

The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends¹

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Abstract

In response to concerns expressed by applicants regarding inconsistent policies in establishing blend uniformity acceptance criteria to demonstrate adequacy of mix, the FDA Office of Generic Drugs (OGD) issued the draft document *Guidance for Industry, ANDAs: Blend Uniformity Analysis* (August 1999)². Both generic and innovator pharmaceutical companies raised a number of concerns following the publication of this document. As a result, the Product Quality Research Institute (PQRI) Blend Uniformity Working Group (BUWG) was established in February 2000. One of the primary goals of this group was to draft a scientifically based alternative to the OGD document. The resulting recommendation addresses both FDA and industry concerns by substantially enhancing product quality assurance without increasing regulatory burden. The PQRI BUWG recommends that these blend and dosage unit uniformity requirements be administered uniformly throughout the industry. PQRI submitted the following recommendation to the FDA on December 31, 2002, providing the Agency with an alternative strategy to consider when drafting future regulatory policy to assess blend and dosage unit uniformity.

PQRI Recommendation

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 applies to both ANDA and NDA 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 is applicable to active ingredient(s) contained in the blend.

The approach described in this document is proposed as a means to satisfy the cGMP requirement for in-process testing to demonstrate adequacy of mix,

¹ 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).

² Document was recalled by FDA in May 2002.

as well as USP compendial 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 testing requirements. Additionally, on-line measurement systems may also be used to demonstrate uniformity (e.g., NIR measurement of in-process blend samples or dosage units).

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.³ 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.

Potency refers to the content of drug substance (also referred to as active ingredient) present in the tested dosage unit. Alternate methods of analysis for the content of drug substance, such as a quantitative spectrophotometric method, may be used in place of a more elaborate HPLC method.

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 document. All weight-corrected potencies are to be expressed as a percentage of the blend target concentration. Calculations to satisfy compendial testing requirements and the 75.0 –125.0% criteria for individual dosage units stated in Attachment 1 are not weight corrected. Further, the potencies are expressed as a percentage of the label concentration.

Absolute as used to define the acceptable range (+/- 10%) in which individual blend sample values must fall is independent of the value of the mean. For example, if the mean of all blend samples is 95.0%, the absolute range is 85-105%, (not 95 +/- 9.5%).

³ Glossary and Tables for Statistical Quality Control, ASQC Quality Press, copyright 1983.

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.

Compendial testing mentioned in this document refers to USP <905> Uniformity of Dosage Units, by Content Uniformity.

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 published a draft guidance in August 1999.⁴ The guidance proposed 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.

In-process dosage unit analysis (of 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 employed to collect in-process dosage units throughout the compression or filling process. In-process dosage unit analysis has many positive aspects:

⁴ *Guidance for Industry, ANDAs: Blend Uniformity Analysis* (August 3, 1999), which was subsequently withdrawn by FDA in May 2002.

- It is an 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 reliable, accurate information about the quality of the product given to the patient.
- Weighing errors during blend sample analysis are eliminated.
- It removes the safety issues surrounding blend sampling of toxic or potent drugs manufactured in isolated environments.
- It accounts for potential segregation after blending.

The following proposal presents strategies for in-process 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 batches, and both ANDA and NDA batches during the validation of the commercial manufacturing process. The rationale for each sample size and acceptance criteria for the proposal contained in Attachment 1 are provided in Attachments 2 and 3. If this proposal is used to test the exhibit and/or commercial scale validation lots, and the results comply, then it may be sufficient to perform stratified sampling and analysis of in-process dosage units for commercial batches in lieu of blend sampling and analysis advocated in the draft ANDA blend uniformity guidance document. The level of testing required to satisfy cGMP requirements would be dependent on the quality of the data generated by testing the batches in accordance with the proposal. For those products that readily pass the defined acceptance criteria, 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 (see Section VI and Attachment 4). Processes that do not readily pass would require additional testing for routine production batches.

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 post-blending segregation of the mixture and thus 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 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.

Blend sampling plans should be designed 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 present. 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 such as the use of methods described in PDA Technical Report 25⁵ should be applied to assess the situation.

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 appropriately 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. Comparisons between the blend and dosage unit data should be performed throughout product development. Investigations should be conducted to identify potential causes of any discrepancies observed between the blend and dosage unit uniformity data.⁶ A basic foundation of this proposal is the strong technical opinion that the proposed approach is likely to reveal formulation and processing problems that might remain hidden if less discriminating techniques are used (e.g. thief sampling; fewer sampling points during dosage form manufacture).

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

During the manufacture of exhibit and/or process validation batches, an assessment of the uniformity of both the powder blend and in-process 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 in-process 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 exhibit and/or process validation batches. Sampling locations and acceptance criteria must be identified prior to the manufacture of the exhibit 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), then the blend is not uniform

⁵ PDA Journal of Pharmaceutical Science and Technology, Technical Report No. 25, Blend Uniformity Analysis: Validation and In-Process Testing.

⁶ JK Prescott and TP Garcia, Pharmaceutical Technology, 25 (3), March 2001, p. 68-88.

and 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 Exhibit and/or Process Validation Batches

Blend	Dosage Unit
<p>Identify at least 10 locations in the blender to pull blend samples. Locations must be carefully chosen to represent potential areas of poor blending. 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.</p> <p>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). Take at least three replicate samples from each location.</p>	<p>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.⁷ Take at least 7 dosage units from each location.</p>

The stratified sampling criteria defined in this document are acceptable for demonstrating blend uniformity in NDA or ANDA submissions. The use of routine stratified dosage unit testing as described in this document for commercial production batches (Section VI) would satisfy the cGMP requirements for in-process testing as defined in 21CFR211.110 (a)(3).

VI. Proposed Stratified Testing Plan and Acceptance Criteria for

⁷ The beginning and end samples are taken from dosage units that would normally be included in the batch.

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) (in lieu of blend testing) and compendial testing, through the analysis of a single set of in-process dosage units (Attachment 4). Rather than analyzing an additional random sample of finished dosage units to satisfy compendial testing requirements, stratified samples of the dosage units are taken in-process during the compression or filling operation. Data generated from analysis of the stratified samples is used to satisfy both cGMP and compendial testing requirements.

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 (sensitivity to lack of uniformity) as the content uniformity data generated during compendial testing of the corresponding finished dosage units. This relationship must be established ideally for each exhibit and/or validation batch 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, then it would not be necessary to perform compendial testing on finished dosage forms to demonstrate content uniformity. In this instance, the results from testing the stratified in-process dosage unit samples would be sufficient to demonstrate acceptable content uniformity for the batch. If the relationship between in-process and compendial testing cannot be demonstrated, then both compendial testing of the finished product and in-process testing of stratified dosage unit samples must be performed separately.

The number of dosage units that must be tested during routine manufacture is based on the content uniformity results obtained for the product during exhibit and/or validation batch manufacture. The following text defines the terms readily pass, marginally pass, standard testing and tightened testing, and summarizes the rules for switching between standard and tightened testing.

Definition of Products That Readily Pass and Marginally Pass the Acceptance Criteria in Section V or Attachment 1

Products are considered to "Readily Pass" the acceptance criteria stated in Section V or Attachment 1 if for each of the exhibit and/or validation batches, the dosage unit means for each location are between 90.0% - 110.0% of target, the RSD is $\leq 4.0\%$, and all individual results are between 75.0%-125.0% of target potency [number of dosage units per batch (n) is at least 60].

Exhibit and/or validation batches yielding marginal results require additional testing to satisfy cGMP compliance during routine production. Products are considered to "Marginally Pass" the acceptance criteria stated in Section V or

Attachment 1 if all exhibit and/or validation batches pass the acceptance criteria (in Section V or Attachment 1), but at least one batch has an RSD $> 4.0\%$ but $\leq 6.0\%$ for the dosage units. The definitions listed above are summarized in Table 2.

Table 2. Definitions for “Readily Pass” and “Marginally Pass”

When	Status
All batches have dosage unit means for each location between 90.0% - 110.0% of target, $RSD \leq 4.0\%$, and all individual results are between 75.0%-125.0% ⁸ of target potency [n = at least 60]	Readily Pass
At least one batch has dosage unit means for each location between 90.0% - 110.0% of target, $4.0 < RSD \leq 6.0\%$, and all individual results are between 75.0%-125.0% ⁸ of target potency [n = at least 60]	Marginally Pass

Definition of Standard Testing and Tightened Testing

Readily passing the above criteria for all validation and exhibit batches qualifies a product to use Standard Testing during routine manufacture. Products that marginally pass during validation must use Tightened Testing during routine manufacture. These testing schemes and acceptance criteria are described in the Table 3.

Table 3. Definition of “Standard Testing” and “Tightened Testing” During Routine Manufacture

Status	Acceptance Criteria
Standard Testing during Routine Manufacture	Stage 1, n=10 (from 10 stratified locations) If the mean is between 90.0% - 110.0% of target and $RSD \leq 5.0\%$, adequacy of mix is demonstrated. If not, proceed to Stage 2 Testing. Stage 2, n=30 total (from same 10 stratified locations) If the mean is between 90.0% - 110.0% of target and $RSD \leq 6.0\%$, adequacy of mix is demonstrated.
Tightened Testing during Routine Manufacture	n=30 (from 10 stratified locations) If the mean is between 90.0% - 110.0% of target and $RSD \leq 6.0\%$, adequacy of mix is demonstrated.
Compendial Requirement	The same dosage units are tested according to the compendial procedure described in the USP. Values are not weight corrected.

At least 10 stratified sampling locations throughout the compression or filling operation to obtain dosage units should be identified. The sampling locations must be representative of the compression or filling process and include samples

⁸ The individual sample criterion is evaluated before weight correcting the assays.

from the beginning and the end of the batch.⁹ Obtain at least 3 dosage units at each location. The product meets specifications if the results comply with the acceptance criteria stated in Table 3.

Switching Between Standard Testing and Tightened Testing

Rules for switching from Standard Testing to Tightened Testing are necessary to ensure that a product that Readily Passes during validation does not undergo change during routine manufacture in which blend uniformity significantly degrades from that previously exhibited for the product. At the same time, these rules must not generate excessive “false” signals, causing a product not undergoing significant change to switch to Tightened Testing. Similarly, products that demonstrate marked improvement in dosage unit uniformity should be allowed to switch from Tightened Testing to Standard Testing. With this in mind, Table 4 provides guidance for switching between Standard Testing and Tightened Testing.

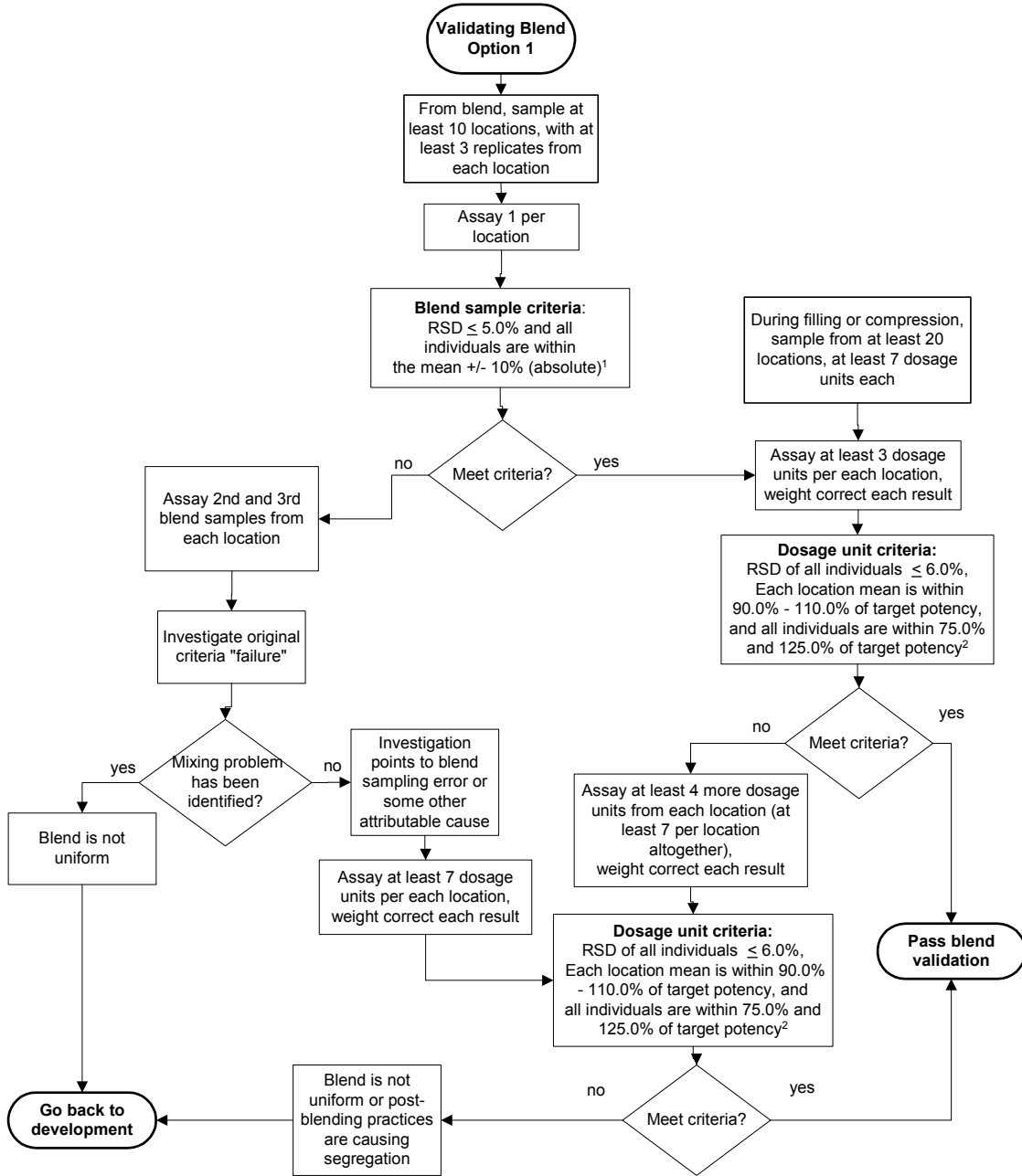
Table 4. Switching Between Standard Testing and Tightened Testing of Dosage Units During Routine Manufacture

When Performing	Switch To
Tightened Testing, when 5 consecutive batches (n=30 dosage units per batch) each have an RSD \leq 5.0%, then	Standard test
Standard Testing, when the RSD of 1 batch following Stage 2 testing (n=30 dosage units per batch) is $>$ 5.0%, then	Tightened test

⁹ The beginning and end samples are taken from dosage units that would normally be included in the batch.

Attachment 1

Demonstration of Adequacy of Mix and Content Uniformity for Exhibit and/or Validation Batches [Option 1]



¹ Examples of "mean +/- 10% (absolute)" are: If the mean potency = 95%, then the interval is 95% +/- 10%; thus, all individuals must fall within 85% - 105%. If the mean potency = 103%, then the interval is 103 +/- 10%; thus all individuals must fall within 93% - 113%.

² When comparing individual dosage units to 75.0 - 125.0% of target potency, use the 'as is' results (not corrected for weight).

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. The 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 powder blends. 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 +/- 10% (absolute) of the mean for validation, to allow 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.

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 components. 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 identify the presence of 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 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 1 - No Between-Location Variability

Population Mean = 100%, Wt. RSD = 1.5%
Within-Location RSD Varies from 1 - 10%

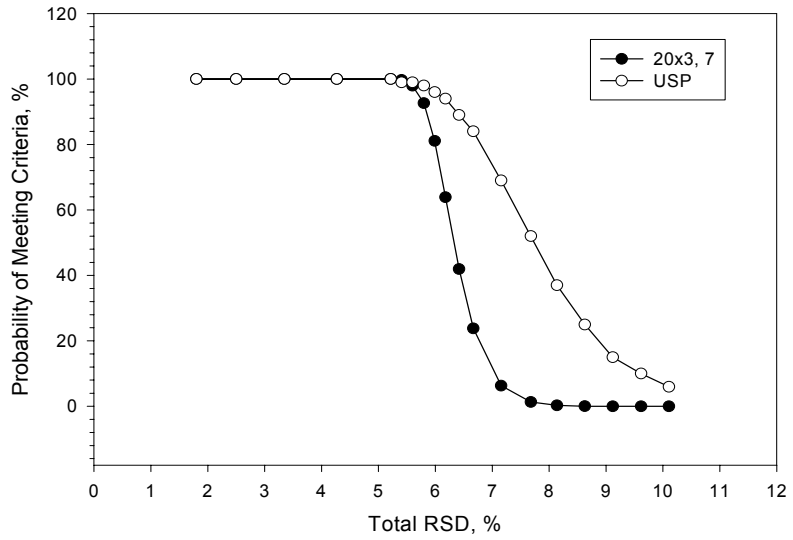
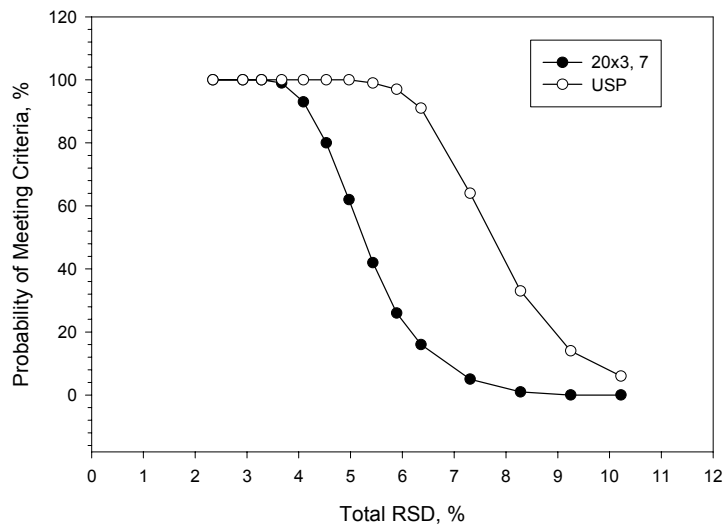


Figure 2 - Between Location Variability Exists

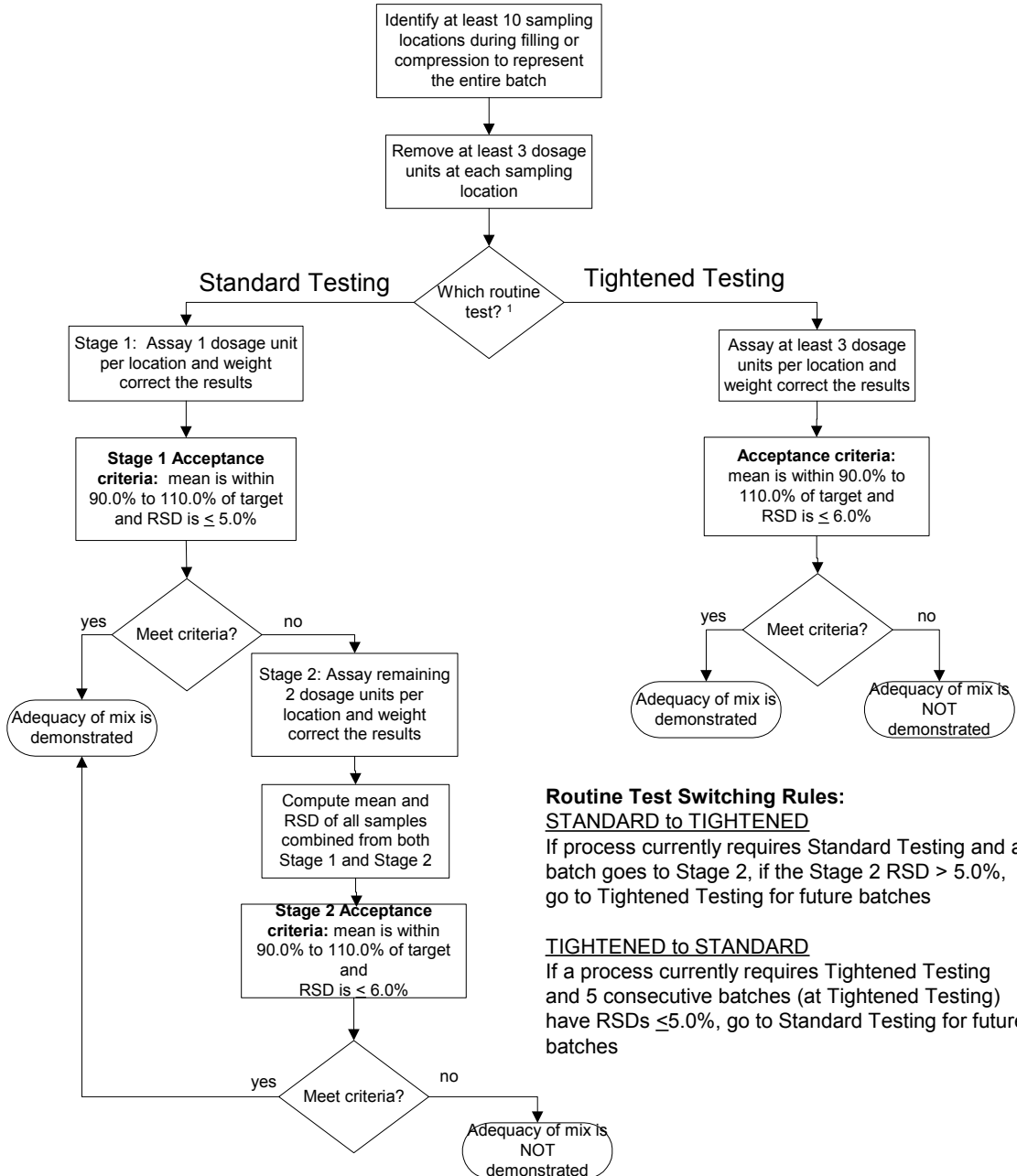
Population Mean = 100%, Assay RSD = 1.5%, Wt. RSD = 1.5%
Between Location RSD varies from 1 - 10%



Attachment 4

Demonstration of Adequacy of Mix and Content Uniformity During Routine Manufacture

Note: Validation and Exhibit batches met dosage unit criteria (Attachment 1) for location means, RSD, and individuals.



¹ If a process "Marginally passes" during validation/Exhibit batches, use Tightened Testing. If a process "Readily passes" use Standard Testing. Apply switching rules post-validation (see Table 4).