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.

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

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(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."*

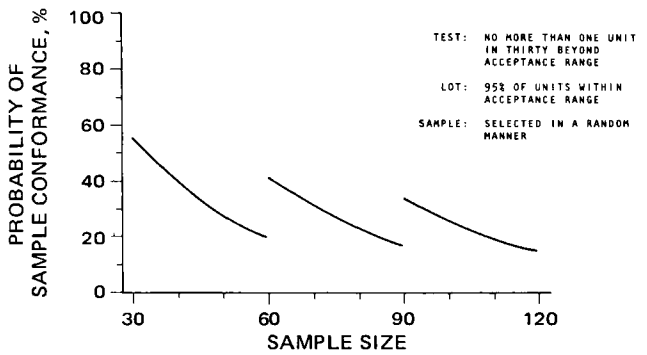

Figure 1—*Example of the effect of sample size on the content uniformity test.*

and:

> *"Where it is directed in an assay or a test that a counted number of dosage units is to be examined, the specified number is a minimal figure chosen only for convenience of analytical manipulation; it is not intended to restrict the total number of units that may be subjected to the assay or test. Regardless of the number of units so examined, the article meets the requirements if the same proportion of units conforms as is stated in the assay or single-stage test, or at the conclusion of a multiple-stage test."*

The employment of sample sizes greater than those stipulated in the monograph increases the discriminatory ability of the acceptance tests and provides a "cushion" in the event that some unit assays are not completed. However, the probability of drawing an unsatisfactory sample is a function of sample size. For example, consider the application of the compendial test for content uniformity to a randomly mixed lot with 5% of the units beyond the acceptance range.

The probability of sample conformance is 0.55, 0.42, 0.34, and 0.28 for samples of 30, 60, 90, and 120 units, respectively (Fig. 1). The lower probability of conformance of a sample of, for example, 59 units as compared to one of 60 units is due to the discrete nature of the dosage units. Only one nonconforming unit in a sample of 59 is acceptable, whereas two are acceptable in a sample of 60. Different, but similar, saw-toothed curves would be obtained for other percentages of units beyond the acceptance range. (For values less than 3.33%, the probability of sample conformance approaches 100% for increasing sample size, whereas the probability approaches 0% for values greater than 3.33%.) A similar situation exists for the other three tests.

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 4.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, p. 11.

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Starch Paste Granulations: Binder Dilution Effects on Granulations and Tablets

Keyphrases □ Starch paste granulations—effect of gelatin binder solution concentrations, tableting characteristics □ Granulations, starch paste—effect of gelatin binder solution concentrations, tableting characteristics □ Dosage forms—tablets, effect of gelatin binder solution concentrations on starch paste granulations and tableting characteristics

To the Editor:

It was reported previously that the dilution factor of a gelatin binder solution used in a fluidized-bed granulating process influenced the friability of the granules (1). Specifically, the more dilute binder solutions resulted in less friable granules. The present communication reports similar results with aqueous dilutions of starch paste and a conventional granulating process.

Starch paste has long been used as a tablet binder in the pharmaceutical industry, but the literature contains few references to studies of this use. Starch paste granulations usually result in faster disintegrating tablets than do many other binders (especially the gum type) and may be preferred for this reason. Despite its wide usage, the effect of starch paste preparation variables on granulation or tablet quality has received little attention. One variable is the viscosity or thickness of the paste. In some cases, starch paste may be made with the maximum amount of water that can be used without overwetting the granulation. In other cases, less water is used and additional water is added to the granulation after some massing, based on the operator's judgment.

The formulations shown in Table I were manufactured in a small planetary-type mixer to find whether dilution of the starch paste affects granulation or tableting characteristics.

The lactose and starch were dry mixed in the mixer bowl for 5 min. The amount of water used to make the paste was varied from a 4:1 to a 6:1 water to starch ratio. The total amount of water used in each experiment was kept constant by varying the amount of water added to the mass after the starch paste had been mixed with the lactose–starch mixture for 1 min. The starch paste was cooked to a temperature of 72 ± 1°, and the total massing time was kept at 5 min

Table I—Starch Paste Dilutions

	Experiment A	Experiment B	Experiment C
Lactose, g	860	860	860
Starch (in dry mix), g	47	47	47
Starch (in paste), g	26	26	26
Water (for paste), ml	100	130	160
Water (used to *qs*), ml	100	70	40

Table II—Percent Fines Formed by Attrition

Experiment	500 Revolutions	1000 Revolutions
A	8.4	11.0
B	5.6	7.1
C	3.4	4.5