represent a viable drug delivery mode, plasma phenytoin levels from 3-pentanoyloxymethyl-5,5-diphenylhydantoin in tributyrin, administered orally to rats at a 30 mg/kg phenytoin equivalent dose were compared with phenytoin from an aqueous solution of sodium phenytoin. Figure 5 is a plot of the mean blood levels for the two dosage forms. The superiority of the lipid vehicle–prodrug combination is obvious. Table VI summarizes the mean (and standard deviations) phenytoin blood levels at each sample time and the AUCs up to 26 hr. Presumably, the poor bioavailability of phenytoin from the sodium phenytoin solution was due to the slow redissolution of phenytoin precipitated when the sodium phenytoin was exposed to stomach acid.

In summary, the lipid solubility of high-melting, sparingly water- and lipid-soluble drugs can be altered by transient molecular modifications. Such modification may act to disrupt the major intermolecular interactions in the crystal lattice responsible for the undesired physical properties. For these poorly lipid and water soluble drugs, improved oral delivery can be effected by the synthesis of low-melting lipoidal prodrugs, which can then be incorporated into metabolizable vehicles. *In vivo* parent drug release from such a vehicle–prodrug combination is speculated to be initial lipolysis of the vehicle giving rise to prodrug release, followed by prodrug absorption and cleavage.

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Computation of In-house Quality Control Limits for Pharmaceutical Dosage Forms Based on Product Variability

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Abstract □ A method for establishing sampling plans for in-house limits that fix both the producer's and consumer's risks is presented for pharmaceutical systems in which both between-batch and within-batch variations are present. Such plans can always be constructed and require more or less sample assays depending on the variability of the process. The computations involve a numerical approximation to the bivariate normal distribution.

Keyphrases □ Product variability—pharmaceutical dosage forms, quality control limits □ Pharmaceutical dosage forms—quality control limits, product variability □ Quality control limits—pharmaceutical dosage forms, product variability

A recent article by Boudreau and Harrison (1) described a method for establishing "House Guides" that achieve "a high degree of assurance at a minimum of cost." These guides were set up in an effort to establish reasonable in-house limits, tighter than official specifications, which would give a high level of assurance that the finished product would not be out of specifications set by the NDA, FDA, official compendia, or company policy. According to Boudreau and Harrison (1), the FDA has recommended that a risk of releasing an out-of-specification product should be ≤5% based on the in-house guidelines. The establishment of in-house specifications is important because of problems that can arise when the assay of a batch of material is close to, but within, the official specifications. In these cases, the true mean potency has a good chance of being outside the official limits. Boudreau and Harrison in developing their formula, EVAL, were prompted by the difficulty of computing house limits using a single formula that would satisfy the 5% criterion and would, at the same time, consistently pass good batches which have a relatively large variation. They recommended the use of three formulas based on the relative amount of variation. It is possible to establish such in-house limits (hereafter referred to as IHLs) for any product based on its variability. If the batch-to-batch variability is so great that many batches truly fall outside the official limits, no plan will consistently pass these batches. In these situations, it is the responsibility of the manufacturer to improve the process so as to reduce the variability.

However, once the sources of variability have been identified, plans can be established with known properties. In the present case, the plans should accept out-of-specification material 5% of the time, at most. Another important criterion is that the plan should pass good material with a known probability, *e.g.*, 90% of the time.

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Table I—Scheme for Nested Design to Estimate Variance

		Batch I Tablet		Batch II Tablet		Batch III Tablet	
		1	2	1	2	1	2
Replicate	1	X	X	X	X	X	X
	2	X	X	X	X	X	X

PRELIMINARY CONSIDERATIONS

If the variability in a dosage form potency is due to assay error only, then the problem of setting IHLs is relatively simple. As previously described (1), the limits for in-house specifications to maintain a 5% error rate or less are (using the authors' notation (1) and assuming that the data are normally distributed):

$$\text{UPS} - 1.65S_a, \quad \text{LPS} + 1.65S_a \qquad \text{(Eq. 1)}$$

where S_a is the assay standard deviation (SD), UPS is the upper product specification, and LPS is the lower product specification. The assay SD, S_a, can be determined from control charts or replicate assays. The IHLs can be made to be as close to the UPS and LPS as we wish by increasing the number of samples assayed. Then the IHLs are:

$$\text{UPS} - 1.65S_a/\sqrt{N}, \quad \text{LPS} + 1.65S_a/\sqrt{N} \qquad \text{(Eq. 2)}$$

where N is the number of samples assayed.

The above probability statements are correct if the product is homogeneous, such as would occur with solutions or other homogeneous mixes. In these situations, the sampling procedure and the number of samples to be assayed are unambiguously defined. If the variability is composed of both assay error and sampling error, which would occur in the case of tablets (when tablets are not identical), then the number of samples to be assayed and the procedure for setting limits require further analysis. For example, a duplicate determination could be two single-tablet assays or one tablet assayed in duplicate. If S_t, the standard deviation due to only tablet differences, is 5%, S_a is 2.5%, and the UPS is 110%, a single assay would yield IHLs of $110 - 1.65\sqrt{5^2 + 2.5^2} = 100.8\%$. Similarly if the LPS is 90%, the lower IHL would be 99.2%. These limits would probably be untenable. A duplicate assay (single assays of two tablets), for example, results in an upper IHL of $110 - 1.65\sqrt{(5^2 + 2.5^2)/2} = 103.5\%$.

The problem of setting limits based on assay variation only, as correctly pointed out (1), is that other sources of variation are not accounted for. In the above example, tablet variation is included in the error, and such a procedure would properly meet the 5% FDA recommendations. Although this takes care of the so-called consumer's risk, the producer's risk (the risk of rejecting good products) is not clearly defined. This report presents a method of constructing in-house guidelines that will define both of these risks.

STATISTICAL CONCEPTS

The problem of defining both the producer's and consumer's risks when setting acceptance/rejection in-house guidelines is more or less difficult, depending on the nature of the variability of a product. The simplest case is a homogeneous system that does not vary from batch to batch but has assay error associated with it. More common are systems that have both assay error and batch-to-batch variability as well as being nonhomogeneous, *i.e.*, having unit-to-unit variation. Thus, all of these sources of variability must be considered in setting up a suitable quality control plan.

The calculation of the aforementioned sources of error can be accomplished in several ways. Quality control records for many batches where replicate assays are performed within each batch may be sufficient to supply the necessary estimates. The use of Shewhart control charts for means and variability (range or, preferably, standard deviation) accomplish the same end. Since the discussion in this paper is based on an assumption that the process is not changing, Shewhart control charts can also help ensure that the process is in "control." An experimental design (known as a nested design) may be implemented where several units from each batch are assayed in replicate (duplicates are usually sufficient) for many batches, as shown in Table I.

Table II—Analysis of Variance for a Nested Design to Estimate Components of Variance

Source	Mean Square Estimates[a]
Batches	$rtS^2_b + rS^2_t + S^2_a$
Tablets (within batches)	$rS^2_t + S^2_a$
Assay error	S^2_a

[a] r = Number of replicate assays on each tablet; t = number of tablets; S^2_a, S^2_t, and S^2_b are the variances associated with the assay, tablets, and batches, respectively.

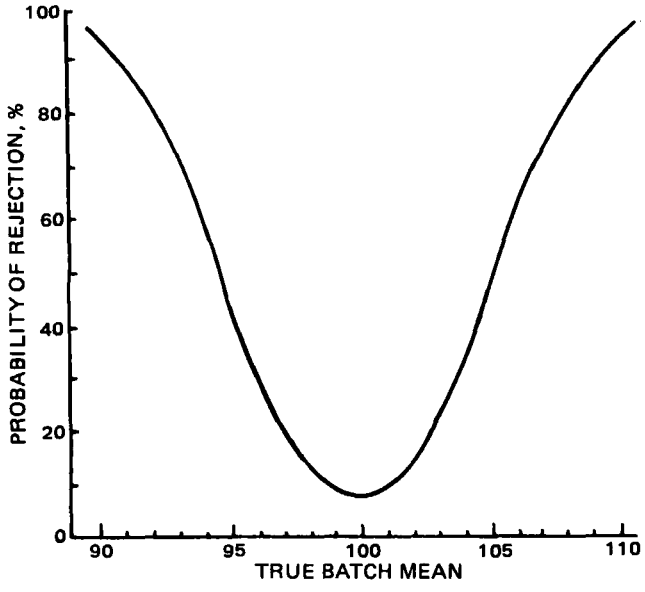

Figure 1—*OC Curve for batch with* $S^2_t + S^2_a = 25$, *true mean = 100,* N *= 3.*

This design allows the estimation of the variance due to assay, unit-to-unit, and batch-to-batch variability (components of variance) (2). The computations in this paper assume that the variances are known (typical Shewhart control charts are constructed under the same assumption). If a sufficient amount of historical data are available, this assumption will not cause problems. For a new process, specifications and/or the sampling plan should be suitably modified as data become available and variance estimates stabilize. The analysis of variance is shown in Table II.

The variance of a single tablet assay is $S^2_t + S^2_a$. If this variance is so large that an unreasonable IHL is obtained to satisfy the 5% criterion, this variability can be effectively reduced by performing replicate assays. This is usually more efficiently accomplished by assaying more than one tablet rather than performing replicate assays on the same tablet, but the optimal procedure depends on the magnitude of S^2_t, S^2_a, and time-cost estimates. For example, the variance of the average of two replicate assays of two tablets is $S^2_t/2 + S^2_a/4$. The variance of the average of four single tablet assays is $(S^2_t + S^2_a)/4$, smaller than that of two replicate assays of two tablets, but which may be more costly to run. Data derived from content uniformity tests can be useful to develop and monitor IHLs because of the relatively large amount of data (at least 20 individual tablet assays per batch) that is readily available for products

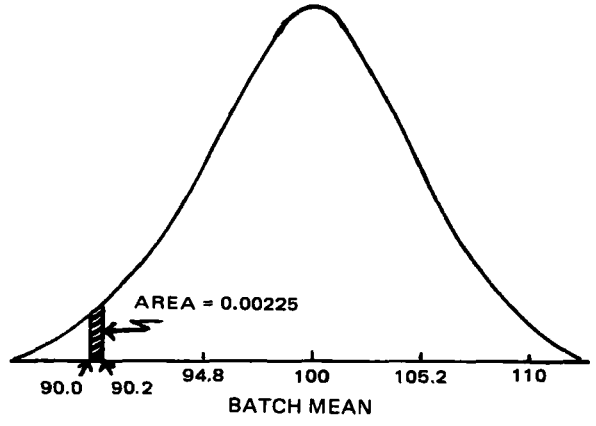

Figure 2—*The shaded area represents the probability of a batch mean falling between 90.0 and 90.2.*

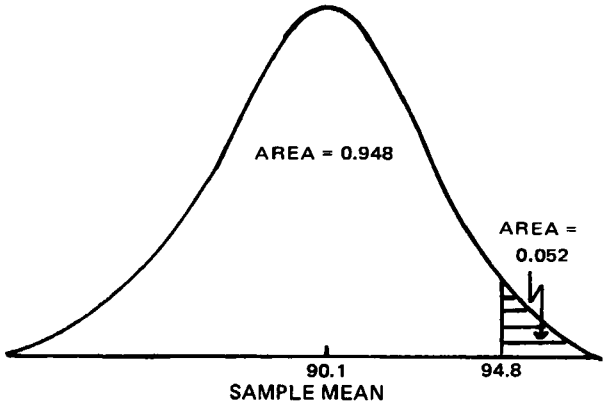

Figure 3—*Normal curve with mean equal to 90.1 showing the probability of a sample mean being below 94.8 (unshaded area, p = 0.948).*

undergoing this test. However, data may also be derived from the usual composite assays performed in replicate. Because most solid dose forms undergo content uniformity tests, and the results of these multiple single tablet (or capsule) assays provide more data for variance estimation, the remaining discussion will consider single-tablet assays. The discussion applies equally well to composite assays where sufficient data are available to precisely estimate the variance components. For composite assays, the variance of a single tablet assay, $S^2_t + S^2_a$, is replaced by $S^2_t/C^2 + S^2_a$, the variance of a single composite assay, where the composite consists of C tablets. The variance in the latter case may be reduced by performing m assays on each of n composites, where the variance of the mean result is $S^2_t/nC + S^2_a/nm$. This is analogous to the variance of the mean of t single tablet assays when $c = M = 1$.

Ignoring batch-to-batch variability for now, it is clear, based on the above discussion, that the IHLs can be made as close to the UPS and LPS as we wish by performing more assays. Consider the following example. Experience has shown that the *SD* (assay error) of a tablet with 100 mg of drug is 5% ($S^2_a + S^2_t = 25$). If single tablets are assayed and the official specifications are 90–110 mg, the IHLs are:

$$110 - 1.65 \times 5 = 101.75 \text{ and } 90 + 1.65 \times 5 = 98.25$$

a very tight specification for a 100-mg tablet. However, if three tablets are assayed, the standard error of the average is $5/\sqrt{3} = 2.89$, and the IHLs are 94.8–105.2, with the same probability (≤5%) of accepting a bad lot. Therefore, if considerable variability exists, the IHLs can be made wider (close to, but not exceeding the UPS and LPS) by performing replicate assays.

SAMPLING PLANS: MANUFACTURER'S RISK

Since there are any number of plans, depending on the number and kind of replicate assays, all of which will ensure that no more than 5% of out-of-specification product will be passed, another criterion can be used to fix the number of assays to be used for a given plan. This criterion, as previously mentioned, the manufacturer's risk, is the chance of rejecting a good batch of product based on the in-house limits. A good batch is one that is truly within the official limits, the UPS and LPS. The following discussion will present a method for establishing plans based on both the α and β risks: the chance of accepting lots of poor quality or rejecting lots of good quality, respectively. Since only one assay will be performed per tablet, the variance of a single assay is $S^2_a + S^2_t$. Also, the α error will be at most 5% for each batch.

Some practical considerations should be emphasized. When considering sampling from batches, the variance of the estimate of a mean value taken from a batch (any batch taken at random) is $S^2_b + (S^2_t + S^2_a)/t$, where t is the number of tablets assayed. Thus, it is not possible to reduce the variance of this estimate below S^2_b by increased sampling of tablets within a batch. The way to reduce batch-to-batch variation (S^2_b) is by careful and controlled manufacturing procedures, as previously noted. If the batch variation is so large that the sample averages consistently border on the official limits, it would be advantageous to the manufacturer to improve the process. Otherwise it will be difficult to pass batches using any plan.

An example will be used to illustrate the general procedure of constructing a sample plan. Consider a product whose overall average as determined from historical data or control charts over many batches is

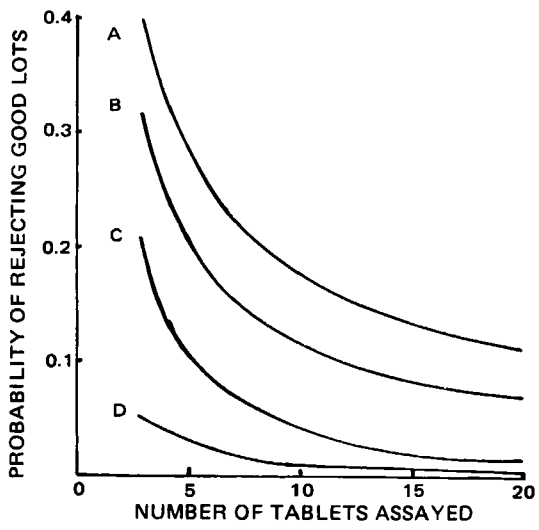

Figure 4—*Probability of rejecting good batches based on in-house limits.*
For curves A, B, and C, $S^2_t + S^2_a = 25$. For curve A, $S^2_b = 50$; for curve B, $S^2_b = 25$; for curve C, $S^2_b = 10$; for curve D, $S^2_t + S^2_a = 10$ and $S^2_b = 10$.

100% of label. The LPS and UPS are 90 and 110%, respectively, and the assay and unit-to-unit variabilities are known. The batch-to-batch variability can be obtained from historical data or by using an experimental design similar to that previously described. Suppose, in this example, that three tablets are assayed and $S^2_a + S^2_t = 25$. The IHLs are $(90 + 1.65\sqrt{25/3},\ 110 - 1.65\sqrt{25/3})$ 94.8–105.2 (Eq. 2). This fixes the consumer's risk at ≤5%. The properties of this plan for any given batch can be described by an operating characteristic (OC) curve, where the probability of rejection is plotted as a function of the true batch mean (Fig. 1). Clearly, the probability of rejection is not constant but changes depending on the true mean of the particular batch being tested. For any given batch, the true mean is not known and the probability of rejection, therefore, is also not known. (It should be again emphasized that the probability of accepting a bad batch is fixed at ≤5% for all batches by application of Eq. 2.)

The problem to be solved is to establish a sampling plan that will reject good batches using the in-house guidelines, a small but known proportion of the time over many batches. This can be accomplished if S^2_b and $S^2_t + S^2_a$ are known and if batch means and assays are normally distributed, by use of the bivariate normal distribution. The probability of rejecting a good batch (one whose true mean is between 90 and 110 mg) using the IHLs as the criteria, can be computed based on a basic probability theorem:

Probability (a sample mean falls outside the IHLs, given that the true batch mean is within the official specifications) = Probability (sample mean falls outside the IHLs and the true batch mean is within official specifications)/Probability (true batch mean is within official specifications)[1]. (Eq. 3)

The following sample calculation will give a close approximation to this probability. The example uses official limits of 90–110 with a long-term average of 100, but this process can be applied to any specified limits or any long-term mean of a product.

1. Divide the region between 90 and 110 into small intervals, *e.g.*, 100 divisions of 0.2 units each.

2. Compute the probability that the true batch mean lies in each of the 100 intervals. For example, if $S^2_b = 25$, the probability of a batch mean falling between 90.0 and 90.2 is 0.002248, as calculated from areas under the standard normal curve (Fig. 2).

3. For each of the 100 intervals, compute the probability that a sample mean from a batch in the interval will fall outside of the IHLs. This can be closely approximated by computing the probability based on a true batch mean midway in the interval. For example, to calculate the probability that the mean if a sample of size 3 will fail the in-house limits if

[1] Note that the producer's risk, the probability of rejecting a good lot, is defined here as a conditional probability, based only on the good lots manufactured. This risk may also be calculated on the basis of all lots produced, both good and bad. In this example, using the results shown in Table III, the former calculation results in a risk of 0.0664/0.955 = 0.0695; the latter calculation results in a risk of 0.0664.

Table III—Properties of a Plan with $N = 20$, $S^2_b = 25$, $S^2_t + S^2_a = 25$

	Probability that a batch is			
	Within Official Specifications (0.955) and		Outside Official Specifications (0.045) and	
Plan A[a]	Passes In-House 0.8881	Fails In-House 0.0664	Passes In-House 0.0004	Fails In-House 0.0446
Plan B[a]	Passes 0.937	Fails 0.017	Passes 0.004	Fails 0.041

[a] Plan A: Assay 20 single tablets. Pass batch if average is within IHLs.
Plan B: Assay 20 single tablets. Pass batch if average is within IHLs. Reject if average outside official specifications. If average is between IHLs and official specifications, assay 20 different tablets and average the 40 tablets. If the average of the 40 tablets is within official specifications, pass the batch. Otherwise, reject the batch.

the batch mean is between 90 and 90.2, consider μ, the true batch mean to be equal to 90.1. The problem, then, is to compute the probability that the sample mean will be <94.8 or >105.2, if the true mean of the batch is 90.1. The probability of the mean being >105.2 is virtually zero. The probability that the sample mean is less than 94.8 can be calculated knowing that the variance of the mean of three tablets is 25/3 ($S^2_t + S^2_a = 25$). Again, using areas under the standard normal curve, this area is equal to 0.948, as shown in Fig. 3.

4. Multiply the probabilities obtained from steps 2 and 3 for each of the intervals in step 1 and sum over all intervals (between 90 and 110). This result closely approximates the probability of observing a sample mean outside of the IHLs and a batch mean within official specifications. This sum is equal to 0.320 for this example.

5. Divide the probability obtained in step 4 by the probability that a batch mean will fall between 90 and 110. In this case the latter probability is equal to 0.955 (95.5% of the batches manufactured will have a true mean between 90 and 110 if $S^2_b = 25$.). This quotient is the answer to the original problem: the *probability that a good batch will fail* based on the IHLs as expressed in Eq. 3. This is equal to 0.320/0.955 = 0.335 in the present example.

There is no explicit solution to the above problem, but by selecting smaller intervals for the batch means (less than 0.2 in step 1, the approximation can be improved slightly. Although this calculation may seem complicated and tedious, it can be accomplished easily by a simple computer program[2].

Figure 4 is a plot of the probability of rejecting good batches as a function of sample size showing the effect of changing $S^2_a + S^2_t$ and S^2_b. With such information a suitable sample size can be chosen to fix the manufacturer's risk at an acceptable level. These plans always have a probability of <5% of accepting lots that are out of the official specifications.

If $S^2_t + S^2_a = 25$, a product with $S^2_b = 25$ would require more than 55 tablets to achieve an erroneous rejection rate of 5%. If $S^2_b = 10$, a sample of 8–9 tablets would suffice. If $S^2_t + S^2_a$ is reduced to 10, and $S^2_b = 10$, 3–4 tablets would give the required protection.

The complete properties of any plan can be calculated using a variation of the same computer program used to compute the probabilities of erroneously rejecting good batches as described above. The probabilities shown in Table III were derived from a plan in which 20 tablets were assayed, with $S^2_b = 25$ and $S^2_t + S^2_a = 25$, a plan that fixes the IHLs at 91.84–108.16. More than 95% of batches of this product will be within official specifications. Of these, 6.64% will fail the in-house specifications. The probability of a good batch failing the in-house specifications is 6.64/95.55 = 0.0695, the producers risk.

The consumer's risk can be defined as the probability that a bad batch will be among those passed by the producer, i.e., the probability that a batch is bad given that it is accepted by the producer. Using the data in Table III, the consumer's risk, according to this definition, is 0.0004/(0.8881 + 0.0004) = 0.00045.

If the sample mean falls between the IHLs and the official specifications, usually it would be prudent not to reject immediately the batch, but to perform further assays to zero in on the true batch average. However, such sequential sampling changes the probabilities as outlined in this paper. The probabilities resulting from sequential sampling plans depend on the nature of the sampling plan, and increase the consumer's risk and decrease the producer's risk. The probabilities resulting from a sequential plan can be closely approximated by using a procedure similar to that previously described for the single stage sampling. A reasonable sequential plan would be as follows. Assay 20 single tablets[3]. Accept the batch if the average falls within the IHLs, and reject the batch if the average is outside the official specifications. If the average falls between the IHLs and official specifications, assay 20 more single tablets and compute the average of the 40 tablets assayed. If the average of the 40 tablets falls within the official specifications, accept the batch. Otherwise, reject the batch. The probabilities of acceptance and rejection using this plan is shown in Table III, Plan B. The producer's risk is reduced to 0.018 and the consumer's risk is increased to 0.0043 as compared with the risks of 0.0695 and 0.00045 for the single-stage sampling plan.

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[2] The author will supply a routine for the TI 59 upon request, which will compute this probability given S^2_b, $S^2_t + S^2_a$, and the sample size for assay.

[3] Of course, a similar plan could be constructed based on composite assays.