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RESEARCH PAPER

Unit Dose Sampling and Final Product Performance: An Alternative Approach

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ABSTRACT

This article documents a proposed plan for validation testing for the content uniformity for final blends and finished solid oral dosage forms (SODFs). The testing logic and statistical justification of the plan are presented. The plan provides good assurance that a passing lot will perform well against the USP tablet content uniformity test. The operating characteristics of the test and the probability of needing to test for blend sampling bias are reported. A case study is presented.

INTRODUCTION

Validation of the uniformity of a final blend is currently a highly debated topic in the pharmaceutical industry. A number of papers (1–19) have recently been published discussing this very matter. It is not the intent to review these articles here, but merely to propose an alternative method of determining blend uniformity with special consideration for sample bias.

The FDA has recently commented on the methods by which an innovator may address final blend content uniformity results that are suspected of having sample bias: change sampling technique, change sample size, or perform extensive final product testing (e.g., tablets or capsules) (19).

An appropriately developed product will have been sampled, as part of its process development, using various sampling thieves and sample sizes to determine the appropriate sampling methodology.

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The formulator must give due consideration to the scale of development at which the methodology was developed, understanding that what may have seemed optimal on a smaller scale may not necessarily be true on a larger scale. Considering the high expense and time necessary, typically only limited experience is available at full scale, before process validation. Even if prior experience has been successful with a specific sampling methodology, there is no guarantee that the success will continue through validation. Therefore, the appropriately developed sampling protocol and acceptance criteria will take into consideration potential sampling biases, which may develop during process validation.

During the time of validation, it is practically impossible to change the sampling technique or the sample size since, in many cases, the blend may have undergone further processing (e.g., compression) or may have been discharged from the sampling container (e.g., blender or bin). Therefore, an innovator is left with only the opportunity to perform extensive final product testing to prove or disprove the uniformity of the final product. Extensive final product testing is important to the proposed alternative presented here.

This article provides details of an alternative sampling procedure and acceptance criteria to ensure final product content uniformity. A case study is presented as well.

PHILOSOPHY AND ASSUMPTIONS

In the development of the sampling protocol, it was assumed that the practical constraints for sampling within a blender (i.e., ceiling height constraints, difficulty in sampling from a large [e.g., 150 cubic foot] V blender) render it impractical. Rather, it was suggested that sampling occur after discharge, from the bins or hoppers.

The method of bin sampling is shown in Fig. 1. Each bin is sampled at multiple locations around its periphery, as well as from its center. For each thief stab indicated in Fig. 1, three samples are retrieved, one each from the top, middle, and bottom of the bin. This yields 30 total samples, 18 from the periphery and 12 from the center of the bin. However, only 12 samples are tested initially, while the remaining samples are kept in reserve. Nine tested samples are from the periphery (locations A, C, and E), and three samples are from sample location G1.

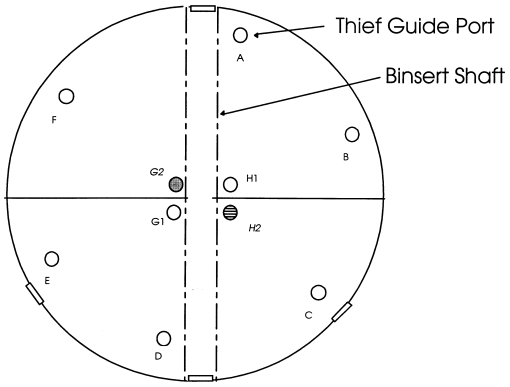

Figure 1. Bin sampling scheme (top view).

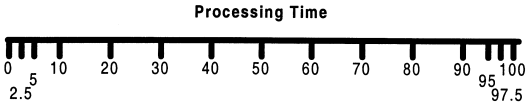

Figure 2. Sampling time points for solid oral dosage forms as a percentage of batch completion.

Reserve samples are important in the event of a loss of sample integrity through lab error, sample-handling error subsequent to sampling, or random acts of god.

Since sampling of the bin/hopper is assumed, the goal then is to profile each individual bin/hopper. Therefore, in a multiple bin/hopper process, each bin would be sampled 30 times. For example, a 4-bin/hopper process would yield 120 blend samples, but only 48 are tested initially.

There are a number of possible final solid oral dosage forms (SODFs), such as tablets, capsules, powder-filled bottles (for reconstitution), and others. An appropriate sampling plan for these unit operations is also critical to the validation process. Sampling of the process throughout the operation is vital in proving that the process performs to and delivers product of acceptable quality.

The proposed sampling procedure for these dosage forms is one by which a number of units are tested at specific points throughout the process (e.g., compression). The sampling time points are graphically depicted in Fig. 2. For each of the 15 sampling time points, a sufficient number of dosage forms are collected to perform all appropriate testing, including content uniformity.

The minimum number of samples to be tested at this stage depends on whether sampling bias has been demonstrated with the blend samples. If sam-

pling bias has been demonstrated for the final blend, then 6 final dosage units are sampled at each of the 15 sampling time points, yielding a total of 90 dosage units tested; otherwise, only 4 final dosage forms are tested at each time point, for a total of 60 dosage units.

VALIDATION SAMPLING PLAN

The validation sampling plan (VSP) for blend/SODF content uniformity is outlined in Fig. 3. Figure 3 presents the plan from the point of view of testing logic and data handling. The following comments detail this aspect of the plan for each step given in Fig. 3.

1. From each of N containers (e.g., bins, hoppers), 30 samples are collected. The sampling plan has been laid out with 10 samples from the top, middle, and bottom of the container. At each level, 4 center samples and 6 peripheral samples (hexagonally arranged) are collected. The sample size is nominally 1–3× unit size,

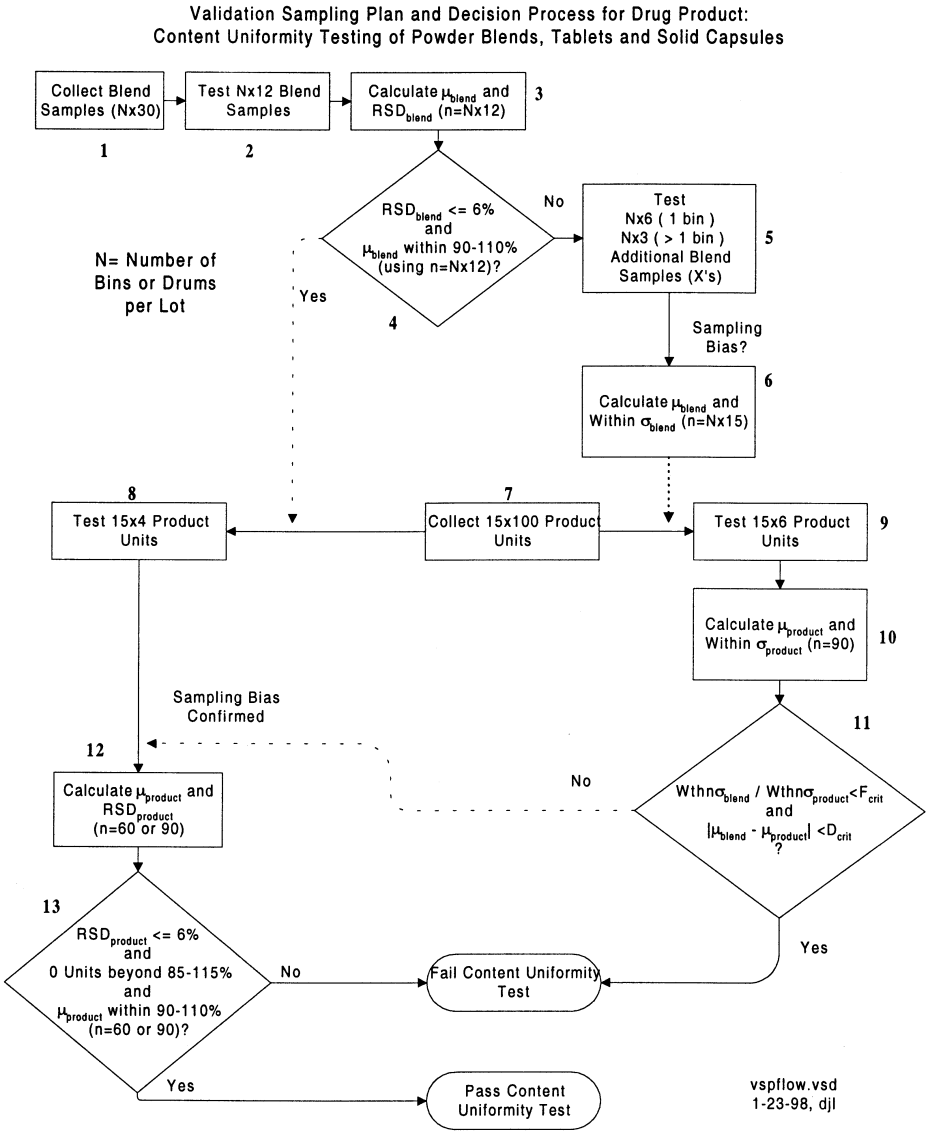

Figure 3. Validation plan decision tree.

unless justified, with a minimum sample weight of 250 mg. An acceptable sample weight must be determined prior to validation.

2. From each container, 12 samples are tested, 4 (4 center and 3 peripheral) from each level.
3. The grand mean and overall relative standard deviation (RSD) of all $N \times 12$ tested samples is calculated. Let N equal the number of bins in the lot, and R_i is the ith blend test result of $12N$. Calculate the following:

$$\overline{X}_{\text{blend}} = \frac{\sum_{i=1}^{12N} R_i}{12N}$$

$$RSD_{\text{blend}} = 100\frac{\sqrt{\dfrac{12N\sum_{i=1}^{12N} R_i^2 - \left(\sum_{i=1}^{12N} R_i\right)^2}{12N(12N-1)}}}{\overline{X}_{blend}}$$

4. The $\overline{X}_{\text{blend}}$ from step 3 must be within 90.0 to 110.0. The $\text{RSD}_{\text{blend}}$ from step 3 must be less than or equal to 6.0. If both are true, proceed to product testing (step 7, then step 8). If either of these specifications fails, calculate the standard error of the blend mean as below and proceed to additional testing (step 5).

$$\hat{\sigma}_{\overline{X}_{\text{blend}}} = \sqrt{\frac{12N\sum_{i=1}^{12N} R_i^2 - \left(\sum_{i=1}^{12N} R_i\right)^2}{144N^2(12N-1)}}.$$

5. Blend sampling bias is suspected if the overall $\text{RSD}_{\text{blend}}$ (step 3) is unexpectedly large or if the $\overline{X}_{\text{blend}}$ (step 3) deviates greatly from 100%. To test the hypothesis of blend sampling bias, additional blend samples are assayed for comparison with product unit content uniformity. If the lot consists of more than 1 bin, 3 additional center points are tested per container (top, middle, and bottom from position H1 in Fig. 1). If the lot consists of only 1 bin, 6 additional center points are tested per container (2 from top, 2 from middle, and 2 from bottom from positions H1 and G2 in Fig. 1) so that the within-position component of variation can be estimated. (Sampling is doubled when only 1 bin is present to raise the degrees of freedom for estimating the within-position variance component from 3 to 6. This will provide reasonable power for the F test in step 11.)
6. The within-location blend variance component $\hat{\sigma}^2_{\text{blend}}$ is estimated from the $N \times 6$ center point results (or 9 results if the lot consists of only 1 bin). For this calculation, each of the three center positions (top, middle, and bottom) from which either 3 (1 bin lot) or 2 (>1 bin lots) replicate test results are available is regarded as a location. The calculations are as follows: Let R_{ij} = the jth replicate blend result from the ith center location, R_i = the mean blend result from the ith center location, and r = number of blend replicates per center location.

$$\hat{\sigma}^2_{\text{blend}} = \frac{\sum_{i=1}^{3N}\sum_{j=1}^{r}\left(R_{ij} - R_{i.}\right)^2}{3N(r-1)}$$

Proceed to product testing (step 7, then step 9).

7. From each of the 15 sampling points, 100 product units are collected during compression or encapsulation. If one or both of the specifications in step 4 failed, proceed to step 9. If both specifications in step 4 were met, proceed to step 8.
8. Four product units are randomly selected and tested from each sampling position if the original blend test (step 4) passes.
9. For testing of sampling bias, more extensive product testing is required. Six product units are randomly selected and tested from each sampling location if the original blend test (step 4) fails.
10. The product grand mean $\overline{X}_{\text{product}}$ and product within location variance component $\hat{\sigma}^2_{\text{product}}$ and the standard error of the product grand mean $\hat{\sigma}_{\overline{X}_{\text{product}}}$ are calculated for the compression or encapsulation run from the 90 results as follows: Let P_{ij} = the jth replicate product result from the ith run location, and $P_{i.}$ = the mean product test result from the ith run location:

$$\overline{X}_{\text{product}} = \frac{\sum_{i=1}^{15}\sum_{j=1}^{6} P_{ij}}{90}$$

$$\hat{\sigma}^2_{\text{product}} = \frac{\sum_{i=1}^{15}\sum_{j=1}^{6}\left(P_{ij} - P_{i.}\right)^2}{75}$$

$$\hat{\sigma}_{\overline{X}_{\text{product}}} = \sqrt{\frac{\sum_{i=1}^{15}\left(P_{i.} - \overline{X}_{\text{product}}\right)^2}{210}}$$

Proceed to step 11.

11. A one-sided F test of the within-location components of variance (Ho: $\hat{\sigma}^2_{\text{blend}} = \hat{\sigma}^2_{\text{product}}$ vs. Ha: $\hat{\sigma}^2_{\text{blend}} > \hat{\sigma}^2_{\text{product}}$) is made. Calculate the observed F ratio as follows:

$$F_{\text{observed}} = \frac{\hat{\sigma}^2_{\text{blend}}}{\hat{\sigma}^2_{\text{product}}}$$

Obtain the statistical significance level of F_{observed} from a standard F table with 75 degrees of freedom in the denominator and either 6 (if $N = 1$ bin/lot) or $N \times 3$ (if $N > 1$ bin/lot) degrees of freedom in the numerator. If the significance level is less than or equal to .05, blend sampling bias is confirmed.

An approximate two-sided t test (Ho: $\overline{X}_{\text{blend}} = \overline{X}_{\text{product}}$ versus Ha: $\overline{X}_{\text{blend}} \neq \overline{X}_{\text{product}}$) is conducted to determine if sampling bias is present. ($\overline{X}_{\text{blend}}$, the blend grand mean, was calculated in step 6, and $\overline{X}_{\text{product}}$, the product grand mean, was obtained in step 10.) The sum of the variances of the means is used in the numerator. The approximate degrees of freedom for the test is obtained from the Satterthwaitte approximation (1):

$$t_{\text{observed}} = \frac{\left|\overline{X}_{\text{product}} - \overline{X}_{\text{blend}}\right|}{\sqrt{\sigma^2_{\overline{X}_{\text{product}}} + \sigma^2_{\overline{X}_{\text{blend}}}}}$$

$$df \cong \frac{\left(\sigma^2_{\overline{X}_{\text{product}}} + \sigma^2_{\overline{X}_{\text{blend}}}\right)^2}{\sigma^4_{\overline{X}_{\text{product}}}/14 + \sigma^4_{\overline{X}_{\text{blend}}}/(12N-1)}$$

Obtain the statistical significance level of t_{observed} from a standard two-sided t table with df the degrees of freedom. If the significance level is less than or equal to .05, blend sampling bias is confirmed.

If either the t test or the F test is significant or if both tests are significant, blend sampling bias is confirmed. Proceed to step 12. If neither is significant, the content uniformity validation fails.

12. If the product grand mean was not calculated in step 10, it is calculated as below from the $n = 60$ (step 8) product testing results:

$$\overline{X}_{\text{product}} = \frac{\sum_{i=1}^{15}\sum_{j=1}^{4} P_{ij}}{60}$$

Let $m = 4$ if results are from step 8 and $m = 6$ if from step 9. Then, the overall $\text{RSD}_{\text{product}}$ is calculated as follows:

$$RSD_{\text{product}} = 100\frac{\sqrt{\dfrac{15m\sum_{i=1}^{15}\sum_{j=1}^{m} P_{ij}^2 - \left(\sum_{i=1}^{15}\sum_{j=1}^{m} P_{ij}\right)^2}{15m(15m-1)}}}{\overline{X}_{\text{product}}}$$

13. The following comparisons are made using values calculated in step 12. For the product to pass the content uniformity test, all three conditions must be met: (a) $\text{RSD}_{\text{product}} \leq 6.0$; (b) no individual product test result P_{ij} outside the range 85% to 115%; (c) $90 \leq \overline{X}_{\text{product}} \leq 110$.

Operating Characteristics of the Validation Sampling Plan

An SAS program was written that exercises (via Monte Carlo simulation) the VSP testing scheme of Fig. 3. The following assumptions are made in the simulations: (1) Content uniformity variation follows a normal distribution; (2) the mean potency does not differ bin to bin (for blending) or throughout the compression run. These assumptions do not represent limitations of the VSP, but merely give the context of the simulation results described here.

Figure 4 gives the operating characteristic (OC) curves for the VSP as a function of true potency standard deviation (1% to 8%) at eight true mean potency levels (100% to 114%). Since the equations deal with standard deviations and not relative standard deviations, generated OC curves will be sym-

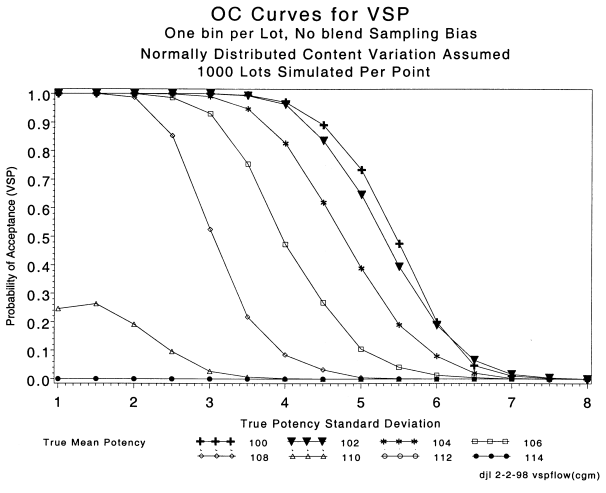

Figure 4. OC curves for proposed validation plan.

metrical about 100%. In Fig. 4, a lot consisting of 1 bin was assumed. As expected, as standard deviation rises and/or mean potency deviates from 100%, the probability of accepting a lot decreases.

Comparison of the Validation Sampling Plan with the Current USP Test for Content Uniformity

The current USP (1) test plan is specifically for testing the content uniformity of tablets and capsules. If the blend is well mixed and is sampled randomly at unit dose levels, the USP test may be regarded as a benchmark for final acceptability of content uniformity.

A validation, being an initial demonstration of process quality (process not yet validated), should be subject to higher assurance requirements than that provided by routine release specifications (for validated processes) such as the USP test. The OC curves for the USP test are given in Fig. 5. The curves in Fig. 5 are in agreement with the performance of the USP test expected from theoretical arguments (2). In all cases, the VSP test provides a higher degree of quality assurance (probability of acceptance is always lower for the VSP than for the USP test).

As an example, consider a lot with a true mean potency of 106% and a standard deviation of potency of 6%. Such a lot has a 50% chance of passing the USP test (see Fig. 5), even though 16% of the material has a potency above 112%. Such a lot has less than a 2% chance of passing the VSP test (see Fig. 4). If the standard deviation of the lot dropped from 6% to 4%, the lot would then have a 50% chance of passing the VSP. This lot would then contain only 7% of its material is above 112% potency. These comparisons show that the additional assurance provided by the VSP is reasonable and not excessive.

The VSP OC curves are also steeper than those of the USP test. This means that the VSP is a more powerful test than the USP test. This likely derives from the larger sample sizes (USP requires 10 samples for stage 1 and 30 for stage 2, whereas the VSP starts with 12 blend samples/bin and 60 final dosage forms).

Rates of Sampling Bias Testing

Blend sampling is fraught with technical difficulty (3). The VSP also has the capacity to detect bias in the blend sampling by comparison with final product (e.g., tablets, capsules). This requires that extra samples be taken at the blend stage (25%–50% more) and at the final processing stage, such as compression or encapsulation (50% more). Figure 6 shows how the probability of performing this extra testing varies with the mean and standard deviation of the potency. The figure shows that the extra testing will be rare unless the mean rises above 108% and/or the standard deviation is above 4%. Thus, a typical content uniformity validation with a mean below 108% and a standard deviation below 4% will

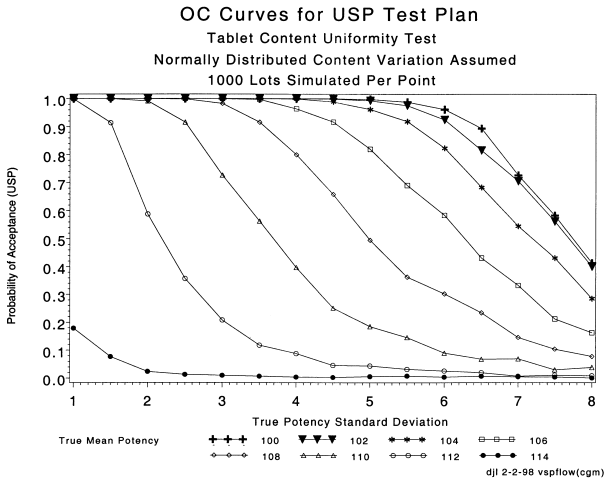

Figure 5. OC curves for USP test plan.

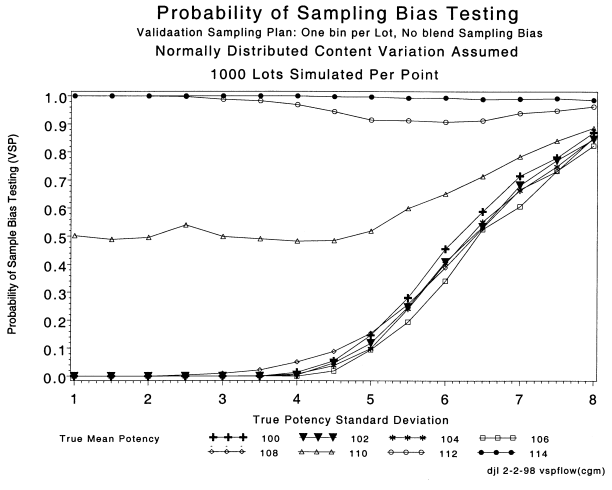

Figure 6. Probability of sample bias testing for proposed validation plan.

require 12 blend tests per bin and 60 compression tests.

While the USP test was not designed to detect sampling bias, it is a two-stage test. The second stage requires an additional testing burden of 200% (20 additional above the initial 10). Figure 7 presents the probability of needing to conduct stage 2 testing as a function of lot true potency mean and standard deviation. The figure shows that the extra testing will be rare unless the mean rises above 106% and/or the standard deviation is above 4%. The extra testing for the USP test becomes necessary at levels of uniformity below that required for extra testing with the VSP. This is likely because the initial sample testing levels with the VSP are slightly higher (12 per bin for VSP vs. 10 for USP).

Interestingly, Fig. 7 shows that when lot quality is extremely poor, the likelihood of needing the stage 2 USP testing decreases. This is because such lots fail the stage 1 test outright with results outside the 75%–125% potency level. This outlier test would not be appropriate at the blend stage with the VSP because of the possibility of blend sampling bias.

Effect of Number of Bins per Lot on the Validation Sampling Plan Performance

Figure 8 demonstrates that the OC curve for the VSP test does not depend on the number of bins in the blend for a given lot. This is likely because the final compression testing is based on 60 to 90 samples and thus controls the power of the test.

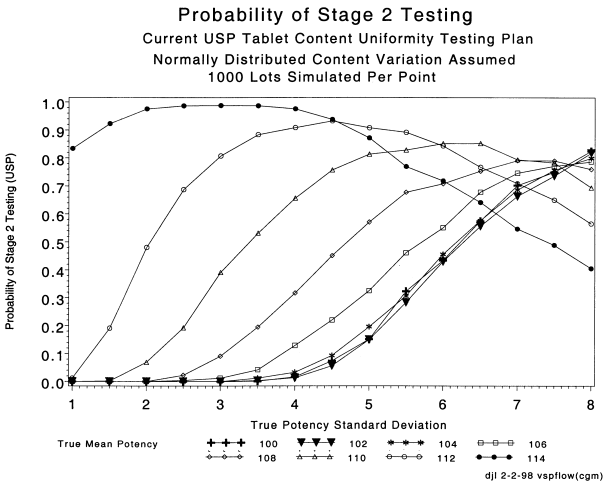

Figure 7. Probability of stage 2 testing for USP test plan.

However, the need for sample bias testing does depend on the number of bins in a lot, as illustrated in Fig. 9. The OC curves become steeper as the number of bins in the blend rises. This is because, with only 1 or 2 bins (12 or 24 samples), the likelihood of incorrectly failing or passing the initial testing is increased. The change in power, however, is not excessive: With a mean of 108% and a standard deviation of 6.6%, sample bias testing will be required 60% of the time regardless of the number of bins per lot.

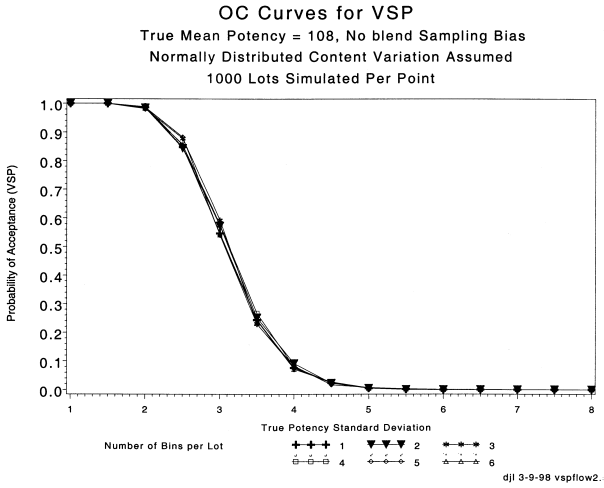

Figure 8. OC curves for proposed validation plan as a function of number of bins/hoppers.

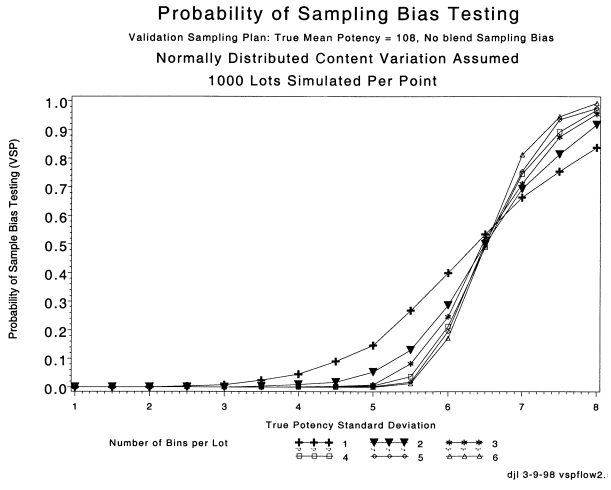

Figure 9. Probability of sample bias testing as a function of the number of bins/hoppers.

Effect of Sampling Bias on USP Criteria and the Proposed Validation Sampling Plan

Figures 10 and 11 report the effect of a 3% sampling bias in the final blend on the operating characteristic curves for the USP and proposed validation sampling plans, respectively. A 3% bias in the final blend data results in a shift of the OC curves for the USP testing plan, resulting in more failed batches. However, the proposed VSP has virtually no change in its OC curves because of its reliance on final product testing once sampling bias has been demonstrated for the final blend. Recall that the sample size for the final product increases from 60 to 90 final dosage forms if sampling bias has been demonstrated. This increased sampling aids greatly in nullifying the effects of sampling bias at the blend stage.

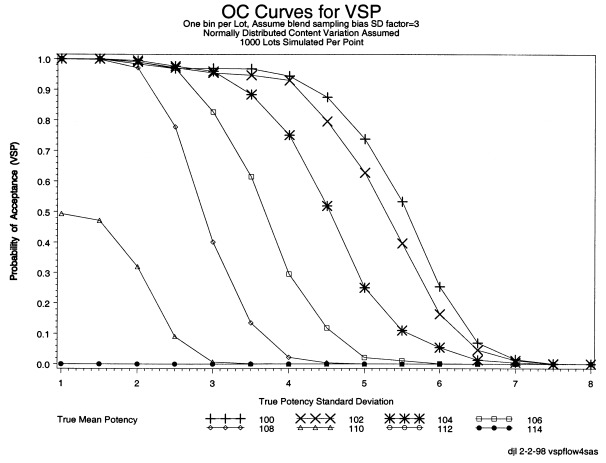

Figure 10. OC curves for proposed validation plan with a 3% sample bias.

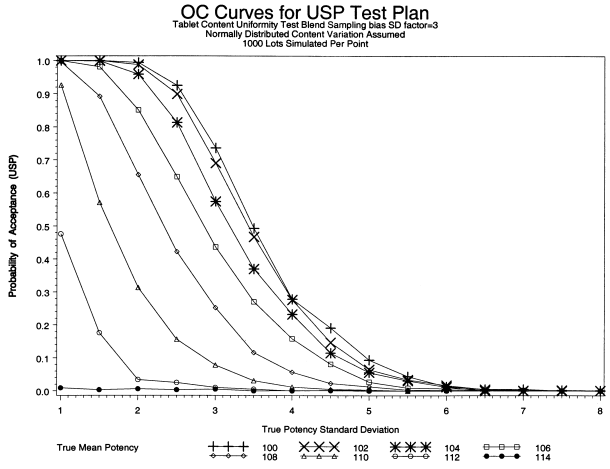

Figure 11. OC curves for USP test plan with a 3% sample bias.

Case Study

The Initial Blend Test Failure

The final blend unit dose and final tablet potency results for a low-dose tablet, product A, were generated and are given in Table 1 and Table 2. The summary statistics are given in Table 3. The grand mean of the initial 12 blend test results was 89.7%, which is below the lower specification of 90.0%. The overall blend RSD (CV in Table 3) is 3.9%, well below the upper specification limit of 6.0%.

Because of the blend mean failure, the validation plan calls for extensive product testing and confirmation of sample bias. Additional testing results are indicated in Tables 1 and 2 by "extra" (6 additional blend center points and 30 additional tablets).

Test for Equality of the Grand Means

The grand means and standard errors are obtained from Table 3 (for blend, $n = 12$) and Table 4 (for product, $n = 90$). The means are provided in Table 5 along with the variances needed to conduct an approximate two-sided t test as described above (step 11). These calculations were performed by calculator and are given below.

$$t_{\text{observed}} = \frac{|99.7 - 89.7|}{\sqrt{1.01.538^2 + 0.35503^2}} = 6.65$$

$$df \cong \frac{\left(0.35503^2 + 1.010538^2\right)^2}{(0.35503^4/14) + (n1.010538^2/11)}\, n$$
$$= 13.72, \text{ which rounds down to } 13$$

This test is based on the null hypothesis of equality of means and variances between blend and product. Because the t_{observed} is greater than 2.16, this hypothesis can be rejected with at least 95% confidence.

Test for Equality of the Within-Location Variances

The within-location variance component for blending and tableting are provided in Table 5 and Table 6, respectively (this is the "ERROR" variance component). The F test is conducted on these

Table 1

Bend Test Results

OBS	Stage at Which Testing Was Done	Sample Guide/Thief Position	Bin Sampling Location	Potency Test Result (%)	Manufacturing Process
1	Initial	A1	Outside1	94.1	Blend
2	Initial	A2	Outside2	83.7	Blend
3	Initial	A3	Outside3	89.7	Blend
4	Initial	C1	Outside4	88.9	Blend
5	Initial	C2	Outside5	95.5	Blend
6	Initial	F3	Outside6	86.5	Blend
7	Initial	E1	Outside7	86.9	Blend
8	Initial	E2	Outside8	86.6	Blend
9	Initial	E3	Outside9	89.6	Blend
10	Initial	G1	center1	93.6	Blend
11	Initial	G2	center2	90.9	Blend
12	Initial	G3	center3	90.6	Blend
13	Extra	H1	center1	97.1	Blend
14	Extra	I1	center1	99.8	Blend
15	Extra	I2	center2	93.9	Blend
16	Extra	I3	center3	100.5	Blend
17	Extra	J1	center1	100.9	Blend
18	Extra	J2	center2	97.5	Blend

Table 2

Tablet Test Results

OBS	Sampling Position (kg Compressed)	Manufacturing Process	Stage at Which Testing Was Done	Tablet Tested	Beyond 85:115 If Flagged (*)	Potency Test Result (%)
1	0	Tablets	Initial	1		102.5
2	0	Tablets	Initial	2		102.0
3	0	Tablets	Initial	3		101.0
4	0	Tablets	Initial	4		102.0
5	0	Tablets	Extra	5		102.0
6	0	Tablets	Extra	6		102.5
7	5	Tablets	Initial	1		101.5
8	5	Tablets	Initial	2		100.0
9	5	Tablets	Initial	3		101.0
10	5	Tablets	Initial	4		100.5
11	5	Tablets	Extra	5		102.5
12	5	Tablets	Extra	6		103.0
13	10	Tablets	Initial	1		99.5
14	10	Tablets	Initial	2		99.0
15	10	Tablets	Initial	3		98.0
16	10	Tablets	Initial	4		101.5
17	10	Tablets	Extra	5		103.0
18	10	Tablets	Extra	6		103.5
19	20	Tablets	Initial	1		99.0
20	20	Tablets	Initial	2		102.0
21	20	Tablets	Initial	3		100.5

(*continued*)

Table 2

Continued

OBS	Sampling Position (kg Compressed)	Manufacturing Process	Stage at Which Testing Was Done	Tablet Tested	Beyond 85:115 If Flagged (*)	Potency Test Result (%)
22	20	Tablets	Initial	4		100.5
23	20	Tablets	Extra	5		103.0
24	20	Tablets	Extra	6		100.5
25	40	Tablets	Initial	1		97.0
26	40	Tablets	Initial	2		99.0
27	40	Tablets	Initial	3		95.5
28	40	Tablets	Initial	4		98.5
29	40	Tablets	Extra	5		99.5
30	40	Tablets	Extra	6		99.5
31	60	Tablets	Initial	1		98.0
32	60	Tablets	Initial	2		98.0
33	60	Tablets	Initial	3		100.0
34	60	Tablets	Initial	4		95.5
35	60	Tablets	Extra	5		102.5
36	60	Tablets	Extra	6		101.0
37	80	Tablets	Initial	1		100.0
38	80	Tablets	Initial	2		98.0
39	80	Tablets	Initial	3		97.5
40	80	Tablets	Initial	4		96.5
41	80	Tablets	Extra	5		101.0
42	80	Tablets	Extra	6		102.5
43	100	Tablets	Initial	1		100.5
44	100	Tablets	Initial	2		101.0
45	100	Tablets	Initial	3		98.5
46	100	Tablets	Initial	4		101.5
47	100	Tablets	Extra	5		100.5
48	100	Tablets	Extra	6		104.5
49	120	Tablets	Initial	1		100.5
50	120	Tablets	Initial	2		98.5
51	120	Tablets	Initial	3		98.5
52	120	Tablets	Initial	4		99.0
53	120	Tablets	Extra	5		100.0
54	120	Tablets	Extra	6		102.0
55	140	Tablets	Initial	1		101.5
56	140	Tablets	Initial	2		102.0
57	140	Tablets	Initial	3		99.5
58	140	Tablets	Initial	4		98.0
59	140	Tablets	Extra	5		100.0
60	140	Tablets	Extra	6		102.5
61	160	Tablets	Initial	1		98.5
62	160	Tablets	Initial	2		98.5
63	160	Tablets	Initial	3		97.0
64	160	Tablets	Initial	4		97.5
65	160	Tablets	Extra	5		101.0
66	160	Tablets	Extra	6		99.5
67	180	Tablets	Initial	1		102.0
68	180	Tablets	Initial	2		98.5

(*continued*)

Table 2

Continued

OBS	Sampling Position (kg Compressed)	Manufacturing Process	Stage at Which Testing Was Done	Tablet Tested	Beyond 85:115 If Flagged (*)	Potency Test Result (%)
69	180	Tablets	Initial	3		96.5
70	180	Tablets	Initial	4		99.0
71	180	Tablets	Extra	5		99.5
72	180	Tablets	Extra	6		99.0
73	190	Tablets	Initial	1		101.0
74	190	Tablets	Initial	2		99.5
75	190	Tablets	Initial	3		98.0
76	190	Tablets	Initial	4		96.0
77	190	Tablets	Extra	5		100.5
78	190	Tablets	Extra	6		99.5
79	195	Tablets	Initial	1		100.0
80	195	Tablets	Initial	2		100.0
81	195	Tablets	Initial	3		100.0
82	195	Tablets	Initial	4		95.0
83	195	Tablets	Extra	5		101.0
84	195	Tablets	Extra	6		95.0
85	200	Tablets	Initial	1		100.0
86	200	Tablets	Initial	2		95.0
87	200	Tablets	Initial	3		98.5
88	200	Tablets	Initial	4		101.5
89	200	Tablets	Extra	5		95.0
90	200	Tablets	Extra	6		92.5

Table 3

Summary Statistics of Initial Testing Results: Blend Manufacturing Process

N	Mean	Variance	SD	Standard Error of the Mean	CV
12	89.7166667	12.2542424	3.5006060	1.010538	3.9018458

Analysis variable: POTENCY, potency test result (%).
CV, coefficient of variation.

Table 4

Summary Statistics of All Testing Results: Tablet Manufacturing Process

N	Mean	Variance	SD	CV
90	99.7000000	5.1224719	2.2632879	2.2700981

Analysis variable: POTENCY, potency test result (%).
CV, coefficient of variation.

Table 5

Components of Variance Analysis for Bias Testing: Blend Manufacturing Process. Nested Random Effects Analysis of Variance for Variable POTENCY

Variance Source	Degrees of Freedom	Sum of Squares	*F* Value	Pr > *F*	Error Term
TOTAL	17	463.636111			
POSITN	11	361.061111			
ERROR	6	102.575000			

Variance Source	Mean Square	Variance Component	Percentage of Total
TOTAL	27.272712	27.984382	100.0000
POSITN	32.823737	10.888549	38.9094
ERROR	17.095833	17.095833	61.0906
Mean		92.57222222	
Standard error of mean		1.49225352	

Table 6

Components of Variance Analysis for Bias Testing: Tablet Manufacturing Process. Nested Random Effects Analysis of Variance for Variable POTENCY

Variance Source	Degrees of Freedom	Sum of Squares	*F* Value	Pr > *F*	Error Term
TOTAL	89	455.900000			
POSITN	14	158.816667	2.864	0.0017	ERROR
ERROR	75	297.083333			

Variance Source	Mean Square	Variance Component	Percentage of Total
TOTAL	5.122472	5.191601	100.0000
POSITN	11.344048	1.230489	23.7015
ERROR	3.961111	3.961111	76.2985
Mean	99.70000000		
Standard error of mean	0.35502813		

variances as described in the accompanying justification document (step 11). These calculations were performed by calculator and are given below.

$$F_{\text{observed}} = \frac{17.095833}{3.961111} = 4.32$$

This test is based on the hypothesis that the blend and product within-component variances are equal versus the hypothesis that the blend component is larger. Because the F_{observed} exceeds the value of 2.22 given in the justification document for a 1-bin blend, the original hypothesis can be rejected with 95% confidence.

Extensive Product Testing

As indicated above, both tests above provide evidence for bias in the sampling of the blend. Thus, the original failure of the blend grand mean is likely due to an inability to sample the blend accurately. It remains to examine the product testing for conformance.

The grand mean and CV of the product test ($n = 90$) are given in Table 4. The grand mean of 99.7 is well within the specification range of 90% to 110% (step 13 of the justification document). The RSD of 2.27 is well below the upper specification limit of 6.0%. As is indicated in Table 2, no individual tablet test result exceeds the specification range of 85% to 115%.

Thus, extensive tablet testing shows the product to be well within the specifications for content uniformity.

CONCLUSIONS

A practical method of performing unit dose sampling has been presented that takes into account sampling bias and extensive final product testing. This method provides reasonable assurance that commercial lots will consistently perform to USP standards once validated. Operating characteristic curves demonstrated the reliability of the method and its ability to take into account sampling bias, the probability of testing for sampling bias, and the effects of varying numbers of bins/hoppers for final blend containment. Comparisons of operating characteristic curves between the USP and proposed final blend validation plan were made and showed that the USP test method is significantly more liberal in comparison to the proposed final blend validation plan, but that the proposed method is much less sensitive to sampling bias. A case study was presented to demonstrate the methodology.

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