The Study of the Applicability of Content Uniformity and Weight Variation Test—The State of Commercial Tablets and Capsules in Japan—

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This study intends to determine the rational criteria (*e.g.*, threshold value) for applying the weight variation test and to investigate the adequacy of the acceptance value for existing commercial products in Japan. The studied products were 489 lots (3 lots×163 products) of compressed tablets (plain, film-coated, sugar-coated) and 42 lots (3 lots×14 products) of hard capsules marketed in Japan. The individual drug content and the weight of 10 units in a lot were determined for each product and the acceptance values were calculated according to the Japanese Pharmacopoeia thirteenth edition (JP13) Content Uniformity Test (M=100.0, k=2.2). Product-specific intra-lot relative standard deviation of content (RSD_D), weight (RSD_W) and concentration (RSD_C) were calculated by analysis of variance (ANOVA) using three lots of data per product. The RSD_D and RSD_C tended to increase with the decrease of the label strength for plain tablets, but not for film-coated and sugar-coated tablets, and hard capsules. A good correlation was found between RSD_D and RSD_C but not between RSD_D and RSD_W. These findings indicate that 1) it is difficult to rationally set the threshold level for weight variation, especially regarding the dosage forms except for plain tablets, 2) the application of weight variation tests should, in principle, be decided on the mixing homogeneity that is RSD_C. 3) Most (99.6%) of the tablets and all the capsules investigated met the requirement of content uniformity test of JP13. Therefore the criteria of the JP13 content uniformity test are considered acceptable from the viewpoint of manufacturing capability.

Key words content uniformity; weight variation; mixing homogeneity; Japanese Pharmacopoeia; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

To assure the therapeutic utility of dosage units such as tablets, capsules, and solids in single-unit containers, the drug content of each unit in a lot should be distributed in a narrow range around the label strength. For this purpose, there are two tests, the content uniformity test and an alternative simplified test, the weight variation test, in pharmacopoeias. The content uniformity test of Japanese Pharmacopoeia (JP) was significantly changed in the thirteenth edition (1996). The new criteria in JP13[1] is the acceptance values which are calculated from standard deviation of drug content and deviation of mean content from label claim[2,3] as follows.

$$\text{acceptance value} = |M - \bar{X}| + ks$$

- M: label claim (100.0%), unless otherwise specified in the individual monograph
- $\bar{X}$: mean of individual contents $(x_1, x_2, \ldots, x_n)$
- $x_1, x_2, \ldots, x_n$: individual contents of the units tested, expressed as a percentage of the label claim
- n: sample size (number of units in a sample)
- k: acceptability constant, k=2.2 when the sample size is 10, and k=1.9 when the sample size is 30.
- s: standard deviation of the sample $= \sqrt{\dfrac{\sum_{i=1}^{n} (x_i - \bar{X})^2}{n-1}}$

If an acceptance value is not larger than the specification limit, the product passes the test. The discussions about global harmonization of the compendial test for uniformity of dosage units were stimulated by the introduction of acceptance values that reflect the current requirements of the JP content uniformity test. United States Pharmacopeia (USP) is also considering the adoption these criteria for uniformity of dosage units.[4] The acceptance values were adopted as the global standards at the International Conference on Harmonistration of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conference. The differences between the harmonization plans and current JP in the criteria are the settings for M and k values of the formula of the acceptance value. In the harmonization plans recommended by The Pharmaceutical Research and Manufacturers of America (PhRMA),[5] "If $\bar{X}$ is less than or equal to 100.0%, then M=the greater of 98.5% or $\bar{X}$. If $\bar{X}$ is greater than 100.0%, M=101.5%." It was also set that k=2.3 and k=2.0 if sample sizes are 10 and 30 respectively." The harmonization plans were looser than JP criteria in biases of average content and slightly stricter in dispersions of the individual contents. It has also been considered for international harmonization in this area to determine the threshold level for the application of the weight variation test. A strong candidate of the requirement for application of the weight variation test is that the content of the active ingredient is 25 mg or more, representing 25% or more of the formulation weight.[5] However, there is no practical data or specific information to support the rationality of these threshold values.

This study was designed to evaluate the content uniformity and weight variation of the formulations released in Japan: plain tablets, film-coated tablets, sugar-coated tablets and hard capsules. The objectives of this study are:

1. to determine the rational application criteria (*e.g.*, threshold value) for weight variation,
2. to investigate the adequacy of acceptance values for existing tablets and capsules based on the actual quality of commercial formulations.

Theoretical Background The sources of variation in the individual content of each product consist of weight variation of units, blend heterogeneity and assay imprecision. If the ef-

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fect of assay precision is neglected, the relationship between the uniformity of dosage units and the sources of variation is approximately described as[6]:

$$s_D^2=s_W^2\bar{C}^2s_C^2\bar{W}^2 \quad (1)$$

where s_D^2, s_W^2 and s_C^2 are the intra-lot variances of dose, weight of a unit and concentration (amount of active ingredient per unit weight of formulation mixture), respectively, and $\bar{C}$ and $\bar{W}$ are lot mean value of concentration and unit weight. The relative standard deviation (RSD) is, of course, standard deviation normalized for the mean, so the lot RSDs of dose, weight and concentration are generally

$$RSD_D=s_D/\bar{D} \quad (2)$$

$$RSD_W=s_W/\bar{W} \quad (3)$$

$$RSD_C=s_C/\bar{C} \quad (4)$$

where RSD_D, RSD_W and RSD_C are the intra-lot RSDs of dose, weight and concentration, respectively, and D is the lot mean of dose. Dividing Eq. 1 by $\bar{C}^2\bar{W}^2$ gives:

$$s_D^2/\bar{C}^2\bar{W}^2=s_W^2/\bar{W}^2+s_C^2/\bar{C}^2 \quad (5)$$

In Eq. 5, $\bar{C}^2\bar{W}^2$ equal $\bar{D}^2$ and then Eq. 5 becomes:

$$s_D/\bar{D}^2=s_W^2/\bar{W}^2+s_C^2/\bar{C}^2 \quad (6)$$

From Eq. 6 and Eqs. 2—4, the relationship of lot RSDs is obtained as:

$$RSD_D^2=RSD_W^2+RSD_C^2 \quad (7)$$

Therefore, if RSD_W and RSD_C are already known, RSD_D can be estimated by the use of Eq. 7. For example, if RSD_W is 8% and RSD_C is 6%, RSD_D is estimated to be 10%. On the other hand, when we want to control the lot RSD_D to be less than 10% and RSD_C is already known to be 6%, RSD_W must be less than 8%.

Experimental

Forty-nine pharmaceutical companies participated in this study.[7] All products studied were released in Japan and details of the sources of products are described in Table 1. The major parts of the products collected were around 1 to 50 mg of content because the purpose of this study was to investigate the threshold value 25 mg/25% for weight variation.

For each individual lot, 10 units were sampled. Measurements were done by the individual manufacture. The assay methods used were HPLC and UV absorption methods. The analytical precisions was below 2.5% of RSD. The mean and SD of drug content, formulation weight and concentration of active ingredient (w/w%) were calculated for each group of 10 units in a single lot, and were used for obtaining the acceptance values of JP13 as described above.

Plain Tablets Each unit was weighed and assayed in succession. The concentration of the active ingredient was calculated by dividing drug content by the formulation weight of each unit.

Film-Coated Tablets Film-coated tablets were tested in the same manner as the plain tablets. The concentration of the active ingredient was calculated by dividing drug content by formulation weight in which the coating weight was contained.

Sugar-Coated Tablets Two types of samples were tested; one is a precoated plain tablet sampled from production lines, another is a sugar-coated tablet as a final product. Whole weight and drug content of each unit were measured and statistical variables and acceptance values were calculated for both samples.

Hard Capsules Each unit was weighed, then the capsule was emptied to weigh the empty shell and the net weight of filling was obtained by subtracting shell weight from the weight of the whole formulation. The filling was used for assay of drug. In the case where the emptied shell weight could not be measured, the filling weight of each unit was assumed by subtracting mean shell weight from the individual whole weight of an intact formulation. The mean shell weight was obtained by weighing the empty shells before filling.

Data Analysis Product-specific RSD was given by ANOVA using three lots of data for each brand. The model associated with the observation is given as:

$$x_{ij}=\mu+a_i+e_{ij} \quad (8)$$

where x_{ij} is the observation of the jth unit in ith lot, μ is the general mean, a_i is the effect of ith lot, and e_{ij} is the residual error consisting of intra-lot variation and analytical error. The intra-lot variation RSD_D, RSD_W and RSD_C were calculated as Eq. 9.

$$RSD_{intra}=\frac{\sqrt{V_{intra}}}{\bar{\bar{x}}} \quad (9)$$

The product-specific inter-lot RSD of content (RSD'_D), weight (RSD'_W) and concentration (RSD'_C) for variation were calculated as below.

$$RSD_{inter}=\frac{\sqrt{(V_{inter}-V_{intra})/10}}{\bar{\bar{x}}} \quad (10)$$

$$V_{inter}=10\sum_i(\bar{x}_i-\bar{\bar{x}})^2/2 \quad (11)$$

$$V_{intra}=\sum_{ij}(x_{ij}-\bar{x}_i)^2/27 \quad (12)$$

Operating Characteristic Curves The probability of acceptance for the Content Uniformity Test was obtained by Monte Carlo simulations under the condition that the lot mean was 100.0% of label strength and RSD_D varies from 0.5 to 15.0%. OC curves of Weight Variation Test were calculated in the same manner as the Content Uniformity Test except for using RSD_W instead of RSD_D. If $RSD_C=0$, then $RSD_D=RSD_W$ because RSD_D is the square root of $RSD_W^2+RSD_C^2$ (from Eq. 7). In this case, the OC curve of Weight Variation Test *versus* RSD_D is the same as that of Content Uniformity Test. If $RSD_C>0$, then $RSD_D>RSD_W$ and the OC curve of Weight Variation Test *versus* RSD_D shifts to the right of the Content Uniformity Test.

Results and Discussion

The characteristics of distribution of label strength of

Table 1. Formulations Studied for Content Uniformity and Weight Variation

Dosage forms	Total	Plain tablets	Film-coated tablets	Sugar-coated tablets	Hard capsules
No. of companies	49	37	29	10	10
No. of Brands	177	93	56	14	14
No. of lots	531	279	168	42	42

Table 2. Distribution Characteristics of Drug Contents

Dosage forms	Total	Plain tablets	Film-coated tablets	Sugar-coated tablets	Hard capsules
Label strength of pharmaceuticals					
Number of brands	177	93	56	14	14
Mean (mg)	25.4	16.8	33.4	22.3	53.5
Median (mg)	10.0	5.0	17.3	17.6	34.3
Max (mg)	255.0	255.0	200.0	50.0	225.0
Min (mg)	0.25	0.25	1.0	5.0	10.0
Intra lot RSD_D of brands					
Mean (%)	1.34	1.26	1.34	1.63	1.56
Median (%)	1.09	1.02	1.20	1.23	1.27
Max (%)	5.20	5.20	3.68	3.07	4.41
Min (%)	0.45	0.45	0.62	0.85	0.76
Skewness	2.35	2.83	1.99	0.87	2.46
Kurtosis	7.30	10.98	4.42	−0.83	7.30

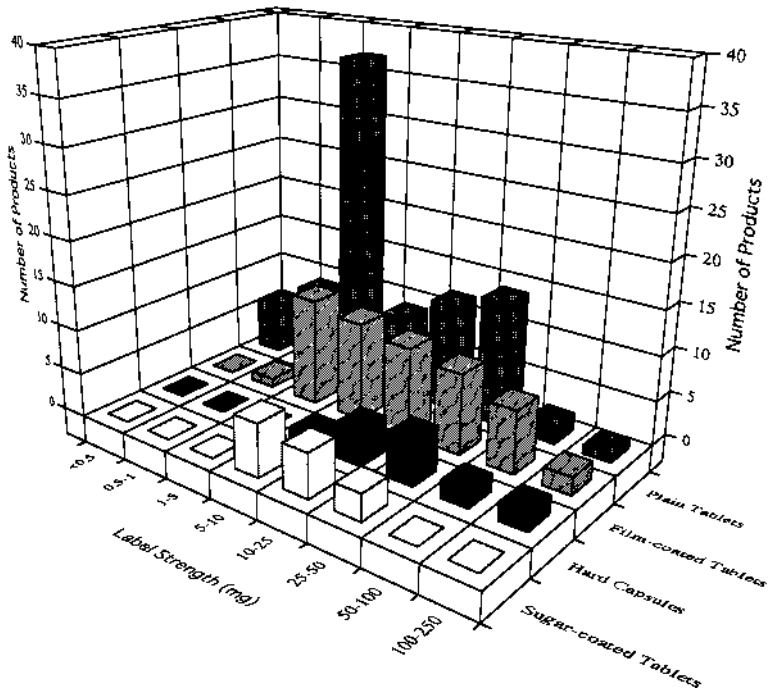

Fig. 1. Distribution of Label Strength in Four Dosage Forms Investigated

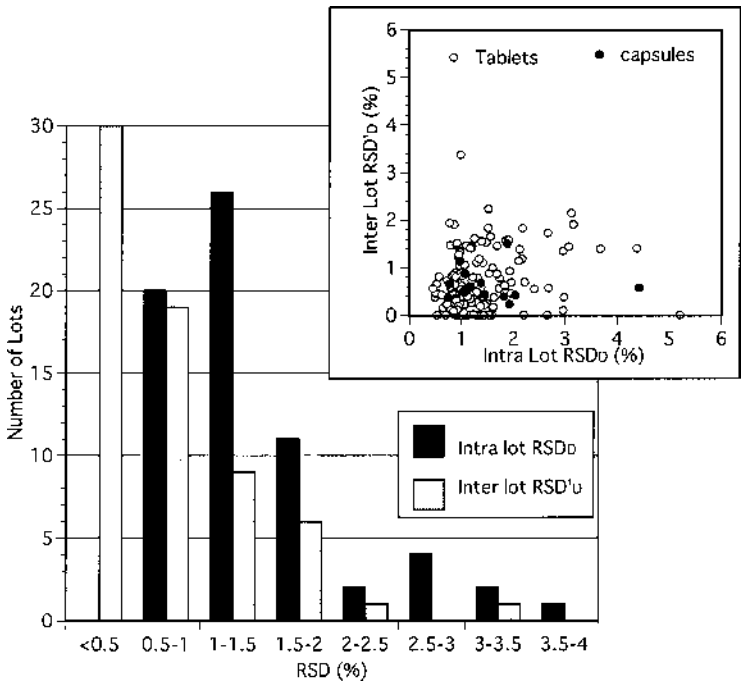

Fig. 2. Intra- and Inter-lot RSD_D of All the Dosage Forms

The small figure shows the relationship between intra and inter lot RSD_D for each brand.

pharmaceuticals tested are shown in Fig. 1 and Table 2. There were large differences in distribution of unit dose strength among dosage forms tested. Most of the plain tablets were low-dose drugs containing less than 1 mg of active ingredient, whereas all the sugar-coated tablets and hard capsules had equal to or higher than 5 mg of dose strength.

The results of ANOVA showed that the inter-lot variation was smaller than intra-lot variation in content uniformity and no relationship was found between intra- and inter-lot variations for any brand (Fig. 2). The small inter-lot variability is based on: 1. the manufacturing process may be well controlled by most of the manufacturers and 2. analytical variation increases intra-lot variability.

Relationship between Content Uniformity and Label Strength or Drug Concentration The content uniformity of a formulation is represented by intra-lot variation (RSD_D). In the case of plain tablets, RSD_D tended to increase with the decrease of the label strength (Fig. 3a). Especially, the plain tablets of label strength that was lower than 10 mg showed large RSD_D. The low-dose drugs having less than 1 mg some-

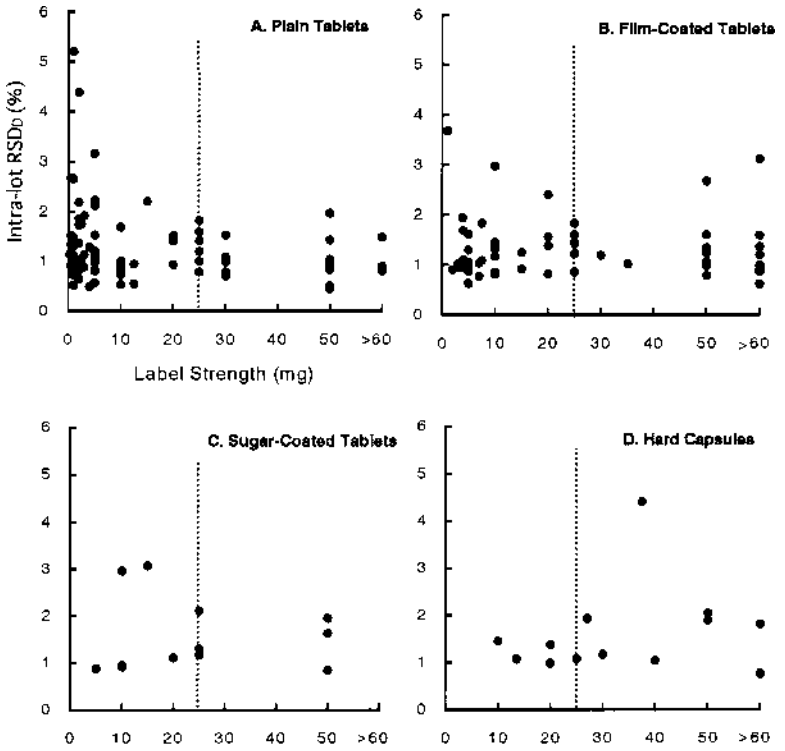

Fig. 3. Relation between Label Strength and RSD of Content Uniformity
Vertical broken lines show the ICH threshold of 25mg of dose.

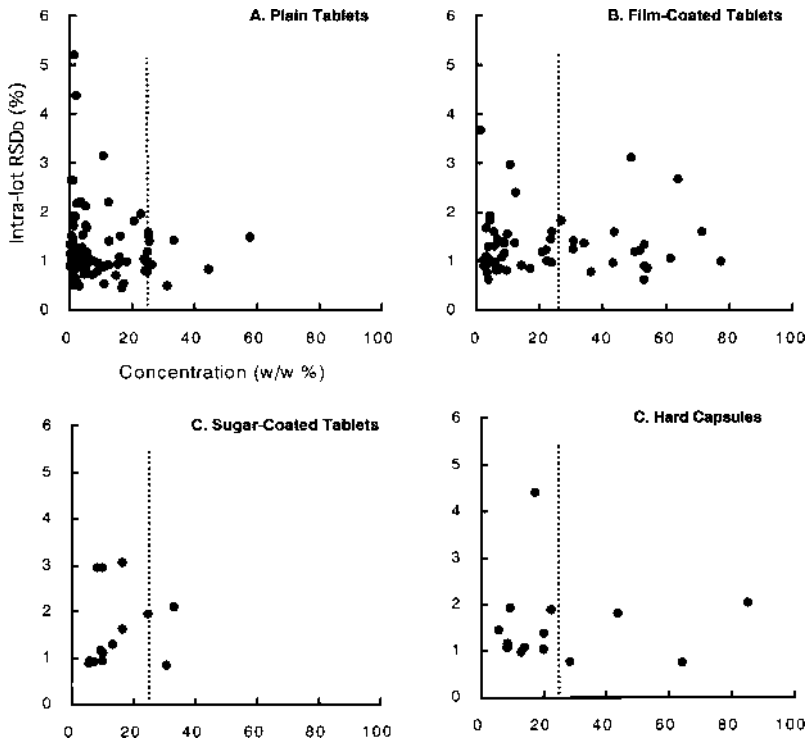

Fig. 4. Relation between Drug Concentration and RSD of Content Uniformity
Vertical broken lines show the ICH threshold of 25% of concentration.

times showed especially large RSD_D (*e.g.*, above 4%). However, these relationships between label strength and RSD_D were not observed for those of the other dosage forms and large RSD_D was also found in high-dose formulations having more than 25 mg for film-coated tablets and capsules (Figs. 3b, d).

The relationship between RSD_D and drug concentration is quite similar to the relationship between RSD_D and unit dose strength; the RSD_D of plain tablets tended to increase with the decrease of the drug concentration (Fig. 4a). However such a tendency was not obvious in the other dosage forms (Figs. 4b—d).

In the PhRMA's recommendation[5] of the ICH draft, it was said that "The weight variation may be applicable for products whose strength and concentration are not less than 25 mg and 25%, respectively" because the RSD_C is theoretically 1.1% when the particle size of active ingredient is well controlled and mixing of active ingredient and additives is completed.[5] However our results did not support the threshold "25 mg/25%." For plain tablets, an allowable threshold of application of weight variation will be that the label strength is not less than 10 mg and the concentration of active ingredient is not less than 10% (w/w). The acceptable threshold for weight variation test in other dosage forms could not be decided. This means that the manufacturers' mixing skill is not always sufficient even when the dose strength is high.

Relationship between Weight Variation and Formulation Weight The characteristics of the weight distribution of the formulations tested are shown in Table 3. There were small differences in the characteristics of the weight distributions among dosage forms tested. Almost all the formulations weighed less than 400 mg. The two plain tablets showing exceptionally larger weight higher than 500 mg were chewable tablets and vaginal tablets.

Table 3. Distribution Characteristics of Formulation Weights

Dosage forms	Plain tablets	Film-coated tablets	Sugar-coated tablets	Hard capsules[a]
Weight of formulations				
Number of brands	93	56	14	14
Mean (mg)	159.3	143.9	157.9	221.3
Median (mg)	120.1	135.0	151.8	211.3
Max (mg)	999.1	309.4	303.9	370.3
Min (mg)	48.89	48.2	74.6	58.3
Intra lot RSD_W of brands				
Mean (%)	0.77	0.91	2.73	1.16
Median (%)	0.72	0.93	2.34	1.04
Max (%)	1.65	1.57	5.66	2.09
Min (%)	0.32	0.41	1.00	0.67
Skewness	0.92	0.25	0.87	0.84
Kurtosis	0.70	−0.80	0.27	−0.45

a) Weight of filling in capsules.

The weight variation of a formulation is represented by RSD_W. There was no relationship between formulation weight and RSD_W (Fig. 5). European Pharmacopoeia adopts the "sliding scale" in the judgment of weight variation test. Sliding scale means setting different specification limits according to the weight of dosage forms. The sliding scales have been used for dealing with the difficulty in controlling the weight of small dosage forms. However, our results did not support the relevance of sliding scale in the weight variation test.

Sugar-coated tablets showed exceptionally large RSD_W (Fig. 5). The large RSD_W of sugar-coated tablets was caused by the large weight variability in the sugar coatings, which shared about 40% of the tablet's weight.

Relationship between RSD_D and RSD_C or RSD_W The RSD_D was well correlated with RSD_C but not RSD_W (Figs. 6, 7). The correlation coefficients between RSD_D and RSD_C were above 0.9 for all the dosage forms except for sugar-coated tablets (Fig. 6), whereas the correlation coefficients between RSD_D and RSD_W were not more than 0.5 in all the dosage forms (Fig. 7). This means that the content variability mostly depended on the variability of concentration rather than weight variation. In the case of sugar-coated tablets, the RSD_D was less correlated with RSD_C than RSD_W. It is suggested that RSD_C (Table 4) is influenced by the weight variability of the sugar coat because the core of the sugar-coated tablets (pre-coated plain tablets) showed good correlation be-

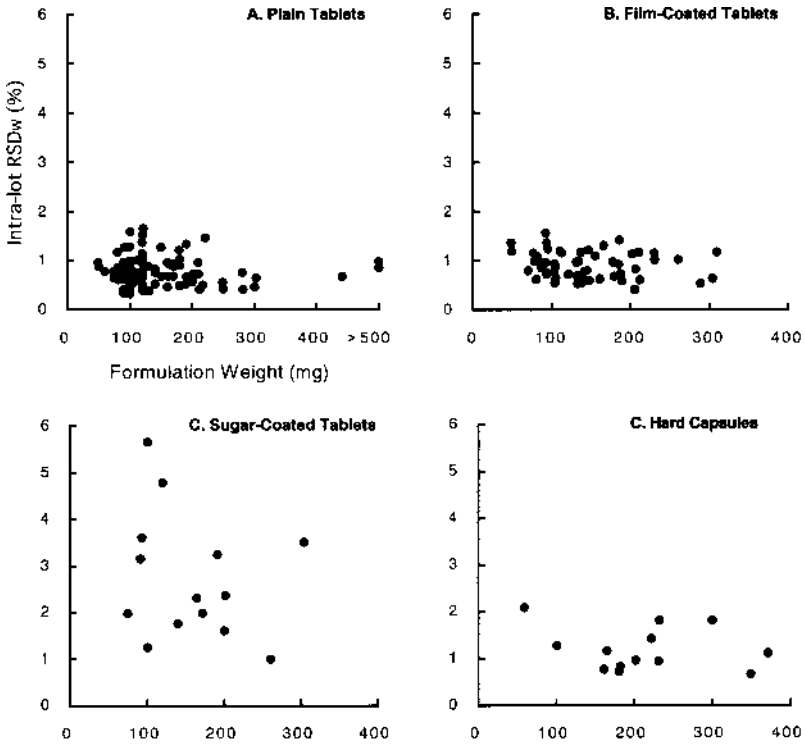

Fig. 5. Relation between Formulation Weight and RSD_W

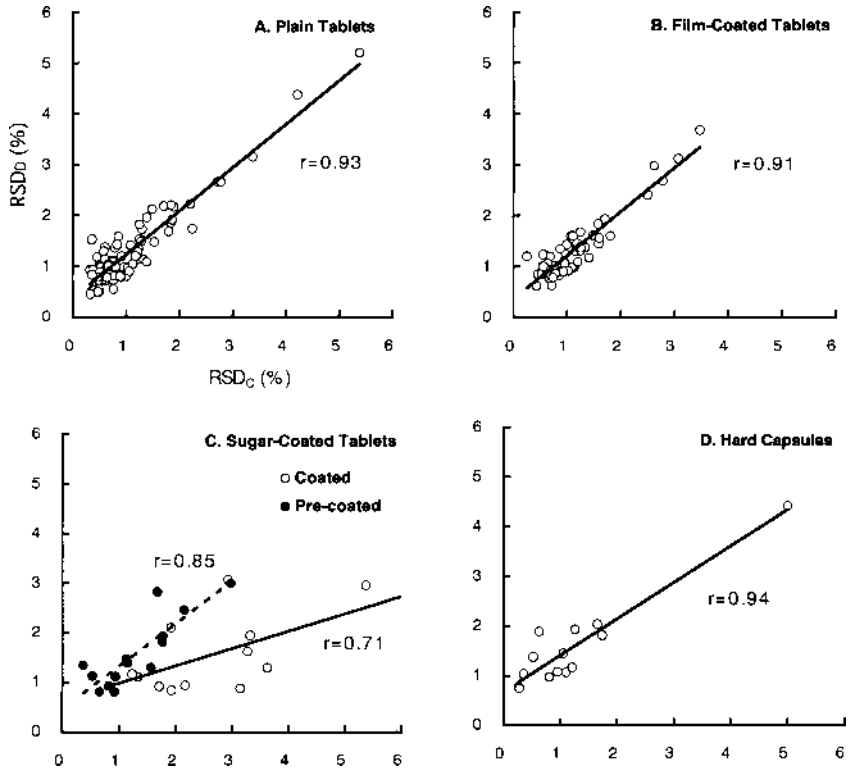

Fig. 6. Relation between Mixing Homogeneity (RSD_C) and Content Uniformity (RSD_D)
Lines are the regression lines.

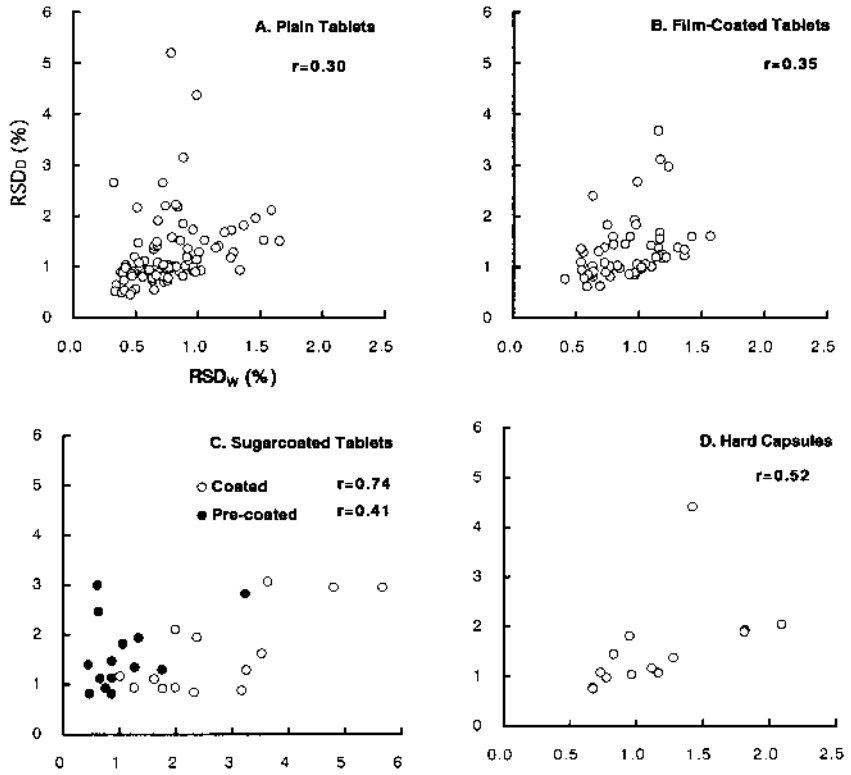

Fig. 7. Relation between Weight Variation (RSD_W) and Content Uniformity (RSD_D)

tween RSD_D and RSD_C as well as plain tablets (Fig. 6c).

The effects of RSD_C on the operating characteristics of JP weight variation test are shown in Fig. 8. The RSD_D of consumer's risk level (5% of probability of acceptance for pharmaceutical products) increases with an increase of the RSD_C of each submitted lot. The acceptable RSD_C for application of the weight variation tests which does not show a significant difference in the quality of the consumer's risk level be-

Table 4. Distribution Characteristics of Drug Concentration and Mixing Homogeneity

Dosage forms	Plain tablets	Film-coated tablets	Sugar-coated tablets	Hard capsules[a)]
Concentration of active ingredient				
Number of brands	93	56	14	14
Mean (w/w%)	9.6	21.9	14.2	25.6
Median (w/w%)	5.1	11.4	10.0	18.5
Max (w/w%)	57.7	77.2	33.0	85.1
Min (w/w%)	0.05	1.4	5.5	5.5
Intra lot RSD_C of brands				
Mean (%)	1.04	1.14	2.84	1.20
Median (%)	0.79	0.98	2.54	1.00
Max (%)	5.38	3.48	7.07	5.00
Min (%)	0.32	0.25	0.82	0.26
Skewness	2.93	1.74	1.32	2.78
Kurtosis	11.21	3.24	1.84	9.02

a) Concentration in capsule filling.

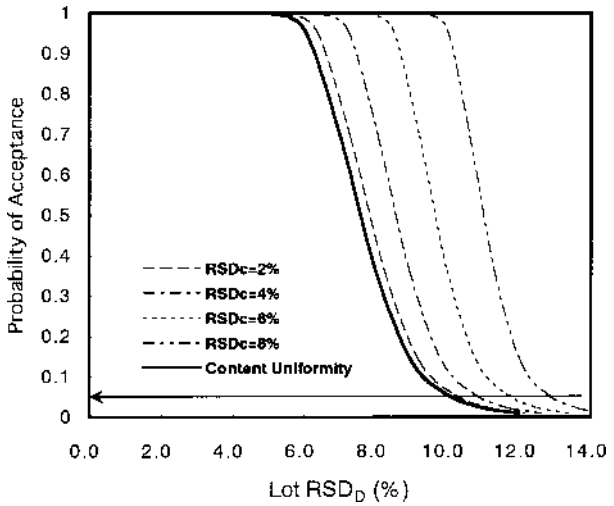

Fig. 8. Effect of RSD_C on Operating Characteristics of Weight Variation Test

Arrow shows consumer's risk (p=0.05).

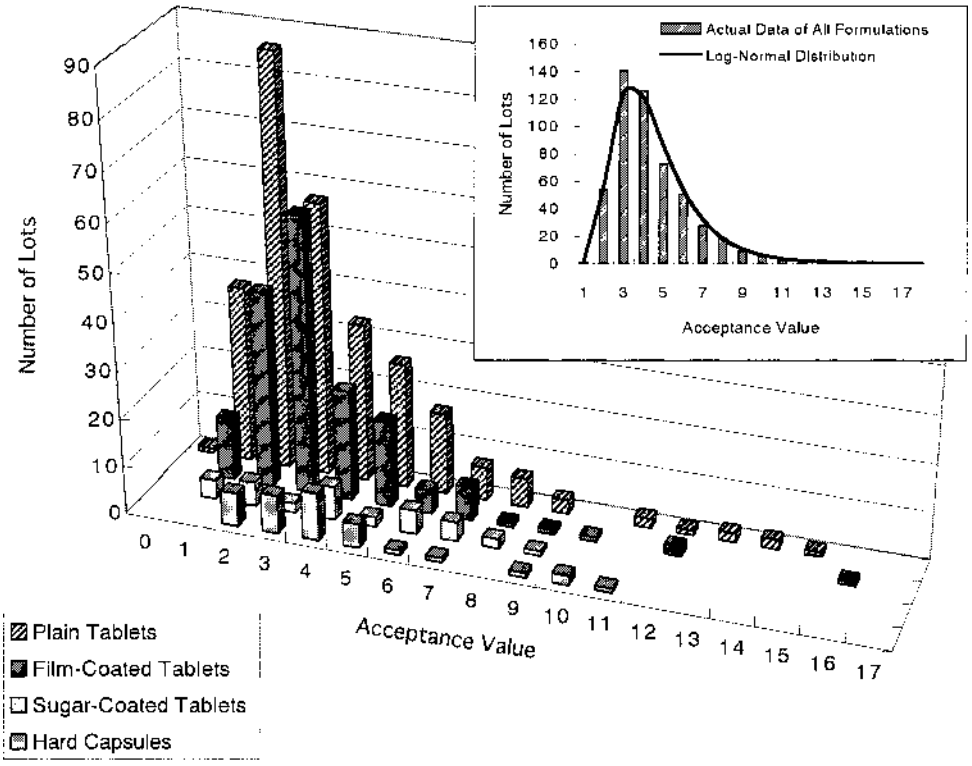

Fig. 9. Distribution of Acceptance Values of Content Uniformity Test for Four Types of Dosage Forms

tween the content uniformity and weight variation tests is considered to be not more than 2%. Therefore, before application of the weight variation test, it is desirable to assess the state of mixing of a submitted formulation by using the product specific RSD_C. If the RSD_C of a product is always below 2%, the weight variation test is applicable for Content Uniformity Tests regardless of any threshold such as "25 mg/25%".

Distribution of Acceptance Value of JP To investigate the characteristics of the content uniformity test, it is important to know the behavior of the distribution manner of acceptance values ($|M-\bar{X}|+ks$). The distributions of the acceptance values of JP Content Uniformity Test of the first step (n=10, k=2.2) are described in Fig. 9 and Table 5. The distributions for all the dosage forms showed a large skewness and kurtosis, and could be well approximated to a log-normal distribution. The number of lots that could not pass the first step of the JP Content Uniformity Test was only one out of 531 for all the dosage forms. The probabilities of passing the tests calculated assuming the log-normal distribution was above 99.5% (Table 5). It was concluded that the risks of failing the JP Content Uniformity Test were very low. One difference between the harmonization plans[5)] and current JP in the acceptance values is the setting of M and k values as

Table 5. Distribution Characteristics of Acceptance Values

Dosage forms	Total	Plain tablets	Film-coated tablets	Sugar-coated tablets	Hard capsules
Acceptance values of JP13 Content Uniformity Test					
Number of lots	531	279	168	42	42
Mean	4.04	3.92	3.98	4.56	4.51
Median	3.45	3.25	3.55	4.22	3.94
Max	16.27	15.01	16.27	9.74	11.08
Min	1.00	1.00	1.02	1.39	1.42
Skewness	2.00	2.08	2.54	0.48	1.46
Kurtosis	5.58	5.70	9.74	−0.63	1.88
95 percentile[a)]	7.93	7.90	7.33	9.25	8.83
99 percentile[a)]	11.03	11.18	9.83	13.00	12.25
Probability of acceptance[a)]	0.9985	0.9982	0.9995	0.9955	0.9970
Acceptance values of JP13 Weight Variation Test					
Number of lots	—	279	168	42	42
Mean	—	2.88	3.05	6.95	3.67
Median	—	2.52	2.89	5.98	3.29
Max	—	11.28	8.62	15.37	10.48
Min	—	0.69	0.85	2.10	1.21
Skewness	—	1.65	1.56	1.16	1.53
Kurtosis	—	5.04	3.84	1.24	4.51
95 percentile[a)]	—	5.61	5.45	12.38	6.98
99 percentile[a)]	—	7.75	7.17	16.23	9.48
Probability of acceptance[a)]	—	0.9999	1.0000	0.9833	0.9996

a) These values are calculated by assuming log-normal distribution.

described above. The PhRMA's recommendation is intended to help the products showing a deviation from label claim to pass the test; however, the test using the JP acceptance value is not too strict thus allowing almost all the commercial products to pass the Content Uniformity Test (Table 5).

The present study revealed that the probabilities of failing the first step of the JP Weight Variation Tests were lower than 0.05% for plain tablets, film-coated tablets and hard capsules (Table 5). This suggested that the Weight Variation Test was less strict than the Content Uniformity Test except for sugar-coated tablets. The probability of failing the Weight Variation Test was calculated to be about 2% for sugar-coated tablets (Table 5). The high failure rate of sugar-coated tablets was caused by the high variability of the weight of the sugar coats.

The differentiation in the specification limits between compressed tablets and capsules has been a topic in the discussion of pharmacopoeial harmonization. The acceptance criteria of the Content Uniformity Test are the same between tablets and capsules in JP but differ in USP. Our results showed that there were small differences between tablets and hard capsules in RSD_D (Table 2) and the risk of failing the JP Content Uniformity Test in capsules was almost the same as in the plain and film-coated tablets (Table 5). It was concluded that additional criteria like USP are not needed for hard capsules in Japan.

Conclusion

The threshold value of 25 mg/25% for application of weight variation for content uniformity was not supported by this study. The threshold of 10 mg/10% is favorable for plain tablets if being applied. However, application of weight variation tests should, in principle, be decided on the mixing homogeneity (RSD_C) because RSD_C depends on the manufacturer's methods. The Weight Variation Test can be applied when the RSD_C is smaller than 2% where consumer's risks are restrained as low as the Content Uniformity Test. The criteria of JP13 Content Uniformity and Weight Variation Test are not considered to be unduly strict and are acceptable because they allow commercial products of ordinal quality.

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References

1) Japanese Pharmacopoeia 13 ed. (1996), General Test 10, Content Uniformity Test.
2) Katori N., Aoyagi N., Kojima S., *JP Forum*, **4**, 71—92 (1995).
3) Katori N., Aoyagi N., Kojima S., *USP Pharmacopeial Forum*, **23**, 5325—5333 (1997).
4) Pharmacopeial Previews, ⟨905⟩ Uniformity of Dosage units, *USP Pharmacopeial Forum*, **23**, 4683—4686 (1997).
5) Members of the Statistics Working Group of PhRMA, *USP Pharmacopeial Forum*, **25**, 8609—8624 (1999).
6) Stanger W. C., Cerimele B. J., Fricke G. H., *Drug Dev. Ind. Pharm*., **17**, 233—244 (1991).
7) Nakanishi A., Tonooka H., Suzuki S., Ohtani S., Okuda H., Kato M., *Iyakuhin Kenkyu*, **32**, 27—33 (2001).