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THE DETERMINATION OF PRODUCT EXPIRY DATES FROM SHORT TERM STORAGE AT ROOM TEMPERATURE

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Increasingly registration authorities are requesting expiry dating of pharmaceuticals. A scheme is suggested based on short term stability data at "room temperature" for obtaining reliable expiry dates. The advantages and disadvantages of this method and methods using elevated temperatures and the Arrhenius plot are discussed. The statistical equations necessary to calculate the minimum predicted shelf life are given and difficulties encountered in their use explained.

INTRODUCTION

In the data given in an application to market or conduct clinical trials on a new pharmaceutical product many registration authorities are now insisting that the product shall bear an expiry date. In many cases stability data will not be available on batches stored for the whole of the foreseen shelf life, and some form of

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prediction based on short term stability data has to be made. A literature search has shown that storage at elevated temperatures with some form of prediction based on the Arrhenius equation is the general method in use.

This paper suggests a scheme to obtain an expiry date for a pharmaceutical product based on short term stability data at "room temperature". By "room temperature" it is not meant the actual temperature encountered in some laboratory storage area over a period of time, as it is considered more meaningful to store the product in a constant temperature environment at say 20 - 22°C for a temperate country, or whatever mean temperature is considered most likely to represent conditions encountered by the marketed product.

A large number of smaller laboratories still do not have access to computer facilities and the mathematics described here are suitable for calculation with bench top calculators. The method is concerned with an expiry date based on testing the chemical stability of pharmaceutical products. Aspects relating to the physical stability of products are excluded.

Arrhenius Prediction

There are a number of papers in the literature on the use of data obtained for samples stored at elevated

temperatures to calculate rate constants which are used in an Arrhenius plot to give a stability prediction for a lower temperature. Garrett[1] first gave the mathematics involved in such an approach, and Bentley[2] suggested modifications to give increased accuracy. Papers on this subject are mainly limited to liquid preparations[3,4] where the chemical kinetics and orders of reactions are fairly easily obtainable and the Arrhenius equation $k = A \exp(-E/RT)$ is applicable over a wide range of temperatures. The Arrhenius equation is not always as simple as that stated and for many systems A and E are also dependant on T[5].

It is always satisfying to be able to publish a paper showing that the Arrhenius equation gave the correct prediction for a pharmaceutical system. However the industrial pharmaceutical formulator must be able to say with confidence that the Arrhenius equation is applicable to his product, without benefit of hindsight, and that a prediction from its use is valid. The Arrhenius equation is probably satisfactory for simple solution systems where solvolytic processes are responsible for the degradation. Simple liquids form only a small percentage of pharmaceutical formulations and for most other types of formulation there are grave objections to the use of the Arrhenius method.

In solid dosage forms e.g. tablets or capsules, the most likely route of degradation is that caused by solvolytic reactions resulting from incomplete removal of granulating solvents or the presence of equilibrium concentrations of moisture associated with the excipients in use. In this type of product the ratio of solvent to drug is very much less than in simple liquid systems and as the degradation reaction often involves one or more of the tablet excipients, the order of the reaction is very difficult to determine. In addition many of the reactions do not go to completion but only to some form of equilibrium state[6]. Apart from the more complicated nature of the reaction mechanisms there are two added objections to using higher temperatures to predict stability. The first is that solvent may escape from the storage containers at higher temperatures which obviously invalidates any Arrhenius prediction on products where solvolysis is the main route of degradation. The second is that the solvent may be redistributed throughout the system e.g. tablets may dry out at the centre, or moisture may transfer from one component to another, e.g. moisture in gelatin capsule shells may be driven off and reabsorbed by the drug or one of the excipients. This will probably occur to differing extents at different temperatures.

Other types of degradation such as oxidation or thermal breakdown of the drug itself often occur only above a certain critical temperature, and below that temperature the product is quite stable. For example some ergot alkaloids will decompose completely within a year above 45°C, but below 35°C their rate of degradation is less than one percent per year.

A major complicating factor is that in many products more than one degradation route is operative at the same time. Each reaction may proceed at a different rate with different Arrhenius constants. This makes any stability analysis lengthy and the stability prediction prone to errors because each reaction rate must be determined separately which is usually impractical.

Another complication is that the thermal degradation of excipients such as sugars may catalyse the degradation of other components[7]. These pyrolyses have high energies of activation and virtually do not proceed at room temperature.

In a number of pharmaceutical forms such as creams, ointments, emulsions and suspensions the physical form of the product may change so drastically that data obtained at a high temperature is meaningless for stability prediction at room temperature. The drug may

have greater solubility at the higher temperature or the partition ratio of the drug between two immiscible solvents may be changed completely or one of the phases may be solid at room temperature and liquid at higher temperatures.

For the reasons outlined it may be preferable to use an alternative method of predicting product shelf lives based on data obtained at the temperature they are stored at in normal use.

This is not to say that high temperature stability data have no place in pharmaceutical development. It may be possible by subjecting a number of possible formulations to elevated temperatures to select, in a short time, one or two which have promising stability profiles in order to cut down the amount of long term stability testing at lower temperatures.

PROPOSED METHOD

1) Stability Limits

The suggested procedure is of application where minimum expiry dates for normal pharmaceutical products i.e. those with shelf lives greater than one year are required. For products with shorter shelf lives it is usually possible to conduct stability tests over the whole of the anticipated shelf life before information is supplied to the registration authorities. The

mathematics to be used to obtain a confidence level for the minimum predicted shelf life are the same, but the analytical errors are normally less significant and a much narrower fiducial interval on the minimum predicted shelf life is obtained. For such short dated products it may also be possible to determine accurately the actual reaction order involved.

It is usually considered good manufacturing practice to give five years as the maximum expiry date for any pharmaceutical product, even if the stability data gives a longer shelf life prediction.

2) Loss Limits

The normally accepted criterion for product expiry dates is that the formulation should contain greater than 90% of the label declaration of intact drug throughout its shelf life. In a number of cases in the literature this 90% of undegraded drug is assumed to be equivalent to 10% drug decomposition. However, in practical terms the acceptable percentage drug degradation should be the difference between the lower Quality Control limit and 90% of label claim. In other words, if the Quality Control acceptance limits are 95% to 105% of label declaration the maximum degradation allowed should be 5%. If the product has a 5% overage and the

Quality Control release limits are say 97.5% to 112.5% of label claim, the maximum degradation allowed should be 7.5%.

When later stability results become available the predicted expiry date often increases and the confidence limits decrease in width. It may be that on six months stability data a 5% loss limit gives too short a minimum shelf life at the required confidence level. In this case the manufacturing limits should be tightened or the possibility of a small overage considered. It may then be possible at a later date when longer stability data is available to relax the manufacturing limits slightly or omit the overage.

The case of limitation of product shelf lives through the appearance of toxic degradation products is discussed later.

3) Confidence Level

In giving confidence limits to a prediction from a regression equation both upper and lower limits are given mathematically. With expiry dating only the lower limit is of interest because only the least optimistic forecast must be relied upon. In choosing a confidence level the formulator is therefore only interested in a one-sided probability level. For example if

P = 0.95 (α = 0.05), and we take a Quality Control lower release limit of 95% label claim together with an acceptable loss limit of 5%, 95 out of 100 samples at the lower Quality Control release limit will contain greater than 90% intact drug at the expiry date. It is important to realise that in practice, since most batches will assay above the lower release limit, more than 95 out of 100 batches can be expected to have the predicted shelf life. If 99 out of 100 batches assay initially at greater than 95.5% label claim it can be shown statistically that at the 95% confidence level only 1 batch in 2000 batches should be below 90% of undegraded drug before the expiry date is reached.

For this reason the probability level to be taken depends to a large extent on the likely variation in drug content obtained on production batches. A batch of tablets that are assayed and if necessary adjusted at the granulation stage, will have less variation in the final tableted form than a batch of tablets compressed from an unassayed dry mix.

As a general rule a probability level of p = 0.95 is used. The actual effect of the probability level chosen on the minimum predicted shelf life will be demonstrated.

4) Analytical Precision

This paper is limited to products with shelf lives of more than one year. For nearly all preparations (those with at most 5% overage) a maximum loss of pure drug of less than 10% is involved. This means that the assay must have good precision to obtain meaningful results. It must be emphasised strongly that the smaller the spread of results due to analytical imprecision the narrower will be the fiducial limits and the longer will be the minimum predicted expiry date.

Most assays for intact drugs will involve some form of chromatography. Relative standard deviations of less than 1.0% should be obtainable for assays using GLC or HPLC and relative standard deviations of less than 1.5% are obtainable with quantitative TLC. These levels of precision are obtainable by trained unqualified technicians.

Assays with a standard deviation of greater than 2.0% are probably unsuitable for obtaining useful predictions from short time periods. This rules out most biological assays. In these circumstances the only alternatives are Arrhenius prediction, waiting for long term storage results, or testing of a larger number of stability batches.

It has been suggested[8,9] that more emphasis should be placed on the rate of accumulation of a degradation product as the accuracy in determining total breakdown is greater i.e. 0.1% degradation product can be measured within say 0.05% to 0.15% whereas 99.9% intact drug can only be measured between say 98.9% and 100.9% In general we feel this approach is to be avoided. Many drugs degrade by more than one route, and many degradation products themselves degrade further. This leads us to emphasise the need for analytical specificity in the intact drug assay method. There is also the danger that as a result of development of new or improved techniques, an additional degradation product may be detected which, although separated from intact drug by the chromatographic technique, was not known when the batch of product was placed on stability test.

If a degradation product has a greater toxicity than the pure drug, then its rate of formation must be monitored. If a maximum limit is set, an expiry date with confidence limits can be calculated in a similar way to that described for loss of intact drug. Such a loss limit may be more stringent than that imposed by potency loss considerations.

5) Reaction Rate

It is impossible, when dealing with less than 10% degradation to determine accurately the reaction order involved, assuming only one reaction is onvolved. It can be shown mathematically[10] that even with good assay precision "first" and "zero" order reactions cannot be distinguished above 90% retained potency.

Unless there is strong evidence to the contrary, a standard procedure is to assume that pseudo first order conditions apply. This is similar to the procedure used by Lordi and Scott[11] who discussed the errors involved in such an approach in relation to Arrhenius prediction.

We choose first order conditions for a number of reasons as listed below :

a) If degradation were of a higher order, then this would result in a more favourable shelf life than would pseudo first order.

b) The ratio between the amount of drug and excipients is generally so much to the disadvantage of the drug than any influence of one upon the other may be expected to lead to pseudo first order conditions.

c) If the reaction was in fact zero order but was plotted as first order it would make little difference to the stability prediction. For example if the following results were obtained Initial = 100% 3 months =

97.5% 6 months = 95.0% i.e. zero order giving a prediction of 12 months for 10.0% degradation, would give a prediction of 12.3 months if plotted as first order. Similarly Initial = 100% 6 months = 99% 12 months = 98% i.e. zero order giving a prediction of 60 months for 10.0% degradation would give a prediction of 63 months if plotted as first order.

d) Most liquid systems give first order kinetics.

e) The few papers giving reaction rates for solid systems give first order kinetics [6,12,13]

f) Many solids degrade topochemically giving pseudo first order kinetics[6].

SUGGESTED PROCEDURE

Most registration authorities require stability results from at least three batches of new product, and three batches is also the minimum number needed to obtain meaningful statistical information.

It is important that the initial assay figure is accurate and so duplicate analysis by each of two analysts, i.e. 4 assays in total is recommended. The analysis at each subsequent stability point is then performed in duplicate by one analyst. The results for each stability point are then averaged to the nearest 0.1%.

Shelf life predictions should not be attempted until results from at least two stability points apart from the initial are available. In general 3 months and 6 months figures are suggested, although shorter periods such as 1 month and 3 months can be used for products where previous knowledge indicates a relatively short shelf life.

The mean assay results for each batch at any one time period are taken rather than the individual assay results, as the regression line required is that giving the functional relationship between intact drug content of a batch of product and time. The variation of assay results at each time period for each batch should not be confused with the variation in drug content of the total population of batches with time.

The mean results should then be scaled to give 100.0% for each initial assay. For example the results in Table I will give those in Table II.

The assay results should then be converted to logarithms. At least 5 and preferably 7 place tables should be used to obtain the necessary accuracy in subsequent calculations. For this reason the use of $\log_{10}$ tables, which are more readily available than 7 place tables for $\log_e$ is preferred. This alteration

TABLE I

	Initial	3 months	6 months
Batch 1	101.2 100.8 100.2 100.5 Mean 100.7%	100.3 100.5 Mean 100.4%	100.2 100.8 Mean 100.5%
Batch 2	99.0 98.7 99.2 98.6 Mean 98.9%	98.9 99.3 Mean 99.1%	97.9 97.9 Mean 97.9%
Batch 3	99.9 99.9 99.7 100.0 Mean 99.9%	99.5 98.7 Mean 99.1%	99.0 98.8 Mean 98.9%

makes no difference to the expiry date prediction but the regression line slope must be multiplied by 2.3026 for the 1st order rate constant.

It should be noted that by converting the assays to logarithms, if there is very little or no degradation and the assay spread is above and below 100% due solely to assay imprecision, then the first order plot will still have a very small negative slope.

TABLE II

	Initial	3 months	6 months
Batch 1	100.0%	99.7%	99.8%
Batch 2	100.0%	100.2%	99.0%
Batch 3	100.0%	99.2%	99.0%

If the slope of the regression line is positive, which will normally only occur with no degradation and a loss in weight of the product e.g Loss of solvent from a cream through the walls of a plastic tube, the predicted shelf life will be at a negative date. However a positive confidence limit can usually still be obtained to enable one to say that the minimum predicted shelf life is greater than this minimum value.

CALCULATION

Expiry dates are calculated by regression analysis from storage results of the type given in Table II

The regression line is given as

$$C = bT + a \qquad (1)$$

Where C is $\log_{10}$ percentage assay, T is time in months, and a and b are constants.

$$S_{TT} = \Sigma T^2 - \frac{(\Sigma T)^2}{n} \qquad (2)$$

$$S_{CC} = \Sigma C^2 - \frac{(\Sigma C)^2}{n} \qquad (3)$$

$$S_{CT} = \Sigma CT - \frac{\Sigma T \Sigma C}{n} \qquad (4)$$

Where n is the total number of mean assay results. The slope of the regression line, b, is given by

$$b = \frac{S_{CT}}{S_{TT}} \qquad (5)$$

The intercept is

$$a = \frac{\Sigma C}{n} - \frac{b\Sigma T}{n} \qquad (6)$$

The slope b should be negative for a loss of intact drug with time.

It may be more correct to calculate separate regression lines for each batch of product, and then compare all the regression lines so obtained. This can only be done with a computer and is outside the scope of this paper.

No weighting is applied to any of the results; the precision of most assay methods for intact drugs is the same at 90% as at 100% intact drug. It would be possible to weight the initial results at T = 0 as these are obtained from four individual assay results instead of two individual results for all other time periods. This is not generally necessary. The fact that all three batches have T = 0 C = 2.0000000 (100%) serves to ensure the intercept on T = 0 is always very close to 2.0000000 without further weighting.

For the example in Table II

$$b = -0.00053278$$
$$a = 2.00009697$$

If the Quality Control limits for this product were 95% to 105%,

Then the predicted time for 5% loss would be given by

$$C_{95} = bT + a \quad C_{95} = 1.9777243$$

Therefore T = 42.0

The predicted time for 5% loss is 42 months.

In obtaining the regression line and in subsequent work to obtain the confidence limits, the assumption is made that the values of C at any given assay time point are normally distributed. This will be true for small losses in intact drug when the distribution in values of C will be governed by assay imprecision. However when the loss of intact drug is greater, say 4%-5% this will not always be true. If for example the degradation route in a tableted product depends on the amount of granulating solvent present, a limit on the residual solvent content of the granules will usually be fixed. This will mean that the distribution in values of C will have a lower limit corresponding to the degradation caused by the maximum permitted amount of solvent. C will then have a positive skew. This should not affect the validity of the statistics.[14]

CONFIDENCE LIMITS

The general formula for the determination of confidence (fiducial) limits is given by Fieller's formula[15,16]. The limits α of a ratio y/x are given by

$$(y^2 - t^2 V_{yy}) - 2\alpha(xy - t^2 V_{xy}) + \alpha^2(x^2 - t^2 V_{xx}) = 0 \quad (7)$$

Where t is the "Student" t deviate, V_{xx} and V_{yy} are the variances of x and y, and V_{xy} is the covariance. The equation of the straight line (equation 1) may be written

$$T - \bar{T} = \frac{C - \bar{C}}{b} \quad (8)$$

Where $\bar{T}$ and $\bar{C}$ are the mean values of T and C respectively.

In this case $y = C - \bar{C}$ and $x = b$ and

$$V_{yy} = \sigma^2 \left(1 + \frac{1}{n}\right) \quad (9)$$

$$V_{xx} = \frac{\sigma^2}{S_{TT}} \quad (10)$$

$$V_{xy} = 0 \quad (11)$$

Where σ is the standard deviation given by

$$\sqrt{\frac{S_{CC} - b^2 S_{TT}}{n - 2}} \quad (12)$$

Therefore the limits for $T - \bar{T}$ are given by

$$\left[(C - \bar{C})^2 - t^2\sigma^2\left(1 + \frac{1}{n}\right)\right] - 2\alpha\left[b(C - \bar{C})\right] + \alpha^2\left[b^2 - \frac{t^2\sigma^2}{S_{TT}}\right] = 0 \quad (13)$$

This is a quadratic equation in α and may be solved in the normal way. The solution may be simplified to give limits for T_L as

$$T_L = T' + \frac{(T' - \bar{T})g \pm \frac{t\sigma}{b}\sqrt{\left(\frac{T' - \bar{T}}{S_{TT}}\right)^2 + \left(1 + \frac{1}{n}\right)(1 - g)}}{1 - g} \quad (14)$$

Where T' is the predicted time (shelf life) from the regression equation.

$$g = \frac{t^2\sigma^2}{b^2 S_{TT}} \quad (15)$$

t is the "Student" t factor for a <u>one sided</u> test for n - 2 degrees of freedom.

A simplified version of this equation

$$T_L = T' \pm \frac{t\sigma}{b}\sqrt{\frac{(T'-\bar{T})^2}{S_{TT}} + 1 + \frac{1}{n}} \qquad (16)$$

is often given in books on statistics for the standard error of a prediction. This equation (16) is an approximation and gives nearly the true answer when g is small. Finney[17] states that when g is less than 0.05, which requires that (for the 0.95 probability level) b is at least nine times its standard error, g may be ignored. For the type of data discussed in this paper b is usually very small i.e. the rate of loss of drug is very small. In fact b is often similar or less than its standard error. The approximate equation (16) should therefore not be used in this type of work.

Because b is very small this gives rise to certain difficulties in solving equation (14). These difficulties are now discussed.

i) $g < 1$

This is the simplest case and the equation will give two values for T_L one above and one below T'. We are interested only in the lower limit, so as to be able to say with a certain confidence level that for a particular percentage loss of intact drug the minimum predicted shelf life is greater than the lower fiducial limit.

ii) $g = 1$ i.e. $b^2 = \frac{t^2\sigma^2}{S_{TT}}$

In this case no solution is possible to equation (14) as the upper limit to T_L is infinity. The lower limit which is the one required can be found from equation (7) and is

$$T_L = \frac{T' + \bar{T}}{2} - \frac{s_{\pi}\left(1 + \frac{1}{n}\right)}{n(T' - \bar{T})} \qquad (17)$$

iii) $g > 1$

In this case both limits for T_L are lower than T' Fieller gives the easiest mathematical interpretation of this[16], but a simple explanation is to say that the lower of the two limits arises from the fact that from the data used to obtain the regression line, there is a finite possibility that b has a positive slope and that the amount of drug in the product is increasing and so C_{95} was reached before T = 0.

This is of course meaningless when applied to stability data and only the upper of the two limits is of practical interest.

In the example quoted earlier, if we take a probability level of 0.99 for a one sided test.

$$g = 1.509$$

and $T_L = 19.5$ or -165.9

We could therefore say for this product that the predicted time for 5% loss is 42 months, with a confid-

ence level of 99% that the time will not be less than 19.5 months.

The effect of different probability levels is shown in Table III. The required fiducial limit is underlined.

It can be seen that for the results quoted in Table I there is little practical difference between say 0.90 probability and 0.95 probability. It also shows that unless the assay precision is very good the minimum shelf life will be very much shorter than that predicted from the regression line

iv) if $\frac{(T' - \bar{T})^2}{S_{TT}} + \left[1 + \frac{1}{n}\right]\left[1 - g\right] < 0$

In this case no solution is possible because at the probability level chosen α can have any value from $+\infty$ to $-\infty$. A result can only be obtained by reducing the probability level and hence t and therefore g until the left hand side is greater than 0. In dealing with stability data this problem will only occur when the

TABLE III

Probability Level	g	Fiducial Limits
0.90	0.3379	27.1 and 96.1
0.95	0.5989	24.3 and 175.1
0.975	0.9336	21.9 and 1152.7
0.99	1.5090	-165.9 and 19.5

assay is very imprecise and results for $T > 0$ are widespread above and below 100%.

While a value of $b > 0$ is unlikely, and although as mentioned earlier the predicted shelf life is meaningless, a positive upper fiducial limit will probably exist and can be calculated using equation (14) similar to that described under iii). If the accumulation of a by-product is assayed b will be positive and limits can be obtained in a similar way to those described previously.

Care must be exercised if the statistical method is used for purposes other than the stability scheme outlined.

In particular the calculation of a prediction from a single batch should be avoided if at all possible. Not only will the results obtained give no information on batch variation but with only two or three individual results at $T > 0$ there is a high probability that one erroneous result, which may be due to assay imprecision, will have a large influence on the final prediction and its calculated confidence limits. Occasionally such results have to be used, eg.in trial comparisons of differing formulations, but great care must be taken before putting weight on any one prediction.

Carstensen discussed the following single batch results [18]

Calculation of these results gives a positive slope and no minimum prediction is possible as the results, due to their imprecision fall into category iv), at the 95% confidence level. If there is evidence that the T = 0 assay can be relied upon to a greater extent than the other figures, eg replicate analyses, then it is possible to constrain the regression. line through T = 0 C = 2.0000000.

In this case it is simpler mathematically to plot

$D = C - \log_{10} 100\%$ against time T, where $D = bT$ (18)

Then the slope $b = \frac{\Sigma DT}{\Sigma T^2}$ (19)

$$\sigma = \sqrt{\frac{\Sigma D^2 - b^2 \Sigma T^2}{n - 1}} \quad (20)$$

If $h = \frac{t^2\sigma^2}{b^2 \Sigma T}$ (t is for n - 1 degress of freedom) (21)

$$\text{then } T = T' + \frac{\acute{T}h \pm \frac{t\sigma}{b}\sqrt{\frac{T'^2}{\Sigma T} + 1 - h}}{1 - h} \quad (22)$$

Doing this with the data in Table IV gives a predicted shelf life of 48 months with a 95% confidence level that the time to reach 10% loss will be greater than 9 months.

This technique has not been applied to the recommended method for two reasons.

1) There is a finite possibility that the T = 0 assays are incorrect

TABLE IV

Time	Initial	1 month	2 months	3 months
Assay	100%	98%	101%	99%

2) If the degradation reaction has a rate order > 1 or if it reaches an equilibrium, by constraining the regression line through T = 0 D = 0 the slope b will be too large and will give too short a predicted expiry date.

CONCLUSION

The suggested procedure has advantages over the Arrhenius method currently in use by many laboratories. For some products, where elevated temperature stability studies are not meaningful, it provides a method for estimating expiry dates for newly marketed products.

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