > w$). If the manufacturer's initial inventory is not sufficient, i.e., $z_{Mt} < I - z_{Ht}$, then the shortfall quantity $(I - z_{Ht} - z_{Mt})$ will be allocated to the two manufacturing facilities using the allocation factor k, where $k(I - z_{Ht} - z_{Mt})$ will be ordered from the manufacturer, and $(1 - k)(I - z_{Ht} - z_{Mt})$ will be allocated to the in-house producer. For any given pairs of

(I, k), the hospital's order quantities from the two manufacturing facilities in period t are given by:

$$q_{Mt} = \min\{(I - z_{Ht})^+, z_{Mt} + k(I - z_{Ht} - z_{Mt})^+ \} \quad (3.13)$$

$$q_{Rt} = (1 - k)(I - z_{Ht} - z_{Mt})^+ \quad (3.14)$$

A Scale Factor Policy

Under a *Scale Factor Policy (SFP)*, at the beginning of the entire time horizon, the hospital chooses two scale factors, S_M and S_H, to determine the order quantities from the manufacturer and the in-house producer, respectively. At the beginning of period t, if the hospital's initial inventory cannot fully satisfy the demand ($z_{Ht} < D$), then the hospital needs to procure an initial shortfall quantity $(D - z_{Ht})$ from the two manufacturing facilities. The hospital's first preferred source for the initial shortfall quantity is the manufacturer's initial inventory, as discussed for a TIP. If the manufacturer's initial inventory is insufficient, then the quantity $(D - z_{Ht} - z_{Mt})$ needs to be produced by the two manufacturing facilities. The hospital will use S_M and S_H to determine the allocation of this quantity: $S_M(D - z_{Ht} - z_{Mt})$ will be ordered from the manufacturer, and $S_H(D - z_{Ht} - z_{Mt})$ will be ordered from the in-house producer. The hospital's order quantities from the two manufacturing facilities in period t are given by:

$$q_{Mt} = \min\{ (D - z_{Ht})^+, z_{Mt} + S_M(D - z_{Ht} - z_{Mt})^+\} \quad (3.15)$$

$$q_{Rt} = S_H(D - z_{Ht} - z_{Mt})^+ \quad (3.16)$$

A Myopic Scale Factor Policy

The hospital can apply a myopic policy by using the optimal solution in the single-period model. Denote this myopic policy a *Myopic Scale Factor Policy* (MSFP), because it has the same structure as a SFP with different scale factors. Let S_M^{MSFP} and S_H^{MSFP} be the scale factors used in a MSFP, and hospital's order quantities from the manufacturer and the in-house producer in period t are given by:

$$q_{Mt} = \min\{ (D - z_{Ht})^+, z_{Mt} + S_M^{MSFP}(D - z_{Ht} - z_{Mt})^+\} \quad (3.17)$$

$$q_{Rt} = S_H^{MSFP}(D - z_{Ht} - z_{Mt})^+ \quad (3.18)$$

The hospital's procurement decisions in the regular phase in period t, q_{Mt} and q_{Rt}, are determined using the same rule as a SFP. However, the optimal values for S_M^{MSFP} and S_H^{MSFP} are not generated using the SAA algorithm as discussed in section 3.5.2, but a direct application of the single period result. According to Proposition 3.2, the parameters in the MSFP are given by $S_M^{MSFP} = 0$, and $S_H^{MSFP} = 1$, if c_R is low, $S_M^{MSFP} = A_H$ and $S_H^{MSFP} = 0$, if c_R is high. The hospital can use a MSFP if she does not have sophisticated analytical tools (such as the SAA algorithm) to obtain the optimal policy parameters for a TIP or a SFP in a multi-period setting. Therefore, we consider the hospital's profit in this scenario as a lower bound for her expected profit in the multi-period model.

3.5.2 Solution and Evaluation Algorithm

Refer (I, K), (S_M, S_H), and (S_M^{MSFP}, S_H^{MSFP}) as the *policy parameters* in a TIP, a SFP and a MSFP, respectively. Let j be the index for the three inventory management policies, $j \in \{TIP, SFP, MSFP\}$. We calculate the approximate optimal values for the policy parameters and the two parties average profit over T periods under each inventory policy using the Sample Average Approximation (SAA) algorithm (Kleywegt et al., 2002). We use the same parameter values as indicated in Table 3.3.

Figure 3.8 illustrates the implementation of the SAA algorithm. The algorithm consists of three main steps: optimization, solution evaluation, and bound calculation. We elaborate on each step as follows.

Optimization

In the optimization step, we solve the optimal parameters for the three inventory management policies. For a TIP and a SFP, the policy parameters need to satisfy the following feasibility constraints: $I > 0$, $0 \leq k \leq 1$, $s_H \geq 0$, and $s_M \geq 0$, respectively.

For a MSFP, the candidate for the policy parameters are limited to two sets of values: $(S_M^{MSFP}, S_H^{MSFP}) = (0,1)$ and $(S_M^{MSFP}, S_H^{MSFP}) = (A_H, 0)$, which are the single period solutions. We first generate one realization of the manufacturer's random yield rate in each period, and define this sample set of yield rates as $\widehat{U}$. Next, for policy j, we compute the optimal policy parameters that maximize the hospital's average profit over T periods with the sample set $\widehat{U}$, $\widehat{\Pi}_i^j = \frac{1}{T}\sum_{t=1}^{T} \widehat{\Pi}_{it}^j$, where $\widehat{\Pi}_{it}^j$ is the hospital's profit in period t with sample $\hat{u}_t$. We record the optimal policy parameters, $(\hat{I}, \hat{K})$ for a TIP, $(\hat{S}_M, \hat{S}_H)$ for a SFP,

1. Optimization

For $t = 1, \dots, T$, generate a realization of the manufacturer's yield rate, $\hat{u}_t$, from i.i.d. uniform distribution $U_t(a, b)$, and define the set of these samples of yield rates as $\widehat{U}$.

a. Compute the optimal policy parameters that maximize the hospital's average profit over T periods with the sample set $\widehat{U}$, $\widehat{\Pi}_H^j = \frac{1}{T}\sum_{t=1}^{T} \widehat{\Pi}_{Ht}^j$, $j \in \{TIP, SFP, MSFP\}$, where $\widehat{\Pi}_{Ht}^j$ is the hospital's profit in period t with sample $\hat{u}_t$.

b. Record the following optimal values:

I. The optimal policy parameters: $(\hat{I}, \hat{K})$, $(\hat{S}_M, \hat{S}_H)$, and $(\hat{S}_M^{MSFP}, \hat{S}_H^{MSFP})$.

II. The manufacturer's average initial inventory under the optimal policy parameters, $\hat{z}_M^j = \frac{1}{T}\sum_{t=1}^{T} \hat{z}_{Mt}^j$, $j \in \{TIP, SFP, MSFP\}$, where $\hat{z}_{Mt}^j$ is the manufacturer's initial inventory in period t with sample $\hat{u}_t$.

2. Evaluation

For $t = 1, \dots, T$, generate another realization of the manufacturer's yield rate, $\check{u}_t$, from i.i.d. uniform distribution $U_t(a, b)$, and define the set of these samples as $\check{U}$.

a. Fix $(I, K) = (\hat{I}, \hat{K})$ for a TIP, $(S_M, S_H) = (\hat{S}_M, \hat{S}_H)$ for a SFP, and $(\hat{S}_M^{MSFP}, \hat{S}_H^{MSFP})$ for a MSFP, respectively.

b. Compute and record the hospital and the manufacturer's average profit over T periods with the sample set $\check{U}$ in the following two scenarios:

Scenario 1: The hospital knows $\check{z}_{Mt}$. Compute and record $\check{\Pi}_i^j$.

Scenario 2: The hospital does not know $\check{z}_{Mt}$, and she uses $\hat{z}_M^j$ as her belief in each period. Compute and record $\check{\Pi}_i^{j\prime}$, $i \in \{H, M\}$ and $j \in \{TIP, SFP, MSFP\}$.

3. Computation of the lower and upper bounds

a. Lower bound: compute the hospital and manufacturer's average profit over T periods under a MSPF, $\check{\Pi}_i^{MSFP}$.

b. Upper bound: compute $\overline{\Pi}_i$ in which case the manufacturer has a perfect yield rate, $i \in \{H, M\}$.

Figure 3.8: Implementation of SAA

and $(\hat{S}_M^{MSFP}, \hat{S}_H^{MSFP})$ for a MSFP, respectively.

We also record the manufacturer's average initial inventory under the optimal policy parameters, $\hat{z}_M^j = \frac{1}{T}\sum_{t=1}^{T} \hat{z}_{Mt}^j$, where $\hat{z}_{Mt}^j$ is the manufacturer's initial inventory in period t with sample $\hat{u}_t$.

Solution Evaluation

In the evaluation step, we evaluate the optimal policy parameters obtained in the optimization step. We first generate another realization of the manufacturer's yield rate in each period, and define the set of these samples as $\check{U}$. We fix the policy parameters at the optimal values obtained from the optimization step, i.e., fix $(I, K) = (\hat{I}, \hat{K})$ in a TIP, $(S_M, S_H) = (\hat{S}_M, \hat{S}_H)$ in a SFP, and $(S_M^{MSFP}, S_H^{MSFP}) = (\hat{S}_M^{MSFP}, \hat{S}_H^{MSFP})$ in a MSFP. Next, we compute and record the hospital and the manufacturer's average profit over T periods with the sample set $\check{U}$ and the optimal policy parameters. In reality, the hospital may not know the manufacturer's actual initial inventory in each period. Therefore, we consider two scenarios with different assumptions regarding the hospital's knowledge about the manufacturer's initial inventory in each period. In Scenario 1, the hospital knows the manufacturer's initial inventory in period t, $\check{z}_{Mt}$. We compute and record the two parties' average profit $\check{\Pi}_i^j$, $i \in \{H, M\}$ and $j \in \{TIP, SFP, MSFP\}$. In Scenario 2, the hospital does not know $\check{z}_{Mt}$, and she uses $\hat{z}_M^j$ (the manufacturer's average initial inventory solved in the optimization step) as her belief in each period. We compute and record the two parties' average profit in this scenario, $\check{\Pi}_i^{j\prime}$. Scenario 2 corresponds to the situation in which the hospital estimates the manufacturer's average inventory level using analytical approaches and uses the result to guide her future actions.

Bound Calculation

To evaluate the hospital's performance under a TIP and a SFP, we define two benchmark values for the worst case and the best case, respectively.

Lower bound:

As discussed previously, in the worst-case scenario, the hospital applies a myopic policy by using the optimal solutions in the single-period model. We consider the profits in this scenario as the lower bound for the hospital's average expected profit. Let $\underline{\Pi_i}$ denote the lower bound on the profit of player i, $\underline{\Pi_i} = \breve{\Pi}_i^{MSFP}$, $i \in \{H, M\}$

Upper Bound:

In the best-case scenario, the manufacturer has a perfect yield rate. Let $\overline{\Pi}_i$ be the average profit of player i over T periods in the best-case scenario, which is considered as an upper bound on the optimal profit of player i, $i \in \{H, M\}$

3.5.3 Performance Evaluation

Let $R_i^j = \hat{\Pi}_i^j / \overline{\Pi}_i$ be the *relative performance* of player i under inventory management policy j compared with the best-case scenario, $i \in \{H, M, \}$ and $j \in \{TIP, SFP, MSFP\}$. We present the relative performance R_i^j when the yield rate changes in three ways. First, we fix the upper limit of the yield rate, b, and only change the lower limit, a (Figure 3.9 and Figure 3.10). Next, we isolate the effect of the mean and the variance of the yield rate, by changing the mean with a fixed variance (Figure 3.11 a and b), and changing the variance with a fixed mean (Figure 3.11 c and d), respectively. We also present the impact of c_R on the relative performance R_i^j by considering a low value of c_R ($c_R = 1.1w$, Figure 3.10) and a high value of c_R ($c_R = 1.5w$, Figure 3.9 and Figure 3.11). Table 3.4 summarizes the main differences among the parameter values for the figures

Table 3.4: Summary of figures presented in subsection 3.5.3

	Mean of u_{Mt}	**Variance of u_{Mt}**	**Knowledge about z_{Mt}**	**Value of c_R**
Figure 3.7 a and b	Changing	Changing	Known	High
Figure 3.7 c and d	Changing	Changing	Unknown	High
Figure 3.8	Changing	Changing	Known	Low
Figure 3.9 a and b	Changing	Constant	Known	High
Figure 3.9 c and d	Constant	Changing	Known	High

Low c_R: $c_R = 1.1w$. High c_R: $c_R = 1.5w$

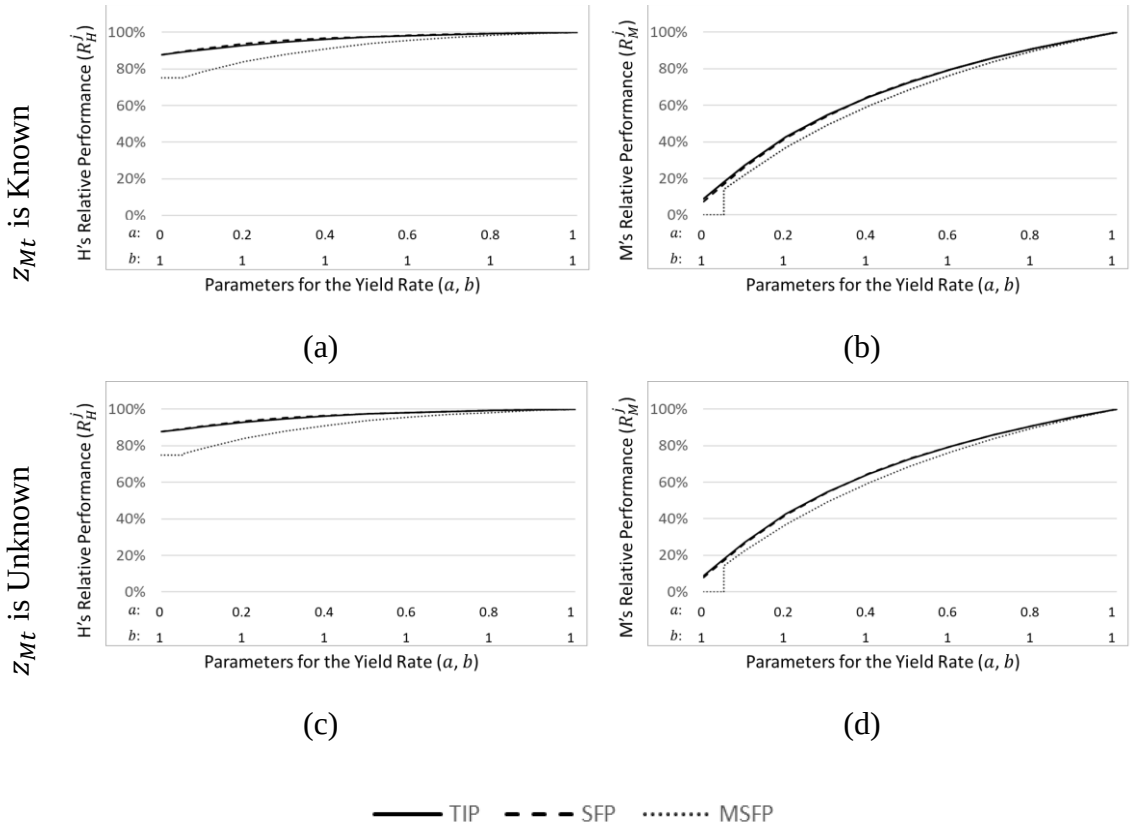

Figure 3.9: The relative performance of player i under inventory management policy j compared with the best-case scenario ($R_i^j = \hat{\Pi}_i^j / \overline{\Pi}_i$) with respect to a with fixed $b = 1$, $i \in \{H, M\}$, $j \in \{TIP, SFP, MSFP\}$. c_R is high ($c_R = 1.5w$). (a) and (b): z_{Mt} is known to the hospital. (c) and (d): z_{Mt} is unknown to the hospital.

presented in this section.

Refer to the TIP and the SFP as the *long-term inventory management policies* as opposed to the myopic policy (MSFP). We discuss some observations as follows. First, the graphs when z_{Mt} is known are very similar to those when z_{Mt} is unknown (Figure 3.9 a and b vs. c and d), indicating that the hospital's knowledge of the manufacturer's initial inventory does not have a significant impact on the performance of the inventory management policies. This may be because the manufacturer's average initial inventory solved in the optimization step is low. For all combinations of parameters considered in this section, $\hat{z}_M^j$ is less than 10% of the total demand. This feature can also be observed when c_R is low (the counterpart of Figure 3.8 when z_{Mt} is unknown), and different combinations of a and b (the counterpart of Figure 3.9 when z_{Mt} is unknown), which

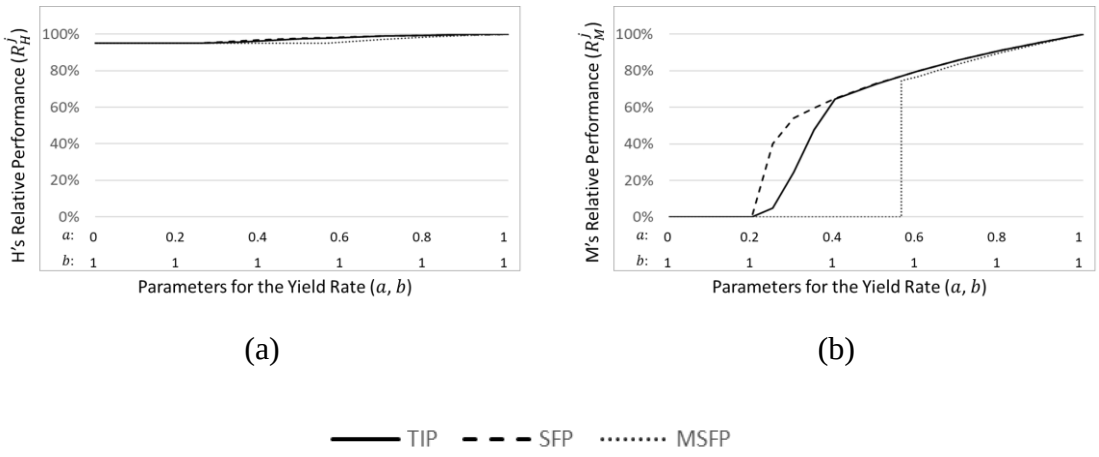

Figure 3.10: The relative performance of player i under inventory management policy j compared with the best-case scenario ($R_i^j = \widehat{\Pi}_i^j / \overline{\Pi}_i$) with respect to a with fixed $b = 1, j \in \{TIP, SFP, MSFP\}$. c_R is low ($c_R = 1.1\ w$) and z_{Mt} is known.

graphs are not presented in this paper due to repetitiveness. Therefore, we conclude that the implementation of the two long-term inventory management policies does not require the hospital to know the manufacturer's exact initial inventory in each period, as long as the hospital could come up with a reasonable estimation of the manufacturer's average inventory using analytical approaches. Another consideration is to let the manufacturer have a certain level of safety stocks, and verify whether this property still holds, which can be a future extension to this study.

Second, R_i^j is low if the manufacturer's yield rate is low (either a is low with a constant b as shown in Figure 3.9 and Figure 3.10, or the mean is low with a constant variance as shown in Figure 3.11 a and b), or the yield is highly uncertain (towards the left of Figure 3.11 c and d where the variance is large with a constant the mean). In other words, the hospital and the manufacturer's profits are low if the manufacturer's yield rate is low and/or highly uncertain. This result is intuitive, because the lower the reliability of the manufacturer (i.e., either the average yield rate is low, or the yield is varying in a wide range which is hard to predict and mitigate the risks), the lower the profits that both player can receive compared with a perfect yield scenario.

Third, a TIP and a SFP have similar performance for the hospital, and both policies perform well with different parameters of the yield rate and the hospital's regular

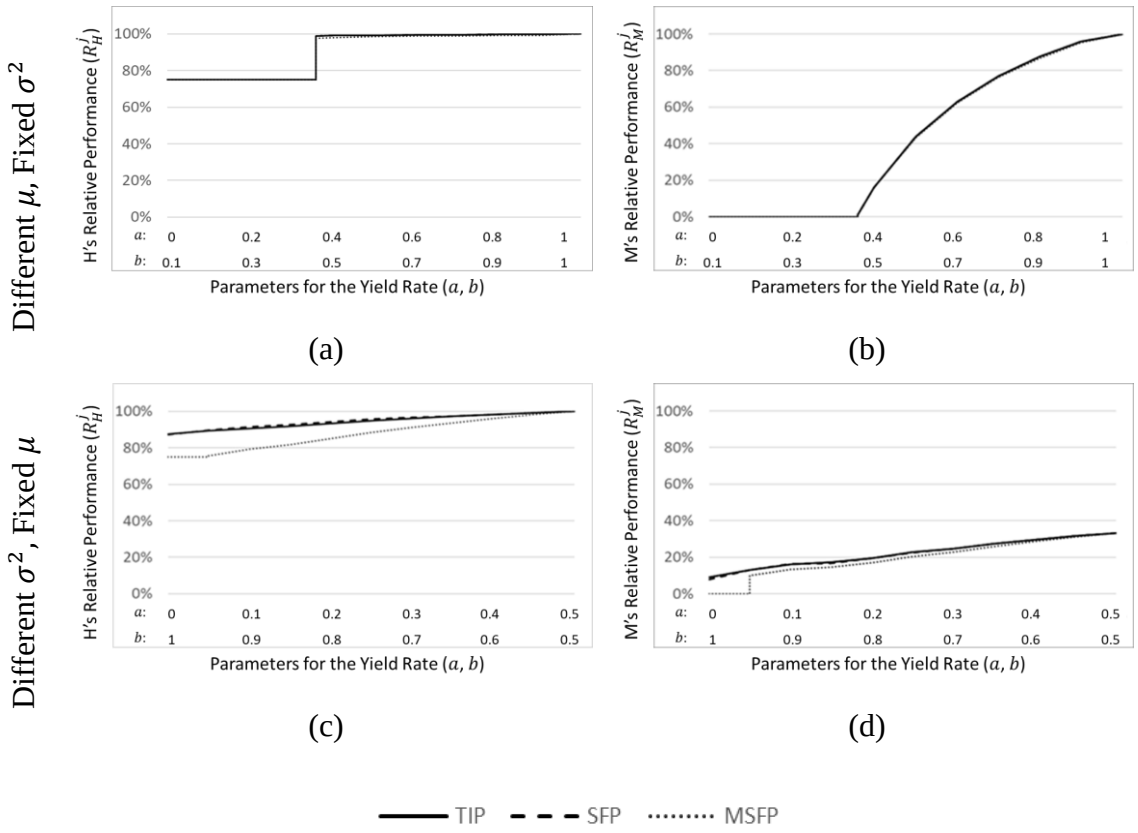

Figure 3.11: The relative performance of player i under inventory management policy j compared with the best-case scenario ($R_i^j = \widehat{\Pi}_i^j / \overline{\Pi}_i$), $j \in \{TIP, SFP, MSFP\}$. c_R is high ($c_R = 1.5w$), and z_{Mt} is known to the hospital. (a) and (b): with respect to σ^2 with fixed μ. (c) and (d): with respect to μ with fixed σ^2.

production cost. For example, when c_R is high, the hospital's relative performance under a TIP or a SFP compared with the best case scenario, R_H^j, is close to or greater than 80% (Figure 3.9 a and c, and Figure 3.11 a and c). When c_R is low, Figure 3.10 a shows that R_H^j is greater than 90%. The graphs for a TIP and for SFP are very close to each other in these figures, indicating a comparable performance of the two policies for the hospital.

In addition, the manufacturer's relative performance is lower than the hospital's relative performance ($R_M^j < R_H^j$) for any given yield rate and inventory management policy, indicating that the impact of the yield uncertainty on the manufacturer's relative performance is larger than that on the hospital's relative performance. For example, Figure 3.9 a and b show that $R_M^j < R_H^j$ holds in all regions. And when $a = 0$ and $b = 1$,

the relative performances of the hospital and the manufacturer are approximately 90% and 10%, respectively, under both a TIP and a SFP. The relationship that $R_M^j < R_H^j, j \in \{TIP, SFP\}$, can also be observed when c_R is low (Figure 3.10 a and b), and with different combinations of parameters for the yield rate (Figure 3.11). This property may be because the hospital moves first, i.e., the hospital takes into consideration the yield uncertainty and the manufacturer's best response function when choosing the policy parameters which determines her procurement quantities in each period. This property means the manufacturer may benefit more from improved yield rate and/or lower variability in his yield rate than the hospital does.

Note that the manufacturer's relative performance is zero under two circumstances. First, the hospital chooses a pure in-house production plan and does not purchase anything from the manufacturer because the benefit of a reliable source outweighs the benefit of a cheap but unreliable source. This situation is more likely to occur if c_R is low (for the same parameter regions $a \in [0, 0.2]$, $R_M^j > 0$ in Figure 3.9 b with a high c_R, and $R_M^j = 0$ in Figure 3.10 b with a low c_R), or the yield rate is highly uncertain. Another situation under which $R_M^j = 0$ is when the mean of the yield rate is sufficiently low such that the it is not profitable for the manufacturer to make any production regardless of the order quantity from the hospital. This observation is consistent with Lemma 3.3 in the single-period setting, because Lemma 3.3 can be rewritten as: if $\frac{a+b}{2} < \frac{c_M}{w+s_M}$, then $x_M^* = 0 \; \forall \; q_M$. For example, Figure 3.11 b shows that $R_M^j = 0$ when $a \leq 0.36$ and $b \leq 0.46$, and $R_M^j > 0$ when $a > 0.36$ and $b > 0.46$. Thus, there is a jump in the hospital's relative performance at $a = 0.36$ and $b = 0.46$ in Figure 3.11 a, which is caused by the change of the manufacturer's decision on whether to make production or not.

Moreover, the performance loss caused by a myopic policy compared with either a TIP or a SFP (i.e., $R_i^j - R_i^{MSFP}$, $i \in \{H, M\}$ and $j \in \{TIP, SFP\}$) depends on several parameters. The performance loss caused by a myopic policy is big if the yield rate is highly uncertain (Figure 3.9, Figure 3.10, and Figure 3.11 c and d). The performance loss

caused by a myopic policy is smaller (bigger) for the hospital (manufacturer) if c_R is lower (compare Figure 3.10 with Figure 3.9 and Figure 3.11 c and d). If the yield rate is less uncertain (with a small and constant variance), then a myopic policy may perform closely to a TIP and a SFP. This can be observed from Figure 3.11, in which the graphs for a MSFP are very close to the graphs for a TIP and a SFP.

Comparison of single-period vs. multi-period solutions

The comparison between a MSFP with the two long-term inventory management policies shows some commonalities and differences between the single-period and the multi-period solutions. One common feature for both the single-period and multi-period models is that if c_R is low, the yield rate is low or is highly uncertain, then the hospital prefers a pure in-house production plan (e.g., Figure 3.10 b, where $R_M^j = 0, j \in \{TIP, SFP, MSFP\}$); if c_R is high, the yield rate is high or is less uncertain, then the hospital prefers a pure-outsourcing plan (e.g., Figure 3.10 b, where R_M^j changes smoothly in the region $a > 0.4$ for $j \in \{TIP, SFP, MSFP\}$, and the region $a > 0.6$ for $j = MSFP$, respectively).

One major difference is whether the hospital will use a mixed strategy or not. Under a MSFP, the hospital will only use a pure procurement strategy (either a pure in-house production or a pure outsourcing strategy). Whereas under either a TIP or SFP, the hospital may use a pure procurement strategy or a mixed procurement strategy (procuring from both the manufacturer and the in-house producer). According to the single period solution, when the benefit of a reliable source (the in-house producer) outweighs the benefit of the cheaper but unreliable source (the manufacturer) (we characterize this situation by $c_R < \bar{c}_R$) , the hospital will only purchase the manufacturer's initial inventory which is cheaper and without any yield risk, but she will not order any additional quantities from the manufacturer. However, if the manufacturer starts a period without any initial inventory, then the hospital will not purchase anything from the manufacturer. This does not provide incentives to the manufacturer to make production when he is also using a myopic policy as assumed. Therefore, the hospital ends up using a pure in-house production plan. On the other hand, under a long-term inventory

management policy, the hospital chooses the policy parameters by considering the advantages and disadvantages of each source over the long term. If the advantages of one source significantly outweigh the other, then the hospital will use a pure strategy. Otherwise, she will use a mixed strategy to balance the advantages and disadvantages of each source.

One more difference is that the hospital is more likely to procure from the manufacturer in a long-term inventory management policy than in a myopic policy. Figure 3.10 b shows that the manufacturer's profit remains zero for a larger region under a MSFP than under a TIP or a SFP.

The differences between the long-term policies and the myopic policy have important implications. For example, in the range $a \in [0.2, 0.4]$ in Figure 3.10 b, the hospital's optimal policy parameters under a TIP or a SFP will result in a mixed procurement strategy, under which both the hospital and the manufacturer will receive positive profit and stay in the supply chain for a long term. Whereas the hospital's optimal policy parameters under a MSFP will result in a pure in-house production plan, under which the manufacturer may exit the supply chain eventually due to the lack of incentives, leaving the hospital's in-house producer the only source of the drug. This is not a favorable situation for a resilient drug supply chain to mitigate shortages. As previously discussed, a MSFP causes performance loss for both the manufacturer and the hospital. These indicate the importance of implementing an inventory management policy from a long-term perspective.

3.6 Discussion

Drug shortages are a serious problem threatening patients' safety and adding a significant financial burden to many health care systems. Several US hospitals created a generic drug manufacturer to mitigate drug shortages. Our study investigates circumstances under which the hospitals would benefit from owning an in-house manufacturer, and we examine the impact on the external pharmaceutical manufacturers.

Our study has theoretical contributions to the existing literature of supply chain

risk management. We creatively integrate a game-theoretic model with a multi-stage stochastic programing model to analyze the interactions between a hospital and an external manufacturer. We analyze the hospital's optimal ordering decisions from two sources (the external manufacturer, and an in-house manufacturer) under the presence of yield uncertainty. We analytically characterize the optimal decisions and profits for the hospital and the external manufacturer in a single-period model setting. Based on the insights from the single period solutions, we then propose two long-term inventory management policies (a Target Inventory Policy and a Scale Factor Policy) and evaluate the performance of the two inventory management policies in a multi-period setting using a heuristic.

Our study also provides managerial insights into the hospital's optimal sourcing strategies and inventory management policies. We show that the hospital would benefit from using an in-house manufacturer to make regular production if the in-house production cost is low, the external manufacturer's yield rate is low, or the external manufacturer's yield is highly uncertain. The hospital can also benefit from making emergency production at the in-house manufacturer, if the emergency production cost is lower than the sum of the drug revenue and the shortage cost caused by the unavailability of the drug. Drug shortages can be mitigated if the hospital operates an in-house manufacturer as her regular source or contingent source, which confirms the value of the establishment of Civica Rx on mitigating drug shortages.

The two long-term inventory management policies that we proposed have comparable and good performance for the hospital, indicating that the hospital can use either policy for the long-term inventory management practice. The manufacturer's yield uncertainty has a larger impact on his own long-term profit than that on the hospital's profit, indicating that it is beneficial for the manufacturer to make investment in improving his reliability.

In addition, this study has important implications for hospitals' drug procurement practice. Our analysis indicates that hospitals should trade-off between the procurement cost and other factors (e.g., shortage cost of the drug, and reliability of different

suppliers), instead of focusing only on procurement costs to choose the cheapest supplier, as observed in drug procurement practices in reality. Considering the long-term impact on the external manufacturers and the drug supply chain, hospitals should also procure drugs from both the internal and external manufacturers to avoid driving out the external manufacturers from the market.

Our study has several limitations. First, our study focuses on drugs shortages caused by manufacturing reasons, which is the major cause of drug shortages. Future studies can incorporate other causes, such as supply disruptions due to natural disasters and unavailability of raw material. Another cause is that Pharmaceutical companies may deliberately create shortages by stopping production or discouraging sales for a cheaper form to favor a newer and more profitable form sold by themselves or their parent companies (Palmer, 2014). Future studies may analyze the impact of this business decision on drug shortages. Second, we assume that there is only one external manufacturer if the hospital does not operate an in-house producer. A direction to extend our study is to consider multiple external manufacturers and to analyze the dynamics of their interactions with the hospital.

In addition, we assume all information is publicly known. However, the hospital and the manufacturer may hold private information about some parameters such as the production cost, and the yield rate. Another extension to our study is to incorporate information asymmetry and to examine the impact on the two parties' optimal decisions and profits. Moreover, our model did not capture the fixed production cost, and may overestimate the benefit of a dual-sourcing strategy. Future studies can capture the fixed production cost and provide further insights into the value of the establishment of the hospital's in-house producer. Furthermore, our model did not capture the impact on other hospitals that do not own an in-house manufacturing facility. It would be interesting to analyze the impact of the establishment of a hospital's in-house producer on other hospitals' benefit.

Finally, drug shortages are a complex problem, and the solutions from the mathematical model should be implemented in the real world with consideration from a

systematic and long-term perspective. For example, our model suggests that the hospital prefers a pure in-house production strategy if the in-house production cost is low, or the external manufacturer's yield rate is either low or highly uncertain. However, without any order quantities from the hospital, the external manufacturer may exit the market, leaving the hospital's in-house producer as the sole source for the drug. This is not a favorable situation for mitigating drug shortages. Therefore, future studies can analyze mechanisms to incentivize the external manufacturer's long-term production, which can be an extension to our work.

There are other ways to further extend our study. For example, one could endogenize drug price as a decision, which applies to the situation where drug prices are not strictly regulated but could be determined or largely influenced by powerful pharmaceutical companies. In addition, due to the limited information of Civica Rx at present, we are not able to estimate the model parameters using real data. As more information becomes available in the future, one could estimate the model parameters for specific drugs and perform case studies to validate the results of our model in a more realistic manner. Moreover, we did not consider hospital's strategy of holding safety stocks to mitigate shortages. This is mainly because many hospitals are using a just-in-time purchasing strategy due to expiration date of many pharmaceutical products as well as the pressure of reducing carrying cost by keeping the drug inventories lean (Green, 2015). Future studies may consider a strategy of holding safety stock to examine the relative benefit of producing drugs at an in-house manufacturing facility compared with carrying sufficient stocks.

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Chapter 4

4 Essay 3: Subsidies or Public Provision: Optimal Government Interventions on Mitigating Drug Shortages

4.1 Introduction

Drug shortages have gained increasing attention from health care policymakers in recent years as they are a major challenge faced by many health care systems (MacLeod, 2020; McGinley, 2019). To mitigate drug shortages, government agencies such as FDA in the US have taken actions to collaborate with the pharmaceutical industry by sharing information, searching for alternative manufacturers, and importing critical drugs in shortage from other overseas manufacturers (Food and Drug Administration, 2018). The health authorities in Canada can also implement an expedited review process to speed up patient access to alternative drugs during a shortage, or use special access programs to provide physicians access to non-marketed drugs for treating life-threatening conditions if conventional drugs are not available (The Multi-Stakeholder Steering Committee on Drug Shortages in Canada, 2017).

However, despite government actions, drug shortages are a persistent problem. Many shortages involve older, hard-to-make generic drugs where there are low-profit margins and high market concentration (Food and Drug Administration, 2019; McGinley, 2019). Among them, sole-source drugs (drugs that are produced by a single manufacturer) are particularly vulnerable to shortages caused by manufacturing problems since the disruption cannot be absorbed by alternative suppliers (Blank, 2018). Due to the low profit margin, other manufacturers have little incentives to enter the market. Some experts concern that the sole-sourcing situation is not likely to change without any interventions (De Weerdt et al., 2015; Dranitsaris et al., 2017; Gagnon, 2012).

Several policymakers argue that more government interventions are required to protect patient safety against drug shortages (MacLeod, 2020; McGinley, 2019; Milne et al., 2017). One strategy for government interventions is to provide subsidies. For

example, in 2018, the FDA appointed a task force to investigate drug shortages, including whether the US should develop a list of "essential drugs" which may get subsidies from the government. Another strategy for government intervention is to establish public manufacturers to produce certain critical drugs. In 2018, Senator Elizabeth Warren, proposed legislation that would create a new office within the Department of Health and Human Services to produce certain generic drugs in shortage (McGinley, 2019). Some Canadian experts also believe that Canada needs a Crown Corporation to manufacture crucial drugs that are not favored by pharmaceutical manufacturers in the private sector (MacLeod, 2020; Milne et al., 2017).

This study analyzes government interventions to mitigate drug shortages. We analyze two mitigating strategies: establishing a government-owned manufacturing facility, and providing subsidies. We evaluate the government's payoff under the two strategies and in the status quo, which captures the monetary health benefit and the shortage cost of a drug, the cost of public provision, and the cost of subsidies. We formulate the problem using a supply chain management approach. We focus on the shortages caused by manufacturing problems (e.g., quality issues, manufacturing delays), which are a major cause or drug shortages in many counties in recent years (JAVMA News, 2019; Malacos, 2019). We model drug shortages as a result of yield uncertainties at the manufacturing facilities.

Pharmaceutical supply chains often have wholesalers (also known as distributors) and manufacturers as the primary stakeholders who make procurement or production decisions. These decisions have significant impacts on the supply and availability of drugs. Wholesalers purchase and distribute a wide variety of pharmaceutical products so that hospitals and pharmacies do not need to deal with different manufacturers for different drugs (Fein, 2017; Healthcare Distribution Alliance, 2018). Wholesalers can increase the efficiency of pharmaceutical supply chains by saving time, effort, and costs for hospitals and pharmacies on drug procurement (The Multi-Stakeholder Steering Committee on Drug Shortages, 2017). Our study focuses on the situation where a single wholesaler is dealing with several hospitals and pharmacies in the jurisdiction of a

government. Our study also focuses on the most vulnerable pharmaceutical supply chain in which there is only one manufacturer.

We investigate the following research questions:

- Whether a government should establish a manufacturing facility to mitigate drug shortages?
- Could the government achieve the same performance level by using subsidies?
- What are the impacts of government intervention on the private sector?

We construct a game-theoretic model to analyze the interactions among three players in a pharmaceutical supply chain: a wholesaler, a private manufacturer, and a government. The wholesaler procures a drug from the manufacturer and sells it to the downstream demand, such as hospitals and pharmacies. The manufacturer's production is subject to random yield, which may cause drug shortages. The wholesaler chooses the order quantity from the manufacturer, and then the manufacturer chooses the planned production quantity. We formulate three individual models depending on the government's actions. The government can either do nothing (basic model/status quo); create a manufacturing facility (dual sourcing model); or provide subsidies to the wholesaler (subsidy model).

We assume the government subsidizes the wholesaler for two reasons. First, pharmaceutical wholesalers' profit margin is much lower than pharmaceutical manufacturers' profit margin. For example, US pharmaceutical manufacturers and wholesalers' average profit margin are 50% and 19% for generic drugs, and 76% and 1% for branded drugs, respectively (Sood et al., 2017). Second, pharmaceutical manufacturers are mainly facing R&D and sales risks, whereas pharmaceutical wholesalers are mostly facing inventory risks (Dai and Tayur, 2018; Sood et al., 2017). Therefore, we assume the government subsidizes the wholesaler to increase the wholesaler's profit margin and incentivize an increase of the wholesaler's order quantity from the manufacturer.

We consider two types of subsidies to the wholesaler: a unit subsidy to its procured quantity, and a unit subsidy to its sales quantity, respectively. These two types of subsides are studied in previous supply chain literature as incentives provided by manufacturers or donors to increase retailers' order quantity under demand uncertainties (Dreze and Bell, 2003; Taylor and Xiao, 2014). In those studies, retailers can be considered as intermediaries between manufacturers and consumers. Whereas in our study, wholesalers can be considered as the intermediary between the manufacturers and the downstream party (hospitals and pharmacies which represent the demand of the drug). Therefore, we adopt the same structure of the unit subsidies and analyze whether they can effectively mitigate supply side uncertainties.

We first analytically characterize the optimal values in each of the three models. Next, we compare the performance of each mitigating strategy (the dual sourcing strategy and the subsidy strategy) with the status quo. This comparison provides insights into the situations in which the government prefers one strategy over the other, or only one particular strategy is available. We finally compare the three models together and examine the government's optimal choice if both strategies are available options.

Our study has several interesting findings. An advantage of both mitigating strategies is that both a subsidy strategy and a dual sourcing strategy can effectively reduce the shortage amounts compared with the status quo. A difference between the two mitigating strategies is their abilities to align the incentives of different parties. A subsidy strategy can be mutually preferred by the three parties and achieve Pareto improvement, whereas a dual sourcing strategy can align the incentives of the government and the wholesaler, but the manufacturer is no better off under a dual sourcing strategy compared with the status quo. Therefore, under a dual sourcing strategy, the government and/or the wholesaler may need to consider incentives to the private manufacturer. Otherwise, the private manufacturer may leave the market in the long term, which is not a favorable situation in which the public manufacturer became the sole source of the supply chain.

This study also has policy implications regarding governments' decisions on the types of shortage mitigating policies under different circumstances. For example, we

found that if the wholesaler's profit margin is low and the shortage cost is high, then the government should implement a subsidy strategy. The subsidy should be paid to the wholesaler based on its unit procurement cost rather than its unit selling price. If the wholesaler's profit margin is intermediate and the shortage cost is high, then the government should produce drugs at a public manufacturer. If the shortage cost is low and the wholesaler's profit margin is either low or high, then the government does not need to take any actions.

4.2 Literature Review

This study is closely related to four streams of literature: (1) supply chain disruptions with multiple decision-makers; (2) lot sizing and sourcing strategies to mitigate supply chain disruptions; (3) subsidies to mitigate supply chain uncertainties ; (4) mitigating strategies for drug shortages from a pharmaceutical supply chain perspective. We discussed streams 1, 2 and 4 in the literature review (section 3.2) in Essay 2 and will skip them in this Essay to avoid repetition. We discuss stream 3 and the contribution of this study as follows.

Subsidy strategies to mitigate supply uncertainties

Xia et al. (2011) studied two contract mechanisms (an option contract and a firm order contract) to share demand and supply risk between an unreliable supplier and a buyer. The authors analyzed two operational strategies that can be used by the buyer to mitigate the supply disruption risk: the use of an alternate reliable supplier and to provide subsidies to the supplier to improve reliability. The subsidy in their study is a costly investment to reduce the probability of disruption, which is a different type of subsidy from our study.

Taylor and Xiao (2014) investigated a donor's optimal subsidy decision to improve the availability and affordability of recommended malaria drugs provided by the private-sector in some developing countries. The authors constructed a game-theoretic model between a donor and a retailer of a malaria drug subject to demand uncertainties. This is the only subsidy study on mitigating demand side uncertainties that we include in

this literature review because of the similarity of their subsidies with our study. Their study compared two types of subsidies that the donor can provide to the retailer to increase the availability of the drug: a per-unit purchase subsidy (paid to the retailer's purchased quantities), and a per-unit sales subsidy (paid to the retailer's sales quantity). The author found that donors should only subsidize retailers' purchase but not the sales.

Raz and Ovchinnikov (2015) analyzed government rebates and subsidies for public interest goods with externalities (e.g., electric vehicles and vaccines). The authors extended the newsvendor framework with price-dependency to account for externalities. Their study found that rebates to consumers are much better than subsidies to manufacturers. Cai et al. (2017) studied contracts to coordinate a vendor-managed inventory (VMI) supply chain with one retailer and one unreliable supplier under the presence of yield uncertainty. The authors compared two contracts: an option contract, and a subsidy contract, and they also considered a replenishment tactic. In their subsidy contract, the retailer will pay the supplier a unit subsidy for unsold products. Guo et al. (2019) studied government subsidy, optimal recovery and production strategies for the closed-loop supply chain with supply disruption. The authors constructed a model with a manufacturing and a remanufacturing system, and assumed that the buyback cost, return rate and remanufacturing cost are function of quality level of returned item. The study showed that the government can apply an appropriate subsidy policy to encourage the recycling of returned items.

Peng and Pang (2019) studied the optimal strategies for an agricultural supply chain consisting of three players: a risk-averse farmer who is subject to a yield uncertainty, a risk-neutral supplier and a risk-neutral distributor. The authors consider a subsidy which can be offered by a government to the farmer in terms of the acreage of the farm size. Ye et al. (2020) studied a bioenergy supply chain consisting of a government, a bioenergy producer, and n risk-averse farmers who grow the biomass feedstocks with yield uncertainties. The authors compared two subsides that can be provided by the government to mitigate supply uncertainties: a farmer subsidy program (subsidy to the farmers per unit acreage) and a bioenergy producer subsidy program (subsidy to the bioenergy producer's per unit of bioenergy produced). They found the

conditions under which each subsidy can more effectively increase the reliability of feedstocks supply.

The contribution of this research

In this research of government mitigating strategies for drug shortages, we make the following contributions:

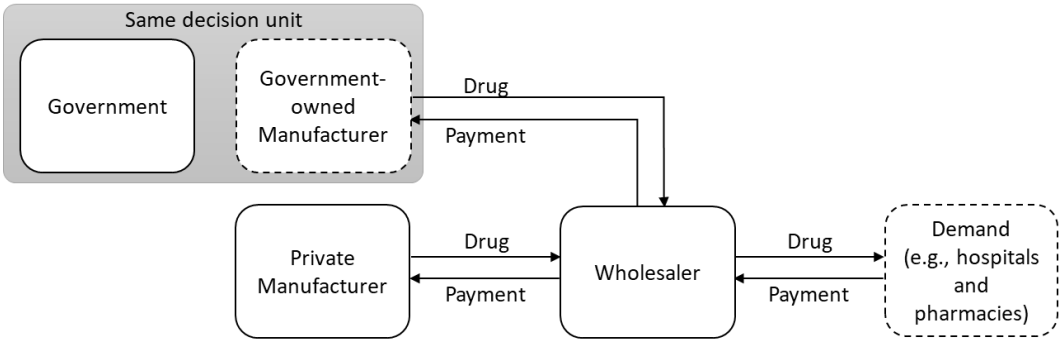
- We develop a pharmaceutical supply chain model that incorporates interactions among three important decision-makers – a manufacturer, a wholesaler, and a government. We are not aware of any previous studies that captured the interactions among these three parties in a single model to study supply chain risk management in either pharmaceutical or non-pharmaceutical settings. Our study incorporates a total number of five decisions that are sequentially made by the three parties, and we are able to analytically characterize the optimal solutions.

- We evaluate two strategies which can be implemented by government agencies: establishing a public manufacturer, and providing subsides to the wholesaler. We are not aware of any existing studies comparing these two types of strategies from the government's perspective. Our study provides economical foundations for the advantages and disadvantages of each strategy. It has theoretical contributions to the existing literature of mitigating supply disruption, and it also has policy implications for government interventions to mitigate shortages.

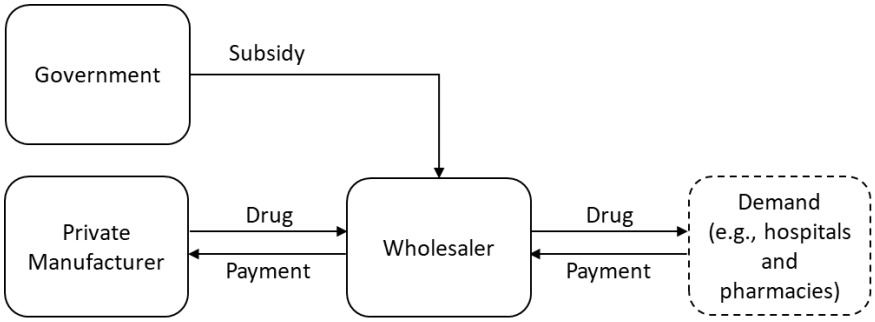
4.3 Model

We develop a pharmaceutical supply chain consisting of three decision-makers: a *wholesaler* (W), a *private manufacturer* (M, the *manufacturer*) that is subject to yield uncertainty, and a *government* (G). Let i be the index for the three decision-makers, $i \in \{W, M, G\}$. We consider a single period setting for one drug. We formulate three individual models depending on the government's actions. The government can either do nothing (basic model/status quo); operate a government-owned manufacturer (dual sourcing model); or provide subsidies to the wholesaler (subsidy model). Figure 4.1

(a) Basic Model



(b) Dual Sourcing Model



(c) Subsidy Model

Figure 4.1: A schematic illustration of the pharmaceutical supply chain. (a) Basic Model/Status Quo (b) Dual Sourcing Model. (c) Subsidy Model.

schematically illustrates the three models in the pharmaceutical supply chain. We assume that all parameters and decisions are publicly known to all parties. We adopt the convention that $A^+ = \max\{0, A\}$, and $E[\cdot]$ denotes the expected value. All model notation is summarized in Table 4.1.

4.3.1 Basic Model

We first describe the basic model (Model B, denoted by superscript B) in which the

Table 4.1: Summary of notation

Symbol	Description
Decisions	
q_i	Wholesaler's order quantity from player i, $i \in \{M, G\}$
x_M	Manufacturer's planned production quantity
x_G	Government's planned production quantity at the in-house producer
γ_w	Government's s subsidy to the wholesaler's unit procurement cost
γ_p	Government's s subsidy to the wholesaler's unit selling price
Random Variable	
u_M	Manufacturer's random yield rate, $u_M \in [\underline{u}, \bar{u}]$, with a PDF $f(\cdot)$, a CDF $F(\cdot)$, a mean μ, and a variance σ^2
Parameters	
i	Index for the three players, $i \in \{G, M, W\}$. G: government; M: the private manufacturer; W: the wholesaler
j	Index for the models, $j \in \{B, S, D\}$. B: basic model; S: subsidy model; D: dual sourcing model
d	Wholesaler's deterministic demand for the drug
s_G	Government's unit shortage cost
c_i	Player i's unit production cost, $i \in \{G, M\}$
w_i	The drug price that the wholesalers pays to player i, $i \in \{G, M\}$
p	Wholesaler's unit selling price of the drug
m	The wholesaler's markup parameter, $m > 1$. $m - 1$ is the markup percentage of the wholesaler's unit selling price over w_M i.e., $p = mw_M$
b	The monetary health benefit of each unit of the drug
Calculated quantities	
y_i^j	The delivered quantity from player i in Model j. The expected delivered quantity for player i is $Y_i^j = E[y_i^j]$
Π_i^j	The expected utility function for player i
z^j	The shortage amount in model j. The expected shortage amount is $Z^j = E[z^j]$

government does not take any action to mitigate shortages. We assume that the wholesaler is facing a deterministic demand d for a drug. This is because a sudden increase in demand is typically not a major cause of drug shortages (Malacos, 2019). This assumption is also used in other modeling studies on supply uncertainties (e.g., Hou et al. (2017) and Tucker et al. (2019)), and it allows us to focus on the supply-side uncertainties. The wholesaler procures the drug from the manufacturer at an exogenous wholesale price w_M. Although drug prices may increase after a drug shortage (Alevizakos et al., 2016), our model applies to the situation in many countries where drug price is

highly regulated and is not likely to be affected by the manufacturer or change in the short run (Hou et al., 2017).

The wholesaler sells the drug to the downstream parties in the drug supply chain at an exogenous price p. The selling price represents a markup over the drug price, i.e., $p = mw_M$, where $m > 1$ is the wholesaler's *markup parameter* which is a constant. This is because the fees from wholesaling and distributing services are generally computed as a percentage of drugs' list price (Fein, 2015). The wholesaler's markup may be affected by legislations, therapeutic class, generic vs. brand-name drugs, and many other factors. We assume that the manufacturer faces a stochastically proportional yield rate u_M. Let u_M be a continuous random variable distributed on the interval $[\underline{u}, \bar{u}]$, $0 \leq \underline{u} < \bar{u} \leq 1$, according to a probability density function (PDF), $f(\cdot)$, and a cumulative distribution function (CDF), $F(\cdot)$, with a mean, μ, and a variance σ^2.

Taking into consideration the yield uncertainty, the wholesaler chooses the order quantity from the manufacturer, q_M. Next, the manufacturer chooses the production quantity, x_M, and produces the drug at a unit production cost $c_M \leq w_M$. The yield uncertainty is realized, and the production is completed. The manufacturer delivers y_M^B to the wholesaler, $y_M^B = \min\{u_M x_M, q_M\}$ (i.e., the manufacturer will deliver the realized production quantity, $u_M x_M$, up to the wholesaler's order quantity). The wholesaler then distributes a total amount of y_W^B to the downstream parties, $y_W^B = \min\{d, y_M^B\}$ (i.e., the wholesaler will distribute all available inventories up to the demand for the drug).

Each unit of the drug has a benefit b, which could be considered as the expected monetary health benefit of consuming one unit of the drug. We assume that the government cares about the net monetary health benefit, $b - p$. This is because of the public nature of the government, i.e., the government cares about the purchasing cost to achieve the health benefit. This assumption is similar to other modeling studies (e.g., Barros (2011) and Mahjoub et al. (2018)).

The drug is subject to shortages due to yield uncertainty and possible double marginalization (i.e., the manufacturer and the wholesaler have different incentives and

markups in the supply chain, and this may cause inefficiency of their production decisions compared with the social optimal level). The shortage amount is the unfulfilled demand, $z^B = d - y_W^B$. The government incurs a unit shortage cost for the unfulfilled demand, $s_G \geq 0$. This shortage cost should include patients' welfare loss, staff time on searching for alternative drugs, and any other costs that are caused by the unavailability of the drug and the government cares about. If the drug enables complex procedures (e.g., saline solution, painkillers, and anesthetics required for surgeries) or is a lifesaving drug which has a large impact on patients' welfare, then s_G can be very high.

The expected profit for player i in the basic model, Π_i^B, is calculated as follows.

$$\Pi_W^B(q_M) = E[py_W^B - w_M y_M^B] \tag{4.1}$$

$$\Pi_M^B(x_M)|q_{WM} = E[w_M y_M^B - c_M q_M] \tag{4.2}$$

$$\Pi_G^B|x_M, q_M = E[(b-p)y_W^B - s_G(d - y_W^B)] \tag{4.3}$$

The wholesaler's expected profit function (Equation 4.1) consists of the revenue of selling the drug and the procurement cost paid to the manufacturer. The manufacturer's expected profit function (Equation 4.2) consists of the payment received from the wholesaler and the production cost. Although the government is not an active decision-maker in the basic model, we calculate its expected utility for comparison with the other strategies. The government's expected utility (Equation 4.3) captures the total net monetary benefit of the drug and the total shortage cost, which can be considered as the patient welfare. The government can be considered as a health authority – it cares about patient welfare but does not concern the benefit of the companies (i.e., the wholesaler and the manufacturer).

4.3.2 Dual Sourcing Model

Under a dual sourcing strategy (Model D, denoted by superscript D), the government operates a government-owned manufacturer to provide additional supplies to the wholesaler to mitigate shortages. The government makes decisions on behalf of the government-owned manufacturer, i.e., they are the same decision unit. To differentiate

the two manufacturer facilities, we refer to the private manufacturer as *the manufacturer*, and we refer to the government-owned manufacturer as *GM*.

GM produces the drug at a unit production cost $c_G > c_M$. We assume that GM is perfectly reliable, i.e., it has a perfect yield rate. The reason is three-fold. First, some manufacturers produce drugs using decades-old equipment, which are vulnerable to manufacturing problems (Woodcock and Wosinska, 2013). The newly established GM may be more reliable than the manufacturer because of the newer equipment and advanced technology. Second, the government's main motivation for operating a manufacturer is to produce the drug in a more reliable way to mitigate shortages. Therefore, GM may have better maintenance and quality control than the manufacturer does. Third, GM may still have random yield, but it keeps on working until the planned quantity is fully produced, which also explains why its production cost is higher than the manufacturer. The assumption of a perfect yield rate for the more reliable supplier is also used in other studies on supply disruptions, such as Tomlin (2006) and Chen et al. (2012).

GM provides the drug to the wholesaler at a wholesale price $w_G > w_M$, i.e., the more reliable source is more expensive. As in the basic model, p still represents a markup on w_M, i.e., $p = mw_M$. Note that we do not make any assumption about the relative ordering of w_G and c_G. This is because the government may be willing to provide the drug at a price that is lower than its production cost, due to the shortage cost and/or benefit of the drug.

At the beginning of the period, the wholesaler chooses the order quantities from the manufacturer and GM, q_M and q_G, respectively. Next, the manufacturer and GM simultaneously choose the production quantities, x_M and x_G, respectively. The two manufacturing facilities produce the drug, and the yield rate u_M is realized. The manufacturer and GM then deliver y_M^D and y_G^D to the wholesaler, respectively.

We assume that the wholesaler may purchase more than the original order quantity from the two manufacturers if needed. To explain this assumption, we imagine dividing y_i^D into two rounds of procurement, y_{i1}^D and y_{i2}^D, respectively, i.e., $y_i^D = y_{i1}^D + y_{i2}^D$, $i \in \{M, G\}$. The first round of procurement is based on the order quantities in the

original procurement contracts (i.e., q_{WM} and q_G). In this first round of procurement, the manufacturer and GM deliver up to the original order quantities, $y_{M1}^D = \min\{u_M x_M, q_M\}$ and $y_{G1}^D = \min\{x_G, q_G\}$.

If there is still a shortage after the first round of procurement, then the wholesaler can procure the leftover stocks from the two manufacturing facilities in the second round, which allows the wholesaler to purchase more than the order quantities indicated in the original contract. Because $w_M < w_G$, the wholesaler will first exhaust the manufacturer's leftover stock before purchasing any additional unit from GM. Therefore, in the second round of procurement, the wholesaler purchases y_{M2}^D unit from the manufacturer, where $y_{M2}^D = \min\{(u_M x_M - q_M)^+, (d - y_{M1}^D - y_{G1}^D)^+\}$. The first term in y_{M2}^D is the manufacturer's leftover stock, and the second term is the quantity still short after the first round of procurement. The wholesaler then purchases y_{G2}^D from GM, where $y_{G2}^D = \min\{(x_G - q_G)^+, (d - y_{M1}^D - y_{G1}^D - y_{M2}^D)^+\}$. The first term in y_{G2}^D is the GM's leftover stock, and the second term is the wholesaler's shortage quantity after exhausting the manufacturer's leftover stocks. The wholesaler then uses its available stocks to satisfy the demand, and its delivered quantity is $y_W^D = \min\{d, y_M^D + y_G^D\}$. Finally, costs and revenues are realized.

Player i's expected profit in Model D, Π_i^D, is calculated as follows.

$$\Pi_W^D(q_M, q_G) = E[p y_W^D - w_M y_M^D - w_G y_G^D] \tag{4.4}$$

$$\Pi_M^D(x_M)|q_M, q_G = E[w_M y_M^D - c_M x_M] \tag{4.5}$$

$$\Pi_G^D(x_G)|q_M, q_G = E[(b-p) y_W^D + w_G y_G^D - c_G x_G - s_G(d - y_W^D)] \tag{4.6}$$

The wholesaler's profit function (Equation 4.4) captures the revenue and the procurement costs paid to the two manufacturing facilities. The manufacturer's profit (Equation 4.5) is the same as in the basic model. The government's utility (Equation 4.6) includes the net monetary benefit, revenue received from the wholesaler, production cost, and shortage cost.

4.3.3 Subsidy Model

Under a subsidy strategy (Model S, denoted by a superscript S), the government does not own a manufacturing facility. Instead, it uses subsidies to mitigate shortages. As discussed in the introduction, we assume that the government provides two types of subsidies to the wholesaler. The first type is a unit subsidy to the wholesaler's unit procurement cost (the procurement cost subsidy), $\gamma_w < w_M$, which brings the wholesaler's actual unit procurement cost down to $w_M - \gamma_w$. The second type is a unit subsidy to the wholesaler's unit selling price (the selling price subsidy), γ_p, which brings the wholesaler's actual unit revenue up to $p + \gamma_p$.

In the subsidy model, the government chooses the value of the subsidy at the beginning, and then, the sequence proceeds as described in the basic model. The expected utility function for Player i in Model S, Π_i^S, can be expressed as follows.

$$\Pi_G^S(\gamma_w, \gamma_p) = E\left[(b-p)y_W^S - s_G(d - y_W^S) - \gamma_w y_M^S - \gamma_p y_W^S\right] \tag{4.7}$$

$$\Pi_W^S(q_M)|\gamma_w, \gamma_p = E\left[(p+\gamma_p)y_W^S - (w_M - \gamma_w)y_M^S\right] \tag{4.8}$$

$$\Pi_M^S(x_M)|q_M, \gamma_w, \gamma_p = E[w_M y_M^S - c_M x_M] \tag{4.9}$$

Where $y_M^S = \min\{u_M x_M, q_M\}$ and. The government's utility function (Equation 4.7) includes the net benefit of the drug, the shortage cost, and the subsidy payments. The wholesaler's profit function (Equation 4.8) captures the actual revenue from selling the drug and the actual procurement cost, including the subsides. The manufacturer's profit function (Equation 4.9) includes revenue and production costs.

Let j be the index for the superscript for each model, $j \in \{B, D, S\}$. Figure 4.2 summarizes the sequence of events in each model.

4.4 Structural Results

In this section, we derive the closed-form solutions and discuss some structural properties. In model j, player i makes decision(s) to maximize its expected utility according to the game sequence. We solve each model using backward induction.

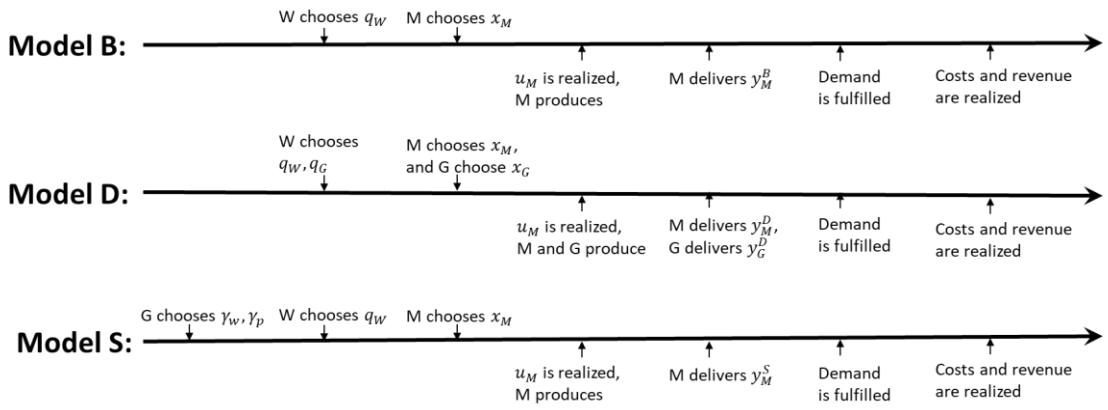


Figure 4.2: The sequence of events in each model

Throughout the analysis, we assume that u_M is uniformly distributed between 0 and 1, to simplify the model and obtain closed-form solutions. This is a commonly used assumption (e.g., Keren, 2009 and Li et al., 2010). The terms "increasing" and "decreasing" in this section are used in the weak sense (i.e., increasing means non-decreasing, and decreasing means non-increasing.)

4.4.1 Model B

We first solve the manufacturer's expected profit function and obtain its best response function for the production decision, $\tilde{x}_M^B$, which is presented in Lemma 4.1. Details of the formal proofs are found in the appendix.

Lemma 4.1: *The manufacturer's best response function for the production decision for any given order quantity from the wholesaler is given by:*

a. When $\mu w_M \leq c_M$, $\tilde{x}_M^B = 0 \; \forall q_M$.

b. When $\mu w_M > c_M$, $\tilde{x}_M^B(q_M) = \alpha q_M$, *where* $\alpha = \sqrt{\frac{w_M}{2c_M}} > 1$.

Lemma 4.1.a indicates that when the expected revenue of producing the drug (μw_M) is less than the production cost, then the manufacturer will not produce anything regardless of the wholesaler's order quantity. Therefore, we assume $\mu w_M > c_M$ (i.e., $w_M > 2c_M$) throughout the analysis to guarantee the manufacturer's participation in the

game. Lemma 4.1.b indicates that when $\mu w_M > c_M$, the manufacturer uses a coefficient, α, to adjust its planned production quantity for any given order quantity from the wholesaler. Based on the assumption that $w_M > 2c_M$, we know $\alpha > 1$, i.e., the manufacturer's planned production quantity is always greater than then wholesaler's order quantity. This is an intuitive result due to the existence of the yield uncertainty.

Let $*$ be the superscript for the optimal values. We solve the wholesaler's expected profit function and obtain its optimal ordering decision, q_M^{B*}, which is summarized in Proposition 4.1.

Proposition 4.1: *The wholesaler's optimal ordering quantity is given by:*

$$q_M^{B*} = \tau d, \text{ where } \tau = \sqrt{\frac{m}{(2\alpha-1)}}.$$

Proposition 4.1 indicates that the wholesaler uses a coefficient τ to adjust its order quantity as a function of the demand. Let S^{j*} be the expected shortage amount under equilibrium in model j. We then present the expected shortage amount in Model B, S^{B*}.

Lemma 4.2: *The expected shortage amount under the optimal solution in Model B is given by*

$$S^{B*} = \frac{d}{2\alpha\tau}.$$

Lemma 4.2 indicates that the expected shortage amount is jointly affected by the manufacturer and the wholesaler's adjustment coefficient α and τ. We examine some properties of the optimal solutions and shortage amount in Proposition 4.2.

Proposition 4.2: *The optimal solutions and shortage amount in Model B have the following properties:*

a. $\frac{\partial q_M^{B*}}{\partial m} > 0;\ \frac{\partial x_M^{B*}}{\partial m} > 0;\ \frac{\partial S^{B*}}{\partial m} < 0$

b. $\frac{\partial q_M^{B*}}{\partial w_M} < 0;\ \frac{\partial x_M^{B*}}{\partial w_M} > 0;\ \frac{\partial S^{B*}}{\partial w_M} < 0$

c. $\frac{\partial q_M^{B*}}{\partial c_M} > 0; \frac{\partial x_M^{B*}}{\partial c_M} < 0; \frac{\partial S^{B*}}{\partial c_M} > 0$

Proposition 4.2.a indicates the impact of the wholesaler's markup (m) on the optimal values. As m increases, the wholesaler will increase its order quantity to pursue a high profit, and the manufacturer will increase its production quantity. As a result, the shortage amount will decrease. Proposition 4.2.b indicates that the manufacturer's selling price (w_M) has an opposite impact on the wholesaler and the manufacturer's optimal decisions. As w_M increases, knowing that the manufacturer will increases the adjustment factor α for any order quantity, the wholesaler will decrease its order quantity accordingly. On the other hand, as w_M increases, the manufacturer will increase its production quantity to pursue a higher revenue. As a result, the shortage amount is decreasing in w_M. Proposition 4.2.c shows that the manufacturer's unit production cost (c_M) has an opposite impact with w_M on the manufacturer and the wholesaler's optimal decisions as well as the shortage amount. This is because w_M is the manufacturer's unit revenue, whereas c_M is its unit production cost.

4.4.2 Model D

In Model D, we first solve the manufacturer and the government's expected utility functions simultaneously to generate their best response functions $\tilde{x}_M^D$ and $\tilde{x}_G^D$, respectively.

Lemma 4.3: *The manufacturer and the government's best response functions for any given order quantities from the wholesaler are given by:*

$$\tilde{x}_M^D(q_M) = \alpha q_M$$

$$\tilde{x}_G^D(q_M) = (d - \beta\alpha q_M)^+$$

Where α *is as defined in Lemma 4.1 and* $\beta = \frac{c_G}{b-p+s_G+w_G}$.

Lemma 4.3 states the following: the manufacturer's best response function is the same as it in the basic model; GM uses an adjustment factor β to adjust the manufacturer's production quantity, and produces the gap between the adjusted quantity

($\beta\alpha q_M$) and the demand. Note that GM will not produce anything if the adjusted quantity $\beta\alpha q_M$ is greater than the demand, i.e., GM only produces to make up an adjusted expected demand shortfall.

We next solve the wholesaler's optimal order quantities. Proposition 4.3 summarizes three possible equilibrium states of the optimal procurement and production plans.

Proposition 4.3: *The optimal procurement and production plan of the three players will be one of the three following cases:*

a. $q_M^{D*} = \theta d,\ q_G^{D*} = 0,\ x_M^{D*} = a\theta d,\ x_G^{D*} = (1 - a\theta\beta)d,\ and\ S^{D*} = \frac{\alpha\beta^2\theta d}{2}$

b. $q_M^{D*} = 0,\ q_G^{D*} = d,\ x_M^{D*} = 0,\ x_G^{D*} = d,\ and\ S^{D*} = 0$

c. $q_M^{D*} = \tau d,\ q_G^{D*} = 0,\ x_M^{D*} = \alpha\tau d,\ x_G^{D*} = 0,\ and\ \ S^{D*} = \frac{d}{2\alpha\tau}$

Where $\theta = \sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+w_M(2\alpha-1)}}$, *and* $\tau > \theta$.

In plan a, the wholesaler anticipates that GM will produce some backup quantities even without any order quantity from the wholesaler at the beginning. Therefore, the wholesaler orders everything from the manufacturer at the beginning and takes advantage of GM's produced quantities when the manufacturer's realized production quantity is lower than demand. In plan b, the wholesaler orders everything from the government at the beginning. Because GM has a perfect yield rate, both the wholesaler's order quantity and the GM's production quantity are equal to the demand, whereas the manufacturer does not produce anything. Plan c is the same as the basic model: GM does not produce anything in both cases. The wholesaler's adjustment factor for its order quantity from the manufacturer in plan c is greater than that in plan a, i.e., $\tau > \theta$, because there are no backup quantities available at GM in plan c.

In Proposition 4.3 we refer plan a as a *mixed procurement plan*; plan b as a strict *public procurement plan*; and plan c as a strict *private procurement plan*. We use the

term "*plan*" for the three equilibrium states in Model D (i.e., the wholesaler's procurement plans in Model D), and we use the term "strategy" for the government's interventions (i.e., no intervention, subsidy, and dual sourcing).

Let Π_W^{Da}, Π_W^{Db} and Π_W^{Dc} be the wholesaler's optimal profit in plan a, b and c in Proposition 4.3, respectively. Proposition 4.4 provides a pairwise comparison of the wholesalers' optimal profits in the three plans depending on different parameter values.

Proposition 4.4: *The relative values of the wholesaler optimal profits in the three procurement plans are as follows:*

a. *Comparing* Π_W^{Da} *with* Π_W^{Db}*:*

   I. *If* $c_G \le c_G^{ab}$*:* $\Pi_W^{Da} > \Pi_W^{Db}$

   II. *If* $c_G > c_G^{ab}$

      i. *If* $s_G \le s_G^{ab}$*:* $\Pi_W^{Da} \le \Pi_W^{Db}$

      ii. *If* $s_G > s_G^{ab}$*:* $\Pi_W^{Da} > \Pi_W^{Db}$

b. *Comparing* Π_W^{Da} *with* Π_W^{Dc}*:*

   I. *If* $c_G \le c_G^{ac}$*:* $\Pi_W^{Da} > \Pi_W^{Dc}$

   II. *If* $c_G > c_G^{ac}$

      i. *If* $s_G \le s_G^{ac}$*:* $\Pi_W^{Da} \le \Pi_W^{Dc}$

      ii. *If* $s_G > s_G^{ac}$*:* $\Pi_W^{Da} > \Pi_W^{Dc}$

c. *Comparing* Π_W^{Db} *with* Π_W^{Dc}

      i. *If* $w_G \le \frac{p}{a\tau}$*:* $\Pi_W^{Db} \ge \Pi_W^{Dc}$

      ii. *If* $w_G > \frac{p}{a\tau}$*:* $\Pi_W^{Db} < \Pi_W^{Dc}$

where $c_G^{ab} = \frac{b-p+w_G}{a}\sqrt{\frac{a^2w_G-(2\alpha-1)w_M}{p-w_G}}$, $s_G^{ab} = ac_G\sqrt{\frac{p-w_G}{a^2w_G-(2\alpha-1)w_M}} + p - b - w_G$, $c_G^{ac} = \frac{b-p+w_G}{a}\sqrt{\frac{(2\alpha-1)w_M}{w_G}}$, *and* $s_G^{ac} = \alpha c_G\sqrt{\frac{w_G}{(2\alpha-1)w_M}} + p - b - w_G$.

Proposition 4.4.a summarizes the wholesaler's preference between a mixed procurement plan and a public procurement plan. If GM's selling price is sufficiently low, then the wholesaler always prefers a public strategy to a mixed procurement plan. This is because the benefit of a reliable source can justify GM's higher selling price. Otherwise, the wholesaler's preference between the two procurement plans depends on c_G and s_G. If either c_G is sufficiently low or s_G is sufficiently high, then GM will be more willing to produce some backup quantities even without any order quantities, and the wholesaler prefers a mixed procurement plan. This is because the wholesaler can take advantage of both the cheaper source and the backup supplier: the wholesaler can first procure the drug from the manufacturer and then purchase the drug from GM if the manufacturer's realized quantity is lower than demand.

Proposition 4.4.b summarizes the wholesaler's preference between a mixed procurement plan and a private procurement plan. In this comparison, the wholesaler only orders from the manufacturer at the beginning, and the difference between the two procurement plans is whether GM voluntarily produces some backup quantities or not. Similarly to the logic explained in the previous paragraph, GM's decision is depending on c_G and s_G: if either c_G is sufficiently low or s_G is sufficiently high, then GM will be more willing to produce some backup quantities even without any order quantities from the wholesaler.

Proposition 4.4.c states the wholesaler's preference between a public procurement plan and a private procurement plan. In this comparison, the wholesaler will procure the drug only from one source throughout the whole period. The wholesaler's preference is based on the trade-offs between the reliability and procurement cost at the two sources. If the wholesaler's selling price is low, then there is not enough profit margin for it to procure the drug from a more expensive source, and it will only procure from the manufacturer which is cheaper. If the wholesaler's selling price and profit margin are

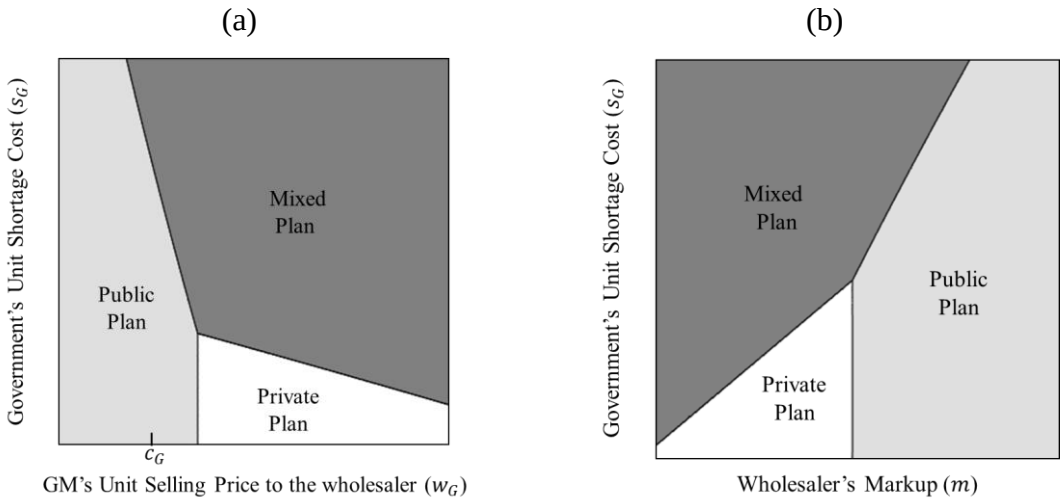


Figure 4.3. The wholesaler's optimal procurement plan in Model D. (a): with respect to the public manufacturer's selling price (w_G) and the government's unit shortage cost (s_G); (b): with respect to the wholesaler's unit markup (m) and s_G.

high, then it will procure the drug from GM if w_G is sufficiently low, and it will procure from the manufacturer if w_G is sufficiently high.

Due to the complicated threshold values in Proposition 4.4, it is difficult to provide a clear analytical comparison of the three procurement plans. Therefore, we graphically illustrate and discuss the wholesaler's preference for the three procurement plans as a function of different parameter values in Figure 4.3. Figure 4.3.a illustrates the wholesaler's optimal procurement plan with respect to the government's selling price (w_G) and the government's unit shortage cost (s_G); If both s_G and w_G are small, then the wholesaler will choose a public procurement plan. If s_G is small and w_G is large, then the wholesaler prefers a private procurement plan; otherwise, the supply chain will reach a mixed procurement plan. The logic is as follows. If s_G is small, then the shortage cost is not severe enough to incentivize GM to voluntarily produce any backup quantities, and the supply chain will reach a pure procurement plan (the wholesaler only procures the drug from one manufacturing facility through the entire period). If both s_G and w_G are small, then GM's reasonably high price and perfect reliability are more attractive to the wholesaler than the unreliable manufacturer. Knowing that GM will not produce anything without any order, the wholesaler will order everything from GM. If s_G is small and w_G is

large, then GM's selling price is too high for the wholesaler, and the wholesaler will order everything from the manufacturer.

If s_G is high, then GM will voluntarily produce some backup quantities even without any order quantities from the wholesaler at the beginning. Therefore, the wholesaler will order from the cheaper supplier (the manufacturer) at the beginning, and it will procure from GM if the manufacturer's realized production quantity is lower than the demand. In this scenario, the supply chain is more likely to reach a mixed procurement plan.

Note that in the region where GM's selling price is less than GM's unit production cost ($w_G < c_G$) in Figure 4.3.a, the government is willing to produce the drug even if GM's selling price is less than its production cost. This is because the additional health benefit and avoided shortage cost from GM's provision of the drug may justify the gap between GM's price and production cost.

Figure 4.3.b illustrates the wholesaler's optimal procurement plan as a function of with respect to the wholesaler's unit markup (m) and the government's unit shortage cost (s_G). We can see that m and w_G have an opposite impact on the wholesaler's optimal plan. This is because m determines the wholesaler's revenue whereas w_G is a cost for the wholesaler.

4.4.3 Model S

For ease of implementation, we assume that the government will only choose one type of subsidy. Define Model SW and Model SP as two sub-models in which the government will only implement a procurement cost subsidy (Model SW) and a selling price subsidy (Model SP), respectively (i.e., $\gamma_p = 0$ in Model SW, and $\gamma_w = 0$ in Model SP). We solve Model SW and Model SP separately.

Because the subsidy is not included in the manufacturer's profit function, its best response function for any given order quantity from the wholesaler has the same form as the basic model, $\tilde{x}_M^S(q_M) = \alpha q_M$, where α is the same as defined in Lemma 4.1. We then

solve the wholesaler's best response function for any given subsidy in Model SW and Model SP, respectively.

Lemma 4.4: *The wholesaler's best response functions for any given subsidy in Model SW and Model SP are given by*

$$\tilde{q}_M^{SW} = \tau^{SW} d$$

$$\tilde{q}_M^{SP} = \tau^{SP} d$$

where $\tau^{SW} = \sqrt{\frac{p}{(2\alpha-1)(w_M-\gamma_w)}}$ *and* $\tau^{SP} = \sqrt{\frac{p+\gamma_p}{(2\alpha-1)w_M}}$.

The wholesaler's ordering decision in the basic model and that in the subsidy model have the same structure. It uses a coefficient to make an adjustment on the demand for the drug, and the coefficient in the subsidy model incorporates the subsidies from the government.

Finally, we solve the government's optimal subsidy and summarize it in Proposition 4.5.

Proposition 4.5: *There exists a unique optimal solution for the government's subsidy in each sub-model, which is given by*

a. In Model SW: $\gamma_w^* = \begin{cases} w_M - \hat{\gamma}_w, if\ m \le \frac{b+s_G}{3w_M} \quad (i.e., p \le \frac{b+s_G}{3}) \\ 0, if\ m > \frac{b+s_G}{3w_M} \quad (i.e.,\ p > \frac{b+s_G}{3}) \end{cases}$

b. In Model SP: $\gamma_p^* = \begin{cases} \hat{\gamma}_p - p, if\ p \le \hat{\gamma}_p \\ 0, if\ p > \hat{\gamma}_p \end{cases}$

where the expressions of $\hat{\gamma}_w$ *and* $\hat{\gamma}_p$ *are defined in the Appendix.*

Proposition 4.5.a indicates that if the government is considering whether to provide a procurement cost subsidy, then it should provide the subsidy only if the wholesaler's profit margin (or revenue) is sufficiently low. With this type of subsidy, the

wholesaler's *effective procurement cost* became $\hat{\gamma}_w$. Proposition 4.5.b states that there exists a unique *effective price* ($\hat{\gamma}_p$) that maximizes the government's utility. When the government is considering whether to use a selling price subsidy, then it should provide the subsidy if p is sufficiently low, and the subsidy should increase the wholesaler's selling price up to the effective price.

Due to the complicated expression of the optimal solutions in Proposition 4.5, we are not able to analytically compare the performance of the two subsidies. Therefore, we conduct numerical analysis and test a wide range of parameter values. We summarize an important observation that holds for all parameter values we tested.

Observation 4.1: $\Pi_G^{SW*} > \Pi_G^{SP*}$.

Observation 4.1 indicates that the government always prefers a procurement cost subsidy to a selling price subsidy. This is because under a selling price subsidy, the wholesaler will not receive the subsidy if it overstocks (i.e., when the manufacturer's delivered quantity is greater than the drug demand). On the other hand, under a procurement cost subsidy, the wholesaler can receive the subsidy for all procured quantities, which has a larger effect on incentivizing it to increase the order quantity and reduce shortages. Because the drug has a positive net health benefit and positive shortage cost for the government, a procurement cost subsidy can better mitigate shortages and improve the government's utility than a selling price subsidy. This result is similar to the main finding in Taylor and Xiao (2014), which investigated a donor's optimal subsidy to improve the availability and affordability of malaria drugs provided by the private-sector and found that the donor should only subsidize the retailers' purchases and should not subsidize their sales. For the rest of the analysis, we only focus on the procurement cost subsidy as it is more effective than the selling price subsidy.

Proposition 4.6 summarizes some properties of the optimal procurement cost subsidy.

Proposition 4.6: *The optimal procurement cost subsidy has the following properties*

$\frac{\partial \gamma_W^*}{\partial m} \leq 0, \frac{\partial \gamma_W^*}{\partial w_M} \geq 0, \frac{\partial \gamma_W^*}{\partial b} \geq 0,$ *and* $\frac{\partial \gamma_W^*}{\partial s_G} \geq 0$

The optimal procurement cost subsidy is decreasing in m, because the government does not need to pay a large subsidy if the wholesaler already charges a high markup. The optimal subsidy increases as the wholesaler's procurement cost increases. The optimal subsidy also increases when the government has a higher incentive to mitigate shortages, such as the health benefit or the shortage cost are high.

4.5 Comparisons of Different Strategies

With the optimal values obtained in each model, we are able to analyze the government's optimal strategy and examine the impact on the wholesaler and the manufacturer. Based on Observation 4.1 (the government always prefers a procurement cost subsidy to a selling price subsidy), we only consider a procurement cost subsidy in Model S for the rest of the analysis. The government chooses from the three strategies to maximize its expected utility, i.e., no intervention (Model B), the subsidy strategy (Model S), and the dual sourcing strategy (Model D). The government prefers a strategy if its utility in the corresponding model is higher than that in the other two models. We first compare each mitigating strategy (Model S and Model D, respectively) with Model B. This comparison provides insights into situations in which the government has a preference for one strategy over the other, or only one certain type of strategy is available. Next, we compare the three models together and examine the government's optimal strategy if both mitigating strategies are available.

4.5.1 Comparison of Model B with Model S

We first investigate the government's preference for whether to provide subsidies to the wholesaler. We first summarize some properties of the optimal values in Proposition 4.7.

Proposition 4.7: *The following properties hold when comparing Model B with Model S*

If $\Pi_G^{S*} > \Pi_G^{B*}$*, then the following are true:*

$\Pi_W^{S*} > \Pi_W^{B*}, \Pi_M^{S*} > \Pi_M^{B*}, Y_W^{S*} > Y_W^{B*}, Y_M^{S*} > Y_M^{B*}$, *and* $S^{S*} < S^{B*}$.

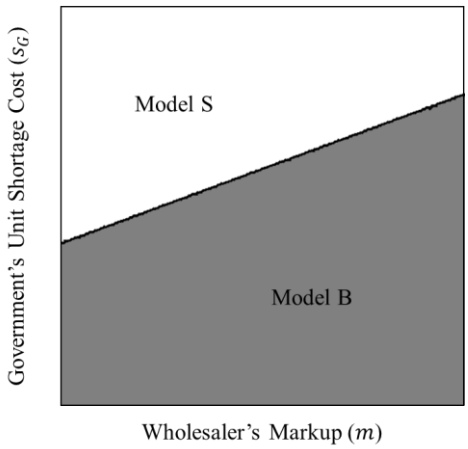


Figure 4.4: The government's preference between Model B (no intervention) and Model S (subsidy strategy) with respect to the wholesaler's markup (m) and the government's unit shortage cost (s_G).

Proposition 4.7 indicates that if the government prefers to provide subsidies, then the two parties in the private sector have the same preferences as the government, indicating that a subsidy strategy can achieve an "all-win" situation compared with the basic model in same cases. Because the government decides whether to provide subsidies or not, it will be better off if it chooses to provide subsidies instead of no intervention. The subsidy increases the wholesaler's profit margin and incentivizes it to increase its order quantity, which in turn increases its profit. As a response to the wholesaler's increased order quantity, the manufacturer will increase the production quantity which in turn increase it profit. As a result, when the government use a subsidy strategy, the delivered quantity from the manufacturer to the wholesaler increases, and the shortage amount decreases, compared with the basic model.

Next, we show a two-way graph of the government's optimal choice between Model B and Model S with respect to the wholesaler's markup (m) and the government's unit shortage cost (s_G). Figure 4.4 illustrates that when the wholesaler's profit margin (i.e., markup) is low and the shortage cost is high, the government should provide subsidies; when the wholesaler's profit margin is high and the shortage cost is low, the government should not provide subsidies. Note that when replacing s_G with the unit monetary health benefit of the drug (b), the two graphs have similar structures. This is because the government has a higher incentive to reduce shortages when either b or s_G

increases.

4.5.2 Comparison of Model B with Model D

We compare the government's optimal utilities in Model B and Model D to investigate the government's preference on whether to operate GM. Note that, if the government implements a dual sourcing strategy, then the wholesaler chooses the optimal procurement plans (a mixed plan, a public plan, and a private plan) to maximize its own profit. In other words, the optimal procurement plan in Model D is the wholesaler's choice. Therefore, the government's expected utility under the wholesaler's optimal procurement plan in Model D may be lower than in Model B.

Proposition 4.8: *The following properties hold when comparing Model B with Model D:*

If $\Pi_G^{D*} > \Pi_G^{B*}$*, then the following are true:*

$\Pi_W^{D*} > \Pi_W^{B*}$, $\Pi_M^{D*} \leq \Pi_M^{B*}$, $Y_W^{D*} \geq Y_W^{B*}$, $Y_M^{D*} \leq Y_M^{B*}$, *and* $S^{D*} \leq S^{B*}$

Proposition 4.8 indicates that if the government prefers Model D to Model B, then the wholesaler also has the same preference. This is intuitive, because the wholesaler has more flexibility on choosing the suppliers in Model D than in Model B, and it is no worse off in Model D. However, the manufacturer is always no better off if the government operates GM. This is because the manufacturer faces competitions with GM, and some or all of its order quantities will be taken by GM in Model D. If the government prefers model D to Model B, i.e., it operates GM, then the wholesaler's fulfilled demand is higher, the manufacturer's delivered quantity is lower, and the expected shortage is lower in Model D then in Model B.

Next, we show the government's choice between Model B and Model D as a function of m and s_G in Figure 4.5. Note that, in the region labeled with "Model D Private Plan", the government prefers a public procurement plan, whereas the wholesaler prefers not to procure from GM even if GM is available. In contrast, in the region labeled with "Model B", the wholesaler prefers to procure from GM if it is available, whereas the government prefers not to produce the drug at GM.

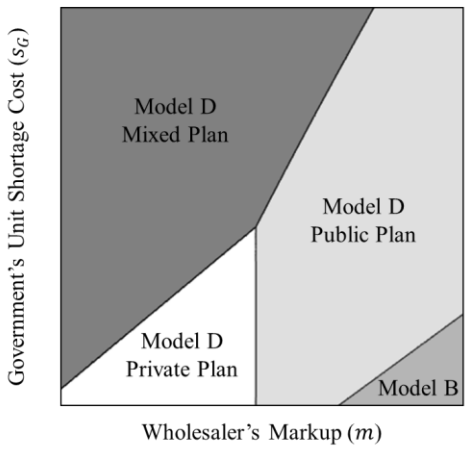


Figure 4.5: The government's preference between Model B (no intervention) and Model D (dual sourcing strategy) with respect to the wholesaler's markup (m) and the government's unit shortage cost (s_G).

If the incentive to mitigate shortages is low, then the government prefers Model B to Model D. This is more likely to occur if the government's shortage cost is low and the wholesaler's profit margin is sufficiently high (the bottom right region labeled with "Model B" in Figure 4.5), so that the government would rely on the wholesaler's ordering decision in a sole-sourcing situation rather than operating a GM to mitigate shortages. The optimal procurement plan within Model D is the same as discussed in subsection 4.4.2.

4.5.3 Comparison of the Three Models

We finally analyze the government's optimal strategy when comparing all three models. Table 4.2 summarizes the optimal values for all possible equilibrium states in the three models. Depending on the different combinations of parameters, the three players will follow their respective optimal decisions, and the supply chain will reach one equilibrium state in Table 4.2.

Figure 4.6 shows a two-way graph of the government's optimal strategy as a function of m and s_G. Recall that, in the region labeled with "Model D Private Plan", the wholesaler prefers not to procure from GM even if GM is available. However, in the region labeled with "Model B", the wholesaler prefers to procure from GM if it is available, whereas the government prefers not to produce the drug at GM.

Table 4.2: Summary of optimal values

		B Model	S Model	D Model		
				Mixed	Private	Public
Optimal Decisions	q_M^{j*}	τd	$\tau^{S*} d$	θd	τd	0
	q_G^{j*}	-	-	0	0	d
	x_M^{j*}	$\alpha\tau d$	$\alpha\tau^{S*} d$	$a\theta d$	$a\tau d$	0
	x_G^{j*}	-	-	$(1 - a\theta\beta)d$	0	d
	γ_w^*	-	$\begin{cases} w_M - \hat{\gamma}_w, if\ p \le \dfrac{b + s_G}{3} \\ 0, otherwise \end{cases}$	-	-	-
Optimal Profits	Π_G^{j*}	$(b-p)\left(1 - \dfrac{1}{2\alpha\tau}\right)d - \dfrac{s_G d}{2\alpha\tau}$	$(b-p)\left(1 - \dfrac{1}{2\alpha\tau^{S*}}\right)d$ $- \dfrac{s_G d}{2\alpha\tau^{S*}} - \gamma_w^*\left(1 - \dfrac{1}{2\alpha}\right)\tau^{S*} d$	$(b-p)\left(1 - \dfrac{\alpha\beta^2\theta}{2}\right)d + w_G \dfrac{1-(\alpha\beta\theta)^2}{2\alpha\theta} d$ $- c_G(1 - a\theta\beta)d - s_G \dfrac{\alpha\beta^2\theta d}{2}$	$= \Pi_G^{B*}$	$(b - p + w_G - c_G)d$
	Π_W^{j*}	$p\left(1 - \dfrac{1}{2\alpha\tau}\right)d - w_M\left(1 - \dfrac{1}{2\alpha}\right)\tau d$	$p\left(1 - \dfrac{1}{2\alpha\tau^{S*}}\right)d$ $-(w_M - \gamma_w^*)\left(1 - \dfrac{1}{2\alpha}\right)\tau^{S*} d$	$p\left(1 - \dfrac{\alpha\beta^2\theta}{2}\right)d - w_M\left(1 - \dfrac{1}{2\alpha}\right)\theta d$ $- w_G \dfrac{1-(\alpha\beta\theta)^2}{2\alpha\theta} d$	$= \Pi_W^{B*}$	$(p - w_G)d$
	Π_M^{j*}	$w_M\left(1 - \dfrac{1}{2\alpha}\right)\tau d - c_M\alpha\tau d$	$w_M\left(1 - \dfrac{1}{2\alpha}\right)\tau^{S*} d - c_M\alpha\tau^{S*} d$	$w_M\theta\left(1 - \dfrac{1}{2\alpha}\right)d - c_M\alpha\theta d$	$= \Pi_M^{B*}$	0
Optimal Calculated Quantities	S^{j*}	$\dfrac{d}{2\alpha\tau}$	$\dfrac{d}{2\alpha\tau^{S*}}$	$\dfrac{\alpha\beta^2\theta d}{2}$	$= S^{B*}$	0
	Y_W^{j*}	$\left(1 - \dfrac{1}{2\alpha\tau}\right)d$	$\left(1 - \dfrac{1}{2\alpha\tau^{S*}}\right)d$	$\left(1 - \dfrac{\alpha\beta^2\theta}{2}\right)d$	$= Y_W^{B*}$	d
	Y_M^{j*}	$\left(1 - \dfrac{1}{2\alpha}\right)\tau d$	$\left(1 - \dfrac{1}{2\alpha}\right)\tau^{S*} d$	$\left(1 - \dfrac{1}{2\alpha}\right)\theta d$	$= Y_M^{B*}$	0
	Y_G^{j*}	-	-	$\dfrac{1-(\alpha\beta\theta)^2}{2\alpha\theta} d$	0	d

where $\tau = \sqrt{\frac{p}{(2\alpha-1)w_M}}$; $\alpha = \sqrt{\frac{w_M}{2c_M}}$; $\tau^{S*} = \tau^{SW*}\sqrt{\frac{p}{(2\alpha-1)(w_M - \gamma_w^*)}}$; $\hat{\gamma}_w$ *is as defined in the Appendix;* $\beta = \frac{c_G}{b-p+s_G+w_G}$; *and* $\theta = \sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+w_M(2\alpha-1)}}$.

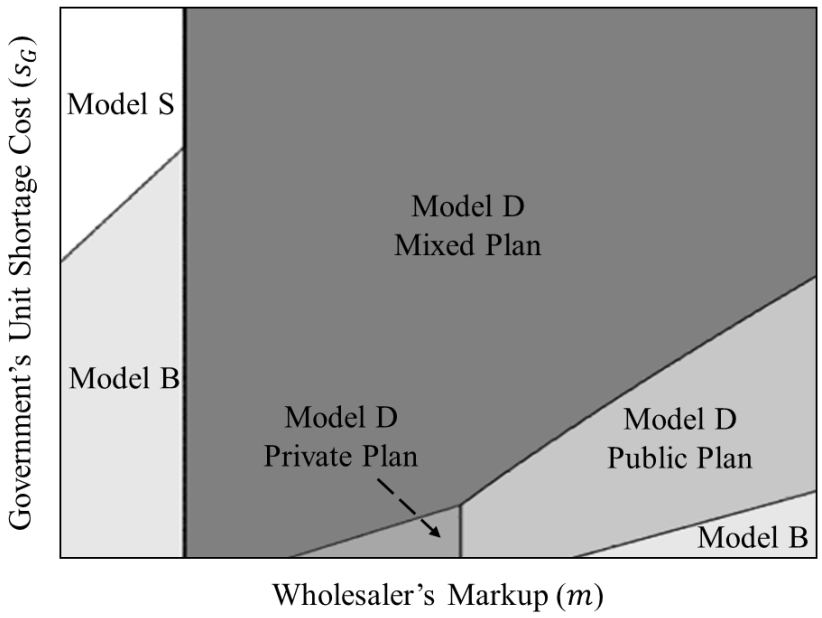


Figure 4.6: The government's optimal strategy among the three policies with respect to the wholesaler's markup parameter (m) and the government's unit shortage cost (s_G).

If the wholesaler's profit margin is sufficiently low, then the government's optimal choice is between Model B and Model S. If the shortage cost is sufficiently low, then the government does not have enough incentives to implement a subsidy strategy (the region labeled "Model B" on the bottom left in Figure 4.6). If the shortage cost is high, then a procurement cost subsidy is an effective strategy to mitigate shortages (the region labeled "Model S" in Figure 4.6), which also improves the utilities of the three players in the pharmaceutical supply chain.

If the wholesaler's profit margin is sufficiently high, then Model D dominates Model S, and the government's optimal choice is between Model B and Model D. In this comparison, if m is sufficiently high and s_G is sufficiently low, then the government prefers not to intervene (the region labeled "Model B" on the bottom right in Figure 4.6). Otherwise, the government will use a dual sourcing strategy to mitigate drug shortages. When the government uses a dual sourcing strategy, the supply chain will reach a mixed procurement plan if m is small and s_G is large (the region labeled "Model D Mixed Plan" in Figure 4.6). This is because when s_G is large, the government will voluntarily produce

some backup quantities even without any initial orders from the wholesaler. If the profit margin is low, then the wholesaler cannot afford sole-sourcing from a more reliable but more expensive public supplier. Therefore, the wholesaler will place an initial order from the manufacturer which is cheaper, and the wholesaler will take advantage of GM's backup quantities if the manufacturer's delivered quantity is lower than the demand. If s_G is small, as the wholesaler's profit margin increases, the supply chain will reach a private procurement plan (the region labeled "Model D Private Plan" in Figure 4.6). This is because the increase of the wholesaler's profit margin incentivizes a higher order quantity which reduces the expected shortage amount, whereas the low shortage cost cannot incentivize GM to produce any back up quantities voluntarily. Because the wholesaler still cannot afford to procure the drug exclusively from GM in this range of profit margin, it will only procure from the manufacturer.

If s_G is small and the wholesaler charges a higher markup, then the wholesaler can afford to procure from GM exclusively, and the supply chain will reach a public procurement plan (the region labeled "Model D Public Plan" in Figure 4.6). However, if m is sufficiently high and s_G is sufficiently low, the government prefer to rely on the wholesaler's order decision in a sole sourcing situation rather than producing the drug at GM to mitigate shortages ("Model B" on the bottom right in Figure 4.6).

4.6 Discussion

In this essay, we analyze the governments' optimal strategy to mitigate drug shortages. We construct a pharmaceutical supply chain model consisting of three decision-makers: a manufacturer, a wholesaler, and a government. We assume the manufacturing process has random yield rate to capture the major known cause of drug shortages, which is manufacturing issues. We consider two mitigating strategies that can be implemented by the government: providing subsidies to the wholesaler, or establishing a public manufacturer. We analytically characterize the optimal decisions for each party in each strategy and analyze the government's optimal strategy under different circumstances. To our best knowledge, this paper is the first modeling study that investigates the interactions among three key decision-makers in a pharmaceutical supply chain while

comparing a subsidy strategy and a dual sourcing strategy to mitigate supply uncertainties from a government's perspective.

This study shows the advantages and disadvantages of each strategy. An advantage for both mitigating strategies is that the expected shortage amount can be reduced by either strategy compared with the status quo in which the government does not take any intervention. An advantage of a subsidy strategy is that, if the government prefers to use a subsidy strategy, then the wholesaler and the manufacturer's profits with subsidies are higher than those without subsidies, indicating a subsidy strategy can achieve an all-win situation. However, a disadvantage is that the supply chain remains a sole sourcing situation under a subsidy strategy, which is more vulnerable to disruptions risks than a supply chain with multiple suppliers.

In contrast, an advantage of a dual sourcing strategy is that it eases the high market concentration by adding a second source of the drug, which makes the supply chain more reliable and resilient to supply disruptions. However, a disadvantage is that a dual sourcing strategy cannot be mutually preferred by all three parties. If the government chooses to establish a public manufacturer, then the wholesale is no worse off, but the manufacturer is no better off compared with the status quo. In some circumstances, the wholesaler may prefer to procure everything from the public manufacturer, and the manufacturer is not making any profit. In these situations, the government and/or the wholesaler may need to provide incentives to the manufacturer to keep it in the market in the long term. This consideration is similar to the discussion in the previous chapter.

This study also provides analysis for the government's optimal strategy under different circumstances. We show that governments should always intervene if the shortage cost is high (i.e., critical and lifesaving drugs without alternatives). For example, if the wholesaler's profit margin is low, then governments should provide subsidies for critical and lifesaving drugs without alternatives to incentivize an increase of the wholesaler's order quantity and reduce shortages. If wholesalers already charge a high markup, then governments should produce critical and lifesaving drugs without alternatives at public manufacturers to provide additional supplies. The results confirm

the importance of establishing a list of critical drugs and take more government interventions to mitigate shortages of the drugs. These analyses along with the advantages and disadvantages of each strategy have important policy implications for government interventions on mitigating drug shortages.

This study has several limitations. First, we construct a single-period model with zero lead time, mainly due to the complexity of our model. Future studies can extend our model to a multi-period setting while considering a positive lead time in drug production and distribution. For example, some drugs require a long time for production and distribution, which require an assumption of positive lead time in the model. Second, we do not consider fixed cost and cost of switching production and maintaining regulatory ability to produce drugs, and our results may overestimate the benefit of producing drugs at public manufacturers. When considering fixed costs, the threshold values may change, but the qualitative properties of our model should remain the same. Future studies may consider possible fixed costs and verify the impacts on our main findings.

In addition, we assume all parameters are known by all parties. However, it is possible that the parameters of cost, revenue, and/or yield rate are private information. Therefore, one extension to our study is to incorporate information asymmetry and provide further insights into possible changes in our findings. Moreover, we do not consider holding costs for the three parties. Our analysis may apply to the situation in which the drug does not require costly storage conditions, and the holding costs are negligible compared with other costs and revenue parameters. We also do not consider shortage costs for the manufacturer and the wholesaler. For example, the failure-to-supply clauses in many contracts are very week, and often suppliers do not incur financial penalties if they fail to supply the contracted quantity to the buyer (Jia and Zhao, 2017). Future studies can extend our study to a richer setting by incorporating parameters for holding costs and/or shortage costs.

There are other directions to extend this study. We consider two types of subsidies that are paid to the wholesaler. Future studies can consider more types of subsidies, such as the subsidies to private manufacturers, or subsidies to induce new manufacturers to

enter the market. Next, we assume all price parameters are exogenous because drug prices are highly regulated in many countries. Future analysis can include drug prices as decision variables, e.g., influential parties may have the power to affect drug prices directly or through discount/rebate. Moreover, we study the most vulnerable supply chain setting, which consists of only one private manufacturer and one wholesaler. Future studies can consider duopoly or more competitive settings to provide insights into different circumstances.

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Chapter 5

5 Conclusion

In this thesis, I investigate several decision-making problems faced by health care decision-makers to manage drug supply and patient access to drugs in the presence of various uncertainties. Using a game-theoretic approach, I analyze the dynamics of the key decision-makers' optimal decisions and the impact of these interactions on their performances. In the first essay, I compare the performance of two drug reimbursement policies between a payer and a pharmaceutical company to mitigate the uncertainties of new and expensive drugs. Different from previous studies, I incorporate several key aspects of the decision making challenge, such as the multiple decision-maker aspects, comparing a volume-based policy with a value-based policy, and capturing the pharmaceutical company's strategic decision of its marketing efforts.

Next, using a supply chain management approach, I examine policies to mitigate drug shortages caused by supply uncertainties from hospitals' and governments' perspectives, respectively. In the second essay, I evaluate hospitals' strategy of establishing an in-house manufacturer to mitigate drug shortages. I construct a multi-period supply chain model consisting of a hospital and an external manufacturer that is subject to supply uncertainty. The hospital owns an in-house manufacturer and can procure the drug from the two manufacturing facilities. The hospital also has a second chance to make emergency production at the in-house producer. I capture the hospital's procurement and production decisions, and the external manufacturer's production decisions. First, I analytically characterize the optimal decisions of each party in a single period setting. Next, I analyze the hospital's long-term inventory management policies in a multi-period setting using a heuristic.

In the third essay, I study mitigating strategies for drug shortages from the governments' perspective. This study distinguished from previous work in several aspects. I construct a pharmaceutical supply chain consisting of three decision-makers: a manufacturer, a wholesaler, and a government. I consider three strategies that can be

implemented by the government: 1) no intervention; 2) a dual sourcing strategy, in which the government operates a public manufacturer; and 3) a subsidy strategy in which the government provides subsidies based on the wholesaler's unit procurement cost or unit selling price. First, I analytically solve the optimal solutions in each model. Next, I analyze the government's optimal policy and its impacts on the performance of the wholesaler and the manufacturer under different circumstances.

5.1 Managerial Insights

The results of the first essay provide insights for health payers who are facing decisions between a volume-based reimbursement policy and a value-based reimbursement policy. I show that under some circumstances, none of the two policies can align the incentives of the two parties. This may lead to resistance from the misaligned party during the implementation and partially explain the lack of consensus between payers and manufacturers on the preferability of a risk-sharing agreement, which has been observed in reality (Bastian et al., 2015). Under some other circumstances, in contrast, a properly selected policy can be mutually preferred by the two parties, which may result in a smooth implementation. A policy implication is that neither policy is a universal solution that can be applied in all situations, and payers should carefully consider the trade-offs between different incentives and costs when making decision, rather than sticking to just one policy (e.g., to use a volume-based policy for ease of negotiation and implementation).

In the second essay, I show that the hospital's optimal decision on whether to establish an in-house manufacturer should depend on the trade-offs between different parameters (e.g., the procurement/production costs, the shortage costs, and the reliability of the external manufacturers), rather than a simple cost consideration for the cheapest source. I show that the shortage amount can be reduced by the hospital's in-house producer, which provides evidence for the value of establishing Civica Rx to mitigate drug shortages. The results may provide one explanation for the rapid growths of the company business: from providing 14 drugs to approximately 500 member hospitals in 2018, to providing 40 drugs to over 1200 members hospitals in July 2020 (Civica Rx, 2020). However, the results show that the external manufacturer is no better off under the

hospital's dual sourcing practice, and the hospital may need to consider incentives to keep the external manufacturer from exiting the market. This consideration is in order to keep the multi-supplier situation for a more reliable pharmaceutical supply chain against supply uncertainties.

The third essay provides insights into government interventions to mitigate drug shortages caused by supply uncertainties. I show that both the subsidy policy and the dual sourcing strategy can reduce the shortage amount compared with the status quo. However, the two strategies differ in several aspects. One difference is their ability to align the incentives of different parties. A subsidy strategy can align the incentives of the government, the wholesaler, and the external manufacturer, whereas a dual sourcing strategy cannot be mutually preferred by all three parties. Due to the competition with the public manufacturer, the external manufacturer is no better off under the government's dual sourcing strategy compared with the status quo. Another difference between the two mitigating strategies is their ability to change the supply structure. Under a subsidy strategy, the supply chain remains a sole supplier situation which is vulnerable to supply disruptions. In contrast, a dual sourcing strategy adds a supplier, which eases the high market concentration and increases the reliability and resilience of the supply chain against supply disruptions. I also provide analysis for the government's optimal policies under different circumstances, which has implications for policymakers regarding the optimal interventions to mitigate supply uncertainties.

The three essays have some common insights regarding the decision-making challenges in a multi-decision-maker setting. First, the second and third essays show the importance of the trade-offs between different factors, rather than a simple cost consideration that favors the cheapest supplier. The two essays show that sourcing from the cheaper but unreliable supplier may result in inferior performance for the wholesaler and the government in the expected form (i.e., long-term average) when taking into consideration the reliability of the suppliers and the shortage cost due to the unavailability of the drug. Second, all three essays show that each policy candidate's ability to align the incentives of different parties may depend on various circumstances. In the first essay, the payer and the pharmaceutical company may or may not prefer the

same reimbursement policy depending on the drug price and patient treatment eligibility. In the second essay, the external manufacturer always prefers a sole-sourcing situation, whereas the hospital may prefer to establish an in-house producer. In the third essay, a subsidy strategy is not always preferred by the three parties, since the government may prefer a dual sourcing strategy or not to intervene, depending on different situations.

5.2 Implications for COVID-19

The three essays have important policy implications in the context of the unprecedented novel coronavirus (COVID-19) pandemic. For example, new vaccines and drugs are being developed to prevent or treat COVID-19. Due to the public crisis nature of this pandemic, it is very likely that many government agencies and health authorities will cover the costs of vaccines and/or drugs for patients. My first essay may provide insights into payers' decisions on selecting a reimbursement policy for the newly developed vaccines or drugs. For example, traditional vaccines and drugs require many years to go through the process of early development, multiple phases of clinical trials to confirm the efficacy and safety of the products. In contrast, vaccines and drugs for COVID-19 are expected to be developed within a very short time period. Therefore, the effectiveness of the drugs and vaccines for COVID-19 may be highly uncertainty. On the other hand, due to the possible multiple waves of the pandemic, the sales volume of the drugs for COVID-19 may be highly uncertain. Payers should carefully weigh the risks and benefits of different products and select a risk-sharing agreement to mitigate uncertainties.

In addition, many pharmaceutical products are undergoing or are expected to experience shortages, due to supply uncertainties at overseas suppliers during COVID-19 (Blank, 2020; Hahn, 2020; Rees, 2020; Russell, 2020). For example, the FDA has identified 20 medicines that sole source the finished drug products or the active pharmaceutical ingredients from oversea manufacturers, which are significantly affected by this pandemic (Hahn, 2020; Russell, 2020). The pandemic revealed the vulnerability of the current pharmaceutical supply chains in many countries, and reconstructions of the existing systems are required. My second and third essays provide insights into the reconstruction towards more reliable and resilient pharmaceutical supply chains.

Many policymakers and experts believe that it is important to increase the diversity of supply sources (in different geographic regions, if possible), as risk management measures for drug suppliers (Linton and Vakil, 2020). This coincides with the dual-sourcing concept discussed in the two essays. The two essays show that it is crucial to trade-off the benefits and risks of cheaper but unreliable sources with more expensive but more reliable sources. Due to the for-profit nature of many drug manufacturers, it is difficult to rely on them to manage drug suppliers and mitigate shortages. The two essays analyze strategies which can be implemented by two types of key stakeholders in mitigating drug shortages: hospitals and governments, which provide theoretical foundations for them to design and implement interventions of drug shortages in reality. It is also crucial for stakeholders to consider the advantages and disadvantages of the shortage mitigating strategies and take a long-term perspective when moving towards supply chain reconstructions in a post-COVID-19 world.

We originally initiated essays 2 and 3 to investigate drug shortages. But recent events during the COVID-19 pandemic also indicated that our results apply to equipment shortages, such as personal protective equipment (PPE) and lab testing equipment. Many PPE and lab equipment require higher production costs at domestic manufacturers than oversea suppliers. But the equipment has a large impact on frontline worker's safety and patient welfare, i.e., the shortage cost is high. Therefore, governments and hospitals should help make additional productions or provide financial supports to mitigate the equipment shortages and better defeat the pandemic,

5.3 Limitations and Future Research

The three studies establish the foundation for several important decision-making challenges faced by health care decision-makers to manage drug supply and patient access to drugs. I made several limiting assumptions to make the models tractable, and there are multiple directions for future extension. In the first essay, I compare two types of risk-sharing contracts. Future studies can consider other types of contracts that are implemented in reality. In the second essay and third essay, I focus on drug shortages caused by supply uncertainties at the manufacturing facilities. Future studies can incorporate other causes, such as demand uncertainties, manufacturers' strategic

decisions on holding inventories, natural disasters, and unavailability of API from upper stream suppliers. Because low drug price is one important underlying factor for drug shortages, future studies may also analyze whether pricing agreement can solve the drug shortage problems (i.e., whether increase drug price may mitigate drug shortages). In the third essays, I consider a single-period setting, mainly due to the number of decisions and decision-makers: I capture five decisions made by the three decision-makers. Future analysis may extend the study to a multi-period setting and analyze the model with reasonable simplifications, numerical analysis, or heuristics. Another direction to extend the third essay is to include more government interventions into consideration.

The three essays also share some common assumptions that may be relaxed in future studies. For example, in all three essays, I assume all parameters are known to all parties. However, it is possible that one or more parties possess private information regarding some parameters. Future research can incorporate information asymmetry to analyze the impact of this change on the model results. Second, drug prices are considered as exogenous parameters in all three essays. This is mainly because drug prices are highly regulated in many countries and jurisdictions and cannot be easily influenced by any party. One possible extension is to model drug price as a decision for one party or as a result of a negotiating process among multiple parties depending on the situation.

In addition, it will be insightful to conduct case studies to estimate the parameters using real-world data and verify the results of the analytical models. This is very challenging for the first essay due to the confidential nature of the details of many drug reimbursement schemes. For the second and third essays, as more information becomes available in the future, one can estimate the model parameters for specific drugs and verify the model results.

Finally, it will be useful to conduct interviews with policymakers, health care practitioners, and other key stakeholders to verify the model setting and understand the key trade-offs in reality – what makes it difficult to make the decision (i.e., choose the right risk-sharing agreement, and choose the right strategy to mitigate drug shortages).

The model frameworks in this dissertation can be revised based on the feedback from the key stakeholders to capture additional factors and their interrelationship, as well as additional decision makers and their decisions. The results should also be communicated with the stakeholders to validate the findings of analytical models and help inform the decision-making in reality.

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Appendices

Appendix A: Essay 1

Derivation of the optimal solutions

With the assumption of uniform distribution, the total sales and total health benefit are given by $q = 1 - (y - m + \epsilon)$ and $b = \frac{1-(y-m+\epsilon)^2}{2}$.

As uniform distribution has boundaries, there are two cases:

(1): $y - m - \bar{\epsilon} > 0$, i.e., the lowest value for the actual treatment eligibility is positive.

(2): $y - m - \bar{\epsilon} \leq 0$, i.e., the lowest value for the actual treatment eligibility is zero (actual treatment eligibilities with $y - m + \epsilon < 0$ are out of the defined boundary for ϵ and therefore the values for them are zeros).

Case 1. ($y - m - \bar{\epsilon} > 0$, i.e., $m < y - \bar{\epsilon}$):

The expected totals sales and the expected total health benefit are $Q = 1 + m - y$ and $B = \frac{1}{6}(3 - \bar{\epsilon}^2 - 3(y - m)^2)$.

1 - a. PVA:

With the assumption $x = Q$, the rebate occurs when $p(q - x) = -p\epsilon > 0$, i.e., when $\epsilon < 0$.Thus, $S^{PVA} = \int_{-\bar{\epsilon}}^{0} p(q - x)g(\epsilon)\,\mathrm{d}\epsilon = \frac{p\bar{\epsilon}}{4}$. The manufacturer's payoff is concave ($\frac{d^2\pi_M^{PVA}}{dm^2} = -2k < 0$). The first derivative of π_M^{PVA} with respect to m is $\frac{d\pi_M^{PVA}}{dm} = p - 2km + c_M$.The first order necessary condition for m^{PVA*} is $\frac{d\pi_M^{PVA}}{dm} = 0$. With the condition for case i, the optimal marketing effort is shown in Table A. 1. The two parties' optimal payoffs are calculated by plugging in m^{PVA*} and shown in Table A. 1.

1 - b. CER:

The rebate occurs when $(p + c_P + a_P^{CER})q - \lambda b > 0$, i.e., when $\epsilon \leq \epsilon^{CER} = \frac{2(p+c_P+a_P^{CER})}{\lambda} - 1 + m - y$. We compare ϵ^{CER} with the boundaries of ϵ and obtain three cases:

(a) $\epsilon^{CER} < -\bar{\epsilon}$; (b) $-\bar{\epsilon} \leq \epsilon^{CER} \leq \bar{\epsilon}$; (c) $\epsilon^{CER} > \bar{\epsilon}$.

1 - b - i. $\boldsymbol{\epsilon^{CER} < -\bar{\epsilon}}$

The condition for this case is $m < 1 - \bar{\epsilon} + y + \frac{2(p+c_P+a_P^{CER})}{\lambda}$. The rebate never occurs and thus $S^{CER} = 0$. The optimal values are solved with the same manner and shown in Table A.2.

1 - b - ii. $\boldsymbol{-\bar{\epsilon} \leq \epsilon^{CER} \leq \bar{\epsilon}}$

The condition for this case is $1 - \bar{\epsilon} + y + \frac{2(p+c_P+a_P^{CER})}{\lambda} < m < 1 + \bar{\epsilon} + y - \frac{2(p+c_P+a_P^{CER})}{\lambda}$.

The expected rebate is $S^{CER} = \int_{-\bar{\epsilon}}^{\epsilon^{CER}} \left((p + c_P + a_P^{CER})q - \lambda b\right) g(\epsilon)\, \mathrm{d}\epsilon = \frac{(2(p+c_P+a_P^{CER}) - (1-m-\bar{\epsilon}+y)\lambda)^2((2+m+\bar{\epsilon}-y)\lambda - (p+c_P+a_P^{CER}))}{12\bar{\epsilon}\lambda^2}$. The optimal values are solved with the same manner and shown in Table A.2.

1 - b - iii. $\boldsymbol{\epsilon^{CER} > \bar{\epsilon}}$

The condition for this case is $m > 1 + \bar{\epsilon} + y - \frac{2(p+c_P+a_P^{CER})}{\lambda}$. The rebate is $S^{CER} = \int_{-\bar{\epsilon}}^{\bar{\epsilon}} \left((p + c_P + a_P^{CER})q - \lambda b\right) g(\epsilon)\, d\epsilon = (p + c_P + a_P^{CER})(1 + m - y) - \frac{1}{6}(3 - \bar{\epsilon}^2 - 3(y - m)^2)\lambda$. The optimal values are solved with the same manner and shown in Table A.2.

<u>Case 2 ($\boldsymbol{y - m - \bar{\epsilon} \leq 0}$, i.e., $\boldsymbol{m \geq y - \bar{\epsilon}}$)</u>:

The expected totals sales and the expected total health benefit are given by $Q = 1 - \frac{(y+\bar{\epsilon}-m)^2}{4\bar{\epsilon}}$ and $B = \frac{1}{2} - \frac{(y+\bar{\epsilon}-m)^3}{12\bar{\epsilon}}$ when $y - m + \epsilon > 0$, $Q = 1$ and $B = \frac{1}{2}$ when $y - m + \epsilon \leq 0$.

2 - a. PVA:

The expected rebate is $\frac{\boldsymbol{p(m+\bar{\epsilon}-y)(y-m+\bar{\epsilon})^2}}{\boldsymbol{8\bar{\epsilon}^2}}$ when $\boldsymbol{y - m + \epsilon \leq 0}$, and $\frac{\boldsymbol{p(y+\bar{\epsilon}-m)^4}}{\boldsymbol{64\,\bar{\epsilon}^3}}$ when $\boldsymbol{y - m + \epsilon > 0}$, and the total expected rebate is the sum of the two quantities. The optimal values are solved with the same manner and shown in Table A. 1.

2 - b. CER:

With similar procedure in other cases, we solve the optimal values and conditions for this case which are shown in Table A. 2.

Table A. 1: Optimal solutions for a PVA

	Optimal solutions
m^{PVA1*} [a]	$\min\left\{y - \bar{\epsilon}, \frac{1}{2k}(p - c_M)\right\}$
m^{PVA2*}	$\min\{y + \bar{\epsilon},$ $\max\{0, y - \bar{\epsilon}, (-4\,3^{2/3}c_M p\bar{\epsilon}^2 + 2\,3^{2/3}p^2\bar{\epsilon}^2 + 163^{2/3}kp\bar{\epsilon}^3 - 3p\bar{\epsilon}(\phi^{PVA})^{1/3} + 3py(\phi^{PVA})^{1/3} - 2\,3^{1/3}(\phi^{PVA})^{2/3})/(3p(\phi^{PVA})^{1/3})\}\}$
π_P^{PVA1*}	$\frac{1}{6}(3 - \bar{\epsilon}^2 - 3\,(y - m^{PVA*})^2)\lambda - (p + a_P{}^{PVA} + c_P)(1 - y + m^{PVA*}) + \frac{p\bar{\epsilon}}{4}$
π_P^{PVA2*}	$(\frac{1}{2} - \frac{(y - m^{PVA*} + \bar{\epsilon})^3}{12\bar{\epsilon}})\lambda - (p + a_P{}^{PVA} + c_P)(1 - \frac{(y - m^{PVA*} + \bar{\epsilon})^2}{4\bar{\epsilon}}) + \frac{p(y - m^{PVA*} - 3\bar{\epsilon})^2(y - m^{PVA*} + \bar{\epsilon})^2}{64\bar{\epsilon}^3}$
π_M^{PVA1*}	$(p - c_M)(1 - y + m^{PVA*}) - k(m^{PVA*})^2 - \frac{p\bar{\epsilon}}{4}$
π_M^{PVA2*}	$(p - c_M)(1 - \frac{(y - m^{PVA*} + \bar{\epsilon})^2}{4\bar{\epsilon}}) - k(m^{PVA*})^2 - \frac{p(y - m^{PVA*} - 3\bar{\epsilon})^2(y - m^{PVA*} + \bar{\epsilon})^2}{64\bar{\epsilon}^3}$

[a] The optimal values with a superscript 1 is for case 1 (when $m \leq y - \bar{\epsilon}$); the optimal values with a superscript 2 is for case 2 (when $m > y - \bar{\epsilon}$).

[b] $\phi^{PVA} = 9c_M p^2\bar{\epsilon}^3 - 9p^3\bar{\epsilon}^3 - 18kp^2\bar{\epsilon}^4 + 18kp^2\bar{\epsilon}^3 y + \frac{1}{48}\sqrt{4(-24c_M p\bar{\epsilon}^2 + 12p^2\bar{\epsilon}^2 + 96kp\bar{\epsilon}^3)^3 + (432c_M p^2\bar{\epsilon}^3 - 432p^3\bar{\epsilon}^3 - 864kp^2\bar{\epsilon}^4 + 864kp^2\bar{\epsilon}^3 y)^2}$

Table A. 2: Optimal solution for a CEA

	When p is small [a]	When p is intermediate [b]	When p is large [c]
m^{CER1*} [d]	$\min\left\{y-\bar{\epsilon}, \max\left\{0, \frac{1}{2k}(p-c_M)\right\}\right\}$	$\min\left\{y-\bar{\epsilon}, \max\left\{0, \frac{1}{\lambda}(-a_P{}^{CER}-c_P-p-4k\bar{\epsilon}-\bar{\epsilon}\lambda+y\lambda+\phi^{CER})\right\}\right\}$ [d]	$\min\left\{y-\bar{\epsilon}, \max\left\{0, \frac{y\lambda-c_M-c_P-a_P{}^{CER}}{2k+\lambda}\right\}\right\}$
m^{CER2*}	$\min\left\{y-\bar{\epsilon}, \max\left\{0, y-\bar{\epsilon}, \frac{(p-c_M)(\bar{\epsilon}+y)}{p-c_M+4k\bar{\epsilon}}\right\}\right\}$	$\min\left\{y-\bar{\epsilon}, \max\left\{0, y-\bar{\epsilon}, \frac{2a_P{}^{CER}+2c_P+2p+2c_M\bar{\epsilon}-2p\bar{\epsilon}+2c_My-2py-\lambda}{2(c_M-p-4k\bar{\epsilon})}\right\}\right\}$	$\min\left\{\frac{-2a_P{}^{CER}-2c_P-2p+\lambda+\bar{\epsilon}\lambda+y\lambda}{\lambda}, \max\left\{0, y-\bar{\epsilon}, \frac{2a_P{}^{CER}+2c_P+2p+2c_M\bar{\epsilon}-2p\bar{\epsilon}+2c_My-2py-\lambda}{2(c_M-p-4k\bar{\epsilon})}\right\}\right\}$
π_P^{CER1*}	$\frac{1}{6}(3-\bar{\epsilon}^2-3(y-m^{CER*})^2)\lambda-(p+a_P{}^{CER}+c_P)(1-y+m^{CER*})$	$\frac{1}{6}(3-\bar{\epsilon}^2-3(y-m^{CER*})^2)\lambda-(p+a_P{}^{CER}+c_P)(1-y+m^{CER*})+\frac{(2(a_P{}^{CER}+c_P+p)+(1+y-m^{CER*}-\bar{\epsilon})\lambda)^2(-a_P{}^{CER}-c_P-p+(2+m^{CER*}+\bar{\epsilon}}{12\bar{\epsilon}\lambda^2}$	0
π_P^{CER2*}	$(\frac{1}{2}-\frac{(y-m^{CER*}+\bar{\epsilon})^3}{12\bar{\epsilon}})\lambda-(p+a_P{}^{CER}+c_P)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})$	$(\frac{1}{2}-\frac{(y-m^{CER*}+\bar{\epsilon})^3}{12\bar{\epsilon}})\lambda-(p+a_P{}^{CER}+c_P)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})+\frac{(m^{CER*}+\bar{\epsilon}-y)(a_P{}^{CER}+c_P+p-\frac{\lambda}{2})}{2\bar{\epsilon}}-\frac{(a_P{}^{CER}+c_P+p-2\lambda)(-2(a_P{}^{CER}+c_P+p)+\lambda)^2}{12\bar{\epsilon}\lambda^2}$	$(\frac{1}{2}-\frac{(y-m^{CER*}+\bar{\epsilon})^3}{12\bar{\epsilon}})\lambda-(p+a_P{}^{CER}+c_P)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})+\frac{(m^{CER*}+\bar{\epsilon}-y)(a_P{}^{CER}+c_P+p-\frac{\lambda}{2})}{2\bar{\epsilon}}-\frac{(a_P{}^{CER}+c_P+p-2\lambda)(-2(a_P{}^{CER}+c_P+p)+\lambda)^2}{12\bar{\epsilon}\lambda^2}$
π_M^{CER1*}	$(p-c_M)(1-y+m^{CER*})-k(m^{CER*})^2$	$(p-c_M)(1-y+m^{CER*})-k(m^{CER*})^2-\frac{(2(a_P{}^{CER}+c_P+p)+(1+y-m^{CER*}-\bar{\epsilon})\lambda)^2(-a_P{}^{CER}-c_P-p+(2+m^{CER*}+\bar{\epsilon}}{12\bar{\epsilon}\lambda^2}$	$(p-c_M)(1-y+m^{CER*})-k(m^{CER*})^2-(a_P{}^{CER}+c_P+p)(1+m^{CER*}-y)-\frac{1}{6}(3(m^{CER*}-y)^2-3+\bar{\epsilon}^2)\lambda$
π_M^{CER2*}	$(p-c_M)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})-k(m^{CER*})^2$	$(p-c_M)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})-k(m^{H*})^2-\frac{(m^{CER*}+\bar{\epsilon}-y)(a_P{}^{CER}+c_P+p-\frac{\lambda}{2})}{2\bar{\epsilon}}+\frac{(a_P{}^{CER}+c_P+p-2\lambda)(-2(a_P{}^{CER}+c_P+p)+\lambda)^2}{12\bar{\epsilon}\lambda^2}$	$(p-c_M)(1-\frac{(y-m^{CER*}+\bar{\epsilon})^2}{4\bar{\epsilon}})-k(m^{CER*})^2-\frac{(m^{CER*}+\bar{\epsilon}-y)(a_P{}^{CER}+c_P+p-\frac{\lambda}{2})}{2\bar{\epsilon}}+\frac{(a_P{}^{CER}+c_P+p-2\lambda)(-2(a_P{}^{CER}+c_P+p)+\lambda)^2}{12\bar{\epsilon}\lambda^2}$

[a] When $p < p^{CER1I}$ for case 1 and $p < p^{CER2I}$ for case 2, where $p^{CER1I} = \max\{0, \frac{\lambda}{2}-a_P{}^{CER}-c_P, \frac{-4a_P{}^{CER}k-4c_Pk+c_M\lambda+2k\lambda-2k\bar{\epsilon}\lambda+2ky\lambda}{4k+\lambda}\}$ and $p^{CER1II} = \frac{\lambda}{2}-a_P{}^{CER}-c_P$.

[b] When $p^{CER1I} < p < p^{CER1II}$ for case 1 and $p^{CER2I} < p < p^{CER2II}$, where $p^{CER1II} = \max\{0, (\frac{1}{2}+\bar{\epsilon})\lambda-a_P{}^{CER}-c_P, \frac{-4c_P-4a_P{}^{CER}+\lambda(2+2y+\lambda+w(2+\lambda)+c_M-c_P-a_P{}^{CER})}{2(2+\lambda)}\}$ and $p^{CER2II} = \lambda-a_P{}^{CER}-c_P$.

[c] When $p > p^{CER1II}$ for case 1 and $p > p^{CER2II}$ for case 2.

[d] The optimal values with a superscript 1 is for case 1 (when $m \le y-\bar{\epsilon}$); the optimal values with a superscript 2 is for case 2 (when $m > y-\bar{\epsilon}$).

[e] $\phi^{CER} = \sqrt{a_P{}^{CER2}+2a_P{}^{CER}c_P+c_P{}^2+2a_P{}^{CER}p+2c_Pp+p^2+8a_P{}^{CER}k\bar{\epsilon}+8c_Pk\bar{\epsilon}+8kp\bar{\epsilon}+16k^2\bar{\epsilon}^2-2a_P{}^{CER}\lambda-2c_P\lambda-2p\lambda-4c_M\bar{\epsilon}\lambda+4p\bar{\epsilon}\lambda+8k\bar{\epsilon}^2\lambda-8k\bar{\epsilon}y\lambda+\lambda^2}$

Appendix B: Essay 2

Proof of Lemma 3.1:

The profit of the centralized system in stage 2 is given by:

$$\pi_C|L_C = r\min\{D, L_C + q_E\} - c_M x_M - c_R q_R - c_E q_E - h_C(L_C + q_E - D)^+ - s_H(D - L_C - q_E)^+$$

There are two cases: $D \le L_C + q_E$, and $D > L_C + q_E$.

- If $D \le L_C + q_E$, i.e., $q_E \ge D - L_C$:

$$\pi_C|L_C = -(c_E + h_C)q_E + (r + h_C)D - c_M x_M - c_R q_R - h_C L_C$$

Since the slope of q_E is $-(c_E + h_C) < 0$, π_C is decreasing in q_E, and thus $q_E = (D - L_C)^+$

- If $D > L_C + q_E$, i.e., $q_E \le D - L_C$:

$$\pi_C|L_C = (r + s_H - c_E)q_E + (r + s_H)L_C - s_H D - c_M x_M - c_R q_R$$

The slope of q_E is $r + s_H - c_E$.

- If $c_E < r + s_H$, then the slope of q_E is positive, and π_C is increasing in q_E. Thus $q_E = (D - L_C)^+$.
- If $c_E \ge r + s_H$, then the slope of q_E is negative and π_C is decreasing in q_E. Thus $q_E = 0$.■

Proof of Proposition 3.1:

Depending on the value of $\tilde{q}_E^C$, there are two cases: 1. $\tilde{q}_E^C = 0$, if $c_E \ge r + s_H$; 2. $\tilde{q}_E^C = (D - L_C)^+$, if $c_E < r + s_H$. We solve each case as follows.

1. $\tilde{q}_E^C = 0$, if $c_E \ge r + s_H$

$$\pi_C = r\min\{D, z_C + q_R + u\,k_M\} - c_M x_M - c_R q_R - h_C(z_C + q_R + u\,k_M - D)^+ - s_H(D - z_C - q_R - u\,k_M)^+$$
$$= rD - c_M x_M - c_R q_R - h_C(z_C + q_R + u\,k_M - D)^+ - (r + s_H)(D - z_C - q_R - u\,k_M)^+$$

We find the limit of u and calculate the expected profit as follows

$$\Pi_C = rD - c_M x_M - c_R q_R - h_C \int_{\frac{D-q_R-z_C}{x_M}}^{b} (z_C + q_R + u\,k_M - D)\, f(u)du - (r + s_H)\int_{a}^{\frac{D-q_R-z_C}{x_M}} (D - z_C - q_R - u\,k_M)\, f(u)du$$

The second order condition (SOC) $\frac{\partial^2 \Pi_C}{\partial q_R^2}\frac{\partial^2 \Pi_C}{\partial x_M^2} - \left(\frac{\partial^2 \Pi_C}{\partial q_R \partial x_M}\right)^2 = 0$, which is non-conclusive. Therefore, we solve the interior solution and boundary solutions as candidates, and compare the profit with the candidate solutions to obtain the optimal solutions.

By solving $\frac{\partial \Pi_C}{\partial q_R} = 0$ and $\frac{\partial \Pi_C}{\partial x_M} = 0$ simultaneously, we obtain the interior solutions: $q_R = D - z_C$ and $x_M = 0$ (which is also a boundary solution at $x_M = 0$);

Another boundary solution is $q_R = 0$, $x_M = \frac{\sqrt{h_C + r + s_H}(D - z_C)}{\sqrt{-2ac_M + b(2c_M + bh_C) + a^2(r + s_H)}} = \hat{x}_M$

We then compare the profit with the two candidate solutions: $\Pi_C(q_R = D - z_c, x_M = 0) \le \Pi_C(q_R = 0, x_M = \hat{x}_M)$ iff. $c_R < \left(\frac{\sqrt{h_C + r + s_H}\sqrt{-2ac_M + b(2c_M + bh_C) + a^2(r + s_H)} - bh_C - a(r + s_H)}{b - a}\right)^+$.

2. $\tilde{q}_E^C = (D - L_C)^+$, if $c_E < r + s_H$.

$$\pi_C = r\min\{D, L_C + (D - L_C)^+\} - c_M x_M - c_R q_R - c_E(D - L_C)^+ - h_C\,(L_C + (D - L_C)^+ - D)^+ - s_H(D - L_C - (D - L_C)^+)^+$$
$$= rD - c_M x_M - c_R q_R - h_C(z_C + q_R + u\,k_M - D)^+ - c_E(D - z_C - q_R - u\,k_M)^+$$

After the transformation of π_C, it is easy to verify that we can obtain π_C in this case from π_C in case 1 by replacing $r + s_H$ (the coefficient of the last term) with c_E. Thus the optimal solutions could be obtained from case 1 by replacing $r + s_H$ with c_E:

$\Pi_C(q_R = D - z_c, x_M = 0) \leq \Pi_C\left(q_R = 0, x_M = \frac{\sqrt{h_C+r+s_C}(D-z_C)}{\sqrt{-2ac_M+b(2c_M+bh_C)+a^2(r+s_C)}}\right)$ iff $c_R < \left(\frac{\sqrt{h_C+c_E}\sqrt{-2ac_M+b(2c_M+bh_C)+a^2c_E}-bh_C-ac_E}{b-a}\right)^+$. ■

Proof of Lemma 3.2: Lemma 3.2 can be proved using the same procedure with Lemma 3.1. ■

Proof of Lemma 3.4 (the proof of Lemma 3.3 is a subcase in Lemma 3.4):

Proof for $\tilde{x}_M$:

- If $q_M \leq z_M$, the manufacturer's expected profit is strictly decreasing in x_M, thus $x_M = 0$.

- If $q_M > z_M$:

1. If $q_M < bx_M + z_M$ (i.e., $\frac{q_M - z_M}{k_M} < b$), then

$$\Pi_M|z_M = w\left(\int_a^{\frac{q_M-z_M}{x_M}} (u\,x_M + z_M)\,f(u)du + \int_{\frac{q_M-z_M}{x_M}}^{b} q_M f(u)du\right) - c_M x_M$$
$$- h_M \int_{\frac{q_M-z_M}{x_M}}^{b} (z_M + u\,x_M - q_M) f(u)du$$
$$- s_M \int_a^{\frac{q_M-z_M}{x_M}} (q_M - z_M - u\,x_M)\,f(u)du$$

Since $\frac{d^2\Pi_M}{dx_M^2} = -\frac{(w+h_M+s_M)(q_M-z_M)^2}{(b-a)x_M^3} < 0$, Π_M is concave in x_M.We solve the first order condition (FOC) $\frac{d\Pi_M}{dx_M} = \frac{(w+h_M+s_M)(q_M-z_M)^2}{2(b-a)x_M^2} - c_M - \frac{2b^2h_M+a^2(s_M+w)}{2(b-a)} = 0$ to obtain $x_M^* = A_M(q_M - z_M)$. We substitute x_M^* in the condition $\frac{q_M-z_M}{k_M} < b$ to

obtain $\frac{1}{A_M} < b$, which is equivalent to $(a+b)(s_M+w) - 2c_M > 0$.

2. If $q_M \geq bx_M + z_M$ (i.e., $\frac{q_M - z_M}{x_M} \geq b$), then

$$\Pi_M | z_M = w(E[u]x_M + z_M) - c_M x_M - s_M\big((q_M - z_M - E[u]x_M)\big)$$
$$= \frac{1}{2}x_M((a+b)(s_M+w) - 2c_M) + \frac{1}{2}(-2q_M s_M + 2(s_M+w)z_M)$$

- If $(a+b)(s_M+w) - 2c_M > 0$, then $x_M = \frac{q_M - z_M}{b}$. However, $\Pi_M\left(x_M = \frac{q_M - z_M}{b}\right) \leq \Pi_M(x_M = A_M(q_M - z_M).)$, therefore this solution is not optimal.
- If $(a+b)(s_M+w) - 2c_M < 0$, Π_M is decreasing in x_M, thus $x_M = 0$, this is also the proof for Lemma 3.2 and Assumption 3.1. ■

Proof of Lemma 3.5:

$(w + h_M + s_M) - (2(b-a)c_M + s_M a^2 + wa^2 + h_M b^2) = (1-b^2)(w + h_M + s_M) + (b-a)\big((b+a)(s_M+w) - 2c_M\big) > 0$ under the assumption that $(a+b)(s_M+w) - 2c_M > 0$, thus, $A_M = \frac{\sqrt{w+h_M+s_M}}{\sqrt{2(b-a)c_M + s_M a^2 + wa^2 + h_M b^2}} > 1$. ■

Proof of Proposition 3.2:

We skip the proof for Proposition 2.A and B, which are straightforward. We show the proof of Proposition 2.C. Depending on the best response function in step 3 and step 2, there are 4 cases as follows:

	$\tilde{q}_E = 0$ **if** $c_E \geq r + s_H$	$\tilde{q}_E = (D-L)^+$ **if** $c_E < r + s_H$
$\tilde{x}_M = 0$ if $q_M \leq z_M$	Case 1	Case 2
$\tilde{x}_M = A(q_M - z_M)$ if $q_M > z_M$	Case 3	Case 4

The superscript is the index for the case number in the following proof.

Case 1. $\tilde{q}_E = 0$ and $\tilde{x}_M = 0$ if $c_E \geq r + s_H$ and $q_M \leq z_M$. The hospital's random profit is as follows.

$$\pi_H^1 = r\min\{D, z_H + q_R + q_M\} - wq_M - c_R q_R - h_H(z_H + q_R + q_M - D)^+ - s_H(D - z_H - q_R - q_M)^+$$

There are two subcases:1.1. $z_H + q_R + q_M \le D$; 1.2. $z_H + q_R + q_M \ge D$.

1.1.$z_H + q_R + q_M \le D$, or $q_R + q_M \le D - z_H$

$$\begin{aligned}\pi_H^{11} &= r(z_H + q_R + q_M) - wq_M - c_R q_R - s_H(D - z_H - q_R - q_M) \\ &= q_R(r + s_H - c_R) + q_M(r + s_H - w) + (r + s_H)z_H - s_H D\end{aligned}$$

π_H^{11} is increasing in both q_R and q_M based on the assumption that $c_R, w < r + s_H$. We compare the slope of q_R and q_M, and obtain the optimal solutions as follows:

$q_R = D - z_H$ and $q_M = 0$ if $c_R \le w$; $q_R = D - z_H - z_M$ and $q_M = z_M$ if $c_R > w$.

1.2.$z_H + q_R + q_M \ge D$, or $q_R + q_M \ge D - z_H$

$$\begin{aligned}\pi_H^{12} &= rD - wq_M - c_R q_R - h_H(z_H + q_R + q_M - D) \\ &= q_R(-c_R - h_H) + q_M(-w - h_H) + rD + h_H(D - z_H)\end{aligned}$$

π_H is decreasing in both q_R and q_M, and by comparing the slope, we know that the optimal solutions for this case are the same as those in case 1.1.

Case 2. $\tilde{q}_E = (D - L)^+$ and $\tilde{x}_M = 0$ if $c_E < r + s_H$ and $q_M \le z_M$.

Following similar steps, this subcase has the same optimal solution with case 1.

Case 3. $\tilde{q}_E = 0$ and $\tilde{x}_M = A_M(q_M - z_M)$ if $c_E \ge r + s_H$ and $q_M > z_M$. We substitute $\tilde{x}_M$ to obtain $y = \min\{q_M, uA_M(q_M - z_M) + z_M\}$. We then generate π_H as follows

$$\begin{aligned}\pi_H^3 = r\min\{D, Q_1, Q_2\} - wy - c_R q_R - s_H \max\{0, D - Q_1, D - Q_2\} \\ - h_H(\min\{Q_1 - D, Q_2 - D\})^+ \\ = rD - wy - c_R q_R - (r + s_H)\max\{0, D - Q_1, D - Q_2\} \\ - h_H(\min\{Q_1 - D, Q_2 - D\})^+\end{aligned}$$

Where $Q_1 = z_H + q_R + q_M$ and $Q_2 = z_H + q_R + z_M + uA_M(q_M - z_M)$.

There are two subcases: 3.1. $Q_1 \ge D$; 3.2. $Q_1 < D$.

3.1. $Q_1 \geq D$, i.e., $q_R + q_M \geq D - z_H$

$$\pi_H = rD - wy - c_R q_R - (r + s_H)\max\{0, D - Q_2\} - h_H(\min\{Q_1 - D, Q_2 - D\})^+$$

We find the limit for u and calculate the expected profit as follows.

$$\Pi_H^{31} = r\,D - w\left(\int_a^{\frac{1}{A_M}} (uA_M(q_M - z_M) + z_M)\,f(u)du + \int_{A_M}^{b} q_M\,f(u)du\right) - c_R q_R$$
$$- (r + s_H)\int_a^{\frac{D-q_R-z_H-z_M}{A_M(q_M-z_M)}} (D - Q_2)\,f(u)du$$
$$- h_H\left(\left(\int_{\frac{D-q_R-z_H-z_M}{A(q_M-z_M)}}^{\frac{1}{A_M}} (Q_2 - D)\,f(u)du + \int_{\frac{1}{A_M}}^{b} (Q_1 - D)\,f(u)du\right)\right)$$

Where $f(u) = \frac{1}{b-a}$ under the assumption that $u \sim U(a, b)$. For the limit of u in the above profit function: it could be easily verified that $\frac{D-q_R-z_H-z_M}{A_M(q_M-z_M)} \leq \frac{1}{A_M}$; we solve for optimal q_R and q_M, and verify that $\frac{D-q_R-z_H-z_M}{A_M(q_M-z_M)} \geq a$ under the optimal values for q_R and q_M; we also solve for the case that $\frac{D-q_R-z_H-z_M}{A_M(q_M-z_M)} \leq a$, and verify that this case is not optimal.

Similar to the proof of Proposition 1, SOC $= 0$ which is non-conclusive. Thus, we solve for the interior solution and boundary solutions as candidates, and compare the profit to obtain the optimal solutions.

Solve $\frac{\partial \Pi_H^{32}}{\partial q_R} = 0$ and $\frac{\partial \Pi_H^{32}}{\partial q_M} = 0$ simultaneously, we obtain interior solution: $q_R = D - z_H - z_M$ and $x_M = z_M$. This solution is not feasible, since $x_M - z_M$ is showing in the denominator in the limit for u in Π_H. However, we could use the profit function in Case 1 Π_H^1, which applies to the solution $q_M = z_M$, to generate the profit for this interior solution, and compare it with other boundary solution.

The only other boundary solution is when $q_R = 0$: Π_H^{31} is concave in q_M and solving

$\frac{\partial \Pi_H^{32}(q_R=0)}{\partial q_M} = 0$ gives $q_M = z_M + \frac{\sqrt{(r+s_H+h_H)}(D-z_H-z_M)}{\sqrt{A_M{}^2a^2(r+s_H-w)+(2Ab-1)(h_H+w)}}$. We compare Π_H^{31} under the two candidate solutions and obtain the optimal solution as follows.

$q_R = D - z_H - z_M, q_M = z_M, if\ c_R = c_R^{32} \leq \frac{\sqrt{(h_H+r+s_H)((2A_Mb-1)(h_H+w)+a^2A_M{}^2(r+s_H-w)}-A_M(bh_H+a(r+s_H))}{A_M(b-a)}$; $q_R = 0, q_M = \max\{D - z_H, z_M + \frac{\sqrt{(r+s_H+h_H)}(D-z_H-z_M)}{\sqrt{A_M{}^2a^2(r+s_H-w)+(2A_Mb-1)(h_H+w)}}\}$ otherwise.

We also solve the optimal solution in case 3.2, and verify that $\Pi_H^{31*} \geq \Pi_H^{32*}$, i.e., case 3.2 is never optimal, since it is dominated by case 3.1.

Case 4. $\tilde{q}_E = (D-L)^+$ and $\tilde{x}_M = A_M(q_M - z_M)$ if $c_E < r + s_H$ and $q_M > z_M$. After substituting $\tilde{q}_E$ and $\tilde{x}_M$, and some manipulation of the min and max functions, we have

$$\pi_H^4 = rD - wy - c_R q_R - c_E \max\{0, D - Q_1, D - Q_2\} - h_H(\min\{Q_1 - D, Q_2 - D\})^+$$

π_H^4 could be obtained by replacing $r + s_H$ in π_H^3 with c_E. Therefore, the optimal solution in case 4 could be obtained by replacing $r + s_H$ in the optimal solution in case 3 with c_E. ■

Proof of Proposition 3.3.a:

- If $c_E \geq r + s_H$:

  $\frac{\partial \bar{c}_R}{\partial s_H} = \frac{(aA_H\sqrt{h_H+r+s_H}-\sqrt{(h_H+r+s_H)((2Ab-1)(h_H+w)+a^2A^2(r+s_H-w))^2}}{2A_H(b-a)\sqrt{h_H+r+s_H}\sqrt{(h_H+r+s_H)((2Ab-1)(h_H+w)+a^2A^2(r+s_H-w)}} \geq 0;$

  $\frac{\partial \bar{c}_R}{\partial r} = \frac{(aA_H\sqrt{h_H+r+s_H}-\sqrt{(h_H+r+s_H)((2Ab-1)(h_H+w)+a^2A^2(r+s_H-w))^2}}{2A_H(b-a)\sqrt{h_H+r+s_H}\sqrt{(h_H+r+s_H)((2Ab-1)(h_H+w)+a^2A^2(r+s_H-w)}} \geq 0;$

  $\frac{\partial \bar{c}_R}{\partial c_E} = 0$

- If $c_E < r + s_H$:

$$\frac{\partial \bar{c}_R}{\partial s_H} = 0; \frac{\partial \bar{c}_R}{\partial r} = 0; \frac{\partial \bar{c}_R}{\partial c_E} = \frac{(aA_H\sqrt{h_H+c_E} - \sqrt{(h_H+c_E)((2Ab-1)(h_H+w)+a^2A^2(c_E-w))})^2}{2A_H(b-a)\sqrt{h_H+c_E}\sqrt{(h_H+c_E)((2Ab-1)(h_H+w)+a^2A^2(c_E-w)}} > 0. \blacksquare$$

Proof of Lemma 3.6:

By substituting the optimal solutions in Π_H^*, we verify that s_H is not showing in Π_H^* in regions A,B and D in Figure 3.3, indicating that there is no shortage in those regions. In region C, the expected shortage amount could be obtained by computing the integral of the s_H term: $\int_a^{\frac{D-q_R-z_H-z_M}{A_M(q_M-z_M)}} (D - Q_2)\, f(u)du = \frac{(q_R+z_H+z_M-D+aA(\hat{q}_M-z_M))^2}{2A_M(b-a)(\hat{q}_M-z_M)}$. $\blacksquare$

Appendix C: Essay 3

All proofs are based on the assumption that $u_M \sim U(0,1)$, i.e., $f(u_M) = 1$.

Proof of Lemma 4.1:

- If $x_M \leq q_M$:

$$\frac{q_M}{x_M} > 1 \rightarrow u_M x_M < q_M \rightarrow \min\{u_M x_M, q_M\} = u_M x_M$$

$$Y_M^B = \int_0^1 u_M x_M f(u_M) \mathrm{d}u_M = x_M E[u_M] = \frac{x_M}{2}$$

$$\Pi_M^B = w_M Y_M^B - c_M x_M = \left(\frac{w_M}{2} - c_M\right) x_M$$

Π_M^B is linear in x_M, and the slope of x_M is $\frac{w_M}{2} - c_M$.

a. If $\frac{w_M}{2} - c_M < 0$, i.e., $w_M < c_M$: Π_M^B is decreasing in x_M, and $x_M = 0 \; \forall \; q_M$, the manufacturer does not produce anything regardless of q_M. Therefore, we assume $w_M > 2c_M$ for the rest of the analysis.

b. If $\frac{w_M}{2} - c_M < 0, i.e., w_M < c_M$: Π_M^B is increasing in $x_M \rightarrow x_M = q_M$.

- If $x_M > q_M$:

$$Y_M^B = \int_0^{\frac{q_M}{x_M}} u_M x_M f(u_M) \mathrm{d}u_M + \int_{\frac{q_M}{x_M}}^1 q_M f(u_M) \mathrm{d}u_M = x_M \left[\frac{u_M^2}{2}\right]_0^{\frac{q_M}{x_M}} + q_M [u_M]_{\frac{q_M}{x_M}}^1$$

$$= q_M - \frac{q_M^2}{2x_M}$$

$$\Pi_M^B = w_M Y_M^B - c_M x_M = w_M \left(q_M - \frac{q_M^2}{2x_M}\right) - c_M x_M$$

The second order condition (SOC) of Π_M^B is $\frac{d^2 \Pi_M^B}{d\, x_M^2} = -w_M \frac{q_M^2}{x_M^3} < 0$: Π_M^B is concave in x_M.

Solve the first order condition (FOC) of Π_M^B, $\frac{d\Pi_M^B}{d\, x_M} = \frac{w_M}{2}\left(\frac{q_M}{x_M}\right)^2 - c_M = 0 \rightarrow \; \tilde{x}_M^B(q_M) = \alpha q_M$, where $\alpha = \sqrt{\frac{w_M}{2c_M}}$ ■

Proof of Proposition 3.1:

It could be proved that $q_M < d$ is not optimal. Therefore, the following proof is based on $q_M > d$.

$$y_W^B = \min\{d, \min\{u_M x_M, q_M\} = \min\{d, u_M x_M\}$$

$$Y_W^B = \int_0^{\frac{d}{x_M}} u_M x_M f(u_M)\mathrm{d}u_M + \int_{\frac{d}{x_M}}^1 df(u_M)\mathrm{d}u_M = d - \frac{d^2}{2x_M}$$

$$\Pi_W^B = pY_W^B - w_M Y_M^B = p\left(d - \frac{d^2}{2x_M}\right) - w_M\left(q_M - \frac{q_M^2}{2x_M}\right)$$

Substitute $\tilde{x}_M^B(q_M) = \alpha q_M$:

$$\widetilde{\Pi}_W^B = p\left(d - \frac{d^2}{2\alpha q_M}\right) - w_M q_M\left(1 - \frac{1}{2\alpha}\right)$$

SOC of $\widetilde{\Pi}_W^B$ is $\frac{d^2\widetilde{\Pi}_W^B}{d\, q_M^2} = -\frac{d^2 p}{a q_M^3} < 0$: $\widetilde{\Pi}_W^B$ is concave in q_M

Solve the FOC of $\widetilde{\Pi}_W^B$, $\frac{d\widetilde{\Pi}_W^B}{d\, q_M} = \frac{p}{2\alpha}\left(\frac{d}{q_M}\right)^2 - w_M\left(1 - \frac{1}{2\alpha}\right) = 0 \rightarrow\ q_M^{B*} = \tau q_M$, where $\tau = \sqrt{\frac{m}{(2\alpha-1)w_M}}$. ■

Proof of Lemma 4.2:

$$S^B = d - Y_W^B = \left(d - \frac{d^2}{2x_M}\right) = \frac{d^2}{2x_M}$$

Substitute $\tilde{x}_M^B(q_M) = \alpha q_M$ and $q_M^{B*} = \tau q_M$: $S^{B*} = \frac{d^2}{2a\tau d} = \frac{d}{2a\tau}$. ■

Proof of Proposition 4.2:

a. $\frac{\partial q_M^{B*}}{\partial m} = \frac{d}{2m}\sqrt{\frac{m}{2\alpha-1}} > 0$; $\frac{\partial q_M^{B*}}{\partial w_M} = \frac{\alpha\tau d}{2w_M(1-2\alpha)} < 0$; $\frac{\partial q_M^{B*}}{\partial c_M} = \frac{\alpha\tau d}{2c_M(2\alpha-1)} > 0$

b. $\frac{\partial x_M^{B*}}{\partial m} = \frac{ad\tau}{2m} > 0$; $\frac{\partial x_M^{B*}}{\partial w_M} = \frac{d\tau(\sqrt{w_M}-\sqrt{2c_M})(\sqrt{2w_M}-\sqrt{c_M})}{4\sqrt{2}c_M^2 a(2a-1)^2} > 0$; $\frac{\partial x_M^{B*}}{\partial c_M} = -\frac{\sqrt{2}ad\tau(\sqrt{w_M}-\sqrt{2c_M})(\sqrt{2w_M}-\sqrt{c_M})}{4c_M^2(2a-1)^2} < 0$

c. $\frac{\partial S^{B*}}{\partial m} = -\frac{d}{4am\tau} < 0$; $\frac{\partial S^{B*}}{\partial w_M} = -\frac{\tau d\left(\sqrt{w_M}-\sqrt{2c_M}\right)}{4mw_M^{\frac{3}{2}}} < 0$; $\frac{\partial S^{B*}}{\partial c_M} = \frac{\tau d(\sqrt{w_M}-\sqrt{2c_M})}{4mc_M\sqrt{w_M}} > 0$ ■

Proof of Lemma 4.3:

It can be proved that $q_M + q_G < d$ is not optimal, therefore, the following proof is based on $q_M + q_G \geq d$.

According to our assumption of the procurement rule in Model D, y_i^D as a function u_M is summarized in Table C. 1.

Table C. 1: y_i^D as a function u_M, $i \in \{M, G, W\}$

$\boldsymbol{u_M}$	$\in \left[\mathbf{0}, \frac{\boldsymbol{d}-\boldsymbol{x_G}}{\boldsymbol{x_M}}\right]$	$\in \left(\frac{\boldsymbol{d}-\boldsymbol{x_G}}{\boldsymbol{x_M}}, \frac{\boldsymbol{d}-\boldsymbol{q_G}}{\boldsymbol{x_M}}\right]$	$\in \left(\frac{\boldsymbol{d}-\boldsymbol{q_G}}{\boldsymbol{x_M}}, \frac{\boldsymbol{q_M}}{\boldsymbol{x_M}}\right]$	$\in \left(\frac{\boldsymbol{q_M}}{\boldsymbol{x_M}}, \mathbf{1}\right]$
$\boldsymbol{y_M^D}$	$u_M x_M$	$u_M x_M$	$u_M x_M$	q_M
$\boldsymbol{y_G^D}$	x_G	$d - u_M x_M$	q_G	q_G
$\boldsymbol{y_W^D}$	$u_M x_M + x_G$	d	d	d

We first obtain Y_i^B, $i \in \{M, G, W\}$:

$$Y_M^B = \int_0^{\frac{q_M}{x_M}} u_M x_M f(u_M) \mathrm{d}u_M + \int_{\frac{q_M}{x_M}}^1 q_M f(u_M) \mathrm{d}u_M = q_M - \frac{q_M^2}{2x_M}$$

$$Y_G^B = \int_0^{\frac{d-x_G}{x_M}} x_G f(u_M) \mathrm{d}u_M + \int_{\frac{d-x_G}{x_M}}^{\frac{d-q_G}{x_M}} (d - u_M x_M) f(u_M) \mathrm{d}u_M + \int_{\frac{d-q_G}{x_M}}^1 q_G f(u_M) \mathrm{d}u_M$$

$$= \frac{2d(x_G - q_G) - x_G^2 + 2x_M q_G + q_G^2}{2x_M}$$

$$Y_W^B = \int_0^{\frac{d-x_G}{x_M}} (u_M x_M + x_G) f(u_M) \mathrm{d}u_M + \int_{\frac{d-x_G}{x_M}}^1 d f(u_M) \mathrm{d}u_M = \frac{2d(x_G + x_M) - (d^2 + x_G^2)}{2x_M}$$

We then obtain the manufacturer and the government's expected utility functions:

$$\Pi_M^D = w_M Y_M^D - c_M x_M = w_M \left(q_M - \frac{q_M^2}{2x_M}\right) - c_M x_M$$

$$\Pi_G^D = (b - p) Y_W^D + w_G y_G^D - c_G x_G - s_G (d - y_W^D)$$

$$= (b - p + s_G) \frac{2d(x_G + x_M) - (d^2 + x_G^2)}{2x_M} + w_G \frac{2d(x_G - q_G) - x_G^2 + 2x_M q_G + q_G^2}{2x_M}$$

$$- c_G x_G - s_G d$$

SOC of Π_M^D is $\frac{d^2 \Pi_M^D}{d\, x_M^2} = -\frac{q_M^2 w_M}{x_M^3} < 0$: Π_M^D is concave in x_M.

SOC of Π_G^D is $\frac{d^2 \Pi_G^D}{d\, x_G^2} = -\frac{b - p + s_G + w_G}{x_M} < 0$: Π_G^D is concave in x_G.

Solve the FOC of Π_M^D and Π_G^D simultaneously, $\frac{d\Pi_M^D}{d\,x_M} = 0$ and $\frac{d\Pi_G^D}{d\,x_G} = 0$: $\tilde{x}_M^D = \alpha q_M$ and $\tilde{x}_G^D = (d - \beta\alpha q_M)^+$, where $\beta = \frac{c_G}{b-p+s_G+w_G}$ ■

Proof of Proposition 4.3:

We first obtain the wholesaler's expected profit function:

$$\begin{aligned}\Pi_W^D &= pY_W^D - w_M Y_M^D - w_G Y_G^D \\ &= p\frac{2d(x_G + x_M) - (d^2 + x_G^2)}{2x_M} - w_M\left(q_M - \frac{q_M^2}{2x_M}\right) \\ &\quad - w_G\frac{2d(x_G - q_G) - x_G^2 + 2x_M q_G + q_G^2}{2x_M}\end{aligned}$$

Depending on the government's best response function, there are two cases: 1. $\tilde{x}_G^D = 0$; 2. $\tilde{x}_G^D = d - \beta\alpha q_M$.

1. $\tilde{x}_G^D = 0$, if $d - \beta\alpha q_M < 0$, i.e., $q_M > \frac{d}{\beta\alpha}$

In this case $q_G = 0$: the wholesaler does not order from the government since it knows that the government will not produce anything. Substituting $\tilde{x}_M^D = \alpha q_M, \tilde{x}_G^D = 0$, and $q_G = 0$, the wholesaler's expected profit function became

$$\widetilde{\Pi}_W^D = p\frac{2\alpha q_M - d^2}{2\alpha q_M} - w_M\left(q_M - \frac{q_M}{2\alpha}\right)$$

The SOC of $\widetilde{\Pi}_W^D$ is $\frac{\partial^2\widetilde{\Pi}_W^D}{\partial q_M^2} = \frac{d^2 p}{\alpha q_M^3} < 0$: $\widetilde{\Pi}_W^D$ is concave in q_M.

Solve the FOC of $\widetilde{\Pi}_W^D$: $q_M^{B*} = \tau q_M$, where τ is the same as defined in Proposition 1.

2. $\tilde{x}_G^D = d - \beta\alpha q_M$ (if $d - \beta\alpha q_M > 0$, i.e., $q_M < \frac{d}{\beta\alpha}$)

Substituting $\tilde{x}_M^D = \alpha q_M$ and $\tilde{x}_G^D = d - \beta\alpha q_M$, the wholesaler's expected profit function became

$$\widetilde{\Pi}_W^D = p\left(d - \frac{1}{2}\alpha\beta^2 q_M\right) - w_M\left(q_M - \frac{q_M}{2\alpha}\right) - w_G\left(q_G + \frac{(d - q_G)^2}{2\alpha q_M} - \frac{1}{2}\alpha\beta^2 q_M\right)$$

We check the SOC of $\widetilde{\Pi}_W^D$:

$$\frac{\partial^2\widetilde{\Pi}_W^D}{\partial q_M^2} = -\frac{(d - q_G)^2 w_G}{\alpha q_M^3} < 0$$

$$\frac{\partial^2 \widetilde{\Pi}_W^D}{\partial q_G^2} = -\frac{w_G}{\alpha q_M} < 0$$

$$\frac{\partial^2 \widetilde{\Pi}_W^D}{\partial q_M^2}\frac{\partial^2 \widetilde{\Pi}_W^D}{\partial q_G^2} - \left(\frac{\partial^2 \widetilde{\Pi}_W^D}{\partial q_M q_G}\right)^2 = 0$$

The SOC of $\widetilde{\Pi}_W^D$ is not conclusive. After examining $\widetilde{\Pi}_W^D$, we conclude that there are two candidates of the optimal solutions: the boundary solution with $q_G = 0$ and the boundary solution with $q_M = 0$. Therefore, we solve the two candidates, and the candidate which maximizes $\widetilde{\Pi}_W^D$ is the optimal solution

- When $q_G = 0$, $\widetilde{\Pi}_W^D$ is concave in q_M, solve the $\frac{\partial \widetilde{\Pi}_W^D}{\partial q_M} = 0 \to q_M = \theta d$, where $\theta = \sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+w_M(2\alpha-1)}}$.
- When $q_M = 0$: $Y_W^D = d - \frac{1}{2}\alpha\beta^2 q_M = d$, $\tilde{x}_G^D = d - \beta\alpha q_M = d$, $y_G^D = \min\{q_M, x_G\} = \min\{q_M, d\}$, $\pi_W^D = pd - w_G \min\{q_M, d\} \to q_M = d$.

Next, we prove $\theta < \tau$: $\frac{w_G}{\alpha^2\beta^2(p-w_G)+w_M(2\alpha-1)} < \frac{p}{(2\alpha-1)w_M} \Leftrightarrow w_G(2\alpha-1)w_M < p\big(\alpha^2\beta^2(p-w_G)+w_M(2\alpha-1)\big) \Leftrightarrow -(p-w_G)(\alpha^2\beta^2 p + (2\alpha-1)w_M) < 0$. The last inequality always holds, thus $\theta < \tau$. ■

Proof of Proposition 4.4:

a. Compare Π_W^{Da} vs. Π_W^{Db}:

$$\Pi_W^{Da} - \Pi_W^{Db} = \frac{d(-w_G + \theta(a^2\beta^2\theta(-p+w_G) + \theta w_M + 2a(w_G - \theta w_M)))}{2\alpha\theta}$$

Compare $-w_G + \theta(a^2\beta^2\theta(-p+w_G) + \theta w_M + 2a(w_G - \theta w_M))$ vs. 0:

Plug in β, θ and τ, the above expression became $2w_G(-1 + a\sqrt{\frac{w_G}{\frac{a^2c_G^2(p-w_G)}{(b-p+s_G+w_G)^2}+(2\alpha-1)w_M}}) =$

$2w_G\delta_2$

$$\delta_2 < 0 \Leftrightarrow a^2 w_G - (2\alpha-1)w_M < \frac{a^2c_G^2(p-w_G)}{(b-p+s_G+w_G)^2}$$

We check the sign of $a^2 w_G - (2\alpha-1)w_M$:

$$a^2 w_G - (2\alpha - 1)w_M = a^2 w_G - (2\alpha - 1)w_G + (2\alpha - 1)w_G - (2\alpha - 1)w_M$$
$$= (a-1)^2 w_G + (2\alpha - 1)(w_G - w_M) > 0$$

the above equation become:

$$b - p + s_G + w_G < a c_G \sqrt{\frac{p - w_G}{a^2 w_G - (2\alpha - 1)w_M}}$$

$$\Leftrightarrow s_G < \bar{s}_G^{D1} = a c_G \sqrt{\frac{p - w_G}{a^2 w_G - (2\alpha - 1)w_M}} + p - b - w_G$$

If $s_G^{ab} \leq 0$, i.e., $c_G < c_G^{ab} = \frac{b-p+w_G}{a}\sqrt{\frac{a^2 w_G - (2\alpha-1)w_M}{p - w_G}}$: $s_G^{ab} > 0$ always holds: $\Pi_W^{Da} > \Pi_W^{Db}$

If $c_G > c_G^{ab}$

$s_G < s_G^{ab} \Leftrightarrow \delta_2 < 0 \Leftrightarrow \Pi_W^{Da} < \Pi_W^{Db}$

$s_G > s_G^{ab} \Leftrightarrow \delta_2 > 0 \Leftrightarrow \Pi_W^{Da} > \Pi_W^{Db}$

b. Compare Π_W^{Da} vs. Π_W^{Dc}:

$$\Pi_W^{Da} - \Pi_W^{Dc} = \frac{d(p\theta(1 - a^2\beta^2\tau\theta) + \tau(a^2\beta^2\theta^2 - 1)w_G + (2a-1)\tau(\tau - \theta)\theta w_M)}{2a\tau\theta}$$

Compare $p\theta(1 - a^2\beta^2\tau\theta) + \tau(a^2\beta^2\theta^2 - 1)w_G + (2a-1)\tau(\tau-\theta)\theta w_M$ vs. 0:

Plug in β, θ and τ, the above expression became $2\left(p\sqrt{\frac{w_G}{\frac{a^2 c_G^2 (p - w_G)}{(b-p+s_G+w_G)^2} + (2\alpha-1)w_M}} - w_G\sqrt{\frac{p}{(2\alpha-1)w_M}}\right) = 2\delta$

$\Pi_W^{Da} > \Pi_W^{Dc} \Leftrightarrow \delta > 0 \Leftrightarrow s_G > s_G^{ac} = \alpha c_G \sqrt{\frac{w_G}{(2\alpha-1)w_M}} + p - b - w_G$

If $\bar{s}_G < 0$ (i.e., $c_G < c_G^{ac} = \frac{b-p+w_G}{a}\sqrt{\frac{(2\alpha-1)w_M}{w_G}}$) $\Leftrightarrow s_G > s_G^{ac}$ always holds: $\Pi_W^{Da} > \Pi_W^{Dc}$

If $\bar{s}_G > 0$ (i.e., $c_G > c_G^{ac}$)

If $s_G > s_G^{ac}$: $\Pi_W^{Da} > \Pi_W^{Dc}$

If $s_G < s_G^{ac}$: $\Pi_W^{Da} < \Pi_W^{Dc}$

c. Compare Π_W^{Db} vs. Π_W^{Dc}:

$$\Pi_W^{Db} - \Pi_W^{Dc} = \frac{d(p + \tau(-2aw_G + (2a-1)\tau w_M))}{2a\tau}$$

Compare $p + \tau(-2aw_G + (2a-1)\tau w_M)$ with 0:

Plug in β, θ and τ, the above expression became $2\left(p - aw_G\sqrt{\frac{p}{(2a-1)w_M}}\right) = 2\delta^{bc}$

$$\delta^{bc} < 0 \Leftrightarrow p - aw_G\sqrt{\frac{p}{(2a-1)w_M}} < 0 \Leftrightarrow w_G > \frac{p}{a\tau}$$

If $\frac{p}{a\tau} > p$, i.e., $a\tau < 1$ then $w_G > \frac{p}{a\tau}$ cannot hold. We compare $a\tau$ vs. 1:$a\tau = a\sqrt{\frac{p}{(2a-1)w_M}} > 1 \Leftrightarrow p > \frac{(2a-1)w_M}{a^2} \Leftrightarrow mw_M > \frac{(2a-1)w_M}{a^2} \Leftrightarrow m > \frac{(2a-1)}{a^2}$.

$(a-1)^2 = a^2 - 2a + 1 > 0 \rightarrow a^2 > 2a - 1 \rightarrow \frac{(2a-1)}{a^2} < 1$ .Thus $m > \frac{(2a-1)}{a^2}$ always hold, and $\frac{p}{a\tau} < p$ always hold. Therefore:

If $w_G \leq \frac{p}{a\tau}$: $\Pi_W^{Db} \geq \Pi_W^{Dc}$

If $w_G > \frac{p}{a\tau}$: $\Pi_W^{Db} < \Pi_W^{Dc}$. ■

Proof of Lemma 4.4:

Since $p = mw_M$, τ^B can be rewritten as $\sqrt{\frac{p}{(2a-1)w_M}}$. *Then*, τ^{SW} can be obtained from τ^B by replacing the unit procurement cost (w_M) by $w_M - \gamma_w$. τ^{SP} can be obtained from τ^B by replacing the unit revenue (p) by $p + \gamma_p$. ■

Proof of Proposition 4.5:

We first simplify Π_G^S as follows:

$$\Pi_G^S = (b-p)Y_W^S - s_G(d - Y_W^S) - \gamma_w Y_M^S - \gamma_p Y_W^S$$
$$= \left(b - p + s_G - \gamma_p\right)Y_W^S - \gamma_w Y_M^S - s_G d$$

Similar to the basic model, $Y_M^S = q_M\left(1-\frac{q_M}{2x_M}\right)$ and $Y_W^S = d\left(1-\frac{d}{2x_M}\right)$. Then, Π_G^S can be expressed as:

$$\Pi_G^S = \left(b-p+s_G-\gamma_p\right)d\left(1-\frac{d}{2x_M}\right)-\gamma_w q_M\left(1-\frac{q_M}{2x_M}\right)-\ s_G d$$

- Model SW

We substitute $\tilde{x}_M^S$, $\tilde{q}_M^{SW}$, and $\gamma_p = 0$ to obtain $\widetilde{\Pi}_G^{SW}$ as a function of γ_w

$$\widetilde{\Pi}_G^{SW}(\gamma_w) = (b-p+s_G)d\left(1-\frac{1}{2\alpha\sqrt{\frac{p}{(2\alpha-1)(w_M-\gamma_w)}}}\right)$$
$$-\gamma_w d\sqrt{\frac{p}{(2\alpha-1)(w_M-\gamma_w)}}\left(1-\frac{1}{2a}\right)-\ s_G d$$

The SOC of $\widetilde{\Pi}_G^{SW}$ is $\frac{\partial^2\widetilde{\Pi}_G^{SW}}{\partial\gamma_w^2} = \frac{d((b-2p+s_G)(w_M-\gamma_w)-3pw_M)}{8\alpha(w_M-\gamma_w)^3\tau^{SW}}$, which is not conclusive. We solve the interior solution and plug it back to the SOC to verify the concavity.

By solving the FOC of $\widetilde{\Pi}_G^{SW}$, $\frac{\partial\widetilde{\Pi}_G^{SW}}{\partial\gamma_w} = \frac{d\left((b-2p+s_G)(w_M-\gamma_w)-pw_M\right)}{4\alpha(w_M-\gamma_w)^2\text{tausW}} = 0$, we obtain the interior solution $\gamma_w^{INT} = \frac{b-3p+s_G}{b-2p+s_G}w_M = w_M-\hat{\gamma}_w$, where $\hat{\gamma}_w = \frac{pw_M}{b-2p+s_G}$.

If $b-2p+s_G<0$ (i.e., $p>\frac{b+s_G}{2}$): $\frac{\partial\widetilde{\Pi}_G^{SW}}{\partial\gamma_w}<0$, i.e., $\widetilde{\Pi}_G^{SW}$ is decreasing in γ_w, thus $\gamma_w^* = 0$.

If $b-2p+s_G>0$ (i.e., $p<\frac{b+s_G}{2}$):

If $b-3p+s_G<0$ (i.e., $p>\frac{b+s_G}{3}$): $\gamma_w^{INT}<0$, and $\gamma_w^* = 0$.

If $b-3p+s_G\geq 0$ (i.e., $p\leq\frac{b+s_G}{3}$): $\gamma_w^* = \gamma_w^{INT}$. We substitute γ_w^{INT} in the SOC to abtain $\frac{\partial^2\widetilde{\Pi}_G^{SW}}{\partial\gamma_w^2} = -\frac{d(b-2p+s_G)^3}{4\alpha p^2 w_M^2\sqrt{\frac{b-2p+s_G}{(2\alpha-1)w_M}}}<0$ to verify the concavity of $\widetilde{\Pi}_G^{SW}$.

- Model SP

We subsititute $\tilde{x}_M^S$, $\tilde{q}_M^{SP}$, and $\gamma_w = 0$ to obtain $\widetilde{\Pi}_G^{SP}$ as a function of γ_p

$$\widetilde{\Pi}_G^{SP}(\gamma_p) = \left(b-p+s_G-\gamma_p\right)d\left(1-\frac{1}{2\alpha\sqrt{\frac{p+\gamma_p}{(2\alpha-1)w_M}}}\right)-\ s_G d$$

The SOC of $\widetilde{\Pi}_G^{SP}$ is $\frac{\partial^2 \widetilde{\Pi}_G^{SP}}{\partial \gamma_p^2} = -\frac{d\left(3(b+s_G)+p+\gamma_p\right)}{8a\left(p+\gamma_p\right)^2 \tau^{Sp}} < 0$: $\widetilde{\Pi}_G^{SP}$is concave in γ_p.

The FOC of $\widetilde{\Pi}_G^{SP}$ is $\frac{\partial \widetilde{\Pi}_G^{SP}}{\partial p} = \frac{d\left(b+s_G+(1-4\alpha)\tau^{Sp}(p+\gamma_p)\right)}{4a(p+\gamma_p)\tau^{Sp}} = 0 \Leftrightarrow b + s_G + (1-4\alpha\tau^{Sp})\left(p + \gamma_p\right) = 0$.

The above equation can be transformed to: $-16\alpha^2 {\Gamma_p}^3 + A{\Gamma_p}^2 + 2A\,B\Gamma_p + AB^2 = 0$, where $\Gamma_p = p + \gamma_p$, $A = (2\alpha - 1)w_M > 0$, and $B = b + s_G > 0$. The left-hand side of the equation is a cubit function of Γ_p, with a discriminant $\Delta = -64\alpha^2 A^2(108\alpha^2 + AB^3) < 0$. Thus, the cubic function has a single root for Γ_p:

$$\hat{\gamma}_p = \frac{1}{48\alpha^2}\left(A + \frac{A(A+96\alpha^2 B)}{\varphi} + \varphi\right)$$

where $\varphi = A^3 + 144\alpha^2 A^2 B + 3456\alpha^4 AB^2 + 192\sqrt{3}\sqrt{\alpha^6 A^2 B^3 (A + 108\alpha^2 B)}$.

Therefore, the interior solution of γ_p is $\gamma_p^{INT} = \hat{\gamma}_p - p$. Taking into consideration the non-negativity constraint of γ_p, the optimal sotluion is

$$\gamma_p^* = \left(\hat{\gamma}_p - p\right)^+.\blacksquare$$

Proof of Proposition 4.6:

We prove the case that $\gamma_w^* = \gamma_w^{INT}$, i.e., $p \le \frac{b+s_G}{3}$:

$$\frac{\partial \gamma_w^{INT}}{\partial m} = -\frac{(b+\mathrm{s_G})\mathrm{w_M^2}}{(b+\mathrm{s_G}-2m\mathrm{w_M})^2} < 0;\ \frac{\partial \gamma_w^{INT}}{\partial w_M} = \frac{b-3p+\mathrm{sG}}{b-2p+\mathrm{sG}} \ge 0;\ \frac{\partial \gamma_w^{INT}}{\partial b} = \frac{pw_M}{(b-2p+s_G)^2} > 0;\ \frac{\partial \gamma_w^{INT}}{\partial s_G} = \frac{pw_M}{(b-2p+s_G)^2} > 0.$$

When $p > \frac{b+s_G}{3}$, $\gamma_w^* = 0$, and the derivative with respect to any parameter equals zero. ■

Proof of Proposition 4.7:

If $\Pi_G^{S*} > \Pi_G^{B*}$, then $\gamma_w^* > 0$. It can be easily verified that τ^{S*} is increasing in γ_w.

Therefore, $Y_W^{S*} = \left(1 - \frac{1}{2\alpha\tau^{S*}}\right)d$ and $Y_M^{S*} = \left(1 - \frac{1}{2\alpha}\right)\tau^{S*}d$ are increasing in γ_w, and

$S^{j*} = \frac{d}{2\alpha\tau^{S*}}$ is decreasing in γ_w. Π_M^{S*} can be rewritten as follows:

$$\Pi_M^{S*} = w_M\left(1 - \frac{1}{2\alpha}\right)\tau^{S*}d - c_M\alpha\tau^{S*}d = \tau^{S*}d\left(w_M\left(1 - \frac{1}{2\alpha}\right) - c_M\alpha\right)$$
$$= \tau^{S*}d\left(\frac{(2\alpha - 1)w_M - 2\alpha^2 c_M}{2\alpha}\right)$$

Plug in $\alpha = \sqrt{\frac{w_M}{2c_M}}$: $\Pi_M^{S*} = \tau^{S*}d\left(\frac{(2\alpha-1)w_M - w_M}{2\alpha}\right) = \tau^{S*}d\left(\frac{(\alpha-1)w_M}{\alpha}\right)$. Because $\alpha > 1$, $\frac{(\alpha-1)w_M}{\alpha} > 0$ and Π_M^{S*} is increasing in τ^{S*}.

If $\Pi_W^{S*} < \Pi_W^{B*}$, then the wholesaler can receive the subsidy from the government, but use its optimal order quantity in Model B to get a profit Π_W^{B*}. Knowing this reaction, the government will not provide any subsidy if the wholesaler prefers its profit in Model B. Therefore, if the government chooses to provide subsidy, then $\Pi_W^{S*} \geq \Pi_W^{B*}$. ■

Proof of

Proposition 4.8:

If $\Pi_G^{D*} > \Pi_G^{B*}$, (i.e., the government chooses a dual sourcing strategy), then the wholesaler has the option to procure the drug from either or both manufacturers. The following proof is based on the on the condition that a public manufacturer has been established (i.e., Model D is available for the wholesaler)

- The wholesaler's expected profit (Π_W^{j*})

In Model D, the wholesaler moves first, and it will make the optimal procurement decisions to maximize its own profit. Since the wholesaler's optimal profit in Model B is equal to its optimal profit under a private procurement plan in Model D, the wholesaler will be no worse off in a Model D than in Model B.

- The shortage amount (S^j)

We first prove the shortage amount. Let S^{Da}, S^{Db} and S^{Dc} be the expected shortage amount if the wholesaler uses procurement plan a, b and c as indicated in Proposition 4.3,

respectively. Since $S^{Dc} > 0$ and $S^{Db} = 0$, we know $S^{Dc} > S^{Db}$. Next, we compare S^{Da} with S^{Dc}: $S^{Da} < S^{Dc}$, i.e., $\frac{\alpha\beta^2\theta d}{2} < \frac{d}{2\alpha\tau} \Leftrightarrow \alpha^2\beta^2\theta\tau < 1$. Plug in θ and τ, we have:

$$\alpha^2\beta^2\sqrt{\frac{p}{(2\alpha-1)w_M}}\sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M}} < 1 \Leftrightarrow \alpha^4\beta^4 p\, w_G$$
$$< (2\alpha-1)w_M(\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M)$$
$$\Leftrightarrow (\alpha^2\beta^2 w_G-(2\alpha-1)w_M)(\alpha^2\beta^2 p+(2\alpha-1)w_M)$$

Since $\alpha^2\beta^2 p+(2\alpha-1)w_M > 0$, we check $\alpha^2\beta^2 w_G-(2\alpha-1)w_M$.

In the proof of Proposition 4.4.b, we have $\Pi_W^{Da} > \Pi_W^{Dc}$ iff $\delta > 0$. We minipulate this condition as follows: $\delta = p\sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M}} - w_G\sqrt{\frac{p}{(2\alpha-1)w_M}} > 0 \Leftrightarrow$ $p\sqrt{\frac{w_G}{\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M}} > w_G\sqrt{\frac{p}{(2\alpha-1)w_M}} \Leftrightarrow p^2\frac{w_G}{\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M} > w_G^2\frac{p}{(2\alpha-1)w_M} \Leftrightarrow$ $p(2\alpha-1)w_M > w_G(\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M) \Leftrightarrow p(2\alpha-1)w_M -$ $w_G(\alpha^2\beta^2(p-w_G)+(2\alpha-1)w_M) > 0 \Leftrightarrow -(p-w_G)(\alpha^2\beta^2 w_G-(2\alpha-1)w_M) >$ $0 \Leftrightarrow \alpha^2\beta^2 w_G-(2\alpha-1)w_M < 0$. Thus, if $\Pi_W^{Da} > \Pi_W^{Dc}$, then $S^{Da} < S^{Dc}$.

If the wholesaler chooses a mixed procurement plan (plan a) or a public procurement plan (plan b), then the shortage amount in the implemented plan is less than that in a private procurement plan (plan c, which is the same as Model B). If the wholesaler chooses a private procurement plan, then the shortage amount is the same as it in Model B. Therefore, if the government chooses to operate a public manufacturer, then the wholesaler will choose the optimal procurement plan to maximize its own profit, and the shortage amount under the wholesaler ‘s optimal procurement plan is less than or equal to the shortage amount in Model B.

- The wholesaler’s expected delivered quantity (Y_W^{j*})

Since $Y_W^{Dc} = \left(1-\frac{1}{2\alpha\tau}\right)d < Y_W^{Db} = d$, we know that if the wholesaler chooses plan a, then it delivered quantity in plan a is greater than that in plan c.

Next, we compare Y_W^{Da} with Y_W^{Dc}: $Y_W^{Da} - Y_W^{Dc} = \left(1 - \frac{\alpha\beta^2\theta}{2}\right)d - \left(1 - \frac{1}{2\alpha\tau}\right)d = \left(\frac{1}{2\alpha\tau} - \frac{\alpha\beta^2\theta}{2}\right)d$. $Y_W^{Da} > Y_W^{Dc}$ iff $\alpha^2\beta^2\theta\tau < 1$. As proved for the shortage amount, this condition holds if $\Pi_W^{Da} > \Pi_W^{Dc}$. Following the similar discussion in the proof for the shortage amount, we know that the wholesaler's expected delivered quantity under its optimal procurement plan is greater than or equal to its expected delivered quantity in Model B.

- The manufacturer's expected delivered quantity (Y_W^{j*})

$Y_M^{Dc} = \left(1 - \frac{1}{2\alpha}\right)\tau d > Y_M^{Db} = 0$. Next, we compare Y_M^{Da} with Y_M^{Dc}: $Y_M^{Da} - Y_M^{Dc} = \left(1 - \frac{1}{2\alpha}\right)\theta d - \left(1 - \frac{1}{2\alpha}\right)\tau d = \left(1 - \frac{1}{2\alpha}\right)d(\theta - \tau) < 0$ (we prove that $\theta < \tau$ in Proposition 4.3). Thus $Y_M^{Da} < Y_M^{Dc}$ always holds. Following the same discussion for the shortage amount, we know that the manufacturer's expected delivered quantity under the wholesaler's optimal procurement plan is less than or equal to the manufacturer's expected delivered quantity in Model B.

- The manufacturer's expected profit (Π_M^{j*})

$\Pi_M^{Dc} > \Pi_M^{Db} = 0$. Next, we compare Π_M^{Da} with Π_M^{Dc}: $\Pi_M^{Da} - \Pi_M^{Dc} = \frac{d(\theta-\tau)(\alpha-1)w_M}{2a}$. Since $\theta < \tau$ and $\alpha > 1$, $\Pi_M^{Da} < \Pi_M^{Dc}$ always holds. Following the same logic with the previous discussion, we know that the manufacturer's expected profit under the wholesaler's optimal procurement plan is less than or equal to the manufacturer's expected profit in Model B. ■

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Publications:

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