

Appendix C

**Clean Copy of the Guidance with the Incorporated Suggestions
(for ease of reading)**

Guidance for Industry

Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**October 2003
Pharmaceutical CGMPs**

Guidance for Industry

Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Pharmaceutical Science (OPS)
Office of Compliance (OC)**

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Guidance for Industry¹

**Powder Blends and Finished Dosage Units — Stratified In-Process
Dosage Unit Sampling and Assessment**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers of human drug products in meeting the requirements of 21 CFR 211.110 for demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished solid oral dosage units (*comment: please add more description here as to the general types of dosage units included. We assume this also includes wet granulations?*). This guidance describes a control procedure for the manufacturer to routinely assess the adequacy of powder mix/drug uniformity by the use of stratified in-process dosage unit sampling and testing instead of routine blend sampling, provided that a feasibility assessment is made prior to implementation of the stratified sampling approach.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

This guidance is the result of an Agency effort to achieve a science-based policy and regulatory enforcement. Experts from industry, academia, and the FDA developed the principles

¹ This guidance has been prepared by the Office of Pharmaceutical Science and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in cooperation with the Product Quality Research Institute (PQRI) (see footnote 3). This guidance document represents the Agency's current thinking on assessment of the uniformity of powder blends and finished dosage units in the absence of new technology development or implementation.

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38 underlying this guidance after extensive public discussion. A brief history of the evolution of
39 this guidance is provided in the following paragraphs.

40
41 In response to industry concerns regarding regulations for demonstrating the adequacy of in-
42 process powder mixing, the FDA published a draft guidance for industry containing new
43 approaches for blend uniformity analysis in August 1999.² Comments submitted to the docket
44 resulted in the formation of the Blend Uniformity Working Group (BUWG) by the Product
45 Quality Research Institute (PQRI).³ The PQRI BUWG conducted a public meeting, PQRI
46 Workshop on Blend Uniformity, on September 7 and 8, 2000.

47
48 Using the consensus reached by participants in this workshop, the BUWG developed a draft
49 recommendation, *The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate*
50 *Adequacy of Mix for Powder Blends*. The draft recommendation received examination and peer
51 review in multiple scientific and public venues. In addition, the Advisory Committee for
52 Pharmaceutical Science (ACPS) reviewed the draft recommendation and received public
53 comment during scheduled meetings of the committee.⁴ The draft recommendation was revised
54 to incorporate the results of peer review and public comment and was presented to CDER's
55 Center Director in final form on December 30, 2002. The recommendation was subsequently
56 published in the *PDA Journal of Pharmaceutical Science and Technology*.⁵ This draft guidance
57 reflects CDER's effort to incorporate the draft recommendation into regulatory policy.

58

59

III. SCOPE

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62 Stratified sampling of dosage units is a process of collecting representative samples from
63 predefined, targeted locations in the dosage unit forming process that have the greatest potential
64 to yield extreme high and low test results. These test results are used to monitor the
65 manufacturing process output from the locations most responsible for finished product
66 variability. Stratified sampling of dosage units can be used to ensure adequate powder mix and
67 in some cases, uniform content in finished products.

68

69 The methods described in this guidance are not intended to be the only methods for meeting
70 Agency requirements to demonstrate the adequacy of powder mix. Traditional powder blend

² The FDA withdrew the guidance for industry *ANDAs: Blend Uniformity Analysis* on May 17, 2002.

³ PQRI is a collaborative body involving FDA's Center for Drug Evaluation and Research (CDER), industry, and academia. Since its inception in January 1996, the mission of PQRI has been to generate scientific information in support of regulatory policies through research. Additional information about PQRI is available at www.pqri.org.

⁴ The PQRI BUWG recommendation appeared on the public ACPS agenda on November 28, 2001 (introduction), May 8, 2002 (distribution and comment), and October 22, 2002 (final comment).

⁵ G Boehm, J Clark, J Dietrick, L Foust, T Garcia, M Gavini, L Gelber, J Geoffry, J Hoblitzell, P Jimenez, G Mergen, F Muzzio, J Planchard, J Prescott, J Timmermans, and N Takiar, "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends, *PDA J. Pharm. Sci Technol.*, 57:59-74, 2003.

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71 sampling and testing, in conjunction with testing for uniformity of content in the finished
72 product, can be used to comply with current good manufacturing practice requirements
73 (CGMPs). Use of at-, in-, or on-line measurement systems can also be appropriate and are
74 described in other guidance documents.⁶ After *readily passing* (Section V.B.2) the validation
75 requirements, products that are allowed to meet USP Uniformity of Dosage Units by weight
76 variation are exempted from future routine blend testing requirements.

77
78 This guidance provides recommendations on how to:

- 79 • Conduct powder blend sampling and analyses.
- 80 • Establish initial criteria for stratified sampling of in-process dosage units⁷ and evaluation
81 of test results.
- 82 • Analyze the stratified samples and evaluate data.
- 83 • Compare the stratified sample data with the powder blend data.
- 84 • Assess powder mix uniformity.
- 85 • Compare the stratified in-process dosage unit data with the finished dosage unit data to
86 determine whether in-process samples may be used to assess uniformity of content.
- 87 • Test exhibit and validation batches for adequacy of powder mix.
- 88 • Test and evaluate routine manufacturing batches.
- 89 • Report the use of stratified sampling in the application.
- 90

91
92 The methods described in this guidance can be used to monitor active ingredient homogeneity of
93 powder blends and to ensure uniform content of the finished product for solid oral drug products.
94 These methods are only one way to satisfy the CGMP and application review requirements for
95 in-process testing to demonstrate adequacy of powder mix and uniform content of the finished
96 product. The method assumes appropriate monitoring of all manufacturing steps as required by
97 the regulations or application commitments. This guidance does not discuss the assessment of
98 the potency and other attributes that can affect the finished dosage units, or the homogeneity of
99 inactive ingredients. Some formulations may call for more rigorous sampling than that described
100 in this guidance to assess the uniformity of powder blends or the uniformity of content of the
101 finished dosage units.

102
103 When using the methods described in this guidance, trends may be observed in the data. We
104 recommend that manufacturers scientifically evaluate research data for trends, determining if
105 they affect the quality of a product and, if so, how. The FDA does not intend to inspect research

⁶ In September 2003, the Agency issued the draft guidance for industry *PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*. Once finalized, it will represent the Agency's perspective on this issue.

⁷ The in-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.

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106 data collected on an existing product for the purpose of evaluating the suitability of proposed
107 methods. Any FDA decision to inspect research data would be based on exceptional situations
108 similar to those outlined in Compliance Policy Guide Sec. 130.300.⁸ Those data used to support
109 validation or regulatory submissions will be subject to inspection in the usual manner.
110

IV. EVALUATION OF POWDER MIX AND IN-PROCESS STRATIFIED SAMPLING DURING PROCESS DEVELOPMENT

114
115 If you plan to follow the procedures described in this guidance document, we recommend that
116 you first complete the evaluation described in this section before using the methods described in
117 sections V and VI. The subsections below describe the initial assessment of powder mix
118 uniformity in the blend and stratified in-process dosage units through evaluation of data from
119 development batch(es). These procedures can reveal deficiencies in the blending operation that
120 may not otherwise be detected. We recommend that manufacturers correct deficiencies in the
121 blending operation before validation and implementation of the routine manufacturing control
122 methods described in this guidance.
123

A. Assessment of Powder Mix Uniformity

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125
126 As part of development, we recommend that you assess critical events in the blending process
127 and determine appropriate sampling techniques for demonstrating a validated blend process. As
128 part of this evaluation, we recommend the assessment of powder mix uniformity using the
129 following procedures:
130

- 131 • Conduct blend analysis on batches by sampling the mix in the blender⁹ and/or
132 intermediate bulk containers (IBCs). When sampling from a blender, identify sampling
133 locations¹⁰ to represent potential areas of poor blending. For example, in tumbling
134 blenders such as V-blenders, double cones, or drum mixers, samples should be selected
135 from at least two depths along the axis of the blender. For convective blenders such as a
136 ribbon blender, a special effort should be made to implement uniform volumetric
137 sampling to include the corners and discharge area.
- 138 • Identify appropriate blending time and speed ranges, dead spots in blenders, and locations
139 of segregation in IBCs.
- 140 • Define the effects of sample quantity (e.g., 1-10X dosage unit range) while developing a
141 technique capable of measuring the true uniformity of the blend. Sample quantities larger
142 than 3X can be used with adequate scientific justification. Appropriate blend sampling
143 techniques and procedures should be developed for each product with consideration to

⁸ FDA/ORA Compliance Policy Guide, Sec. 130.300, *FDA Access to Results of Quality Assurance Program Audits and Inspections* (CPG7151.02)

⁹ Sampling can be done from other equipment that is being used to mix the blend, such as a fluid bed.

¹⁰ Typically, at least 10 locations for tumbling blenders and at least 20 locations for convective blenders are selected.

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144 various designs of blend powder sampling and the physical and chemical properties of
145 the blend components.

146 • Quantitatively evaluate the variability that is present among the samples. Attribute the
147 sample variability to either lack of uniformity of the blend or sampling error. High
148 within-location variance in the blend data can be an indication of one factor or a
149 combination of factors such as inadequacy of blend mix, sampling error,¹¹ analytical
150 error, or agglomeration.^{12, 13} High between-location variance in the blend data can
151 indicate that the blending operation is inadequate.

152 • Based upon the results of the development work, identify a sampling and testing plan
153 appropriate for validation of powder mix uniformity (e.g., sampling locations, sample
154 quantity, appropriate statistical analyses).

155

156 **B. Evaluation of Powder Mix Uniformity using Stratified In-Process Dosage** 157 **Unit Data**

158

159 As part of development, we recommend that you assess the in-process dosage unit data to
160 identify locations throughout the forming operation that have a higher risk of producing failing
161 finished product uniformity of content results due to segregation or poor powder mix. We
162 recommend the following steps:

163

164 • Conduct periodic sampling and testing of the in-process dosage units by sampling them at
165 defined intervals throughout the compression or filling process. A minimum of 20
166 appropriately spaced in-process dosage unit sampling points is recommended. There
167 should be at least 7 samples taken¹⁴ from each of these locations for a total minimum of
168 at least 140 samples.

169 • Take at least 7 samples from each additional location to further assess each significant
170 event,¹⁵ such as filling or emptying of hoppers and IBCs, start and end of the
171 compression or filling process and equipment shutdown.

¹¹ If blend sampling error is detected, more sophisticated, statistical analyses should be applied to assess the situation, such as the use of methods described in J Berman, DE Elinski, CR Gonzales, JD Hofer, PJ Jimenez, JA Planchard, RJ Tlachac, PF Vogel, "Blend Uniformity Analysis: Validation and In-Process Testing." *Technical Report No. 25, PDA J Pharm. Sci. Technol.* 51(Suppl 3i-iii), S1-99, 1997.

¹² OS Sudah, PE Arratia, D. Coffin-Beach, FJ Muzzio, "Mixing of Cohesive Pharmaceutical Formulations in Tote (Bin)-Blenders," *Drug Dev. Ind. Pharm.*, 28(8): 905-918, 2002.

¹³ V Swaminathan, DO Kildsig, "Polydisperse powder mixtures: effect of particle size and shape on mixture stability," *Drug Dev. Ind. Pharm.*, 28(1):41-48, 2002.

¹⁴ A minimum of 3 (of the 7) dosage units per location should be assayed.

¹⁵ A *significant event* is any operation during the solid dosage production process that can affect the integrity of the in-process materials – see section IX Glossary.

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- 172 • Significant events may also include observations or changes from one batch to another
173 (e.g., batch scale-up and observations of undesirable trends in previous batch data).
- 174 • Prepare a summary of the data (and analysis), identifying the significant events observed
175 in the manufacturing process that may impact blend uniformity. From this, identify 20
176 stratified sampling locations that may be used to verify or validate blend uniformity¹⁶.
- 177 • Compare the powder mix uniformity data with the in-process dosage-unit uniformity data
178 described above.
- 179 • Investigate any discrepancies observed between powder mix and dosage-unit data and
180 establish root causes. At least one trouble-shooting guide is available that may be helpful
181 with this task.¹⁷ Possible corrections may range from going back to formulation
182 development to improve powder characteristics to process optimization. Sampling
183 problems may also be obviated by use of alternate state-of-the-art methods of in situ real-
184 time sampling and analysis (e.g., P.A.T.).

V. EVALUATION OF EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY

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187 We recommend that during the manufacture of exhibit and process validation batches, you assess
188 the uniformity of the powder blend and the in-process dosage units to ensure adequacy of blend
189 uniformity. We recommend that sampling locations for blend and stratified samples should be
190 identified per Section IV. This comparison of powder mix uniformity and stratified in-process
191 dosage unit uniformity is completed before establishing the criteria and controls for routine
192 manufacturing.

A. Demonstrating Powder Mix Uniformity

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199 This section describes sampling and testing the powder mix of exhibit and process validation
200 batches used to support implementing the stratified sampling method described in this guidance.
201 Some powder blends may present unacceptable safety risk or be physically impractical (e.g.,
202 large V-blender) when directly sampled. Once described, these situations may justify an
203 alternate procedure. In such cases, process knowledge and data from indirect sampling
204 combined with additional in-process dosage unit data may be adequate to demonstrate the
205 adequacy of the powder mix. Data analysis used to justify using these alternate procedures
206 should be described in a summary report that is maintained at the manufacturing facility. In
207 general, we recommend:

¹⁶ Validation of blend uniformity should include both the verification of adequate powder mix and of adequate blend uniformity in the dosage units.

¹⁷ JK Prescott, TJ Garcia, "A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram," Pharm. Technol., 25 (3):68-88, 2001.

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1. Identify at least 10 locations to collect powder blend samples. If taken from the blender, they should include areas that may be problematic in terms of uniform blend¹⁸. For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least two depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling to include the corners and discharge area (at least 20 locations are recommended to adequately validate convective blenders).
 2. Collect at least 3 replicate samples from each location.
 3. Assay one sample per location, with the number of samples (n) ≥ 10. (n ≥ 20 for convective blender). Samples should meet the following criteria:
 - RSD (*relative standard deviation*) of all individual results ≤ 5.0 percent.
 - All individual results are within 10.0 percent (absolute) of the mean of the results.

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If samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage form samples (7 from at least 20 locations) may be analyzed. These samples should have been obtained following the procedure described below in Section V.B. If the cause of failure is identified as a mixing problem, we recommend that you do not proceed further with implementation of the methods described in this guidance until a new mixing procedure is developed. If the cause of failure is not because of mixing, but is attributed to sampling error or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section V.B (see also Attachment 1).

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As an alternative, you can substitute the procedures described in the PDA Technical Report No. 25, (see reference in footnote 11) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above.

241 **B. Assessment and Classification of Stratified In-Process Dosage Unit** 242 **Uniformity** 243

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This section describes the sampling, testing, and evaluation of in-process dosage units collected using stratified sampling. These exhibit and process validation batch data are used to support implementing the stratified sampling method described in this guidance. The manufacturing process will be classified as either *readily pass* (all batches have an RSD ≤ 4.0%), *marginally pass* (all batches have an RSD ≤ 6.0%) or *inappropriate* for demonstration of batch homogeneity (at least 1 batch has an RSD > 6.0%). The procedures are discussed in the following sections:

¹⁸ Developing an appropriate sampling and testing plan is described in Section IV.A of this guidance.

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1. In-Process Dosage Unit Sampling and Analysis

We recommend the following steps:

- Carefully identify locations¹⁹ throughout the compression or filling operation to sample in-process dosage units. The sampling locations should also include significant process events such as hopper changeover, filling or machine shutdown and the beginning and end of the compression or filling operation.²⁰ There should be at least 20 locations with 7 samples each for a minimum total of 140 samples. These include periodic sampling locations and significant event locations.
- Sample at least 7 in-process dosage units from each sampling location.
- Assay at least 3 of the 7 and weight correct each result. (The number of samples should be specified and justified for a given product and process.) Assay all 7 per location if required in Section V.A.
- Analyze the dosage units according to the flowchart in Attachment 1. Adequate Powder Mix is demonstrated, if for each batch:
 - RSD of all individuals is $\leq 6.0\%$
 - Each location mean is within 90.0% - 110.0% of target potency
 - All individuals (not weight corrected) are within 75.0% and 125.0% of the target potency
- Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or a distribution other than bell-shaped should be evaluated. If these occurrences significantly affect your ability to ensure batch homogeneity, they should be corrected.
- Prepare a summary of this analysis. Potential investigation results along with a description of batch distribution should be included in the summary. Submit this summary as described in section VII of this guidance.

2. Classifying the Test Results

Additionally, we recommend that you classify the test results as *readily pass* or *marginally pass* according to the following procedure:

¹⁹ Prior identification of appropriate sampling locations is described in Section IV.B of this guidance.

²⁰ The beginning and end samples are taken from dosage units that would normally be included in the batch.

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Criteria to Meet the *Readily Pass* Classification

For each separate batch, compare the weight corrected test results to the following criteria:

- For all individual results (for each batch $n \geq 60$) the RSD ≤ 4.0 percent.
- Each location mean is within 90.0 percent to 110.0 percent of target potency.
- All individual results without weight correction are within the range of 75.0 percent to 125.0 percent of target potency.

If your test results meet these criteria for all batches, they are classified as *readily pass* and you can start routine batch testing using the Standard Criteria Method (SCM) described in section VI. If your test results for any of the batches fail to meet these criteria, you may choose to test additional location samples and include these results to compare to *readily pass* criteria. Alternatively, you may compare the results to the *marginally pass* criteria described below with or without including additional test results.

Criteria to Meet the *Marginally Pass* Classification

If your dosage unit test results fail to meet the criteria for the *readily pass* classification, you should compare the weight-corrected test results to the following criteria:

- For all individual results (for each batch $n \geq 60$) the RSD ≤ 6.0 percent.
- Each location mean is within 90.0 percent to 110.0 percent of target potency.
- All individual results without weight correction are within the range of 75.0 percent to 125.0 percent of target potency.

If your test results meet these criteria, results can be classified as *marginally pass*. If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and if appropriate, repeat the powder mix homogeneity assessment, in-process dosage unit sampling comparison, and initial criteria establishment procedures. The disposition of batches that have failed the *marginally pass* criteria is outside the scope of this guidance.

C. Establish the Relationship Between Stratified In-Process Samples and the Finished Product

In order to use in-process samples to fulfill the compendial uniformity of dosage units requirement for finished products, we recommend the following steps (this does not need repeated, if the comparison was performed during development):

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- 329 • Conduct testing for uniform content of the finished product using an appropriate
330 procedure or as specified in the Abbreviated New Drug Application (ANDA) or the New
331 Drug Application (NDA) for approved products.
- 332 • Compare the results of stratified in-process dosage unit analysis with uniform content of
333 the finished dosage units from the previous step. This analysis should be done without
334 weight correction.²¹
- 335 • Prepare a summary of the data and analysis. If the stratified in-process data provides
336 assurance of uniform content of the finished product, then the in-process data may be
337 routinely used to demonstrate both uniformity of blend and final product content. See
338 section VII of this guidance for reporting requirements.
- 339 • If the in-process samples cannot be used to assure uniformity of dosage units, then the
340 compendial test on the final product will need to be continued in addition to in-process
341 stratified testing for blend uniformity.

D. Sample Locations for Routine Manufacturing

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345 We recommend that you prepare a summary of the data analysis from the powder mix
346 assessment and stratified sample testing. From the data analysis, you should establish the
347 stratified sample locations for routine manufacturing, taking into account significant process
348 events and their effect on in-process dosage unit and finished dosage unit quality attributes. You
349 should identify 10 sampling locations (or more) during capsule filling or tablet compression to
350 represent the entire routine manufacturing batch.

VI. ROUTINE MANUFACTURING BATCH TESTING METHODS

351
352
353 We recommend that you evaluate routine manufacturing batches using in-process stratified
354 samples against the following criteria, after completing the procedures described above to assess
355 the adequacy of the powder mix and uniform content in finished dosage form.

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358 These routine manufacturing batch-testing methods include the Standard Criteria Method (SCM)
359 and the Marginal Criteria Method (MCM). The SCM consists of two stages, each with the same
360 *accept/reject* criteria. The second of the two stages recommends using a larger sample size to
361 meet these criteria. The MCM uses *accept/reject* criteria that are different from the SCM.

362
363
364 If the batch data fail to conform to the SCM criteria, we recommend continued sampling and
365 testing to intensified criteria (MCM). Both verification methods and the procedures for
366 switching from one to the other are detailed below and in the flow chart in Attachment 2.

²¹ Weight correction is a mathematical correction to eliminate the effect of potentially variable dosage unit weight on measurement of mix adequacy—see Glossary.

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A. Standard Criteria Method (SCM)

We recommend using the SCM when any of the following conditions are met:

- Results of establishing initial criteria are classified as *readily pass* and no previous batch failed SCM criteria.
- Previous routine batch was appropriately evaluated using SCM and met SCM criteria.
- Results of testing the previous routine batches using the MCM pass the criteria for switching to the SCM (see section C below).

The SCM should meet the same criteria using a different number of sample test results as described below:

1. Stage 1 Test

To perform the stage 1 test, we recommend that you (1) collect at least 3 dosage units from each sampling location, (2) assay 1 dosage unit from each location, (3) weight correct the results, and (4) compare the results with the following criteria:

- RSD of all individual results ($n \geq 10$) ≤ 5.0 percent.
- Mean of all results is 90.0 percent to 110.0 percent of target assay.

If your results pass these criteria, the adequacy of mix for the batch is adequate and you can use stage 1 of SCM for the next batch. If test results fail stage 1 criteria, you should conduct extended testing to stage 2 acceptance criteria.

2. Stage 2 Test

To perform the stage 2 test, we recommend that you assay and weight correct the remaining two dosage units (from stage 1) for each sampling location. Compute the mean and RSD of data combined from both stage 1 and stage 2. Compare the results with the following criteria:

- For all individual results ($n \geq 30$) the RSD ≤ 5.0 percent.
- Mean of all results is 90.0 percent to 110.0 percent of target assay.

If your results pass these criteria, the adequacy of mix for the batch is adequate and you can use stage 1 of SCM for the next batch. If test results fail the criteria, use the MCM described in the next section.

B. Marginal Criteria Method (MCM)

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413 We recommend using the MCM when any of the following conditions are met:

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415 • Results of initial criteria establishment qualified as *marginally pass*.

416

417 • Previous routine batch was appropriately evaluated using MCM and met MCM criteria.

418

419 • The current routine batch was tested according to SCM and the test results failed both
420 stage 1 and stage 2 criteria.

421

422 • Previous batch was first tested using SCM, but had to switch to MCM to pass.

423

424 To perform the MCM test, we recommend that you (1) have assayed at least 3 dosage units from
425 each sampling location, (2) weight correct the results, and (3) compare the results with the
426 following criteria (note: the weight-corrected results from the stage 2 SCM analysis are
427 compared to this MCM criteria if stage 2 SCM does not pass):

428

429 • For all individual results ($n \geq 30$) the RSD ≤ 6.0 percent.

430

431 • Mean of all results is 90.0 percent to 110.0 percent of target assay.

432

433 We recommend that all results from analysis of any remaining location samples be computed
434 with the stage 2 SCM data. No test results should be removed from the analysis. If the test
435 results pass these criteria, the adequacy of mix for the batch is adequate, and we recommend that
436 you continue to test routine manufacturing batches with MCM criteria. If the test results fail the
437 criteria, you should no longer use the Routine Manufacturing Batch Testing Methods (Section
438 VI) to ensure adequacy of mixing or uniformity of content until you investigate the failure (per
439 21 CFR 211.192). That is, to establish justified assignable cause(s), take necessary corrective
440 actions, and if appropriate, repeat the powder mix assessment, stratified sample comparison, and
441 initial criteria establishment procedures. Or, adopt at, in, or on-line measurement systems to
442 ensure adequate powder mix assessment.

443

C. Switching to Standard Criteria Method from Marginal Criteria Method

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445 It is appropriate to switch to the SCM when the following criterion is met:

446

447 • Five consecutive batches pass the MCM criteria and for each batch the RSD ≤ 5.0 percent

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VII. REPORTING THE USE OF STRATIFIED SAMPLING

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A. Applications Not Yet Approved

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455 This section refers to the scientific data analysis and other information that should be submitted
456 to an NDA or ANDA. Information submitted in the application should include summary reports

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457 and scientific analyses or statements about the method being used. The raw data collected to
458 support using this method should be maintained at the manufacturing site.

459 We recommend that when available²², you provide the following information in the
460 Manufacturing Process and Process Controls section of the application (CTD²³ 3.2.P.3.3).

- 461
- 462 • Method that will be used to demonstrate the adequacy of powder mix.
 - 463 • Summary of data analysis from the powder mix assessment and from stratified sample
464 testing
 - 465 • Summary of the in-process dosage unit stratified sampling data analysis evaluating the
466 distribution of active ingredient in the batch
 - 467 • Summary of the powder mix sampling data analysis demonstrating that it met the
468 minimum criteria for validation and establishing initial criteria
- 469

470 We recommend that you provide the following information in the Drug Product Specification
471 section of the application (CTD 3.2.P.4.1), if applicable:

- 472
- 473 • Statement in the product specification stating that the methods in this guidance are being
474 used to demonstrate finished product uniformity of content or a description of alternative
475 methods used to demonstrate finished product uniformity of content
- 476

477 We also recommend that you provide the following information in the Pharmaceutical
478 Development Information section of the application (CTD 3.2.P.2.2):

- 479
- 480 • Summary of data analysis for comparison of in-process dosage unit stratified sampling
481 with finished product uniformity of content
 - 482
 - 483 • Summary of data analysis for comparison of powder mix uniformity with in-process
484 dosage unit stratified sampling
- 485

B. Postapproval Change

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488 If you plan on changing the existing controls for adequacy of mix and uniformity of content to
489 the methods described in this guidance, the change should be considered a minor change as
490 described in the postapproval changes guidance.²⁴ We recommend you provide a notice of the
491 change in the next annual report along with the information indicated in section A, above. The
492 raw data collected to support changes can be maintained at the manufacturing site.

493

²² Sufficient data may not be available from full-scale batches at the time of the initial submission. If data summaries are not included in the application, they should be included in validation or development documents maintained at the site. Preliminary data at small-scale may be submitted, but the final analyses and comparisons should be performed on data from full-scale batches.

²³ *M4Q: The CTD – Quality*, one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the FDA.

²⁴ FDA's guidance for industry on *Changes to an Approved NDA or ANDA*.

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GLOSSARY

Absolute as used to define the acceptable range (+/- 10%) in which individual blend sample values must fall and which is independent of the value of the mean. *For example, if the mean of all blend samples is 95.0%, the absolute range is 85.0% to 105.0%, (not 95.0% +/- 9.5%).*

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

In-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.

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

Significant event is any operation during solid dosage production process that can affect the integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a blender to a bin or from the bin to a hopper are two examples of significant events in the blending and compression process.

Stratified sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process. Stratified sampling of dosage units specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content; then, random dosage units are selected within these identified locations.

Target assay/Target potency is the intended strength or intended amount of active ingredient in the dosage unit.

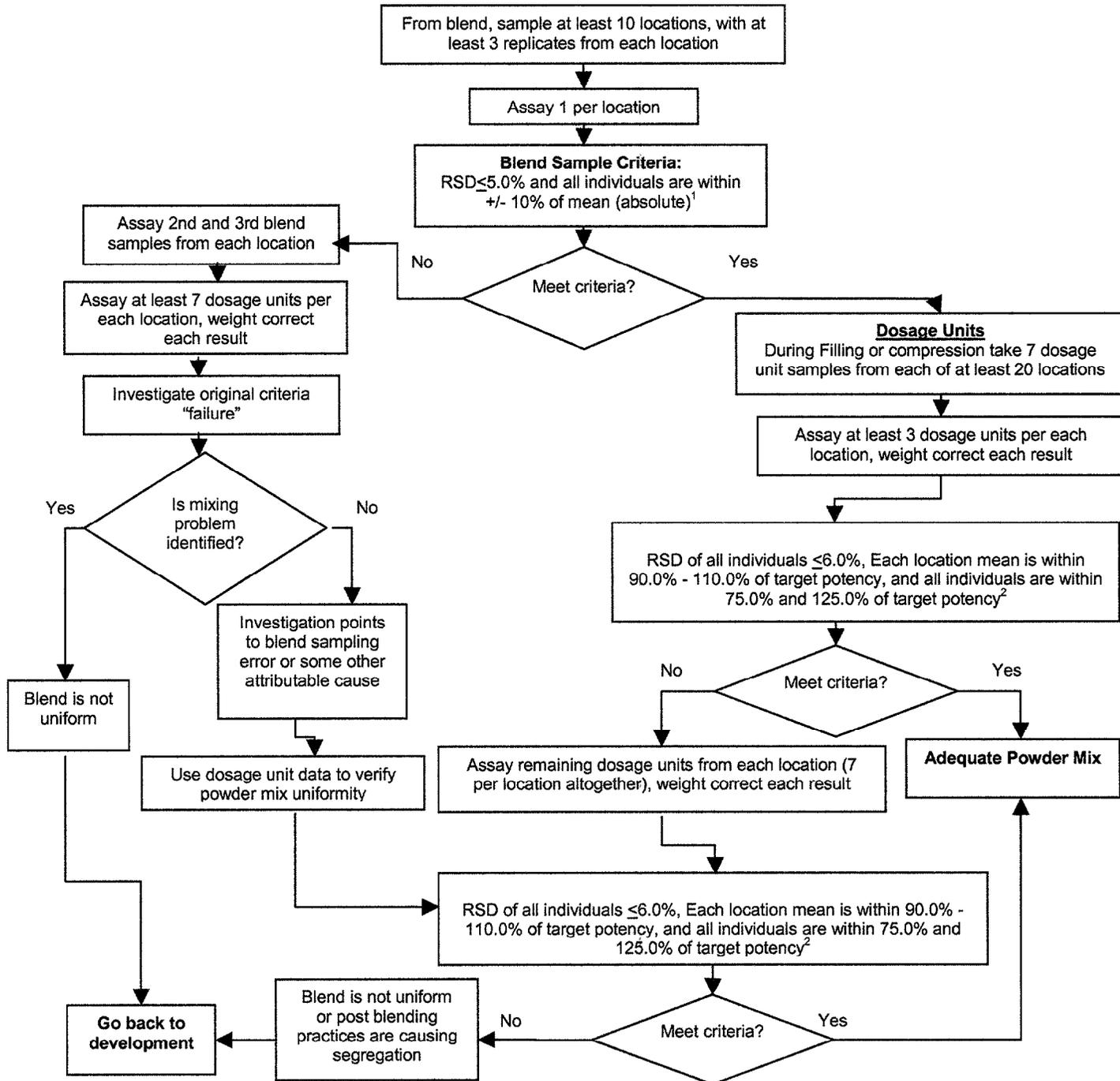
Validation batch is a batch manufactured and tested to verify the proposed routine manufacturing process controls are adequate.

Weight correct is a mathematical correction to eliminate the effect of potentially variable dosage unit weight on measurement of mix adequacy. *For example, a tablet with a strength 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 $0.198 \div 0.20 \times 100 = 99\%$ of target blend assay.*

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ATTACHMENT 1: EVALUATION OF EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY



¹ Examples of "mean +/- 10% (absolute)" are: If the mean potency = 95%, then the interval is 95% +/- 10%; thus, all individuals must fall within 85.0% to 105.0%. If the mean potency = 103.0%, then the interval is 103.0% +/- 10.0%; thus all individuals must fall within 93.0% to 113.0%.

² 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: ROUTINE MANUFACTURING BATCH TESTING

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Before using this chart to demonstrate adequacy of mix and content uniformity during routine manufacture conduct an assessment of the powder mix and compare to stratified sample data and establish initial criteria. Identify at least 10 sampling locations during filling or compression to represent the entire batch. Remove 3 or more dosage units at each sampling location.

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Use SCM routine criteria if:

1. Validation result was *readily pass* and production is just starting
2. Routine test for previous batch was SCM and it passed SCM criteria
3. Routine test for previous batch was MCM, but switching rule is met

Use MCM routine criteria if:

1. Validation result was *marginally pass* and production is just starting
2. Routine test for previous batch was MCM and it passed MCM criteria
3. Routine test for previous batch started as SCM, but had to switch to MCM to pass

