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# DRUG SHELF-LIFE ESTIMATION

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*Abstract:* The shelf-life of a drug product is the time that the average drug characteristic (e.g., potency) remains within an approved specification after manufacture. The United States Food and Drug Administration (FDA) requires indication for every drug product of a shelf-life on the immediate container label. Since the true shelf-life of a drug product is typically unknown, it has to be estimated based on assay results of the drug characteristic from a stability study usually conducted during the process of drug development. Furthermore, the FDA requires that the estimated shelf-life be so constructed that it is statistically evident that the estimated shelf-life is less than the true shelf-life, i.e., the estimated shelf-life should be a conservative (negatively biased) estimator. In this paper, we study and compare several shelf-life estimators, one of which is adopted by the FDA's 1987 guidelines, in terms of their asymptotic biases and mean squared errors. Finite sample performance of some shelf-life estimators is examined in a simulation study.

*Key words and phrases:* Asymptotic bias, asymptotic mean squared error, batch-to-batch variation, inverse regression, lower confidence bound, lower prediction bound.

## 1. Introduction

The expiration dating period or shelf-life of a drug product is defined as the time at which the average drug characteristic (e.g., potency) remains within an approved specification after manufacture (FDA, 1987). The United States Food and Drug Administration (FDA) requires that a shelf-life be indicated on the immediate container label of every drug product. Since the true shelf-life of a drug product is usually unknown, it is typically estimated based on assay results of the drug characteristic from a stability study conducted during the process of drug development. Let $y_j$ be the assay result of a pharmaceutical compound at time $x_j$, $j = 1, \ldots, n$. A simple linear regression model is usually assumed:

$$y_j = \alpha + \beta x_j + e_j, \quad j = 1, \ldots, n, \tag{1.1}$$

where $\alpha$ and $\beta$ are unknown parameters, $x_j$'s are deterministic time points selected in the stability study, and $e_j$'s are measurement errors independently and identically distributed as $N(0, \sigma^2)$. Under (1.1), the average drug characteristic

at time $x$ is $\alpha + \beta x$. Throughout the paper, we assume that the drug characteristic decreases as time increases, i.e., $\beta$ in (1.1) is negative, and that the drug product expires if its average characteristic is below a given specification constant $\eta$. Thus the true shelf-life, denoted by $\theta$, is the solution of $\eta = \alpha + \beta x$, hence $\theta = (\eta - \alpha)/\beta$. Note that $\alpha$ is the average drug characteristic at the time of manufacture (i.e., $x = 0$) which is usually larger than $\eta$. Thus $\theta > 0$.

Let $\hat{\theta}$ be an estimator of the true shelf-life $\theta$ based on $(y_j, x_j)$'s. It is desirable that $\hat{\theta} \leq \theta$ be statistically evident, i.e., $\hat{\theta}$ is a conservative estimator. According to FDA guidelines (FDA 1987), the probability of $\hat{\theta} \leq \theta$ should be nearly 95%, i.e., $\hat{\theta}$ is approximately a 95% lower confidence bound for $\theta$. Thus $\hat{\theta}$ has a negative bias of the same order of magnitude as the standard deviation of $\hat{\theta}$. Studying the magnitude of the bias of $\hat{\theta}$ is particularly important for pharmaceutical companies, because the closeness of $\hat{\theta}$ to $\theta$ is directly related to the bias of $\hat{\theta}$ and a less biased shelf-life estimator is preferred. In Sections 2-4, we study the bias and variance of three different shelf-life estimators, using two different asymptotic approaches. Finite sample performance of these three shelf-life estimators is studied in Section 5 through a simulation study.

In the pharmaceutical industry, drug products are usually manufactured in different batches. The FDA requires testing of at least three batches, preferably more, in any stability analysis to account for batch-to-batch variation. When there is batch-to-batch variation, (1.1) holds for data from each batch but the values of $\alpha$ and $\beta$ in different batches are different. A discussion of shelf-life estimation in the presence of batch-to-batch variation is given in Section 6.

## 2. FDA's Method

Let $(\hat{\alpha}, \hat{\beta})$ be the least squares estimator of $(\alpha, \beta)$ based on $(y_j, x_j)$'s under (1.1). For any fixed time $x$, a 95% lower confidence bound for $\alpha + \beta x$ is

$$L(x) = \hat{\alpha} + \hat{\beta}x - \hat{\sigma} t_{n-2} \sqrt{\frac{1}{n} + \frac{(x - \bar{x})^2}{S_{xx}}},$$

where $t_{n-2}$ is the 95th percentile of the t-distribution with $n - 2$ degrees of freedom, $\bar{x}$ is the average of $x_j$'s, $\hat{\sigma}^2 = (S_{yy} - S_{xy}^2/S_{xx})/(n-2)$, $S_{yy} = \sum_{j=1}^n (y_j - \bar{y})^2$, $S_{xx} = \sum_{j=1}^n (x_j - \bar{x})^2$, $S_{xy} = \sum_{j=1}^n (x_j - \bar{x})(y_j - \bar{y})$, and $\bar{y}$ is the average of $y_j$'s. FDA's shelf-life estimator is $\hat{\theta}_F = \inf\{x \geq 0 : L(x) \leq \eta\}$, the smallest $x \geq 0$ satisfying $L(x) = \eta$. By definition, $\hat{\theta}_F > \theta$ implies $L(\theta) > \eta$ and $P(\hat{\theta}_F > \theta) \leq P(L(\theta) > \eta) = 5\%$, since $L(\theta)$ is a 95% lower confidence bound for $\alpha + \beta\theta = \eta$. This means that $\hat{\theta}_F$ is a (conservative) 95% lower confidence bound for $\theta$. We

now study its asymptotic bias and asymptotic mean squared error. Define

$$A_n = \hat{\sigma}^2 t_{n-2}^2 \left( \frac{1}{n} + \frac{\bar{x}^2}{S_{xx}} \right), \quad B_n = -\frac{\bar{x}\hat{\sigma}^2 t_{n-2}^2}{S_{xx}}, \quad C_n = \frac{\hat{\sigma}^2 t_{n-2}^2}{S_{xx}}. \tag{2.1}$$

Without loss of generality, assume that $S_{xx}$ is exactly of order $n$. Then $A_n$, $B_n$, and $C_n$ are exactly of order $n^{-1}$. Thus, asymptotically, $\hat{\theta}_F$ is the unique solution of $L(x) = \eta$. A straightforward calculation shows that the solution should be

$$\frac{(\eta - \hat{\alpha})\hat{\beta} + B_n - \sqrt{[(\eta - \hat{\alpha})\hat{\beta} + B_n]^2 - (\hat{\beta}^2 - C_n)[(\eta - \hat{\alpha})^2 - A_n]}}{\hat{\beta}^2 - C_n}.$$

Removing terms of order $n^{-1}$, we obtain that

$$\hat{\theta}_F = \frac{\eta - \hat{\alpha}}{\hat{\beta}} - \frac{\sqrt{A_n\hat{\beta}^2 + 2B_n(\eta - \hat{\alpha})\hat{\beta} + C_n(\eta - \hat{\alpha})^2}}{\hat{\beta}^2} + o_p\left(n^{-1/2}\right). \tag{2.2}$$

From the asymptotic theory for the least squares estimators, and Taylor's expansion, we know that

$$\left( \frac{\eta - \hat{\alpha}}{\hat{\beta}} - \frac{\eta - \alpha}{\beta} \right) \Big/ \frac{\sigma}{|\beta|} \sqrt{\frac{1}{n} + \frac{(\theta - \bar{x})^2}{S_{xx}}} \to N(0,1) \quad \text{in law.} \tag{2.3}$$

Since $\theta = (\eta - \alpha)/\beta$, the asymptotic expectation of $\frac{\eta - \hat{\alpha}}{\hat{\beta}} - \theta$ is 0. Since $\hat{\alpha} \to_p \alpha$, $\hat{\beta} \to_p \beta$, and $\hat{\sigma} \to_p \sigma$, the asymptotic expectation of the second term on the right side of (2.2) is

$$-\frac{\sigma t_{n-2}}{\beta^2} \sqrt{\left( \frac{1}{n} + \frac{\bar{x}}{S_{xx}} \right) \beta^2 - \frac{2\bar{x}(\eta - \alpha)\beta}{S_{xx}} + \frac{(\eta - \alpha)^2}{S_{xx}}} = -\frac{\sigma t_{n-2}}{|\beta|} \sqrt{\frac{1}{n} + \frac{(\theta - \bar{x})^2}{S_{xx}}}. \tag{2.4}$$

This is the asymptotic bias of $\hat{\theta}_F$ as $n \to \infty$ and is of order $n^{-1/2}$. Furthermore, it follows from (2.3) and (2.4) that the asymptotic mean squared error of $\hat{\theta}_F$ is

$$\frac{\sigma^2(1 + t_{n-2}^2)}{\beta^2} \left[ \frac{1}{n} + \frac{(\theta - \bar{x})^2}{S_{xx}} \right]. \tag{2.5}$$

Stability studies are often conducted under controlled conditions so that the assay measurement error variance $\sigma^2$ is very small. This leads to the study of the "small error asymptotics". When $n$ is fixed and $\sigma \to 0$,

$$\hat{\beta} = \frac{S_{xy}}{S_{xx}} = \frac{\sum_{i=1}^n (x_i - \bar{x}) y_i}{S_{xx}} = \beta + \frac{\sum_{i=1}^n (x_i - \bar{x}) e_i}{S_{xx}} = \beta + O_p(\sigma) \to_p \beta,$$

where $O_p(\sigma)$ denotes a random variable of order $\sigma$ as $\sigma \to 0$. This result holds because $e_i/\sigma$ is $N(0,1)$. Similarly, $\hat{\alpha} = \bar{y} - \hat{\beta}\bar{x} = \alpha + O_p(\sigma) \to_p \alpha$. Furthermore, $(n-2)\hat{\sigma}^2/\sigma^2$ has the chi-square distribution with $(n-2)$ degrees of freedom. Thus (2.2) holds with $o_p(n^{-1/2})$ replaced by $o_p(\sigma)$. The asymptotic ($\sigma \to 0$) bias of the second term on the right side of (2.2) is given by (2.4), which is now of order $\sigma$. Using Taylor's expansion and the fact that $\hat{\alpha} - \alpha$ and $\hat{\beta} - \beta$ are jointly normal with mean 0 and covariance matrix

$$\frac{\sigma^2}{S_{xx}} \begin{pmatrix} \bar{x}^2 + n^{-1}S_{xx} & -\bar{x} \\ -\bar{x} & 1 \end{pmatrix},$$

we conclude that (2.3) holds when $\sigma \to 0$ and $n$ is fixed. Hence the asymptotic bias and mean squared error of $\hat{\theta}_F$, in the case of $\sigma \to 0$, are the same as those for the case of $n \to \infty$, given by (2.4) and (2.5), respectively.

Formulas (2.4) and (2.5) indicate that, when $n$ and $x_i$'s are fixed, the asymptotic bias and mean squared error of $\hat{\theta}_F$ depend mainly on the noise-to-signal ratio $\sigma/|\beta|$. If $\sigma/|\beta|$ cannot be controlled to a desirable level, then an increase of sample size $n$ is necessary in order to reduce bias and mean squared error.

## 3. The Direct Method

From the asymptotic theory (either $n \to \infty$ or $\sigma \to 0$),

$$\left(\frac{\eta - \hat{\alpha}}{\hat{\beta}} - \theta\right) \Big/ \frac{\hat{\sigma}}{|\hat{\beta}|}\sqrt{\frac{1}{n} + \frac{1}{S_{xx}}\left(\frac{\eta - \hat{\alpha}}{\hat{\beta}} - \bar{x}\right)^2} \to N(0,1) \quad \text{in law.}$$

Let $z$ be the 95th percentile of the standard normal distribution. Then an approximate (large $n$ or small $\sigma$) 95% lower confidence bound for $\theta$ is

$$\hat{\theta}_D = \frac{\eta - \hat{\alpha}}{\hat{\beta}} - \frac{\hat{\sigma} z}{|\hat{\beta}|}\sqrt{\frac{1}{n} + \frac{1}{S_{xx}}\left(\frac{\eta - \hat{\alpha}}{\hat{\beta}} - \bar{x}\right)^2}.$$

We call this the direct method (of obtaining a shelf-life estimator). Using $A_n$, $B_n$ and $C_n$ given in (2.1), we find

$$\hat{\theta}_D = \frac{\eta - \hat{\alpha}}{\hat{\beta}} - \frac{z}{t_{n-2}} \frac{\sqrt{A_n\hat{\beta}^2 + 2B_n(\eta - \hat{\alpha})\hat{\beta} + C_n(\eta - \hat{\alpha})^2}}{\hat{\beta}^2}. \tag{3.1}$$

When $n \to \infty$, $z/t_{n-2} \to 1$. It follows from (2.2) and (3.1) that $\hat{\theta}_D - \hat{\theta}_F = o_p(n^{-1/2})$. Hence the shelf-life estimators obtained by using FDA's method and the direct method are asymptotically equivalent, and their large sample asymptotic bias and mean squared error agree.

The small error asymptotic bias and mean squared error of $\hat{\theta}_D$ are given by (2.4) and (2.5), respectively, with $t_{n-2}$ replaced by $z$. When $n$ is fixed, $z/t_{n-2}$ is a fixed constant less than 1. Hence, $\hat{\theta}_D > \hat{\theta}_F$ holds asymptotically as $\sigma \to 0$, i.e., $\hat{\theta}_D$ is less conservative than $\hat{\theta}_F$. This result indicates that, when $\sigma^2$ is small, $\hat{\theta}_D$ is preferred. The same conclusion can be made based on the simulation result in Section 5.

## 4. The Inverse Method

Another shelf-life estimator can be obtained using the so-called *inverse regression method* (Krutchkoff (1967); Halperin (1970)). Start with

$$x_j = \alpha^* + \beta^* y_j + e_j^*, \quad j = 1, \ldots, n, \tag{4.1}$$

which is the same as (1.1) except that $x_j$ and $y_j$ are switched. In a stability study, however, the $x_j$'s are deterministic time points and the $y_j$'s are assay results and, therefore, the error term $e_j^*$ is not independent of $y_j$. Nevertheless, suppose that we fit model (4.1) based on $(x_j, y_j)$'s. Since the true shelf-life is the $x$-value when the mean of $y$ is $\eta$, the shelf-life estimator $\hat{\theta}_I$ based on the inverse method is the 95% lower confidence bound for $\alpha^* + \beta^*\eta$. Treating (4.1) as an ordinary linear regression model, we obtain the least squares estimators $\hat{\alpha}^* = \bar{x} - \bar{y}S_{xy}/S_{yy}$, $\hat{\beta}^* = S_{xy}/S_{yy}$, and the following "unbiased" estimator of the variance of $\hat{\alpha}^* + \hat{\beta}^*\eta$:

$$\frac{1}{n-2}\left(S_{xx} - \frac{S_{xy}^2}{S_{yy}}\right)\left[\frac{1}{n} + \frac{(\eta - \bar{y})^2}{S_{yy}}\right] = \hat{\sigma}^2 \frac{S_{xx}}{S_{yy}}\left[\frac{1}{n} + \frac{(\eta - \bar{y})^2}{S_{yy}}\right].$$

Consequently, the shelf-life estimator based on the inverse method is

$$\hat{\theta}_I = \bar{x} + \frac{S_{xy}}{S_{yy}}(\eta - \bar{y}) - \hat{\sigma} t_{n-2} \sqrt{\frac{S_{xx}}{S_{yy}}\left[\frac{1}{n} + \frac{(\eta - \bar{y})^2}{S_{yy}}\right]}. \tag{4.2}$$

Under (1.1) with $S_{xx}$ having order $n^{-1}$ as $n \to \infty$, $\hat{\theta}_I$ has the same limit as

$$\bar{x} + \frac{\beta}{\beta^2 + \frac{\sigma^2 n}{S_{xx}}}(\eta - \alpha - \beta\bar{x}) = \frac{\frac{\sigma^2 n}{S_{xx}}}{\beta^2 + \frac{\sigma^2 n}{S_{xx}}}\bar{x} + \frac{\beta^2}{\beta^2 + \frac{\sigma^2 n}{S_{xx}}}\theta,$$

which is a convex combination of $\bar{x}$ and $\theta$. Unless $\bar{x} = \theta$, $\hat{\theta}_I$ has a non-zero limiting bias as $n \to \infty$. Since $\bar{x}$ is the average of the time values used in stability study, it is usually much smaller than the true shelf-life $\theta$. Hence the limiting bias of $\hat{\theta}_I$ is negative, i.e., $\hat{\theta}_I$ can be too conservative. In fact, if $\bar{x} < \theta$ for all $n$, then $\lim_{n\to\infty} P(\hat{\theta}_I < \theta) = 1$.

When $n$ is fixed but $\sigma \to 0$, the difference between the last term on the right side of (4.2) and the quantity on the right side of (2.4) is of the order $o_p(\sigma)$. Thus $\hat{\theta}_I - \hat{\theta}_F = o_p(\sigma)$ and the small error asymptotic properties of $\hat{\theta}_I$ are the same as those of $\hat{\theta}_F$.

The inverse method has a better asymptotic performance in case $\sigma \to 0$ than if $n \to \infty$ since (4.1) and (1.1) are asymptotically the same as $\sigma \to 0$, but asymptotically different as $n \to \infty$. Note that (1.1) and (4.1) are the same if and only if $\sigma = 0$, regardless of how large $n$ is.

The inverse method is appealing because of its simplicity. However, it is not valid unless $\sigma \to 0$. Our simulation study shows that the inverse method is too conservative unless $\sigma$ is very small, so $\hat{\theta}_I$ is not recommended.

## 5. Simulation Results

A simulation study is conducted to examine the finite sample performance of $\hat{\theta}_F$, $\hat{\theta}_D$ and $\hat{\theta}_I$. We also study whether the asymptotic bias and mean squared error formulas (2.4) and (2.5) are close to the bias and mean squared error given by simulation.

We consider a typical stability study design: $x_j = 0, 3, 6, 9, 12, 18,$ and 24 months, with 3 replications at each $x_j$. Thus $n = 21$. Values of $\alpha$, $\beta$ and $\eta$ are chosen to be 105, $-0.5$ and 90, respectively, so that $\theta = 30$. To see the asymptotic effect, we consider values of $\sigma$ ranging from 0.1 to 2.0.

Based on 2,000 simulations, Table 1 lists (1) the bias (BIAS) and mean squared error (MSE) of $\hat{\theta}_F$, $\hat{\theta}_D$ and $\hat{\theta}_I$; (2) the asymptotic bias (ABIAS) and asymptotic mean squared error (AMSE) computed using formulas (2.4) and (2.5); (3) the coverage probability (CP) when $\hat{\theta}_F$, $\hat{\theta}_D$ and $\hat{\theta}_I$ are considered to be 95% lower confidence bounds for $\theta$. The results can be summarized as follows.

1. The performance of $\hat{\theta}_F$ and $\hat{\theta}_D$ is good, especially when $\sigma$ is small. The coverage probability for $\hat{\theta}_F$ and $\hat{\theta}_D$ is close to 95% and never below 94%. Comparing $\hat{\theta}_F$ with $\hat{\theta}_D$, we find that $\hat{\theta}_D$ is slightly better when $\sigma$ is small whereas $\hat{\theta}_F$ is slightly better when $\sigma$ is large.
2. For $\hat{\theta}_F$ or $\hat{\theta}_D$, asymptotic bias and mean squared error from (2.4) and (2.5) are very close to exact bias and mean squared error when $\sigma$ is small. For large $\sigma$, the asymptotic bias (or the asymptotic mean squared error) is quite different from the exact bias (or the exact mean squared error).
3. In general, $\hat{\theta}_I$ is too conservative unless $\sigma$ is very small, which supports our theory in Section 4. Even when $\sigma = 0.2$, the bias and mean squared error of $\hat{\theta}_I$ are still much larger than those of $\hat{\theta}_F$ (or $\hat{\theta}_D$), and the coverage probability of $\hat{\theta}_I$ is over the nominal level by more than 2%.

Table 1. Simulation averages of bias, mean squared error, and coverage probability of shelf-life estimators.

| $\sigma$ | Estimator | BIAS | ABIAS | MSE | AMSE | CP |
|---|---|---|---|---|---|---|
| 0.1 | $\hat{\theta}_F$ | -0.2002 | -0.2044 | 0.0545 | 0.0557 | 0.9510 |
| | $\hat{\theta}_D$ | -0.1922 | -0.1944 | 0.0513 | 0.0518 | 0.9460 |
| | $\hat{\theta}_I$ | -0.2136 | -0.2044 | 0.0603 | 0.0557 | 0.9615 |
| 0.2 | $\hat{\theta}_F$ | -0.4042 | -0.4088 | 0.2193 | 0.2230 | 0.9585 |
| | $\hat{\theta}_D$ | -0.3917 | -0.3889 | 0.2093 | 0.2071 | 0.9525 |
| | $\hat{\theta}_I$ | -0.4571 | -0.4088 | 0.2667 | 0.2230 | 0.9720 |
| 0.3 | $\hat{\theta}_F$ | -0.5850 | -0.6132 | 0.4617 | 0.5017 | 0.9475 |
| | $\hat{\theta}_D$ | -0.5715 | -0.5833 | 0.4462 | 0.4660 | 0.9430 |
| | $\hat{\theta}_I$ | -0.7020 | -0.6132 | 0.6170 | 0.5017 | 0.9760 |
| 0.4 | $\hat{\theta}_F$ | -0.7757 | -0.8176 | 0.8138 | 0.8920 | 0.9445 |
| | $\hat{\theta}_D$ | -0.7646 | -0.7777 | 0.7972 | 0.8284 | 0.9425 |
| | $\hat{\theta}_I$ | -0.9824 | -0.8176 | 1.1865 | 0.8920 | 0.9755 |
| 0.5 | $\hat{\theta}_F$ | -0.9437 | -1.0219 | 1.2001 | 1.3937 | 0.9505 |
| | $\hat{\theta}_D$ | -0.9382 | -0.9721 | 1.1909 | 1.2944 | 0.9485 |
| | $\hat{\theta}_I$ | -1.2599 | -1.0219 | 1.9117 | 1.3937 | 0.9820 |
| 0.6 | $\hat{\theta}_F$ | -1.1588 | -1.2263 | 1.7660 | 2.0069 | 0.9580 |
| | $\hat{\theta}_D$ | -1.1623 | -1.1666 | 1.7742 | 1.8639 | 0.9580 |
| | $\hat{\theta}_I$ | -1.6088 | -1.2263 | 3.0227 | 2.0069 | 0.9915 |
| 0.8 | $\hat{\theta}_F$ | -1.4868 | -1.6351 | 2.9398 | 3.5678 | 0.9495 |
| | $\hat{\theta}_D$ | -1.5169 | -1.5554 | 3.0291 | 3.3135 | 0.9535 |
| | $\hat{\theta}_I$ | -2.2552 | -1.6351 | 5.8382 | 3.5678 | 0.9915 |
| 1.0 | $\hat{\theta}_F$ | -1.8407 | -2.0439 | 4.4785 | 5.5747 | 0.9555 |
| | $\hat{\theta}_D$ | -1.9111 | -1.9443 | 4.7305 | 5.1774 | 0.9615 |
| | $\hat{\theta}_I$ | -3.0114 | -2.0439 | 10.128 | 5.5747 | 0.9970 |
| 1.5 | $\hat{\theta}_F$ | -2.5670 | -3.0658 | 8.8510 | 12.543 | 0.9490 |
| | $\hat{\theta}_D$ | -2.7854 | -2.9164 | 9.8985 | 11.649 | 0.9630 |
| | $\hat{\theta}_I$ | -4.9163 | -3.0658 | 26.042 | 12.543 | 0.9990 |
| 2.0 | $\hat{\theta}_F$ | -3.2363 | -4.0878 | 13.940 | 22.299 | 0.9475 |
| | $\hat{\theta}_D$ | -3.6868 | -3.8885 | 16.659 | 20.710 | 0.9710 |
| | $\hat{\theta}_I$ | -6.9898 | -4.0878 | 51.426 | 22.299 | 0.9990 |

## 6. Shelf-Life Estimation Under Batch-To-Batch Variation

Drug products are usually manufactured in batches. The values of $\alpha$ and $\beta$ in (1.1) may be different for different batches, referred to as batch-to-batch variation. The FDA requires testing of at least three batches, preferably more, in any stability analysis to account for this variation so that a single estimated shelf-life can be used for all future drug products. Some procedures for testing

batch-to-batch variation are proposed in Shao and Chow (1994). If there is no batch-to-batch variation, then the results in Sections 2-4 can be applied after combining data from different batches.

When there is batch-to-batch variation, the batches used in a stability study should constitute a random sample from the population of all future batches. Since a single estimated shelf-life should be applicable to all future batches, it is more appropriate to treat the batch-to-batch variation as a random effect. Suppose that there are $k$ batches in a stability study. Let

$$y_{ij} = \alpha_i + \beta_i x_{ij} + e_{ij} \tag{6.1}$$

be the $j$th assay result at time $x_{ij}$ for the $i$th batch, $j = 1, \ldots, n$, $i = 1, \ldots, k$. The shelf-life for the $i$th batch is $\theta_i = (\alpha_i - \eta)/\beta_i$. Let $(\alpha_0, \beta_0)$ be the regression parameters for a future batch. Then the shelf-life for the future batch is $\theta_0 = (\alpha_0 - \eta)/\beta_0$. If $\alpha_i$'s and $\beta_i$'s are random variables, then $\theta_0$ is random and a 95% lower prediction bound for $\theta_0$ should be considered as a shelf-life estimator.

Assume that $(\alpha_i, \beta_i)$, $i = 0, 1, \ldots, k$, are independent and have a bivariate normal distribution $N((\alpha, \beta), \Sigma)$ with $\beta < 0$ and the second component truncated at 0 (so that all $\beta_i$'s are negative). In practice, this truncation has a negligible effect if $|\beta|$ is more than 4 times the standard deviation of $\beta_i$. Shao and Chen (1997) derived the following approximate ($n \to \infty$ or $\sigma \to 0$) 95% lower prediction bound as a shelf-life estimator: $\hat{\theta}_{SC} = \inf\{x \geq 0 : \tilde{L}(x) \leq \eta\}$ with $\tilde{L}(x) = \hat{\alpha} + \hat{\beta}x - \rho_k\sqrt{v_{11} + 2v_{12}x + v_{22}x^2}$. Here $(\hat{\alpha}, \hat{\beta})$ is the average of $(\hat{\alpha}_i, \hat{\beta}_i)$, $i = 1, \ldots, k$, and $(\hat{\alpha}_i, \hat{\beta}_i)$ is the least squares estimator of $(\alpha_i, \beta_i)$ under (6.1) for fixed $i$; $v_{ij}$ is the $(i, j)$th element of the matrix

$$V = \frac{1}{k(k-1)} \begin{pmatrix} \sum_{i=1}^k (\hat{\alpha}_i - \hat{\alpha})^2 & \sum_{i=1}^k (\hat{\alpha}_i - \hat{\alpha})(\hat{\beta}_i - \hat{\beta}) \\ \sum_{i=1}^k (\hat{\alpha}_i - \hat{\alpha})(\hat{\beta}_i - \hat{\beta}) & \sum_{i=1}^k (\hat{\beta}_i - \hat{\beta})^2 \end{pmatrix};$$

$\rho_k$ is the 95th percentile of the random variable $T_k(U)$ with $U$ being a uniform (0,1) random variable, $T_k(u)$ being the non-central t-random variable with $k-1$ degrees of freedom and non-centrality parameter $\sqrt{k}\Phi^{-1}(1-u)$ (for any given $u$), $\Phi$ being the standard normal distribution function (values of $\rho_k$ are listed in Shao and Chen (1997)). That is, for the future shelf-life $\theta_0$, $P(\hat{\theta}_{SC} \leq \theta_0) \approx 0.95$ as $n \to \infty$ or $\sigma \to 0$, where $P$ is the joint probability of $\hat{\theta}_{SC}$ and $\theta_0$.

Using the argument of Section 2, we find

$$\hat{\theta}_{SC} = \frac{(\eta - \hat{\alpha})\hat{\beta} + \rho_k^2 v_{12} - \sqrt{[(\eta - \hat{\alpha})\hat{\beta} + \rho_k^2 v_{12}]^2 - (\hat{\beta}^2 - \rho_k^2 v_{22})[(\eta - \hat{\alpha})^2 - \rho_k^2 v_{11}]}}{\hat{\beta}^2 - \rho_k^2 v_{22}}.$$

The exact bias of $\hat{\theta}_{SC}$ is $E(\hat{\theta}_{SC} - \theta_0)$, which does not have a simple form. We may use the following measure of closeness of $\hat{\theta}_{SC}$ to $\theta_0$:

$$\frac{(\eta-\alpha)\beta + \rho_k^2\bar{v}_{12} - \sqrt{[(\eta-\alpha)\beta + \rho_k^2\bar{v}_{12}]^2 - (\beta^2-\rho_k^2\bar{v}_{22})[(\eta-\alpha)^2 - \rho_k^2\bar{v}_{11}]}}{\beta^2-\rho_k^2\bar{v}_{22}} - \frac{\eta-\alpha}{\beta}, \tag{6.2}$$

which is obtained by replacing random variables in $\hat{\theta}_{SC}-\theta_0$ by their expectations, where $\bar{v}_{ij}$ is the $(i,j)$th element of the matrix

$$E(V) = \frac{1}{k}\left[\Sigma + \frac{\sigma^2}{k}\sum_{i=1}^{k}\begin{pmatrix} n & \sum_{j=1}^n x_{ij} \\ \sum_{j=1}^n x_{ij} & \sum_{j=1}^n x_{ij}^2 \end{pmatrix}^{-1}\right].$$

As $\sigma \to 0$ and $\Sigma \to 0$ (which means that the variance matrix $\Sigma$ for the random batch effects is relatively small compared with the mean $(\alpha, \beta)$), the quantity in (6.2) simplifies to the asymptotic bias of $\hat{\theta}_{SC}$, which is

$$-\beta^{-2}\rho_k\sqrt{\bar{v}_{11}\beta^2 - 2\bar{v}_{12}(\eta-\alpha)\beta + \bar{v}_{22}(\eta-\alpha)^2}.$$

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