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a stochastic dynamic programming approach

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Production and Inventory of Personalized Drugs: A Stochastic Dynamic Programming Approach

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We consider a supply chain for personalized drugs facing several unique challenges in modeling and analysis of production-inventory system, such as separate demand streams for different product categories, random lifetime, and several substitution options. For a drug that has two different grade categories, we develop a discrete time, discrete state space, infinite-horizon Markov decision process model to obtain a joint optimal replenishment and issuance policy that minimizes the total discounted cost. We introduce an upward substitution with double picking quantity which is a procedure to substitute two low-grade drugs for one high-grade drug, in order to satisfy the dose requirement requested by customers. Our analysis shows that the structure of the issuance policy is complex and highly depends on the initial state when the optimal ordering follows a base-stock policy. Numerical experiments are performed to gain insights on how the decay rate and the double picking quantity procedure influence the optimal value and solution. Furthermore, we find that the optimal cost is generated by applying the most flexible substitution setting under different decay rates and financial characteristics.

Key words: perishable inventory; replenishment and issuance policies; Markov decision process; separate demand streams; random lifetime; substitution

1. Introduction

A personalized approach for medical treatment has received increasing acceptance due to the belief that every patient has a unique variation of the human genome that affects the patients' predicted response to a disease (of Medical Sciences 2015). This patient-to-patient variation leads to a special medical procedure that is designed to mitigate risks and treat diseases with precision. The direct impact of this approach is the classification of patients into different groups with specific medical decisions, practices, and interventions. In this article, we narrow down into the personalization of medical drugs context which each patient group receives a specified level of dose according to each individual's genomic information or other molecular or cellular analysis (Katsios and Roukos 2010). Currently, many people suffer from imprecise drugs that do not effectively help them in treating their illnesses. According to Schork (2015), efficacy of the top ten grossing drugs in the United States is as low as 4% to 25% and even lower still for other drugs. These facts motivate

health care practitioners to shift their paradigm from conventional to personalized drugs. From the manufacturers' perspective, managing the production-inventory system of personalized drugs is essential as this system highly affects the availability of drugs with the requested level of dose. In this study, we focus on the production and inventory of personalized drugs conducted by a pharmaceutical company as part of its supply chain optimization efforts. This topic is of relevance given the widespread use of personalized drugs and the low efficacy of imprecise medicines.

This paper is an outcome of a practice-driven research conducted in a close collaboration with a large pharmaceutical company. In order to properly provide the background of the system, we first describe the underlying features of its personalized drug supply chain. At the beginning of each period, customers, i.e. hospitals or physicians, order personalized drugs based on a specified level of dose according to patients' treatment plans for the medicine. We classify the level of dose into two different grades, namely high and low-grades. Each drug grade, which has a dedicated storage, represents a range of dose level. At this moment, the inventory on hand and the customer demand for every drug grade are already known. In the practice, high-grade drugs are compatible for meeting demands for both high and low-grade drugs, as the Active Pharmaceutical Ingredient (API) available in high-grade drugs is more than what is requested by the demands for low-grade drugs. We define this interaction of substituting high-grade drugs for low-grade drugs as *downward substitution*, meanwhile *upward substitution* refers to the use of low-grade drugs to meet the demands for high-grade drugs. However, the upward substitution can only be applied if the company picks two low-grade drugs to fulfill the demand of one high-grade drug. The second drug is depleted to satisfy the dose requirement requested by customers and is free of charge. We use the term *upward substitution with double picking quantity or second drug scheme* to denote this unique case. After receiving information about the inventory on hand and the demand realization, the system takes issuance and replenishment decisions simultaneously. Here, the issuance decision means the allocation of drugs available to meet both demand streams given several substitution options. For example, four low-grade drugs available are allocated to satisfy two demands of the low-grade drug (without substitution) and one demand of the high-grade drug (upward substitution). The replenishment decision tells the production quantity to be ordered from the manufacturing facility, with one period of production lead time. At the end of each period, unused high-grade drugs have a probability to decay to low-grade drugs and the remaining low-grade drugs could be inactive and scrapped. At the beginning of the next period, new high-grade drugs arrives and are added to the corresponding storage.

The production and inventory system of personalized drugs introduces several challenges, such as multiple demand classes, random lifetime, and different substitution options. The decay process of pharmaceuticals follows a particular rate that is affected by the chemical stability of the API

(Waterman 2009). The drug shelf-life determines the period of time when a drug is effective and safe to be consumed under relevant storage conditions. However, many other factors affect the degradation of API availability, whether it either accelerates or slows down the decay process, such as temperature, humidity, and damage. No one would understand the real status of API, unless product testing is conducted, or advanced technology is applied to automatically detect the current status. This shelf-life uncertainty influences the availability of drugs and further influences how multiple demand streams are fulfilled under several substitution settings in order to ensure that the total cost incurred in production-inventory system is maintained to be as low as possible.

In the current practice, the company uses some heuristic techniques to determine the ordering and allocation decisions. Generally, the company has a tendency to set a high production quantity on daily basis to prevent drug shortages. As a result, the stock-out rarely occurs, but the inventory on hand and the number of inactive drugs are substantially high. For the issuance decision, the company always applies a combined upward and downward (*full*) substitution although it incurs an opportunity cost per second drug unit delivered. Even though several system parameters, such as decay rate and shortage cost, include circumstances that could vary from time to time due to the uncertainty of external factors, the company does not really react to the change of these parameters. This behavior can be identified from its heuristic techniques that do not consider these parameters on the calculation. We believe that by investigating the impacts of these parameters, the company can decide what actions are needed to optimize the supply chain of personalized drugs under different conditions.

In this article, we identify the research motivations and opportunities to improve the production-inventory system according to the business case. Next, we provide an optimization model that considers the system complexity and uncertainties occur in the system and answer these research questions: (*i*) For a given current condition of the company, what are the optimal replenishment and issuance policies that minimize the total cost involved in the production-inventory system? (*ii*) What is the sensitivity of the model to different system parameters, i.e. decay rate and cost parameters? What are the impacts of changes in these parameters towards the optimal value and solution? (*iii*) Is the full substitution truly dominant to other substitution options under the company's existing condition? Which substitution option is economically dominant to others under different decay rates and financial characteristics? In order to answer these questions, we model the production-inventory system as an infinite-horizon Markov decision process and solve the model via stochastic dynamic programming. We analyze the behavior of actions taken under different state combinations and generalize the solution into an optimal policy. Next, a sensitivity analysis is conducted by varying system parameters and the impact of these parameter changes is observed. Furthermore, we modify the model to capture different substitution settings (i.e.

without substitution, upward, downward, and full substitutions) and conduct a scenario analysis to understand the best substitution option given various system parameter settings.

The remainder of this paper is organized as follows. Section 2 presents a review of the relevant existing literature. The mathematical model is developed in Section 3, and the base model according to the current condition of the company is solved in Section 4. Numerical experiments in Section 5 assess the sensitivity of the optimal value and solution to decay rates and financial characteristics, and compare the performance of several substitution options under different scenarios. Lastly, Section 6 provides concluding remarks.

2. Literature Review

This study is related to two main research streams: replenishment and issuance policies of perishable inventory systems and substitution in the area of inventory management. Even though the object of this study is medical drugs, we extend the review to general perishable products without losing important characteristics of pharmaceutical products.

The basic inventory problem consists of at least two optimization problems: determining optimal replenishment policy and issuance policy. The replenishment or ordering policy prescribes how much to order in order to optimize the performance measure, depending on the stakeholders' interest. The issuance, dispatching, or withdrawal policy sets which product is allocated to meet the demand. In current literature, most studies only solve one of these problems, meanwhile assuming another policy as given. For example, Nahmias (1982) reviews 67 academic papers having a similar objective: determining suitable replenishment policy, given first-in-first-out (FIFO) or least-in-first-out (LIFO) issuance policies, for both single product with different ages and multiple products. The latter case includes perishable and non-perishable products, but no-substitution is considered in this review papers. Similarly, Ishii (1993) and Ishii and Nose (1996) focus on the optimization of ordering policy considering a hybrid FIFO-LIFO policy for the fulfillment of two different demand classes (high and low priorities). The hybrid policy arises from a possibility to substitute old products for new products (upward substitution) experienced by the low priority customers. On the other way around, Pierskalla and Roach (1972) develop a mathematical model to investigate the optimality of issuance policies, given a random supply in the context of blood bank inventory. In the blood bank application, demand for each of the categories could be satisfied by units from that category or from any "younger" category (downward substitution). Within many studies about the perishable inventory control, however, the joint replenishment and issuance policy optimization has rarely been discussed in prior works. Replenishment and issuance decisions may be interconnected, hence more careful analysis is needed to understand the interplay between these decisions.

There are only a few studies that jointly optimize ordering and issuing policies. For example, Fujiwara et al. (1997) develop an optimization model and a heuristic algorithm for modeling a two-echelon inventory system with perishable multiple products, where the first stage consists of the whole product made up of multiple sub-products, while the second stage consists of the sub-products. Lee et al. (2014) formulate a modified Economic Manufacturing Quantity (EMQ) model to represent a perishable inventory system with a minimum inventory volume constraint. The proposed model is used to optimize the issuing policy given a fixed ordering quantity, as well as the joint ordering and issuing policy problem. Deniz et al. (2010) focus on how to simultaneously replenish and issue the inventory of a perishable product considering heterogeneity in customers' preferences and product substitutions. For a product with two periods of lifetime, they provide analytical results that compare the cost performance of different ordering and issuing policy pairs and identify sufficient conditions that ensure one pair to dominate the others. The existing studies that simultaneously optimize ordering and issuing policies generally focus on fixed lifetime perishable inventory models, while we consider the deterioration to be random (no fixed shelf-life) that follows a particular probability distribution.

Several studies focus on multiple demand streams for perishables. For example, Goh et al. (1993) analyze a two-stage perishable inventory problem having two different demand streams. The study is motivated by applications in blood inventory. They computationally compare two policies, i.e. no-substitution and downward substitution. Considering shortage and outdating costs, they conclude that the downward substitution option is preferable if the shortage unit cost of fresh products is not substantially high. Ishii and Nose (1996) divide customer demands into high priority demands that order fresher products and low priority demands that do not have any preference. They focus on the ordering problem for a single period inventory under a warehouse capacity constraint. Haijema et al. (2007) consider two types of demand, two different issuance policies, and one day of production lead time in the context of blood platelets. They propose two replenishment heuristics (i.e. single and double order-up-to policies) that are shown to be near optimal. We identify that the motivation for many of the papers that involve multiple demand streams mainly come from the health care industry, such as blood banks. Summary of the literature on blood bank applications can be found in Prastacos (1984), Pierskalla (2005), and Beliën and Forcé (2012). According to these studies, it can be observed that, again, a pre-determined fixed shelf-life is used. In our context, shelf-life is considered to be random due to batch-to-batch variation and uncertainties during transport and storage period, like vaporization, damage, spoilage, and dryness (Goyal and Giri 2001; Dye et al. 2007). Furthermore, the studies that include multiple demand classes mainly aim to optimize either replenishment or issuance policies, while we focus on the joint ordering and issuing problem.

Random lifetime refers to the condition that the exact lifetime of stock items cannot be determined in advance. This term is used in the review papers by Nahmias (1982) and Goyal and Giri (2001) to describe the uncertainty occur in the shelf-life of perishable products. More recently, Bakker et al. (2012) divide the lifetime uncertainty based on the variable involved, into two different terms: age dependent deterioration rate, and time or inventory dependent deterioration rate. Most of the studies that consider the lifetime uncertainty deal with a continuous review inventory system. For instance, Nahmias (1977) is the first research that incorporate the uncertainty in both the demand and the lifetime of the perishable product. The study shows that if products perish in the same sequence as they were ordered, the results obtained from the fixed lifetime model continue to hold. A random lifetime perishable inventory model with a Markovian renewal demand is developed by Lian et al. (2009). In this paper, they assume that the product lifetime is exponentially distributed and the order lead time is zero. Using the model they obtain analytical results for the expected recycle time, total cost rate function, and the optimal ordering policy. Kouki and Jouini (2015) discuss the effect of lifetime variability on the performance of inventory systems. The research incorporates the random lifetime by using Erlang distribution that captures various cases of lifetime variability in the practices. An example of studies that consider a discrete inventory review is given by Jain and Silver (1994). They provide a stochastic dynamic programming model to determine the best replenishment decision for a random lifetime. An arbitrary probability distribution is used to describe the lifetime uncertainty. They assume that the total inventory leftover is worthless or unusable for at least the next period.

Substitution refers to the utility of particular products to meet the demand of different products. Depending on the decision maker, substitution can be grouped into supplier-driven substitution and customer-driven substitution (Shin et al. 2015). When the suppliers decide on substitution, the concept of substitution significantly affects the issuance policy in a single perishable product inventory control. In practices, products of different ages are available in the inventory. This fact motivates the supplier to issue the inventory using some rules that are more complicated than FIFO or LIFO issuance policies which considering substitution issues. Pierskalla and Roach (1972) is considered as the first paper that involves product substitutions and age-dependent demands. They assume that demands of a particular class can be satisfied by either stocks from that class or stocks that are fresher. In their study, they prove that FIFO issuance policy minimizes both lost sales and outdates. Similarly, Cohen et al. (1981); Haijema et al. (2007); and Haijema et al. (2009) also incorporate substitutions and multiple demand streams in the blood bank context. In general, their substitution models benefit the flexibility given by demand classes that have no-strong preference of a particular blood age. Notice that in the previous studies, demands are independent to the issuance policy, as in blood banks the primary objective is to save human lives. Hospitals

always accept product substitutes as long as they are compatible with the individual's blood type or other genomic information. For the products other than medical products, customers usually decide whether or not to substitute for their unavailable desired products, depending on customers' choices and preferences. The supplier usually influences this decision by markdown pricing. An example of papers than study the interaction between inventory and pricing decisions is provided by Ferguson and Koenigsberg (2007). The paper develops a two period model that captures the effect of internal competition or substitution on the production and pricing decisions. They investigate whether it is better to provide both or only the new product in the second period. Our model differs from the existing studies as we introduce a unique procedure of product substitution that is derived from the current practice in our collaborator. Two items of low-quality products can be used as substitutes for the demand of one high-quality product. We use the term upward substitution with double picking quantity or second drug scheme to represent this case.

In this article, we formulate an infinite-horizon MDP model that considers separate demand streams for different drug grades, random lifetime, and product substitution. We let the model decides the best ordering and issuing decisions without having pre-determined policies. We introduce double picking quantity or second drug scheme for the upward substitution. To our knowledge, no-existing studies has captured the double picking quantity in product substitutions.

3. Model Formulation

We model the personalized drugs production and inventory system as a discrete time, discrete state space, infinite-horizon Markov decision process. The objective is to identify the best replenishment and issuance policies in order to minimize the total discounted cost.

States: The state is denoted by (s_1, s_2, d_1, d_2) on state space $\mathcal{Y} = \mathcal{S}_1 \times \mathcal{S}_2 \times \mathcal{D}_1 \times \mathcal{D}_2$, where $\mathcal{S}_1 \in [0, \bar{S}_1]$, $\mathcal{S}_2 \in [0, \bar{S}_2]$, $\mathcal{D}_1 \in [0, \bar{D}_1]$, and $\mathcal{D}_2 \in [0, \bar{D}_2]$. The state $s_i \in \mathcal{S}_i$ denotes the number of drugs of drug grade i remaining in storage at the beginning of a period, where $i \in \{1, 2\}$ denotes the drug grade, where $i = 1$ and $i = 2$ represent high and low-grade drug respectively. The drug availability of each drug grade is limited by $\bar{S}_i$ due to the maximum storage capacity. Similarly, state $d_j \in \mathcal{D}_j$ denotes the number of realized demand of demand class j known at the beginning of a period, where $j \in \{1, 2\}$ denotes the demand class. $j = 1$ and $j = 2$ represent demand class of high and low-grade drug respectively. $\mathcal{D}_j$ is a discrete non-negative random variable and is bounded by a threshold value $\bar{D}_j$. Probability mass function of demand class j is represented by $g_j(\cdot)$.

Actions: The action is denoted by an ordered triplet (x_{11}, x_{12}, u) and the action space is defined by $\mathcal{A} = \mathcal{X}_{11} \times \mathcal{X}_{12} \times \mathcal{U}$. The first two actions represent the issuance decision under several possible substitution settings. $x_{1j} \in \mathcal{X}_{1j}$ denote the number of demand of demand class j planned to be fulfilled by high-grade drugs ($i = 1$), where $\mathcal{X}_{11} \in [0, d_1]$ and $\mathcal{X}_{12} \in [0, d_2]$. Therefore, the remaining

demand of each demand class j will be met by low-grade drugs ($i = 2$) implicitly. Action $u \in \mathcal{U}$ represents planned number of drugs to be produced at the manufacturing facility, where $\mathcal{U} \in [0, \bar{U}]$. Note that there is a maximum number of production quantity $\bar{U}$ due to limited production capacity.

Transitions: The transition equation is formulated based on a defined sequence of events that occurs during a period. At the beginning of each period, the current state is observed. The observation aims to identify the drug availability and the demand realization. Then, allocation and production quantity are decided based on the current state information and the costs involved in the production-inventory system are assessed. At the end of a period, the remaining drugs could decay from high-grade to low-grade drugs and from low-grade to inactive drugs. Finally, new high-grade drugs arrive in warehouse and added to the storage in the beginning of next period as we assume that lead time is one period. The number of drugs available at the beginning of next period is denoted by $s_i^{'}$, where k_i represents the number of drugs of drug grade i that decay to lower grade at the end of each period, ranging from zero to maximum drugs available after actions are taken.

$$s_1^{'} = (s_1 - x_{11} - x_{12})^+ - k_1 + u \tag{1}$$

For the low-grade drugs' storage, the number of drugs available at the beginning of next period is additionally affected by decayed high-grade and low-grade drugs. At the end of each period, the storage for low-grade drugs can receive decayed high-grade drugs and send decayed low-grade drugs to the scrapping facility. Once a drug becomes inactive, it cannot be used to fulfill demands and will be scrapped. The double picking quantity is also applied here. Two low-grade drugs should be picked in order to meet one demand for high-grade drug via upward substitution.

$$s_2^{'} = \left[s_2 - 2(d_1 - x_{11}) - (d_2 - x_{12})\right]^+ - k_2 + k_1 \tag{2}$$

Notice that the above transition equations refers to our full substitution option. A minor adjustment is needed to model the other three (upward, downward, and no-substitution) settings.

Immediate cost: The immediate reward in this system is the total cost that needs to be minimized. The total immediate cost involved, denoted by C, consists of holding cost, shortage cost, second drug cost, and manufacturing cost. The total cost not only depends on current state (s_1, s_2, d_1, d_2), but also depends on actions taken at every period (x_{11}, x_{12}, u).

$$\begin{aligned} &C\big((s_1, s_2, d_1, d_2)|(x_{11}, x_{12}, u)\big) \\ &\qquad = C_h(s_1, s_2, d_1, d_2, x_{11}, x_{12}) + C_\pi(s_1, s_2, d_1, d_2, x_{11}, x_{12}) + C_{2nd}(d_1, x_{11}) + C_m(u) \end{aligned} \tag{3}$$

The holding cost is the cost incurred to store the drugs so that it can be used optimally during their shelf-life. We only consider variable cost so that it is linear in total inventory.

$$C_h(s_1, s_2, d_1, d_2, x_{11}, x_{12}) = h\Big\{(s_1 - x_{11} - x_{12})^+ + \left[s_2 - 2(d_1 - x_{11}) - (d_2 - x_{12})\right]^+\Big\} \tag{4}$$

The shortage cost is the cost made due to the inability to satisfy the demand on time. In order to maintain customer service level, a costly solution has to be found, e.g. getting drugs from another manufacturer or short-term production. As a consequence, the shortage unit cost is considerably higher than any other unit costs.

$$C_\pi(s_1, s_2, d_1, d_2, x_{11}, x_{12}) = \pi\Big\{\big[-(s_1 - x_{11} - x_{12})\big]^+ + \big[-\big(s_2 - 2(d_1 - x_{11}) - (d_2 - x_{12})\big)\big]^+\Big\} \quad (5)$$

The second drug cost reflects the revenue loss due to additional drug shipment to substitute low-grade drugs for desired high-grade drugs. Since the second drug is given for free, the second drug unit cost is estimated as being the same as the unit revenue that is similar for both drug grades.

$$C_{2nd}(d_1, x_{11}) = r(d_1 - x_{11}) \quad (6)$$

The manufacturing cost mainly includes raw material, labor, and equipment costs, which can be divided into fixed and variable costs. In this study, manufacturing cost is assumed to be linear in production quantity, without considering fixed cost incurred in investment.

$$C_m(u) = mu \quad (7)$$

Value function: The value function represents the expected total discounted cost incurred on the ordering and issuing problem. We formulate an infinite-horizon discounted MDP model with the following value function $V(s_1, s_2, d_1, d_2)$. The value function can be generated via the Bellman equation and is obtained by evaluating all possible actions and selecting the best possible actions (x_{11}, x_{12}, u) at each period such that the value function is minimized. The discount factor is denoted by λ.

$$\begin{aligned} V(s_1, s_2, d_1, d_2) = \underset{x_{11}\in\mathcal{X}_{11}, x_{12}\in\mathcal{X}_{12}, u\in\mathcal{U}}{\text{minimize}} \Big\{ & C\big((s_1, s_2, d_1, d_2)|(x_{11}, x_{12}, u)\big) \\ & + \lambda\mathbb{E}\Big[V\big((S_1', S_2', D_1', D_2')|(s_1, s_2, d_1, d_2), (x_{11}, x_{12}, u)\big)\Big]\Big\} \end{aligned} \quad (8)$$

The expected future cost is calculated based on the decay of an individual drug and the demand probability distributions. We assume that the decay of an individual drug follows a geometric distribution, where $p_i \in [0, 1]$ denotes the decay probability of an individual drug from drug grade i to corresponding one lower grade. Note that the future state (S_1', S_2', D_1', D_2') is random variable due to the random lifetime and the random demand for next period.

$$\begin{aligned} &\mathbb{E}\Big[V\big((S_1', S_2', D_1', D_2')|(s_1, s_2, d_1, d_2), (x_{11}, x_{12}, u)\big)\Big] \\ &\quad = \sum_{k_1=0}^{(s_1 - x_{11} - x_{12})^+} \sum_{k_2=0}^{[s_2 - 2(d_1 - x_{11}) - (d_2 - x_{12})]^+} \sum_{d_1'=0}^{\bar{D}_1} \sum_{d_2'=0}^{\bar{D}_2} \Big[p_1^{k_1}(1 - p_1) p_2^{k_2}(1 - p_2) g_1(d_1') g_2(d_2') \\ &\qquad V\Big((s_1 - x_{11} - x_{12})^+ - k_1 + u, \big[s_2 - 2(d_1 - x_{11}) - (d_2 - x_{12})\big]^+ - k_2 + k_1, d_1', d_2'\Big)\Big] \end{aligned} \quad (9)$$

4. Optimal Policy of Current Condition

In this section, we solve the formulated MDP model with settings representing the current condition of the company. The model is solved via stochastic dynamic programming using the value iteration algorithm to obtain optimal replenishment and issuance policies.

Table 1 Parameter settings for base model

Parameter	Notation	Value
Discount factor	λ	0.99
Error gap	ϵ	0.01
Decay rate	p_i	0.3
Manufacturing cost	m	1
Holding cost	h	0.07
Shortage cost	π	20
Second drug cost	r	7
Random demand for high (low)-grade drugs	$g_j(\cdot)$	$B(n,p)$

Table 1 shows the parameter values for the current setting of the company. The discount factor is set to 0.99 meaning that the future total cost is slightly discounted. This factor is used to describe that the future total cost is less valuable than the cost involved at the current period. The maximum error gap used for stopping criteria is 0.01 or 1% of value function difference between two iterations. For the drug under this study, there is no difference in the decay rate of an individual drug for both drug grades ($p_1 = p_2$) and the average decay rate identified in the system is approximately 0.3. The cost parameter values considered in the model are normalized for confidentiality purposes. We set the manufacturing unit cost to 1 unit of measure and use it as a standard to normalize other unit costs. The holding unit cost is estimated to be 0.07 times the manufacturing unit cost per period, while the shortage unit costs vary between 10 to 20 times higher than the manufacturing unit cost. The second drug unit cost which represents the cost incurred due to the double picking quantity is estimated to be the same as the unit revenue which is 7 times higher than the manufacturing unit cost. The probability distribution of demands is derived from historical demand data of the company. According to the fitting procedure by Adan et al. (1995), we do a discretization of the demand data. The daily demand of both demand classes follow binomial distributions with corresponding parameters for each drug grade.

In current practice, the company uses the full substitution option to meet all demand classes. This full substitution means that both upward and downward substitutions are allowed for the picking process. The only difference between these substitutions is that a double quantity of drugs is needed for the demand fulfillment via upward substitution, in order to meet the dose requested by patients. For visualization convenience, we set two states (either d_1 and d_2, or s_1 and s_2) as

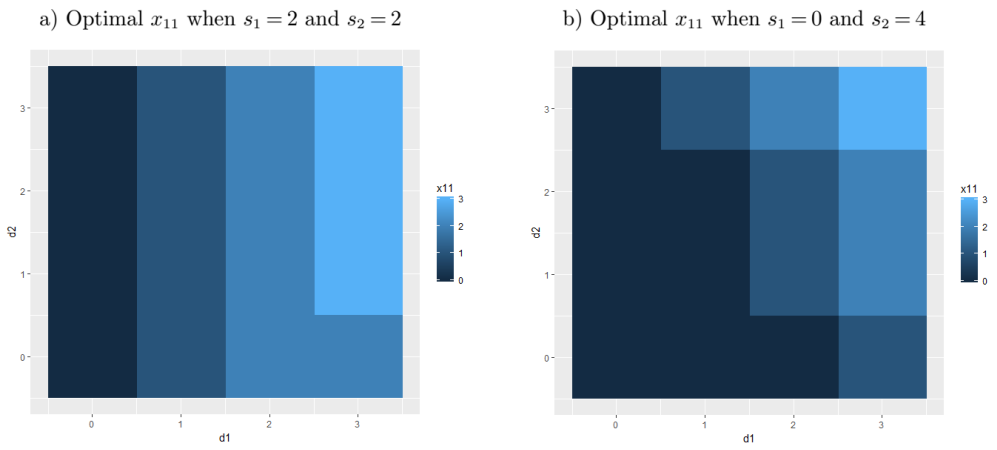

Figure 1 Optimal issuance of s_1 to meet d_1

given. Also, as the structure of optimal policy differs for every given two states, we discuss some special behaviors of different fixed states to give more detailed explanations.

Figure 1(a) depicts the optimal x_{11} or issuance of s_1 to meet d_1, given $s_1 = 2$ and $s_2 = 2$. It can be observed that if $s_1 \geq d_1$, the system allocates the s_1 available as much as possible to fulfill d_1, disregarding any demand for low-grade drugs at the same period ($x_{11} = \{min(s_1, d_1)\}$). For example, if $d_1 = 1$, the system assigns one high-grade drug ($x_{11} = 1$) to satisfy the demand. This behavior explains that given the current situation of the company, the system tries to minimize upward substitutions and shortages, which lead to additional costs. Note that s_2 and d_2 are irrelevant in the decision of x_{11} under this condition.

However, if $s_1 < d_1$, both s_2 and d_2 are taken into account in deciding the x_{11}. First, the system sets the x_{11} to the maximum s_1 available, if the remaining s_2, after meeting d_2, can fully serve upward substitution for the remaining d_1. Second, if some d_1 left can be met by substituting s_2 for s_1, the system sets the x_{11} to the maximum s_1 available plus stock-outs, which refers to the number of d_1 that cannot be met by either s_1 or s_2. Lastly, if the remaining s_2 cannot serve any upward substitution, the system reacts by getting requested drugs from alternative sources (stock-outs occur) and sets $x_{11} = d_1$. Figure 1(b) shows the example of these cases. When $d_1 = 2$ and $d_2 = 0$, the system allocates the maximum high-grade drugs available, which is equal to zero, to meet the demand for high-grade drug. The upward substitution is performed to fulfill this demand, meaning that the system delivers four low-grade drugs to hospitals. Also, when $d_1 = 2$ and $d_2 = 2$, one demand for high-grade drug is satisfied by two low-grade drugs left, and another one met by an alternative source ($x_{11} = 1$).

The optimal x_{12} or issuance of s_1 to meet d_2, given $s_1 = 3$ and $s_2 = 3$ is presented in Figure 2(a). This action defines how many downward substitutions are performed in the system which

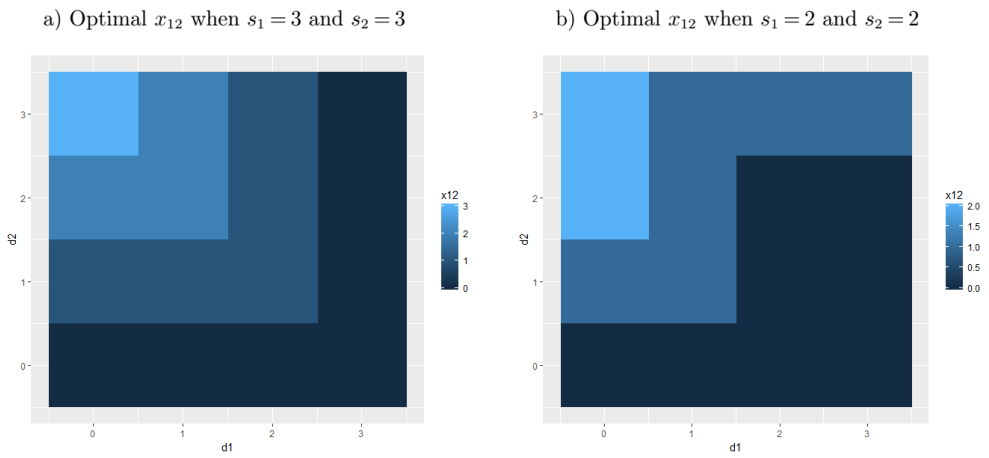

Figure 2 Optimal issuance of s_1 to meet d_2

does not incur any special cost. From the graph, we can observe that when $d_1 = 1$ and $d_2 = 2$, the system picks two high-grade drugs available instead of two low-grade drugs. A similar case occurs when $d_1 = 1$ and $d_2 = 3$. All remaining high-grade drugs, after meeting the demand of high-grade drug, are allocated to fulfill the demand of low-grade drug. In other words, the inventory prefers to consume high-grade drugs first before satisfying the remaining demand using low-grade drugs. This practice could occur as there is no cost involved in the downward substitution. Note that this condition holds if d_2 can be met by using s_1 and s_2 available in the inventory.

If stock-outs occur due to the insufficiency of s_1 and s_2, the system asks for an expedition of deficit drugs in the form of high-grade drugs. It can be identified that indeed high-grade drugs are more prioritized to be used to fulfill d_2. Aside from the fact that no additional cost made for the downward substitution, another reason behind this practice is that there is no difference in the shortage unit cost between high and low-grade drugs. An example of this behavior can be seen in Figure 2(b). When $d_1 = 2$ and $d_2 = 3$, no s_1 left in the inventory and the s_2 available is less than what is demanded. Thus, one high-grade drug is procured from another source that is denoted by $x_{12} = 1$.

Figure 3(a) and Figure 3(b) present the optimal production quantity obtained from the current condition, given $d_1 = 0$ and $d_2 = 0$, and $d_1 = 3$ and $d_2 = 3$ respectively. Optimally, each combination of initial states tends to transition to the optimal states at the next period. The desired future states are known to be optimal since they provide the minimum total discounted cost. According to Figure 3(a), we generalize the optimal production quantity obtained from all possible states into three different zones. In the first zone, the system produces the drugs on maximum capacity. In this zone, the system does not have enough production capacity to bring s_1 to the desired future

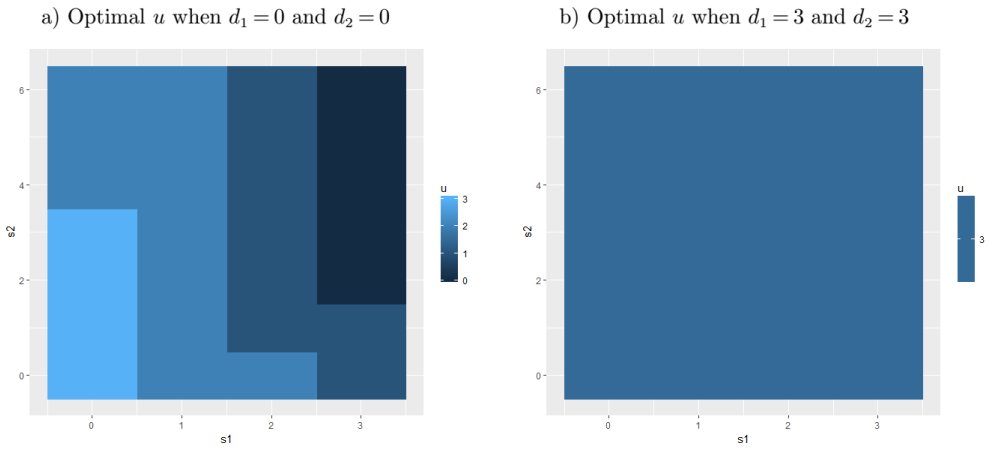

Figure 3 Optimal production quantity when $d_1 = 0$ and $d_2 = 0$

states. To approach the desired states as close as possible, it puts the maximum capacity into the production planning. The second zone refers to the base-stock policy. it can be observed that the optimal production quantity reduces with the increase of s_1 and s_2, meaning that both states are considered in the decision making. Due to demand and decay uncertainties involved in this model, the calculation of base-stock level is not straightforward. The expectation of realized demands and decayed drugs based on their probability distributions must be taken into account. The last zone suggests not to produce any drugs, which is only relevant if there is no demand for both drug grades at the initial states. Another behavior identified is that when $d_1 + d_2$ approach $\bar{S}_2$, number of zones will reduce. Also, if $d_1 + d_2 = \bar{S}_2$ (see Figure 3(b)), only the first zone is generated for the optimal ordering policy.

5. Numerical Experiments

In this section, we conduct several numerical experiments to understand the sensitivity of the optimization framework under several parameter settings. Furthermore, we investigate which substitution option gives the best optimal cost under several conditions.

5.1. Effect of Decay Rate.

5.1.1. Impact of Decay Rate on Optimal Cost. A medical drug deteriorates over time at a specific rate which depends on its active ingredient. The decay rate, shelf-life, and expiry date are normally determined under an assumption of standard conditions. In reality, the shelf-life of pharmaceuticals is random, commonly affected by external factors that occur in transport and storage. In order to understand the effect of the decay rate of an individual drug on the optimal cost, a sensitivity analysis by varying the decay rate is conducted.

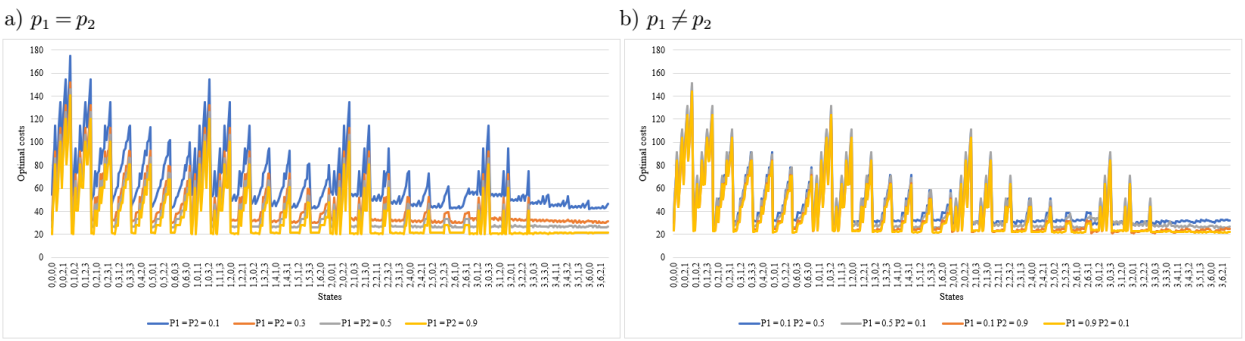

Figure 4 Comparison of optimal cost under different decay rates

We use two different approaches to vary the decay rate. First, we assume that the decay rates of high and low-grade drugs are similar. This approach is applicable for drugs which have a constant decay rate over time. In other words, the decay rate does not depend on the level of API left in the drug. For this case, we set some decay rates to near extreme values (i.e. 0.1 and 0.9), and some values in the middle (i.e. 0.3 and 0.5). Second, we assign a pair of different decay rates for each scenario. Different decay rates between two drug grades can occur on pharmaceuticals that degrade according to dose-dependent rates, either accelerating or slowing with the reduce of API. Two scenarios are assigned to a condition of $p_1 < p_2$, while other two scenarios are set to the contrary condition. Using the system characteristics of the company's current situation, we run all scenarios and observe the optimal values obtained.

Figure 4 plots the result of the analysis, assuming that (a) $p_1 = p_2$ and (b) $p_1 \neq p_2$. From the line graphs, it can be seen that when p_1 and p_2 are increased, the optimal cost involved at each state reduces. The minimum optimal cost is always provided by $p_1 = p_2 = 0.9$, regardless of the initial state of the system. This might occur as the system consumes high-grade drugs first to satisfy both demand classes when the decay rate is considerably low. However, when decay rate approaches one, the system tries to minimize the number of scrapping by utilizing low-grade drugs as much as possible. Note that the scrapping unit cost is implicitly covered by the manufacturing unit cost used in the model, referring to the over production. When the deterioration rates of both drug grades are different, the optimal cost reduces with the increase of the decay rate difference between high and low-grade drugs. It can be seen from Figure 4(b) that the condition of $p_1 = 0.1$ and $p_2 = 0.9$ always provides a lower optimal cost at each state combination than the condition of $p_1 = 0.1$ and $p_2 = 0.5$. The same pattern also holds when $p_1 > p_2$. The reason behind this behavior is similar to the previous case. A lower optimal cost can be obtained if the decay rate approaches one. However, when we compare the cost performance of two different conditions, i.e. $p_1 < p_2$ and $p_1 > p_2$, using a pair of decay rates, no superior condition exists for all state combinations. From these facts, we can conclude that under the current condition of the company, (1) having a fast decaying drug is

economically superior than the slow ones, and (2) if the drug follows the dose-dependent decay rate, a dramatic change of decay rate is preferable by the system.

As the decay rate depends on the stability of API and external factors, the company cannot really control the impact of it on the optimal cost, given fixed cost parameters. If the company has some flexibility to manage the cost structure, e.g. the shortage unit cost that mainly depends on which alternative source selected by the company, the company might benefit from the decay rate uncertainty by setting the best possible cost parameters. Note that this implication is subject to the sensitivity analysis of varying cost parameters that will be discussed in the latter subsection.

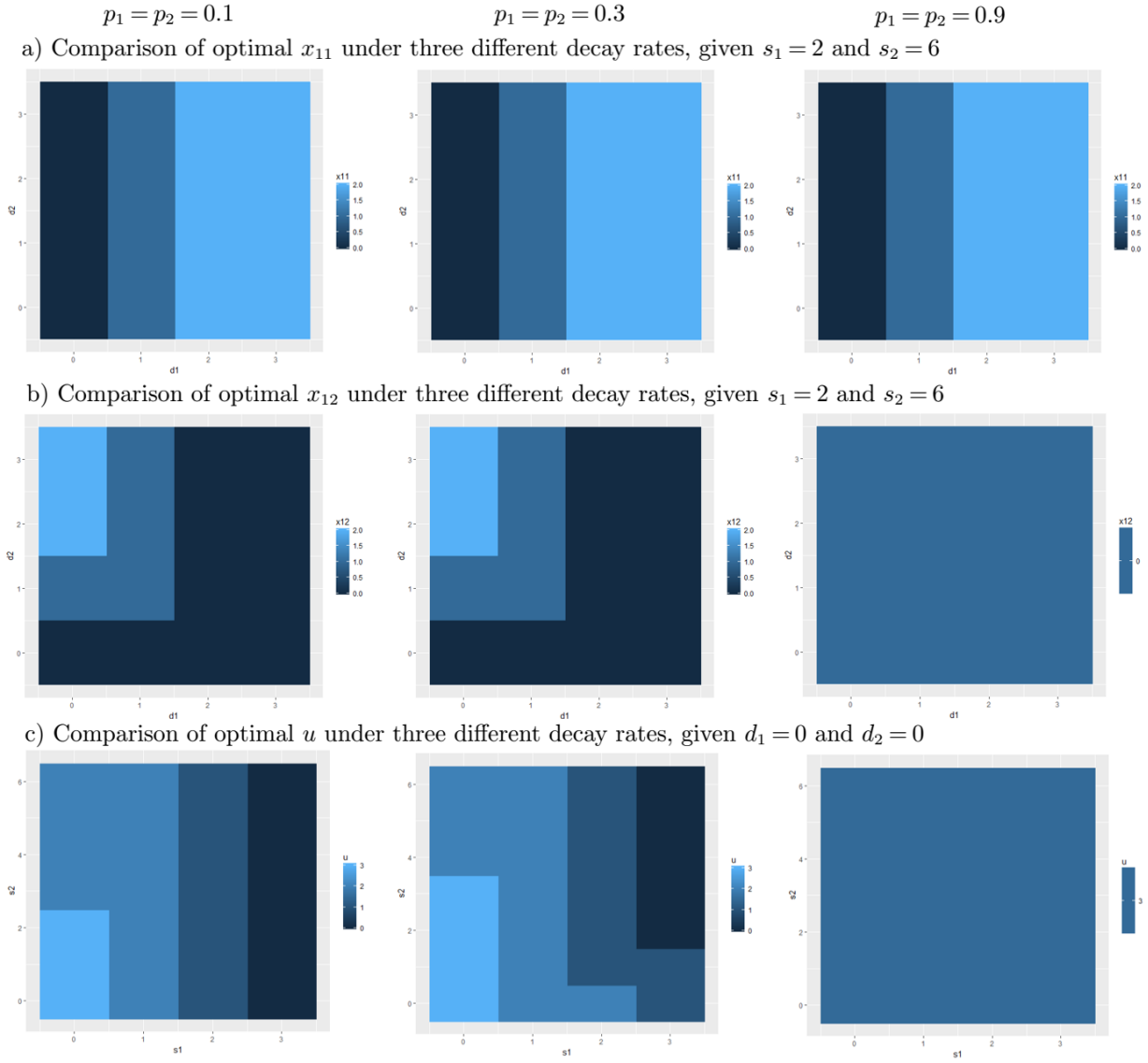

Figure 5 Comparison of optimal structure under three different decay rates

5.1.2. Impact of Decay Rate on Optimal Structure. Next, we analyze the influence of the decay rate on the optimal policy structure. For this purpose, we assume that the decay rate is independent of the API remaining in the drugs ($p_1 = p_2$). We select three various decay rates (i.e. $0.1, 0.3, 0.9$) and compare the optimal policy of each action. For analysis convenience, we set some states as given (either s_1 and s_2, or d_1 and d_2).

Figure 5 shows the comparison of all three actions under low, base, and high decay rates. In Figure 5(a), we can observe that for all decay rates, the system prioritizes the fulfillment of demands for the high-grade drug. It can be seen that the system allocates the s_1 available as much as possible to meet d_1, regardless of the decay rate of an individual drug. Next, Figure 5(b) depicts the comparison of the optimal x_{12} under various decay rates. For the low decay rate, the optimal policy does not differ with that in the current condition. The inventory of high-grade drugs is the first priority to be picked. After all s_1 available are depleted, s_2 is used to satisfy the remaining demands. However, for the high decay rate, an interesting solution is obtained. In this condition, the system does not assign any s_1 to meet demands for low-grade drug. This fact indicates that the system wants to consume s_2 as much as possible as they will most likely decay in the next period.

The behavior of optimal production quantity under various decay rates can be seen in Figure 5(c). It can be identified that when the decay rate is considerably low, there are three optimal zones, similar to the structure of the optimal ordering policy in the current condition. Using the expected number of decayed drugs, we can calculate and compare the base-stock level for both high and low decay rate. It shows that base-stock level for the low decay rate is slightly higher than that in the base decay rate. An interesting optimal production quantity is obtained from the high decay rate case. In this case, the production quantity is always set to the maximum capacity, regardless of the initial inventory. It can be concluded that there is only an optimal zone generated in this decay rate. The system sets production quantity at its maximum capacity as the capacity available is not sufficient to transition the initial state to the desired optimal state.

From these three analyses, we can conclude that for the same initial state combination, the optimal structures of both replenishment and issuance policies are considerably sensitive toward the change of the decay rate when fixing all other parameters. The implication of this result is that the company should be able to adapt with this sensitive behavior of optimal structures. An adaptive decision making is needed for the implementation, especially for the issuance policy. As previously mentioned in Section 4, the issuance decision has special cases, depending on the initial state combination. These special cases need to be considered in the implementation. Understanding the real decay rate is also crucial in this phase since it affects the decision making. Ideally, the company should have historical data regarding realized decay rates with the corresponding external conditions. These data can be used as an input parameter in the optimization framework.

5.2. Effect of Cost Configuration.

Table 2 Cost scenarios and impact on optimal value and base-stock level

	Current condition	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Manufacturing cost (m)	1	1	1	1	1
Holding cost (h)	0.07	5	10	15	20
Shortage cost (π)	20	20	20	20	20
Second drug cost (r)	7	7	7	7	7
Ratio $\frac{h}{\pi}$	0.0035	0.25	0.5	0.75	1
Ratio $\frac{r}{\pi}$	0.35	0.35	0.35	0.35	0.35
Optimal value (normalized) $V(2,6,0,0)$	1.000	7.18	12.50	17.70	22.77
Base-stock level (entire system)	9	5	5	4	4
	Current condition	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Manufacturing cost (m)	1	1	1	1	1
Holding cost (h)	0.07	0.07	0.07	0.07	0.07
Shortage cost (π)	20	20	20	20	20
Second drug cost (r)	7	10	15	20	25
Ratio $\frac{h}{\pi}$	0.0035	0.0035	0.0035	0.0035	0.0035
Ratio $\frac{r}{\pi}$	0.35	0.5	0.75	1	1.25
Optimal value (normalized) $V(2,6,0,0)$	1.000	1.04	1.09	1.12	1.12
Base-stock level (entire system)	9	9	9	9	9

A sensitivity analysis is conducted to gain more insights about how the optimal cost and policy react toward the change of unit cost parameters. Here, we are interested in getting more understanding of the relationship between pairs of unit cost parameters and their impacts on the optimal value and solution. First, we vary the ratio between holding and shortage unit costs by increasing the value of holding unit cost. Similarly, we assess the effect of increasing the second drug cost, so that the ratio between the second drug and shortage unit costs becomes higher than that in the current condition. Table 2 displays detailed costs parameter settings for all scenarios. Note that other model parameters, e.g. decay rate and discount factor, are fixed to the same values as those in the model of the current condition.

From scenario 1 to 5, it can be identified that the optimal value increases with the holding cost. Notice that we only compare the normalized optimal cost of a specific state, i.e. $(2,6,0,0)$. However, in terms of the optimal solution, when the ratio of holding and shortage unit costs increases, the base-stock level reduces. This impact is intuitive because when the difference between those unit costs is minimized, the well-known inventory trade-off is balanced, and the system does not need to store much inventory. Notice that we refer to the base-stock level of the entire system (sum of s_1 and s_2 base-stock levels) in this analysis.

Then, the impact of the second drug unit cost on the system is assessed by increasing the ratio between the second drug and shortage unit costs. The second drug unit cost is defined as the cost

incurred when the upward substitution option is taken by the system. In the model, we refer to this cost as an opportunity cost due to the free second drug shipment. We are interested to understand the effects of giving an additional price discount to compensate the inability to supply desired drugs. We reflect this price discount in the form of a second drug unit cost rise.

From the numerical experiment, the change of the ratio between second drug and shortage unit costs slightly affects the optimal value obtained from our infinite optimization model. This effect is not as big as the effect of the holding unit cost on the optimal value. The optimal values generated by all scenarios increase by less than 12%, although the ratio between second drug and shortage unit costs has been increased to one. Notice that when the ratio is further increased to more than one, the optimal value almost does not change. A similar result holds in regard to the base-stock level. The base-stock level of the entire system remains the same as that in the current condition, disregarding various second drug costs. Theoretically, for the given state combination under this analysis, the change of the second drug unit cost should not affect both the optimal value and solution. For $d_1 = d_2 = 0$, there is absolutely no upward substitution performed by the system, hence no second drug cost generated. The small increase of the optimal value observed in the experiment might be due to the considerably large value of the epsilon used in the model that leads to less accurate results. This analysis concludes that under the given initial state combination, the optimal value and solution are insensitive to the second drug unit cost or the cost involved in the upward substitution. Note that this insight is only applicable when the system does not perform any upward substitution.

5.3. Optimal Substitution Option.

In this subsection, we investigate whether the substitution option that is applied in the current practice provides the minimum total discounted cost under several decay rates. Furthermore, we set the cost parameters to some extreme values and identify the best substitution setting under the extreme conditions.

5.3.1. Best Substitution under Different Decay Rates. Although our collaborator currently uses the full substitution as the common practice, we are interested to identify if this option is indeed dominantly optimal given the current financial characteristic of the company.

Four substitution settings are defined: (*i*) no-substitution, (*ii*) upward substitution, (*iii*) downward substitution, and (*iv*) full substitution. We compare the optimal total discounted cost incurred at each possible state in each scenario. For this analysis, we apply similar parameter settings used in the current condition, but setting the decay rate to various values between 0.1 and 0.9.

Figure 6 depicts four different graphs, comparing the optimal cost generated by four substitution options under different decay rates. Given the default parameter setting, it can be identified that

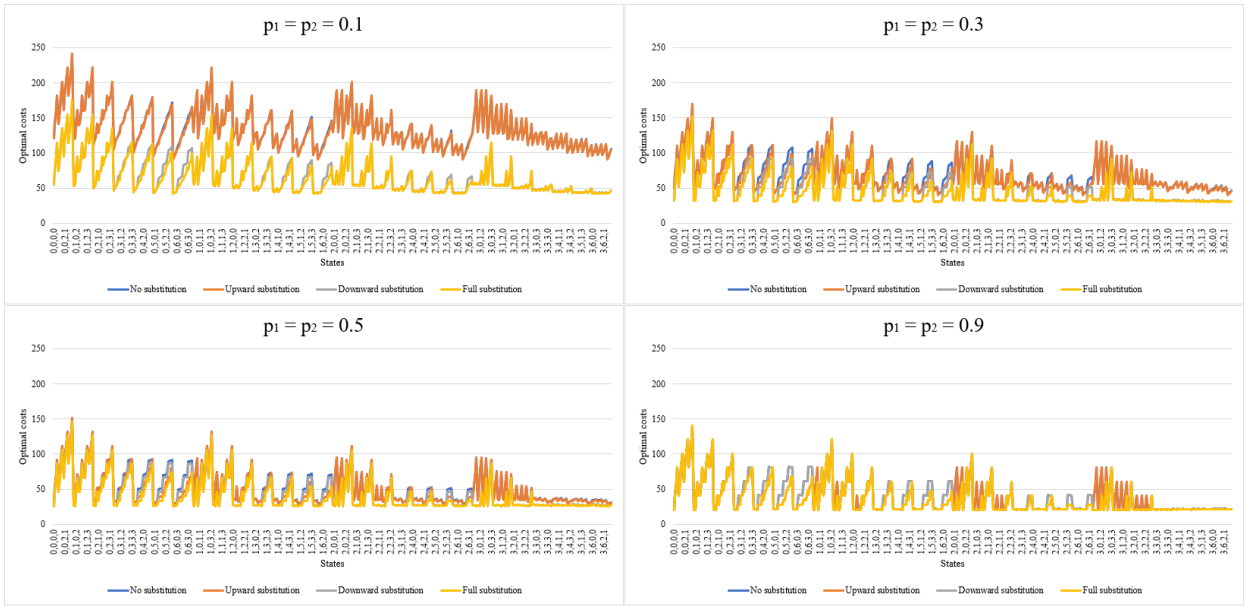

Figure 6 Comparison of substitution settings under different decay rates

the full substitution provides the lowest total discounted cost for each possible state and all defined decay rates, while the highest cost given by ignoring any substitution options. When the decay rate is considerably low, the optimal cost incurred by applying the full substitution is not significantly different with those in the downward substitution. This behavior is also applicable for another two options, which provide similar costs, but on the higher range of values. Also, we can observe that the higher the decay rate, the optimal values obtained by each substitution option are getting close to each other.

From this performed analysis, it can be concluded that full substitution exploits the most flexibility among the other options in satisfying demand. Although there is an additional cost for the second drug scheme, the improvement of the stock-out performance outweighs the cost involved. Additionally, when the decay rate is considerably high, the cost performances of all substitution options are not meaningfully different. This fact might occur since these substitution settings share similar policies to react toward the high decay rate.

The implication of these findings is that the company should further analyze whether the full substitution is indeed economically dominant, especially when the cost difference between full and downward substitutions is not substantial. In the implementation of the picking processes, the total cost involved does not only depend on production and inventory related costs. Other operational costs, such as labor and handling costs should also be considered when deciding the best issuance policy. From the hospital's point of view, receiving two drugs is also less preferable as it generates additional costs. For example, in the form of liquid drugs, getting two drugs means two injections are needed, thus two times the service cost needs to be covered by customers.

5.3.2. Best Substitution under Different Financial Characteristics. We consider some extreme cost ratio conditions to understand whether the best substitution option depends on the financial characteristic. We define the extreme cost ratio as the condition when the ratio between unit cost pairs is on the other way around of the current condition. Table 3 presents the cost ratios of the current condition and the extreme conditions that are defined in this analysis. Note that the other parameters, such as the decay rate, are fixed to the same values as those in the current condition.

Table 3 Cost ratios of current and extreme conditions

	Current condition	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Manufacturing cost (m)	1	1	1	1	25
Holding cost (h)	0.07	25	0.07	10	0.07
Shortage cost (π)	20	20	20	20	20
Second drug cost (r)	7	7	25	7	7
Ratio $\frac{h}{\pi}$	0.0035	1.25	0.0035	0.0035	0.0035
Ratio $\frac{r}{\pi}$	0.35	0.35	1.25	0.35	0.35
Ratio $\frac{h}{r}$	0.01	0.01	0.01	1.43	0.01
Ratio $\frac{m}{\pi}$	0.05	0.05	0.05	0.05	1.25

The shortage unit cost includes components that could vary from alternative solution to alternative solution. The various shortage unit costs might occur, for example due to different purchasing costs of other manufacturers. This reason motivates us to include the ratios between the shortage unit cost and other three unit costs in the analysis. Another cost ratio that is considered in the numerical experiment is the ratio between the holding and second drug unit costs. Notice that we do not focus on the ratios between the manufacturing cost and two other unit costs (i.e. the holding and second drug unit costs). In common practices, the holding unit cost is usually estimated by the percentage of the product value, so it is impossible to have higher holding unit cost than the manufacturing unit cost. A similar reason applies to the ratio between the manufacturing and second drug unit costs. Since we define the second drug unit cost as the revenue loss due to the free second drug shipment, and the unit revenue is always higher than the manufacturing unit cost, it does not make sense to consider the ratio between these unit costs.

The comparison of the optimal costs that are generated by using several substitution options under different extreme conditions is presented in Figure 7. We can conclude that under several extreme cost ratio conditions, the full substitution is still dominant to other options. The highest dynamic range of optimal costs throughout the state combinations can be seen in scenario 1, while scenario 4 shows the least dynamic range the cost. These facts relate to the impact of the costs on the optimal value. As identified in the previous sensitivity analysis, the holding unit cost highly affects the optimal cost.

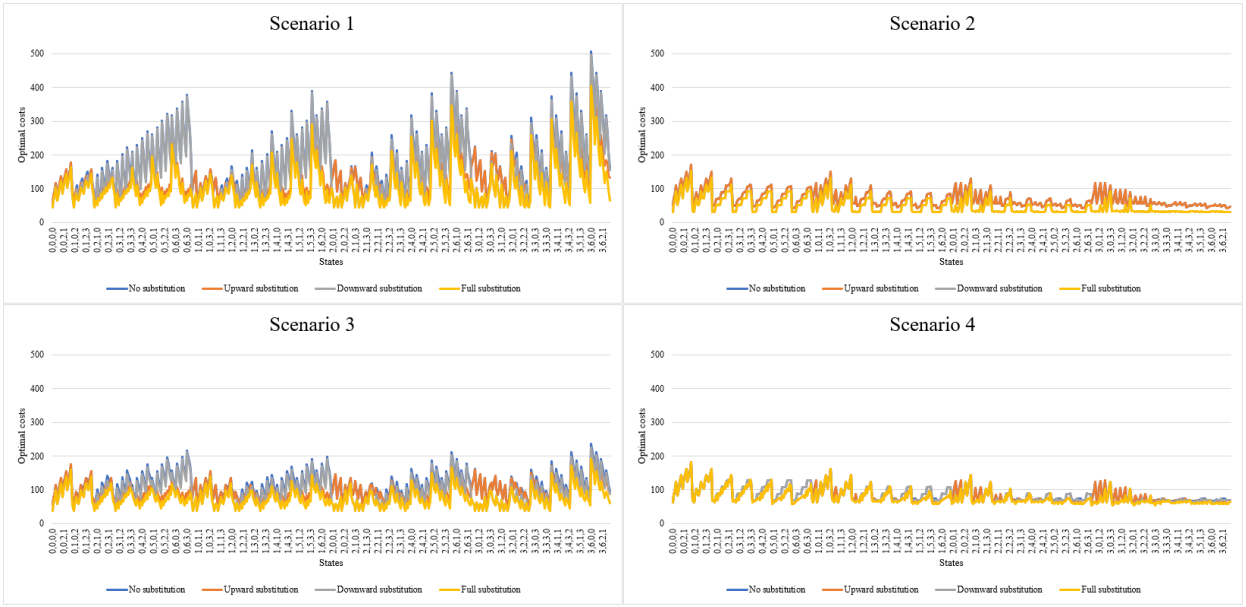

Figure 7 Comparison of substitution settings under different financial characteristics

A managerial insight obtained in this analysis is that the company should keep the full substitution as the current practice as it is numerically proven to be the best substitution setting under the current and extreme conditions. We can also generally conclude that the full substitution is also the best option for the case of different decay rates according to the previous analysis.

6. Conclusion

Personalized drugs are given to patients in a specific dose based on the individuals' genomic information. This relatively new approach of medical treatment introduces several challenges in modeling and analysis of production-inventory system due to multiple random demand streams, random lifetime, and several substitution options. The second drug scheme is introduced according to the current practice of our collaborator. A free additional low-grade drug has to be sent to substitute a high-grade drug.

We develop an infinite-horizon MDP model to simultaneously identify the best replenishment and issuance policies in order to minimize the total discounted cost. The cost involved in the model includes the manufacturing, holding, shortage, and second drug unit costs. The second drug unit cost refers to an additional cost incurred due to the upward substitution. The MDP model is solved via stochastic dynamic programming, using value iteration algorithm.

Our decisions that relates to the issuance policy describe the number of demand for high and low-grade drug planned to be satisfied by using high-grade drugs. The optimal structure of these actions, under the system parameter setting in the current condition indicates that, for the high-grade drugs demand fulfillment, (i) the system assigns high-grade drugs available as much as

possible to meet the demand. (*ii*) When high-grade drugs available are not sufficient, low-grade drugs leftover after satisfying the demand for low-grade drug are checked. If the low-grade drugs left can partially serve the upward substitution, the system allocates high-grade drugs equal to the maximum drugs available plus the number of stock-out. Thus, the demand fulfillment done by all possible ways: using high-grade drugs available, substituting low-grade drugs for high-grade drugs, and using alternative sources. (*iii*) If the remaining low-grade drugs cannot serve any substitution, all demands are served by using high-grade drugs (both by the stock available and by the alternative sources). Next, for the low-grade drugs demand fulfillment, (*i*) the system checks the status of the high-grade drugs inventory. If there are some high-grade drugs left in the inventory, the system allocates them to meet the demand at first. (*ii*) Remaining demands (if any) are satisfied by using the low-grade drugs available. (*iii*) Lastly, if stock-out occurs, the system gets the unmet demand in the form of high-grade drugs. The optimal production quantity obtained from the model behaves according to the base-stock policy. The production quantity reduces with the increase of the entire inventory (both high and low-grade drugs).

Next, we analyze the impact of the decay rate on the optimal value and structure given by the model. The performed analysis shows that the optimal cost decreases with the decay rate, meaning that drugs with decay rate that is close to one generates the least cost. In terms of the optimal solution, replenishment and allocation rules are considerably sensitive to the change of the decay rate. The sensitivity analysis by varying the ratio of two pairs of unit costs are conducted to understand the impacts of the financial characteristic on the optimal cost and policy.

We compare the cost performance of four substitution options under several decay rates to check if the current practice is numerically proven as the optimal substitution setting. We find that the full substitution is economically superior at each possible initial state, compared to the other three settings. There is also an interesting fact that the cost obtained from the downward substitution option is only marginally different than those in the full substitution, especially when the decay rate is low. A similar analysis is also conducted by setting the financial characteristic to some extreme cost ratio conditions. Considering four different cost ratios, we conclude that the full substitution setting is still optimal under these extreme conditions.

Future research could include the interaction between substitution and demand. Substituting other drugs for desired drugs could generally affect the demand from hospitals, especially in the context of the perfect market competition. The model assumes that there is no dependency between the substitution decision and the demand, which could be a limitation in the decision making. Another future research could explore the disposal policy in personalized drugs. One could argue that the manufacturer want to dispose the lowest grade drugs if the stock level is high, as providing high grade drugs is more effective in the medical treatment.

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