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COMMUNICATION

RSD Requirement for Different Sample Size for Blend Sampling

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ABSTRACT

A formula for calculating the equivalent relative standard deviation (RSD) for different sample sizes other than the Office of Generic Drugs (OGD) draft guidance was derived. These critical values vary with the population RSD and the sample size and guarantee the same confidence of passing a batch similar to the OGD blend uniformity test. Simulation results showed that the normal approximations give very close results to the simulation results. An assessment of the proposed OGD blend uniformity criteria against the first-stage USP content uniformity (CU) criteria for tablets was also made.

Key Words: *Blend uniformity; Equivalent RSD; Normal approximation.*

INTRODUCTION

The Office of Generic Drugs (OGD) (1) draft guidance for blend uniformity analysis applies two criteria: (*a*) the average of the individual assay values falls within prespecified limits and (*b*) sample relative standard deviation (RSD) has to be no more than the prespecified value for the recommended sample size. But, for some practical reasons, analysts may assay fewer samples than stated in the guidelines or the sample size stated in the analysts' standard operating procedure (SOP). In this context, consulting statisticians are frequently asked questions concerning the RSD requirement for a particular sample size to be equivalent to the OGD test or the test stated in an SOP.

For example, let us assume that 5 samples were assayed from a granulation bin rather than the usual 10 samples. The draft OGD guideline and the FDA recommendation on validation issues (2) states that the RSD of the sample size should not be more than 5% to demonstrate that the blend homogeneity provides a high degree of assurance that the individual dosage units would meet USP requirements for content uniformity (CU). The analyst wants to know the equivalent RSD requirement for his or her sample size. For two RSD criteria to be equivalent, we need to have the same acceptance probability from both criteria, that is,

$$\Pr(RSD_{10} \leq 5) = \Pr(RSD_5 \leq d)$$

The solution of d of the above equation gives the equivalent OGD guidance RSD requirements for the given sample size.

Table 1

Critical Relative Standard Deviation (RSD) for Sample Sizes 4 to 9 Equivalent to Sample Size 10 with RSD = 6% (USP CU for Tablet Stage 1 Criterion) for Given Population Relative Standard Deviation

Population RSD (%)	Sample Size					
	4	5	6	7	8	9
3.5	7.84	7.25	6.86	6.56	6.33	6.15
3.6	7.76	7.20	6.82	6.54	6.32	6.15
3.7	7.69	7.15	6.79	6.52	6.31	6.14
3.8	7.61	7.10	6.75	6.50	6.30	6.13
3.9	7.54	7.05	6.72	6.47	6.28	6.13
4.0	7.47	7.00	6.68	6.45	6.27	6.12
4.1	7.40	6.95	6.65	6.43	6.25	6.11
4.2	7.32	6.90	6.62	6.40	6.24	6.11
4.3	7.25	6.85	6.58	6.38	6.22	6.10
4.4	7.17	6.80	6.55	6.36	6.21	6.09
4.5	7.10	6.75	6.51	6.34	6.20	6.09
5.0	6.73	6.50	6.34	6.22	6.13	6.06
5.2	6.60	6.40	6.27	6.18	6.11	6.05
5.4	6.44	6.30	6.20	6.13	6.10	6.03
5.6	6.30	6.20	6.14	6.10	6.05	6.02
5.8	6.15	6.10	6.07	6.04	6.02	6.01
6.0	6.00	6.00	6.00	6.00	6.00	6.00

Table 2

Critical Relative Standard Deviation (RSD) for Sample Sizes 4 to 9 Equivalent to Sample Size 10 with RSD = 5% (OGD Criterion) for Given Population Relative Standard Deviation

Population RSD (%)	Sample Size					
	4	5	6	7	8	9
3.5	6.10	5.75	5.51	5.34	5.20	5.09
3.6	6.03	5.70	5.48	5.31	5.19	5.08
3.7	5.95	5.65	5.44	5.29	5.17	5.08
3.8	5.88	5.60	5.41	5.27	5.16	5.07
3.9	5.81	5.55	5.38	5.25	5.15	5.07
4.0	5.73	5.50	5.34	5.22	5.13	5.06
4.1	5.66	5.45	5.31	5.20	5.12	5.05
4.2	5.59	5.40	5.27	5.18	5.11	5.05
4.3	5.51	5.35	5.24	5.16	5.09	5.04
4.4	5.44	5.30	5.20	5.13	5.08	5.04
4.5	5.37	5.25	5.17	5.11	5.07	5.03
5.0	5.00	5.00	5.00	5.00	5.00	5.00
5.2	4.85	4.90	4.93	4.96	4.97	4.99
5.4	4.72	4.80	4.86	4.91	4.95	4.97
5.6	4.56	4.70	4.80	4.87	4.92	4.96
5.8	4.42	4.60	4.73	4.82	4.90	4.95
6.0	4.27	4.50	4.66	4.78	4.87	4.94

OGD = Office of Generic Drugs.

Table 3

Probability (%) of Passing the Relative Standard Deviation Requirement For Three Criteria for Different Population Relative Standard Deviations

Population RSD (%)	$N = 10$, $r = 6\%$	$N = 6$	r (%)	$N = 6$, $r = 6\%$
3.5	99.88	99.77	6.86	98.71
3.7	99.47	99.51	6.79	97.76
3.9	98.83	98.80	6.72	96.22
4.1	97.80	97.66	6.65	94.08
4.3	96.10	96.06	6.58	91.50
4.5	93.12	93.53	6.51	88.30
5.2	78.30	79.82	6.27	75.34
5.6	67.18	69.00	6.14	66.22
6.0	56.28	58.90	6.00	58.92

CALCULATION OF CRITICAL RELATIVE STANDARD DEVIATION

Let us assume that we are sampling from a normal population with mean μ and standard deviation σ and also assume that $\bar{x} + ks$ is approximately normally distributed, that is,

$$\bar{x} + ks \sim N\left(\mu + k\sigma, \frac{\sigma^2}{n} + \frac{k^2\sigma^2}{2(n-1)}\right)$$

where $\bar{x}$, s, and n are the sample mean, sample standard deviation, and the sample size, respectively, and k is a constant. Let the recommended OGD sample size and the critical RSD value be n_0 and d_0 and the analyst's sample size and the equivalent critical RSD be n_1 and d_1, respectively, and also assume the population RSD is r(%). Using the normal approximation, one can derive the following equation, which gives the solution for d_1:

$$\frac{r - d_0}{\sqrt{\frac{d_0^2}{n_0} + \frac{10^4}{2(n_0 - 1)}}} = \frac{r - d_1}{\sqrt{\frac{d_1^2}{n_1} + \frac{10^4}{2(n_1 - 1)}}}$$

This equation can be solved iteratively to obtain the solution for d_1, and we obtain the critical values of RSD equivalent to USP the first-stage CU of dosage units criterion and the OGD blend uniformity criterion (Tables 1 and 2, respectively) for sample sizes 4 to 9.

SIMULATION STUDY

The accuracy of the normal approximation was examined by a simulation study. Five hundred random samples of size 10 and 6 were drawn from a normal distribution with mean 100 and given a standard deviation ranging from 3.5 to 6. First, for sample size 10 and 6, a critical value of 6% was used, and the percentage of samples that passed the criteria were calculated. Second, for the same set of samples of size 6, different critical values were given (see Table 1), and the percentage of samples that passed the criteria were also calculated. The procedure was repeated 50 times, and the average percentages of the three criteria are reported in Table 3. The results

Table 4

Percentage of Batches Meeting the Current USP Uniformity of Dosage Units and Proposed Office of Generic Drugs (OGD) Blend Uniformity Criteria for Different True Process Means (μ)

	$\mu = 100$		$\mu = 94$		$\mu = 93$		$\mu = 92$	
Population RSD (%)	Current USP	Proposed OGD[a]	Current USP	Proposed OGD[a]	Current USP	Proposed OGD[a]	Current USP	Proposed OGD[a]
3.5	99.8	92.9	96.8	92.7	93.3	91.6	85.5	87.1
3.7	99.6	89.4	95.2	89.3	90.0	88.6	81.8	82.8
3.9	98.9	85.1	92.8	85.4	87.1	84.0	77.0	78.3
4.1	97.5	81.0	90.0	80.7	83.4	78.3	72.0	73.2
4.3	95.5	75.9	86.0	75.6	78.7	73.8	66.7	68.5
4.5	92.9	70.6	82.0	69.7	73.8	68.1	62.2	63.0
5.2	78.3	54.2	64.3	52.7	56.8	50.2	44.8	46.3
5.6	67.4	44.9	53.6	43.6	45.7	42.3	36.5	37.7
6.0	55.5	37.4	43.0	36.0	36.6	33.8	29.1	31.0

[a] With sample size 6.

showed that the normal approximation gives very close estimates to the simulation results.

CONCLUSION

In this paper, a formula is derived to convert the OGD draft guidance for blend uniformity stated RSD requirement to an equivalent criterion for different sample size. The results of this study suggest that a provision should be made for less stringent criteria for RSD for a small sample size. One needs to know the information about the population RSD of the product to use Tables 1 and 2. It may be estimated either from the historic data or from a simulation study of a normal distribution.

The results of this study also showed that the recently proposed OGD criteria (sample size usually 6–10, RSD $\leq$ 5% and the average within 90–110%) for abbreviated new drug applications (ANDAs) in-process blend uniformity is much tighter than the criteria currently being used for tablet CU. For example, if the population RSD is within 4 to 5, Table 1 shows that the equivalent RSD requirement to the current criteria vary from 6.68 to 6.34 for sample size 6. If we observed RSD = 6.2% of a sample of 6 of this population, the test fails the proposed OGD criteria, but would have passed the first-stage USP CU of dosage unit criteria. This observation is also supported by the estimated percentage of batches meeting both criteria by 500 bootstrap samples drawn from normal populations (see Table 4).

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REFERENCES

1. Guidance for Industry, *ANDAs: Blend Uniformity Analysis*, U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), Office of Generic Drugs, Washington, DC, August 1999.
2. J. M. Dietrick, Food and drug administration recommendations on validation issues, Reg. Affairs, 5, 363–366 (1993).