Determination of Release Limits: A General Methodology

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Received October 24, 1990; accepted March 27, 1991

Release limits of drug dosage forms are defined as the bounds on the potency at which an individual lot can be released for marketing which will ensure that it remains within registered limits throughout its shelf life. A statistically based method is described for calculating release limits for any type of dosage form and any parameter for which the rate of change with time is predictably uniform and linear. When the mean release assay result for a specific product lot is at or within the calculated release limit bounds, assurance is provided at the specified confidence level that the average assay results obtained at any subsequent time within the shelf life will remain within registered limits.

KEY WORDS: release limits; average slope; expiration dating; batch release; covariance analysis; Satterthwaite approximation.

INTRODUCTION

All products are required to remain within registered limits throughout their shelf life. For the case where potency is the limiting factor, the degradation rate determined from the results of stability studies conducted during the development phase is used to establish the initial expiration dating period for the product. The expiration dating period (and the degradation rate) are then refined based on the results of postapproval stability studies. The ability of an individual lot to remain within registered limits throughout its assigned shelf life is directly related to its initial potency. Therefore, an objective method for setting a limit on initial potency is needed.

DISCUSSION

Of primary concern in the assignment of a shelf life to an individual product lot is the level of confidence that it will remain within its registered limits during that time period. For physical attributes such as appearance and dissolution, prior stability experience will indicate whether changes may be anticipated, but it is either difficult or impossible to develop a model to predict the change accurately. The level of confidence in these cases is based on experience under accelerated and label storage conditions as well as a sound process validation program. For potency changes, on the other hand, a quantitative degradation rate may be determined which can be used to calculate the level of confidence that the lot average will remain within registered limits throughout its shelf life. For the purposes of this paper, the following assumptions are used.

1. Potency is the stability limiting factor.
2. The desired level of confidence, unless otherwise stated, is 95% (one-sided) in accordance with the FDA's stability guidelines (1).
3. The manufacturing process has been validated and the underlying distribution for the potency values is normal or can be approximated by a normal distribution.
4. The potency has a predictable rate of change. (This also includes no change.)
5. The potency change is linear at least through the shelf life for all batches produced by the process. For a loss of potency of the order of 10 to 20%, this assumption is usually valid, regardless of the order of the reaction.
6. The reaction mechanism is the same for all lots and the true rate of change is a constant.
7. The assay is stability indicating (it has been validated with regard to specificity, ruggedness, and linearity).

There are a number of factors which must be considered to ensure, with at least 95% confidence, that potency remains within its registered limits during the shelf life. For the simplest case, consider a product for which no changes are expected for any attribute.

Case I: Products with No Degradation

In order to ensure that the potency will remain within registered limits over the shelf life, it is necessary only to determine, with 95% confidence, that the true potency upon release is within the registered limits. The lowest potency at which a lot could be released under these conditions may be defined as the lower release limit. The calculation in this case is very simple and straightforward as shown in Eq. (1).

$$\mathrm{LRL} = \mathrm{LR} + t \times \frac{S}{\sqrt{n}} \tag{1}$$

where

LRL = lower release limit
LR = lower registration limit
S = assay standard deviation
DF = degrees of freedom for S
t = 95% confidence (one-sided) t-value with DF degrees of freedom
n = number of replicate assays used for batch release

At The Upjohn Company, the assay standard deviation is determined from all assay results obtained from a laboratory standard (a single lot which is tested whenever the assay is run). If no value for assay standard deviation is available, the average residual variation term computed as part of the re-

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0724-8741/91/0900-1210$06.50/0

gression analysis of the stability data may be used. It is composed of the desired assay and sampling variation, but it also includes variation associated with how well the linear model fits the data, thus providing a somewhat more conservative value for the release limit. In this case, DF would be the number of points minus the number of lots in the regression line minus 1. An upper release limit could also be calculated by subtracting the error term from the upper registration limit (UR).

Case II: Products with Degradation

A slightly more complex case is that given by a product, such as a tablet, which exhibits a significant degradation rate. For this case, a measure of the degradation rate and its associated variability is needed in order to calculate a lower release limit. To obtain these, the stability data are analyzed using standard covariance analysis techniques. It is outside the scope of this paper to describe the methods which could be used to select lots and perform testing for poolability. We use the average slope instead of the pooled slope because the pooled slope is influenced by the intercepts of the individual lots.

Since the release assay results and the average slope are independent measurements, the uncertainties due to the variation associated with the mean release assay result and the average slope may be added in quadrature as shown in Eq. (2) and illustrated in Fig. 1 (2).

$$\mathrm{LRL} = \mathrm{LR} - EAC_T + t \times \sqrt{S_T^2 + \frac{S^2}{n}} \qquad (2)$$

where

EAC_T = average slope of tablet * shelf life (This term is negative when describing degradation of an active ingredient.)

S_T = standard error of average slope * shelf life (standard error of EAC_T)

t = 95% confidence (one-sided) t value with DF degrees of freedom

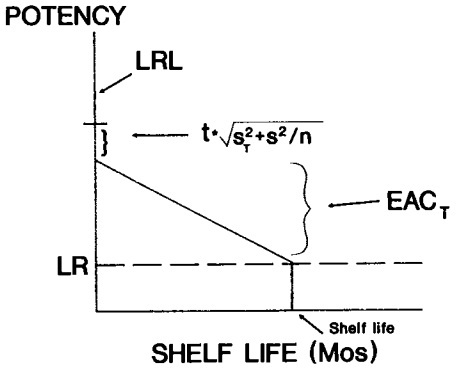

Fig. 1. Case II: products with degradation.

The degrees of freedom used to determine t may be calculated by the Satterthwaite approximation (3) as shown below.

$$\mathrm{DF} = (V_1 + V_2)^2 \Big/ \left(\frac{V_1^2}{\mathrm{DF}_1} + \frac{V_2^2}{\mathrm{DF}_2}\right)$$

where V_1,DF_1 and V_2,DF_2 are the variance and degrees of freedom associated with the assay and the average slope, respectively, and all other terms are as defined for Eq. (1).

Note: An upper release limit could be calculated by Eq. (2), subtracting the error term from the upper registration limit (UR). This would, however, not be meaningful unless the average slope is positive.

A release limit calculation of this type is shown as example A.

Example A

Consider tablet X with the following parameters:

LR = 90% of label
S = 1.1% of label
average slope = −0.20% of label/month
standard error of average slope = 0.03% of label
EAC_T = −4.8% of label
S_T = 0.72% of label
n = 2
t = 1.67 (DF = 58)
shelf life = 24 months

$$\mathrm{LRL} = 90 + 4.8 + 1.67 \times \sqrt{0.72^2 + \frac{1.1^2}{2}}$$
$$= 96.6\% \text{ of label}$$

Calculation of the lower release limit without adding the variances in quadrature [i.e., simple addition of the uncertainty of the mean release assay result and the amount of degradation expected over the shelf life (at the 95% one-sided confidence level)] would result in an unnecessarily conservative value (97.3% of label for the example given above). The penalty for this incorrect calculation increases as the error terms become similar in magnitude. (See also Ref. 4.)

Case III: Products Requiring Reconstitution Prior to Use

A more complex case involves a product which must be reconstituted prior to use, in which there are more interdependent factors (both fixed and variable) which must be considered. For a given formulation, manufacturing process, assay method, and stability data base, the fixed and variable factors are given in Table I.

In similar fashion to the case described above, the release assay results and the average slopes of the dry powder and the reconstituted solution are independent measurements, allowing the addition in quadrature of the variances

Table I. Fixed and Variable Factors for Products Requiring Reconstitution Before Use

Fixed factors
• Dry powder degradation rate
• Reconstituted solution degradation rate
• Variances associated with the dry powder degradation rate, the reconstituted solution degradation rate, and the mean release assay result
Variable factors
• Dry powder shelf life
• Reconstituted solution shelf life
• Number of replicate release assay results

associated with these measurements. The lower release limit for this case may be calculated by Eq. (3) and is illustrated by Fig. 2.

$$LRL = LR - EAC_P - EAC_S + t \times \sqrt{S_P^2 + S_S^2 + \frac{S^2}{n}} \quad (3)$$

where

EAC_P = average slope of dry powder * shelf life (dry powder)

S_P = standard error (SE) of average slope of dry powder * shelf life (standard error of EAC_P)

EAC_S = average slope of reconstituted solution * shelf life (reconstituted solution)

S_S = standard error of average slope of reconstituted solution * shelf life (standard error of EAC_S)

The degrees of freedom used to determine t may be calculated by the Satterthwaite approximation (3) as shown below.

$$DF = (V_1 + V_2 + V_3)^2 \Big/ \left(\frac{V_1^2}{DF_1} + \frac{V_2^2}{DF_2} + \frac{V_3^2}{DF_3}\right)$$

where V_1,DF_1, V_2,DF_2, and V_3,DF_3 are the variance and degrees of freedom associated with the assay, the average slope of the dry powder, and the average slope of the reconstituted solution, respectively, and all other terms are as previously defined.

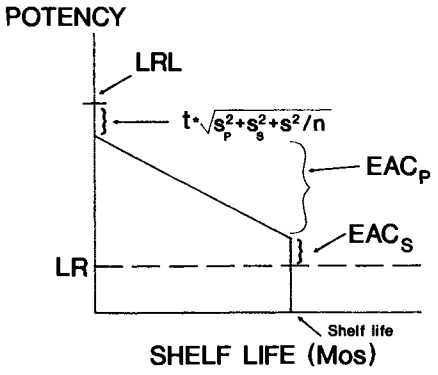

Fig. 2. Case III: products requiring reconstitution prior to use.

Note: An upper release limit may be calculated in a manner analogous to that shown for Eq. (2).

It is readily apparent that the release limit represents a balance between all of the variable factors. For a given release limit, a change in one of the variables requires a counterbalancing change in one or more of the others. Conversely, a change in one of the variables, with all others held constant, will cause a change in the release limit. This is illustrated in example B.

Example B

Consider reconstitutable product Y with the following parameters:

LR = 90% of label

average slope of dry powder = −0.15% of label/month

average slope of reconstituted solution = −0.12% of label/day

SE of average slope of dry powder = 0.02% of label

SE of average slope of reconstituted solution = 0.02% of label

S = 1.0% of label

t = 1.67 (DF = 64)

n = 2

Various combinations of dry powder shelf lives and reconstituted solution shelf lives will result in different release limits as shown in Table II. For example, the combination of a 24-month dry powder shelf life and a 7-day reconstituted solution shelf life results in a 95.9% release limit. Holding the dry powder shelf life constant at 24 months and increasing the reconstituted solution shelf life to 21 days result in an increase in the lower release limit to 97.7%. Conversely, holding the reconstituted shelf life constant at 7 days and increasing the dry powder shelf life to 48 months result in an increase in the lower release limit to 100.0%.

The results from this type of calculation may be combined with process capability data and marketing preferences to determine the optimal combination of shelf-life assignments to be filed in the NDA. This calculation method can also indicate the impact of changes in the fixed factors on the release limit and provide an objective means for focusing attention on the relative benefits possible from in-

Table II. Effect of Variation of Dry and Reconstituted Solution Shelf Life on Release Limit

Shelf life (dry)	Shelf life (reconstituted)		
	7 days	14 days	21 days
24 months	95.9%	96.8%	97.7%
36 months	97.9%	98.8%	99.7%
48 months	100.0%	>100%	>100%

creased assay precision, a more robust formulation, or a more extensive stability data base. In contrast, the current method in the FDA stability guidelines for analyzing stability data to determine a shelf life inappropriately penalizes manufacturing processes and assay methodology which are highly reproducible. As the precision of the data within each lot increases, small differences between lots take on exaggerated statistical significance, decreasing the likelihood that the data from all of the lots will pool.

For releasing individual batches of a marketed product with fixed shelf lives, the primary variable is the number of replicate release assays. This is a particularly important factor in those cases where the standard error of the assay is relatively large. For example, in the case of an assay with a standard error of 5.0% of label, a change from one to four replicates reduces the release limit by as much as 4% of label. Of course, the option is also available to assign a shorter shelf life, which will also reduce the calculated release limit.

Release limits should be reevaluated on a regular basis, since the degradation rates and the various standard deviations will become more refined as the stability data base matures.

It is important to understand that there is an inherent limitation to this method. Since the upper bound of a lower release limit is the theoretical potency of the product when the process is run at nominal values with no variation, it is obvious that the sum of all terms after LR in Eqs. (1), (2), and (3) must be less than theory minus LR (usually 10%). For example, in those cases where the assay has a relatively large variability (e.g., biological or microbiological assays) or the limits are very tight (e.g., bulk drugs), alternate methods may be necessary.

CONCLUSIONS

(1) Release limits are defined as the bounds on the potency at which an individual product lot can be released for marketing which will ensure that it remains within registered limits throughout its shelf life.

(2) A statistically based method is described which is capable of calculating release limits for any type of dosage form and any parameter for which the rate of change with time is predictably uniform and linear.

(3) When the mean release result for a specific product batch is at or within the calculated release limit bounds, assurance is provided at the specified confidence level that the average assay results obtained at any subsequent time within the shelf life will remain within registered limits.

(4) Release limits are dynamic in that they are derived from a number of interdependent variable factors and the influence of each of the variables can be isolated to allow cost-benefit analysis of the impact of changes.

(5) Release limits calculated by this method provide an objective basis for the release of individual product lots.

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