Testing for Uniformity: Sampling Plans in Pharmacopeias for Weight, Volume, and Content Uniformity

VALERIA PIETRA and IVO SETNIKAR

Abstract □ A procedure for analyzing the unit-to-unit uniformity specifications given by several pharmacopeias and for translating them into coefficients of variation is presented. Since the pharmacopeias fail to give the probability level of the compliance with the specifications, two largely adopted probability levels were considered: the 95% level which is important to the producer and the 10% level which is important to the consumer. The coefficients of variation implied by official uniformity specifications for the weights of tablets, capsules, miscellaneous oral forms, and sterile solids; for injection volume; and for content were calculated. The examined pharmacopeias show remarkable differences, both with regard to the sampling strategy and to the allowed variability of the considered dosage forms.

Keyphrases □ Pharmacopeias, dosage form uniformity testing—comparison □ Uniformity specifications—coefficient of variation calculations □ Coefficient of variation, dosage forms—equations □ Variability determination—dosage form units

The USP and NF introduced their first uniformity test, for unit-to-unit weight variability of tablets, in the 1950 editions. Since then uniformity specifications have been extended to the weight of other dosage forms (capsules and sterile solids) and, in other pharmacopeias, to the volume of injectable solutions (1–3). Finally, a uniformity specification for the content of the active ingredient of some tablets was introduced by USP XVII and NF XII (4).

As a general rule the official uniformity tests state the sample size and limit the number of specimens which may be outside certain limits. The allowed variability is difficult to evaluate since it depends on two factors: on the sampling plan and on the limits which discriminate the "inside" from the "outside" specimens. The pharmacopeias do not inform either on the maximum variability that a product complying with the specification may have (important information for the consumer) or on the maximum variability compatible with the compliance of the product (important information for the producer).

The uniformity specifications given by several pharmacopeias were therefore analyzed, translated into coefficients of variation, compared, and their efficacy and weaknesses commented upon.

THEORY

Although concerned with measurements of continuous variables, uniformity specifications of pharmacopeias involve sampling plans worked out for attributes, *i.e.*, for the restriction of "defectives." However, since in the context defectives are the specimens which have a weight, volume, content, *etc.*, outside some established limits, there is nothing intrinsically wrong with these specimens, provided that their incidence in the product does not exceed a certain percentage. Defectives in the context is therefore a misnomer and is properly substituted by the word "outsiders."

When the acceptance of a lot is based on a sampling plan defined by the sample size n and the acceptance number c, the probability of acceptance P_a depends on the percentage of outsiders in the submitted lot and is shown by the operating characteristic curve (*OC* curve) which may be calculated by the binomial expansion. The *OC* curve does not, of itself, give information about the percentage of outsiders which is considered critical for accepting a lot, but rather gives a general picture of the performance of the sampling plan on which it is based. In order to define, through the *OC* curve, the maximum percentage of outsiders allowed, the P_a must be agreed on and specified. Conventionally, two P_a values are considered as particularly important in sampling-inspection procedures (5): the P_a of 95%, representative of the "producer's risk" (R_P), and the P_a of 10%, used for defining the "consumer's risk" (R_C). A possible alternative value for defining the R_C may be the 5% acceptance probability.

In Table I the percentages of outsiders in the population corresponding to these three levels are given for the most common sample sizes asked by official specifications or used in pharmaceutical inspections.

The values of Table I were calculated using the central F distribution (6) for sample sizes $n \leqslant 30$, owing to the fact that in the expansion of the binomial:

$$\tfrac{1}{2}(n_1 + n_2 - 2)$$

$$[p + (1 - p)]$$

P_a is the sum of the first $n_1/2$ terms and $(1 - P_a)$ is the sum of the remaining $n_2/2$ terms when:

$$\frac{p}{1-p} = \frac{n_1}{n_2} \cdot F_{P_a};\ n_1,\ n_2 \qquad \text{(Eq. 1)}$$

For sample sizes n = 50, 60, and 100, the percentages of outsiders were calculated with the aid of the tables of Cameron (7), *i.e.*, using Poisson's approximation (6).

Table I shows the capability of a plan to detect and to limit the outsiders in a lot. But this is only one step toward the assessment of variability, which depends also on the limits used for discriminating the insiders from the outsiders. These limits are symmetrically set about the mean and are expressed as fractions of the mean. The official uniformity specifications can be converted into an appropriate measure of variability (coefficient of variation, *CV*) by means of the factors given in Table II, the entries of which are the reciprocals of the abscissas of the normal curve, corresponding to the fractions of outsiders, multiplied by 100. A numerical example of this conversion is shown in the section *Specifications for Uniformity of Tablet Weights*.

In fact, for the evaluation of the variability through the percentage of outsiders and the amplitude of limits, the distribution pattern of the variable must be recognized. Unfortunately the sample sizes prescribed by official codexes are inadequate for the identification of the distribution type and larger samples may not be available in field inspections, in inspections performed by the

Table I—Percentage of Outsiders which Will Be Accepted with the Stated Probabilities[a] for Samples of Stated Sample Size and Rejection Number[b]

$O_{tol.}$	Accept. Prob.	Sample Size 5	6	7	8	9	10	11	12	13	14	15	18	20	25	30	50	60	100
0	0.95	1	0.9	0.8	0.7	0.6	0.5	0.5	0.4	0.4	0.4	0.3	0.27	0.25	0.20	0.17	0.10	0.09	0.05
	0.10	37	32	28	25	23	21	19	17	16	15	14	12	11	9	7.5	4.5	3.8	2.5
	0.05	45	39	35	31	28	26	24	22	21	19	18	15	14	11	9.5	6	5	3
1	0.95	8	6	5	4.5	4	3.5	3.3	3	2.8	2.5	2.5	2.2	2	1.5	1	0.7	0.6	0.35
	0.10	58	51	45	41	37	34	31	29	27	25	24	20	18	15	12.5	8	6.5	4
	0.05	66	58	52	47	43	39	36	34	32	30	28	24	22	18	15	9.5	8	4.5
2	0.95	19	15	13	11	10	9	8	7	7	6	5.5	5	4.5	3.5	2.5	1.5	1.4	0.8
	0.10	75	67	60	54	49	45	42	39	36	34	32	27	24.5	20	17	10.5	9	5.5
	0.05	81	73	66	60	55	51	47	44	41	39	36	31	28	23	20	12.5	10.5	6.5
3	0.95	34	27	23	19	17	15	14	12	11	10	9.5	7.5	7	5.5	4.5	2.5	2.3	1.5
	0.10	89	80	72	66	60	55	51	48	45	42	39	33	30.5	25	21	13.5	11.1	6.5
	0.05	92	85	77	71	66	61	56	53	49	47	44	38	34	28	24	15.5	13	8
4	0.95		42	34	29	25	22	20	18	17	15	14	12	10.5	8.5	7	4	3.3	2
	0.10			83	76	70	65	60	55	52	49	46	40	36	30	25	16	13.3	8
	0.05			87	81	75	70	65	61	57	54	51	44	40	33	28	18.5	15.3	9
5	0.95				40	34	30	27	25	22	21	19	16	14	11	9	5	4.4	2.5
	0.10					79	73	68	63	59	56	53	46	41	34	29	18.5	15.5	9.5
	0.05					83	78	73	68	64	61	58	50	46	38	32	21	17.5	10.5
6	0.95							35	32	29	26	24	20	18	14	12	6.5	5.5	3.5
	0.10										63	60	51	46	38	33	21	17.6	10.5
	0.05										67	64	55	51	42	36	23.5	19.7	12
7	0.95										33	30	24	22	17	14	8	6.6	4
	0.10												56	51	43	36	23.5	19.6	12
	0.05												61	56	46	39	26.5	22	13
8	0.95												29	26	21	17	9.5	7.8	4.5
	0.10													56	47	40	26	21.7	13
	0.05													61	50	43	29	24.1	14.5
9	0.95													30	24	19	11	9	5.5
	0.10														50	43	28.5	23.7	14
	0.05														54	47	31.5	26.2	15.5
10	0.95														27	22	12.5	10.3	6
	0.10														55	47	31	25.7	15.5
	0.05														58	50	34	28.3	17
11	0.95														31	25	14	11.5	7.0
	0.10															50	33	27.7	16.5
	0.05															53	36.5	30.3	18.0
12	0.95															28	15.5	12.8	7.5
	0.10																35.5	29.6	18
	0.05																39	32.4	19.5

[a] Accept. prob. [b] $O_{tol.}$

average consumer, or in outgoing quality inspection of the producer. This obstacle may be overcome assuming a normal distribution. But the variables involved do not always conform to the normal distribution, since sometimes they are truncated normal, skew, lepto- or platy-curtic, or bimodal, *etc.* (8–10). Nevertheless, a normal distribution is very frequent, and therefore it is still meaningful to assume it for analyzing uniformity specifications and for comparing those of different official codexes. Obviously this assumption must be kept in mind in critical situations and in borderline conditions. In these cases the distribution type ought to be checked with large samples before drawing final conclusions.

Table II—Factors (u) for Calculating CV[a] in Relation to the Percentage of Outsiders

Outsiders, %[b]	0	1	2	3	4	5	6	7	8	9
0	[c]	39	43	46	49	51	53	55	57	59
10	61	63	64	66	68	69	71	73	75	76
20	78	80	81	83	85	87	89	91	93	95
30	97	99	101	103	105	107	109	112	114	116
40	119	121	124	127	130	132	135	138	142	145

[a] $CV = u \cdot L$; L is the limit about the mean and expressed as fraction of the mean. [b] *E.g.*, for 22% outsiders, $u = 81$. [c] Factors for percentages between 0.05 and 0.90:

Percent	0.05	0.10	0.20	0.25	0.30	0.40
Outsiders, %	29	30	32	33	34	35
Percent	0.50	0.60	0.70	0.80	0.90	
Outsiders, %	36	36	37	38	38	

ANALYSIS OF THE UNIFORMITY SPECIFICATIONS OF PHARMACOPEIAS

With the exception of the "Pharmacopée Française" (11), the most important recent pharmacopeias demand the compliance with uniformity tests for several dosage forms. In the present study the pharmacopeias listed in Table III were examined, their uniformity tests analyzed, and the percentages of outsiders calculated with the aid of Table I at the acceptance probability levels of $R_P = 95\%$ and of $R_C = 10\%$ and then converted into CV values using Table II.

Table III—Pharmacopeias Examined and Abbreviations Used

Pharmacopeias	Year of Issue	Abbreviation
British Pharmacopoeia	1968	BP
Deutsches Arzneibuch 7 (of the DDR)	1964	DA-E
Deutsches Arzneibuch 7 (of the BR)	1968	DA-W
Farmacopea Ufficiale della Repubblica Italiana 7	1965	FU
Österreichisches Arzneibuch 9	1960	OA
Pharmacopée Belge 5	1962	PB
Pharmacopoeia of Japan 7	1961	PJ
Pharmacopoea Nordica	1964	PN
State Pharmacopoeia of the USSR 9	1961	PUSSR
Spécifications pour le Contrôle de la Qualité des Préparations Pharmaceutiques (WHO)	1967	WHO
United States Pharmacopeia XVII	1965	USP
National Formulary XII	1965	NF

Table IV—Official Specifications for Tablet Weight Uniformity

Codex	Sample Size	Acceptance Conditions[a]								CV[b]			
		I Condition				II Condition				Producer		Consumer	
		Plan	Limits	O_P	O_C	Plan	Limits	O_P	O_C	I	II	I	II
BP	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm L'$	0.25	11.0	2.5–5.0	3.3–5.0	4.3– 8.6	6.3– 9.5
DA-E[c]	10	1/10	$m \pm L$	3.5	34.0	0/10	$m \pm 2L$	0.50	21.0	2.4–7.2	3.6–10.8	5.2–15.7	8.0–24.0
DA-W	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–7.5	3.3–9.9	4.3–12.9	6.3–18.9
FU	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–5.0	3.3–6.6	4.3– 8.6	6.3–12.6
OA	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 1.5L$	0.25	11.0	2.5–5.0	2.5–4.9	4.3– 8.6	4.7– 9.5
PB	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–7.5	3.3–9.9	4.3–12.9	6.3–18.9
PJ	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–5.0	3.3–6.6	4.3– 8.6	6.3–12.6
PN	100, 30	3/30	$M^d \pm L$	4.5	21.0	0/30	$M^d \pm 2L$	0.17	7.5	2.9–5.0	3.8–6.4	4.6– 8.0	6.5–11.2
PUSSR	10	0/10	$m \pm L$	0.5	21.0					1.8–3.6		4.0– 8.0	
WHO	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–7.5	3.3–9.9	4.3–12.9	6.3–18.9
USP–NF	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	2.5–5.0	3.3–6.6	4.3– 8.6	6.3–12.6

[a] The actual values of L are given in Table V. [b] The ranges shown reflect the ranges of L values for different tablet weights. [c] *Cf. Footnote*[a] of Table V. [d] *Cf. Footnote*[b] of Table V.

Table V—Limits for Tablets

Codex	L					
	0.05 m	0.075 m	0.08 m	0.10 m	0.125 m	0.15 m
BP	>250	81–249		⩽80		
BP (L′)				⩾250	81–249	⩽80
DA-E[a]	>300	151–300		51–150		⩽50
DA-W	>300	151–300		26–150		⩽25
FU	>300	151–300		⩽150		
OA	>500		251–500	⩽251		
PB	⩾300	150–299		25–149		<25
PJ	⩾300	120–299		<120		
PN[b]	Sliding[b]					
PUSSR	⩾120			<120		
WHO	>324	131–324		14–130		⩽13
USP–NF	>324	131–324		⩽130		

[a] Same specifications for granules, dragee-cores, and pastilles. [b] Weigh 100 tablets and calculate the average weight M. $L = 0.10\ M$ for tablets weighing less than 80 mg.; $L = 4$ mg. $+ 0.05\ M$ for tablets weighing 80 mg. or more; values of L from 0.058 to 0.10 M were considered for calculating CV.

Some specifications set their limits about the sample mean m and some about the true mean μ. In the first case the same specimen may be sometimes an outsider and sometimes an insider, according to the value of the mean of the sample which includes it. As a consequence the probability of acceptance depends also on the random difference between the sample mean and the true mean, as shown in a previous paper (12). No correction was made, however, for this situation or for the influence of double-sampling plans on the OC curve, since these corrections require propositions not given in the examined pharmacopeias.

Specifications for Uniformity of Tablet Weights—Table IV summarizes the uniformity specifications and the acceptance conditions given for tablets.

Most pharmacopeias set two interlinked conditions shown in Table IV under the headings I and II. These conditions may be analyzed even by the trinomial expansion (13).

Table VII—Notes for Capsules

(*a*) Type A specification for contents of hard capsules. Limits: $L = 0.10\ m$ for contents of 120 mg. or less; $L = 0.075\ m$ for contents of more than 120 mg. Type B specification for contents of soft capsules (chlortrianisene, ethchlorvynol, ethosuximide, halibut liver oil, paramethadion, phytonanadione, tetrachloroethylene).

(*b*) For hard and for soft capsules.

Content, mg.	>300	151–300	51–150	⩽50
L	0.05 m	0.075 m	0.10 m	0.15 m

If the weight of content is labeled, m is the label weight. If the weight of content is not labeled, m is the sample average weight.

(*c*) $L = 0.05\ m + 10$ mg. Values from 100 to 1000 mg. were considered for calculating CV.

(*d*) Type A specification for the weights of whole capsules. In the event of noncompliance, type B specification is applied to contents. The definition of specification B is obscure.

(*e*) Type A specification for the weights of whole capsules. In the event of noncompliance, type B specification is applied to the contents. If the contents fail to comply with test B1, test B2 is allowed, provided that not more than 6/20 contents fall outside the limits $m \pm 0.10\ m$. These conditions correspond to a producer's CV ⩽7.5 and a consumer's CV ⩽13.5.

The implied maximum percentages of outsiders are given in the O_P column (for a $P_a = 95\%$, *i.e.*, the producer's risk) and in the O_C column (for a $P_a = 10\%$, *i.e.*, the consumer's risk). The limits which discriminate the outsiders are set by most pharmacopeias symmetrically about the sample mean. Usually different limits are given according to the average tablet weight. The "Pharmacopoea Nordica" makes an exception since it relates the weight limits to the mean obtained on a larger sample than that used for measuring variability and considers a sliding variation instead of a step-by-step one. From Tables IV and V it may be noted that both the limits and the tablet weights which define them are quite different in the examined codexes.

The actually allowed unit-to-unit variabilities are given as CV values in Table IV, the ranges of which reflect the ranges of the

Table VI—Official Specifications for Capsule Weight Uniformity

Codex	Step or Type	Sample Size	Acceptance Conditions[a]								CV[b]			
			I Condition				II Condition				Producer		Consumer	
			Plan	Limits	O_P	O_C	Plan	Limits	O_P	O_C	I	II	I	II
BP[c]	A	20	2/20	$m \pm L$	4.5	24.5	0/20	$m \pm 2L$	0.25	11.0	3.8–5.0	4.9– 6.6	6.4– 8.6	9.5–12.6
	B	10	1/10	$m \pm 0.075\ m$	3.5	34.0	0/10	$m \pm 0.15\ m$	0.5	21.0	3.6	5.4	7.9	12.0
DA-E		10	1/10	$m \pm L^d$	3.5	34.0	0/10	$m \pm 2L^d$	0.5	21.0	2.4–7.2	3.6–10.8	5.3–15.7	8.0–24.0
DA-W		20	2/20	$m \pm 0.10\ m$	4.5	24.5	0/20	$m \pm 0.15\ m$	0.25	11.0	5.0	5.1	8.6	9.5
PB		20	2/20	$m \pm L^e$	4.5	24.5	0/20	$m \pm 2L^e$	0.25	11.0	3.0–7.5	4.0– 9.9	5.2–12.9	7.6–18.9
PN		20	2/20	$m \pm 0.10\ m$	4.5	24.5	0/20	$m \pm 0.20\ m$	0.25	11.0	5.0	6.6	8.6	12.6
WHO[f]	A	20	0/20	$m \pm 0.10\ m$	0.25	14.0					3.3		6.8	
	B	20	2/20	$m \pm 0.10\ m$	4.5	24.5	0/20	$m \pm 0.20\ m$	0.25	11.0	5.0	6.6	8.6	12.6
USP–NF[g]	A	20	0/20	$m \pm 0.10\ m$	0.25	14.0					3.3		6.8	
	B1	20	2/20	$m \pm 0.10\ m$	4.5	24.5	0/20	$m \pm 0.25\ m$	0.25	11.0	5.0	8.2	8.6	15.8
	B2	60	6/60	$m \pm 0.10\ m$	5.5	17.6	0/60	$m \pm 0.25\ m$	0.09	3.8	5.2	7.5	7.4	12.0

[a] The actual values of L are given in Table VII. [b] The ranges shown reflect the ranges of L values for different capsule weights. [c] *Cf. Note* (*a*) in Table VII. [d] *Cf. Note* (*b*) in Table VII. [e] *Cf. Note* (*c*) in Table VII. [f] *Cf. Note* (*d*) in Table VII. [g] *Cf. Note* (*e*) in Table VII.

Table VIII—Official Specification for Weight Uniformity of Miscellaneous Oral Dosage Forms

Dosage Form	Acceptance Conditions: I Condition Plan	I Condition Limits	O_P	O_C	II Condition Plan	II Condition Limits	O_P	O_C	CV: Producer I	Producer II	Consumer I	Consumer II
DA-E												
Dragees	1/10	$m \pm 0.15\,m$	3.5	34.0					7.2		15.8	
Pills[a]	2/20	$m \pm 0.10\,m$	4.5	24.5	0/20	$m \pm 0.15\,m$	0.25	11.0	5.0	5.0	8.6	9.5
DA-W												
Pills	3/30	$m \pm 0.10\,m$	4.5	21.0	0/30	$m \pm 0.30\,m$	0.17	7.5	5.0	9.6	8.0	16.8
OA												
Pills	3/30	$m \pm 0.10\,m$	4.5	21.0	0/30	$m \pm 0.30\,m$	0.17	7.5	5.0	9.6	8.0	16.8
Divided powders	0/10	$m \pm L$[b]	0.5	21.0					2.9–5.4		6.4–12.0	
PB												
Cachet-gelules	2/20	$m \pm L$[c]	4.5	24.5	0 20	$m \pm 2\,L$[c]	0.25	11.0	2.8–5.0	3.7–6.6	4.8– 8.6	7.1–12.6
PN												
Pills	3/30	M[d] $\pm 0.15\,M$	4.5	21.0					7.5		15.0	
Dragees and boles	2/20	$m \pm 0.10\,m$	4.5	24.5	0 20	$m \pm 0.20\,m$	0.25	11.0	5.0	6.6	8.6	12.6

[a] Comprehensive of all formed oral dosage forms.

[b] Content, mg. >1000 | 501–1000 | 201–500 | ≤200
L 0.08 m | 0.10 m | 0.12 m | 0.15 m

m must be within ±10% the labeled weight. [c] $L = 0.05\,m + 5$ mg. Values from 100 to 2000 mg. were considered for calculating CV. [d] The grand mean M is calculated on 100 pills.

L values given in Table V for weights of different tablets. Remarkable differences may be noted between the uniformity levels required by the different codexes.

The following example, based on the BP uniformity specifications for tablets greater than 250 mg., shows how the CV values were obtained. The sampling plan is defined by $n = 20$ and $c = 2$ (Table IV). According to Table I there is a 95% probability of accepting the submitted lot if 4.5% (O_P) of the items of the lot are outside the limits, which are $m \pm 0.05\,m$ (Table V). From the table of the normal distribution, it is found that 4.5% outsiders (O_P), namely, 2.25% at each end, lie beyond the limits $m \pm 2\,SD$. Therefore, $2\,SD = 0.05\,m$, so that $CV = 100\,SD/m = 2.5$.

The CV values may be obtained using the factors of Table II:

$$CV = u \cdot L = 50 \cdot 0.05 = 2.5 \qquad \text{(Eq. 2)}$$

Specification for Uniformity of Capsule Weights, for Weights of Miscellaneous Oral Forms, and for Suppository Weights—Tables VI and VII show the weight uniformity specification for capsule weights, Table VIII shows those for miscellaneous oral dosage forms, and Table IX shows those for suppositories.

These tables were prepared following the same criteria adopted for tablets and, as for tablets, there is little similarity between the different sampling plan strategies and procedures.

Specifications for Uniformity of Injectables—Tables X and XI summarize the specifications for weight uniformity of sterile solids. There are large differences with regard to the allowed CV values and still more with regard to the weight classes for which the sizes of limits change (Table XI).

The specifications for uniformity of volume of injectables are more regular (Table XII). These specifications are given in four of the examined pharmacopeias.

Content Uniformity—USP–NF are the first pharmacopeias to introduce a specification on content uniformity. The prescribed two-step procedure is summarized in Table XII and the operating characteristic curve is given in Fig. 1.

Table IX—Official Specifications for Suppository Weight Uniformity

Codex	Sample Size	Acceptance Conditions: I Condition Plan	I Condition Limits	O_P	O_C	II Condition Plan	II Condition Limits	O_P	O_C	CV: Producer I	Producer II	Consumer I	Consumer II
DA-E	5	0/5	$m \pm 0.05\,m$	1.0	37.0					2.0		5.6	
DA-W	10	1/10	$m \pm 0.05\,m$	3.5	34.0	0/10	$m \pm 0.10\,m$	0.5	21.0	2.4	3.6	5.3	8.0
PB	20	2/20	$m \pm 0.05\,m$	4.5	24.5	0/20	$m \pm 0.10\,m$	0.25	11.0	2.5	3.3	4.3	6.3
PN	20	2/20	$m \pm 0.10\,m$	4.5	24.5	0/20	$m \pm 0.20\,m$	0.25	11.0	5.0	6.6	8.6	12.6
PUSSR	10	0/10	$m \pm 0.05\,m$	0.5	21.0					1.8		4.0	

Table X—Official Specifications for Weight Uniformity of Sterile Solids

Codex	Step	Sample Size	Acceptance Conditions: I Condition Plan	I Condition Limits	O_P	O_S	II Condition Plan	II Condition Limits	O_P	O_C	CV: Producer I	Producer II	Consumer I	Consumer II
BP		10	1/10	μ[a] $\pm L$	3.5	34.0	0/10	$m \pm 2\,L$	0.5	21.0	2.4– 4.8	3.6– 7.2	5.3–10.6	8.0–16.0
DA-E[b]		10	0/10	$m \pm L$	0.5	21.0					2.2– 5.4		4.8–12.0	
DA-E[c]		5	1/5	$m \pm L$	8.0	58.0	0/5	$m \pm 2\,L$	1.0	37.0	2.8– 8.6	3.9–11.7	9.1–27.1	11.2–33.6
PB		10	0/10	$m \pm L$	0.5	21.0					1.1– 3.6		2.4– 8.0	
PJ		10	0/10	μ[d] $\pm L$	0.5	21.0					5.0–10.8		11.2–24.0	
USP–NF[e]	1	20	2/20	$m \pm 0.10\,m$	4.5	24.5	0/20	$m \pm 0.15\,m$	0.25	11.0	5.0	5.0	8.6	9.5
	2	60	6/60	$m \pm 0.10\,m$	5.5	17.6	1/60	$m \pm 0.15\,m$	0.6	6.5	5.2	5.4	7.4	8.1

For the values of L *cf.* Table XI.

[a] μ is the labeled weight. [b] The pooled mass of the 10 units must be within ±10% of the labeled mass, if this is smaller than 2000 mg., and within ±15% of the labeled mass if this is larger than 2000 mg. [c] The specification concerns the implants. [d] The sample average must be within $\mu \pm 0.5\,L$ (*cf.* Table XI). μ is the labeled weight. [e] Step 2 is allowed when the sample does not comply with Step 1 and when less than 7/20 weights are outside $m \pm 0.10\,m$. The producer's CV may therefore reach a value of 7.5 and the consumer's CV a value of 13.5. The sample average m must be between $\mu \pm 0.07\,\mu$, where μ is the labeled weight. The USP–NF do not state if the last rule applies to the sample of 20, or of 60, or to both.

Table XI—*L* Values for Sterile Solids

Codex	BP	DA-E	DA-E	PB	PJ
L =					
0.03 *m*				>300	
0.05 *m*	⩾300		>300	151–300	
0.06 *m*		>1000		51–150	
0.075 *m*	121–299		151–300	26–50	
0.08 *m*		501–1000			
0.10 *m*	⩽120	201–500	51–150	<26	
0.12 *m*		101–200			
0.14 *m*					⩾300
0.15 *m*		⩽100	⩽50		120–299
0.20 *m*					15–119
0.30 *m*					<15

DISCUSSION

The specifications for uniformity tests prescribed in several important pharmacopeias are remarkably different, even in the same codex for different dosage forms, and lack essential information for establishing the variability actually allowed. If the specifications are analyzed with constant criteria, their comparison becomes possible and reveals discrepancies as *CV* at the consumer's risk level from 8.0 to 15.7 for tablets, from 6.8 to 15.7 for capsules, from 8.0 to 12.0 for miscellaneous oral forms, from 4.3 to 8.6 for suppositories, from 8.6 to 27.1 for sterile solids, and from 8.0 to 15.8 for injection volume.

For some dosage forms, different variabilities are allowed, depending on the average weight. The criteria adopted for establishing these weight classes differ markedly in the examined pharmacopeias as shown by Table V for tablets, Table VII for capsules, and Table XI for sterile solids. The differences are difficult to understand since they are not related to technical reasons because most dosage forms are produced with a narrower weight variability than that necessary for the compliance with the official specifications. The differences are even not justified by some needs of the consumer, who may be prepared to accept differences in uniformity according to the safety margin or to the therapeutic efficacy of a drug, but not according to the dosage form or to the size of the dosage form by which the drug is administered.

Uniformity specifications with two interlinked compliance conditions (I Condition and II Condition in the tables) imply a larger *CV* for the second condition than for the first, both for the producer and for the consumer. Probably the second condition aims to establish absolute limits to variability or to protect from abnormal variability. Compliance with absolute limits, however, cannot be assured by sample inspections, and abnormal variability can be investigated only with much larger sample sizes than those considered by the official specifications.

Most specifications consist of a one-step sampling plan. There are some exceptions, *e.g.*, USP–NF describe a two-step sampling plan for capsules, for sterile solids, and for content of active ingredient. These double plans are difficult to comment on since the second step in the three plans has different effects, both on the variability allowed to the producer and on the protection for the consumer.

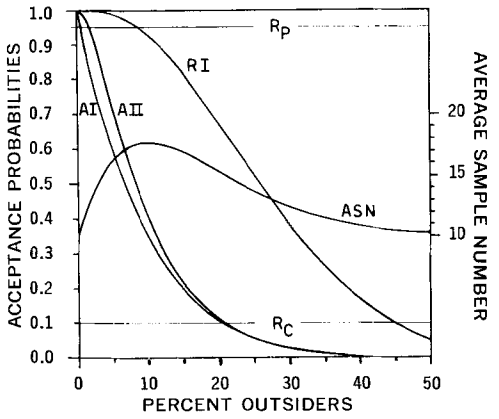

Figure 1—*Characteristics of two-step sampling plan for content uniformity of USP–NF. Key:* AI, *operating characteristic* (OC) *curve for acceptance after the first sampling* {*10,0*}; RI, OC *curve for rejection after the first sampling* {*10,2*}; AII, OC *curve for acceptance after the second sampling* {*10,1;20,0*}; ASN, *average sample number related to percent outsiders;* R_p, *producer's risk level* (P_a = *0.95*); R_c, *consumer's risk level* (P_a = *0.10*).

Perhaps the most critical uniformity specification is the two-step sampling plan for content, required by USP–NF for some drugs dosed in tablets. The operating characteristic (*OC*) curves, given in Fig. 1, show that the second step adds a very small amount of tolerated outsiders at the level of the R_P and that there is practically no difference of tolerated outsiders at the level of the R_C. The advantage of the second step, therefore, is not clear.

The specification for content uniformity apparently restricts variability to the same order of magnitude as that allowed for tablet weights. The *CV* allowed for content, however, is comprehensive both for variability of actual content and for the apparent variability, *i.e.*, that linked to the analytical error, which may reach values of 3% and more and is different for each analytical method. Therefore, the allowances for content variability are actually different for each drug, depending on the precision of the analytical method.

In conclusion, the official uniformity specifications may be analyzed in order to obtain useful information on the variabilities actually allowed. The relevant *CV* values may be calculated and used for production-control charts and for acceptance inspections performed with other sample sizes. They inform also the consumer about the variability which may inhere in accepted products.

The approach presented in this paper complements that of Roberts (14) who studied the relationship between *CV* of the lot and the probability that a sample fails the USP–NF uniformity tests for weight of tablets, capsules, or sterile solids.

SYMBOLS AND DEFINITIONS

P_a = acceptance probability
n = sample size
c = acceptance number
p = fraction of defectives (or outsiders) in the population

Table XII—Official Specifications for Uniformity of Injection Volume and for Content Uniformity

Codex	Sample Size	Acceptance Conditions				*CV*	
		Plan	Limits	O_P	O_C	Producer	Consumer
BP	10	0/10	$\mu \pm L^a$	0.5	21.0	1.8–3.6	4.0–8.0
PB	10	1/10	$\mu^b \pm 0.15\,\mu$	3.5	34.0	7.2	15.8
PJ	10	1/10	$\mu^b \pm 0.15\,\mu$	3.5	34.0	7.2	15.8
WHO	10	1/10	$\mu^b \pm 0.15\,\mu$	3.5	34.0	7.2	15.8
USP–NF	10	0/10	$\mu^c \pm 0.15\,\mu$	0.5	21	5.4	12
	30	1/30	$\mu^c \pm 0.15\,\mu$	1.5	21.5	6.2	12

[a] For labeled volumes ⩽2.0 ml., L = 0.10 μ (μ = prescribed volume) and the sample average volume within $\mu \pm 0.05\,\mu$. For labeled volumes >2.0 ml., L must be within the labeled volume and $+0.05\,\mu$. The prescribed volume μ is given in a table. [b] μ is the prescribed volume given in a table of the codex. Directions are given for the limits of the average sample volume. [c] Specification for content uniformity. The second step, with additional 20 contents, is allowed when not more than one value in Step 1 exceeds $\mu \pm 0.15\,\mu$. This implies a producer's *CV* of 7.2 and a consumer's *CV* of 15.7. μ is the labeled content. The specification applies to tablets of hydrocortisone, prednisolone, prednisone, chlorpromazine, prochlorperazine, digitoxin, ergonovine, and phenobarbital.

OC = operating characteristic curve
R_C = consumer's risk (set at a 10% level)
R_P = producer's risk (set at a 95% level)
CV = coefficient of variation [$CV = (s/m) \cdot 100$]
s = sample standard deviation
m = sample mean
μ = population or true mean
T = prescribed value
L = limit symmetrically set about the mean
k = fraction of the mean by which limits are expressed ($L = km$)
u = factor for calculating CV from k when a normal distribution is assumed ($CV = uk$)

Outsiders = specimens outside mean $\pm L$
Insiders = specimens inside mean $\pm L$

REFERENCES

(1) "British Pharmacopoeia," Pharmaceutical Press, London, England, 1968.

(2) "Pharmacopée Belge," **5**, 1962.

(3) "Pharmacopoeia of Japan," 7th ed., Hirokawa Publishing, Tokyo, Japan, 1961.

(4) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965; "National Formulary," 12th ed., Mack Publishing Co., Easton, Pa., 1965.

(5) E. L. Grant, "Statistical Quality Control," McGraw-Hill, New York, N. Y., 1964, p. 344.

(6) A. Hald, "Statistical Theory with Engineering Applications," Wiley, New York, N. Y., 1965, pp. 674, 688.

(7) J. M. Cameron, *Ind. Quality Control*, **9**, 37(1952).

(8) P. M. A. section meetings, 1963, Quality Control Section, pp. 458, 471.

(9) J. D. Haynes, M. Schnall, and A. S. Doniger, "Types of Unit-to-Unit Variation and Their Implications," Third Annual Eastern Regional Meeting, Industrial Pharmacy Section, APhA, New York, N. Y., 1963.

(10) C. W. Dunnett and R. Crisafio, *J. Pharm. Pharmacol.*, **7**, 314(1955).

(11) "Pharmacopée Francaise," 8th ed., Impr. Maisonneuve, St. Ruffine, France, 1965.

(12) I. Setnikar and V. Pietra, *J. Pharm. Sci.*, **58**, 112(1969).

(13) J. D. Haynes, M. Schnall, and R. A. Lamm, "Variability Tests in Acceptance Sampling from Non-normal Populations," presented at the American Statistical Association annual meeting, Cleveland, Ohio, 1963.

(14) C. Roberts, *Technometrics*, **11**, 161(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received May 26, 1969, from the *Research Division, Recordati s.a.s., Milano, Italy.*

Accepted for publication September 12, 1969.

Quantitative Gas-Liquid Chromatographic Determination of Estrone in Dermatological Products

PRAMOD P. KARKHANIS and JON R. ANFINSEN

Abstract □ A gas-liquid chromatographic procedure employing an internal-external standard ratioing technique is described for the analyses of estrone in dermatological preparations. The analysis of a cream or lotion is performed by the addition of an internal standard, extraction of sample with 10% sodium hydroxide, filtration, adjustment of the filtrate pH to 9–9.5, and chromatography on a 3% OV-1 column.

Keyphrases □ Estrone dermatological products—analysis □ Extraction procedure, estrone—internal-external standard ratioing technique □ GLC—analysis □ Equilenin solution—internal standard

Estrone has been incorporated in creams primarily for the treatment of senile vaginitis, pruritus vulvae, leukoplakia vulvae, and in emollients for the relief of local antikeratotic and trophic therapy in skin of the climacteric. In addition to the base, these preparations frequently contain vitamin A, hydrocortisone, and pyrilamine maleate for local antihistaminic and analgesic effect.

Several chemical methods for the estrone are found in the literature (1–5). However, due to the small amount of the steroid and the interference from the other ingredients in these pharmaceutical preparations, the results obtained with some of these methods were unreliable. The biological assay of estrone (6), based on the cellular change in the vagina of the spayed mouse or rat, gave erratic results.

Kroman *et al.* have quantitatively determined the concentration of estrone in the human plasma using a combination of chemical extraction and gas chromatography (7) and Wotiz and Chattoraj have described a method to determine estrone in low- and high-titer urine employing TLC and gas chromatography (8).

A GLC procedure has been described for ethinyl estradiol in both sesame oil solutions and solid dosage forms, using estrone as an internal standard, by Talmage *et al.* (9); Boughton *et al.* have determined ethinyl estradiol in tablets and granulations by gas chromatography using estrone as an internal standard (10). The proposed method, with a simple clean-up procedure, allows the separation and determination of estrone by gas chromatography while eliminating interferences from excipients commonly present in the creams and lotions.

EXPERIMENTAL

Instrument—Hewlett-Packard 5754A research chromatograph equipped with Hewlett-Packard 3370A electronic integrator and Honeywell Electronic 16 recorder.

Column—A 1.22-m. (4-ft.) helical glass column, 4 mm. i.d.

Liquid Phase—Three percent OV-1 on diatomite aggregate[1] (HP), 80–100 mesh (Supelco, Inc., Bellefonte, Pa.). The column is conditioned overnight at 300° with a helium flow rate of 45 ml./min.

[1] Chromosorb G, Johns-Manville Products Corp., New York, N. Y.