Weight Variations of Rectal Suppositories: Suggestions for Weight Uniformity Specifications

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Abstract □ Samples of 50 suppositories were taken from 42 batches, representing one year's production. As no difference exists between the weights of "naked" suppositories, as obtained during the production process, and "wrapped" ones, as those actually released for distribution, quality control charts can be set to control weight uniformity during the production. Since USP XVII does not give weight uniformity specifications for suppositories, the most stringent specification for tablets was analyzed and adapted to suppositories. A sampling plan, combining practicality for the consumer and a satisfactory discrimination between "good" and "bad" batches was worked out and its implications for the producer outlined and examined for compatibility with these data.

Keyphrases □ Rectal suppositories—weight variation □ Weight uniformity—rectal suppositories □ Specifications—suppository weight uniformity □ Sampling techniques—suppository weight variation □ Tolerance limits—suppository weight variation

The German (1) and Russian (2) pharmacopeias state that individual weight deviations of rectal suppositories are tolerated within ±5% of the average weight. The Pharmacopoea Nordica (3) tolerates weight deviation up to ±10% of the average weight for 90% of the suppositories, provided that the variations do not exceed ±20%. The International 1967, USP XVII, NF XII, BP 1963, Italian VII, Austrian IX, Gallica VIII, and Japanese VII pharmacopeias give no specification for weight uniformity for suppositories.

Apart from these different attitudes in the official texts, there is little published experimental evidence for suggesting standards for the establishment of specifications on weight uniformity of rectal suppositories.

To obtain information on this subject, the weights of rectal suppositories of one year's production were analyzed.

EXPERIMENTAL

Outline of the Manufacturing Process of Rectal Suppositories[1]—Suppositories are produced by the melting-casting process. A machine[2] pours the melted suppository mass into divided hinged molds, each of which has 12 housings for suppositories of the "adult" size, or 10 for the "child" size. The capacity of the individual housings is 2.2 ml. in the adult size and 1.1 ml. in the child size. The production rate is 1,000 molds/hr., with a yield of 12,000 adult or 10,000 pediatric suppositories. The cooled suppositories are expelled from the molds and stored for 2 days in a cool room. Then they are wrapped in aluminum thermo-adhesive foils and released for packaging.

Sampling and Weighing—A random sample of 50 naked and 50 wrapped suppositories was taken from each batch. The naked suppositories were individually weighed with a precision of 1 mg. The same procedure was followed for the wrapped suppositories, after detaching the aluminum foil.

[1] At Recordati.
[2] Model GS03, Ing. Franco Crespi, Milan, Italy.

Abbreviations and Symbols—A = adult; C = child; N = naked W = wrapped (the weight of W suppositories is without the wrap) CV = coefficient of variation; $CV = SD/\text{mean} \cdot 100$.

RESULTS

Suppository Weight and Weight Variability—The average weights of N and W suppositories and their coefficients of variation are given in Table I for the A type and in Table II for the C type. The weight variations found were reasonably low, the CV of A suppositories being between 1.88 and 0.80 and of C suppositories between 2.05 and 0.94.

The confidence limits ($CL_{0.05}$) of CV with $p = 0.05$ are given in Eq. 1.

$$CL_{0.05} = \overline{CV}\left[1 \pm \frac{1.96}{\sqrt{2df}}\sqrt{1 + 2\left(\frac{\overline{CV}}{100}\right)^2}\right] \quad \text{(Eq. 1)}$$

where $\overline{CV}$ is the average CV estimated by past experience and df is degrees of freedom of the samples to be drawn for control (*cf. Control Charts*).

Table III shows an agreement between the $CL_{0.05}$ calculated according to Eq. 1 and those calculated directly on the CV values of

Table I—Adult Suppositories[a]

Drug (Coded by Initials)	Batch	Naked wt.	Naked CV	Wrapped wt.	Wrapped CV	Weight Difference, mg.
Bis	1	2.472	1.29	2.502	1.51	−30
Din	1	2.264	1.41	2.278	1.10	−14
	2	2.293	1.13	2.270	1.88	23
Fe	1	1.976	1.72	1.958	1.07	18
	2	1.965	1.27	1.958	1.25	7
Mal	1	2.070	1.30	2.061	1.05	9
	2	2.046	1.08	2.056	1.09	−10
	3	2.057	1.17	2.048	1.21	9
	4	2.060	1.21	2.036	1.37	24
Mal Ant	1	2.084	1.20	2.083	1.38	1
	2	2.080	1.49	2.063	0.80	17
	3	2.070	1.40	2.047	1.39	23
	4	2.053	1.07	2.059	1.41	−6
	5	2.047	1.22	2.050	0.96	−3
	6	2.066	1.02	2.061	1.13	5
Sed	1	2.001	1.05	2.005	1.12	−4
	2	2.004	1.50	1.993	1.22	11
Tef	1	2.090	1.39	2.096	1.03	−6
	2	2.093	1.48	2.086	1.43	7
	3	2.081	0.80	2.082	1.60	−1
	4	2.086	1.25	2.089	1.16	−3
	5	2.082	1.20	2.092	0.96	−10
	6	2.099	1.48	2.089	0.93	10
Tef Ef	1	2.094	1.10	2.092	1.09	2
	2	2.089	0.96	2.088	0.92	1
Tef Pa	1	2.112	0.80	2.121	1.02	−9
	2	2.116	1.28	2.111	1.49	5
	3	2.107	1.00	2.116	1.40	−9
	4	2.115	1.09	2.108	1.06	7
	5	2.116	1.23	2.115	1.36	1
	6	2.123	1.13	2.101	1.01	22
Val	1	1.974	1.17	1.959	0.96	15
	2	1.963	1.50	1.967	1.01	−4
	3	1.965	1.32	1.963	1.42	2
	4	1.973	0.96	1.978	0.87	−5

[a] Average weights in grams and coefficients of variations (CV).

Table II—Child Suppositories[a]

Drug (Coded by Initials)	Batch	Naked Wt.	Naked CV	Wrapped Wt.	Wrapped CV	Weight Difference, mg.
Bis	1	1.209	1.74	1.214	2.05	−5
Mal	1	1.020	1.27	1.019	0.94	1
	2	1.004	1.39	0.995	1.49	9
Mal Ant	1	1.024	1.27	0.999	1.17	25
	2	1.000	1.20	1.018	1.74	−18
	3	1.010	1.19	1.008	1.20	2
	4	0.997	1.30	0.997	1.11	0

[a] Average weights in grams and coefficients of variation (*CV*).

Tables I and II. This fact supports the hypothesis that the found *CV* originates from homogeneous populations of A suppositories or of C suppositories, respectively.

The analysis of variance on the data of Tables I and II is given in Table IV. It shows that the differences between batches within each drug are highly significant. This corroborates the importance of considering each batch individually, as demanded by the rules for good manufacturing practice.

Table IV shows that wrapping does not affect suppository weight to a statistically significant degree. The weight of N suppositories is therefore representative of that of the W suppositories, after unwrapping. This is an essential datum for quality control on this production, since the N suppositories can be subjected to immediate weight control, whereas the W suppositories cannot be controlled during production, but are actually used in therapy and are subjected to outgoing quality control and possibly to weight control by a third party.

Control Charts—For the authors' control charts the directives given by the British Standard Institution (4) were adopted for samples of 12 suppositories in the A case and of 10 suppositories in the C case, in order to perform the weight control on the yield of one combined mold.

The outer average limits (OAL), or action limits, embracing 99.8% of the individuals. were calculated in Eq. 2.

$$\text{OAL} = \bar{m} \pm 3.09 \frac{s'}{\sqrt{n}} \qquad \text{(Eq. 2)}$$

where $\bar{m}$ is the average of the weight averages of the samples taken from the different batches, n is the number of items to be drawn for control (n = 10 or 12), and s' is calculated by

$$s' = \sqrt{s^2 + \frac{1}{50}(s_P^2 - s^2)}$$

s_P^2 being the mean square between batches, s^2 the error mean square and 50 the number of suppositories in the samples of past experience.

The warning average limits (WAL), embracing 95% of the individuals, were calculated in Eq. 3.

$$\text{WAL} = \bar{m} \pm 1.96 \frac{s'}{\sqrt{n}} \qquad \text{(Eq. 3)}$$

The outer-range limits (ORL) were calculated by multiplying s' by the 0.001 and 0.999 *P*-fractiles of the distribution of the range. The warning range limits (WRL) were found by multiplying s' by the 0.025 and 0.975 *P*-fractiles. The *P*-fractiles were taken from Table 14 of *Reference 4*.

Table III—Averages and Confidence Limits of the Coefficients of Variation for A and C Suppositories

Suppository Type	Average	Confidence Limits of CV[a] Calcd. by Eq. 1	Confidence Limits of CV[a] Calcd. from the Values of Tables I and II
A	1.21	0.70–1.71	0.78–1.64
C	1.36	0.73–1.99	0.77–1.95

[a] p = 0.05.

Table IV—Analysis of Variance of Weights of A and C Suppositories (Tables I and II)

Sources of Variability[a]	Sum of Squares	*df*	Mean Squares	*F*
Drugs	673.9637	12	56.1636	10597[b]
Batches (within drugs)	0.1540	29	0.0053	9.08[b]
Wrapping	0.0086	1	0.0086	2.32[c]
Drugs × wrapping	0.0410	12	0.0034	0.92[c]
Batches × wrapping (within drugs)	0.1076	29	0.0037	6.34[b]
Samples	674.2749	83	(8.1238)	(13910.60[b])
Error	2.4068	4115[d]	0.000584	
Total	676.6817	4198[d]		

[a] For the analysis of variance a mixed-effects model was chosen; drugs and wrapping effects are fixed, batches and samples effects are random. [b] $p < 0.001$. [c] Statistically not significant. [d] One degree of freedom lost for substitution of an aberrant value.

Possible causes of aberrant averages or ranges of the samples taken from the manufacturing process are: defective closing of the two hinged mold halves, defective agitation and sedimentation in the melted suppository mass, erratic pouring, defective detachment of suppositories from the molds, air trapping, *etc.*

The actual figures of control charts for suppository production are given in Tables V and VI.

Most of the range tolerance limits are narrow enough to ensure compliance with the proposed specification limits. For the drugs whose outer, or even warning, upper tolerance limit exceeds the specification limit, it is necessary to substitute the latter for the outer upper limit.

Distribution Type—All the foregoing statistical considerations are based on the assumption that suppository weights are normally distributed. Even the most unhomogeneous weight values of the suppositories, *i.e.*, those of Mal Ant A, are still consistent with a normal distribution (χ^2 = 22.95 is lower than the critical χ^2 = 23.68 for α = 0.05 and 14 degrees of freedom, as the 300 weights were divided into 16 frequency classes).

It is also important to know whether or not the population contains aberrant individuals, *i.e.*, individuals whose weight is clearly outside the general weight range.

In this production the incidence of aberrant weights seems extremely low, as only one suppository was found, out of the 4,200 examined, for which the test for rejection (USP XVII, p. 844) was significant.

DISCUSSION

Weight Uniformity Specifications—There is an obvious need for official specifications on weight uniformity for suppositories, at least for those vehicling drugs with a general action, because weight

Table V—Mean Value and Tolerance Limits for Average Weights, Given in Grams

Drugs		Mean Value	Tolerance Limits for Average Weight: Warning Lower	Warning Upper	Outer Lower	Outer Upper
Bis	A[a,b]	2.502	2.481	2.523	2.468	2.536
Din	A	2.274	2.254	2.294	2.242	2.306
Fe	A	1.958	1.945	1.971	1.938	1.978
Mal	A	2.050	2.035	2.065	2.026	2.074
Mal Ant	A	2.060	2.044	2.076	2.035	2.085
Sed	A	1.999	1.985	2.013	1.977	2.021
Tef	A	2.089	2.075	2.103	2.066	2.112
Tef Ef	A	2.090	2.078	2.102	2.071	2.109
Tef Pa	A	2.112	2.097	2.127	2.088	2.136
Val	A	1.967	1.954	1.980	1.947	1.987
Bis	C[b,c]	1.214	1.199	1.229	1.190	1.238
Mal	C	1.007	0.994	1.020	0.987	1.027
Mal Ant	C	1.006	0.996	1.016	0.990	1.022

[a] A = Adult size. [b] The values are estimated by the data of the sample taken only from one batch. [c] C = Child size.

Table VI—Mean Value, Warning, Outer, and Specification Limits for Range, Given in mg.

Drugs	Mean Value	Tolerance Limits for Range[a] —Warning— Lower	Upper	—Outer— Lower	Upper	Specification,[b] Upper Limits
Bis A[c]	123	71	185	49	229	220[d]
Din A	115	66	174	46	215	200[d]
Fe A	74	42	111	29	138	172
Mal A	86	50	130	34	160	180
Mal Ant A	90	52	136	36	168	181
Sed A	80	46	121	32	150	176
Tef A	83	48	125	33	155	184
Tef Ef A	69	40	104	27	129	184
Tef Pa A	87	50	132	35	164	186
Val A	74	43	111	29	138	173
Bis C[c]	76	41	119	27	148	101[e]
Mal C	64	35	99	22	123	84[e]
Mal Ant C	50	27	78	18	97	84[d]

[a] The limits are not symmetrical about the mean value, according to the exact distribution of the range. [b] The rationale of the specification limits is given in the discussion section. [c] The values are estimated by the data of the sample taken only from one batch. [d] Between upper WRL and ORL. [e] Lower than WRL.

variations may involve dosage variations, as happens in some instances with tablets (5).

A discussion on this subject may start from the weight variations allowed for other enteral dosage forms. Since there are substantially different specifications among the most important pharmacopeias, and even within the single pharmacopeias, between the different oral dosage forms (6), the authors assigned their suppositories the most stringent specification for oral dosage forms of the USP XVII, *i.e.*, that for tablets weighing more than 324 mg.

The USP states; "Weigh individually 20 whole tablets and calculate the average weight: the weight of not more than two of the tablets may differ by more than 5% from the average weight and no tablet may differ by more than ±10%."

This type of specification, as already pointed out by other investigators (7–9), has certain drawbacks: (*a*) it cannot be translated into statistical terms unless certain assumptions are agreed; (*b*) it is not sufficiently discriminating between acceptable and unacceptable batches; (*c*) it does not give a basis for settling disputes.

To analyze the implications of the USP XVII specification, the following were assumed: (*a*) a normal distribution; (*b*) a 0.95 probability level; (*c*) the identification of the sample mean with the true mean of the population, for locating the limits which define defectives (*k* value of Table VIII).

This last assumption is appropriate because a prefixed average weight of dosage forms such as suppositories, tablets, *etc.*, is not critical from the therapeutic point of view. Conversely, it is very useful to allow some flexibility in the average weight of the different batches, in order to facilitate production.

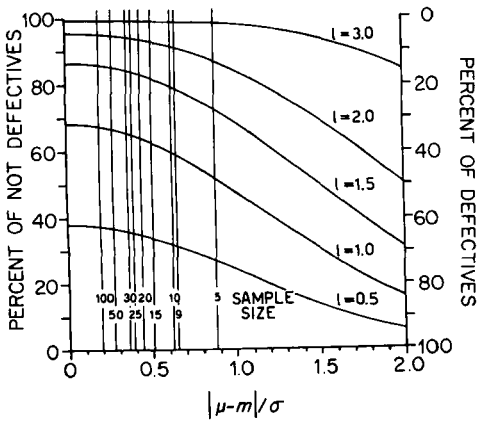

Figure 1—*Effects of the difference between the true mean* (μ) *and the sample mean* (m) *on the percentage of defectives, considering defectives the specimens of a normal population which fall outside the limits* $\mu \pm l\sigma$. *The differences are given on the abscissa in absolute values. The* p = *0.95 fiducial limits of* m, *as a function of several sample sizes, are also shown.*

Table VII—Acceptance Probability with Not More Than Two Defectives or with No Defective in a Sample of 20 (Approximated from *Reference 11*)

True Percentage of Defective in the Population	Acceptance Probability with two Defectives Tolerated	Acceptance Probability with no Defective Tolerated
0.3	—	0.95
1	—	0.82
2	0.99	0.66
4	0.95	0.44
8	0.78	0.19
10	0.68	0.12
12	0.56	0.08
14	0.46	0.05
15	0.40	
20	0.20	
28	0.05	

As a consequence, however, the probability level of acceptance or rejection depends also on the random difference between the sample mean and the true mean.

This effect becomes negligible with large sample sizes. With small sample sizes it diminishes the consumer's risk and increases the producer's risk (Fig. 1) and must be kept in mind when evaluating batches with borderline quality.

Furthermore the outer absolute acceptance limits of the USP specification (*i.e.*, ±10%) were ignored, the variability being already defined by the inner limits. Besides, should technological reasons require absolute acceptance limits, these must be obviously related to a theoretical value, *e.g.*, the true mean, and not to a sliding value like the mean of a sample. Absolute acceptance limits can be a good tool for identifying and rejecting batches containing a fairly large amount of aberrant individuals as may happen with tablets prepared in very small quantity (10). But this problem does not seem to be relevant to suppositories produced in a conventional industrial plant.

As shown by Table VII, obtained on the basis of the previously outlined assumptions, batches with a percentage of defectives as high as 28% may be accepted and batches with 4% defectives may be rejected, according to the mentioned USP specification.

Since the specification is tested by an extremely large experience on tablets, it seems justified to set the limit of defectives tolerated ($p = 0.05$) on the 28% level. This condition corresponds to a $CV = 4.6$ according to Table VIII (for a sample size of 20, two defectives tolerated, 0.05 acceptance probability, and $k = 5$). Incidentally, this $CV = 4.6$ is not far from 4.5, specified by the "Swedish Pharmacopoeia" (1946) for tablets (12), though later on abandoned by the "Pharmacopoea Nordica," because it was felt that the limits for weight variability should decrease as the size of tablets increases (10).

In order to choose the best sampling strategy on these premises, the implications of different sampling plans were tabulated. Table VIII shows that the guarantee, with regard to the borderline quality, given by the USP specification under discussion, is given also by cheaper sampling plans as: "not more than one defective in fifteen," or "no defectives in nine." The last sampling plan may therefore be considered as a first step for testing weight variability of suppositories.

On the other hand, good batches, *i.e.*, with a $CV < 4.6$, may not comply. The border separating possible good batches from bad ones is represented by the inspection result "more than four defectives in a sample of nine." In fact, this inspection result corresponds to $p = 0.92$ for accepting a batch with 28% defectives.

When the sample of nine contains one, two, three, or four defectives, a sample of 30 specimens may be examined.

Table VIII shows that the finding of not more than four defectives in a sample of 30 guarantees that the defectives in the batch are less than 28%. It was also calculated that more than 12 defectives in a sample of 30 are probably ($p = 0.95$) found when the defectives in the batch are higher than 28%.

Thus the operating instructions may be the following ones.

1. Draw a random sample of nine suppositories, weigh indi-

Table VIII—Percentage of Defectives in the Population (Perc) and CV/k[a] Ratios, Related to Defectives Tolerated, Acceptance Probabilities, and Sample Sizes

Defectives Tolerated	Acceptance Probabilities	Sample Size 5		9		10		15		20		25		30	
		Perc	CV/k	Perc	CV/k	Perc	CV/k	Perc	CV/k	Perc	CV/k	Perc	CV/k	Perc	CV/k
0	$p = 0.95$	1	0.39	0.6	0.36	0.5	0.36	0.30	0.34	0.25	0.33	0.20	0.32		
	$p = 0.50$	13	0.66	7.5	0.56	6.5	0.54	4.5	0.50	3.5	0.47	2.50	0.45		
	$p = 0.05$	45	1.33	28	0.93	26	0.88	18	0.75	14	0.68	11	0.63		
1	$p = 0.95$	7	0.55	4	0.49	3.5	0.47	2.5	0.45	2.0	0.43	1.5	0.41	1.0	0.39
	$p = 0.50$	31	0.99	18	0.75	16	0.71	11	0.63	8.0	0.57	6.5	0.54	5.5	0.52
	$p = 0.05$	66	2.27	43	1.27	40	1.19	28	0.93	21	0.80	18	0.74	15	0.69
2	$p = 0.95$	19	0.76	10	0.61	9	0.59	5.5	0.52	4.5	0.50	3.5	0.47	2.5	0.45
	$p = 0.50$	50	1.48	28	0.93	26	0.89	18	0.74	13	0.66	11	0.63	7.5	0.56
	$p = 0.05$	81	4.16	55	1.67	50	1.48	36	1.09	28	0.93	24	0.85	20	0.77
3	$p = 0.95$			17	0.73	15	0.69	9.5	0.60	7.0	0.55	5.5	0.52	4.5	0.50
	$p = 0.50$			39	1.16	36	1.09	24	0.85	18	0.75	15	0.69	12	0.64
	$p = 0.05$			66	2.27	60	1.91	44	1.30	34	1.05	28	0.93	24	0.85

[a] CV is the coefficient of variation; k is the limit value, expressed as a percentage of the mean and symmetrically set about the mean.

vidually each suppository to the nearest milligram, calculate the average weight (m), and the acceptance limits (AL) as $m \pm 0.05\ m$. If no weight exceeds the AL, accept the batch. If more than four weights exceed the AL, reject the batch. If one, two, three, or four weights exceed the AL proceed to 2.

2. Weigh individually to the nearest milligram 21 other suppositories randomly sampled. Pool these weights with those previously found in order to have a sample of 30. Calculate the average weight m and the acceptance limits (AL) as $m \pm 0.05\ m$. If no more than four weights exceed the AL, accept the batch. If more than 12 exceed the AL, reject the batch.

In case of uncertainty the CV of the sample of 30 may be calculated. A CV of 3.4 or less guarantees ($p = 0.95$) that the CV of the batch is equal or smaller than 4.6 so that the batch can be accepted. A CV of 5.8 or more shows that the CV of the batch is 4.6 or more ($p = 0.95$) and the batch must be rejected. Between a CV of 3.4 and one of 5.8 an area of uncertainty exists. Cases in which these values of CV are found must be settled by previous agreements between consumer and producer. For instance, the probability of the CV found being lower or higher than the theoretical critical CV value of 4.6 may be calculated, the sample may be expanded, *etc.*

The authors do not suggest, however, adopting a very large sample size in the first sampling step, *e.g.*, of 100 specimens, as asked for tablets by the "Pharmacopoea Nordica" (3), because such a sampling plan could be either unfeasible, or very expensive for the consumer (*e.g.*, when the control becomes destructive, as in cases where the dosage forms are wrapped, in strips, in blisters, or in sealed containers, *etc.*). Admittedly, large samples permit the identification of batches containing aberrant individuals, a problem which seems to be important in some cases of tablet production

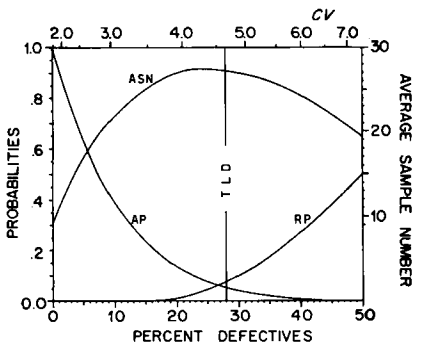

Figure 2—*Left ordinate: probability of acceptance (for Curve AP) or rejection (for Curve RP) on the basis of a sample of* 9 *specimens. Right ordinate: Average sample number (ASN) according to the proposed sampling plan. Abscissa: Percent of defectives in the batch. The upper abscissa gives the corresponding* CV, *provided that acceptance limits are set at* $\mu \pm 0.05\ \mu$. *Key: AP, probabilities that the first sample* ($n_1 = 9$) *has no defectives; RP, probabilities that the first sample* ($n_1 = 9$) *has more than four defectives; TLD, tolerance limit for defectives according to the proposed weight uniformity specifications.*

(10). This aspect, however, is not relevant to suppositories and in fact for this dosage form even the Pharmacopoea Nordica asks for a sample of 20 units.

Economy of the Proposed Sampling Plan—Figure 2 gives the average number of specimens that must be weighed, either in relation to the CV values for weight or to the percentage of defectives in the batch. Assuming that the production of suppositories has an average variability defined by a CV of 1.21–1.36 (*cf.* Table III), the corresponding percentage of defectives is about 0.02% and the average number of suppositories sufficient to reach a decision is nine. Conversely, if a CV value of 2.7 is assumed, which represents the borderline CV complying with the producer's specification, the average number of suppositories to be inspected is 18.5.

Fixed Versus Mobile Tolerance Limits—The limits for weight variability established by most pharmacopeias are mobile, *i.e.*, they are narrower for large tablets than for small ones. This principle is justified insofar as tablets may differ greatly in size and as the manufacturing process is known to yield tablets of more uniform weights when their size is large (7, 10). It implies, however, that for small tablets a larger dosage variability is accepted, a fact on which the therapist may not agree, because dosage variability tolerance should depend on the pharmacological properties of a certain drug rather than on the size of the dosage form by which it is administered. Therefore, even if corrected by other specifications such as those for content uniformity, mobile limits for weight variability are not free of substantial inconsistencies. There is thus a good case for fixed limits for weight variability of suppositories such as those that have been suggested, apart from the fact that rectal suppositories are not so variable in size as tablets, another reason for adopting fixed tolerance limits.

In this connection it may be of some interest to translate the USP specifications for weight uniformity of tablets into CV values, calculated according to the assumptions previously made. These CV values are given in Table IX, and may be the starting point for devising new strategies for testing weight uniformity of tablets.

Implications for the Producer—The object of an official codex is to safeguard the consumer by establishing specifications which guarantee a satisfactory quality level. Since the producer must have the certainty or a high probability that his product complies with the official specifications, he must work out internal specifications, which are more stringent than the official ones.

Considering as official for suppositories the proposed specifications, a batch is accepted by the consumer if a sample of 30 yields

Table IX—Coefficients of Variation for Consumer's and Producer's Risk Corresponding to USP XVII Specifications for Tablets

Tablet Wt., mg.	Limits not to be Exceeded by More Than Two Tablets out of 20	CV Values for Consumer	CV Values for Producer
More than 324	± 5% of the mean	4.6	2.5
130–324	± 7.5% of the mean	7.0	3.7
Less than 130	± 10% of the mean	9.3	4.9

a CV value for weight of 3.4 or less. In consequence, the producer must make every effort to produce batches with a CV whose upper fiducial limit is 3.4 or less. This borderline CV, evaluated on a sample of 30, corresponds to 2.7, because in this case the fiducial limits ($p = 0.05$) are 3.4 and 2.0. Batches meeting these CV specifications are therefore very likely to be accepted by the consumer's control. In fact a batch with a CV of 2.7 has already 0.57 probabilities of being accepted at the first of the proposed inspection steps, *i.e.*, that asking for no defectives in a sample of nine.

Going by the authors' experience of suppository production, it should not be too difficult to meet the requirement that the CV must be lower than 2.7. In fact, the highest CV values observed in the authors' samples was of 2.05 (bis suppositories of the C type, Table II), a value substantially smaller than 2.7, which is critical for the producer.

Specification Limits on Control Charts—The critical CV of 2.7 corresponds to an upper-range specification limit of 0.088 m for the 12 specimens sample, and of 0.083 m for the 10 specimens sample considered by the control charts (m = average weight). As already said, in most instances these specification limits are outside the upper ORL (outer range limit).

In a few instances they are between the ORL and the WRL (warning range limit), and even so the limits can still be met. For two drugs they are below the WRL. In these cases it is necessary either to adjust the production process, or to accept a higher probability of rejection of the product by the outgoing or by the consumer's quality control.

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Assay of Quinacrine Hydrochloride

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Abstract □ Comparison of USP method for the assay of quinacrine hydrochloride involving precipitation of the dichromate salt and determination of the excess dichromate with the nonaqueous titration using a visual end point and a proposed nonaqueous titration with a potentiometric end point, shows that all three methods give the same results, with the nonaqueous methods superior in reproducibility and rapidity. The proposed method is also satisfactorily applied to the assay of quinacrine hydrochloride tablets.

Keyphrases □ Quinacrine HCl and tablets—analysis □ Titration, nonaqueous—analysis □ Mercuric acetate T.S.—reagent □ Potentiometric determination—titration end point

Many types of analytical methods have been proposed for the determination of quinacrine hydrochloride including fluorescimetric (1–10), absorptimetric (11, 12), gravimetric (13), polarographic (14), amperometric (15), complexometric (16, 17), chloridometric after Parr bomb fusion (18), and various titrimetric methods (19–21). The method of Auerbach (22), has been the basis for the official methods of assay in the "United States Pharmacopeia" (23–28), since the compound was first recognized as official. This method has been adopted by other compendia (29–31). The procedure involves precipitating quinacrine dichromate from a buffered aqueous solution by addition of an excess of standard dichromate solution, removal of the precipitate by filtration, and determination of the excess dichromate in an aliquot of the filtrate by addition of potassium iodide and titration of the liberated iodine with standard thiosulfate solution, using starch indicator. The procedure is lengthy and involved and requires correction of the results for the solubility of quinacrine dichromate. In this laboratory, the reproducibility was not as good as desired.

Pifer and Wollish (32), state that they have titrated quinacrine hydrochloride as a base in nonaqueous systems but present no supporting data. Phoryles and Cohen (33), report the nonaqueous titration of quinacrine hydrochloride in glacial acetic acid after the addition of mercuric acetate using crystal violet indicator. The end point is a change from red to green when the solution is viewed by transmitted light. No end point is detected by reflected light. The "British Pharmacopoeia" (34), calls for a similar titration in chloroform, but omits directions for viewing the end point by transmitted light.