Monte Carlo Approximations in Bayesian Decision Theory Part II: Constructing Release Targets for Drug Products

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MONTE CARLO APPROXIMATIONS IN BAYESIAN DECISION THEORY

PART II:

CONSTRUCTING RELEASE TARGETS FOR DRUG PRODUCTS

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SUMMARY

Constructing release targets for drug products in the pharmaceutical industry is considered. To account for the cost and profit of the drug company, a useful decision theory approach is proposed. The release targets are constructed by minimizing the company's expected loss (or maximizing the expected gain). An example from a pharmaceutical company concerning the decision of releasing a batch of drug product is presented.

Key words: Release targets; USP specifications; Loss function; Optimal action.

1. INTRODUCTION

In a pharmaceutical company, before a batch of a drug product can be released for sale, it is necessary to test whether the drug meets some United States Pharmacopiea (USP) specifications, such as drug potency, dissolution and disintegration. For example, for drug potency, the Food and Drug Administration (FDA) requires that the average drug potency of the batch is within an interval (L,U), where $0<L<U$ are USP specification limits. Since the average potency is unknown, the test is based on the potency assay result of a sample (or the average potency results of n samples) from the batch. A batch might be released for sale if its potency assay result is within (L,U). However, a released batch according to such a test criterion could have average potency outside (L,U) with a high chance. A batch having average potency outside USP specifications during the expiration date period is subject to recall. To have a certain degree of assurance that the average potency of a released batch is within (L,U), a set of limits, denoted by a and b, is usually selected as an in-house guide for releasing a batch. We will refer to a and b as release targets. Thus, a batch is released for sale if its potency assay result is within (a,b).

Assuming that the potency assay result is normally distributed, customarily used release targets are

$$a_c = L + 1.645\sigma/n^{1/2} + s \quad \text{and} \quad b_c = U - 1.645\sigma/n^{1/2}, \tag{1.1}$$

where s is the estimated stability loss in potency over the expiration period, n is the number of assays and σ^2 is the estimated variability of an assay. The release targets (1.1) are commonly used, yet the following are some disadvantages:

(i) The idea behind the release targets (1.1) is that if all future batches have the *same* average potency, then the use of release targets (1.1) guarantees that among all the future batches released for sale, 95% of them have the average potency within (L,U). However, usually the average potencies for different batches are *different* (more precisely, they should be considered as random variables). Hence this 95% assurance does not hold and the use of release targets

(1.1) lacks statistical basis.

(ii) The use of release targets (1.1) does not take into account the company's costs and profits. The interval (a_c, b_c) could be too narrow and the chance of passing is extremely low (only a few batches can be released). Also, even if one has 95% assurance that the average potency is within (L, U), with a 5% chance of the true average potency being outside (L, U), the pay off for recall and possible penalty could be a disaster for the company.

In this paper we propose an alternative for constructing release targets using a statistical decision theory approach. The release targets a and b are viewed as the company's action (decision). After establishing an appropriate loss function, which takes into account the company's profits and possible costs, an action is chosen to minimize the company's expected loss over all the possible actions (release targets) that the company may have. Such an action is referred to as an optimal action. The decision theory approach is shown to be successful, both in theory and in practice. For details, see Ferguson (1967) and Berger (1985), which also provide many other useful references.

Procedures for constructing release targets (optimal action) are described in Sections 2-4, where Section 2 contains a general description, Section 3 studies the distribution of the average drug characteristics and other parameters, and Section 4 shows an example of constructing loss function through the company's utility analysis. As an illustration, Section 5 presents some numerical results for an example from a pharmaceutical company.

2. CONSTRUCTION OF THE OPTIMAL ACTION

Let μ be a k-vector of averages of drug characteristics (e.g., potency, dissolution and disintegration) for a batch and y be the k-vector of corresponding assay results of a sample from the batch (y can be the average of n assay results). Assume that the density of y, denoted by $f(y \mid \mu, \nu)$, is known when μ and ν are given, where ν is a q-vector of nuisance

parameters. In practice, $f(y \mid \mu,\nu)$ is often the density of a normal distribution. Since usually there is batch-to-batch variation, μ is considered to be random. Let $p(\mu,\nu)$ be the believed joint density of μ and ν at the time of decision making. The construction of $p(\mu,\nu)$ will be discussed in Section 3.

Let a and b be release targets and L and U be the USP specification limits. a, b, L and U are k-vectors. Denote the ith component of a (b, L or U) by a_i (b_i, L_i or U_i). The pair $d=(a,b)$ is called an action or a decision of the company. d will be chosen from the collection (action space)

$$\mathbf{D}=\{\, d: L_i \le a_i \le b_i \le U_i \text{ for all } i \,\}.$$

For a particular batch with assay result y, the batch is released for sale if

$$a_i \le y_i \le b_i \quad \text{for all } i, \tag{2.1}$$

where y_i is the ith component of y. Otherwise the batch has to be disposed of or recovered for future use. Then the utility of the company depends on μ, y and the action d.

Let $u(\mu,y,d)$ be the utility of the company if the action d is taken and μ turns out to be the *true* average (of the drug characteristic) of the batch. Then the loss of the company is $l(\mu,y,d)=-u(\mu,y,d)$. The function $l(\mu,y,d)$ can usually be determined through a utility analysis (see Section 4). The average (over all the future batches) loss of the company when the action d is taken is then

$$\rho(d) = E^{(\mu,y)}[l(\mu,y,d)],$$

where $E^{(\mu,y)}$ is the expectation taken under the joint distribution of μ and y. Thus,

$$\rho(d) = \iiint l(\mu,y,d) f(y \mid \mu,\nu) p(\mu,\nu) \mathrm{d}y \, \mathrm{d}\mu \, \mathrm{d}\nu.$$

$\rho(d)$ is often called the expected loss in the statistical literature. An optimal action is an action $d^* \in \mathbf{D}$ such that

$$\rho(d^*) = \min_{d \in \mathbf{D}} \rho(d). \tag{2.2}$$

Usually the function $\rho(d)$ does not have a closed form. A numerical method for solving (2.2) is required. Shao (1988) proposed the following Monte Carlo method for approximating the optimal action d^*. Generate independent and identically distributed random $(k+q)$-vectors $\{ (\mu^{(j)}\ \nu^{(j)}),\ j=1,2,...,m \}$ from a density $h(\mu,\nu)$ which has the same support as $p(\mu,\nu)$ (If $(\mu^{(j)}\ \nu^{(j)})$ can be easily generated from $p(\mu,\nu)$, then h is chosen to be $p(\mu,\nu)$). Approximate $\rho(d)$ by

$$\rho_m(d) = \frac{\sum_{j=1}^m l(\mu^{(j)},y,d) f(y \mid \mu^{(j)},\nu^{(j)}) p(\mu^{(j)},\nu^{(j)})/h(\mu^{(j)},\nu^{(j)})}{\sum_{j=1}^m f(y \mid \mu^{(j)},\nu^{(j)}) p(\mu^{(j)},\nu^{(j)})/h(\mu^{(j)},\nu^{(j)})}$$

and d^* be d_m^* satisfying

$$\rho_m(d_m^*) = \min_{d\in\mathbf{D}} \rho_m(d). \tag{2.3}$$

For solving (2.3), algorithms from nonlinear programming and optimization can be used.

The convergence of d_m^* to d^* (as $m\to\infty$) was shown in Shao (1988). Thus, we can use $d_m^*=(a_m^*,b_m^*)$ as an optimal action.

For some characteristics, such as drug potency, stability loss should also be taken into account. That is, at the expiration date (e.g, 60 months after the drug is produced), the drug characteristic may not be μ but $\mu-s$, where s is a k-vector of stability losses. In this case, the loss function depends on s, say $l(s,\mu,y,d)$. If s is believed to be equal for all the batches and is estimated by $\bar{s}$ based on some other data through a stability analysis (FDA, 1987; Chow and Shao, 1988), then the expected loss is

$$\rho(d) = E^{(\mu,y)}[l(\bar{s},\mu,y,d)].$$

If different batches have different stability losses, then s is random and the expected loss is

$$\rho(d) = E^{(s,\mu,y)}[l(s,\mu,y,d)], \tag{2.4}$$

where $E^{(s,\mu,y)}$ is the expectation taken under the joint distribution of s, μ and y.

3. THE DISTRIBUTION OF PARAMETERS

The joint distribution of μ and ν (and s if the stability loss is considered) can be obtained from (i) an accuracy and precision study from an assay validation; (ii) the stability data of the drug.

Let the distribution obtained from past experience be $\pi(s,\mu,\nu)$. For example, μ may have a normal distribution with mean $(L+U)/2$ (the center of (L,U)) and the conditional distribution of s given μ has mean 0.05μ. A noninformative distribution (Berger, 1985, Chapter 3) can be used for ν if there is no information available.

The data collected from a stability analysis often are

$$x_{it}, \quad i=1,...,n, \; t=0,t_1,...,t_T,$$

where x_{it} is the ith replication (assay result) for a sample batch after t months from the production date. For given μ and s, x_{it} are independently distributed with mean $\mu-(t/t_T)s$. Let $g(x \mid s,\mu,\nu)$ be the joint distribution of x_{it} for given μ, ν and s. Then an updated distribution of μ, ν and s is given by

$$p(s,\mu,\nu) = g(x \mid s,\mu,\nu)\pi(s,\mu,\nu)/m(x), \tag{3.1}$$

where

$$m(x) = \iiint g(x \mid s,\mu,\nu)\pi(s,\mu,\nu)\mathrm{d}s\,\mathrm{d}\mu\,\mathrm{d}\nu.$$

From a Bayesian point of view (Berger, 1985, Chapter 4), $\pi(s,\mu,\nu)$ is the prior density of s, μ and ν and $p(s,\mu,\nu)$ is their posterior density.

Typically, the conditional distribution of x_{it} is normal. That is, for given μ and s,

$$x_{it} = \mu-(t/t_T)s + e_{it},$$

where e_{it} are independently $N(0, \sigma^2\mathrm{I}_{k\times k})$, $\mathrm{I}_{k\times k}$ is the $k\times k$ identity matrix and σ^2 is a nuisance parameter. As an example, we consider the case where $k=1$, $L=90$ and $U=110$. Assume that for given σ^2, μ and s have a joint normal distribution with mean $(100\ 100r)^\tau$ and covariance matrix

$$\sigma^2 G, \quad G = \begin{bmatrix} \tau_1 & r\tau_1 \\ r\tau_1 & \tau_2 \end{bmatrix},$$

where r is the expected percentage of stability loss. Note that for given μ and σ^2, $E(s \mid \mu,\sigma^2)=r\mu$. The distribution for σ^2 can be chosen to be a noninformative distribution with $\pi(\sigma^2) = \sigma^{-2}$. Let $\nu=\sigma^{-2}$, $\eta=(100\tau_1^{-1}\ 0)^\tau$,

$$\xi = (\sum_{i,t} x_{it} \quad -t_T^{-1} \sum_{v=1}^{T} t_v \sum_{i=1}^{n} x_{it})^\tau,$$

and

$$M = n \begin{bmatrix} (1+T) & -t_T^{-1} \sum_{v=1}^{T} t_v \\ -t_T^{-1} \sum_{v=1}^{T} t_v & t_T^{-2} \sum_{v=1}^{T} t_v^2 \end{bmatrix}.$$

Then $p(s,\mu,\nu)$ defined in (3.1) is equal to

$$p_1(s,\mu \mid \nu)\, p_2(\nu), \tag{3.2}$$

where $p_2(\nu)$ is the density of a gamma distribution with shape parameter $(1+T)n/2$ and scale parameter $2[\sum_{i,t} x_{it}^2 - (\xi+\eta)^\tau (M+G^{-1})^{-1}(\xi+\eta)+10{,}000/\tau_1]^{-1}$, and $p_1(s,\mu \mid \nu)$ is the density of a bivariate normal with mean $(M+G^{-1})^{-1}(\xi+\eta)$ and covariance matrix $\nu^{-1}(M+G^{-1})^{-1}$.

4. THE LOSS FUNCTION

Another crucial step is to construct an appropriate loss function, which usually can be done by a utility analysis (Berger, 1985, Chapter 2). Information about the company's costs involved for releasing a batch is essential. In this section, we derive a loss function, which may be useful in practice, through an analysis of the company's profits and costs. Typically, the company's costs include the following:

(i) *Costs when the batch is not released.* When it is decided not to release a batch for sale, the batch is either disposed of or the active ingredient is recovered for future use. Let C be the cost of a batch due to disposal or recovery when the batch fails to pass the USP test (i.e, (2.1) does not hold).

(ii) *Costs when the batch is released.* When a batch is released for sale, the batch will be packaged and distributed. Let C_1 be the sum of the packaging cost, distribution cost and storage cost, and D be the cost and penalty of a recall by the FDA. Then the company's cost is C_1 if a released batch has μ within the USP specification limits and is C_1+D otherwise.

(iii) *Fixed costs.* The fixed costs include the production and laboratory testing cost. Let C_0 be the total fixed costs.

Let B be the company's profit from a released batch. From the above considerations, we derive the following loss function:

$$l(s,\mu,y,d) = C_0 + C(1-\prod_{i=1}^{k} I_i) + (C_1+D)\prod_{i=1}^{k} I_i(1-J_i) + (C_1-B)\prod_{i=1}^{k} I_i J_i, \qquad (4.1)$$

where $I_i=I_{(a_i<y_i<b_i)}$, $J_i=I_{(L_i+s_i<\mu_i<U_i)}$ and I_A is the indicator function of the set A. Assume that the components of $(y\ s\ \mu\ \nu)$ are independent. The expected loss is then

$$\rho(d) = C_0 + C[1-\prod_{i=1}^{k} E^{(s,\mu,\nu)}(p_i)]$$

$$+ (C_1+D)\prod_{i=1}^{k} E^{(s,\mu,\nu)}[p_i(1-J_i)] + (C_1-B)\prod_{i=1}^{k} E^{(s,\mu,\nu)}(p_i J_i),$$

where $p_i=P(\ a_i<y_i<b_i\ )$. If y_i follows a normal distribution $N(\mu_i,\sigma_i^2)$, then

$$p_i = \Phi(\frac{b_i-\mu_i}{\sigma_i}) - \Phi(\frac{a_i-\mu_i}{\sigma_i}),$$

where $\Phi(t)$ is the standard normal distribution function.

5. AN EXAMPLE

We present the following example to illustrate the use of the proposed decision approach for constructing a set of release targets. For simplicity, we consider the potency test only. The USP specifications for the product under consideration are 90-110 (% of claim). The following table gives the information about the cost, profit and penalty for the batch of drug product to be released:

Item	Description	Amount (in dollars)
C_0	Total fixed costs	2,000
C_1	Packaging, distribution and storage costs	1,000
C	Disposal or recovery cost	c
B	Profit	3c
D	Cost and penalty of a recall	40c - 150c

where c is a fixed constant. Note that from (4.1), only the ratios D/C and B/C affect the selection of d. Hence the actual value of c is not relevant to the construction of release targets.

The loss function (4.1) is used. To account for stability loss, the following stability data (% of claim) from a released batch are collected:

Age (month)	0	6	12	24	36	60
x_t	104.0	104.9	100.5	92.2	99.2	94.4

The joint distribution of s, μ and ν is given by (3.2) with r=0.05, τ_1=10 and τ_2=1. Since the densities $p_1(s,\mu|\nu)$ and $p_2(\nu)$ have known forms, $\rho(d)$ in (2.4) is approximated by Monte Carlo with 20,000 samples $(s^{(j)}\ \mu^{(j)}\ \nu^{(j)})$ from $p_1(s,\mu|\nu)p_2(\nu)$. The release targets a and b are obtained by minimizing $\rho(d)$ over $d=(a,b)\in\{\ L\le a<b\le U\ \}$. Table 1 gives the constructed release targets for various D's ranging from 40c to 150c. For example, if the cost and penalty of a recall is 125c, to account for the stability loss, the recommended release targets are 97.0 and 107.5, i.e., the batch is released if the mean potency assay result is between 97.0 and 107.5. It can also be seen that the width of the release targets becomes narrow when the cost and penalty of a recall increases (Figure 1). For example, the width of the release targets is

reduced by 6.5 (from 17.4 to 10.9) as the cost and penalty increases from 60c to 120c.

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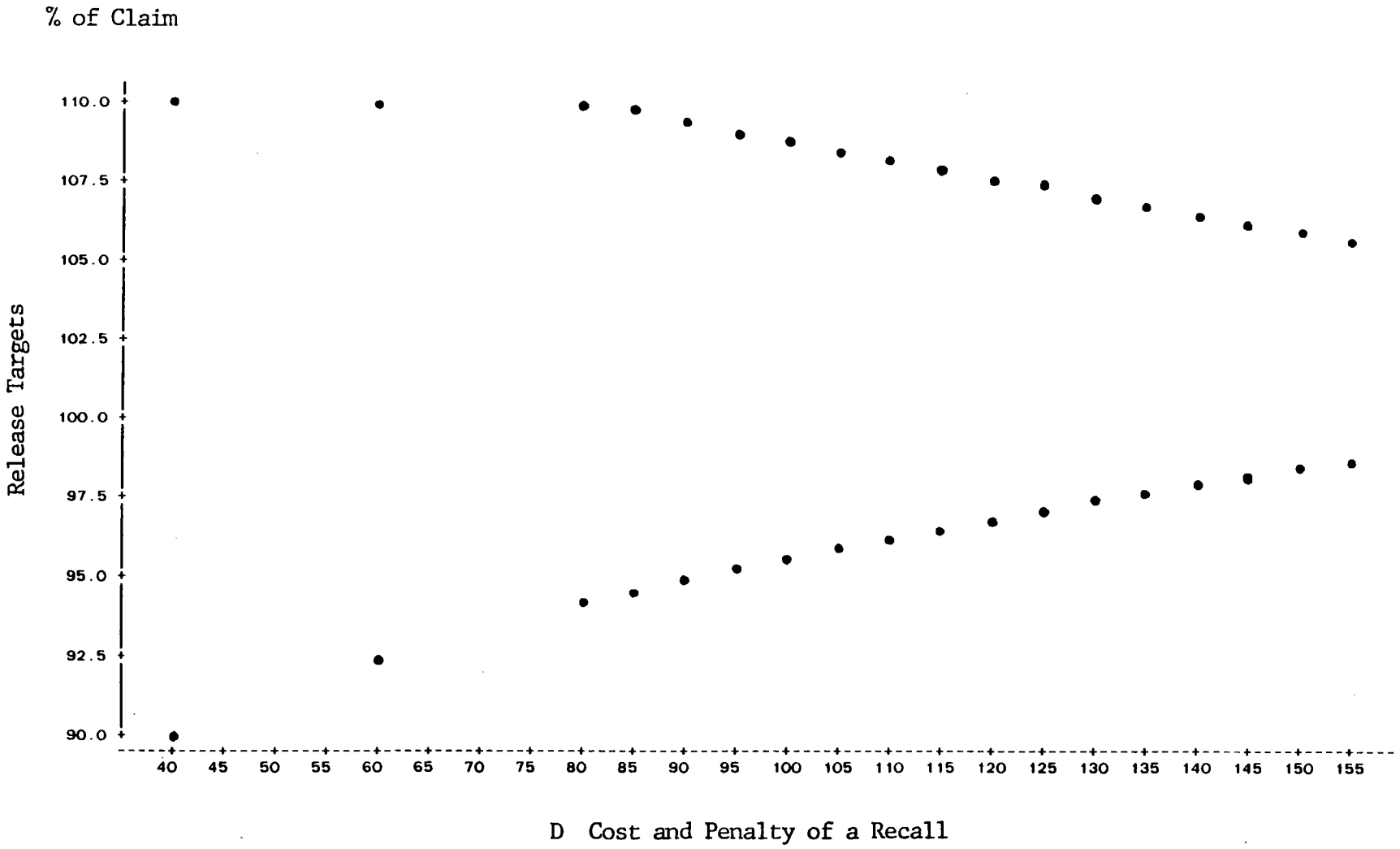
Table 1

Release Targets for Various D

a	b	D
90.0	110.0	40
92.6	110.0	60
94.3	110.0	80
94.7	109.8	85
95.0	109.5	90
95.4	109.1	95
95.7	108.8	100
96.0	108.5	105
96.2	108.3	110
96.5	108.0	115
96.8	107.7	120
97.0	107.5	125
97.3	107.2	130
97.5	106.9	135
97.8	106.7	140
98.0	106.4	145
98.3	106.2	150
98.5	105.9	155

Note: a = lower release target
b = upper release target
D = cost and penalty of a recall

Figure 1


% of Claim
Release Targets
110.0
107.5
105.0
102.5
100.0
97.5
95.0
92.5
90.0
40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155
D Cost and Penalty of a Recall