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Analysis of Government Policies in the Pharmaceutical Industry

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Abstract: A model of the pharmaceutical manufacturing system is established in this paper to analyze how government policies affect pharmaceutical manufacturers' business decision. The government policies considered includes inventory buy-back and pre-order. In the model, the manufacturer is assumed to minimize its financial risk while satisfying various other constraints and the conditional value-at-risk of the loss function of the manufacturer is used to measure the risk associated with its manufacturing plans. Simulation results show that government intervention can reduce the risk of manufacturers significantly. These results also serve as a reference for other countries to implement their own pharmaceutical manufacturing regulatory policies.

Key words: Government policies, financial risk, loss function

INTRODUCTION

Pharmaceutical industry and many other industries generally involve the management of its supply chain from the long-term strategic planning to the detailed short-term device and task scheduling (Verderame *et al*., 2010). This is due to the features of the manufacturing processes of such industries. In pharmaceutical production for example, the whole manufacturing process can be divided into two phases, i.e., primary production and secondary production (Bennett and Cole, 2003). In both phases, various devices and instruments are required and most of them can be used to produce different products. In this case, manufacturers often shift their production efforts to the products with high profitability or/and low risk and leave high-risk pharmaceuticals such as vaccines vulnerable to shortage. Sharing manufacturing facilities among different products also makes it hard to implement current good manufacturing practices and the whole system also becomes fragile to equipment failures. Concordant with the above analysis, manufacturing and supply/demand reasons are the two major known reasons of the drug shortage in 2010 according to the data from University of Utah Drug Information Service (UHC, 2011).

Drug shortage occurs every year and the number of new shortage identified generally keeps increasing since 2004 (ASHP, 2011). Although, drug shortages have little influence on the manufacturers, it may have great impact on the health care system. In the case that there is no alternative medications, drug shortages can cause change or delay of therapy for patients and if there is alternative medications there is also chances of misses and errors that lead to adverse patient outcomes. A recent survey indicates that all these outcomes yield high level of frustration and low level of safety for everyone that is involved in the health care system (ISMP, 2010).

Without any control, drug shortages may further lead to other social and economic problems. Therefore, the government should play an active role in preventing drug shortages. One possible way is through government contract order and another way is inventory buy-back which is suggested by people from the industry (Nevel *et al*., 2005). In the influenza vaccine industry for example, the demand is difficult to predict since it is affected by many uncertain factors and the manufacturer has to predict it six month before realization (Gerdil, 2003). Hence, manufacturers tend to make conservative manufacturing plans and produce less to avoid risks. If the government can buy-back portion of the manufacturers' inventories at a reasonable cost, this may help to maintain a steady supply, avoid drug shortage and is good to the government and society on the whole (Congressional Budget Office, 2008).

In this study, a model is established for the decision making problem of pharmaceutical manufacturers and all the above mentioned policies are taken into consideration. The effect of different policies on the manufacturers' decision making process is studied based on the simulation of the model. The results are potentially useful for other countries, such as China where the manufacturing and market of some vaccines is still in its infant stage, to implement their regulatory policies.

SYSTEM MODEL

Description: The system considered in this study is briefly shown by the diagram in Fig. 1. The system is

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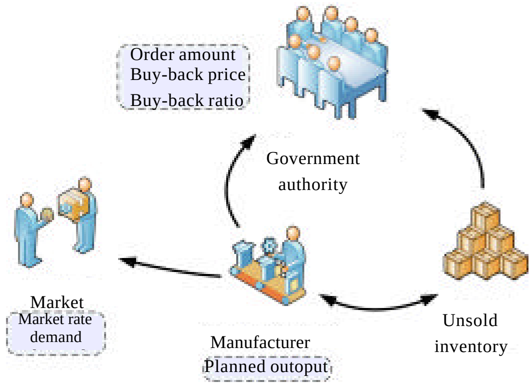

Fig. 1: Diagram of the overall system

centered with the manufacturer and the manufacturer is connected with the market and government authorities. The manufacturing plan of the manufacturer is affected by parameters or policies of the peripheral entities. The detailed description of each entity is as follows.

Manufacturer: As mentioned in the previous section, the pharmaceutical manufacturer has to plan and schedule its manufacturing resources among multiple products. In this model, we assume that the manufacturer attempts to minimize its financial risk while making such plans and schedules and therefore some "risky" products may be underproduced and lead to shortages in the future. However, exterior interventions may make the product less risky.

Market: Each product has a known and fixed price in the market and it also has an unrealized demand. But an estimation of the underlying distribution of the demand is assumed available.

Government authorities: Government authorities can affect the manufacturers' decision in two ways. One is contract order at a price equivalent to or lower than the market price, such as the Centers for Disease Control and Prevention (CDC)'s contract order of prepandemic influenza vaccine. The other way is inventory buy-back, i.e., the government authorities buy back a portion or all of the manufacturers' unsold inventory at a reasonable price. The buy-back price and ratio are all determined by the government authorities.

Parameters, variables and constraints: Based on the above description, the tuning parameters and variables that are used later in the mathematical formulation of the problem are summarized as follows.

Manufacturer
Parameters:

C_H: Manufacturing cost of high-risk product
C_L: Manufacturing cost of low-risk product
I_U: Upper bound of the manufacturer's investment
I_L: Lower bound of the manufacturer's investment
R: Manufacturer's expected return
Lb_H: Minimal amount of high-risk to produce

Variables:

x_H: Planned output of high-risk product
x_L: Planned output of low-risk product

Market
Parameters:

P_H : Market price of high-risk product
P_L : Market price of low-risk product
$\tilde{d}_H$: The demand of high-risk product
$\tilde{d}_L$: The demand of low-risk product

Government authorities
Parameters:

P_B: Government buy-back price
γ_H: Government buy-back ratio
O_G: Government pre-order amount of risky product

Using these notations, the mathematical model of the manufacturer's decision making problem involves the following constraints.

Expected return constraint:

$$\bar{d}_H \cdot x_H + \bar{d}_L \cdot x_L \geq R \quad (1)$$

where, $\bar{d}_H = E[\tilde{d}_H]$ and $\bar{d}_L = E[\tilde{d}_L]$. This constraint is commonly imposed to guarantee the expected return of certain investment.

Total investment constraints:

$$C_H \cdot x_H + C_L \cdot x_L \geq I_L \quad (2a)$$

$$C_H \cdot x_H + C_L \cdot x_L \leq I_U \quad (2b)$$

This constraint is imposed to set lower and upper bounds on the manufacturer's total investment on production.

Capacity constraints: Normally manufacturer has a production capacity. Since we focus on the analysis of the system at a general level but not the details, we assume the manufacturer capacity is reflected by investment constraints (2).

Minimal output constraint:

$$x_H \geq Lb_H \quad (3)$$

The constraint is used to guarantee the minimal planned output of the high-risk product. It is quite useful in the following analysis and may not be present in practice.

With the above notations, the manufacturer is assumed to make its manufacturing decisions generally by minimizing its financial risk subject to the mentioned constraints.

RISK MEASURE

The well known conditional value-at-risk (CVaR) of the loss of the manufacturer is utilized to measure the risk of the manufacturer's production plan.

Loss function and its convex formulation: With the decision variable $x_H(x_L)$ and the unrealized random demand $\tilde{d}_H(\tilde{d}_L)$, the associated profit is also a random variable as a function of $x_H(x_L)$ and $\tilde{d}_H(\tilde{d}_L)$ and define loss of a product as its negative profit. The profit, of the high-risk product is composed of two parts:

- Profit due to regular selling
- Profit due to government buy-back

Hence, the loss function of the high-risk product can be express as:

$$Loss_H(x_H, d_H) = C_H \cdot x_H - p_H \cdot \min\{x_H, \hat{d}_H\} \quad (4a)$$

$$-P_B \cdot \gamma_B \cdot (x_H - \hat{d}_H)^+ \quad (4b)$$

where, for any $\alpha \in R$, $\alpha^+ = \{a, 0\}$ $\alpha^- = \max\{-\alpha, 0\}$ and additionally:

$$\hat{d}_H = \max\{O_G, \tilde{d}_H\} \quad (5)$$

$\tilde{d}_H$ is the demand that the manufacturer finally take. The last term in (4a) and the term in (4b) correspond, respectively to the two parts of the profit mentioned above. As in (4), the loss function $Loss_H(x_H, \tilde{d}_H)$ not directly convex function of x_H. However, $Loss_H(x_H, \tilde{d}_H)$ can be reformulated as a convex piecewise linear function of x_H and this result is stated in the next theorem.

Theorem 1: The loss function of the high-risk product defined in (4) is equivalent to:

$$Loss_H(x_H, d_H) = \max\begin{Bmatrix}(C_H - P_B \cdot \gamma_B)x_H - (P_H - P_B \cdot \gamma_B)d_H \\ (C_H - P_H)x_H\end{Bmatrix} \quad (6)$$

under the condition $P_H \geq C_H \geq P_H \cdot \gamma_B$.

Proof: The loss function is equivalent to:

$$Loss_H = C_H \cdot x_H - P_H \cdot \min\{x_H, \hat{d}_H\} \quad (7a)$$

$$-P_B \cdot \gamma_B \cdot \max\{x_H - \hat{d}_H, 0\} \quad (7b)$$

Therefore, when $x_H \geq \hat{d}_H$:

$$Loss_H = C_H \cdot x_H - P_H \cdot \min(x_H, \hat{d}_H) \quad (8a)$$

$$= (C_H - P_B \cdot \gamma_B)x_H - (C_H - P_B \cdot \gamma_B)\hat{d}_H \quad (8b)$$

and when, $x_H < \hat{d}_H$:

$$LossH = C_H \cdot x_H - P_H \cdot x_H \quad (9a)$$

$$= (C_H - P_H)x_H \quad (9b)$$

Note that $P_H \geq C_H \geq P_B \cdot \gamma_B$, $Loss_H$ express by 8 and 9 in this case is roughly shown in Fig. 2 and clearly it equivalent to 6. The analysis of the above two cases completes the proof.

Remark 1: The requirement that $P_H \geq C_H \geq P_B \cdot \gamma_B$ in Theorem 1 is quite reasonable. If the condition is not satisfied, the manufacturer's production planning problem becomes trivial and the solution can be determined simply by observation.

Clearly, the loss function (6) is a convex piecewise linear function of the planned output. Similar to the loss of the high-risk product, the loss of the low-risk product without government interventions and emergency supplies is:

$$Loss_L(x_L, \tilde{d}_L) = C_L \cdot x_L - P_L \cdot \min(x_L, \tilde{d}_L) \quad (10)$$

Which is also a convex and piecewise linear function of the decision variable x_L With (6) and (10), the loss of the overall system is:

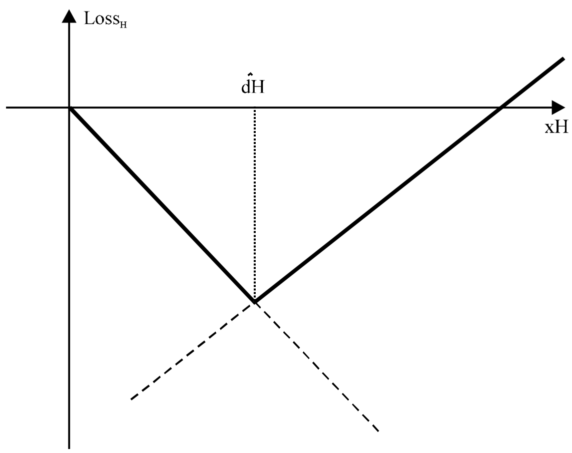

Fig. 2: Loss function

$$Loss(x_L, x_H, \tilde{d}_L, \tilde{d}_H) := Loss_H(x_H, \tilde{d}_H) + Loss_L(x_L, \tilde{d}_L) \tag{11}$$

Conditional value-at-risk: In the sequel, the CVaR of the loss function (11) of the overall system is used to measure the risk of the manufacturer's production plan. The definition and properties of CVaR is briefly reviewed first. Before CVaR is proposed, Value-at-Risk (VaR) is one of the most well known risk measures and has been widely applied and studied in the 1990s (Duffie and Pan, 1997). For a loss $L(x,\tilde{d})$ associated with the decision vector x and the random vector $\tilde{d}$ and a given threshold $\alpha \in (0, 1)$, the VaR of the loss is defined as:

$$VaR_\alpha(x) := \min\{\varsigma \in \Re : \int_{L(x,\tilde{d}) \le \varsigma} P(\tilde{d}) d\tilde{d} \ge \alpha \tag{12}$$

where, $p(\tilde{d})$ is the density function of $\tilde{d}$. Although, VaR is a popular risk measure, it is lack of desirable mathematical characteristics such subadditivity and convexity and hence is less appealing for the control and optimization of risk (Krokhmal *et al*., 2011). Later based on VaR, CVaR was proposed in the early 2000s (Rockafellar and Uryasev, 2002, 2000; Uryasev, 2000) and it is defined as:

$$CVaR_\alpha(x) := (1-\alpha)^{-1} \int_{L(x,\tilde{d}) \ge VaR_\alpha(x)} L(x,\tilde{d}) p(\tilde{d}) d\tilde{d} \tag{13}$$

Unlike VaR, CVaR enjoys numerous nice properties. Specifically, CVaR is a coherent risk measure (Artzner *et al*., 1999) and hence, it is a desirable risk measure. Besides the nice properties, CVaR is also not as difficult to compute as it appears in the definition (13). To show this, the following auxiliary function is required.

$$F_\alpha(x,\beta) = \beta + (1-\alpha)^{-1} \int [L(x,\tilde{d}) - \beta]^+ P(\tilde{d}) d\tilde{d} \tag{14}$$

The properties of $F_a(x, \beta)$ and its relationship with VaR and CVaR have been well studied (Rockafellar and Uryasev, 2000). To be self-contained, these results are summarized in the following theorem. For detailed proof of the results, refer to (Rockafellar and Uryasev, 2000, 2002).

Theorem 2:

- As a function of α, $F_a(x, \beta)$ is convex and continuously differentiable
  Additionally, $F_a(x, \beta)$ is convex with respect to (x, α) when $L(x,\tilde{d})$ is convex with respect to x
- For a given x, the VaR and CVaR of the associated loss $L(x,\tilde{d})$ can be determined as:

$$VaR_\alpha(x) = \min\{\arg\min_{\beta \in \Re} F_\alpha(x,\beta)\}, \tag{15}$$

$$CVaR_\alpha(x) = \min_{\beta \in \Re} F_\alpha(x,\beta) \tag{16}$$

- Minimizing $CVaR_a(x)$ over the feasible set $\aleph$ is equivalent to minimizing $F_a(x, \beta)$ over $(x,\beta) \in \aleph \times \Re$, i.e.:

$$\min_{x \in \aleph} CVaR\alpha(x) = \min_{(x,\beta) \in \aleph \times \Re} F_\alpha(x,\beta) \tag{17}$$

Remark 2: From Theorem 2, CVaR and VaR can be determined simultaneously determined by minimizing the auxiliary function $F_a(x, \beta)$. Furthermore, the multidimensional integral in (14) can also be approximated in various ways. For example, if a enough number of samples $d_1 \ldots d_k$ of $\tilde{d}$ is available, then $F_a(x, \beta)$ can be approximated by:

$$\hat{F}_\alpha(x,\beta) = \beta + [k(1-\alpha)]^{-1} \sum_{i=1}^{k} L(x,d_i) - \beta]^+ \tag{18}$$

which is a convex and piecewise linear function of α. Other variants of CVaR and various applications are also available in the literature (Huang *et al*., 2010; Tong *et al*., 2009). But this paper just focuses on the original concept of CVaR of the loss defined in (11). The approach introduced in Remark 2 is used to approximate the auxiliary function:

$$F_\alpha(x_H, x_L, \beta) = \beta + (1-\alpha)^{-1} \int [Loss(x_H, x_L, \tilde{d}_H, \tilde{d}_L - \beta]^+ P_H(\tilde{d}_H) P_L(\tilde{d}_L) d\tilde{d}_H d\tilde{d}_L \tag{19}$$

finally takes the form:

$$\min_{x_h, x_L, \beta} F_\alpha(x_H, x_L, \beta) \tag{20a}$$

s.t. (1)-(3), etc. (20b)

A number of simulations are done based on the optimization (20).

SIMULATION RESULTS AND ANALYSIS

In the example, the manufacturer produces two vaccine-like products, one high-risk and the other low-risk. The high-risk product is analogous to influenza vaccine demand of which is uncertain and is realized only at the end of the year in the northern hemisphere. The low-risk product is analogous to a regular vaccine demand of which is steady and can be roughly predicted based on birth rate and other factors. The data of the two products in this example are extracted from that provided by CDC (2011) and is described as follows. The high-risk product demand $\tilde{d}_H$ is assumed to be truncated normally distributed on the interval [50 200] and the original normal distribution has mean $\mu_H = 125$ (million) and variance $\delta_H 2$, i.e., N (125, 75). The low-risk product demand $\tilde{d}_L$ is also truncated normal distribution N (40, 5) on [30 50]. Other parameters include $C_H = 8$, $P_H = 12$, $C_L = 25$ and $P_L = 40$. Additionally, α in all the simulations.

Risk-averse decision maker: In this simulation, the government intervention is assumed void. Furthermore, R = 0 and $Lb_H = 0$, therefore constraints (1) and (3) are relaxed. The intention is focused on the manufacture's behavior in choosing products. The value of I_L in constraint (2) is increased from 1350 to 1750 and we observe how the total investment distributes between the high-risk and low-risk products as the total investment increases. The simulation result is shown in Fig. 3 from the figure; it can be observed that as the total investment increases more is invested on the low-risk product. This shows that if the financial return is guaranteed or is not the major concern, manufacturers always try to avoid additional risk (Chen and Sim, 2009). This can explain why the vaccine manufacturers kept quitting the business in 1990s. Hence, to keep a steady supply of certain pharmaceutical, the risk associated with the product should be reduced to keep the manufacturers in the market. In the rest of this section, the role of government intervention and emergency supply in reducing manufacturers, risk is analyzed by simulations.

Government intervention

Contract order: In this simulation, the high-risk product is assumed to be the only product of the manufacturer. The government buy-back is assumed void and how the government order affect the manufacturer's decision and risk is studied. Constraints (1) and (2) are relaxed and Lb_H in (3) is set to 150 to maintain an minimal output. The value of government order O_G is increased from 50 to 210, the corresponding planned output and the manufacturer's risk during this change are plotted in Fig. 4. In Fig. 4, the manufacturer's risk keeps decreasing with the increase of government order although the planned output does not change due to the minimal output constraint. After government order exceeding the minimal output value, the risk keeps decreasing at a smaller rate, i.e., the manufacturer keeps making profit at a certain rate. This result is expected since the government order shifts the risk from the manufacturer to the government. However, the government does not face too much risk since the order is for those who benefit from immunization grant funds, i.e., state health departments, certain large city immunization projects and others.

Buy-back: This simulation is similar to the previous one except that the government order is avoided and the government buy-back is valid. The buy-back ratio $\gamma_B = 1$ and the buy-back price vary from 0 to 7.8. The minimal

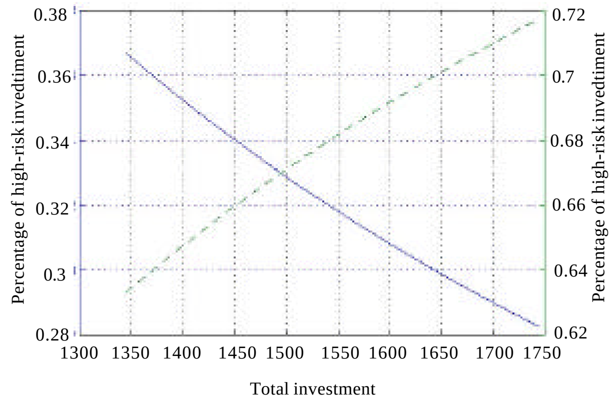

Fig. 3: Distribution of total investment in different products

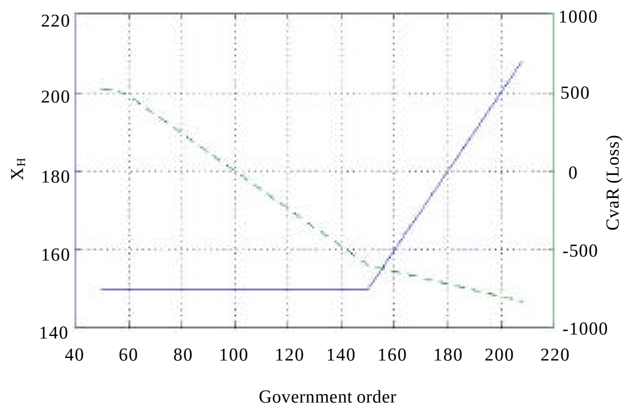

Fig. 4: x_H and CVaR (loss) vs. O_G

Fig. 5: Risk of manufacturer and government vs. P_B

output is also 150. By buy-back, the government's loss function is simply $P_B(\tilde{d}_H - x_H)^+$ and the CVaR of this loss is easily computable. The simulation result indicates that x_H remains at 150 as P_B varies, but the CVaR of the manufacturer and the government change. This change as a function of the buy back price P_B is shown in Fig. 5. From Fig. 5, it can be observed that the manufacturer's risk is reduced by increasing P_B but the risk shifted to the government is always positive and is relatively high compared with the risk of contract order.

CONCLUSIONS

A model of general pharmaceutical manufacturing system is proposed in this study. The model is manufacturer-centered and also includes the market and government authorities as factors that affect the manufacturer's production plans. Based on this model, the loss function of the manufacturer is a convex piecewise linear function. Assuming that the manufacturer attempts to minimize its conditional value at risk of the loss function, the decision making problem of the manufacturer can be formulated as a linear programming problem. By tuning the parameters in the optimization, simulations show that the government intervention can reduce the manufacturer's risk while keeping a steady drug supply. Using the proposed approach, different government policies can be compared to determine the optimal policy. The proposed approach can also be generalized to handle problems with a similar setting.

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