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RESEARCH PAPERS

Blending Validation and Content Uniformity of Low-Content, Noncohesive Powder Blends

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ABSTRACT

Blending validation has become mandatory, partly through good manufacturing practice (GMP), partly through a court action (the Barr decision) in 1993. Although feasibly carried out with existing technology, there are situations where the methodology for sampling causes a suspected bias in the figures, and one such case is where the drug content (expressed as fraction x in the following) is low. In particular, this dilemma is predominant where the blended materials are not cohesive. Possible explanations for this are voiced, as are suggestions on how to proceed rationally in such cases.

INTRODUCTION

The wording of Barr decision is outlined in the Civil Action No. 92-1744 Order by Alfred Wolin, dated February 1993. Pertinent excerpts from this are:

- Page 28, paragraph 60: "In accordance with the preamble to the CGMP regulations, the Court must construe the as appropriate phrase to permit reasonable, albeit variable interpretations'."
- Page 28, paragraph 63: "Content uniformity testing, designed to detect the adequacy of the mix by measuring variations in the potency of the blend . . . should be conducted with a sample that resembles the dosage size. Any other practice likely would blur differences in portions of the blend."
- Page 31, paragraph 69. "Expert testimony revealed that firms test from both the drum and the mixer and that either practice is acceptable under CGMP. . . . Thus, the Court is not prepared to prescribe a particular location for the blend testing."
- Page 31, paragraph 71: "Experts did suggest, however, that sampling from the mixer is preferable. . . ."

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> Page 50, under "(4) *Sample Size*" "The Court noted above . . . the proper blend sample size for content uniformity testing is three times the run weight of the finished product. . . ."

The general result of this decision has been an industry-wide change of testing procedures from arbitrary numbers of arbitrary (although often reasonable) sample sizes to ten samples of one to three times the dose weight of the product. In an internal Food and Drug Administration (FDA) memorandum from M. A. Danello to "Colleagues," dated May 14, 1993, the Barr decision appears to have been given the following simple form: "the appropriate sample size for blend content uniformity in both validation and ordinary production batches is three times the active ingredient dosage size. . . ."

The above reflects the guidance of the Court and the intent of the authors is not to discredit the legal system nor the FDA's adoption of the above Order. Carstensen and Rhodes (1) have, however, taken scientific issue with the findings of the Court (and in particular their enforceability), and this writing further establishes flaws in the *general* procedure, using presently available technology for sampling. It is often difficult to establish a procedure which is all-encompassing, and the following demonstrates some of the fallacies of small-cavity testing.

Ultimately, the rigorous enforcement of the procedures ordered would be that many companies would abandon the practice of direct compression (since wet granulation is guaranteed to behave with less sampling bias), which would not guarantee a better product but would surely make it more expensive, more prone to degradation, and hence less safe.

EXPERIMENTAL

Drug Content

The binomial aspects of blending sampling have been dealt with in previous publications (1); and the problems associated with sampling with a thief were predicted by these authors and recently have been addressed by Berman and Planchard (2).

The first author, furthermore, had experience with the problem addressed in several consultantships, and the pattern is *always* that the assay value or % label claim (% LC) appears to be low when the in-process powder is sampled with a thief and then "increases" when tablets are assayed for content uniformity.

The trend is also that the assay "increases" when the sample size is increased (from one to two times dose weight). And, again, the assay "increases" to acceptable levels when the compressed tablets are sampled and assayed.

Berman and Planchard (2) in their Fig. 12 show that there is a linear (or pseudolinear) correlation between thieved sample size and assay, but that this has the wrong direction, and that "apparently for this product the thief sample is more likely to be 'overfilled' with excipient than with drug. . . ."

Homogeneity

The problem of thief sampling is furthermore accentuated by the effect on content uniformity. Considering the construction of a thief (Fig. 1), one realizes that (a) the powder mix is disturbed as the thief is lowered into the powder mass, i.e., powder is pushed to the side of the thief; (b) powder is caught (captured) in the space of the "hole" in the outer shell of the thief and the "closed" inner shell, as the thief is lowered; and (c) the powder that enters the sampling cavity is primarily this "captured" powder sample.

For a large sample (e.g., 30 g as frequently used in engineering applications) this is of little importance, because it will constitute only a fraction of the powder sample, but if one takes a sample which is no larger than (even smaller than) the "captured" powder sample, there is a definite bias of the sample. Segregation during the flow of the sample into the cavity was predicted by Carstensen and Rhodes (1) and demonstrated by

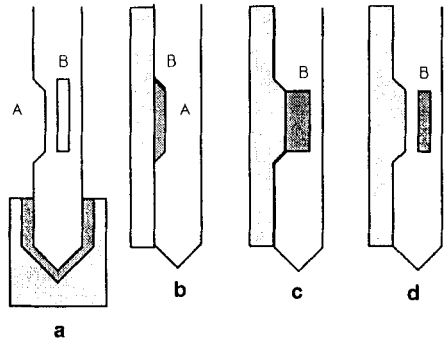

Figure 1. Action of a thief where (a) the powder directly outside the thief is disturbed; (b) gets caught in the space between the shell and the core at the sampling port; (c) the powder that enters the sampling port is of a perturbed nature (d) The sample which is removed.

Berman and Planchard (2), but the additional segregation occurring in the formation of the "captured" sample adds to the problem. The statement by Berman and Planchard (2) that "apparently for this product the thief sample is more likely to be overfilled with excipient than with drug" can be expected to be general.

Segregation potential is quite predominant in powders that exhibit no cohesive tendency (1,3), and the magnitude of the effect is obviously accentuated when the content of drug is small.

To demonstrate these points a powder blend was validated in a Collette bowl and the process of blending validation carried out with a thief.

To compare the effect of concentration of drug (denoted A in the following), it was decided to make batches of two concentrations, $x = 0.03$ and $x = 0.015$. To demonstrate the effect of concentration of ingredient (x), an excipient, B, present in a concentration of 0.78 was assayed as well. The drug in some of the studies was in a concentration of 0.03 and in some in a concentration of 0.15. It is recalled that these were large-scale batches, and that uninhibited manipulation of variables was not possible.

A best first recommended step in blending validation is to ascertain that the material "blends" according to expected laws. The general law (4) is that

$$\ln[RSD] = -kt + \ln[RSD_0] \quad (1)$$

where RSD = relative standard deviation, and

$$\ln[RSD_0] = 100[(1 - x)/x]^{1/2} \quad (2)$$

The blending data for A and B using seven positions are shown in Table 1. The data are plotted in Fig. 2.

What Is a Good Average Assay for the Blend?

According to common practice samples were taken by thief. In the case in point the compression weight was 425 mg. Samples of 2500 mg (pooled, thieved samples) were taken in triplicate and assayed, and results are shown in Table 2.

Table 1

Blending Time Traces of Components A and B

	Time (min)		
	5	10	15
For A ($x = 0.03$)			
Average (% theory)	105	101	102
RSD	5.44%	1.88%	1.35%
For B ($x = 0.78$)			
Average (% theory)	99	99	99
RSD	1.99%	1.15%	0.93%

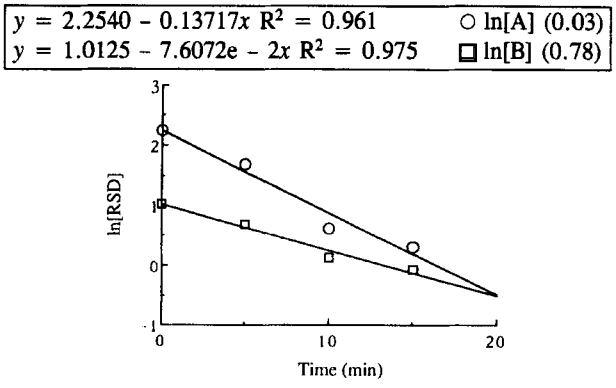

Figure 2. Data from Table 1, where the initial point is the random standard deviation (i.e., not an experimental point).

Note that when x is high (abundant), there is consistency; whereas the data when x is low (meager) are inconsistent. Hence it is probably never advisable to take a sample from a mixer and adjust the fill weight to assay, unless there is a compelling reason (manufacturing loss) to do so. (Some industrial practices make use of "tablet weight by assay.")

Is there a Correlation Between Thief Samples and Content Uniformity?

This question is addressed in Table 3.

These data are shown as a bar graph in Fig. 3 and the blend assay data are shown in Fig. 4.

What Is More Representative: Thieved Samples or Content Uniformity Samples?

The thesis of this presentation is to demonstrate that thieving is not a representative method of sampling,

Table 2

Blending Samples of a Mixture of 0.015 Fraction of A and 0.78 Fraction of B

	Sample No.			Content Uniformity of Tablets
	1	2	3	
A				
Mean (*%LC*)	107.6	87.1	88.0	96.5
RSD	0.86	1.79	2.39	1.71
B				
Mean (*%LC*)	97.0	99.7	99.1	99.1
RSD	0.17	0.11	0.11	0.46

Table 3

Comparative Sampling Results from a Mix Containing $x_A = 0.03$ and $x_B = 0.78$

	A		B	
N	Thieved Granulation 10 (2 × 10)	Content Uniformity of Tablets 3 × 10	Thieved Granulation 10 (2 × 10)	Content Uniformity of Tablets 3 × 10
Mean (% *LC*)	98.3	101.1	95.6	102.7
		101.5		102.8
		100.1		103.3
RSD (%)	9.0	0.29	1.3	0.34
		0.68		0.81
		0.59		0.58
Mean (% *LC*)	93.3	91.8	98.8	928
	91.1	93.0	99.9	99.1
		94.0		98.7
RSD (%)	5.46	1.09	3.55	0.34
	4.97	1.43	0.55	0.40
		1.61		0.32

while admitting that in bulk blenders it is the only available method. For products with large drug contents (large x values), the distortion is not too serious, but it takes on disturbing proportions when x is small, i.e., the drug is in a fairly dilute powder mixture.

If we examine the individual (milligram assay) data from which Table 3 was constructed, we find the following as an example:

1. Thirty tablets in one case had a mean of 9.11 and a standard deviation of 0.45 (more than significant figures included—truncation will be effected at a later point).
2. In the data from the thieved samples from the blender, the lowest assays were 8.14 and 8.55, and the mean was 9.11 mg per dose weight. One might now ask: What is the possibility of two of the tablets really being below 8.55?

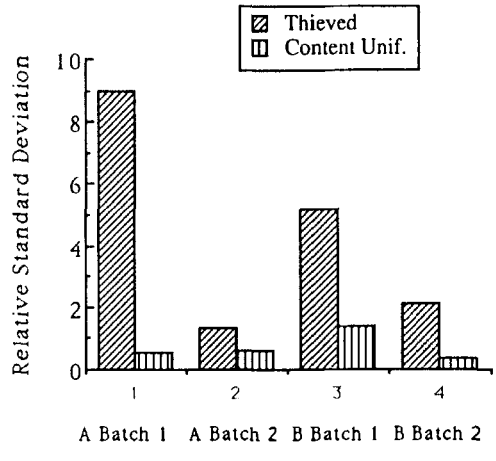

Figure 3. Standard deviations of blends versus standard deviations of assays (two to three content uniformity tests). 1 and 2 are $x = 0.03$, and 3 and 4 are $x = 0.78$. For the x axis 1 and 3 are A, and 2 and 4 are B.

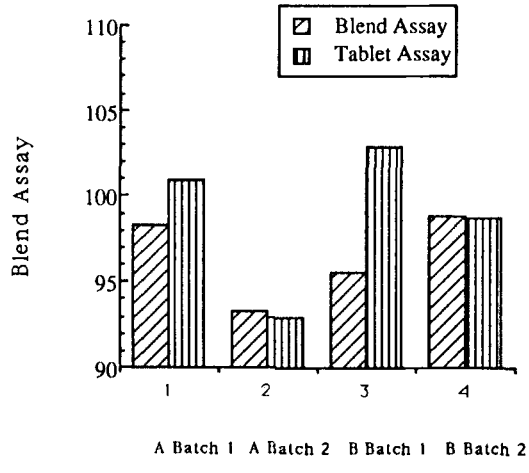

Figure 4. Assays of blend versus assays of tablets (two to three content uniformity tests).

3. 8.55 is removed from the mean (9.11) by 0.56 mg or 0.56/0.45 = 1.24 standard deviations. The probability of a tablet assay being below the mean minus 1.25 *sd* is 10%, yet 20% of the blender assays were below this figure. Furthermore, what would the possibility of finding an assay of 8.14 be? This is now 0.97/0.45 = 2.2 *SD*, and the possibility of finding tablet assays below this figure is 1.5%.

So the data are not really out of line; except it is a consistent trend. *The RSD of thieved samples is consistently higher than that of the final dosage form.*

Are There Other Sampling Methods Available?

The authors, in the present study, attempted to take samples by spoon, but this essentially becomes an artificial type of sampling. It cannot be carried out in a blender. One might fill a drum one-third of the way, sample by thief, and repeat this, but this is an artificial type of sampling. Further cascading of powder into the storage drum disturbs and causes turbulence in the lower levels, so that the sampling is not representative.

Berman and Planchard (2) applied the method of Hahn and Meeker (5) for adjustment of observed relative standard deviations.

$$S_{cr} = S_M/[F_{1-a,\ N-1,\ M-1}]^{1/2} \quad (3)$$

The nomenclature in the Hahn and Mecker formula is:

S_{cr} = critical value of the *RSD* from a size N sample
N = number validation sample size (i.e., 10)
S_M = upper limit for the RSD of expanded content uniformity test
M = the number of samples in the expanded content uniformity test
$1-a$ = confidence interval (e.g., 0.90)
F = value of F for the appropriate degrees of freedom

The upper United States Pharmacopeia (USP) limit for the *RSD* for content uniformity, using 10 samples, is 6%. For 30 samples it is 7.8.
A recent statement in the Pink Sheet stated that the *RSD* in a blender should be 5%. For this number

$S_{cr} = 5$
$N = 10$
$S_M = 0.06$
$M = 10$

Therefore

$$S_{cr} = S_M/[F_{1-a,9,9}]^{1/2} = 0.06/2.44^{1/2} = 0.04$$

So that if the two samples were "of the same nature," then the relative standard deviation in sampling should be 4%. On the surface, then, the 5% figure published in the Pink Sheet would have some value. It should be pointed out that the above treatment was not within the scope of the article by Berman and Planchard but is added here for illustrative purposes: the two numbers are not "of the same nature," so that the comparison really cannot be made.
The use of the Hahn–Mecker formula is rational (as, e.g., used by Berman and Planchard in Ref. 2); however, it is inconsistent with the practices of the USP. Because a sample of $N = 10$ should give a *RSD* of 0.06, then a sample of $N = 30$ should give a *RSD* of 7.8, i.e.

$$0.078/0.06 = 1.3 \text{ should equal } 1/[F_{0.9,9,9}]^{1/2} = 1.56$$

which is not the case.

Intensified Sampling Plans

One might ask whether, if one sampled more than 10/30 tablets for "content uniformity," the "acceptable" *RSD* would increase (as it, e.g., increases from 6% to 7.8% in the case of $M = 10$ versus $M = 30$). If a blend sample has a *RSD* of S^*, at what sample size in content uniformity would this value be reached, assuming the *RSD* for a sample of 10 to be 6%)?

Several criteria could be used for this, and one such is that suggested by Carstensen et al. (6). This is shown in Fig. 5. The relative standard deviation of the blend (if above 6) will dictate the number of samples taken for the content uniformity test for the tablets or capsules made from the blend *for blending validation only*.

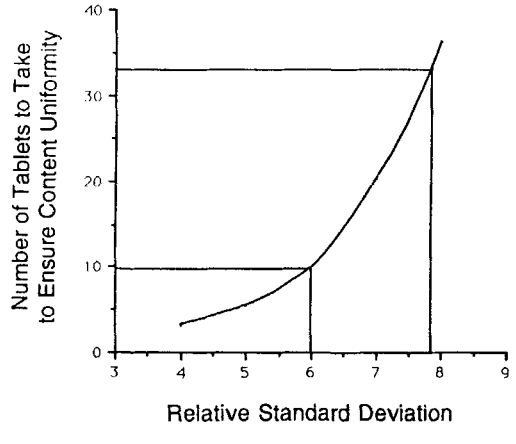

Figure 5. Proposed intensified sampling scheme for blending validation.

The proposed method for blending validation (only) would then be, if the standard deviation of a blend sample were high, to sample more than the required 10 samples for the first USP content uniformity test. For instance, if the standard deviation of the blend were 7, then the graph would show that 20 samples should be sampled in the first stage of a content uniformity test for the compressed tablets (or capsules), and 40 samples more for the second stage (should there be one minor defect (75–85% or 115–125% of label claim).

The method recognizes that there is a bias in blend sampling with a thief, or to paraphrase an old saying: "There is error among thieves." It recognizes that at the present time there is no better practical method of taking the sample, and it suggests that intensified sampling of the produced tablets will be an adjunct to the blending validation which assures the quality expected in usual regulatory fashion, be it USP or FDA.

REFERENCES

1. J. T. Carstensen and C. R. Rhodes, Drug Dev. Ind. Pharm., 19, 2699 (1993).
2. J. Berman and J. A. Planchard, Drug Dev. Ind. Pharm., 21, 1257 (1995).
3. C. F. Harwood and T. J. Ripley, Powder Bulk Solids Technol., 20, 28 (1977).
4. J. T. Carstensen and M. R. Patel, Powder Technol., 17, 273 (1977).
5. G. J. Hahn and W. Q. Meeker, *Statistical Intervals: A Guide for Practitioners*, Wiley & Sons, New York, 1991.
6. J. T. Carstensen, M. V. Dali, and M. Pudipeddi, Pharm. Dev. Technol., in press (1996).