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STATISTICAL ANALYSIS OF PHARMACEUTICAL STABILITY DATA

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SUMMARY

A method is presented for establishing the shelf-life for a pharmaceutical product using data from long-term stability studies. The method utilizes the work of Fuller and Battese (1973). An example is given which illustrates the use of the method with a set of pharmaceutical stability data.

1. INTRODUCTION

Modern pharmaceutical products must bear an expiration date, usually a fixed period of time from the date of manufacture. The legal requirement is stated in the Current Good Manufacturing Practices Regulations (1978). These regulations state that the expiration date must be based on stability studies and that "valid estimates of stability" must be obtained based on statistical criteria. Stability studies must include studies of the marketed pharmaceutical product in which the manufacturer retains samples of several batches and tests each batch at regular intervals according to a written stability testing protocol. In a typical stability study a batch would be tested at time of manufacture, then at least once per year until the expiration date. The testing would include assays of the active ingredients and a number of other chemical and physical tests designed to assess the stability of the product. In these studies, the product is stored according to the conditions specified on the product labeling. The purpose of this paper is to present a statistical method for establishing an expiration period or shelf-life for pharmaceutical products which has advantages over other methods currently available. The shelf-life is the period of time between the date of manufacture and the expiration date. The method utilizes the one-fold nested-error model of Fuller and Battese (1973).

2. TWO CURRENTLY AVAILABLE METHODS

2.1 Prediction Interval Method

This method is described by Carstensen and Nelson (1976). An ordinary linear regression model is used to estimate potency as a

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function of age, the date of manufacture being zero. Then one computes the prediction interval belt or envelope on a future assay or mean assay. This well-known procedure is described in Snedecor and Cochran (1967). The shelf-life estimate is the age at which the lower limit of the prediction interval envelope reaches the lower specification or compendial limit for the product potency. See Figure 1.

This method is reasonable when the manufacturing process producing the product can be controlled so that each batch has very nearly the same initial potency. When significant batch to batch variation exists, however, this method leads to biased estimates for the rate of loss of potency and hence to improper prediction intervals. (To appreciate the amount of bias which could be introduced, referring to Figure 1, suppose data were added on a second batch having an age of 1 unit and a mean potency of 95 percent label. The addition of this data would lead to an upward bias in the estimated slope or equivalently a downward bias in the estimated loss rate.) Furthermore, this method fails to address the expiration dating of batches for which the initial potency is below historically established limits, derived from analyses of data on previously produced batches.

2.2 Confidence Bound Method

This method is described by Haynes et al (1959). Norwood (1980) and Dykstra (1980) also discuss this method. One fits an analysis of covariance model using batches as "treatments" and age as the covariate. Attention is centered on the covariate; the batch effects are nuisance parameters. First one estimates the rate of loss of potency (age effect) and places an upper confidence bound on this loss rate. Then assuming the actual rate of loss equal to the upper confidence bound, one can establish an expiration period corresponding to a minimum acceptable initial potency or release limit. The release limit is the lowest initial potency required for a batch of a drug product to be released for sale. (The release limit is always higher than the lower specification or compendial limit since the batch must remain above the lower specification or compendial limit for its entire expiration period.) For example, suppose the upper confidence bound for the rate of loss is 2 percent per year, the release limit is 95 percent, and the lower specification or compendial limit is 90 percent of labeled potency. Then the expiration period would be 2.5 years. Conversely, one can start with a desired expiration period of 3 years and establish the associated release limit, 96 percent.

It is assumed that the manufacturer performs adequate testing to assure compliance with the release limit. The issue of what constitutes adequate testing is not addressed here.

Two key assumptions in this analysis and in the previous one are: independent, identically distributed residuals and no batch by age interaction. This analysis does not require the initial batch potencies to be equal; whereas in the previous analysis (2.1), this was an important assumption.

3. THE NESTED-ERROR STRUCTURE

3.1 Rationale

While estimating the rate of loss along with an upper confidence bound is a useful approach to the analysis of pharmaceutical

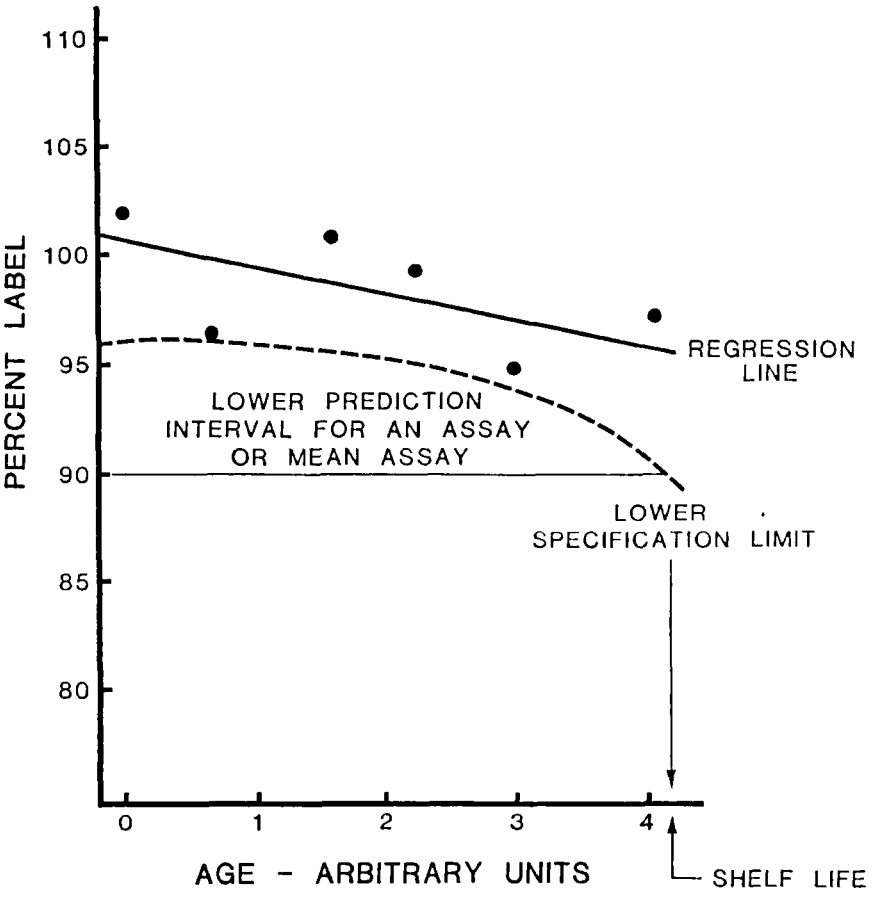

Figure 1. PREDICTION INTERVAL METHOD

stability data, in many cases the usual analysis of covariance model does not fit the data adequately. Figure 2 shows the typical pattern of variability. The assays are grouped by age with the mean assay at each age determined by a linear effect of age plus group to group (age to age) variation. The group to group variation is due to the fact that each group of assays was performed at the same time by the same analyst using the same instruments and reagents. This error structure is well-known to chemists; see for example Youden and Steiner (1975), who give an excellent description of the pattern of variability of data from analytical chemistry laboratories.

3.2 Proposed Method

We propose the confidence bound approach of 2.2 using the one-fold nested-error model of Fuller and Battese (1973) instead of the ordinary ANCOVA model. The proposed model, which differs from that model only in the error terms, is given below:

$$Y_{ijk} = \mu_i - x_{ij\gamma} + \delta_{ij} + \varepsilon_{ijk} \quad (1)$$

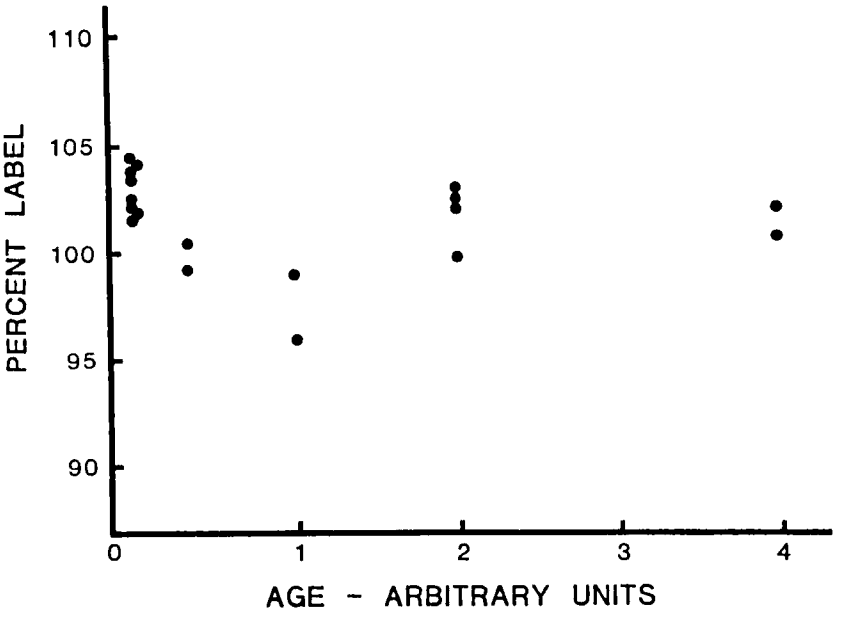

Figure 2. STABILITY DATA ON A TYPICAL BATCH

$(i = 1, \ldots, b;\ j = 1, \ldots, r_i;\ k = 1, \ldots, n_{ij})$

where Y_{ijk} is the k^{th} assay at the j^{th} test point for the i^{th} batch,

μ_i is the initial potency for the i^{th} batch, assumed to be a fixed effect,

x_{ij} is the age at the j^{th} test point for the i^{th} batch,

γ is the rate of loss of potency,

δ_{ij} is the error component associated with the ij^{th} batch, age combination, $\delta \sim N(0,\sigma^2_\delta)$, and

ε_{ijk} is the error component within a batch, age combination, $\varepsilon \sim N(0,\sigma^2)$.

The error components δ and ε are distributed independently of each other. We assume that all samples at each batch, age combination are assayed at the same time and comprise a distinct analytical determination or instrument run. The data would consist of $r_1 + r_2 + \ldots + r_b = r$ "runs". This is usually a reasonable assumption in a laboratory.

3.3 Fitting the Model

To estimate the rate of loss, we fit the model (1) following Fuller and Battese (1973). Express the model in matrix notation separating the random and fixed effects,

$$Y = X\beta + Z\delta + \varepsilon \qquad (2)$$

where Y_{nx1} is the vector of assays, $n = \sum_i \sum_j n_{ij}$,

$X_{nx(b+1)}$ is the design matrix for the fixed effects,

$\beta_{(b+1)x1} = [\mu 1, \mu 2, \ldots, \mu b, \gamma]'$ is the fixed effect parameter vector,

Z_{nxr} is the design matrix of random "run" effects,

δ_{rx1} is the vector of random "run" effects, and

ε_{nx1} is the within-run error vector.

In order to estimate the rate of loss using this model, we derive the generalized least squares estimator for the rate of loss. This is done by applying a transformation (to be derived) to both sides of (2), then performing linear regression on the transformed variables.

Since

$$Y \sim N(X\beta, ZZ'\sigma_\delta^2 + I_n\sigma^2),$$

let

$$V_{nxn} = \mathrm{Var}(Y)/\sigma^2$$

$$= ZZ'\,\sigma_\delta^2/\sigma^2 + I_n, \text{ where } I_n \text{ is an identity matrix of dimension } n.$$

Then the generalized least squares estimator for β is

$$(X' V^{-1} X)^{-1} X' V^{-1} Y$$

which may be approximated by

$$\hat{\beta} = (X' \hat{V}^{-1} X)^{-1} X' \hat{V}^{-1} Y$$

where $\hat{V}$ is the covariance matrix for Y divided by σ^2, with σ_δ^2 and σ^2 estimated from the data. Note that $\hat{V}$ is obtained from V by substituting variance component estimates, calculated as shown in section 3.4.

The estimator $\hat{\beta}$ can be derived by ordinary least squares regression of $\hat{T}Y$ on $\hat{T}X$ where

$$\hat{T} = \hat{V}^{-1/2}.$$

Following Fuller and Battese (1973) T can be shown to be a block diagonal matrix

$$T = \mathrm{Diag}(T_{ij})$$

where

$$T_{ij} = I_{n_{ij}} - \left\{1 - [\sigma^2/(\sigma^2 + n_{ij}\,\sigma_\delta^2)]^{1/2}\right\} J_{n_{ij}}/n_{ij} \text{ and}$$

$J_{n_{ij}}$ is a square matrix of 1's with dimension n_{ij}.

3.4 Estimating the Variance Components

Fuller and Battese (1973) recommend Henderson's "fitting of constants" method discussed by Searle (1971). There are other methods available and no "best" method has been identified. To use the "fitting of constants" method, first estimate σ^2 using the mean square within runs. Then compute the residual mean square from regression of Y on X, set it equal to its expectation,

$$\sigma^2 + \left\{n - \mathrm{tr}[Z' X (X'X)^{-1} X'Z]\right\} \sigma^2_\delta/(n-b-1),$$

and solve for σ^2_δ. The non-negative estimator for σ^2_δ should be used. Note that if the estimate for σ^2_δ is zero, the estimator for γ is the ANCOVA estimator. On the other hand if the estimate for σ^2_δ is large relative to that for σ^2, the estimator for γ approximates the estimator obtained from ANCOVA on the run means.

4. EXAMPLE

Table I shows a set of stability data on a pharmaceutical product. The ages have been transformed to arbitrary units, but the pattern of variability has been preserved.

The standard ANCOVA estimate for the rate of loss is 0.65 percent per age unit with a standard error of 0.31 percent per age unit (62df). The proposed method yields a rate of loss estimate of 0.50 percent per age unit with a standard error of 0.64 percent per age unit. The estimates for σ^2_δ and σ^2 are 5.2 and 2.6 respectively.

Note that the standard error is considerably larger with the proposed method. We assign r-b-1 = 9 degrees of freedom for the standard error which corresponds to the residual degrees of freedom from ANCOVA on the run means.

Assuming a 3 age unit expiration period and a lower specification or compendial limit of 90 percent, the minimum acceptable initial potency is 93.5 percent of label by the ANCOVA method and 95.0 percent of label by the proposed method, using an upper 95 percent confidence bound on the rate of loss.

5. SUMMARY

We have presented a method for establishing the shelf-life for a pharmaceutical product, together with associated limits on the minimum acceptable initial potency. The method of Fuller and Battese (1973) is utilized to obtain an upper confidence limit for the rate of loss of potency, recognizing the nested-error structure of the data. Using this confidence limit, the initial potency limit is derived from the desired shelf-life, or the shelf-life is derived from a desired initial potency limit.

The assumption of negligible batch by age interaction is usually reasonable but should be checked. A batch by age interaction test could be performed after fitting the model (1) with an additional fixed effect term for interaction. Since rates of loss of potency are usually less than 1 percent per year, however, this test often has low power. A plot of the data is usually at least as effective in revealing interaction as a test of hypothesis.

TABLE 1

STABILITY DATA FOR THREE BATCHES
UNITS: PERCENT OF LABELED QUANTITY

AGE Arbitrary Units	BATCH A	BATCH B	BATCH C
0	100.4 100.0 100.4 100.1		105.6 101.6 103.8 104.8 103.0 102.6 103.2 103.8 98.8 98.0 103.4 104.0 100.4 104.2 101.2 103.8
0.5	97.1 96.4 96.8 99.0	98.1 97.4 98.1 97.4	96.0 101.8
2.0	96.5 94.4 95.1 91.7 94.5 93.2	96.4 96.8 96.6 96.8	98.6 98.0 99.8 98.0
2.5	100.0 98.1 98.0 95.9 98.3 101.7	93.2 95.2 93.3 94.9	
3.0	97.2 97.5 99.9 101.1	100.0 100.8 100.1 100.0	
3.5		96.4 95.8 95.8 94.9	

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