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Acceptance Sampling of Finished Pharmaceutical Products

By H. LATHAM BREUNIG and E. P. KING

In this paper we describe some problems inherent in acceptance sampling of finished pharmaceuticals, and provide an expository account of the power and effectiveness of modern statistical methods in the solution of these problems.

STATISTICAL techniques form an integral part of every effective quality control program. Sound statistical procedures for accepting or rejecting batches of finished product based on evidence obtained from samples were given tremendous impetus during World War II through their recognition and application by military procurement agencies. Since that time, these methods have enjoyed a continually expanding circle of usage in the chemical and process industries.

On the other hand, criteria currently used for acceptance sampling of medicinal products, based upon chemical or biological assay, are susceptible to considerable improvement. It would further appear that as this need for improvement becomes recognized and as changes in the sampling procedures are proposed, even these revisions do not incorporate the efficient statistical methods now available.

The sampling procedures of today are probably the result of a natural process of evolution. For many years the majority of active drugs were dispensed in the form of fluid extracts and solutions. The first official sampling procedure to appear in the United States Pharmacopeia (1) pertained to the assay of crude drugs which were to be extracted. Because the liquid extract was recognized as homogeneous, it was natural that attention be shifted from the finished product and focused on accurately estimating the amount of active principle in a shipment of crude drug. It was logical to strive for a "representative sample" of the shipment, ignoring variation from portion to portion within a shipment, because the entire shipment would ultimately be extracted as one unit to form a homogeneous fluid. Hence the procedure called for taking core samples, compositing, quartering, and the like.

However, as time passed, new dosage forms came into prominence. Tablets and filled capsules replaced fluid extracts and solutions. Since this was a gradual process, the sampling procedures for crude drugs were carried over unchanged to the new forms. Unfortunately, however, the problem had changed. Unit-to-unit variation among finished tablets or capsules from the same batch is inherently greater than the variation from one portion of a fluid to another. A thoroughly mixed fluid is homogeneous throughout, but two tablets from the same batch can differ in potency because of composition variation in granulation and because of weight variation among the tablets after compression.

Both physician and patient are concerned with whether or not the amount of drug in a single dose conforms to label claim. Estimating the average amount of drug per unit weight in the parent batch is only a first step. The older sampling methods, aimed at assessing the amount of active ingredient in a crude drug shipment, simply cannot be depended upon to provide information about unit-to-unit differences in tablets and filled capsules. Hence the "representative sample" approach, although adequate for its original purpose, must now make room for techniques which concentrate on individual units of finished product; methods which are concerned not only with average drug content but also with variation in potency from unit to unit. Such a program is given further impetus by the development, in recent years, of analytical methods which permit

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accurate assay for the relatively small amount of active ingredient in each unit.

The need for this type of change has been recognized by many responsible individuals—both within the Food and Drug Administration and within the pharmaceutical industry. Reports such as that by Pernarowski and co-workers (2) have discussed dosage variation among single tablets of several items. However, some of the proposals which have been made still fall far short of the effectiveness that could be achieved through the use of statistical methods of acceptance sampling. Furthermore, reference to sampling plans in *Interim Federal Standard No. 00140 (Navy-Bu Med)* (3) concerning procurement of tablets for medicinal purposes underlines the need for an understanding of the properties of such plans. Our purpose in the following expository discussion is to illustrate the advantages to be had through the application of these modern statistical principles.

Inherent Variation.—The inescapable fact upon which statistical sampling plans are built is that there is inherent variation in the output of any manufacturing process. No two ball bearings have precisely the same diameter. No two capsules, tablets, or ampules will contain exactly the same amount of active ingredient. Even if it were possible to produce two identical units of product, we could never verify that they were exactly alike because there is no test procedure known to modern science which is capable of producing absolutely error-free measurements. The widespread belief that each tablet in a bottle contains exactly the same amount of active ingredient is every bit as erroneous as the notion that every male child in the United States will attain exactly the same weight at his fifth birthday. The difference is not one of kind—only of degree.

Hence, the problem of constructing an efficient acceptance sampling procedure is not simply one of determining whether or not each unit of product contains exactly the amount of active ingredient specified on the label. The problem is rather one of assuring that a "sufficiently large" percentage of the units falls "sufficiently close" to label claim.

Components of Variation.—In the discussion which follows, when we refer to the variation exhibited by a series of measurements we will be referring to *total* variation, unless otherwise specified. This total variation is not attributable to the product alone nor to the method of assay alone; it is actually the composite result of several variables simultaneously exerting their influences. For example, if a random sample of several tablets is drawn from a parent batch of a particular pharmaceutical product and an individual assay performed on each tablet, the observed variation among the resulting determinations represents the joint contribution of the following major factors: (*a*) differences in weight from tablet to tablet; (*b*) differences in the proportion of active ingredient from one tablet to another, resulting from inhomogeneous mixing of the drug with inert excipients in the granulation from which the tablets are compressed or molded; and (*c*) variation in assay, reflecting not only the precision of the measurement process but also such laboratory variables as sample preparation, equipment, and analysts.

In addition to the above, a lot-to-lot component of variation can reflect such additional factors as variation in raw material potency and variation in raw material assays.

A Typical Statistical Sampling Problem.—In order to illustrate the effectiveness of a statistical plan, together with the rationale behind it, let us take a realistic sampling problem and sketch the steps in its solution. Suppose an acceptance sampling procedure is required for finished lots of a particular tablet item. In other words, we wish to develop an efficient method for classifying a given production lot as "acceptable" or "unacceptable," basing this decision solely upon the information obtained from a small random sample of tablets drawn from the lot.

The first step is to arrive at explicit meanings for the terms "acceptable" and "unacceptable." If the product were an automobile tire, acceptable quality would be defined to reflect the mileage requirements of the consumer under typical driving conditions. If the product were an incandescent lamp, quality standards would incorporate the length of life that should be expected in normal usage. Similarly, quality requirements for an ethical drug should bear a close relationship to the therapeutic needs of the patient. If the range between the minimum effective dose and a toxic dose is small, tolerances on the product should tend to be narrow. On the other hand, if there is a broad dose range within which each dose is nontoxic and of equal therapeutic effect, the tolerances on the product should tend to be broad. By contrast, it appears that present official tolerances on drugs are frequently based, instead, upon the precision and accuracy that is attainable with current assay procedures. It may well be that more reasonable standards should reflect both factors.

A statistical sampling plan normally requires that four quality standards be specified: (*a*) an acceptable quality level (*AQL*), (*b*) an unacceptable quality level (*UQL*) (*c*) the risk of misclassifying an acceptable quality lot, sometimes referred to as the "Producer's Risk"(R_p), and (*d*) the risk of misclassifying an unacceptable quality lot, sometimes referred to as the "Consumer's Risk" (R_c).

When these four basic standards have been established, the corresponding sampling plan is completely determined. If the *AQL* and *UQL* are quite far apart and high risks of misclassification can be tolerated, as might well be the case with sodium chloride tablets, the plan will call for very few units in the sample. If the *AQL* and *UQL* are close together and very small risks of misclassification must be maintained, as on potent steroids, a large sample will normally be required.

In terms of our example, let us set up hypothetical quality standards that might be considered reasonable for a particular tablet product. We will assume that the unit of product from the point of view of the patient is a single tablet. Let us further assume that the definition of acceptable quality shown in Fig. 1 conforms to the therapeutic requirements for this item.

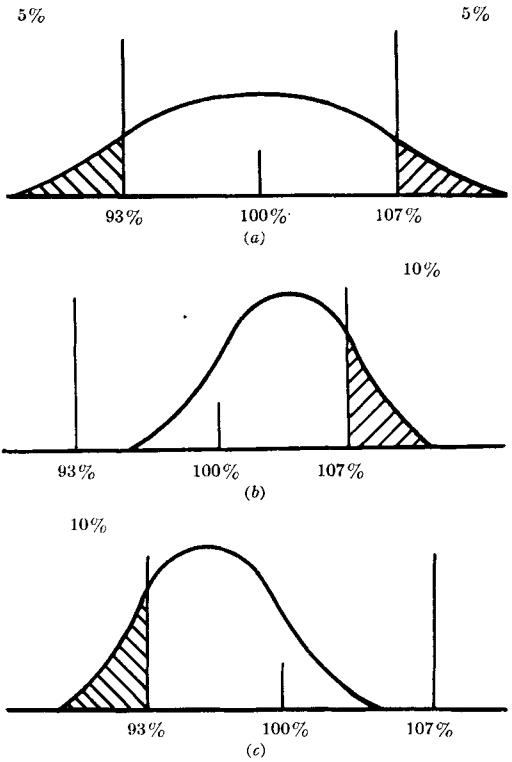

Fig. 1.—Distributions of single tablet assay values, acceptable quality, showing shifts in mean (*a*), mean at label claim; (*b*), upward shift; (*c*) downward shift.

A very large number of single tablet assay values should, when tabulated, distribute themselves under a bell-shaped curve in such a way that, for example, 90% of the tablets would fall within ±7% of label claim. This corresponds to an $AQL = 10\%$. In an analogous fashion let us define UQL as a lot of finished tablets with, say, 40% of its units outside of ±7% of label claim. Examples could be of the types illustrated in Fig. 2.

Let us assume further that we can tolerate misclassifying an acceptable lot no more than 10% of the time and an unacceptable lot no more than 10% of the time. We now have the four required standards: AQL, 10% of units outside ±7% of label claim; UQL, 40% of units outside ±7% of label claim; R_n, Producer's Risk = 10%; and R_c, Consumer's Risk = 10%.

It should be emphasized that we have chosen the numerical values for these standards quite arbitrarily for purposes of illustration. In actual practice this choice would, of course, rest with whatever official group was responsible for this type of policy decision.

Operating Characteristic Curve.—We have pointed out that R_p and R_c, the producer's and consumer's risks, are inherent in any sampling plan. A convenient graphical way of presenting these risks is through the operating characteristic (OC) curve.

In preparing to graph an OC curve, we take for the horizontal scale running from zero to 100%, the quality of submitted lots expressed as per cent defective, *i.e.*, the percentage of units in a lot which falls outside of the official tolerances for the product. On the vertical scale, also running from zero to 100%, is the percentage of lots of a given quality which is expected to be accepted if submitted to the sampling plan.

In an ideal situation, if we agree that a manufacturer is doing a good job if he submits to the sampling plan batches containing 10% defective units, we would accept all batches containing this proportion (or less) of defectives, and reject every batch containing 10.1% or more defectives (Fig. 3).

Such a plan would exhibit perfect discrimination. But it would be unrealistically stringent, for it would make no allowance for batch-to-batch variation about the 10% figure. What we want is a plan which will pass a high percentage of acceptable batches but at the same time guard against poor quality by accepting only a small proportion of bad lots if submitted. This would lead to a plan such as is shown in Fig. 4.

If we still concede that the manufacturer is doing a good job in submitting material containing 10% defective units ($AQL = 10\%$), we may want to be reasonably sure of passing this quality 95% of the time ($R_p = 5\%$). On the other hand, we may decide that 20% defective is intolerable ($UQL = 20\%$), and

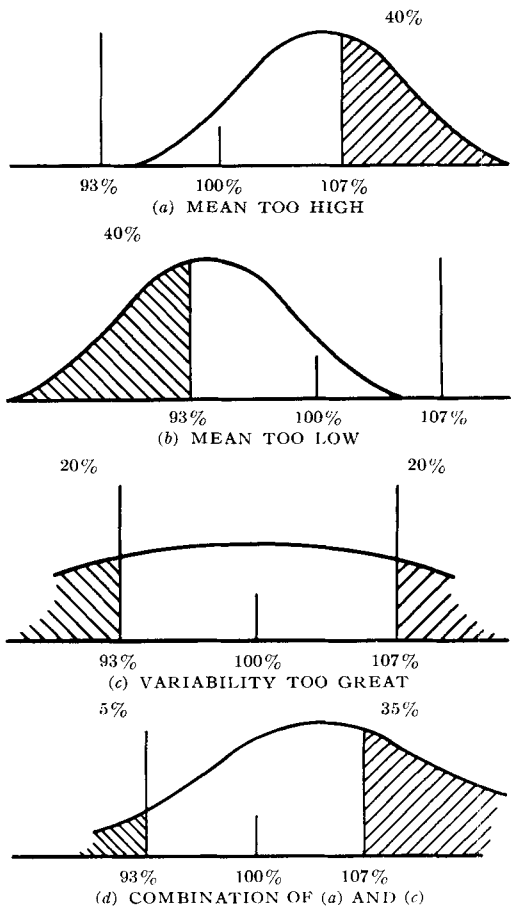

Fig. 2.—Distributions of single tablet assay values, unacceptable quality, showing shifts in location and dispersion.

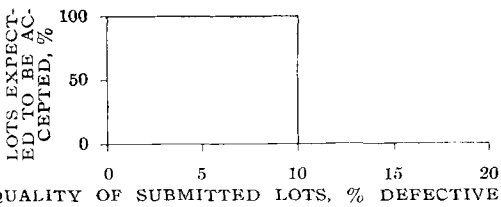

Fig. 3.—Ideal operating characteristic (*OC*) curve illustrating perfect discrimination but unrealistic stringency.

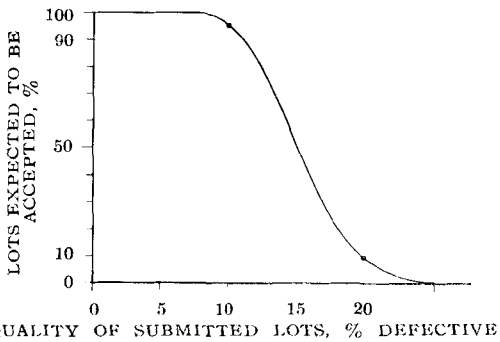

Fig. 4.—Typical *OC* curve from MIL-STD-414 (5), p. 27, illustrating $AQL = 10\%$; $UQL = 20\%$; $R_p = 5\%$; $R_c = 10\%$; $n = 85$.

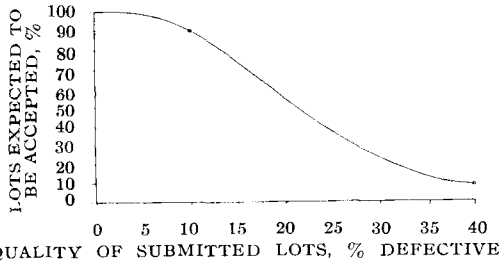

Fig. 5.—*OC* curve for tablet example, from MIL-STD-414 (5), p. 11, illustrating $AQL = 10\%$; $UQL = 40\%$; $R_p = 10\%$; $R_c = 8\%$; $n = 10$.

rarely want to pass this, certainly not more than 10% of the time ($R_c = 10\%$). Such a scheme, in practice, would be fair to both the manufacturer and to the patient.

Once these four characteristics of a plan have been agreed upon, the sample size is automatically determined. For the example cited, the sample size would be $n = 85$. Various *OC* curves for different values of sample size and per cent defective may be drawn, and judgment made as to properties of various sampling plans before agreeing upon one which balances the producer's and consumer's risks against the cost of assay. This balance has been discussed by Davies (4).

Construction of the Plan.—For single characteristics which may be measured on a continuous scale, and for which quality may be expressed in terms of per cent defective, the Military Standard 414 [MIL-STD 414 (5)] is an appropriate source of statistical plans if the measurements may be considered random, independent observations from a normal (bell-shaped) distribution. The mathematical and statistical principles underlying Military Standard 414 are described in a document of the same name (6). This reference also contains the specific methods used in computing the various tables and *OC* curves. In the case of pharmaceutical products we have defined per cent defective as that percentage of single dosage units which may be expected to fall above or below specified tolerances, such as those stated in the several individual monographs of the official compendia.

To illustrate the application of MIL-STD-414 (5), we refer again to our example for which tolerances were set at 93–107% of the labeled amount. Suppose this corresponds to 16.2 ±1.13 mg. of pure drug per tablet, *i.e.*, 15.07–17.33 mg./tablet. An inspection lot of tablets is presented for examination. We have previously specified $AQL = 10\%$; $UQL = 40\%$; $R_p = 10\%$; and $R_c = 10\%$. Searching through the operating characteristic curves of MIL-STD-414 (5) for the curve which most nearly corresponds to these requirements (Fig. 5), we find it associated with "Sample Size Code Letter F."

This *OC* curve tells us that lots of $AQL = 10\%$ (10% or less tablets outside of 15.07–17.33 mg./tablet) will be accepted 90% of the time (R_p). This is shown in Fig. 5 where the curve crosses the 10% abscissa at the 90% ordinate. We also see that lots of $UQL = 40\%$ will be accepted only 8% (R_c) of the time, *i.e.*, where the curve crosses the 40% abscissa at the 8% ordinate.

Referring to the appropriate master table for double specification limits, variability unknown, in MIL-STD-414 (5), we find the sample size corresponding to Code Letter F to be $n = 10$, and that the "acceptability criterion," estimated per cent defective, which balances the risks is 21.06%.

The final statistical plan then takes the following form: Select 10 tablets at random from an inspection lot and individually assay each tablet. Estimate the per cent defective in the lot from these 10 determinations. If this estimate does not exceed 21.06% defective, accept the lot. Otherwise, reject it.

Suppose that we obtain the following values: 16.20, 16.18, 15.70, 15.80, 16.05, 15.54, 16.19, 16.40, 17.00, 15.90 mg./tablet.

The details of computation are spelled out in Appendix I. In this instance the total estimated per cent defective is zero and the lot would be passed. Incidentally, the lot would also be passed on the basis of this sample if $AQL = 1\%$; $UQL = 11\%$; $R_p = 10\%$; $R_c = 20\%$.

Current Sampling Practices.—Let us now compare the discriminating ability of the above procedure with that of the typical plan currently specified in the U.S.P. (1) for a tableted product. The latter stipulates that a single assay on a composite sample of n tablets shall fall within $\pm y\%$ of the declared value. We are not concerned here with whether or not the numerical values of n and y are chosen properly. Our purpose is rather to point out that even with ideal choices of n and y, a plan of this type cannot be as effective as a statistical plan. The detailed derivations for this section are given in Appendix II.

Recalling the basic (but arbitrary) requirements specified for our example, and choosing $n = 10$ as the sample size in order to obtain an unbiased com-

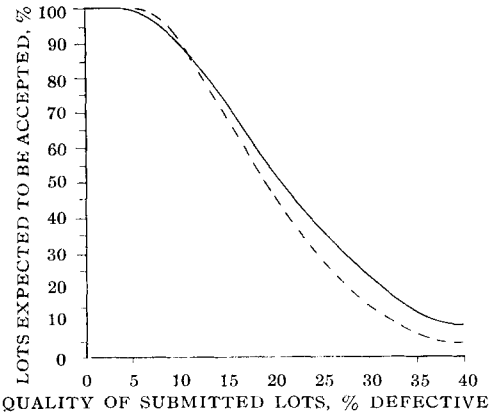

Fig. 6.—Comparison of *OC* curve for statistical plan (Fig. 5) with a curve computed for current plan (dashed line) when mean shifts.

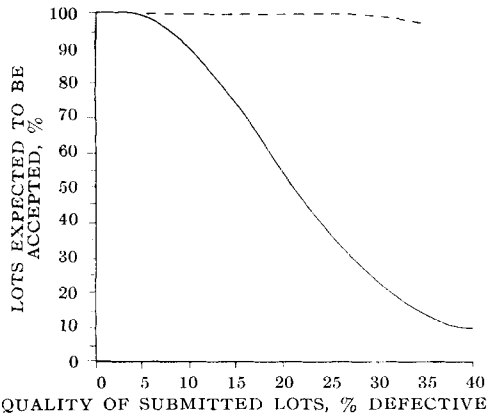

Fig. 7.—Comparison of *OC* curve for statistical plan (Fig. 5) with curve computed for current plan (dashed line) when variation becomes excessive.

parison with the statistical plan just derived, we find the ideal value for y to be approximately 5%. In other words, we have chosen the following specific plan: Perform a single assay on a composite sample of 10 randomly selected tablets and accept the parent lot only if the result falls within ±5% of the decleared value. The *OC* curve for this plan is shown in Fig. 6 for the situation in which inferior quality results from shifts in mean only. Note that this plan provides comparable discrimination to the statistical plan.

If the parent lot has mean potency low enough to force 10% of the tablets below 93% of label claim, both plans will pass this lot approximately 90% of the time. If 40% of the tablets in a lot fall below 93% of label claim because the mean potency of the lot is too low, the statistical plan will accept this type of lot about 8% of the time; the current type plan will accept it about 3% of the time.

Figure 7 shows the *OC* curve for the current plan when inferior quality results from increase in variation from tablet to tablet, the mean always at label claim.

It is clear that the plan is practically powerless to detect this type of trouble. For example, if 40% of the tablets in a lot fall outside ±7% of the declared value (and the lot mean is at 100%), this lot will be passed by the current plan about 94% of the time. The statistical plan, however, because it takes into account both mean and variation, will pass this lot only about 8% of the time, as before.

In actual practice one would expect unsatisfactory lots to exhibit some combination of simultaneous shift in mean and increase in variation. The power of the current plan varies considerably with the type of combination present. Two examples are shown in Fig. 8. The performance of the current plan is clearly inferior to the statistical plan for these combinations.

The reason for poor performance is clear. Because the current method relies on a single assay on a composite sample, it provides no way of estimating the variability in the amount of active ingredient from one tablet to another.

Recent Revisions.—The above shortcoming has been recognized; revisions in the official compendia have been recently proposed which take tablet-to-tablet variation into account. These proposals employ two separate criteria, one for detecting shift in mean only and another for detecting increase in variation only. Revisions of this type are certainly a step in the right direction, but they are still unable to compete with statistical plans because they cannot readily detect the unacceptable lot which has both difficulties operating simultaneously.

Using our example, a specific proposal might read as follows: Select 10 tablets at random from the inspection lot and accept the lot if the following two conditions hold. (*a*) the average drug content of the 10 individually assayed tablets falls within ±5% of the declared value, and (*b*) of the 10 results, not more than two shall differ from the average by more than ±7%.

Let us now examine the performance of this "2-step" plan relative to the statistical plan. If a lot of the quality shown in Fig. 9 is submitted, both the "2-step" plan and the statistical plan will accept it 90% of the time. Since this lot is, by definition,

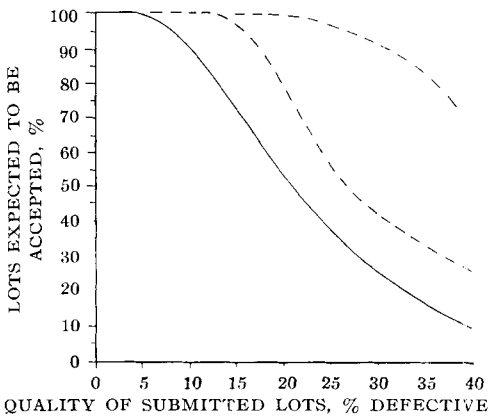

Fig. 8.—Comparison of *OC* curve for statistical plan (Fig. 5) with curves computed for proposed "2-step" plan (dashed line) for detecting shifts in (*a*) location and (*b*) dispersion.

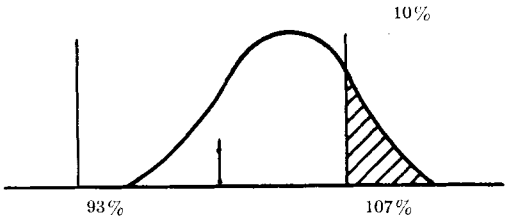

Fig. 9.—Distribution of single tablet assay values for lots expected to be accepted by both the statistical plan and proposed "2-step" plan. Upward shift in mean.

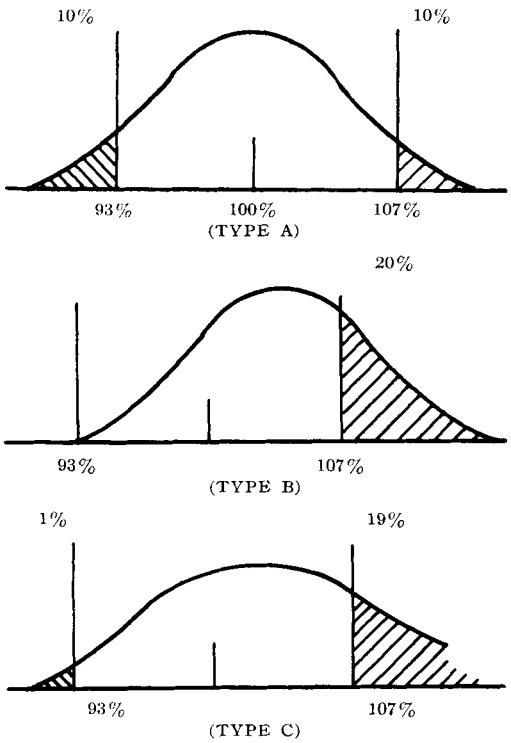

Fig. 10—Distribution of single tablet assay values for unacceptable quality lots of types shown in Table I. Type A, excessive variation; Type B, upward shift in mean; Type C, combination of excessive variation and upward shift in mean.

an acceptable quality lot, both plans are performing as desired. Next, let us consider three different types of lots, each having 20% of its tablets outside limits as illustrated by Fig. 10.

In Table I are shown the percentages of lots containing 20% defective tablets which we would expect to be accepted by each of the two plans, depending upon the type of distribution of the defective tablets outside the postulated official tolerances.

TABLE I.—PER CENT OF LOTS ACCEPTED

	Type A %	Type B %	Type C %
"2-Step" plan	74	50	86
Statistical plan	53	53	53

It is evident from Table I that the "2-step" plan is quite ineffective in detecting a lot of Type *C*, even though this lot has the same proportion of its tablets outside limits as do the other two. The shift in mean in lot *C* is not sufficient to be detected on this basis alone, the variation from tablet to tablet is not sufficient to be detected on this basis alone, and the plan cannot take into account the simultaneous operation of both. See Appendix III for details. By contrast, the statistical plan has the same effectiveness on all three lots.

Advantages of Statistical Plan.—It is clear from the preceding discussion that a statistically designed acceptance sampling plan has many advantages over a plan of any other type.

(*a*) It provides performance that is equal or superior to other plans using the same number of units of product in the sample. This is a result of efficient utilization of the information contained in the sample.

(*b*) Its performance can be studied in advance of its use, by examination of its operating characteristic curve. One can determine beforehand the quality levels that will be consistently accepted and those that will be consistently rejected, when stipulating appropriate risks. It aids in evaluation of official tolerances, not only from these standpoints, but also from that of practical economics in the determination of reasonable sample sizes.

(*c*) The statistical plan lends itself not only to the need of the manufacturer for sound acceptance sampling of his production lots, but also to that of the regulatory agencies who, having little information concerning in-plant quality controls, must perforce base their decisions on packages picked up in the market place. (It should be pointed out that such a package may not be expected to contain units which are randomly chosen from an entire production lot but will represent, rather, a small random sublot.)

The Contrasting Functions of Acceptance Sampling and Process Control.—We feel that this discussion would be incomplete without a word of caution regarding acceptance sampling in general. One characteristic common to all sampling programs is that a lot consisting of a large number of units is accepted or rejected on the basis of information obtained from a very small number of units. It is quite unreasonable to expect even the most efficient statistical plans to guarantee that practically all accepted lots will be of the desired quality. Although such a plan can be quite effective in detecting an occasional bad lot when all others are of high quality, it should be borne in mind that this is basically a checking device. A little reflection should convince even the most confirmed skeptic that an inspection operation which utilizes no prior information and which examines a very small percentage of the total output of a production process could easily overlook moderate departures from ideal quality a large percentage of the time. (For example, the statistical sampling plan discussed in this paper would accept lots containing 20% of their tablets outside tolerance limits about 53% of the time. If we wished to develop a plan which accepted lots of this quality only 1% of the time, it would require a prohibitively large number of units in the sample.) If a process were producing unacceptable quality consistently, acceptance sampling of the finished product would be singularly ineffective in preventing

TABLE II.—TABLET ACCEPTANCE PROTOCOL

Double specification limit.
Variability unknown.
Average range method.
One AQL value for both upper and lower specification limits combined.

Item: Tablets
Assay: ——————————
Label Claim: 16.2 mg./tab.
AQL: 10%

Tablet Assay Data: 16.20, 16.18, 15.70, 15.80, 16.05, R_1 = 16.20–15.70 = 0.50; 15.54, 16.19, 16.40, 17.00, 15.90, R_2 = 17.00–15.54 = 1.46.

Line	Information Needed	Value Obtained	Explanation
1	Sample size: n	10	
2	Sum of measurements: Σx	160.96	
3	Sample mean, $\bar{x} = \Sigma x/n$	16.096	160.96/10
4	Average range, $\bar{R} = \Sigma R$/no. subgroups	0.98	(0.50 + 1.46)/2
5	Factor c[1]	2.405	Table C-3
6	Upper specification limit: U	17.33	
7	Lower specification limit: L	15.07	
8	Quality index: $QU = (U - \bar{x})c/\bar{R}$	3.028	(17.33 − 16.096)2.405/0.98
9	Quality index: $QL = (\bar{x} - L)c/\bar{R}$	2.518	(16.096 − 15.07)2.405/0.98
10	Est. lot % def. > U: p_U	0.00	Table C-5
11	Est. lot % def. < L: p_L	0.00	Table C-5
12	Total est. % def. in Lot: $p = p_U + p_L$	0	
13	Max. allowable % of def.	21.06	
14	Acceptability criterion	$p < 21.06$	Accept. Lot

[1] For the derivation of Factor c, see pp. 23–24 of reference (6).

units of inferior quality from reaching the consumer.

A reputable pharmaceutical manufacturer must maintain production methods capable of sustaining the desired quality level and a quality control system which continuously monitors each process from raw material to finished product. This alone assures acceptable quality in the long run. The practice of sampling finished products serves as a check to insure that such a system is actually in use by detecting gross departures from desired quality if they occur.

APPENDIX I

Example of the Application of MIL-STD-414.—Table II shows a specimen protocol which includes details of computation of estimated per cent defective tablets in the lot from which were taken the tablets of our example. The particular situation deals with symmetrical double specification limits about the mean [(5) p. 69]. Other examples are given (5) where per cent defective beyond a single specification limit either above or below the mean may be estimated and also for double specification limits which are not symmetrical about the mean.

Since the procedure is spelled out in such detail, it may appear at first glance to be inordinately long. In practice, however, computation of quality indices and looking up the corresponding estimated per cent defective in Table C-5 (5) takes approximately 3 minutes.

Entries No. 1, 5, 6, 7, and 13 would normally be made in advance of the assay.

APPENDIX II

Operating Characteristic Curves for Current Plan.—The OC curves for the current plan were derived under the assumption that a sufficiently replicated assay of a composite sample of n tablets is equivalent to the average of n individual tablet assays. The mathematical formulation then takes the following form:

Let $x_1, x_2, \ldots, x_{10}$ be independently and identically distributed random variables, each having a normal distribution with mean μ and variance σ^2. Compute their arithmetic mean, $\bar{x}$. If $0.95\ \mu_0 < \bar{x} < 1.05\ \mu_0$, accept the parent lot; otherwise, reject it.

Let $P_A(\mu, \sigma)$ denote the probability of acceptance. Then we have

$$P_A = P_r\left\{0.95\,\mu_0 < \bar{x} < 1.05\,\mu_0\right\} = P_r\left\{\frac{0.95\,\mu_0 - \mu}{\sigma/\sqrt{10}} < u < \frac{1.05\,\mu_0 - \mu}{\sigma/\sqrt{10}}\right\} = F\left(\frac{1.05\,\mu_0 - \mu}{\sigma/\sqrt{10}}\right) - F\left(\frac{0.95\,\mu_0 - \mu}{\sigma/\sqrt{10}}\right) \quad \text{(Eq 1)}$$

where

$$u = \frac{\bar{x} - \mu}{\sigma/\sqrt{10}} \quad \text{and} \quad F(t) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-y^2/2}\,dy$$

The per cent defective (% outside $\mu_0 \pm 0.07\ \mu_0$) which corresponds to $P_A\ (\mu, \sigma)$ can be expressed as

$$p(\mu, \sigma) = p_u + p_L$$

where

$$\begin{cases} p_u = \%\text{ above upper limit} = 1 - F\left(\dfrac{1.07\,\mu_0 - \mu}{\sigma}\right) \\ p_L = \%\text{ below lower limit} = F\left(\dfrac{0.93\,\mu_0 - \mu}{\sigma}\right) \end{cases}$$

The OC curve for shift in mean only (Fig. 6) was obtained by plotting $P_A(\mu, \sigma)$ *vs.* $p(\mu, \sigma)$ for various values of μ, keeping σ fixed at $\sigma = \sigma_0$. The curve for increase in variation only (Fig. 7) was obtained in analogous fashion by varying σ with μ fixed. Finally, the curves in Fig. 8 were obtained by simultaneous variation of μ and σ.

APPENDIX III

Performance Characteristics of Revised Plans.—The "2-step" plan described in *Recent Revisions* can be defined as follows:

Compute the arithmetic mean, $\bar{x}$, of the 10 sample values and accept the lot if the following conditions hold: (A) $0.95\ \mu_o < \bar{x} < 1.05\ \mu_o$, and (B) $|x_i - x| < 0.07\ x$ for at least 8 of the 10 samples values, x_i.

In the notation of the previous section, the probability that condition (A) holds is simply $P_A(\mu, \sigma)$, as given in Eq. 1. The probability, $P_B(\mu, \sigma)$ that condition (B) holds can be approximated by assuming that $x_i - \bar{x}$ and $x_j - \bar{x}$ are statistically independent when $i \neq j$. Letting $h = P_r\ [|x_i - \bar{x}_1| < 0.07\ \bar{x}]$ we obtain for P_B the binomial type expression

$$P_B(\mu, \sigma) = \sum_{r=8}^{10} \binom{10}{r} h^r (1-h)^{10-r}$$

where $h = 2F(0.0738\ \mu/\sigma) - 1$.

The value in Table I corresponding to a particular normal distribution was obtained by first computing μ, σ, $P_A(\mu, \sigma)$, $P_B(\mu, \sigma)$, and then approximating the probability of acceptance for the revised plan as $P'_A(\mu, \sigma) = P_A(\mu, \sigma)\, P_B(\mu, \sigma)$.

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Notes

The Occurrence of *iso*Pelletierine in *Withania somnifera*

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INVESTIGATION of the root alkaloids of *Withania somnifera* Dunal has resulted in the delineation of the alkaloid complex by paper partition chromatography (1), the isolation of tropine and pseudotropine (2), and the isolation and characterization of a new alkaloid, anaferine (3). Compound VII of the chromatogram, cited above, is *dl-iso*pelletierine. The occurrence of this alkaloid in the *Solanaceae* was first reported (4) for the leaves of *Duboisia myoporoides* R. Br.; the previously acknowledged occurrence being the root of *Punica granatum* L., family *Punicaceae*. This finding amplifies the known biochemical heterogeneity of the *Solanaceae* and extends a lysine related alkaloid to yet another genus in the plant kingdom.

EXPERIMENTAL [1]

The alkaloid was isolated from an ethanol extract of the defatted granulated root (81 Kg.). The concentrated extract diluted with water and adjusted to pH 4.7 was adsorbed on a column of Amberlite IRC-50-Na resin and was eluted by a gradient acid-buffer method. The fraction containing *iso*pelletierine hydrochloride was further purified by chromatography on acid alumina (Woelm, grade 1) using ethyl acetate as the eluent. The alkaloid salt (5.67 Gm.) was recrystallized from ethyl acetate.

***iso*Pelletierine Hydrochloride.**—The infrared spectrum was identical to that of a synthetic sample[2] and a natural sample;[3] m.p. 145°, undepressed in admixture with each of the above samples; $[\alpha]_D^{2.5} = 0.00$ (0.21% in ethanol).

Anal.—Calcd. for $C_8H_{16}ClN$: C, 54.07; H, 9.07; Cl, 19.95; N, 7.88. Found: C, 54.38; H, 9.59; Cl, 20.21; N, 7.67.

***iso*Pelletierine Picrate.**—The compound was prepared from the hydrochloride and was crystallized from ethanol; m.p. 148.5 to 149.5°, reported 149–150°. The melting point of a mixture with the picrate of an authentic sample[2] was undepressed.

***iso*Pelletierine 2,4-Dinitrophenylhydrazone Hydrochloride.**—The compound was prepared from the hydrochloride and was crystallized from ethanol-ethyl acetate; m.p. 240–241.5° (decompn.), lit. 242°.

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[1] Analysis by Geller Microanalytical Laboratories, Bardonia, N. Y. All melting points are corrected. Infrared spectra were determined in KBr pellets, using a Perkin-Elmer model 21 spectrophotometer.

[2] Supplied by Prof. J. B. Wibaut and Prof. H. O. Huisman, Holland.

[3] Supplied by Dr. P. I. Mortimer and Dr. J. W. Clark-Lewis, Australia.