Characterization of the Content Uniformity Plan

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Abstract □ The operating characteristic of the official content uniformity plans is developed in terms of proportion defective in a lot. This proportion defective is represented as a function of the means and variances, respectively, of the drug substance weight and the tablet weight. It is then shown that the probability of acceptance of a lot can be derived for each process from knowledge of only: (*a*) the coefficient of variation, and (*b*) the proportional process bias. That is, the proportion defective in a lot is considered in terms of departures from theoretical drug substance weight and target tablet weight and their coefficients of variation which can arise in normal manufacturing operations. A completely worked example of these calculations outlines the procedure. The tables show, through computer calculation, the probability of acceptance arising through the interplay of several selected values of the coefficients of variation and of the proportional process bias.

Keyphrases □ Tablet content uniformity—determination □ Content uniformity, tablets—sampling plan □ Defective tablets, proportion—determination □ Formulas, tablet—content uniformity determination

The content uniformity sampling plans for tablets in USP XVII and NF XIII have the disadvantages that all information available to the analyst is not efficiently utilized and that the probability of acceptance of a lot cannot be evaluated in terms of departures from the theoretical drug content and target tablet weight.

A new procedure for estimating content uniformity in pharmaceutical products has been proposed by Comer *et al.* (1). Information from both tablet weights and assays may be utilized to provide more efficient estimates of mean potency and tolerance limits. In the present paper, the authors develop the operating characteristics of current official sampling plans for content uniformity tests. Formulas are presented for studying the effect of slight changes in drug content and tablet weight during manufacture upon the probability that a lot of material will meet the official content uniformity limits. These formulas include not only the coefficients of variation of both tablet weight and assay data but also what are described as proportional process biases in these variables. Similar statements concerning the USP weight variation test have been made by Roberts (2).

STRUCTURE

The primary forces which determine the amount of drug substance in the unit dose of pharmaceutical tablet forms are: (*a*) the weight of drug substance per weight of formulation material as estimated by assay, say P, and (*b*) tablet weights, say Y.

If a population is assumed to be normal, then the population parameters of interest are the mean, μ, and the variance, σ^2. Such a normal distribution is denoted by the conventional $N(\mu,\sigma^2)$. Then, restating the assumption of normality, the population of tablet weights is assumed to be normally distributed with mean μ_y and variance σ_y^2, *i.e.*, $N(\mu_y,\sigma_y^2)$. Similarly, the distribution of single-unit assay measurements is $N(\mu_p,\sigma_p^2)$. For consistency, say that Y is measured in milligrams per tablet and P in milligrams of drug substance per milligram of formulation material. It is further assumed that the concentration of drug, P, is independent of the weight of the tablet, Y. The unbiased estimates of μ_p, μ_y, σ_p^2, and σ_y^2 are denoted by $\bar{p}$, $\bar{y}$, s_p^2, and s_y^2, respectively. These estimates are based on n_p observations on the P distribution and n_y observations on the Y distribution.

The variable of interest is PY, the weight of drug substance in milligrams per tablet. Some distribution-free results concerning the mean and variance of PY are now presented. Since P is assumed to be independent of Y, the population mean, μ_{py}, is given by the product of the respective population mean, $\mu_p\mu_y$, and the population variance, σ_{py}^2, is equal to $\mu_p^2\sigma_y^2 + \mu_y^2\sigma_p^2 + \sigma_p^2\sigma_y^2$. [See, for example, Goodman (3).] The unbiased estimates of μ_{py} and σ_{py}^2 are easily shown to be

$$\hat{\mu}_{py} = \overline{py} \qquad \text{(Eq. 1}a\text{)}$$

$$\hat{\sigma}_{py}^2 = \bar{p}^2 s_y^2 + \bar{y}^2 s_p^2 + \left(1 - \frac{1}{n_p} - \frac{1}{n_y}\right) s_p^2 s_y^2 \qquad \text{(Eq. 1}b\text{)}$$

The distribution of PY is not easily determined, but some exact distribution results have been reported by Craig (4), Aroian (5), and DeZur and Donahue (6). These results are somewhat mathematically intractable and are not readily amenable to practical utilization. However, Aroian (5) has demonstrated that as the ratios σ_p/μ_p and σ_y/μ_y, singly or together, become small, the distribution of PY approaches normality. These ratios, denoted by γ_p and γ_y, respectively, are called population coefficients of variation.

Also, approximate formulas for skewness and kurtosis have been worked out for the product of two random variables. [See Burr (7).] Skewness and kurtosis are measures of shape of distribution which, along with the mean and variance, characterize most distributions fairly well. Skewness is a measure of symmetry and has a value of zero for symmetric distributions. Kurtosis measures flatness or peakedness and equals 3.0 for a normal distribution and 1.8 for the rectangular (uniform) distribution.

Sampson (8) evaluated the skewness and kurtosis formulas, performed some Monte Carlo simulations, and concluded that, for the coefficients of variation of magnitudes usually encountered and considered acceptable in tablet manufacture, the assumption of normality for the distribution of PY is reasonable, provided P and Y have normal distributions.

With this structure in mind, the probability of meeting content uniformity requirements for various population coefficients of variation for the respective populations of single-unit assays and of tablet weights is developed.

OPERATING CHARACTERISTIC FORMULAS

The current content uniformity sampling plan for tablets in USP XVII (9) and NF XIII (10) may be summarized as follows: Individually assay 10 tablets. If all 10 are within 85–115% of the mean of the tolerances specified in the official monograph, then the requirements are met. If one of 10 fails, *i.e.*, falls outside the limits, then 20 more tablets are individually assayed. If only one of the combined sample of 30 falls outside limits, the lot is passed. All other possibilities result in failure to meet requirements.

A tablet outside of limits is defined as a "defective." The probability of accepting a lot with a proportion, π, of defective units

under this sampling plan is

$$P_\pi = (1 - \pi)^{10} + 10\pi(1 - \pi)^{29} \quad \text{(Eq. 2)}$$

P_π is easily derived from the criteria for the sampling plan and delineates the operating characteristic curve for various values of the proportion defective π. Once π is evaluated in light of this structure, Eq. 2 characterizes the content uniformity plan.

The lower and upper allowable limits for a particular characteristic of a product unit are denoted by L and U, respectively. If the mean of the tolerances specified by the official monograph is μ, then $L = 0.85\mu$ and $U = 1.15\mu$ for the official plan. If label claim is μ, then the process is expected to operate such that $\mu = \mu_p\mu_y$; therefore, $1 - \pi = Pr[L < PY < U] = Pr[0.85\mu_p\mu_y < PY < 1.15\mu_p\mu_y]$ may be evaluated. It is probable that the parameter mean for the drug substance in formulation material may be running not exactly at μ_p but at $\mu_p + \Delta_p$ for a given point in time, where Δ_p is some incremental change and may be positive or negative. Similarly the process may not be making tablets that weigh on the average μ_y but rather $\mu_y + \Delta_y$. With this in mind, π is computed as a function of the coefficients of variation, $\gamma_p = \sigma_p/\mu_p$ and $\gamma_y = \sigma_y/\mu_y$, and also of what may be termed proportional process biases, $\delta_p = \Delta_p/\mu_p$ and $\delta_y = \Delta_y/\mu_y$. That is, π is a function only of γ_p, γ_y, δ_p, and δ_y; when the processes are running on target so that δ_p and δ_y both equal zero, then π is dependent only upon γ_p and γ_y, the population coefficients of variation.

From these definitions,

$$\mu_{py} = (\mu_p + \Delta_p)(\mu_y + \Delta_y) = \mu_p\mu_y(1 + \delta_p)(1 + \delta_y) \quad \text{(Eq. 3)}$$

$$\sigma_y^2 = (\mu_p + \Delta_p)^2\sigma_y^2 + (\mu_y + \Delta_y)^2\sigma_p^2 + \sigma_p^2\sigma_y^2$$
$$= \mu_p^2\sigma_y^2(1 + \delta_p)^2 + \mu_y^2\sigma_p^2(1 + \delta_y)^2 + \mu_p^2\mu_y^2\gamma_p^2\gamma_y^2 \quad \text{(Eq. 4)}$$

Furthermore:

$$1 - \pi = Pr[L < PY < U]$$
$$= Pr\left[\frac{L - \mu_{py}}{\sigma_{py}} < \frac{PY - \mu_{py}}{\sigma_{py}} < \frac{U - \mu_{py}}{\sigma_{py}}\right]$$
$$= F\left[\frac{U - \mu_{py}}{\sigma_{py}}\right] - F\left[\frac{L - \mu_{py}}{\sigma_{py}}\right] \quad \text{(Eq. 5a)}$$

where $F[\,]$ may be found in tables of the cumulative distribution of the standardized normal function. [For example, see Beyer (11).] From Eqs. 3 and 4,

$$\frac{U - \mu_{py}}{\sigma_{py}} = \frac{1.15\mu_p\mu_y - \mu_p\mu_y(1 + \delta_p)(1 + \delta_y)}{[\mu_p^2\sigma_y^2(1 + \delta_p)^2 + \mu_y^2\sigma_p^2(1 + \delta_y)^2 + \mu_p^2\mu_y^2\gamma_p^2\gamma_y^2]^{1/2}} \quad \text{(Eq. 5b)}$$

By combining and cancelling terms on the right-hand side, this becomes

$$\frac{U - \mu_{py}}{\sigma_{py}} = \frac{1.15 - (1 + \delta_p)(1 + \delta_y)}{\gamma_{py}} \quad \text{(Eq. 6)}$$

where

$$\gamma_{py} = [\gamma_y^2(1 + \delta_p)^2 + \gamma_p^2(1 + \delta_y)^2 + \gamma_p^2\gamma_y^2]^{1/2} \quad \text{(Eq. 7)}$$

Similarly,

$$\frac{L - \mu_{py}}{\sigma_{py}} = \frac{0.85 - (1 + \delta_p)(1 + \delta_y)}{\gamma_{py}} \quad \text{(Eq. 8)}$$

By carrying out the calculations of Eqs. 7, 6, 8, and 5*a* and inserting into Eq. 2, the probability of accepting a lot for given values of γ_p, γ_y, δ_p, and δ_y may be computed.

ILLUSTRATION

Suppose that for a given tablet item labeled at 10 mg. drug per tablet, the process specifications stipulate that the target weight for the granulation is 0.1 mg. of drug substance per milligram of formulation material, *i.e.*,

$$\mu_p = 0.1 \text{ mg./mg.} \quad \text{(Eq. 9)}$$

Table I—Probability of Meeting Content Uniformity Requirements when $\delta_p = \delta_y = 0$[a]

γ_p	γ_y 0.01	0.02	0.03	0.04	0.05
0.01	1.0000	1.0000	1.0000	1.0000	0.9975
0.02		1.0000	1.0000	0.9998	0.9936
0.03			1.0000	0.9983	0.9786
0.04				0.9861	0.9331
0.05					0.8322

[a] When $\delta_p = \delta_y = 0$, the tables are symmetrical.

The repeatability of assay determinations, which also reflects homogeneity, is given by a standard deviation of, say,

$$\sigma_p = 4 \times 10^{-3} \text{ mg./mg.} \quad \text{(Eq. 10)}$$

Similarly, the target weight for compression and weighing may be

$$\mu_y = 100 \text{ mg./tablet} \quad \text{(Eq. 11)}$$

and the repeatability of compression and weighing may be

$$\sigma_y = 3.0 \text{ mg./tablet} \quad \text{(Eq. 12)}$$

Assume, however, that for a particular lot the process is running low on formulation and high on compression so that

$$\mu_p + \Delta_p = 0.093 \text{ mg./mg.} \quad \text{(Eq. 13)}$$

and

$$\mu_y + \Delta_y = 101 \text{ mg./tablet} \quad \text{(Eq. 14)}$$

with the standard deviations remaining the same.

Then, by definition, $\delta_p = -0.07$, $\delta_y = 0.01$, $\gamma_p = 0.04$, and $\gamma_y = 0.03$. Calculating from Eq. 3,

$$\mu_{py} = (0.1)(100)(1 - 0.07)(1 + 0.01)$$
$$= 9.393 \text{ mg. drug/tablet} \quad \text{(Eq. 15)}$$

and from Eq. 7,

$$\gamma_{py} = [(0.04)^2(1 + 0.01)^2 + (0.03)^2(1 - 0.07)^2 + (0.04)^2(0.03)^2]^{1/2}$$
$$= 0.04911 \quad \text{(Eq. 16)}$$

From Eq. 6:

$$\frac{U - \mu_{py}}{\sigma_{py}} = \frac{1.15 - (1 - 0.07)(1 + 0.01)}{0.04911}$$
$$= 4.29 \quad \text{(Eq. 17)}$$

And, similarly, from Eq. 8,

$$\frac{L - \mu_{py}}{\sigma_{py}} = \frac{0.85 - (1 - 0.07)(1 + 0.01)}{0.04911}$$
$$= -1.818 \quad \text{(Eq. 18)}$$

By Eq. 5*a*,

$$1 - \pi = F[4.29] - F[-1.818]$$
$$= 1.00 - 0.03454 \textit{ (Reference 11)} \quad \text{(Eq. 19)}$$

and thus $\pi = 0.03454$.

By Eq. 2

$$P_{0.03454} = (0.96546)^{10} + 10(0.03454)(0.96546)^{29}$$
$$= 0.8283 \quad \text{(Eq. 20)}$$

for the values given for γ_p, γ_y, δ_p, and δ_y.

That is, if the label claim is 10 mg. of drug substance per tablet and if the processes are running at $\mu_p = 0.093$ mg./mg. and $\mu_y =$

Table II—Probability of Meeting Content Uniformity Requirements

γ_p	γ_y 0.01	0.03	0.05
	when $\delta_p = -0.04$, $\delta_y = 0.02$		
0.01	1.0000	1.0000	0.9954
0.03	1.0000	0.9997	0.9663
0.05	0.9896	0.9539	0.7871
	when $\delta_p = 0.09$, $\delta_y = -0.08$		
0.01	1.0000	1.0000	0.9986
0.03	1.0000	1.0000	0.9786
0.05	0.9836	0.9459	0.7943
	when $\delta_p = 0.07$, $\delta_y = -0.01$		
0.01	1.0000	0.9986	0.7794
0.03	0.9996	0.9560	0.6310
0.05	0.8593	0.6823	0.4063

101 mg./tablet with coefficients of variation of 3% for P and 4% for Y, then the probability of meeting the content uniformity requirements as specified in USP XVII and NF XIII is 0.8283.

Although it is not feasible to publish complete tables of $P[\pi]$ for even a representative indexing of γ_p, γ_y, δ_p, and δ_y, a few additional examples (Tables I and II) are included.

DISCUSSION

Recalling that the probabilities of meeting content uniformity requirements depend only upon the four parameters δ_p, δ_y, γ_p, and γ_y, it is convenient to note that these probabilities are symmetric with respect to the pairs (δ_p, γ_p) and (δ_y, γ_y). That is, if $(\delta_p, \gamma_p) = (0.07, 0.03)$ and $(\delta_y, \gamma_y) = (-0.01, 0.05)$, then the probability of acceptance is the same as if $(\delta_p, \gamma_p) = (-0.01, 0.05)$ and $(\delta_y, \gamma_y) = (0.07, 0.03)$. This can be easily verified from Eqs. 6 and 7.

The IBM Mathpack Subroutine NDTR (12) was used to calculate the function $F[\,]$. Since this particular subroutine has a maximum error of $7(\times 10^{-7})$, the computed probabilities are in general more accurate than if they were computed using $F[\,]$ from usual tabled sources of the cumulative normal distribution. The difference is in the fourth decimal place and of little practical significance.

Note that several probabilities in Tables I and II are given as 1.0000. This means that, even though it is not absolutely certain that a lot will meet content uniformity requirements under the indexed parameter conditions, the probabilities of acceptance are so high that rounding to four decimal places carries these values to 1.0000.

The formulas in this paper compute the probability of meeting content uniformity requirements for given population parameters γ_p, γ_y, δ_p, and δ_y. They characterize the content uniformity sampling plan and are to be used as supplemental information in making decisions before and during the production of particular products.

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Solid-Phase Synthesis and Degradation of a Model Polypeptide by an Automated Approach

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Abstract □ The solid-phase synthesis and degradation of a model polypeptide, L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-alanine, was carried out using a computer-oriented automated approach. Two computer programs were used to generate control paper tapes for the total synthesis and degradation of the model peptide. Encouraging results were obtained in automating the degradation of polypeptides on the solid phase and in carrying out the degradation in a nonaqueous solvent system. The course of the synthesis and the degradation was monitored by amino acid analysis of acid hydrolyzates of the resin which were taken periodically. The automated solid-phase degradation of naturally occurring polypeptides and proteins should be possible through modifications of the described approach.

Keyphrases □ Polypeptide—automated synthesis, degradation □ Amino acid sequence, computer controlled—polypeptide synthesis □ Degradation, polypeptide, Edman—automated □ Automated system—peptide synthesis, degradation

Classical methods have been employed in the chemical synthesis (1–6) and Edman degradation (7–10) of polypeptides and proteins. Recently, a number of laboratories have automated solid-phase polypeptide synthesis (11–14); in one instance (15), the automation of classical sequential analysis of polypeptides has been reported.