Assessment of Shelf-Life Equivalence of Pharmaceutical Products

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An alternative method to an analysis of variance (ANOVA)for assessing stability variation among batches, packaging, or formulations is proposed. The new method assesses the shelf-life equivalence based on the range of the shelf-life estimate obtained for each product of a given batch, packaging, or formulation. The power of this analysis was not significantly affected by assay error, whereas that of ANOVA decreased markedly as assay error increased. Therefore, the proposed method does not exhibit a tendency to overlook stability variation from stability data of a larger assay error as does ANOVA. If the critical point is assumed to be 15% of the largest shelf-life estimate, 25% stability variation can be detected at a probability of more than 80% for degradation faster than 0.2%/month. When smaller stability variation is desired to be detected, the critical point must be smaller than 15%.

Key words stability variation; shelf-life equivalent; range

The ICH Tripartite guideline of stability testing for new drug substances and products[1] describes that if batch to batch variation is small, stability data from several batches can be combined into one overall estimate in order to determine the shelf-life of a pharmaceutical product in which quantitative characteristics decrease with time. This can be performed if batch-variation is not found to be significant according to appropriate statistical tests. A similar situation involves the case in which the shelf-life of a pharmaceutical product of different packaging and formulations is estimated by matrixing, which is described in the ICH Tripartite guideline as an experimental design for reducing the number of stability data. Stability variation among packaging and formulations should be assessed before combining stability data from different packaging and formulations into one overall estimate. One method for assessing stability variation among batches, packaging, or formulations, is an analysis of variance (ANOVA). However, the power of ANOVA depends largely on the assay error, such that it decreases markedly with increasing error.[2,3] A notable disadvantage of ANOVA is the increasing difficulty in detecting stability variation among batches, packaging, or formulations from stability data with larger assay error.

In the present study, another method for assessing stability variation among batches, packaging, or formulations is proposed, in which the effect of assay error on the power of analysis is less than that of ANOVA. In the proposed method, shelf-life equivalence is assessed based on the range of the shelf-life estimates obtained for all batches, packaging or formulations. The relationship between the power of analysis and assay error is discussed.

Experimental

Stability data from three batches (or packaging, or formulations) were generated using the Monte Carlo method under the assumption that degradation of a drug product can be described by zero-order kinetics. The slope of the degradation curve was assumed to be either 0.2% or 0.7%/month. A 0%, 10% or 25% larger slope was assumed for one of the three batches. For example, the slope was 0.2%/month for two batches and 0.25%/month for the remaining batch in the case of 0.2%/month degradation and 25% stability difference. Theoretical drug content was determined from these degradation curves at 0, 3, 6, 9, 12, 18, 24 and 36 months, and expressed as a percentage of the content at time zero. Random numbers selected from a normal distribution with a mean of zero and a standard deviation ranging from 0.5% to 2.0% were added to the theoretical data in order to obtain experimental data with an assay error.

The shelf-life (the 95% lower confidence limit of the time when the regression curve intersected 90%, t_{90}) of each batch was calculated using Woolfe's equation,[4] and the range of three t_{90} estimates (the difference between the largest and smallest of three estimates) was calculated. Five hundred values of range were obtained from 500 data sets.

Generation of experimental data and calculation of shelf-life were performed using BASIC programs.

Results and Discussion

Figure 1 shows a typical set of stability data from the three batches. The average and standard deviation of 500 t_{90} estimates obtained for the product having the smallest t_{90} (batch, packaging or formulation) of each set are shown in Fig. 2 as a function of assay error. For degradation of 0.7%/month, which corresponds to approximately 1 year of t_{90}, t_{90} could be estimated even at an assay error of 2.0%. In contrast, the t_{90} estimate for slower degradation of 0.2%/month, which corresponds to approximately 3 years of t_{90}, exhibited very large standard deviation at an assay error of 2.0%.

Figures 3 and 4 show the distribution of the range of t_{90} estimates for the three batches obtained for each of

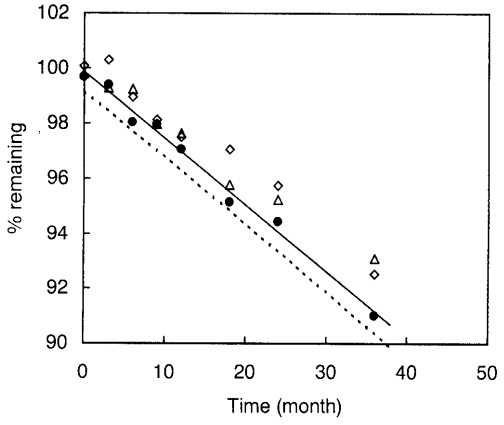

Fig. 1. An Example of the Degradation Time Course of Three Batches

●: batch having the smallest t_{90}; △: batch having the largest t_{90}; ◇: batch having medium t_{90}. Assay error (standard deviation): 0.5%. Degradation: 0.2%/month for two batches and 0.25%/month for the remaining batch (stability variation of 25%). ——:linear regression curve for batch having the smallest t_{90}. – – –: 95% significance limit for batch having the smallest t_{90}.

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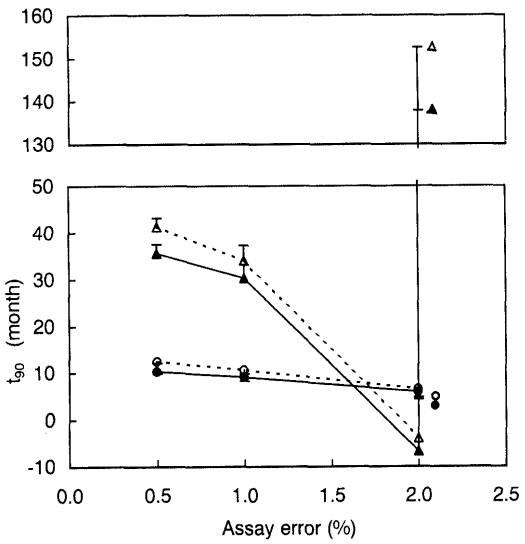

Fig. 2. Effect of Assay Error on t_{90} Estimate of Batch Having the Smallest t_{90}

Stability variation: 0% (--△--○--) and 25% (—▲—●—). Degradation: 0.2 (△▲) and 0.7 (○●) %/month. Bars represent standard deviation.

500 data sets, for degradation of 0.2% and 0.7%/month, respectively. In the case of 0.2%/month degradation and an assay error of 0.5% (Fig. 3A), the 20% point of the distribution was approximately 7 months when there was 25% stability variation among the batches, packaging or formulations. The value of 7 months corresponds to 15% of the average of 500 t_{90} estimates obtained for the product having the largest t_{90} estimate. In other words, 25% stability variation can be detected at a probability of approximately 80%, if the critical point is assumed to be 15% of the largest of the three t_{90} estimates. In this case, the probability of falsely determining that the variation was not significant (β-error) was approximately 20%, and the probability of falsely determining that the variation was significant (α-error) was also approximately 20%.

The distribution of the range for 25% stability variation becomes much closer to that for the case when there is no stability variation among batches, packaging or formulations, as assay error increases (Figs. 3A, B and C).

As degradation becomes faster (0.7%/month), the

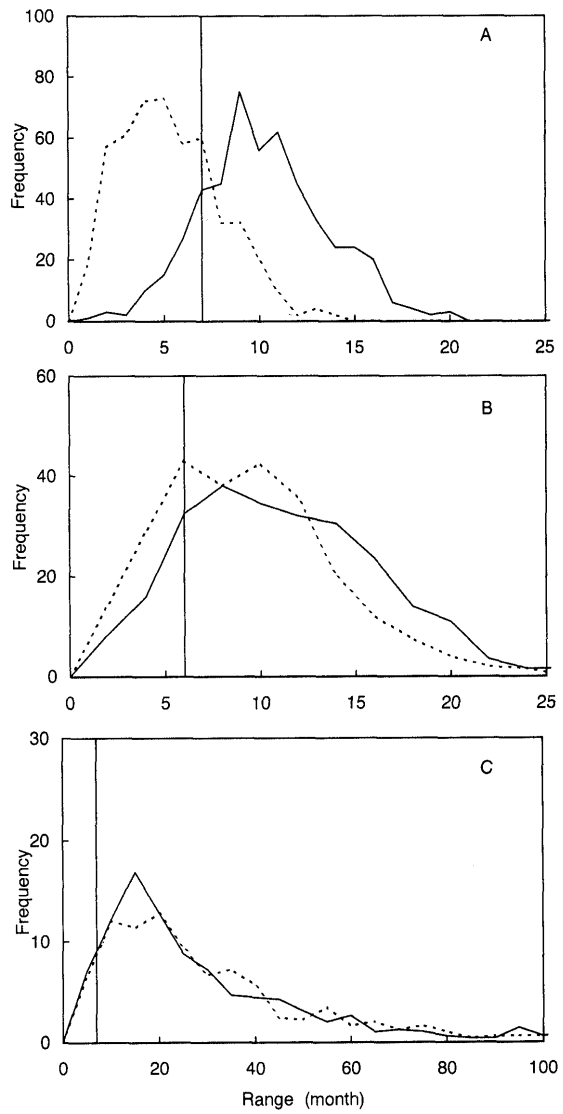

Fig. 3. Distribution of Range of t_{90} Estimates for 0.2%/month Degradation

Assay error: 0.5 (A), 1.0 (B), and 2.0% (C). Stability variation: 0% (---) and 25% (——). Bars represent the 20% point of the distribution for 25% stability variation.

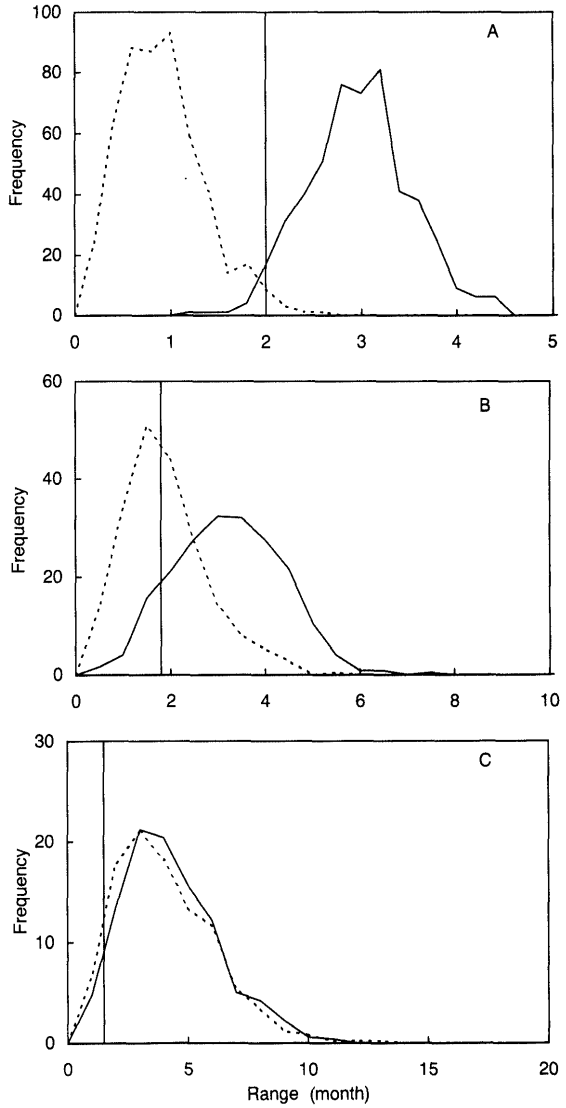

Fig. 4. Distribution of Range of t_{90} Estimates for 0.7%/month Degradation

Assay error: 0.5 (A), 1.0 (B), and 2.0% (C). Stability variation: 0% (---) and 25% (——). Bars represent the 20% point of the distribution for 25% stability variation.

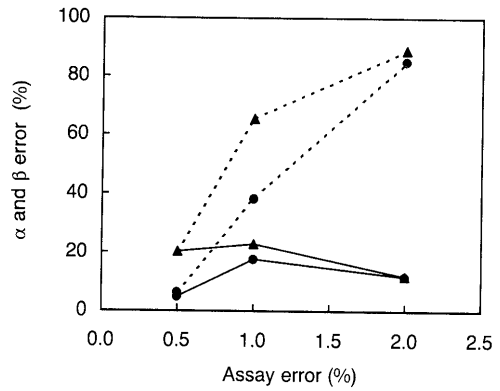

Fig. 5. Effect of Assay Error on α- (---) and β-Error (——)

Degradation: 0.2 (▲) and 0.7 (●) %/month. Stability variation: 25%. Critical point: 15% of the largest t_{90} estimate.

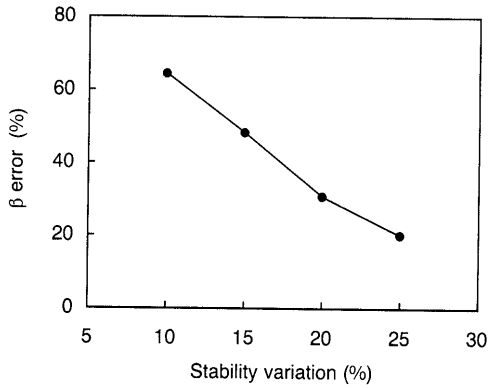

Fig. 6. Dependence of β-Error on Stability Variation

Degradation: 0.2%/month. Assay error: 0.5%. Critical point: 15% of the largest t_{90} estimate.

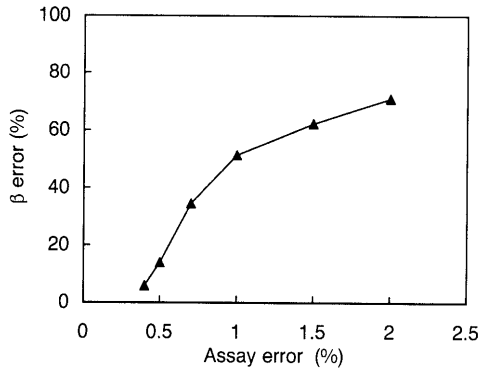

Fig. 7. Effect of Assay Error on β-Error in ANOVA Analysis

Degradation: 0.2%/month. Stability variation: 25%. Significance level: 0.25.

difference in the distribution of the range between 25% and 0% stability variation becomes larger, as shown in Figs. 4A, B and C. If the critical point is assumed to be 2 months, that is, 15% of the average of 500 t_{90} estimates obtained for the product having the largest t_{90}, the β-error becomes less than 20% at assay errors of 0.5, 1.0 and 2.0%.

The effect of assay error on α-error and β-error is shown in Fig.5. As the assay error increases, the α-error increases markedly, while the increase in β-error is less pronounced. This finding indicates that 25% stability variation can be detected with a β-error of less than 20% for degradation faster than 0.2%/month if the critical point is specified to be 15% of the largest of the three estimates. However, when stability variation of less than 25% is assessed by this method, the β-error becomes larger than 20%, as shown in Fig. 6.

In conclusion, shelf-life equivalence among different batches, packaging, and formulations can be assessed based on the range of all the t_{90} estimates obtained. The β-error of this analysis was not pronouncedly increased by increased assay error (Fig. 5). As shown in Fig. 7, which was reported in a previous paper,[2] ANOVA exhibited a marked increase in β-error that resulted from increased assay error. Therefore, ANOVA has a tendency to overlook stability variations from stability data with a larger assay error. In contrast, the proposed method for assessing stability equivalence based the range of t_{90} estimates has a power which is not significantly affected by assay error. If the critical point is assumed to be 15% of the largest estimate, then the 25% stability variation can be detected with a β-error of less than 20% for degradation faster than 0.2%/month. When smaller stability variation is desired to be detected, the critical point must be smaller than 15%.

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