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Estimation of Mean Potency and Content Uniformity of Tablets: A New Approach

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Abstract □ Current official procedures for the estimation of mean drug level and of content uniformity in individual tablets do not efficiently utilize all information available to the analyst, nor can confidence statements be made concerning the reported results. The authors present here a plan for combining readily available weight data with that from assays to generate distributions of potency per tablet. Tolerance limits on these distributions reflect not only the proportion of tablets bracketed, but also the degree of confidence to be placed in the finding. Reference is made to Monte Carlo studies on theoretical distributions as well as to examples from production lots of certain tablet items. The efficient utilization of this combined information leads to an improved method for estimating mean potency and content uniformity.

Keyphrases □ Tablets—mean potency, content uniformity □ Drug content uniformity, mean potency estimations—tablets □ Equations—tablet drug uniformity, mean potency □ Computer simulation—drug distribution, tablets

When considering drug dosage forms, the primary concern of the ethical pharmaceutical industry is that the patient receive in his individual dose an amount of medicament close to that claimed on the label. If this is so, the physician may prescribe the product with confidence that the desired drug substance will be available to perform its intended function. There are many facets to pharmaceutical quality assurance but all lead toward ensuring the identity, safety, and bioavailability of the drug of interest. This paper is solely concerned with the amount of drug substance in the unit dose. Such considerations as particle size, rates of dissolution and of absorption, freedom from impurities, and numerous others, while understood to be parts of pharmaceutical quality assurance, are not directly considered here.

Although this paper refers to compressed tablets, the techniques presented could also apply to filled capsules, ampuls, and other dry product dosage forms. Because of variation in homogeneity of granulation and in individual tablet weights, it is obviously unrealistic to expect every unit of product to possess *exactly* the same amount of physiologically active drug, but with good manufacturing practice these variations may be controlled. The subject of drug substance variability has been considered by a number of authors. Olson and Lee (1) have summarized much of the discussion and present an extensive list of references. A more recent paper is that by French *et al.* (2). Breunig (3) has emphasized the importance of weight control for individual units of product. Roberts (4) points out how easily many tablets (and filled capsules and sterile solids) may fail the USP weight variation test when based upon a sample of 20. He develops four rules for acceptance based upon the coefficient of variation of unit weights and provides charts which may be used for evaluation.

PRODUCT SPECIFICATIONS

The existence of variability in pharmaceutical products is recognized by USP XVII (5) and NF XII (6). These official compendia include at least three types of product specifications:

Rubric Limits—Referred to in the separate monographs, they are the bounds within which the mean response of samples of N units of product must fall based upon physiological, biological, or chemical assay. This response is in terms of the weight of drug substance per unit of product as determined upon individual units or as drug substance weight per average unit where test methods applicable to single units are not available. The bounds and the

mean response are generally given in terms of percentage of the labelled amount of drug.

Weight Variation Requirements—These are sampling plans for controlling the variation in weight of units of product about their sample mean. A certain proportion of the sample is expected to fall within various percentages of the mean sample weight, according to the weight class of the item. In the case of dry products, no statement is made relating the mean sample weight to the expected weight for the batch.

Content Uniformity Limits—Official at this time for certain tablet items only, these limits are specifications on drug substance weight present in individual units of product such that at least 96.7% of the assayed units are expected to fall between 85 and 115% of the mean of the rubric limits "average of the tolerances" (see *Reference 5*, p. 906).

None of the above specifications contains any provision for stating the degree of confidence to be placed on the experimental finding. Depending on how a sample is taken, the requirements listed may or may not characterize the population, *i.e.*, the batch or lot from which it is drawn.

PRESENT PROPOSAL

A major unexplored area in this field has been the effective utilization of information from two sources: (*a*) the distribution statistics obtained from large (100–200) numbers of tablets weighed on automatic recording balances, and (*b*) the information recorded for single unit assays on smaller numbers (3–10) of units from the same lot.

A plan is presented for combining the information from these two sources to place approximate tolerance limits on the drug substance weight in individual dosage units of the product from a lot. Several computer simulation studies have been completed. The results of these studies suggest that the proposed method for setting tolerance limits is reasonable. Since this paper is directed towards the pharmaceutical scientist, it contains no mathematical derivations. These may be the subject of a subsequent paper.

THEORY AND REFERENCES

Tolerance limits for normal distributions are discussed by several authors, including Hald (7) and Dixon and Massey (8). The assumption of normality was made for both types of populations under consideration. This assumption should be checked for a particular item by any of the usual tests for normality that the reader may judge pertinent. The following populations are considered: (*a*) tablet weights, say Y, and (*b*) drug substance in formulation material, say P.

Y is measured in milligrams per tablet (mg./tablet) and P in milligrams of drug substance per milligram of formulation material. It is also assumed that the concentration of drug, P, is independent of the weight of the tablet, Y. The relevant distribution statistics are the sample means, $\bar{Y}$ and $\bar{P}$, and the sample variances, S_Y^2 and S_P^2. These estimates are based on N_Y observations of the Y-distribution and N_P observations of the P-distribution.

The variable of interest is YP, the weight of drug substance per tablet. The unbiased estimates of the population mean and variance of YP are easily shown to be

$$\bar{Y}\bar{P} \qquad \text{(Eq. 1)}$$

and

$$S_{YP}^2 = \bar{Y}^2S_P^2 + \bar{P}^2S_Y^2 + \left(1 - \frac{1}{N_Y} - \frac{1}{N_P}\right)S_Y^2S_P^2 \qquad \text{(Eq. 2)}$$

respectively, *e.g.*, Goodman (9).

The distribution of YP (even when P and Y are both normally distributed) is, in general, somewhat unmanageable, but Aroian (10) has shown that as the population coefficients of variation, of which $S_Y/\bar{Y}$ and $S_P/\bar{P}$ are estimates either singly or together, become small, then the distribution of YP is approximately normal. This being so, normal theory can be utilized and approximations thereof to set tolerance limits on the distribution of YP by constructing the interval

$$\bar{Y}\bar{P} \pm K(\gamma_1, \gamma_2, F)S_{YP} \qquad \text{(Eq. 3)}$$

where $K(\gamma_1, \gamma_2, F)$ is the multiplicative factor indexed by the degree of confidence, γ_1, the proportion of distribution covered, γ_2, and the degrees of freedom, F. For values of K see *References 7*, p. 315, and *8*, p. 436. In other words,

$$\bar{Y}\bar{P} \pm KS_{YP} \qquad \text{(Eq. 3}a\text{)}$$

gives approximate γ_1/γ_2 tolerance limits on the distribution of values of YP, based on F degrees of freedom. For instance, if $\gamma_1 = 0.95$ and $\gamma_2 = 0.99$, the expression 95/99 indicates that one can expect, with 95% confidence, that 99% of the individual values of YP are bounded by $\bar{Y}\bar{P} \pm KS_{YP}$ utilizing the amount of information provided by F. In this case, F is not simply some linear function of N_Y and N_P, but is approximately given by

$$F = \frac{(\bar{P}^2S_Y^2 + \bar{Y}^2S_P^2)^2}{[(\bar{P}^2S_Y^2)^2/(N_Y - 1)] + [(\bar{Y}^2S_P^2)^2/(N_P - 1)]} \qquad \text{(Eq. 4)}$$

Equation 4 may be rewritten

$$F = \frac{(C_P^2 + C_Y^2)^2}{[(C_P^2)^2/(N_P - 1)] + [(C_Y^2)^2/(N_Y - 1)]} \qquad \text{(Eq. 5)}$$

where C_Y and C_P are sample coefficients of variation (also called relative standard deviation), derived from either past data, current data, or both. This formula for F was adapted from the results of Welch (11).

Additional Monte Carlo studies suggest that F, as computed in Eq. 5, will be, on the average, too large in some parametric situations. A more comprehensive treatment of the theory, as well as some suggested improvements, will be the subject of a future paper as previously mentioned.

In the next sections some of the Monte Carlo results and the application of the above equations are reported, using actual control laboratory data.

COMPUTER SIMULATIONS

As mentioned in the previous section, Aroian has shown that the distribution of YP is approximately normal if the coefficients of variation of Y and P are "small." To examine this empirically, several Monte Carlo simulations were carried out on an IBM 360-30 computer with various population coefficients of variation. As an illustrative example, the following are presented.

Initially, the histogram (Y-distribution) of 2000 hypothetical tablet weight observations shown in Fig. 1 was generated from a normal distribution with a population mean of 122.58 and variance of 4.0466. The sample mean and variance from these data were calculated to be 122.55 and 4.1299, respectively. The population coefficient of variation is 1.64%.

Secondly, the histogram (P-distribution) of 2000 hypothetical assays shown in Fig. 2 was generated from a normal distribution with a population mean of 0.7106×10^{-3} and a population variance of 0.2760×10^{-10}. The sample mean and sample variance from these data were calculated to be 0.7104×10^{-3} and 0.2730×10^{-10}, respectively. The population coefficient of variation is 0.757%.

Finally, the histogram shown in Fig. 3 is that of the products of the two random variables, Y and P, *i.e.*, YP-distribution. From the data thus generated, the sample mean and variance are 87.065×10^{-3} and 2.4610×10^{-6}, respectively. The theoretical mean and variance obtained by the proposed calculation are 87.105×10^{-3} and 2.490×10^{-6}, respectively. The population coefficient of variation is 1.81%.

It should be noted that the sample estimates of skewness and kurtosis for the YP-histogram are of the same magnitude as those for the Y- and P-histograms, thus supporting Aroian's work. Neither of these two latter sample statistics is significantly different from zero in any of the cases illustrated by Figs. 1–3.

These sampling results, in addition to Aroian's work, provide justification for using normal theory approximations for the YP-distribution.

APPLICATIONS

To test the calculations further, sufficient data from a tablet product were needed to obtain reliable estimates of sample mean potency and tolerance intervals. Fortunately, such data were available on a steroid tablet assayed by a method described in the

Lower Limit of Cell × 10^{-3}	No. of Observations	Histogram (Each X = 5 Observations)
<116.55048	4	X
116.55048	9	XX
117.47868	24	XXXXX
118.40691	72	XXXXXXXXXXXXXX
119.33513	154	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
120.26334	252	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
121.19156	338	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
122.11978	336	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
123.04799	333	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
123.97621	235	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
124.90443	140	XXXXXXXXXXXXXXXXXXXXXXXXXX
125.83264	64	XXXXXXXXXXXX
126.76086	27	XXXXX
127.68909	9	XX
>128.61729	3	X
	2000	

	Mean	Variance
Population	122.58	4.0466
Computed	122.55	4.1299
Skewness	0.02538	
Kurtosis	0.006658	

Figure 1—*Histogram and distribution statistics for variable* Y.

Analytical Methods section under *Mestranol Assay*. The assay has been found to be very precise and accurate. Routine control computer computations for S_Y and S_P had been made on 200 lots of this product. A summary of the information from these lots is presented in Table I. There were 103 lots with a target dose of 84 mcg./tablet and 97 lots with a target dose of 86 mcg./tablet. Nine tablets per lot were assayed and this information was used to calculate drug dosage. The results of this method are reported under column heading A. The results under B are from the calculations recommended in this paper; *i.e.*, there is information from 100 tablet weighings per lot which were ignored in the A calculations but were utilized in the B calculations. When this information was combined with assay information, the 95/99 tolerance limits (in percentages of sample means) were reduced considerably by the additional degrees of freedom gained from including the tablet weight data. The mean potencies found by the two methods were not significantly different from each other.

Table II summarizes data taken from routine computer printouts for production lots of several official and proprietary items. These printouts display results computed for the conventional assay procedure as well as for the composite procedure, described in this paper. In the conventional procedure, N_x tablets are weighed and the mean weight $\bar{Y}_{N_x}$ is obtained. These N_x tablets are assayed and the mean drug weight per tablet, $\bar{x}$, and the standard deviation, S_x, reported. From these are computed the 95/99 tolerance limits

$$\bar{x} \pm KS_x$$

with $F_x = N_x - 1$ degrees of freedom. It should be noted that these N_x assays are the same ones which give N_P values of P, the proportion of drug in the tablet substance, so that $N_x = N_P$. Table II thus compares the several statistics calculated from both the conventional procedure and the authors' composite procedure. It is noted that, as a rule, the composite procedure results in shortened tolerance intervals. In the isoniazid examples, this represents the difference between rejecting and passing a lot.

Table III gives some guidance to the average number of assays and tablet weights required in order to set 95/99 tolerance limits to ±15% of label claim if the target is label claim and if the process is running at label claim with the population coefficients of variation, λ_Y and λ_P, listed in the first two columns of the table. This table should be used only as a rough guideline. Equations 1 through 5 may be used to prepare similar tables for various confidence levels, portions of population distribution, and postulated tolerance limits.

ANALYTICAL METHODS

Mestranol Assay—A direct reference standard tablet method previously published (12) for the determination of a 17α-ethynylestradiol 3-methyl ether (mestranol) was selected for this study because of its good precision and accuracy as used in these laboratories. In the course of development and production, both domestic and foreign, more than 17,000 determinations have been made by this procedure. Nine test tablets plus three reference tablets may be assayed in 1 hr. of analyst's time. The average difference in the means of single tablet assays comparing this direct method with a manual extraction method on composite samples for a series of 260 assays was 0.56%. During an 18-month period the absorbance values per gram of the reference tablets were found to change no more than absorbance values from color reactions on freshly prepared standard solutions of mestranol. The average assay relative standard deviation for the 1800 determinations on the 200 lots

Lower Limit of Cell × 10^{-3}	No. of Observations	Histogram (Each X = 5 Observations)
<0.69487	2	X
0.69487	8	XX
0.69729	42	XXXXXXXX
0.69972	72	XXXXXXXXXXXXXX
0.70214	121	XXXXXXXXXXXXXXXXXXXXXXXX
0.70456	251	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
0.70698	335	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
0.70941	372	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
0.71183	333	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
0.71425	226	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
0.71668	145	XXXXXXXXXXXXXXXXXXXXXXXXXX
0.71910	60	XXXXXXXXXXX
0.72152	24	XXXXX
0.72395	4	X
>0.72637	5	X
	2000	

	Mean	Variance
Population	0.7106×10^{-3}	0.2760×10^{-10}
Computed	0.7104×10^{-3}	0.2730×10^{-10}
Skewness	−0.0263	
Kurtosis	−0.0969	

Figure 2—*Histogram and distribution statistics for variable* P.

Lower Limit of Cell × 10^{-3}	No. of Observations	Histogram (Each X = 5 Observations)
<82.44057	4	X
82.44057	10	XX
83.15900	36	XXXXXXXX
83.87743	69	XXXXXXXXXXXXX
84.59586	148	XXXXXXXXXXXXXXXXXXXXXXXXXXXX
85.31429	252	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
86.03271	316	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
86.75114	350	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
87.46957	320	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
88.18800	260	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
88.90643	145	XXXXXXXXXXXXXXXXXXXXXXXXXXX
89.62486	58	XXXXXXXXXXX
90.34329	25	XXXXX
91.06172	5	X
>91.78015	2	X
	2000	

	Mean	Variance
From Data	87.065×10^{-3}	2.4610×10^{-6}
From Calcd.	87.110×10^{-3}	2.4900×10^{-6}
Skewness	−0.09520	
Kurtosis	−0.05849	

Figure 3—*Histogram and distribution statistics for variable* YP.

Table I—Data from 200 Lots of a Steroid Tablet

Lots →	103		97	
Determinations →	927		873	
Target →	84 mcg./Tablet		86 mcg./Tablet	
	A[a]	B[b]	A[a]	B[b]
Mean potency mcg./tablet	85.1	85.2	86.2	86.3
Mean *SD*	1.5	1.6	1.4	1.5
Av. tolerance limits (95/99) (in percent of mean)	±7.5	±5.7	±7.5	±5.5

[a] Average results from estimating mean and content uniformity by weighing and assaying nine tablets. [b] Average estimates from the use of the procedure recommended in this paper.

of Table I was less than 0.7%. The direct method cannot be used with tablets whose excipients react with sulfuric acid to form colored components. For such tablets, a selective method such as that reported by Tsilifonis and Chafetz (13) may be used.

Isoniazid Assay—The isoniazid from a single tablet was dissolved in water and filtered. An aliquot of filtrate was diluted with 0.003 *N* HCl. The absorbance of the sample solution at 265 mμ was compared to that of a standard solution similarly prepared using 0.003 *N* HCl as the blank. The relative standard deviation of the method was found to be about 0.6%.

Diethylstilbestrol Assay—The diethylstilbestrol tablets were assayed by the USP procedure (5).

Atropine Sulfate—The atropine sulfate tablets were assayed by a modification (14) of an automated procedure (15) using a bromocresol purple dye complex. The tablets were dissolved in 10 ml. water and placed in the liquid sampler. Ethylene dichloride was used as the extraction solvent.

Methyltestosterone Assay—The methyltestosterone tablets were assayed by the NF procedure (6).

Phenobarbital Assay—A single tablet was disintegrated in water, made alkaline, and filtered. An aliquot of the filtered solution was diluted to a concentration of 8 mcg. of phenobarbital per ml. of 0.04% sodium hydroxide soution. The absorbance at 241 mμ of the sample solution was compared to that of a standard solution similarly prepared using 0.04% sodium hydroxide as the blank. The relative standard deviation of the method was found to be about 1.2%.

Table II—Comparison of Data from Computer Printouts on Production Lots

	Isoniazid USP (Lot A)	Isoniazid USP (Lot B)	Diethylstilbestrol USP	Atropine Sulfate USP
Label claim, mg./tablet	100	100	0.250	0.40
No. tablets weighed (N_Y)	199	199	201	198
No. determinations (N_x, N_P)	9	3	10	10
$\bar{Y}$ (N_x), mg.	320.2	312.9	70.28	35.5
$\bar{Y}$ (N_Y), mg.	311.8	315.1	69.87	36.7
Mean assay ($\bar{x}$), mg.	99.3	97.8	0.252	0.395
$F_{(x)}$	8	2	9	9
$\bar{Y}\bar{P}$ (calcd.), mg.	96.7	98.5	0.253	0.409
$F_{(YP)}$	22	200	27	163
Tol. Int. (x), %	81.1–117.5	42.1–153.0	90.7–110.6	83.3–114.1
Tol. Int. (YP), %	85.5–107.9	93.4–103.0	91.1–111.4	91.5–112.8
Percent of S^2_{YP} due to weight of tablets	40.6	99.1	43.3	85.2

	Methyltestosterone NF	Phenobarbital USP	Aspirin, Phenacetin, and Caffeine NF (Caffeine Assay)	Paramethasone Acetate NF XIII (Tentative)
Label claim, mg./tablet	10.0	30.0	32.0	1.0
No. tablets weighed (N_Y)	200	199	199	200
No. determinations (N_x, N_P)	10	4	9	10
$\bar{Y}$ (N_x), mg.	129.26	121.9	528.5	303.6
$\bar{Y}$ (N_Y), mg.	129.50	120.7	516.1	303.5
Mean assay ($\bar{x}$), mg.	10.05	29.8	33.1	1.015
$F_{(x)}$	9	3	8	9
$\bar{Y}\bar{P}$ (calcd.), mg.	10.07	29.5	32.3	1.014
$F_{(YP)}$	39	38	17	18
Tol. Int. (x), %	89.1–112.0	86.6–111.9	88.0–116.4	96.4–106.5
Tol. Int. (YP), %	91.8–109.7	93.9–102.6	91.3–108.2	95.8–107.0
Percent of S^2_{YP} due to weight of tablets	53.0	73.3	31.4	30.2

Table III—Minimum Estimated Number of Determinations Needed for 95% Confidence That 99% of the Tablets Will Be Within ±15% of Label Claim

λ_Y, %	λ_P, %	K	F	Number of Tablets Weighed 10	20	30	100	∞
				Number of Assays Needed				
1.0	1.0	10.61	2	2	2	2	2	2
1.0	2.5	5.57	6	6	6	6	6	6
1.0	3.5	4.12	12	12	12	12	12	12
2.0	1.0	6.71	4	2	2	2	2	2
2.0	2.5	4.69	8	5	5	5	5	4
2.0	3.5	3.75	17	12	12	12	11	11
3.0	1.0	4.74	8	2	2	2	2	2
3.0	2.5	3.80	16	9	5	5	4	4
3.0	3.5	3.25	30	26	15	14	12	11
3.5	3.5	3.03	67	—	143	41	22	18
4.0	1.0	3.64	20	—	3	2	2	2
4.0	2.5	3.18	40	—	—	13	5	5
4.0	3.0	3.00	75	—	—	—	15	11

Caffeine Assay—The caffeine from a single tablet of aspirin, phenacetin, and caffeine tablets (NF XII) was dissolved in chloroform and determined by an IR spectrophotometric procedure previously published (16). The relative standard deviation of the method was found to be about 1.1%.

Paramethasone Acetate—The paramethasone acetate tablets were dissolved in 50 ml. of 50% methanol and determined by the semiautomated procedure using only the steroid manifold in the previously published method for propoxyphene hydrochloride and paramethasone acetate (17).

CONCLUSIONS

Formulas have been proposed for combining tablet weight and assay data into estimates of mean potency and content uniformity. Based on Monte Carlo simulations and also 20,000 tablet weighings and 1800 assays on 200 lots of a steroid tablet, this approach was found to be reasonable. More specific information on tolerance intervals is obtained by the proposed method than by existing or suggested tests for content uniformity in the official compendia.

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