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AN ALTERNATIVE APPROACH TO THE ASSIGNMENT OF EXPIRATION DATES FOR DRUG PRODUCTS

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Label claims equivalent to "Store below 30°C" in all countries of the globe are often the goal of pharmaceutical companies. It is also in the patients' interest that, wherever possible, the longest expiration date which can be fully justified for the environment in which the product is used, is allocated. In some countries this requires assessment of data generated by continuous storage at 30°C. In other countries the claim can be based on continuous storage at 25°C. For most products where such a label claim is likely, there is usually little, if any, difference between data generated at 25°C and 30°C at early timepoints. At later timepoints significant differences may emerge which allow different shelf-lives to be allocated.

This paper describes a technique which allows both claims to be supported statistically without the need to perform parallel testing at both 25°C and 30°C at early timepoints.

INTRODUCTION

The expiration date of a Drug Product is normally determined by estimating the time at which the 95% one-sided lower confidence interval of a quantitative drug characteristic (e.g. assay) intercepts the lower specification limit (1). For Drug Product characteristics which increase with time (e.g. content of related impurities) the 95% one-sided upper confidence limit would be used to estimate the expiration date.

At the point of submission of the regulatory dossier (typically after data at the 12 months time point have been generated) the stability data of the batches on test will be evaluated. If analysis of the data by appropriate statistical tests shows that the stability profiles of all of the batches under examination are

similar, then the data from all batches would be pooled and an overall estimate of expiration date obtained. If the stability data from all of the batches on test cannot be pooled then the overall expiration date will be defined using the data from the least stable batch on test.

Label claims of store below 30°C in all countries of the globe are often the goal of pharmaceutical companies. However it is also in the interest of the patient that, wherever possible, the longest expiration date, which can be fully justified for the environment in which the product is used, is allocated. (This is the principle underlying the international zoning principles).

Currently, practices in some countries require that such a label claim is based on continuous storage at 30°C (with a suitable controlled humidity). In other countries such a label claim can be based on continuous storage at 25°C (and a suitable controlled humidity). Following ICH, in practice, it will still be necessary in many instances to perform stability testing at both 30°C and 60% relative humidity and 25°C and 60% relative humidity for up to 12 months.

For most products where a storage label claim equivalent to room temperature (either "Store below 25°C" or "Store below 30°C" etc., based on assessment of data as described above) it is likely that there is little, if any, difference between the data generated at 25°C and 30°C, particularly at the early time points. However at later time points differences in stability at 25°C and 30°C may emerge which mean that significantly different expiration dates may be allocated on the basis of considering data generated at 25°C rather than 30°C.

One method by which stability data may be assessed and extrapolated to temperatures other than 30°C is to apply the Arrhenius equation which requires stability data at a range of temperatures to be generated. However, the application of this equation is often not valid, particularly for solid dosage forms.

This paper describes a technique whereby the labelling of a drug product to meet all the necessary requirements may be fully supported without the need to perform parallel testing at both 25°C and 30°C throughout life.

SUMMARY

Where a product is extremely stable, samples are stored and tested only at the long term storage condition of 30°C and expiration dates are estimated and confirmed on the basis of data generated at this temperature.

For other products, long term testing samples are placed on store at both 25°C and 30°C. At the early time points, e.g. 3, 6, and 9 months, analysis is performed only at 30°C. At later time points e.g. 12 months and subsequent, testing is performed at 25°C (and possibly also 30°C if required) until the end of life. At the first time point of testing at 25°C, a statistically appropriate number of replicate analyses are performed. Expiration dates are estimated using the data generated at 25°C with the confidence interval being drawn using estimates of data variability from data generated at both 25°C and 30°C (see figure 1). Expiration dates are subsequently confirmed by continuing stability testing at either 25°C alone, if stability data at 30°C are clearly unacceptable, or at both 25°C and 30°C.

DISCUSSION

Occasionally, although a 'Store below 30°C' label claim for all countries is expected to be supported from an evaluation of stability data generated after storage at 30°C, there may be some slight uncertainty when long-term stability studies are initiated whether a label claim based on assessment of data generated after continuous storage at 25°C may lead to a more acceptable expiration date. In these circumstances, it is proposed that for the long-term stability studies, samples of the Drug Product are placed on test at both 30°C and 25°C. Whilst samples are placed on test at both 25°C and 30°C, only samples stored at 30°C are analysed. Samples are also stored at an accelerated condition e.g. 40°C and 75% relative humidity and tested at appropriate times e.g. 3 and 6 months.

Acceptable precision for the particular quantitative Drug Product characteristics which are to be subsequently evaluated must be ensured through a consideration of the number of replicate determinations which must be performed. In general terms, a standard stability protocol will have an equal number of samples analysed at initial, then at 3 monthly intervals for the first year.

At the 12 month time point, or at the point of submission of the regulatory dossier, stability data obtained from samples of the Drug Product stored at 30°C are evaluated promptly using appropriate statistical techniques and an expiration date estimated. Should the estimate of expiration date be unacceptably short for samples stored at a constant 30°C, samples stored at 25°C are removed from the stability incubators and analysed. As at the initial time point, it is essential that sufficient replicate determinations are performed to allow a precise and accurate estimate of all quantitative Drug Product characteristics to be made.

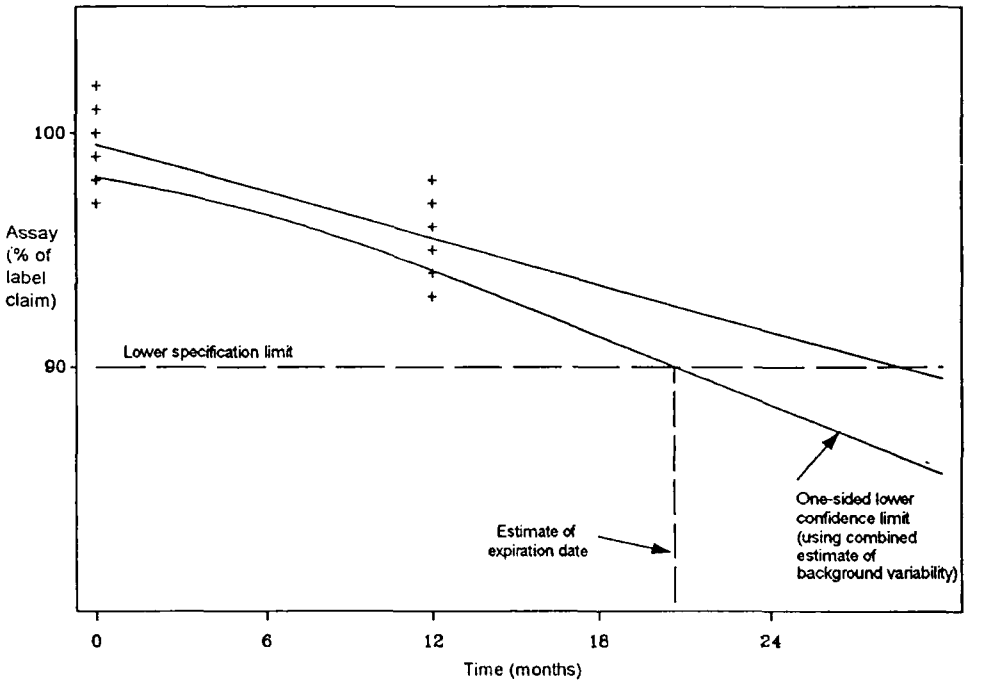

FIGURE 1
Estimate of Expiration Date after 12 Months Storage at 25°C

At this stage, it is important to establish the nature of the degradation relationship to enable a linear regression analysis to be performed. Usually the relationship can be represented by a linear function on arithmetic or logarithmic scales (i.e. zero or first order kinetics). In general terms, when determining the slope of a linear regression line, the points at the extremities of the line (in this case the data generated at the initial and 12 month time points) contain relatively more information than the intermediate time points (i.e. 3, 6 and 9 months). This means that, by dropping the intermediate time points and modestly increasing the replication at the initial and 12 month time points, the slope of the fitted line for the 25°C data can be estimated to the same precision as that which would be obtained for the 30°C data with standard replication at all time points.

The intermediate time points for the data generated after storage at 30°C do, however, provide two other types of useful information, namely:

- They allow the assumption of linearity to be checked (as required in the latest ICH guidelines).
- They provide additional information on the background variability in the study. This is one of the factors that determines the width of the confidence interval about the fitted line and hence the expiration date.

Having established the relationship for the stability data obtained after storage at 30°C it is valid to assume the same relationship for the stability profile of the Drug Product at 25°C. Although the rate of degradation is likely to be different for 25°C and 30°C it is unlikely that the mechanisms underlying the degradation process will change. Under these circumstances we may conclude that if the 30°C data is adequately represented by a straight line then so will be the 25°C data. In addition, the background variability is unlikely to be different for the data generated at the two temperatures. The estimate of background variability obtained from the 30°C data can therefore be combined with that obtained from the 25°C data to obtain a better overall estimate of expiration date as follows:

Let S_{1i}^2 be the variance between the n_{1i} replicates at time point i (excluding the initial time point) for the 25°C data and S_{2j}^2 be the variance between the n_{2j} replicates at time point j (excluding the initial time point) for the 30°C data. Let S_0^2 be the variance between the n_0 replicates at the initial time point.

The pooled estimate of variability is then given by

$$S_p^2 = \frac{(n_0-1)S_0^2 + \sum_i (n_{1i}-1)S_{1i}^2 + \sum_j (n_{2j}-1)S_{2j}^2}{(n_0-1) + \sum_i (n_{1i}-1) + \sum_j (n_{2j}-1)} \qquad \text{Equation 1}$$

At any time t^* the fitted line gives a predicted response Y^* and the 95% one-sided lower confidence limit associated with this value is

$$Y^* - tvalue \times S_p \times \sqrt{\left\{ \frac{1}{\sum_{0,i} n_{1i}} + \frac{(t^*-\bar{t})^2}{\sum_{0,i} n_{1i}(t_{1i}-\bar{t})^2} \right\}} \qquad \text{Equation 2}$$

where *tvalue* is the 95% point of the t-distribution based on

$(n_0-1) + \sum_i (n_{1i}-1) + \sum_j (n_{2j}-1)$ degrees of freedom,

$\sum_{0,i}$ implies include the initial point in the summation

t_{1i} is the ith time point used in the 25°C programme

and $\bar{t}$ is the mean given by

$$\bar{t} = \frac{\sum_{0,i} n_{1i} t_{1i}}{\sum_{0,i} n_{1i}}.$$

(Note that if access to a good statistical package is available then the analysis can be completed using a single analysis of variance).

In the circumstances where a shelf life claim based on assessment of stability data generated by continuous storage at 25°C is then going to be progressed, samples stored in the stability incubators at 25°C will be removed from test at all subsequent stability time points (i.e. 18, 24 months etc.) and the data obtained on these samples evaluated.

To demonstrate this approach, the stability data presented in Table 1 have been assessed as described above.

Note that twice as many samples have been analysed at the initial time point as have been analysed at other time points.

These data yield the following analysis of variance results shown in Table 2.

Since the 'Lack of Fit' term is not significant at the 5% level a straight line model is taken to be a good representation of the data.

The fitted model for the content Y at time t following storage at 30°C is therefore given by:

$$Y = 100.1875 - 0.2592t$$

which by the usual analysis yields an expiration date of approximately 16 months. If this is unacceptably short then four samples are assayed from those on store at 25°C and the data shown in Table 3 obtained.

The fitted model for the content Y at time t following storage at 25°C is

$$Y = 100.3250 - 0.1396t$$

TABLE 1
Drug content expressed as a percentage of label claim after storage at 30°C

Storage Temperature °C	Storage Time (months)				
	0	3	6	9	12
30	100.2 99.9 100.9 100.3	99.5 98.5	97.7 99.3	98.4 98.1	97.2 96.7

TABLE 2
Analysis of Variance for 30°C Data

Source of Variation	Degrees of Freedom	Mean Square	Variance Ratio	Probability
Regression Slope	1	16.1202	45.6	0.0003
Lack of Fit	3	0.2638	0.8	0.56
Pure Error	7	0.3539		

TABLE 3
Drug content expressed as a percentage of label claim after storage at 25°C

Storage Temperature °C	Storage Time (months)	
	0	12
25	100.2 99.9 100.9 100.3	97.8 98.1 99.0 99.7

The variance for each time/temperature combination is given below in Table 4.

Thus the pooled estimate of variability using Equation 1 is

$$S_p^2 = \frac{3\times 0.1758 + 3\times 0.7500 + 1\times 0.5000 + 1\times 1.2800 + 1\times 0.0450 + 1\times 0.1250}{3+3+1+1+1+1}$$

$$= 0.4727$$

and so

$$S_p = \sqrt{0.4727} = 0.6876$$

Also,

$$tvalue = t(0.05, 10) = 1.81$$

$$\bar{t} = \frac{4\times 0 + 4\times 12}{4+4} = 6$$

$$\sum_{0,i} n_{1i}(t_{1i} - \bar{t})^2 = 4\times(0-6)^2 + 4\times(12-6)^2 = 288$$

$$\sum_{0,i} n_{1i} = 4 + 4 = 8$$

At 27 months (ie $t^* = 27$) the predicted mean response is

$$Y^* = 100.3250 - 0.1396\times 27 = 96.5558$$

TABLE 4
Between Sample Variances

Storage Temperature °C	Storage Time (months)				
	0	3	6	9	12
25	0.1758				0.7500
30	0.1758	0.5000	1.2800	0.0450	0.1250

and the lower 95% confidence limit given by Equation 2 is

$$96.5558 - 1.81 \times 0.6876 \times \sqrt{\frac{1}{8} + \frac{(27-6)^2}{288}} = 94.9541$$

Therefore the expiration date is approximately 27 months at 25°C.

CONCLUSIONS

It is not always possible to be absolutely confident of the eventual label claim which may be applied to a Drug Product when long-term stability studies are initiated. One process by which stability data could be generated to support potential label claims would be to perform long-term stability studies at a variety of different temperatures (e.g. 30°C, 25°C etc.). Clearly, this approach is extremely labour intensive and unnecessary.

A more efficient approach has been described whereby data are generated on samples stored at 30°C to the 12 month time point. At this point an estimate of the expiration date can be made. If the estimated expiration date appears to be unacceptably short a decision can be taken as to whether different expiration dates may be allocated on the basis of considering the effects of continuous storage at 25°C rather than 30°C. Samples which had been stored at 25°C (but not previously analysed) would be examined. Having established a linear relationship over time for the samples stored at a constant 30°C, a linear regression analysis can be performed on the data obtained (at the initial and 12 month time points) on the samples stored at 25°C. The estimate of variance obtained from the samples stored at 30°C is then pooled with that obtained from the samples stored at 25°C and used in the estimation of expiration date (i.e. the time at which the 95% one-sided confidence interval intercepts the specification limit). In this way, label claims can be fully supported without generating unnecessary long-term stability data at a variety of different storage temperatures without compromising the quality of the estimate.

REFERENCES

(1) Center for drugs and biologics, Food and Drug Administration, Department of Health and Human Services; Guideline for submitting documentation for the stability of human drugs and biologics, February 1987.