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## THE USE OF STRATIFIED SAMPLING OF BLEND AND DOSAGE UNITS TO DEMONSTRATE ADEQUACY OF MIX FOR POWDER BLENDS<sup>1</sup>

### I. Scope

This proposal is meant to address concerns raised following the issuance of the FDA document *Guidance for Industry, ANDAs: Blend Uniformity Analysis*, (August 3, 1999) as it relates to filing requirements and post-approval commitments. It also applies to process validation and marketed batches for solid oral drug products. It does not apply to those drug products where the determination of dosage-form uniformity by weight variation is allowed. This proposal may only be applied for active ingredients introduced into the blend.

The approach described in this document may be used to satisfy the cGMP requirement for in-process testing to demonstrate adequacy of mix, as well as USP compendial release requirements for the content uniformity of finished dosage forms. Alternatively, traditionally employed methods (such as the direct sampling and analysis of powder blends, in conjunction with content uniformity testing of finished dosage forms) may continue to be used to satisfy cGMP and compendial release requirements.

### II. Definitions

**Stratified sampling** is the process of selecting units deliberately from various locations within a lot or batch or from various phases or periods of a process to obtain a sample.<sup>2</sup> Stratified sampling of the blend and dosage units specifically targets locations either in the blender or throughout the compression/filling operation which have a higher risk of producing failing content uniformity results.

To **weight correct** is to adjust the dosage unit potency result to eliminate the unit weight effect. This method is used to demonstrate blend uniformity using dosage unit results. *For example, a tablet with potency of 19.4 mg and weight of 98 mg =  $19.4 \div 98 = 0.198$  mg/mg. Label claim is 20 mg per each 100 mg tablet, so the weight corrected result is  $0.198 \div 0.20 * 100 = 99\%$  of target blend potency.*

Unless otherwise specifically stated, all dosage unit potencies are to be weight corrected prior to evaluating the acceptance criteria described in this

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<sup>1</sup> The proposals in this document assume that an on-line, in-process measurement system is not currently available for demonstrating blend uniformity (e.g., on-line NIR measurement of in-process blend or dosage units).

<sup>2</sup> Glossary and Tables for Statistical Quality Control, ASQC Quality Press, copyright 1983.

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document. All weight corrected potencies are to be expressed as a percentage of the blend target concentration. Exception - calculations to satisfy compendial release testing are not weight corrected. Further, the potencies are expressed as a percentage of the label concentration.

**ANDA Exhibit Batches** refer to any batch submitted in support of an ANDA. This includes bioequivalence, test and commercial production batches of a drug product.

**RSD** is relative standard deviation.  $RSD = [(standard\ deviation)/(mean)] \times 100\%$

## III. Background

In response to concerns by ANDA applicants regarding inconsistency in review chemists' recommendations, the FDA Drug Product Technical Committee published a draft guidance in August 1999. The guidance proposes routine blend sample analysis on commercial batches for ANDA products when USP Content Uniformity testing is required on the product.

As a result of industry feedback on this draft guidance, a primary goal of the Product Quality Research Institute (PQRI) Blend Uniformity Working Group (BUWG) was to address the gap between scientific principles and the regulatory policy stated in this document. In September 2000, the working group sponsored a workshop on blend uniformity. At the conclusion of the workshop, it was recognized that limitations in current sampling technology and subsequent handling (powder segregation) might limit the effectiveness of using blend sample analysis to ensure adequacy of blending. Alternative solutions were sought to address the shortcomings of sampling and analyzing blends. The PQRI BUWG felt that any solution should possess the following three qualities:

1. The test should be simple to perform, maximizing the use of the data.
2. Acceptance criteria should be easy to evaluate and interpret.
3. Acceptance criteria should demonstrate when lack of homogeneity is suspected.

Dosage unit analysis (of in-process tablet cores, hard gelatin capsules, or other solid dose forms) is proposed as an alternative to routine blend sample analysis. Current GMPs state "control procedures shall include...adequacy of mixing to assure uniformity and homogeneity." [21CFR 211.110 (a)(3)]. Dosage unit analysis satisfies this in-process control requirement by indirectly measuring the uniformity of the blend by sampling and testing in-process dosage units. Stratified sampling techniques are incorporated to collect in-process dosage units throughout the compression or filling process. Dosage unit analysis has many appealing aspects:

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- It is the most accurate and reflective measure of homogeneity of the product.
- It eliminates blend sampling error issues related to thief sampling.
- It applies resources where they produce the most reliable, accurate information about the quality of the product given to the patient.
- Weighing errors when trying to assay blend samples are eliminated.
- It removes the safety issues surrounding blend sampling of toxic or potent drugs manufactured in isolated environments.
- It improves detection of subsequent segregation after the blending process.

The following proposal presents strategies for dosage unit analysis and blend sample analysis. The PQRI BUWG advocates the use of the proposed strategy defined in Section V or Attachment 1 during the manufacture of ANDA exhibit batch(es) and during the validation of the commercial manufacturing process. If the following proposal is used to test the ANDA exhibit batch(es) and three commercial scale validation lots, and the results comply, it may not be necessary to perform routine blend uniformity testing for routine commercial batches as advocated in the current draft of the ANDA Blend Uniformity Guidance Document. However, additional cGMP compliance requirements as defined in 21CFR 211.110 (a)(3) will continue to be applicable. The level of testing required to satisfy cGMP requirements will be dependent on the quality of the data generated by testing the batches in accordance with the proposal. For those products that readily comply with the defined acceptance criteria (see Section VI), a modification of the USP Content Uniformity Test may be used to satisfy the cGMP requirement for routine monitoring of production batches for adequacy of mix (Section V). Processes that do not readily comply may require additional testing for routine production batches. The rationale for each sample size and acceptance criteria for the proposal contained in Attachment 1 are provided in Attachments 2 and 3.

To date, the elements of the sampling proposal have been challenged with computer simulations. Data mining will be conducted in an effort to further substantiate the elements of this proposal.

## IV. Process Development

In general, content uniformity of the final dosage form is dependent on the homogeneity of the powder mixture in the blender. The development of robust blending and transfer processes that will not cause segregation of the mixture post-blending and result in manufacture of a product of acceptable content uniformity remains a critical objective during formulation and process development. Blend sample analysis should be conducted on development batches by extensively sampling both the blender and intermediate bulk containers (IBCs), when applicable, to identify an appropriate range of blending

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times, dead spots in blenders, segregation in IBCs, and the presence of sampling error. Appropriate blend sampling techniques and procedures should be developed for each product, including the consideration of sampling thieves of various designs, and defining the impact of sample size (for example, 1-10X dosage unit range) in an effort to develop a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3X can be used if they can be scientifically justified. Stratified sampling techniques should be utilized to allow variance component analysis to be performed on the data to quantitate the variability attributed to the uniformity of the blend as well as any sampling error that may be occurring. If there is high between-location error in the blender, the deficiencies in the blending operation must be addressed. If blend sampling error is detected, more sophisticated statistical analysis should be applied to assess the situation such as the use of methods described in PDA Technical Report 25.<sup>3</sup>

In addition to extensively sampling the blend, stratified sampling and testing of the dosage units should also be performed, taking samples at defined intervals and locations throughout the compression or filling process. During development, a minimum of 20 uniformly spaced dosage unit sampling points must be defined. Additional samples may be taken to further assess events such as filling or emptying of hoppers during the compression or filling process. A basic foundation of this proposal is the strong technical opinion that the proposed approach is likely to reveal formulation problems that might remain hidden if less discriminating techniques (e.g. thief sampling) are used.

### V. Use of Stratified Blend and Dosage Unit Sampling During Manufacture of ANDA Exhibit and Process Validation Batches to Demonstrate Uniformity of the Blend

During the manufacture of both ANDA exhibit and process validation batches, an assessment of the uniformity of both the powder blend and dosage units should be made. However, for some products, sampling errors make it very difficult to validate blending operations using only blend data. As a result, it is proposed to use the dosage unit data in conjunction with blend sample data to demonstrate blend uniformity for those instances where sampling error has been shown to exist. Both blend sampling and dosage unit sampling are proposed according to sampling plans defined in Table 1 during the manufacture of ANDA exhibit batch(es) and/or process validation batches. Sampling locations must be identified prior to the manufacture of the ANDA exhibit batch(es) and/or validation batches. Blend uniformity is demonstrated by assaying blend samples and dosage unit samples. If a blending problem exists (for example, significant variability is attributed to between-location error) the blend is not uniform and

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<sup>3</sup> PDA Journal of Pharmaceutical Science and Technology, Technical Report No. 25, Blend Uniformity Analysis: Validation and In-Process Testing

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further process development exercises should be conducted to address the deficiencies in the blending process.

### **Demonstrating Blend Uniformity, Option 1:**

See Attachment 1 for the flowchart of this option.

### **Demonstrating Blend Uniformity, Option 2:**

Alternatively, procedures described in the PDA Journal of Pharmaceutical Science and Technology, Technical Report No. 25, "Blend Uniformity Analysis: Validation and In-Process Testing" can be used to obtain assurance that the blend is uniform.

Table 1. Sampling Plans for ANDA Exhibit and Process Validation Batches

| Blend                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Dosage Unit                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Identify at least 10 locations in the blender to pull blend samples. Locations must be carefully chosen to represent potential areas of poor blending.<br>For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least 2 depths along the axis of the blender.<br>For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling, including the corners and discharge area (at least 20 locations are suggested to adequately validate convective blenders).<br>Remove at least three samples from each location. | Identify at least 20 locations throughout the compression or filling operation to obtain dosage units. The sampling locations must be carefully chosen to represent significant events (e.g. hopper changeover) during the compression or filling process including samples from the beginning and end of the compression or filling operation. <sup>4</sup> Remove at least 7 dosage units from each location. |

If acceptable results are generated demonstrating the adequacy of mix during the manufacture of the ANDA exhibit batch(es) and validation batches using either of the above proposals, the Office of Generic Drugs will not require further blend uniformity analysis for routine monitoring as part of the ANDA submission. However, additional testing may be necessary to satisfy cGMP compliance requirements for in-process testing as defined in 21CFR 211.110 (a)(3).

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<sup>4</sup> The beginning and end samples are taken from dosage units that would normally be included in the batch.

## VI. Proposed Stratified Testing Plan and Acceptance Criteria for Routine Monitoring of Production Batches

The following section proposes a method to satisfy both the cGMP requirement for an in-process test to demonstrate adequacy of mix [as defined in 21CFR 211.110 (a)(3)] and compendial release testing, through the analysis of a single set of dosage units. To utilize this approach, the content uniformity results (not weight corrected) obtained for the in-process stratified dosage unit samples must be demonstrated to provide the same or better control as the content uniformity data generated during compendial release testing of the corresponding finished dosage units. This relationship must be established for each of the validation batches manufactured. If the stratified sample is representative of the final dosage unit (e.g., if the final dosage unit is an uncoated tablet), or the previous relationship is established, it is not necessary to perform compendial release testing on finished dosage forms to demonstrate content uniformity. In this instance, the results from testing the stratified in-process dosage unit samples are sufficient to demonstrate acceptable content uniformity for the batch. If the relationship between in-process and compendial release testing cannot be demonstrated, both compendial release testing of the finished product and in-process testing of stratified dosage unit samples must be performed separately.

### Products Which Readily Comply with Acceptance Criteria in Section V or Attachment 1

Products with an RSD  $\leq 4.0\%$ , all mean results within 90.0 – 110.0%, and all individual results between 75.0 – 125.0%, for each exhibit and validation batch, are considered to have readily complied with the Section V or Attachment 1 criteria. These products may use a modification of the USP Content Uniformity Test to satisfy cGMP compliance requirements for routine monitoring of production batches for adequacy of mix, as well as for product release testing. Rather than pulling random samples for compendial testing at the conclusion of the manufacture of the product, stratified samples of the dosage units are taken in-process during the compression or filling operation.

Identify at least 10 locations throughout the compression or filling operation to obtain dosage units. The sampling locations must be representative of the compression or filling process and include samples from the beginning and the end of the batch.<sup>5</sup> Remove at least 3 dosage units from each location. The product meets specifications if the results comply with the acceptance criteria stated in Table 2.

Alternatively, if the product complies with the criteria stated in PDA 25, then the procedures outlined in Table 2 may be used.

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<sup>5</sup> The beginning and end samples are taken from dosage units that would normally be included in the batch.

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## Products Which Marginally Comply with Acceptance Criteria in Section V or Attachment 1

Processes yielding marginal results (e.g. validation and ANDA exhibit batches have one or more RSD values > 4.0%, but comply with the criteria for mean and individual values when tested in accordance with the procedure described in Section V or Attachment 1) require additional testing to satisfy cGMP compliance during routine production batches. Stratified sampling should be performed by taking a minimum of three dosage units from at least 10 locations during the compression or filling operation. At least 30 dosage units are assayed and weight corrected, then compared against the following acceptance criteria: mean of all individual dosage units lies between 90.0 – 110.0% of target, and RSD of all individual dosage units is  $\leq 6.0\%$ . If after testing 5 consecutive batches the criteria for the mean is met and the RSD routinely is  $\leq 5.0\%$ , testing to satisfy the cGMP requirement may be performed according to the procedure defined in Table 2.

Table 2. Acceptance Criteria to Demonstrate Blend Adequacy of Mix and Dosage Unit Content Uniformity for Routine Commercial Batches for Products that Readily Comply with the Acceptance Criteria Discussed in Section V or Attachment 1.

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cGMP Requirement       | Stage 1: Sample at least 3 dosage units from at least 10 locations. Assay one dosage unit from each of at least 10 locations and weight correct the result. If the mean is between 90.0 - 110.0% of target and the RSD is $\leq 5.0\%$ , adequacy of mix is demonstrated.<br>Stage 2: Assay the remaining 2 samples from each location and weight correct the results. If the mean of all individual samples from Stage 1 and Stage 2 testing is between 90.0 – 110.0% of target and the RSD is $\leq 6.0\%$ , adequacy of mix is demonstrated. |
| Compendial Requirement | Dosage units are tested according to the compendial procedure described in the USP. Values are not weight corrected.                                                                                                                                                                                                                                                                                                                                                                                                                            |

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## VII. Next Steps

The PQRI BUWG is soliciting public comment on the approaches defined in this recommendation to demonstrate both blend and dosage unit uniformity. Comments should be sent to the following address no later than October 1, 2001. Both electronic and postal mail is acceptable.

Ms. Sylvia Gantt  
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Simultaneously during the public review, the PQRI BUWG will challenge the recommendations contained in this document with actual data. The PQRI BUWG is calling upon pharmaceutical firms to submit blinded blend and dosage unit data meeting the following criteria:

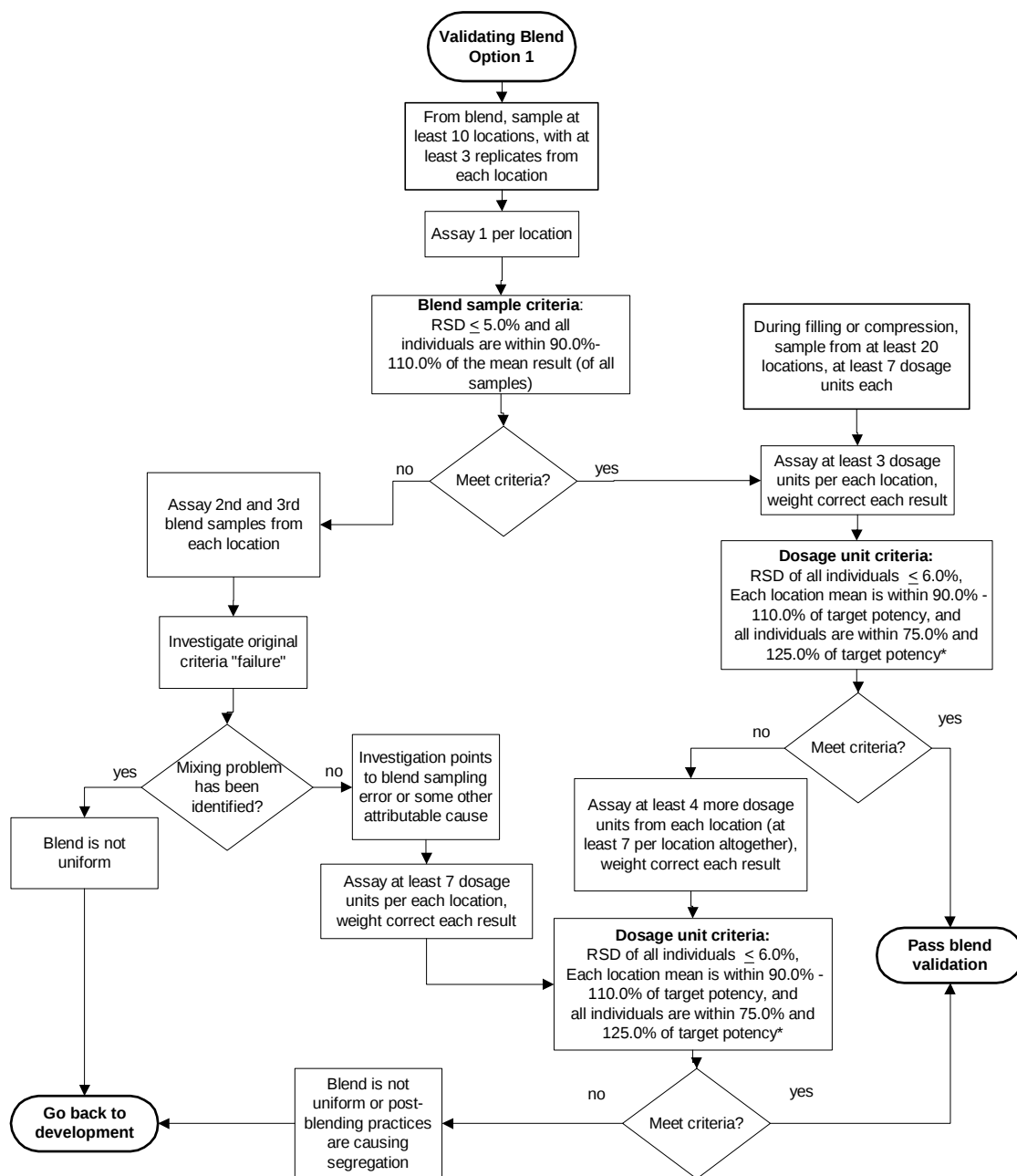
- Containing active ingredient in quantities < 5% and between 15-25%.
- Generated from direct compression and granulation processes (either dry or wet granulation).
- Data for tablets and capsules.
- Commercial scale data from both small (50-100 kg) and large (>400 kg) commercial scale batch sizes.

Pharmaceutical firms should consult the PQRI website ([pqri.org](http://pqri.org)) for instructions regarding how to submit blinded data for challenging the recommendations described in this document.

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## Attachment 1

### Demonstration of Adequacy of Mix and Content Uniformity for ANDA Exhibit Batch(es) and Validation Batches [Option 1]



\* When comparing individual dosage units to 75.0 - 125.0% of target potency, use the 'as is' results (not corrected for weight).

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## Attachment 2

### Rationale for Blend Samples and Acceptance Criteria

#### **Sampling Locations**

The minimum number of sampling locations suggested is based upon current scientific knowledge of blenders. PQRI BUWG supports the use of 10-15 locations to validate a tumbling blender and at least 20 locations to validate a convective blender. Sampling less than 10 locations will not adequately identify lack of blend uniformity.

#### **Acceptance Criteria**

In the past the FDA has proposed that in the testing of blends, either as part of a validation exercise or in routine blend testing, the RSD of the samples should not exceed 5.0% when the assays are expressed as a percent of the target concentration. In the current proposal we have retained the use of this limit during the testing of blend powders. We find this standard consistent with the intent of providing sufficient assurance, given the relatively small sample size, that the blend is adequately mixed.

In addition to the RSD criteria, it is proposed that all individuals fall within “90.0–110.0% of the mean result” for validation (allowing for thief bias). This is a reasonable requirement for blends given the adjustment of thief sample quantity to accommodate for thief error (see Section IV, Process Development), and the use of dosage unit data to validate the blending process if the blend data continue to demonstrate thief error.

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## Attachment 3

### Rationale for Dosage Unit Sample Sizes and Acceptance Criteria

The number of locations and sample sizes within each location were chosen along with the acceptance criteria such that the test would:

1. Always be tighter (more stringent) than the USP test for content uniformity.
2. Be harder to pass for a process with significant between-location variability (indicating blend uniformity issues) across filling or compression, but easier to pass when the process did not demonstrate between-location variability in the dosage units.

The dosage unit criteria have three requirements. For results that have been weight corrected:

- The RSD limit defines the uniformity requirements when there is no between-location variability.
- A comparison of each location mean to 90.0% - 110.0% of target identifies between-location variability

For results not weight corrected:

- A comparison of each individual to 75.0% and 125.0% of target is used to pick up super-potent or sub-potent units. A value outside 25.0% of the target potency may indicate inadequate blend uniformity.

Numerous computer simulations were performed to identify a sampling plan and acceptance criteria that would meet the above requirements. At the same time, consideration was also given to requiring a sufficient number of locations to adequately represent all parts of the batch while trying to minimize the excessive use of analytical resources.

Two of the simulations will be described below. In these simulations, the batch mean was centered at 100%, while the weight variation was set at 1.5%. Data for 5000 batches were generated for a given level of variability, and the results compared to the acceptance criteria. The percent of batches meeting the criteria was computed for each variability level. This process was continued until the percent passing was established for batches with total variability up to approximately 10% (RSD).

In the first simulation, it was assumed that there was no between-location variability (no blend uniformity issues after filling/compression), but only increasing within-location variability. Figure 1 is the plot of these results. The legend indicates the sampling plans being compared. The plot labeled "20x3, 7" represents the sampling plan recommended for validation. "USP" indicates the plot for the USP content uniformity test for tablets. As seen in this figure, the "20x3, 7" plan is equivalent to or tighter than the USP test at all levels of

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variability, and shows good discrimination (the curve is very steep) once it breaks away from the horizontal. Batches have a high probability of passing with an RSD of up to 5.5%. As the RSD increases beyond 5.5% the probability of failure rapidly increases.

A second simulation assumed that there was increasing between-location variability, while maintaining the % RSD values for both weight variation and assay each at 1.5%. Figure 2 is a plot of these results. The key is the same as in Figure 1. All results obtained using the “20x3, 7” sampling plan are tighter than the USP test. Further, as the between-location variability increases (in other words, as blend uniformity issues arise), batches have a higher probability of failure. At RSD's greater than 4%, the probability of failure starts to significantly increase.

Thus, the “20x3, 7” proposal meets the requirements described above.

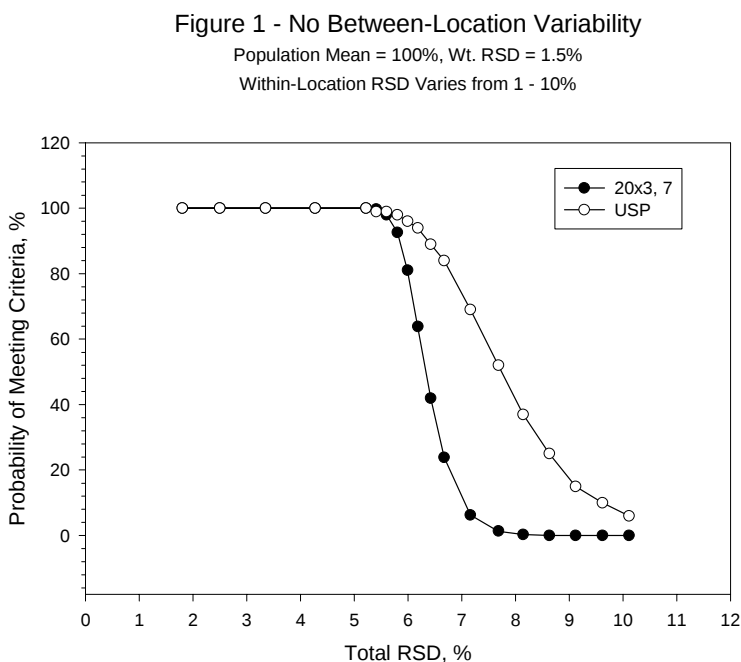


Figure 2 - Between Location Variability Exists  
Population Mean = 100%, Assay RSD = 1.5%, Wt. RSD = 1.5%  
Between Location RSD varies from 1 - 10%

