Terminology Regarding Labeled and Contained Amounts in Dosage Forms

Keyphrases □ Dosage forms—terminology regarding labeled and contained amounts, definitions suggested for the terms shelflife, outdate, expiration date, label date □ Terminology—regarding labeled and contained amounts in dosage forms, definitions suggested for the terms shelflife, outdate, expiration date, label date

To the Editor:

Dating of pharmaceutical preparations has become standard practice in this country. To this end, an acceptable nomenclature for various phases of the decay cycle of a product is of essence; we should like to suggest definitions for the terms "shelflife," "outdate," "expiration date," and "label date."

As pointed out by Crout (1), concise definitions of terms are necessary for the sake of rational debate. The difficulties encountered without such definitions are, for instance, evident in Canadian Regulations C.01.004[7]. Here, such statements are used as: "Where evidence indicates that . . . a drug[1] . . . does not maintain its potency, purity, or physical characteristics for at least three years from the date of manufacture . . . ." If definition of the pertinent terms existed, the wording could be much simpler.

Of the mentioned terms, only label date is a defined quantity at present; it is simply the date appearing on the label. The following discussion does not suggest that more than the label date should appear on the label. However, certain definitions for the other three terms would make scientific and technological dialog more precise, particularly in light of the proposed new Current Good Manufacturing Practices, paragraph 133.14.

In general, the stability of a drug is followed by storing it at constant temperature and assaying it from time to time. The points plotted are the assays, which are estimates of the true contents. The decay curve may be of many types [zero order, first order, with or without lag times, downward parabolic (autocatalytic), and any of these types with or without equilibrium levels (2, 3)]. Although an uncomplicated zero-order decomposition is used as an example here, this usage in no way places any restriction on the definitions to follow. That the statistics of drug decomposition in a dosage form generally may not be this simple is granted; the work by Fusari (4) is an example.

If all dosage units of all batches of a product were of identical content and stability, a decay plot such as the one shown in bold in Fig. 1, the stability line ($y = -ax + b$), would result. The ordinate is percent label claim but could be any scale that linearizes the decay. The initial content is 100% label claim plus excess. In the example in Fig. 1, the excess is $(10 - e)$%; *i.e.*, the initial content is $(100 - e)$% label claim[2]. The point where the stability line reaches 100% is denoted shelflife in our definition. In reality, the stability line will not be an "exact" line but will be subject to variation. The stability line then is the least-squares fit line, and the shelflife is defined as the point where this line cuts the 100% label claim line; it is a function of the excess used.

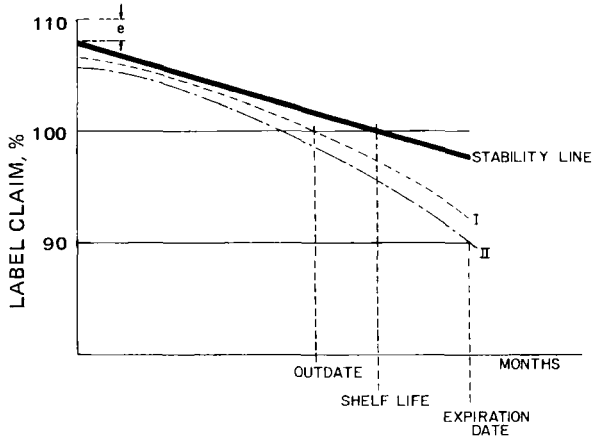

Figure 1—*Plot of stability of product, starting at (110 − e)% label claim.*

To define the pertinent quantities, let us assume that the study involves q batches. A sample of size p dosage units[3] is taken at time x and assayed *in toto*[4]; the assay of the sample divided by p is the y value, which is plotted on the stability line. In the uncomplicated case with which the definitions are illustrated, the variance of the y values is assumed not to change with time. This assumption, as shown by Fusari (4), is an oversimplification but poses no restrictions on the definitions.

At the time a stability report is prepared, there are n assays, the times involved being $x_0, x_1, \ldots, x_k$, where k and n may (or may not) be identical (since several samples may be assayed at one storage time). The true mean of the assays of all possible samples at time x_i lies in the interval (5):

$$\{[b - ax_i - f(x_i)]\|[b - ax_i + f(x_i)]\}$$

where:

$$f(x_i) = t_{0.10,n-2} s_{yx} \sqrt{\frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum (x_j - \bar{x})^2}} \qquad \text{(Eq. 1)}$$

where the summation is from $j = 1$ to $j = n$ and the statement is made with 90% confidence (since $t_{0.10}$ is

[1] The word "drug" in regulations encompasses (among other factors) the dosage form as well.

[2] It is assumed here that the process and assay variances, with 95% confidence, contribute $\pm e$% to the initial assay (which is an average of p units). The specification limits are assumed to be the conventional 90–110% label claim, so initial assays lie between $(110 - 2e)$% and 110% label claim with a frequency of 0.95.

[3] Alternatively, a subsample of p units from a sample of P units could be used.

[4] This, for instance, could be obtained by grinding up p units and either assaying the total sample or performing k chemical determinations on $(1/k)$ segments of a uniformly blended mix of the ground-up sample. In the latter case, information regarding assay variance can be inferred.

being used). Hence, it may be stated with 95% confidence that the true mean of all assays will be above $b - ax_i - f(x_i)$. Here n is the number of assays, t is the Student t value, $\bar{x}$ is the mean of the x values, and s_{yx}^2 is the mean square about the regression (6).

The line marked I in Fig. 1 is denoted the lower (one-tailed) 95% confidence line about the least-squares fit line[5], *i.e.*, $\bar{y} - f(x)$; we should like to define the outdate as the point where this line cuts the 100% label claim line.

An individual assay (average of p units) will, with 90% confidence *at time* x_i, lie in the interval (7):

$$\{[b - ax_i - g(x)][b - ax_i + g(x)]\}$$

where now:

$$g(x) = t_{0.10,n-2}s_{yx}\sqrt{\frac{n+1}{n} + \frac{(x_i - \bar{x})^2}{\sum(x_i - \bar{x})^2}} \qquad \text{(Eq. 2)}$$

The line marked II in Fig. 1 is the 95% confidence line[5] for individual assays by the same argument as already given, *i.e.*, $y - g(x)$. As stated previously, it is assumed that the lower specification limit is 90%; the point where line II cuts the horizontal 90% line. we should like to denote the expiration date. The January or July immediately preceding this date should be denoted the label date and is the date appearing on the label. The other three defined terms do not appear on the label but may occur in documents (regulations, New Drug Application, *etc.*).

In using the nomenclature, it would (except in the case of the label date, which simply is the date that appears on the label) be advisable to indicate the excess (xs) and confidence limits (CL) in parentheses. The number of batches (N), the number of assays (n), the sample size (P), and the subsample size (p) are also pertinent. Thus, the suggested mode of writing would be shelflife s months (xs = 8%, CL = 95%, N = 5, n = 20, P = 100, and p = 10) to denote an 8% excess, 95% confidence, five batches, 20 points, a sample size of 100 dosage units, and a subsample size of 10 units assayed.

A similar statement would apply to the outdate, and the difference between the shelflife and the outdate would show the goodness of fit. For expiration dates, the lower specification limit (SL) would have to be added, *e.g.*, expiration date July 1975 (xs = 8%, CL = 95%, N = 5, n = 20, P = 100, p = 10, and SL = 90%). It is suggested that omission of the last figure implies a 90% lower limit.

These definitions do not help solve all dilemmas of stability testing. For instance, a good product with a high assay variance may still require a higher excess than a product with poorer stability and smaller assay variance. In assays with notoriously high variance (*e.g.*, microbiological assays), an increase in n or a decrease in SL is usually the means used if the assay method cannot be improved.

The 95% confidence limits can be replaced by other confidence limits provided the proper t value is used. The excess used is based on the considerations in Footnote 2 and on stability considerations and will, of course, vary from product to product; it should be calculated by a systematic method, such as an overage chart (8). The excess used also depends on the lower specification limit, which, of course, depends on the product (*e.g.*, *via* compendial standards) and particular company policies.

[5] A single-tailed test is employed since one is interested in the assay falling above a lower limit. It is already known that it will fall below 110% label claim (Footnote 2). It is possible to conceive situations where the potency increases with time (*e.g.*, when an assay is not stability indicating and a degradation product contributes more to the assay than the parent compound or in the case of improper closures), but the study is always invalid in such cases.

(1) J. R. Crout, conference on "Bioavailability—Scientific and Legal Implications for IND/NDA Submissions," Extension Services in Pharmacy, University of Wisconsin, Madison, Wis., Oct. 21–28, 1974.

(2) J. T. Carstensen, "Pharmaceutics of Solids," Badger-Freund Inc., Fond Du Lac, Wis., 1974, pp. 156–158.

(3) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N.Y., 1973, pp. 329–341.

(4) S. Fusari, *J. Pharm. Sci.*, **62**, 2012(1973).

(5) N. R. Draper and H. Smith, "Applied Regression Analysis," Wiley, New York, N.Y., 1966, p. 23.

(6) *Ibid.*, p. 19.

(7) *Ibid.*, p. 24.

(8) J. Haynes, J. T. Carstensen, J. C. Callahan, and R. Card, "Third Stevens Symposium on Statistical Methods in the Chemical Industry," Hoboken, N.J., Jan. 24, 1959, p. 1.

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Sample Size Changes in USP XIX and NF XIV

Keyphrases □ Sampling—effect of sample size, USP and NF tests for content uniformity, dissolution, disintegration, and weight variation, changes from previous editions □ Test specifications—USP and NF tests for content uniformity, dissolution, disintegration, and weight variation, sample size changes from previous editions □ Compendial tests—changes in sample size, effects

To the Editor:

Changes in USP XIX and NF XIV regarding sample size introduce an inconsistency into the tests for content uniformity, dissolution, disintegration, and weight variation. In USP XVIII and NF XIII, the sample size for the final stage of the sequential tests for content uniformity, dissolution time, and disintegration time and for the nonsequential test for weight variation was uniquely determined by the description of the test. However, in the General Notices of USP XIX (1) and NF XIV (2), the following sentences have been inserted under the heading "Procedures":

> *"In the performance of assay or test procedures, not less than the specified number of dosage units should be taken for analysis."*