BACKGROUND

A review of the PQRI ‘recommendation’ on which this guidance is based was submitted, on 25 September 2003, to CDER’s Ombudsman, Warren Rumble, (via e-mail: ombudsman@ceder.fda.gov) and, on 30 September 2003, to Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services (via e-mail: hussaina@ceder.fda.gov).

On 15 November 2003, FAME Systems provided comments based on that review and an in-depth reading of the FDA’s "Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [G:\5831dft.doc 10/27/03]."

That review added elements that connect various issues in the Draft provided by the Agency to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which this guidance is required to be congruent.

INTRODUCTION

On further review of the FDA’s Draft and after in-depth discussions with Jon E. Clark, it became obvious that the FDA’s Draft was clearly at odds with the fundamentals of CGMP, the clear strictures of 21 CFR 210 and 21 CFR 211, and many aspects of sound inspection science.

The procedures outlined in the FDA draft:

- Provide neither a scientific basis for nor guidance for any of the specifications it sets.
- Attempt to substitute a non-batch-representative sampling regime, stratified sampling, for the representative sampling requirements as set forth in 21 CFR 210 and 21 CFR 211.
- Ignore the clear statistical quality control requirements set forth in 21 CFR 211.165(d).
- Deliberately and knowingly ignore the recognized national and international (ISO) 95-%-confidence-level consensus standards that are directly applicable to the inspection (sampling and evaluation) of batches or lots of dosage units.

\[\text{ANSI/ASQC Z1.9-1993, SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING, American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989).}\]
Even when the few tested dosage-unit samples meet the specifications in the FDA’s Draft, provide, at best, less than 20-% confidence that the batch or lot is truly acceptable.

Based on the preceding, it would seem that the PQRI, an organization controlled by the pharmaceutical industry, and others apparently have no problem in reaching a consensus that ignores the clear requirements of the CGMP regulations governing drugs and drug products, the recognized applicable statistical inspection standards for discrete materials, and sound science.

To address the obvious scientific and regulatory deficiencies as well as others in the Draft published by the FDA, Facility Automation Engineering (FAME) Systems has rewritten that Draft and offers the “Revised Draft Guidance” that follows to the Agency as a CGMP-compliant scientifically sound alternative that, when followed, provides a confidence level of 95-% or higher that the uniformity of the content of the dosage units in each batch or lot tested will be acceptable when the requisite batch- or lot-representative samples are inspected (sampled and evaluated) for content and found to meet the specifications established in compliance with the guidance provided.

Further, since the uniformity of the dosage units in a batch with respect to ingredients other than the active ingredient or ingredients (e.g., release control ingredients) is often critical to the safety and efficacy of the dosage units, the revised guidance does not, as the original draft seems to blatantly do, falsely assert that batch dosage-unit content uniformity is equivalent to batch uniformity.

The revised draft that follows provides detailed guidance with respect to establishing the uniformity of the content of each batch.

In doing so, it also defines the controls for dosage unit weight (21 CFR 211.110(a)(1) “Tablet or capsule weight variation”) and provides general approaches that can be used to establish the uniformity of each batch with respect to the other “critical characteristics of in-process material and the drug product” (21 CFR 211.110(a)) including the explicit example in 21 CFR 211.110(a)(4), “Dissolution time and rate” that, based on the available drug-products’ recalls data, is a significant batch uniformity problem.

Should anyone who reads this “Revised Draft Guidance” find that its guidance is at odds with sound inspection science or the applicable CGMP regulations, or that additional clarification is needed in a given area, then, in addition to providing the sound science or rationale that refutes the guidance provided, or his or her clarifying comments to the public docket, he or she is asked to e-mail drking@dr-king.com a copy of that sound science, rationale, or commentary.

Respectfully,

Dr. King
Guidance for Industry

Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity

REVISITED 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.

For questions regarding this draft document contact Jon E. Clark, 301-594-5613 or Mike Gavini, 301-827-9053.

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

January 2004
Pharmaceutical CGMP
Guidance for Industry

Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity

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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)

January 2004
Pharmaceutical CGMP
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Guidance for Industry

Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity

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 content uniformity of in-process powder blends, and in-process and finished dosage units. This guidance describes scientifically sound and appropriate statistics-based (21 CFR 211.110(b)) procedures for assessing powder mix adequacy for the active content, comparing in-process dosage unit content test results with powder mix content test results, and establishing the initial criteria for the content control procedures used in routine manufacturing. This “content uniformity assessment” guidance applies only to drug products that are:

- Single-“uniform”-layer tablets that are uncoated or coated with non-active films and/or sugar in a manner that does not significantly erode the tablet core, or
- Uncoated capsules that are filled with a uniform mixture of solids.

However, the applicable principles and approaches developed may be used for other solid and semi-solid dosage forms in many instances.

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. Similarly, the use of the word may indicates an optional course or action and the use of the words must or shall indicates an action mandated by specific regulatory or statutory requirements.

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 content uniformity of powder blends and finished dosage units in the absence of new technology development or implementation.
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 underlying this guidance after extensive discussion. A brief history of the evolution of this guidance is provided in the following paragraphs.

In response to industry concerns regarding the regulations for demonstrating the adequacy of in-process powder mixing, the FDA published a draft guidance for industry on blend uniformity analysis in August 1999. Comments submitted to the docket resulted in the formation of the Blend Uniformity Working Group (BUWG) by the Product Quality Research Institute (PQRI). The PQRI BUWG conducted a meeting open to the public, PQRI Workshop on Blend Uniformity, on September 7 and 8, 2000.

Using the consensus reached by participants in this workshop, the BUWG developed a draft recommendation, The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends. The draft recommendation received examination and peer review in multiple scientific and public venues. In addition, the Advisory Committee for Pharmaceutical Science (ACPS) reviewed the draft recommendation and received comment during scheduled meetings of the committee. The draft recommendation was revised to incorporate the results of peer review and comment and was presented to CDER's Center Director in final form on December 30, 2002. The recommendation was subsequently published in the PDA Journal of Pharmaceutical Science and Technology.

This draft guidance reflects CDER's effort to incorporate the draft recommendation into regulatory policy in a manner that complies with the applicable clear requirement minimums (21 CFR 211.1(a)) set forth in 21 CFR Part 211. This approach was used because, as the United States Supreme Court ruled in 1988, the United States Food and Drug Administration cannot legally publish any guidance that contradicts any clear regulation.

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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).


III. SCOPE

Stratified sampling is the process of sampling dosage units at predefined intervals and collecting representative samples from specifically targeted locations in the compression/filling operation that have the greatest potential to yield extreme highs and lows in test results. In the PQRI’s recommendations, these test results are used to monitor the manufacturing process output that the PQRI claims is most responsible for causing finished product variability. The PQRI then recommends that the content test results can be used to develop a single control procedure to ensure adequate powder mix uniformity and uniform content in finished products.

Unfortunately, though recommended by the PQRI, this approach does not meet the clear current good manufacturing practice (CGMP) minimum requirement that all in-process sample sets must be representative (as that term representative is defined in 21 CFR 210.3(b)(21)) of the batch or lot from which they were taken (21 211.160(b)(2)) nor does it comply with the “appropriate statistical quality assurance criteria” requirement set forth in 21 CFR 211.165(d). Thus, this guidance must, of necessity, provide a different approach that should, if properly implemented, comply with the aforesaid CGMP requirements. Where they comply with CGMP regulations, the ideas and concepts proposed by the PQRI have been appropriately incorporated into this guidance.

The methods described in this guidance are not intended to be the only methods for meeting Agency requirements to demonstrate the “batch uniformity and integrity of drug products” (21 CFR 211.110(a)) using statistics-based inspection (21 CFR 211.110(b)) to appropriately establish a multi-tiered sampling plan that can minimize the level of inspection required to satisfy the in-process minimums of 21 CFR 211.110. In most cases, traditional powder blend sampling and testing, in conjunction with CGMP-compliant testing for uniformity of content in the finished product, can be used to comply with current good manufacturing practice requirements (CGMPs). Use of at-, in-, or on-line measurement systems may, in some cases, also be appropriate and are described in other guidance documents.

This guidance provides scientifically sound CGMP-compliant recommendations on how to:

- Conduct batch- or lot- representative powder blend sampling and analyses.
- Establish initial criteria for dynamic sampling of in-process dosage units and evaluation of test results.
- Analyze the dynamically acquired samples and evaluate data.

7 21 CFR 210.3(b)(21) “Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.”

8 21 CFR 211.110(b) “Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures . . .”

9 In August 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.

10 The in-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.
The methods described in this guidance can be used to monitor active ingredient homogeneity (“Content Uniformity”) of powder blends and ensure uniform content for each batch or lot of the finished product for solid oral drug products. These methods are only one way to satisfy the CGMP and application review requirements for in-process testing to demonstrate each batch’s or lot’s in-process blend and product content uniformity for the finished product with respect to active content. The methods presume appropriate monitoring and control of all components, materials, and manufacturing steps as required by the drug CGMP regulations and, where they exceed the CGMP minimums, the firm’s application commitments.

However, this guidance does not discuss the firm’s assessment of the potency, other critical variable factors that can affect the acceptability of each batch or lot of finished dosage units, or the assessment of the homogeneity of inactive ingredients that can adversely affect the acceptability of the batch or lot. Formulations with extremely low dose and/or high potency may call for more rigorous sampling than that described in this guidance to assess the uniformity of powder blends or the uniformity of content of the finished dosage units. When using the methods described in this guidance as a Periodic Quality Indicator Test (PQIT), described in a recent drug product draft guidance\(^1\), for approved products for which other procedures have been accepted, certain data or trends may be observed. We recommend that manufacturers scientifically evaluate these types of data to determine if they affect the quality of each batch of a drug product and, if so, how.

Except where the data triggers an investigation that determines the batch contains valid out of specification (OOS) values that fail to meet: a) the USP’s post-release lifetime criteria or b) predicts that the batch or lot contains such units, the FDA does not intend to inspect such data collected on an existing product for the purpose of evaluating the suitability of proposed methods. Any other FDA decision to such research data would be based on exceptional situations like those outlined in Compliance Policy Guide Sec. 130.300.\(^2\) However, all such data acquired in support of, or bearing on, validation or the validity of any regulatory submissions will be subject to inspection in the usual manner.

\(^1\) In January 2003, the Agency issued “Draft Guidance for Industry—Drug Product Chemistry, Manufacturing, and Controls Information.” Once finalized, it will represent the Agency’s perspective on the use of PQIT in the monitoring of a process.

\(^2\) FDA/ORA Compliance Policy Guide, Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG7151.02)
IV. ESTABLISHING VALID CONTENT SPECIFICATIONS

Since the methods proposed in this guidance are intended for new or improved products that “build in” quality, the first thing that a manufacturer needs to establish it its target specifications. To simplify the discussion, the example drug product is a 250 mg tablet containing 0.2 mg of a single stable active ingredient (“0.08 %” wt./wt.). To further simplify the definition process, the drug product is targeted to contain, on average, 100.5 % of its labeled content (21 CFR 211.101(a)). Though the USP allows for a few (“1 in 30”) tablets with contents outside of 85 % to 115 % of the label claim, the USP’s expectations is that all should be inside of the range from 85 % to 115 % of the label claim. Since firms want to test the minimum number of tablets that they can and still comply with CGMP, the specification expectation limits must be appropriately inside of the range from “85 % to 115 %.” Though there are practical limits to how narrow the range can be, firms that truly “build quality into” their products will set these limits as close to the target as the process (process steps, equipment and controls) permits. When the firm uses a “statistical quality control” approach, today’s CGMP should be a “Six Sigma” approach to content uniformity. When a firm adopts a “Six Sigma” approach, then that firm should set a maximum RSD of (115 – 85)/12 or 2.5 % RSD for the finished tablets. If the firm corrects for a target of 100.5 % and presumes a symmetrical distribution about the target, the maximum RSD is reduced to about 2.4 %.

Based on the preceding, for the simple tablet example outlined, the limiting relative variance for the content in the tablets (RSD^2_Tablet) should be about 5.76 %. Accepting the preceding variance as the upper limit allowed, the firm can use that variance value and the other relevant relative variances in the process to estimate the formulation goal for the “final blend.” Using the variance equation:

\[ \text{RSD}^2_{\text{Tablet}} = \text{RSD}^2_{\text{Tablet Weight}} + \text{RSD}^2_{\text{Tableting}} + \text{RSD}^2_{\text{Final Blend}} + \text{RSD}^2_{\text{Error}} \]  

(1)

the firm can use the variance values it establishes for Tablet Weight, Tableting, and Error to solve for RSD^2_FinalBlend. In general, a firm can validly set RSD^2_Error to between 0.25 %^2 and 2.25 %^2 depending upon whether the sampling and testing is performed under ISO 17025 standards or not. For this example, the firm will be presumed to know that, on average, its RSD^2_Error is not more than 1 %. Substituting these estimates of RSD^2_Tablet and RSD^2_Error into Equation 1, the firm should find that:

\[ \text{RSD}^2_{\text{Tablet Weight}} + \text{RSD}^2_{\text{Tableting}} + \text{RSD}^2_{\text{Final Blend}} \approx 4.76 \%^2 \]  

(2)

Wishing to build quality into its product, the firm selects an automated tableting press that is capable of forming “250 mg” tablet cores within a nominal weight range of 4 mg (target ± 2 mg) that weighs all tablets with a scale having a maximum weighing uncertainty of 0.2 mg and rejects any tablet that is more than 2.3 mg from the target. Based on this selection, RSD^2_Tablet Weight is not more than 1 %. Inserting that value into Equation 2, the firm should find that:

\[ \text{RSD}^2_{\text{Tableting}} + \text{RSD}^2_{\text{Final Blend}} \approx 3.76 \%^2 \]  

(3)

When the firm has a formulation program that only develops formulations that are mechanically stable on storage and in the tableting operation, then, the firm can validly set RSD^2_Tableting to be much less than RSD^2_Final Blend (RSD^2_Tableting ≪ RSD^2_Final Blend), for example, 0.16 %^2 (for an RSD Tableting of “0.4 %”), and, solving Equation 3, find that:
\[ RSD_{\text{Final Blend}}^2 \approx 3.6 \%^2 \] (4)

or

\[ RSD_{\text{Final Blend}} \approx 1.9 \% \] (5)

Since, for most firms, the variability contribution in storage and tableting is closer to or exceeds “1 %” than the “0.4 %” value used for Equation 4, most firms (using an automated tablet press like the one in the example) should set \( RSD_{\text{Final Blend}} \) at between “1 %” and “1.7 %.” [Note: Practically, even with careful granulation, it is difficult to manufacture final blends with an RSD of less than about 0.9 % (n = 200). Based on the preceding, most firms should set their practical \( RSD_{\text{Final Blend}} \) limit to not more than 1.5 %.] Reviewing the properties of normal distributions of non-discrete materials with respect to the testing of a small number of samples from a given batch or lot, the firm should note that the most probable range of values should be within ± 3 RSD of the target. Based on that approximation, the firm’s final blend’s expectation range should be not more than about ± 5.7 % (1.9 % times 3) or, for the example tablet’s target of 100.5 % of label claim, 94.8 % to 106.2 % of label claim. Similarly, the tablets’ relative content expectation range should be 100.5 % ± 7.2 % of label claim or 93.3 % to 107.7 % of label claim.

Because experience has shown that the distribution of dosage-unit content values is approximately Gaussian (normal), the firm, not wishing to develop a first-principles approach to the statistical treatment of its testing results, decides that, for statistics-based in-process and release inspection of the dosage units, it will use the recognized 95%-confidence-level consensus standard for inspection by variables for percent nonconforming \(^{13}\). Given it has set its expectations range at the 3 RSD level (approximately 99.72 % of the population), the firm appropriately selects a 0.4 % level as the limit for the allowable percentage of non-conforming units (units outside of the established specification for tablet samples) in recognition of the possible level of “sample set” variability inherent in the set chosen. However, recognizing the lifetime post-release limits imposed by the USP on any article in the batch, the firm should set two auxiliary acceptance criteria for the batch. Those criteria are:

- No valid “unit dose” result or dosage unit value can be outside of the range from 75 % to 125 % of the label claim, and

- For the dosage units tested, not more than 1.6 % of the samples tested can be outside of 85 % to 115 % of the label claim (for a safety factor of 2+ over USP’s “3.33 %” for any article).

Thus, based on the example and the requirements of CGMP, the blend and tablet specifications can be set for the example presented (e.g., as shown in Table 1 on the next page). Having established CGMP-compliant specifications for content, the firm now needs to establish an appropriate CGMP-compliant statistics-based sampling plan for both the “Final Blend” and the dosage form (tablet cores and finished tablets in the example presented).

Though ANSI/ASQC Z 1.9-993 establishes the numbers required for the testing of units, it does not establish the number of units that should be sampled at any stage. Moreover, there are no similar consensus standards that are directly applicable to non-discrete materials such as the final blend.

\(^{13}\) ANSI/ASQC Z1.9-1993, SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING, American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989).
Therefore, the next section provides an example that may be used as the basis for the sampling and testing of the “Final Blend,” and the in-process and finished dosage units.

V. ESTABLISHING APPROPRIATE SAMPLING AND SAMPLE EVALUATION PLANS

A. GENERAL CONSIDERATIONS

For the purposes of this discussion, the “Final Blend” being sampled will be considered to have been developed in a formulation program that had, as its primary goal, developing the formulation to the point that:

- The content for the active in the wall layer is, on average, less than 2% different from the average content in the bulk blend (e.g., 1.4% to 1.6%; n = 6) in developmental studies at one-fifth or larger of the planned production scale.
- The “Final Blend” flow index, as measured by bulk density divided by tapped density for three samples from each development blend, is not less 0.75 (e.g., 0.78 to 0.81; n=3) in developmental studies at not less than (NLT) one-fifth planned scale.
- The worst-case uniformity (for the magnesium stearate added to the formulation as a tableting lubricant) has a reproducible RSD that is less than 6% RSD (e.g., 4.2% to 5.7%; n = 4) on developmental studies at NLT one-fifth planned scale.

Table 1 – Content Specifications For Final Blend and Tablets

<table>
<thead>
<tr>
<th>Specification Stage</th>
<th>Expressed In Terms Of The Percentage Of Label Claim</th>
<th>Mean^1</th>
<th>RSD Limit</th>
<th>Expectation Range (3 RSD)</th>
<th>AQL^2</th>
<th>No Value Can Be Outside Of</th>
<th>NMT^2 1.6 % Outside Of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Blend</td>
<td></td>
<td>NLT^3 100</td>
<td>1.5</td>
<td>96.0 – 105.</td>
<td>N/A</td>
<td>75 - 125</td>
<td>N/A</td>
</tr>
<tr>
<td>Tablet Core</td>
<td></td>
<td>NLT 100</td>
<td>2.4</td>
<td>93.0 – 108.</td>
<td>0.4</td>
<td>75 - 125</td>
<td>85 - 115</td>
</tr>
<tr>
<td>Specific Tablet Core</td>
<td></td>
<td>NLT 100</td>
<td>1.9</td>
<td>94.8 – 106.2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Finished Tablet</td>
<td></td>
<td>NLT 100</td>
<td>2.4</td>
<td>93.0 – 108.</td>
<td>0.4</td>
<td>75 - 125</td>
<td>85 - 115</td>
</tr>
</tbody>
</table>

1 Required to meet the intent of 21 CFR 211.101(a), “The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.”
2 See ANSI/ASQC Z1.9 for an explanation of the term “AQL” and how to use it and the sample values measured in an appropriately sized representative sample to assess the acceptability of the batch or lot from which the samples tested were selected.
3 “NMT” is an abbreviation for “not more than.”
4 “NLT” is an abbreviation for “not less than.”
5 Specific tablet core values are computed by multiplying each content result by the tablet target weight divided by the observed weight for the unit tested.
Post-blend 30-day low-frequency vibration studies on the intermediate containers of the blend shows:

- Segregation in the average level of the active between the top and bottom of the container that is less than 2\% (justifying a 15-day [2-week] hold time)

- The post-study flow index was not less than 0.7 (e.g., 0.72 to 0.75; n = 3).

The other goals are to control the particle size distribution and flow of the components blended such that all intermediate blends and the final blend met their specifications and the one-fifth scale final blends are not less than 5\% inside of the limits established for the planned full scale batches.

Because of the level of active (<0.1 \% wt./wt.), the active ingredient is dry granulated onto a suitable carrier component with the goal of producing mixed/slugged/milled/mixed granulation blends having an average Assay of not less than 101\% of the target level to compensate for a known small loss (typically, not more than 0.5\%) in the subsequent handling, mixing, and transfer operations.

Having established an approach for setting CGMP-compliant specifications and with the preceding approach to developing the drug product formulation in mind, let us next carefully consider the general scientific realities associated with the sampling of non-discrete materials that are mixtures of solids of differing densities, size distributions, affinities, particle shapes and shape distributions, and particle surface and permeability properties. For an in-depth discussion of the development of a robust blend, the firm should consult applicable scientific literature (e.g., Lee Dudley’s recent article, “Unlock Better Blending”\(^{14}\) and the references cited therein).

1. Scientifically Sound And Appropriate Sampling Volume (Or Weight) For Non-Discrete Materials

   In complex mixtures of the type discussed, the size (amount) of the sample sampled must be large enough that the bias in the sampling procedure used is negligible. In addition, although this guidance only addresses the assessment of the uniformity of the blend with respect to the content of the active, the final blend should also be evaluated for the uniformity of any release enhancers or retardants added (or their surrogates) to ensure that the release of the active meets the criteria established for it. Finally, in some cases, the firm may need to evaluate the uniformity of the lubricant added (or a surrogate thereof). Each sample should be large enough to permit the withdrawal of at least three (3) unbiased subsamples (aliquots) for each chemical test (such as, content, of the active or actives, level of the release-control components, level for impurity or impurities, level of flow agent) for components that may affect the uniformity of the drug product, as well as, when physical testing is required, at least one unbiased aliquot for each physical test that must be performed. In general, the preceding are the baseline requirements for scientifically sound and appropriate sampling of unbiased samples from a batch or lot of a non-discrete material. [Note: In general, for a 250-mg tablet, blend samples in studies where no physical properties are to be assessed should be on

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the order of 4 g when a 5-mL sample vial is used. When physical properties are to be assessed, 15-g samples should be sampled into appropriate 20-mL containers or 20-g samples should be sampled into appropriate 25-mL containers to ensure that the sample containers are completely filled. In all cases, the vials should be pre-cleaned wide-mouthed vials or bottles that are pre-labeled and stored/contained in an appropriate rack that holds them upright.

2. Establishing The Scientifically Sound And Appropriate “Sampling Size” Requirements For Non-Discrete Materials

The lower limits on multiple-dose sample’s size (weight or volume) should be established during product development by comparing the results found for unit-dose samples with the results found for unit-dose aliquots from larger multiple-dose samples taken and handled in a manner that neither additionally mixes nor promotes post-sampling segregation. In general, the closer the results for the mean of the unit-dose samples are to: a) the formulation’s targeted mean content level and b) the mean of the results from the unit-dose aliquots from the multiple-dose samples, the more uniform the formulation is and/or the less concerns one should have about sampling tool (typically, stainless steel) and container (typically, borosilicate glass) surface-interaction effects.

3. Scientifically Sound and Appropriate Test Aliquot Volume (or Weight) For Non-Discrete Materials

Trained analysts can easily remove minimally biased singlet aliquots that are within 5% of the weight of the targeted unit-dose aliquot for aliquots down to 50 mg (and within 10% down to 10 mg to 15 mg [a level smaller than most tablets]). Since the goal must be to determine the uniformity at the dosage-unit level, all test aliquots should be taken at a unit-dose or, if justified by the uniformity of the blend, a fraction of the dosage-unit weight. [Note: In general, aliquoting at less than unit-dose weight should be limited to cases where the active content is NLT 10 % of the weight of the dose.]

4. Representative Sampling Requirements For Non-Discrete Materials

Unlike the sampling of discrete materials, the representative sampling of non-discrete in-process materials, as required by 21 CFR 211.160(b)(2), can be accomplished with fewer samples. However, the sampling plan used must still “span” the batch and take the samples in a manner that one sampling does not significantly bias the next sampling. In addition, sampling plan must include an appropriate sample for each interface region in the mixer (e.g., the mixer wall/blend boundary layer, the air/blend interface layer, and, when sampled from plastic-bag-lined storage containers, the bag/blend interface layer). In general, at least duplicate aliquots should be evaluated from each location sampled.

Using the PQRI’s recommendations concerning the identification of regions of poor blending and the CGMP’s requirements for batch- or lot-representative sampling, the manufacturer should initially choose a sampling pattern, based on developmental studies and at least one confirmatory batch manufactured in the intended type of blender at one-fifth planned production scale or larger, that:
Includes more than fifteen (15) sampling locations in the blender with half the sampling locations chosen from the areas where the developmental data found the least homogeneous material (including the blender wall, around the agitator shaft [if any] and in the discharge valve) and the other half in locations where the developmental data found the most homogeneous material – to ensure a batch- or lot-representative sampling.

In tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from not less than two depths along the axis of the blender (the number of levels should increase as the size of the mixer increases); based on the PQRI’s recommendation for choosing at least 10 locations where the least uniform blend is expected to be found, the PQRI initially recommends choosing at least 20 locations to adequately assess the blend homogeneity in such tumbling blenders.

In convective blenders (such as ribbon blenders, screw blenders, plow and paddle mixers, and air jet mixers), a special effort should be made to implement uniform volumetric sampling that, in addition to the general wall and agitator regions, include the corners, the two end “shaft pass through” areas, and discharge area (by analogy, the PQRI initially recommends choosing at least 40 locations to adequately assess the blend homogeneity in convective blenders).

When the data from such in-depth studies clearly demonstrate that the final blend is acceptably uniform with respect to all of its critical variables, the manufacturer should choose that subset of batch- or lot-spanning locations which most consistently provides the same range of uniformity values as the full set. In cases where there are multiple equally representative subsets that could be used, the manufacturer should choose that subset that has the least risk of “between sampling location” biasing.

Having discussed the general considerations for the sampling of non-discrete materials, let us discuss some general sampling plans.

**B. INSPECTION PLANS FOR A FINAL BLEND IN THE MIXER**

For the purposes of this discussion, the blender is a tumble mixer from a vendor that makes blenders that permit the “blend container” to be separated from the mixer drive and agitator.

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15 In general, this approach should be limited to blenders having a nameplate volume not larger than about 30 ft.\(^3\) (0.028 m\(^3\)).

16 The use of sampling from the blender is an approach that should mostly be used in a process development environment where the true final blend uniformity after blending needs to be assessed along with the uniformity of the blend after transfer into an intermediate storage container. This information is needed to measure “blend” resistance to resegregation after the mixing stops. Coupled with the “post-dosage-forming” uniformity information provided by the formed dosage units, this information is valuable in determining that a given formulation is, or is not, adequately resistant to post-mixing “demixing.” At the production scale, where the mechanical stability of the formulation should have been established before transferring the blend from the developmental stage to the pre-production study stage, the more appropriate sampling point for the “Final Blend” is, in general, shortly before the batch is scheduled to be converted into the dosage form. Thus, even when “sampling from the blender” can validly be accomplished, the better sampling point is from the intermediate sampling containers before dosage-unit forming.
With the preceding as the basis for discussing sampling from the blender, let us proceed to discuss plans for Sampling and Evaluation of a blend in the mixer.

1. **Sampling Plans**

With the preceding as the basis for discussing sampling from the blender, this guidance leaves it up to each firm to establish the appropriate sampling locations in a manner that produces a *representative* sample. Based on the PQRI’s input, the industry recommends initially choosing not less than twenty sampling locations when sampling at production scale (implicitly this number is the number recommended for initial “validation” studies where the performance of the blending process is first being assessed at full scale).

To minimize the risk of sampling bias, the sampling locations at each level should be appropriately offset from the sampling locations at the next level. In general, the samplings should proceed by level from the topmost level to the bottommost level with randomized sampling for the samples taken at each level. To minimize “top biasing,” the sampler probes should be inserted slowly. For example, if a three-level, eight-samples-per-level sampling pattern is selected, then the general setup should offset each level’s sampling locations by one-third of the distance between the locations at the top level. As the blend is being sampled, each sample should be transferred into a properly labeled clean sample container that it fills and that container sealed with an appropriate compression-screw cap. When all of the samples have been collected, the sample set should be transferred to the appropriate testing facility for evaluation.

2. **Evaluation Plans**

In general, the firm should adopt a *scientifically sound* hierarchical sample-evaluation plan that initially tests multiple aliquots of all samples and, as the history of the results found dictates, reduces or increases the number of sampled samples tested and the number that are tested in duplicate to estimate the within-sample variability. Initially, *for not less than three (3) consecutive batches (or lots)*, not less than two (2) approximately unit dose aliquots should be taken and tested for active content from each sample sampled. This should be done to establish sound estimates of both the within-sample uniformity and the between-location uniformity of the final blend.

Based on the results found, the nature of the blend should be assessed. From that

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17 The use of such blenders not only facilitates the use of the “sampling from the blender” approach but also can increase production throughput. This is the case because one blend can be mixed while the one being sampled is being sampled, the one previously sampled is being transferred into intermediate containers, and another “mix container” is being loaded for mixing (allowing these operations to proceed in parallel).

18 The test procedures used for evaluating uniformity should be chosen from those analytical evaluation techniques that have inherently high precision and provide integral sample-response averaging (e.g., direct spectrophotometric procedures). Thus, each firm should take this into consideration during the development of the formulation and, to the extent possible, develop a formulation where a pre-separation (e.g., extraction or HPLC) is not required before the test can reliably respond to the level of the active or actives in the formulation. For multiple actives, a firm may be able to use rapid-scan UV/Vis systems equipped with suitable response deconvolution software here.
initial assessment, the number of samples for which duplicates are required should, if indicated, be reduced. Provided the results found are within the limits established for a given final blend and the “within” RSD is consistently less than the “between” RSD, the replicates can be appropriately reduced as long as at least two batch-spanning samples are tested in duplicate. As the production of final blends continues, the history observed should permit the firm to similarly adjust the number of sample locations that should be evaluated. The more uniform the history, the fewer locations that should need to be evaluated. However, the minimum number selected in such decisions should be not less than three (3) samples chosen in a way that they “span” the batch. In addition, the minimum number of samples from which duplicate aliquots should be taken and evaluated should not be less than two (2) batch-spanning samples. Thus, the sample evaluation plans hierarchical structure should range from not less than twenty (20) batch spanning (representative) samples evaluated in duplicate (not less than 40 evaluations) to not less than three (3) batch-spanning samples with duplicate evaluation for the most far apart samples.

In summary, to address all contingencies, all samples should be sampled and an appropriate justified history-based hierarchical sample-evaluation plan should be used to adjust the number of the sampled samples that should be tested initially. The hierarchical sample-evaluation plan should also provide for increased evaluation whenever an apparent nonconformity (valid OOS) is encountered or the test values observed are significantly outside of the historical norms seen for the final blend.

C. INSPECTION PLANS FOR A FINAL BLEND CONTAINED IN “N” INTERMEDIATE STORAGE CONTAINERS

1. Sampling Plans

For blends stored in separately “bagged” 10-kg or smaller identified portions contained in a larger container, sample one appropriately sized multiple-dose sample from each bag into an appropriately labeled and identified sample container. For blends stored in “n,” 25-kg to 35-kg containers, sample one appropriately sized multiple dose sample from the top and the bottom of each container (“2n” samples). For blends stored in “n,” 50-kg to 60-kg containers, sample the appropriately sized multiple-dose sample from the top, middle, and bottom of each container (“3n” samples). In all cases, all sample containers should be sampled at all locations to ensure that all samples needed for any contingency are available without having to resample the containers.

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19 This is the sampling plan that should be used when the blender is larger than 30 ft.³ (0.028 m³) or the developmental studies have established that the final formulation is mechanically stable and the manufacturer plans to store the final blend in an identified (numbered) series of labeled intermediate storage containers (commonly, plastic-bag lined 50-kg or 25-kg drums).

20 These general sampling plans are based on the requirements stated for components in 21 CFR 211.84(c)(4), “If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing” that were developed in the 1970’s with the 50-kg container in mind as the most common container size for such materials. The plans in this guidance appropriately reduce the number of levels as the size of the smallest containment unit decreases.
2. Evaluation Plans

Again, the firm should adopt a scientifically sound hierarchical sample-evaluation plan that initially tests multiple aliquots of all the sampled samples and, as the history of the results found dictates, reduces or increases the number of sampled samples tested and the number that are tested in duplicate to estimate the within-sample variability. Initially, for not less than three (3) consecutive batches (or lots), not less than two (2) approximately unit dose aliquots should be taken and tested for active content from each sample sampled. This should be done to establish sound estimates for both the within-sample uniformity and the between-location uniformity of the final blend.

Based on the results found, the nature of the blend should be assessed and, based on the initial assessment, the number of samples for which duplicates are required should, if indicated, be reduced or increased. Provided the results found are within the limits established for a given final blend and the “within” RSD is consistently less than the “between” RSD, the replicates can be appropriately reduced as long as sample in the bottom of the first, “middle” and last containers are tested in duplicate. As the production of final blends continues, the history observed should permit the number of sample locations that must be evaluated to be similarly adjusted. The more uniform the history, the fewer locations that should need to be evaluated. However, the minimum number selected in such decisions should be not less than the three (3) “batch or lot-spanning” samples previously identified. Minimally, duplicate aliquots should be taken and evaluated for the limiting three (3) batch-spanning samples discussed previously. Thus, the sample evaluation plan’s hierarchical structure should range from not less than “n,” “2n” or “3n” batch spanning (representative) samples evaluated in duplicate (not less than “2n,” “4n,” or “6n” evaluations) to not less than the three (3) identified batch-spanning samples with duplicate evaluation on each (or six (6) evaluations).

In summary, to address all contingencies, all samples should be sampled and an appropriate justified history-based hierarchical sample-evaluation plan should be used to adjust the number of the sampled samples evaluated initially. The firm’s hierarchical sample-evaluation plan should also provide for increased evaluation whenever an apparent non-conformity (valid OOS) is encountered or the test values observed are significantly outside of the historical norms seen for those “locations” in the containers in which the final blend is stored.

D. INSPECTION PLAN FOR IN-PROCESS TABLET CORES AND FILLED CAPSULES

1. Sampling Plans

For the in-process inspection of a batch or lot, most manufacturers want to dynamically assess the quality of the batch or lot as it is being produced whenever the operation lends itself to such sampling. This is especially true when the process step requires several hours to complete. In general, tablet core formation and capsule filling are process steps that require hours to complete. Thus, this guidance presumes that the manufacturers generally dynamically sample the dosage units as they are being
produced. Beyond the usual strictures for a representative sample, dynamic sampling imposes a requirement that each sample taken must be representative of the process at the time of that sampling. Because tablet presses and encapsulation systems are a collection of a significant number of individual dosage-forming stations, each sampling should contain some integer multiple of the number of dosage-unit-forming stations. Since, as the discussion will show, a firm needs a sample of not less than 1600 to 3200 units for its inspections (attribute [done on the firm’s own quality initiative] and variable [required by regulation]), each sampling point should collect “1600 divided by the number of sampling points,” or more, representative dosage units subject to the constraints that the total number of units collected at each point:

- Must be an integer multiple of the number for forming stations in the equipment,
- Should be not less than the next larger integer of “1600/number Sampling Points” dosage units.

In general, the firm should collect each sampling point’s sample in a separate appropriately labeled container (in most cases, a resealable plastic bag may be used and, after sampling, the sampled set of samplings accumulated in an appropriately sized container21). Since most firms perform attribute assessment22 using Military Standard 105E or, more properly, its official replacement ANSI/ASQC Z1.4, and those evaluations are non-destructive, the sample collected for a firm’s attribute quality inspections can, when it passes, be used as the sample for the required variable assessment studies23. This is the case because the number of units required for such assessments is on the order of 800 to 1250 units for production-scale batches of tablets and capsules. Moreover, since many firms do double sampling attribute inspection, this sample should contain from 1600 to 2500 or more units. Thus, the number sampled for dosage-unit attribute inspection should, if preserved, be more than sufficient for content uniformity assessments as well as for all the other appropriate

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21 When the samples from each sampling point are segregated, then, when physical problems are found during attribute inspection, the time sequence of the problem sample set or sets can be identified when the problem does not pervade the batch.

22 The current consensus standard, ANSI/ASQC-Z1.4, spells out a set of attribute sampling and evaluation procedures that provide 95%-confidence level assessment of a batch- or lot representative sample of tablet cores for attributes like chipping, capping, cracking, surface pitting, incorrect punching, and broken, or, for capsules, cracked shell, improper closure, incorrect capsule, and shell defects. Simplistically, the manufacturer assigns an allowable projected percentage level for defective dosage units for each attribute and accepts batches when all attributes are found to have defect levels that are less than the allowable number for each attribute assessed.

23 This strategy ensures that the sample submitted for variables assessment is from the physically acceptable batch. In cases where the batch fails the physical properties, at best, the batch of tablet cores is appropriately screened and, after this screening and an appropriate revised in-process sample is generated that represents the screened batch. When this sample passes attribute inspection, the revised batch- or lot-representative core or capsule sample is then submitted for the requisite variables testing under ANSI/ASQC Z1.9. In the worst case, the batch is rejected for failing its physical attributes inspection. When this approach is used, the risk of non-productive sample evaluation is minimized.
variable factor evaluations including, but not limited to, the chemical property evaluations such as rate of active release (using a USP-like “Dissolution” or “Drug Release” test), assay, impurity, water content, and physical property evaluations such as hardness, friability and disintegration.

In summary, a firm can minimize the number of formed dosage units sampled by appropriately conserving the overall sample collected for attribute inspection and appropriately using it for the requisite assessment of the content uniformity for the formed dosage units in each batch or lot for as well as other variable factors “that may be responsible for causing variability in the characteristics of in-process material and the drug product” (21 CFR 211.110(a)).

2. Evaluation Plans

Broadly, there are two statistical approaches that one can take to evaluating a representative sample from a batch or lot of freshly formed dosage units. Those general approaches are characterized by the distribution assumption made for the units sampled. If no distributional assumption is made, the firm should use a suitable “distribution free” assessment procedure. When the firm can justify classifying the dosage units as belong to a “normal” or “near normal” distribution, the firm should use an appropriate “normal distribution” statistical approach which, in general, requires a significantly smaller number of sample units. This guidance presumes that the manufacturers of tablets and capsules are justified in using “normal distribution” statistical approaches for assessing content uniformity.

With respect to appropriate “normal distribution” statistical approaches, this guidance presumes that manufacturers should use statistical procedures that provide a 95% or higher level of confidence that the results for the representative samples tested should be predictive of the acceptability of the remaining batch or lot of untested units. Given this “confidence level” presumption, this guidance further presumes that each manufacturer should use ANSI/ASQC Z1.9 (or its ISO equivalent, ISO 3951) as the basis for its sample evaluation plans. This presumption is made because ANSI/ASQC Z1.9 and ISO 3951 outline CGMP-compliant sample evaluation plans that test the least number of representative sample units that a firm can justify testing for active content whose active content result values can validly be used to predict the acceptability of the entire batch or lot of units at the 95%-% confidence level.

The cited consensus standards provide evaluation plans for two (2) cases, the “process
variability known’’ case and ‘‘process variability unknown’’ case. To justify using the ‘‘process variability known’’ case, the manufacturer should be able to establish that its acceptance criteria for all incoming components, including the active, and all in-process materials include appropriately restrictive controls on all the critical variable factors for each component or material. In addition, the firm should have sufficient results data from the intensified testing on final stage developmental and initial production-scale validation batches or lots that demonstrates that the process mean and process variability for each such batch are, within their respective uncertainties, the same \(^{25}\) for all such batches or lots. When the overall results support the use of an appropriate ‘‘process variability known’’ evaluation plan, then that plan, when it is

\(^{25}\) For the example tablet product, having a targeted mean of 100.5 % of label claim, consider the following scenarios in which all components are presumed to be from different lots:

- Batch evaluation: 200 or more representative samples were tested for content uniformity in each case
- Batches intensively tested: One (1) “technology transfer” and three (3) “initial validation lots

Results found:

For a **Scenario 1** (process variability known; all critical variable factors well controlled) product:

<table>
<thead>
<tr>
<th>Process Identifier</th>
<th>Content Uniformity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Mean</td>
</tr>
<tr>
<td>Technology transfer</td>
<td>100.4</td>
</tr>
<tr>
<td>Initial Val-1</td>
<td>100.6</td>
</tr>
<tr>
<td>Initial Val-2</td>
<td>100.4</td>
</tr>
<tr>
<td>Initial Val-3</td>
<td>100.6</td>
</tr>
<tr>
<td>Weighted Process</td>
<td>100.5</td>
</tr>
</tbody>
</table>

Based on the results observed for the 1000 units tested, the estimated % non-conforming for the process is about 0.1 %, the range of relative means is 0.2 %, and the range of RSD values is 0.2 % (a relative range of about 11 %). The batches are acceptable and, coupled with the process expectations developmental outcomes, the consistency of the data supports setting a process mean of 100.5 % with a process RSD of 1.8 %. Provided the facts are as presented in this scenario, the firm would be justified in choosing an appropriate “process variability known” sampling plan.

For a **Scenario 2** (process variability unknown; all critical component factors not well controlled) product:

<table>
<thead>
<tr>
<th>Process Identifier</th>
<th>Content Uniformity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Mean</td>
</tr>
<tr>
<td>Technology transfer</td>
<td>100.3</td>
</tr>
<tr>
<td>Initial Val-1</td>
<td>100.0</td>
</tr>
<tr>
<td>Initial Val-2</td>
<td>100.3</td>
</tr>
<tr>
<td>Initial Val-3</td>
<td>100.6</td>
</tr>
<tr>
<td>Weighted Process</td>
<td>100.2</td>
</tr>
</tbody>
</table>

Based on the results observed for the 1200 units tested, the estimated % non-conforming for the process is about 0.25 %, the range of relative means is 0.6 %, and the range of RSD values is 1 %. While the batches are acceptable, the data does NOT support setting a process mean of 100.5 % (as the formulation is expected to generate). In addition, the relative range for the process RSD values (of about 50 %) does NOT support the premise that the process has a global “process variability”. In this instance, the firm should use the appropriate “process variability unknown” plan.
contains nonbinding recommendations

draft — not for implementation

properly established, should be used as the “stage 1” evaluation plan for each batch. When the data does not support the use of a “process variability known” approach to batch assessment (see Footnote 25, Scenario 2), an appropriate “process variability unknown” evaluation plan should be used as the “stage 1” evaluation plan for each batch or lot. In those cases where it is valid to use an appropriate “process variability known” plan for stage 1, the firm’s “stage 2” acceptance evaluation plan, when such is needed, can simply be to switch to the corresponding appropriate “process variability unknown” plan and use it. For an appropriate “stage 2” plan for products that require the “stage 1” plan to be a “process variability unknown” plan, the firm should adopt an appropriate “intensified sample evaluation” plan based on a process capability approach. Thus, the statistical evaluation of an appropriate number of sample units can be globally thought of as a three-tiered plan. The first two tiers of which, “process variability known” and “process variability unknown,” should be based on an appropriate plan from the sets of plans contained in the cited consensus standard documents. The third tier should be based on a “process capability” approach that requires the evaluation of more representative sample units than the “process variability unknown” case. The sections that follow discuss the general requirements for, and limitations on, the use of the approach upon which each tier is based. It is left up to each manufacturer to justify the exact general decision tree that is appropriate for each of their drug products. To simplify this discussion, ANSI/ASQC Z1.9-1993 is the consensus standard used and each batch, or lot, is presumed to contain NLT 250,000+ tablet cores or filled capsules.

a. Tier 1 – Process Variability Known – Evaluation Plans Appropriate To Drug Product Manufacture

In general, the number of population-representative sample unit evaluations required in Tier 1 for a valid batch inspection plan depends upon the tolerable percentage of nonconforming tablet content values (AQL Content). The relationship between sample number and AQL is inverse. Thus, subject to the design limits and verified outcomes established during product development, a firm wishing to minimize the number of samples that should be tested should choose the smallest “Acceptance Quality Level” (“AQL”) that the design, development, and, where available, historical records factually support. Because the validity of the use of this approach is totally dependent on the validity of the firm’s assertion that the process variability is a known value, the use of a “Tier 1” plan in the firm’s overall evaluation plan should be restricted to products manufactured from components and in-process materials whose critical chemical and physical properties are both identified and well controlled. Moreover, as discussed previously, the determination of the “process variability” value should be based on intensified testing on a sufficient number of production-scale related batches or lots manufactured using differing lots of components. [Note: Though a “reduced inspection” option exists, the allowable variability in the chemical and physical properties of the components and in-process materials does not support the use of this option for tablet, capsule, and other solids containing drug products.] Thus, for content uniformity and batches larger than 250,000 units, Row “P” in “Table D-3” of ANSI/ASQC Z1.9 (pages 90 and 91) outlines the number of samples (n), the
acceptance criterion (M), and adjustment factor (v) for a given choice of AQL. Those sample numbers range from 42 for an AQL of 0.1% to 127 for an AQL of 10%. For the example tablet product (see Table 1) used in this guidance where the AQL established is 0.4%, not less than 54 batch representative sample units should be tested. A “500-unit lot” example showing how the results found for the samples tested are used to determine the acceptability of the batch or lot is shown on page 88 in ANSI/ASQC Z1.9-1993. When the batch or lot results are evaluated and, in conjunction with the other acceptance criteria established for the drug product (see Table 1), the batch or lot is found to have an acceptable content uniformity, then not only does the batch or lot evaluated have an acceptable content uniformity but the continued use of this “Tier 1” evaluation plan is also validated. In general, the firm’s use of the “Tier 1” level of inspection should be limited to solid dosage forms for which every variable factor (component, material, process and test) that may adversely affect the uniformity of the content in the formed dosage units is

26 Should a batch or lot not meet its AQL criteria when evaluated using the firm’s “Tier 1” evaluation plan, then, provided the other critical batch acceptance criteria are met, the firm should switch to their “Tier 2” – Process Variability Unknown – plan. When the number of sample units already tested is at least the number specified in the appropriate “Reduced Inspection” option of this “Tier 2” plan, the firm should first evaluate the probable acceptability of the population based on the observed sample variability rather than the sample’s projected “process variability.” This decision is appropriate when, for whatever reason, a process operating in control under a “Tier 1” plan indicates that the product may not be acceptable even though the sample units tested meet all of the other acceptance criteria established for content uniformity. If this evaluation finds the product is acceptable, then the entry point into the “content uniformity” evaluation decision matrix should be set to the “Tier 2 – Reduced Inspection.” If the samples tested are otherwise acceptable but the batch or lot is still found to be not acceptable, then, the firm should switch to the “Tier 2 – Normal Inspection” plan, evaluate the remaining number of units required to satisfy the 200-unit requirements for batches larger than 150,000 units, and ascertain whether or not the batch or lot is acceptable under this evaluation condition. When it is, then the firm should switch their entry point into the “content uniformity” evaluation decision matrix to “Tier 2 – Normal Inspection.” When all of the results are otherwise acceptable but the data do not meet the firm’s “Tier 2 – Normal Inspection” criteria, the firm may elect to switch to their “Tier 3 – Process Capability” plan and proceed as it directs. If the “Tier 3” plan finds the batch acceptable, then the firm should switch their content-uniformity entry point to “Tier 3” and use it for subsequent batches. (Note: the rules for switching from “Tier 3” to “Tier 2 – Normal Inspection,” or “Tier 2 – Normal Inspection” to “Tier 2 – Reduced inspection” or from “Tier 2 – Reduced Inspection” to “Tier 1” are complex and depend upon the:

- General past production history,
- Proximity of changes in the source of or acceptance criteria for a component or in-process material, or processing to the current inspection entry point,
- Steadiness of the production of consecutive batches, and
- Whether or not the dosage units are produced on a dedicated production line.

Though ANSI/ASQC Z1.4 provides some general guidelines, each firm should appropriately justify the decision tree that they use to control switching among the inspection plans the firm chooses to use.

27 Since switching to the ANSI standard’s “tightened” inspection plans: a) does NOT address the acceptability issues associated with the “currently non-acceptable” batch and b) only increases the probability that a subsequent batch or lot will not meet its acceptance criteria, this guidance has elected to switch plans rather than switch to “tightened inspection.” This choice is justified by the current and foreseeable future state of the complexity of, and level of “built in” uniformity for, solid dosage forms.
well controlled.

b. **Tier 2 – Process Variability Unknown – Evaluation Plans Appropriate To Drug Product Manufacture**

In general, the plans in **Tier 2** are appropriate for manufacturers who identify:

- All critical chemical and physical factors for the components, materials and process steps but do not rigorously control all of them, or

- All of the critical chemical factors but only control some of the critical factors relying instead on one or more process steps (usually granulation related) to minimize or eliminate the non-uniformity that the uncontrolled critical component factors can contribute and choose to use the formed dosage units to define the uniformity of:
  - the formed units, and
  - the ‘Powder Blend” from which the dosage units were formed, or

- All chemical factors but rely on the process steps to minimize or eliminate the non-uniformity that the uncontrolled critical component factors can contribute and use the results for the formed units to determine the content uniformity of both the “Powder Blend” used and the dosage units produced.

For the tablet example (see Table 1) produced in batches larger than 250,000 units, the appropriate batch- or lot-representative “normal” inspection sample number is 200 units. In cases where the manufacturer can justify the use of a “reduced” inspection plan, a firm using ANSI/ASQC Z1.9 as the basis for its batch acceptance assessments can chose to test as few as fifty (50) batch- or lot-representative sample units. However, on a generalized statistical basis, evaluating a representative set of 75 is a better choice. When the use of this “reduced inspection” option is justified, any “samples conform but batch or lot

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28 In general, the following conditions should apply before a drug manufacturer can justify switching from the “normal” inspection level to a “reduced” inspection level when all of the following conditions have been met:

- The not less than 10 or more lots or batches have been on normal inspection and none has been rejected
- Production is at a steady rate
- Reduced inspection has been included as an option in the manufacturer’s filing for the drug product and accepted by the Agency.

Thus, the choice of this option should be limited to dedicated manufacturing facilities or facilities in which the production campaign or “run” encompasses more than 10 lots or batches. In general, this choice is not appropriate to short-run production unless the firm is justified in using the “process variability known” option (Tier 1) and a non-conformance to the requirements for that case contains a provision for switching to the “process variability unknown – reduced inspection” option. [Note: Since the ANSI standard’s “tightened” inspection plans: a) do NOT address the acceptability issues associated with the “currently non-acceptable” batch and b) only increase the probability that a subsequent batch or lot will not meet its acceptance criteria, this guidance has elected to switch plans rather than switch to “tightened inspection.”]
is predicted to fail” assessment should trigger switching to the “normal inspection” option with the evaluation of the additional representative dosage units needed to generate the requisite 200 batch- or lot-representative content results. Should the test results from a batch or lot under “normal inspection” meet its sample criteria but fail to meet the acceptance criteria for the batch or lot, the recommended course of action is to switch to a Tier 3 (based on a process capability approach) plan that the manufacturer has justified and submitted in the appropriate filing that has led the FDA to approve or license that drug product. This is the case because a firm’s switching to the “tightened inspection” option presented in the ANSI/ASQC Z1.9 would lead not only to the rejection of the non-conforming batch or lot but also to the tightening of the acceptance criteria in a manner that would increase the risk that an acceptable batch would be rejected.

1. Process Variability Unknown – Normal Inspection

Though ANSI/ASQC Z1.9 provides two approaches, a range-based procedure and a standard-deviation-based procedure, this guidance recommends that the manufacturers elect to use the standard-deviation-based procedure because: a) it requires the testing of fewer samples than the range-based procedure, and, more importantly, b) it results do not depend upon how the samples being evaluated are grouped. For batches larger than 150,000 dosage units, not less than 200 representative dosage units should be tested when this inspection plan is used. For tablet and capsule batches down to 35,000 units, the firm need only evaluate 150 representative dosage units. In general, this, or an appropriate process-capability-based inspection plan, is the minimum inspection plan that a manufacturer should use during the development of the manufacturing process for a tablet or capsule product when the developmental batch size exceeds about 500 dosage units. The text and appropriate tables in pages 37 through 53 of ANSI/ASQC Z1.9-1993 contain the information and examples that are needed for a manufacturer to determine the acceptability of a batch or lot based on finding acceptable sample results generated by the testing of any set of “200” or more representative units.

29 Though “tightened inspection” does not increase the number of samples tested, it has the “effect” of reducing the acceptable percentage of non-conforming units. Since drug product tablet and capsule batches are a high-value product, the better choice is to switch to a “process capability” approach even though that approach requires the testing of more units. As with any approach, a firm may elect to rigorously adhere to the guidance in ANSI/ASQC Z1.9 and adopt the “process variability unknown – tightened inspection” option as that firm’s “Tier 3” plan.

30 To meet the requirements of the standard, an equal number of dosage units should be selected from the sample collected at each sampling point in the dynamic sampling procedure that firms use. If a process interruption generates an additional sampling point (a “restart”), the firm’s inspection plans may include a provision to allow the number of samples evaluated from each routine point to be appropriately reduced to include an appropriate number from each such “restart” without increasing the total number of representative units that must be evaluated.
2. Process Variability Unknown – Reduced Inspection

Provided the manufacture can justify the use of a “reduced inspection” plan, the manufacturer should again, where possible, elect to use the standard-deviation-based procedure described in the text and the appropriate tables in pages 37 through 53 of ANSI/ASQC Z1.9-1993 to assess the acceptability of a batch or lot when the valid content results found from the evaluation of the requisite number of representative sample units meet their acceptance criteria (sample specifications). In general, a firm using this ANSI/ASQC Z1.9 procedure is justified in evaluating as few as 50 representative units and using the results obtained to ascertain whether or not the batch or lot is acceptable. When the firm is justified in using this inspection plan to evaluate the content uniformity of the batch or lot based on the sample units tested, the firm’s inspection plan should provide an explicit provision for switching to “normal inspection” option when a batch or lot is found to be nonconforming (not meeting the acceptance criteria for reduced inspection). Firms wishing a higher level of confidence may elect, where this option exists, to use the next larger sample size as its “reduced inspection” number. In the tablet example that this guidance uses, this would translate into testing 75 dosage units instead of the 50-unit minimum that the consensus standard requires.

In summary, the preceding “Tier 2” inspection plans are those that most of today’s manufacturers should be using for routine production-scale batch acceptability assessments. This is the case because:

- The goal of this CGMP-based in-process content assessment is to ensure that each batch or lot produced has acceptable content uniformity (21 CFR 211.110(a), “To assure batch uniformity …”), and
- Most of today’s firms do not identify and rigorously control all of the critical physical property characteristics of the components and in-process materials used in the manufacture of a solid dosage form product.

Thus, contrary to the assertions of some, the appropriate minimum goal cannot simply be to find that the content results are acceptable for the few tested units. Provided a confidence level of 95 % is acceptable, the plans in ANSI/ASQC Z1.9 provide the minimum plans that a firm can use and meet the drug-product CGMP regulation’s minimums.

c. **Tier 3 – Process-Capability-Based – Evaluation Plans Appropriate To Drug Product Manufacture**

In general, the plans in **Tier 3** are appropriate when the variability of the batches produced is such that use of the consensus standards cited is deemed or found not to be appropriate for a given product. Often, a suitable “Tier 3” inspection plan is the plan of choice for use in the development of a solid dosage form when the controls for the components, in-process materials, and processing steps have not yet been completely developed. Because there a variety of approaches that can be used to evaluate the
manufacturability of a product using a given set of inputs and operations, this guidance
does not propose to address exactly which “process capability” approach should be
used. This guidance instead focuses on the issues associated with the minimum:

a) number of representative dosage units that a firm should evaluate and

b) capability result value that a firm should use
to comply with the requirement minimums of CGMP with respect to 21 CFR 211.110.

1. Minimum Number of Units To Inspect

Since capsule content and tablet-core content values are close to being
normally distributed in a well-controlled process, this guidance will presume
this is the case for the content values in each batch or lot. Because the general
form of all capability assessment approaches is based on a specification range
divided by some standard deviation (“s”) or, using this guidance’s relative
approach, a relative range divided by some relative standard deviation (RSD),
the validity of that “s” or “RSD” depends upon how close it is to the true value
for the population. Consulting appropriate statistical texts (e.g., Chapter 2 in
EXPERIMENTAL STATISTICS, Handbook 91 [see Other References: 15]), that
discuss the analysis of measurement data from normal populations, a firm
should find that a significant number of units must be tested when, for
confidence levels that are 95 % or higher, the estimate of the RSD derived
from the samples tested must be close to the true population relative variability
“R_\sigma_{Batch or Lot}”. Practically, not less than about 400 population representative
units should be tested ensure that the RSD computed (RSD_{Sample}) is definitely
within 10 % of the true relative variability of the batch or lot (“R_\sigma_{Batch or Lot}”).
Though this number is a suggested minimum number for those firms who
choose to use this approach to determining the acceptability of a batch, a firm
may be able to justify using a smaller number when their production history
indicates that testing a smaller subset provides adequate assurance of batch
acceptability at a confidence level that is not less than 95 % provided the
RSD_{Sample} uncertainty vis-à-vis the true value for the batch or lot is estimated
to be within “8 %” or less of the true population value (when a firm can justify
using a 95 % confidence level) and within “9 %” of the true population
variability (when a 99 % confidence level is determined to be appropriate).^{31}

2. Minimum “Process Capability” Assessment

Since the current recognized state of “good” quality in today’s industrial
America is “Six Sigma,” CGMP dictates that that standard should be the one

^{31} For manufacturers who wish to reduce their RSD uncertainty to the point that the error in assigning a process
variability from the sample variability observed is less than “5 %,” not less than about 900 representative
units should be selected when a 95 % confidence level is deemed appropriate. Moreover, at the 99 %
confidence level, not less than 1400 units should be tested. In developmental studies, the firms are
couraged to inspect larger numbers and choose a 99 % confidence level for decision making because
doing so reduces the risk that the data from the developmental lots does not adequately describe the
performance of the projected or observed production-scale batches or lots.
used by today’s drug product manufacturers. Remembering: a) the general form of the process capability equation for a set of relative values is that a relative range divided by six times the RSD observed is equal to the capability “C” and b) “Six Sigma” quality expects all values to be within a relative range from the “mean minus 6 RSD” to the “mean plus 6 RSD” or a “12 RSD” range, the firm should set a minimum process capability that is not less than “12 RSD”/“6 RSD” or 2.0. [Note: Looking at process capability in terms of the number of standard deviations from the process target that are tolerated, a process capability of “1.33” or “1.34,” a value that most authors consider the minimum acceptability, roughly translates into a targeted quality level of “Four Sigma.”]

In summary, inspection based on a “capability” approach and today’s “Six Sigma” expectations for “good” quality require the manufacturer to evaluate more representative sample units than the procedures outlined in ANSI/ASQC Z1.9. In general, this is the approach that a firm should use in developing a drug product. This is the case because the specifications developed from the testing of more units are more likely to provide the firm with solid evidence as to what the true population limits are and properly drive process improvement to the point that the developed process probably should, when implemented, consistently produce batches or lots that meet or exceed the established specifications that the firm’s data clearly justify.

In routine production, this inspection option should only be the starting point for a firm’s evaluation of content uniformity and determination of batch or lot acceptability when the firm elects to use a confidence level higher than 95 % or, because of the nature of the process (e.g., infrequent production of the drug product in very short campaigns [1 to 3 per year]), the outcomes from a given campaign do not provide a sufficient production and evaluation background to justify use of any of the plans in ANSI/ASQC Z1.9.

E. INSPECTION PLAN FOR FINISHED TABLETS AND CAPSULES

1. Sampling Plans

In general, the sampling plans for the finished dosage units are similar to those for the in-process dosage units with respect to the need to take a batch- or lot-representative sample and the number of units required. Moreover, when a firm elects to collect the sample units required during the final packaging of the finished dosage into its commercial packaging system or systems, a dynamic system that is similar to that used in-process can be used. However, when a firm elects to collect the final dosage units after the last processing step (e.g., for a film color-coated tablet, after coating, or for a pre-printed capsules product, after final post-polishing screening, simple random sampling from each post-step container (e.g., from the coating pan or the final capsule storage container) may be used.

32 Since “process capability” is a derived value that is essentially the ratio of the allowed range divided by the observed variability, firms should be able to fully justify the range selected where the justified range should be no larger than the projected population content range derived from the range observed for the number of samples tested to meet the requirements for the 99-% confidence level.
Because a finished dosage-unit “appearance” attribute sample for inspection under ANSI/ASQC Z1.4 is generally collected and examined, that sample should be conserved and used for the requisite variable factor evaluations required. With this in mind, let us turn to the evaluation of the finished dosage units sampled for the simple tablet and capsule products that this guidance directly addresses.

2. Evaluation Plans

When in-process testing establishes the batch’s or lot’s content uniformity, there should, in general, be no need to reassess this variable factor for the instances (addressed by this guidance) in which the post forming operations do not change the content of the dosage units formed. However, when a firm needs to assess uniformity at the finished drug product stage, the procedures used for the in-process assessment can be appropriately adapted for use here. If the drug product assessment for content uniformity is meant to be a confirmation of the in-process assessment, then, in cases where the process steps after dosage unit forming cannot change the content of the dosage units, the firm should be able to justify using an evaluation plan that uses the RSD established in the in-process testing and a suitable ANSI/ASQC Z1.9-based “process variability known” procedure. In such cases, the firm may be justified in using the “process variability known – reduced inspection” plan because this inspection is meant to be confirmatory in nature. This guidance leaves it up to the manufacturer to specify and justify the content evaluation plan, if any, that the firm should be used.

However, though outside the scope of this guidance, one critical process parameter that should be evaluated at the finished product stage is the release profile of the solid dosage form. This is the case because the post-dosage-forming processing and handling steps in the manufacture of tablets (e.g., color coating, inking) and capsules (e.g., polishing and gel coating) are known to affect the release of the active from the dosage unit. For example, when a firm’s process adds an “enteric” coating designed to delay the release of the active until after the dosage unit has passed into the small intestine, the drug product is designed to delay the release of the active. Since evaluating the release of the active is outside the scope of this guidance, the manufacturers should consult other published articles, documents, and texts that provide general guidance that the firm may use to justify the evaluation plan the firm establishes for such “active release” evaluations. Because “active release” and “active content” are correlated variable factors when the active is being released, their correlated nature may be used to justify, in some cases, “active release” examination plans that need only use one of the appropriate “reduced inspection” procedures in ANSI/ASQC Z1.9.

VI. ESTABLISHING APPROPRIATE TEST PROCEDURES

A. GENERAL CONSIDERATIONS

Since the goal of in-process testing (21 CFR 211.110(a)) is to assess batch uniformity – not just the uniformity of the samples evaluated, the analytical test procedures chosen should be
those that have the minimum imprecision subject to the constraint that the procedure’s verified inaccuracy is on the order of 1% or less. Further, because a firm may need to test on the order of 50 to 1000 dosage units in order to make a CGMP-compliant determination of the acceptability of a batch or lot with respect to its content uniformity, the test procedures chosen should maximize sample throughput and, where possible, choose or develop procedures that inherently provide instrument averaged assessments of the response or responses used to compute the content for each dosage unit tested. In cases where the results from the testing of the dosage units evaluated for content indicate that the batch is acceptable and downstream processing has been verified not to affect the content level, the average of the content values found may, in many cases, be validly used as the firm’s “Assay” for the batch or lot being tested.

B. CHOICE OF ANALYTE MEASUREMENT SYSTEM

Historically, the tendency has been to develop and use procedures based on the use of high-performance liquid chromatographic (HPLC) separation of the chemical components in the dosage unit coupled with single-wavelength quantitation of the response produced by the active at some suitable wavelength using a compact spectrophotometer with a limited linear range as the analyte measurement system.

Unfortunately, such HPLC/Spectroscopic procedures are not ideally suited for high throughput and, if response measurement uncertainty is to be minimized, require at least duplicate assessment on each dosage-unit preparation. Furthermore, most of the USP-type procedures tend to have inherent “test result” uncertainties (in result precision and result accuracy) that are larger than the “1% or less” uncertainty that is desirable for batch uniformity assessment.

Fortunately, progress in instrumentation design and the advent of increasingly powerful microprocessors has made it possible to use rapid scan spectrophotometers and sophisticated component deconvolution software to accurately determine an averaged analyte response that provides the high throughput and response averaging capabilities needed to obtain highly precise and suitably accurate determinations of the content in the dosage units tested. Moreover, robotics has progressed to the point that the entire sample preparation and measurement procedure can be automated. With the Agency’s renewed interest in process analytical technology (PAT), manufacturers are encouraged to use such separationless assessment procedures to speed the testing of the requisite number of sample units that CGMP requires a firm to test.

In summary, firms are encouraged to develop and use quantitative analyte assessments procedures that do not require component separation. In this regard, the Agency will also be encouraging the USP to seek out or develop such separationless methods for tests that measure the uniformity of content, drug release, and dissolution as well as for other tests whose analyte is amenable to spectrophotometric measurement.

Since these test procedures are only intended to assess the acceptability of the in-process batch for release to further processing (21 CFR 211.110(c)), the manufacturer should not feel compelled to use a test procedure based on, or derived from, the USP’s “in commerce” test procedure whenever that procedure includes HPLC. Instead, wherever possible, rapid-scan computerized spectrophotometric procedures using spectral deconvolution should be used to assess the uniformity of content for the batch or lot being tested.
VII. ESTABLISHING A CGMP-COMPLIANT INSPECTION PLAN FOR THE ACTIVE CONTENT IN A DRUG-PRODUCT PROCESS

One of the fundamental tenets of quality system is that requisite level of quality required by the customer must be designed into all aspects of the process that produces the product. A second tenet is that all process inputs and processing steps must be properly controlled before one can ensure that the product will reliably meet its established quality criteria. A third tenet is that the costs associated with a quality failure are reduced when the failure is detected as soon as possible in the process. This guidance presumes that the manufacturer understands and develops the firm’s drug product processes for solid dosage units in a manner that fully complies with the first two of these quality tenets.

Further, to minimize the complexity of this discussion by including explicit discussions for the known variety of steps leading up the final blend, this guidance begins its discussion at the end of the process step that generates the final blend. Unless a manufacturer can justify combining the generation of the final blend and the dosage forming operation into a single process step, a firm is required to develop and use some batch- or lot-representative procedure for the assessment of the acceptability of each final blend for release that the firm’s quality control unit (QCU) can use to release each final blend for use in the dosage forming step (21 CFR 211.110(c)). By performing in-depth studies during process development, a firm can determine the material-representative sample number assessment minimums that should be used to meet the requirements minimums of the CGMP regulations for each dosage-unit processing stage that can adversely impact the uniformity of the in-process material or the drug product with respect to any of its critical variable factors (21 CFR 211.110(a)). For the simple tablet and capsule products covered by this guidance, a firm can, in general, justify excluding packaging operations from the set of process steps that can affect the uniformity of the content and other variable factors directly related to level of the active. In such cases, the generalized set of steps where a content and/or other uniformity release is required can be labeled as “Powder Blend,” “Formed Dosage Units,” and “Finished Dosage Units.” To simplify discussion, this section also uses the tablet product example introduced initially (a 250 mg uncoated tablet containing 0.2 mg of a single stable active ingredient [“0.08%” wt./wt] targeted to contain, on average, 100.5% of its labeled content).

A. “POWDER BLEND” INSPECTION

This guidance leaves it up to the manufacturer to justify the sampling and evaluation approach that it uses during the early stages of the development of a process. However, once a firm has established the type of dosage form, the components to be used and the general processing steps that will be used to produce the drug product, the Agency expects to see the manufacturer use scientifically sound and appropriate representative-sample-based statistical inspection plans in the final stages of development as well as in all pre-production-scale batches or lots. Should a firm elect to pursue a “process variability known” approach, the Agency expects to see proof that the firm has determined the critical physical and chemical variable factors for each component, process step and processing choice that can affect the in-process material and drug product content uniformity and has established sufficiently stringent controls for each.

For those firms who elect to approach the determination of the content uniformity for each batch or lot of the final “Powder Blend” indirectly (by determining the weight-corrected
content for the freshly formed dosage units tested and using those values to provide assurance
that the final “Powder Blend” did meet its uniformity criteria), the Agency expects to see an
in-depth justification for choosing that option. That justification should include appropriate
batch-or lot- acceptability for release evaluations 34, 35. With the preceding Agency
expectations in mind, the manufacture should then proceed in the manner that is dictated by
the level of quality that the firm’s controls and process steps have built into the dosage unit
forming operation.

In general, for a developed process, the firm should either have two types of inspection plans
for “Powder Blend” inspection or a single multiple-tier inspection plan. These should address
two (2) general situations, Evaluation Qualification (“EQ”) inspection (commonly referred to
as the Performance Qualification [“PQ”] phase of validation) and Routine Production
Qualification inspection (referred to as the Maintenance Qualification [“MQ”] phase of
validation).

1. **Exhibit, Initial Validation, Initial Production-Scale And Nonconformance
Evaluation Qualification Inspection (“EQI”)**

The inspection plans for EQI should include an appropriate in-depth assessment of
uniformity of the final “Powder Blend.” Based on the input provided by the PQRI, the
number of sampling locations should be on the order of 20 or more. In general, for “in
the mixer” sampling, the manufacturer should provide a body of evidence that
justifies the amount of sample, the number of sampling locations, and the positions
chosen by a manufacturer for sampling. The manufacturer’s evidence should prove
that the samples sampled are indeed representative of the final blend. In general,
increases in blend size and/or the mixer’s design complexity calls for more sampling

34 For example, a manufacturer has identified and appropriately controlled all of the critical physical and
chemical variables for each component and established in development that the maximum difference in
Assay for unbiased representative samples from an in-process blend occurs between the Assay found for the
bulk blend and the Assay for the in-process material remaining in the mixer after it is emptied. For batches
that demonstrated uniformity meeting the criteria established for that “Powder Blend,” this maximum
observed difference could be, for example, 1.4 % of the label claim. Therefore, when both Assay values are
appropriately performed on a sufficient number of appropriately sized aliquots taken from unbiased sample
aliquots large enough to be population representative, the firm may be justified in setting this Assay
difference as a part of its routine-production “Powder Blend” acceptance criteria provided the observed
value for the Assay “Powder Blend” batch or lot is not less than 100 % of the targeted value or, when that is not the
case, the firm’s dosage forming procedure explicitly requires the formed weight to be adjusted “to provide
not less than 100 percent of the labeled or established amount of active ingredient” (21 CFR 211.101(a)).

35 For processes like the ones outlined in Footnote 34 where the “Powder Blend” is mixed in a tote that is
attached to a mixer head for blending and then detached and, after inspection, the tote containing the released
final “Powder Blend” is directly transferred to the feed hopper of the dosage forming system, the firm should
be able to justify relying on the computed Assay for the batch or lot of blended powder provided: a) a valid
batch- or lot- representative Assay “Powder Blend” batch or lot Value is determined from the sample aliquots tested
and b) that Assay “Powder Blend” batch or lot is not less than 100 % of the level targeted or c), when the calculated
Assay “Powder Blend” batch or lot is less than 100 % of the level targeted, the production process has explicit
language to require production to adjust the dosage unit slug or fill weight to “to provide not less than 100
percent of the labeled or established amount of active ingredient” (21 CFR 211.101(a)).
locations when the samples are taken directly from the blender. When the firm elects to locate the completion of the final “Powder Blend” step at the “post-mixing filled intermediate storage container” point, then an appropriate number of samples should be taken from \( \text{NLT} \) two levels (“Top” and “Bottom”) in each container when the intermediate-storage containers are 25-kg or less and \( \text{NLT} \) three levels (Top, Middle, and Bottom) when these containers contain more than 25 kg each.

Whenever an EQI is being conducted, an appropriate number of unit-dose (or smaller) aliquots should be evaluated from each sample location. This is the case because the firm needs valid estimates of the local (within-sample), global (across the sample locations) and residual error variability values in order to properly use the valid results to ascertain whether or not a lot or batch of non-discrete material is or is not acceptably uniform with respect to its content. Since the content level and content level variability found for all valid results for the sample aliquots evaluated from a given location can validly be projected to adjacent locations, in addition to the observed content range, other indicators of built-in quality can be found in the reproducibility of: a) the extreme and mean values; and b) the locations of the sample containing the lowest content and the sample containing the highest content level.  

[Note: For moderately uniform blends, the range of values found in the blend is significantly larger than the within-sample location range and the location of the historical least and highest content levels tend to be reproducibly localized. For a “perfectly uniform” blend, the within-location ranges and between-location ranges are not significantly larger than the test procedure uncertainty and the location of the least and highest levels should be approximately random.]

Thus, in addition to its initial use when the full-scale production of a drug product commences, EQI should be the initial inspection plan whenever production of a given drug product is resumed in a facility that campaigns various products or when a routine production batch has a blend that fails to meet its established MQI acceptance criteria. This is one reason that a manufacturer who wishes to minimize its inspection overhead is encouraged to use dedicated production facilities, where possible, and, in any case, produce drug product batches or lots in campaigns that are as long and as steady as the firm can support.

For short campaigns (runs) in non-dedicated equipment, it will be hard for a firm to justify using an MQI plan. In such cases, a manufacturer should do all that it can to ensure that the drug-product production process have been developed to the point that the firm has built in rigorous controls on the critical physical and chemical variables, process steps, and process controls that could, if not so controlled, adversely impact the content uniformity of the in-process powder “Powder Blend.” Unless the firm develops its production process to the level that its “built in” quality controls ensure that a small number of sampling locations are reliably representative of the batch or lot, it will be difficult for that firm to justify testing less than all of the samples sampled in “short run” situations. Then, for a well-controlled process, after sufficient history is accumulated, a firm may be able to justify routinely testing a fraction of the

\[ \text{Since these test procedures used have overall limiting relative accuracy of a given content value is on the order of 1% or larger, a highly uniform blend cannot be expected to exhibit a measured RSD that is significantly less than 1% unless a large number of aliquots are prepared for each sample location.} \]
samples sampled even in short-run situations.

2. Routine Manufacturing or Maintenance Qualification Inspection ("MQI")

In MQI, the EQI history is used to justify the use of an MQI plan which tests less than all of the samples sampled. By analyzing the EQI results’ history for not less than the previous ten (10) consecutive acceptable blends, the firm may be able to define a subset that, on average, provides the same results’ range pattern. In favorable cases, where the final blend is highly uniform, the firm may be able to justify initially testing a defined subset of the full set sampled containing as few as one-fourth of the sampled set. The reduced set may reliably describe an acceptable lot or batch at least 90 % of the time (with full testing being required about 10 % of the time).

As alluded to previously in Footnotes 34 and 35, in well controlled processes, a firm may be able to justify using a batch- or lot-representative Assay and Assay Range approach\(^{37}\) to justify the release of the final “Powder Blend” to the dosage-forming step provided a post-release conformity content uniformity evaluation on the formed dosage units (using the weight corrected content data for the tablet cores or capsule contents at the formed-dosage-unit stage) is used to verify the content uniformity of the final “Powder Blend” was within its acceptance envelope\(^{38}\). When it is valid to

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\(^{37}\) When this approach is used, the Assay and Assay Range must include an evaluation of all of the components in the blend whose uniformity may affect the overall safety and efficacy of the dosage units formed from the “Powder Blend,” not just the Assay for the active or actives in the formulation. The variables whose level should be assessed in the Assay case are the same ones that should also be assessed in when the uniformity of the final blend is being determined. Those components are, in order of importance, a) stabilizers (components that stabilize the active or actives in the formulation [e.g., sodium citrate, typically, added in a “granulating” solution, used to stabilize Penicillin V Potassium]), b) components that facilitate active adsorption, c) components that regulate (accelerate or retard) the release of the active from the dosage unit (e.g., cross carmellose sodium, sodium starch glycolate, modified cellulose polymers), d) binders that increase tablet core or capsule fill cohesion, and e) lubricants that promote the flow of the final blend through the dosage forming system. Since lubricants are typically added at the end and blended for the least time, the uniformity of the lubricant directly impacts the uniformity of the final blend. For example, if a blend were perfectly uniform up to the point that the lubricants are added and the lubricant weight percentage is 2 % of the tablet weight of 5 mg in the example 250-mg tablet, the lack of uniform dispersion of the lubricant can easily result in level of lubricant that range from near zero to 20 mg (0 % to 8 % of the unit-dose’s weight). This translates into a relative active content range impact of from +2 % to −8 % or a 10 % range. This problem is particularly severe when a non-rotating-shell blender is used and the material in the discharge port (which contains no lubricant) is not removed from the port and added back to the blend midway through the blending of the lubricants and this “discharge port recycling” is not repeated at one minute before the final blend step is completed. [Note: In known cases where no recycling was performed, the level of the active in discharge-port material has been found to be, on average, up to 10 % higher than it should be. This is one of the reasons that, absent continual discharge port recycling, such blenders should not be used to produce drug products.]

\(^{38}\) The downside of this approach is the problem that such a “retrospective” assessment may generate when the weight-corrected content values fail to meet the pre-established acceptance criteria for the “Powder Blend.” At a minimum, the number of representative dosage units evaluated will need to be appropriately increased. Worst case, the much higher “lack of quality” costs associated with rejecting a batch or lot at the formed dosage stage may outweigh the apparent cost savings afforded by using this approach. Moreover, it is both more difficult and more costly to validly “rework” the product at the formed dosage unit stage than it is at the final blend stage.
use this approach, the inspection plan should include switching to a blend content-uniformity inspection plan when the requisite Assays do not meet the manufacturer’s relative mean or RSD acceptance criteria.

B. “FORMED DOSAGE UNIT” INSPECTION

This guidance again leaves it up to the manufacturer to justify the sampling and evaluation approach that it uses during the early stages of the development of a process. However, once a firm has established the type of dosage form, the components to be used and the general processing steps that will be used to produce the drug product, the Agency expects to see the manufacturer use scientifically sound and appropriate representative-sample-based statistical inspection plans in the final stages of development as well as in all pre-production-scale batches or lots. Should a firm elect to pursue a “process variability known” approach, the Agency expects to see proof that the firm has determined the critical physical and chemical variable factors for each component, process step and processing choice that can affect the in-process material and drug product content uniformity and has established sufficiently stringent controls for each. With respect to the dosage units evaluated, the firm should weigh each tablet core or the contents of each capsule as a part of the evaluation process and maintain the link between that weight and the content level found in all cases.

For those firms who elect to approach the determination of the content uniformity for each batch or lot of the final “Powder Blend” indirectly (by determining the weight corrected content for the dosage units tested and using those values to provide assurance that the final “Powder Blend” did meet its uniformity criteria, the Agency expects to see an in-depth justification for choosing that option.

1. Exhibit, Initial Validation, Initial Production-Scale And Nonconformance Evaluation Qualification Inspection (“EQI”)

The inspection plans for EQI should include an appropriate in-depth assessment of uniformity of the dosage units. Minimally, based on either ANSI/ASQC Z1.9 or ISO 3951, initial studies should evaluate no less than 200 batch- or lot-representative dosage units. Firms seeking not only a better understanding of the uniformity of the formed dosage units in a batch but also to establish a sound value for the process variability based on the evaluation of a few initial lots or batches should initially use a 99% confidence level and test not less than 330 representative units. When the firm is in the process of finalizing their understanding of the post-blending handling impacts on the uniformity of the dosage units, the average of the differences in an initial set of not less than three (3) production-scale batches or lots when 330 representative dosage-units are tested from each batch or lot (or not less than five (5) batches or lots when 200 representative dosage units are tested) between the weight-corrected relative dosage-unit content variance (RSD\textsuperscript{2}\text{Wt-Cor. Dosage Unit Content}) and the relative blend content variance (RSD\textsuperscript{2}\text{Blend Content}) can be used to establish the initial post-blending variance (RSD\textsuperscript{2}\text{Post-Blend Content}). Provided the dosage-unit content variances observed for each batch are similar (the range of values observed should be such that the largest variance is not more than about 20% larger than the smallest variance), the firm may be able to justify the use of an appropriate “process variability known” approach to batch inspection as opposed to a “process variability unknown” approach that initially...
requires testing significantly more representative units (about 4 X).

When an EQI is conducted using a dynamic sampling plan, an equal number of dosage units should be selected at each predefined sampling point (e.g., start, i\textsuperscript{th} interval, and end). As previously discussed, that number should be some integer number of the number of dosage forming stations in the equipment used to form the dosage units. The number of units to be selected from each “added” sampling point should be determined by the cause (e.g., PQRI, power failure, mechanical breakdown) for the “added” sampling point. In general, the number of samples selected for evaluation in EQI should be NLT 200 representative dosage units. Therefore, the firm’s EQI plans should take a suitable random subsample from each interval sample. The subsampling plan should randomly take an equal number of dosage units from each predetermined sampling point and the same or a lesser number of dosage units from each “added” sample point provided the total sampled for evaluation is NLT the minimum 200 or more units required for a statistically valid batch- or lot- representative sample.

When evaluating each dosage unit, a minimum of two determinations should be made for the response generated by the sample unless the detection/quantitation system automatically averages the responses measured\textsuperscript{39}.

Thus, in addition to its initial use when the full-scale production of a drug product commences, EQI should be the initial inspection plan whenever production of a given drug product is resumed in a facility that campaigns various products or when a routine production batch does not meet its established MQI acceptance criteria. This is one reason that a manufacturer who wishes to minimize its inspection overhead is encouraged to use dedicated production facilities, where possible, and, in any case, produce drug product batches or lots in campaigns that are as long and as steady as the firm can support.

For short campaigns (runs), in non-dedicated equipment, it will be hard for a firm to justify using other than an EQI plan. In such cases, a manufacturer should again do all that it can to ensure that the drug-product production process has been developed to the point that the firm has built in rigorous controls on the critical physical and chemical variables, process steps, and process controls that could, if not so controlled, adversely impact the content uniformity of the in-process powder “Powder Blend” from which the dosage units are fabricated. Second, the post-blending handling and equipment loading procedures and equipment should be optimized to minimize demixing of the blend being formed into the dosage units. In addition, to the extent possible, the manufacturer should minimize the weight control range for the tablet

\textsuperscript{39} The reason for requiring duplicate determinations is to provide for an internal check on the validity for a given response. In general, the firm should set an appropriate “value agreement” limit on the maximum allowable difference or percentage difference between the first and any subsequent measurement. In cases where the reported measurements are, in fact, the averages of multiple system assessments (e.g., a direct UV/Visible spectrophotometric measurement or an automatic averaging of multiple UV/Visible scans by a diode-array or rapid-scanning spectrophotometer) a firm may be justified in reducing the number of sample workups that are measured in duplicate to some percentage of the determinations made in order to establish valid estimates of the measurement uncertainty.
cores and capsule fills. Unless the firm develops its production process to the level that its “built in” quality controls ensure that a reduced number of dosage-unit determinations are reliably representative of the batch or lot, a firm may have difficulty justifying testing less than 200 or more representative dosage units in “short run” situations. After sufficient history is accumulated in such cases, a firm may be able, for a well-controlled process, to justify routinely testing a reduced number of representative dosage units even in short-run situations.

2. Routine Manufacturing or Maintenance Qualification Inspection (“MQI”)

In MQI, the EQI history is used to justify the use of an MQI plan that tests less than the full number of dosage units required by the firm’s CGMP-compliant EQI plan for evaluating the samples. By analyzing the EQI results’ history for not less than the previous ten (10) consecutive acceptable blends, the firm may be able to justify using either a suitable ANSI-based “process variability unknown” reduced-inspection plan or, provided the batch or lot variabilities observed are sufficient close to each other, switching to a suitable “process variability known” normal-inspection plan. In such cases, the justifiable number of samples should be between one-fourth and one-half of the number required for by the firm’s EQI plan.

However, even when the physical and chemical characteristics of the components are tightly controlled, the limiting ranges for some of the key physical characteristics are still wide enough that the characteristics of each lot of component do affect the uniformity of the batch or lot to some degree. Because this is the case, a firm would be hard pressed to justify a further reduction of the number evaluated from the number in the “process variability known” normal-inspection plan to a lesser number. In cases where the content results are used for confirmation of the adequacy of the uniformity of the final blend as well as for determining that the dosage units are acceptably uniform, a firm should not even attempt to justify any further number reduction and, even when a “process variability known” normal-inspection plan can be justified, should, in most cases, use a suitable “normal inspection” plan that evaluates between one-third and one-half the number of dosage units that the firm’s CGMP-compliant “process variability unknown” normal-inspection plan requires. In cases, where the uniformity of the final blend is determined directly and the accumulated history (for more than the last 10 batches or lots evaluated) indicates that the final blend samples and dosage units tested are acceptable, highly uniform, and strongly correlated, the firm may be able, for the “process variability known” case to justify starting with a “process variability known” reduced-inspection plan provided that plan tests at least one-third of the number of samples required for the firm’s justified “process variability known” normal-inspection plan. This reduced set can be expected to reliably describe an acceptable lot or batch at least 90% of the time (with full testing being required about 10% of the time).

Thus, a firm’s overall dosage-unit inspection plan should be hierarchical in nature and consist of the appropriate set of stages and stage controls for evaluating the lot and switching among the sample numbers required based on the outcomes observed. Based on the production history, the starting point should be the smallest justifiable set (governed by the historical outcomes observed and controlled by the outcomes [blend
and dosage unit] observed for the previous batch or lot). In cases where the previous
batch was found to be unacceptable at the formed-dosage-unit stage, the starting point
should be either a) the firm’s “process variability unknown” normal-inspection plan
when the investigation finds a proven operator error or mechanical failure as the root
cause of the non-acceptability of the batch or lot tested, or the manufacturer’s
scientifically sound process-capability-based inspection plan whenever the firm’s
investigation does not definitively find the root cause of the non-acceptability
observed.

C. “FINISHED DOSAGE UNIT” INSPECTION

Here, this guidance suggests that the initial inspection plans suitable for use at the “Finished
Dosage Unit” stage should test the same number of batch- or lot-representative units as that
required for the “Formed Dosage Unit” stage. In general, the sampling approach should be
simple random sampling and, while recommended, there is no requirement for weighing each
tablet or the contents of each capsule before the unit is tested for content uniformity. In many
cases, after some justified number of initial production-scale batches or lots, the firm may be
justified in switching to a plan that initially omits the content uniformity testing of the
“Finished Dosage” units provided:

- A suitable content uniformity evaluation is conducted whenever the uniformity of the
  content at the “Formed Dosage Unit” stage, while acceptable, is outside of its established
  expectations.
- A PQIT test is used to periodically confirm the agreement between the uniformity at the
  “Formed Dosage Unit” stage and at the “Finished Dosage Unit” stage.
- The manufacturer’s quality plan includes the appropriate CGMP-compliant, statistically
  sound and appropriate evaluation of the “Dissolution” or “Drug release” variable and,
  where required, “Impurity level” that tests a scientifically sound number of units that is
  sufficient to establish the acceptability of each batch or lot at a level of confidence that is
  95 % or higher.
- A set of batch- or lot-representative Assay\textsuperscript{40} results on the dosage units finds the mean
  Assay is not less than 100 % of the label claim in the case of a stable active or not less
  than 100 % of the filed target level when a small percentage of degradation is permitted.

However, the Agency expects to see the manufacturer use scientifically sound and appropriate
representative-sample-based statistical inspection plans in the final stages of development as
well as in all pre-production-scale batches or lots. The Agency has this expectation because

\textsuperscript{40} Provided the analysis procedures used do not introduce a significant content accuracy bias, the average of the
content uniformity results found at the “Formed Dosage Unit” stage can be used as one estimate of the
“Assay” of the batch or lot. In general, at least one or, preferably, two “Assay” evaluations should
be conducted at the “Finished Dosage Unit” stage on a batch- or lot-representative number of units of
sufficient size (number [not the USP’s any 20; nominally, 50 to 200 or more representative units]) to ensure
that the “Assay” results obtained are batch- or lot-representative. In cases where a suitable content
uniformity assessment is made at the “Finished Dosage Unit” stage, the mean of the content values found
may be used in lieu of one “Assay” evaluation provided the analysis procedures used do not introduce a
significant content accuracy bias. To satisfy 21 CFR 211.101(a), the average of all of such “Assay” results
on the formed units must have a value that is not less than 100 % of the label claim or targeted level.
the firm should provide proof that the content uniformity established at the “Formed Dosage Unit” stage is the same at the uniformity for the content at the “Finished Dosage Unit” stage.

1. **Exhibit, Initial Validation, Initial Production-Scale And Nonconformance Evaluation Qualification Inspection (“EQI”)**

The inspection plans for EQI should include an appropriate in-depth assessment of uniformity of the dosage units. In general, the plans should be the same as those used for the “Formed Dosage Unit” case (see VII.B.1).

2. **Routine Manufacturing or Maintenance Qualification Inspection (“MQI”)**

In MQI, the EQI and MQI histories contained in the “Formed Dosage Unit” datasets coupled with the EQI history for the “Finished Dosage Unit” evaluations should be used to establish and justify the MQI plan that the manufacturer sets up. In cases where the content uniformity has been proven to be fixed at the dosage forming stage, the firm could simply treat the “MQI” content uniformity test for the “Finished Dosage Unit” stage as a PQIT whose evaluation frequency should be controlled by, in order of importance, the:

- Acceptability of the previous batch or lot manufactured
- Number of previous acceptable batches in the current campaign
- Length of the production history for the drug product (appropriately increase the separation interval as the unbroken number of accepted batches or lots increases).

The switching rules in ANSI/ASQC Z1.9 may be used to justify the firm’s decision tree for switching among the manufacturer’s inspection plans (“normal inspection,” “reduced inspection” and “PQIT inspection”) for content uniformity assessment.

**VIII. REPORTING THE USE OF THE PROCEDURES OUTLINED IN THIS GUIDANCE**

**A. APPLICATIONS NOT YET APPROVED**

This section refers to the scientific data analysis and other information that should be submitted to an NDA or ANDA. Information submitted in the application should include summary reports and scientific analyses or statements about the method being used. The raw data collected to support using this method should be both submitted and maintained at the manufacturing site. The Agency recommends that the manufacturer should provide the following information in the Manufacturing Process and Process Controls section of the application (CTD41 3.2.P.3.3):

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41 *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.
Contains Nonbinding Recommendations
Draft — Not for Implementation

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- A statement that the procedures in this guidance are being used to establish the content uniformity of the final “Powder Blend” and the dosage units, or a description of the alternative sound statistical-based methods proving the content uniformity of the blend and the drug product.

- An overview of data analyses used for the uniformity assessment of the final blend, the in-process formed dosage units and the finished dosage units.

- A review of the in-process formed dosage units’ “content result” data that demonstrates that the active content and weight corrected active content results for the formed units indicate that the batches or lots evaluated can validly be considered to be normally distributed with respect to each active ingredient in the drug product.

- A summary of the “Powder Blend” sampling data’s analysis that demonstrating that each final blend is appropriately uniform and meets the minimum qualification criteria established for the level of testing performed.

- Tables showing all of the relevant batch and step identification information, sampling location or time point, assigned test identifier, weight of sample or dosage unit tested, results found, weight corrected result values, and the raw data values used to compute the “results found” values.

In the Drug Product Specification section of the application (CTD 3.2.P.4.1), the Agency also recommends that the manufacturer should provide the following information:

- A statement in the product specification affirming either that the applicable procedures used in this guidance were used to develop the specifications for the content uniformity of each active and are being used to demonstrate finished product uniformity of content, or a description of the alternative CGMP-complaint methods used to demonstrate finished product uniformity of content.

- A narrative outlining the justification used for the content uniformity specifications established for each active ingredient.

In the Pharmaceutical Development Information section of the application (CTD 3.2.P.2.2), the Agency recommends that the drug product manufacturer should provide the following information:

- An overview of the data analysis for each batch or lot in the submission that establishes the relationship between the content mean and content distribution for the final blend and the content mean and content distribution for the in-process dosage units.

- A summary of data analysis for each batch or lot in the submission that establishes the correlation between: a) the content mean and content distribution for the in-process dosage units and b) the content mean and content distribution for finished dosage units.

- A detailed data-supported justification for the overall hierarchical inspection plans and switching rules used by the manufacturer of the drug product for the each blend (including the final blend [covered by this guidance]), the in-process formed dosage units and the finished dosage units. [Note: Where appropriate, the justification should include the scientifically sound rationale that clearly establishes the ability of the inspection plans to determine the acceptability of the batch or lot at a confidence level of 95 % or higher based on the results obtained for the small percentage of the population tested.]
B. POSTAPPROVAL CHANGES

If you plan on changing the firm’s existing controls for blend content uniformity and dosage-unit content uniformity to the methods described in this guidance, the change may be considered a minor change as described in the postapproval changes guidance. When this change results in an increase in the level of confidence in the content uniformity of each batch or lot deemed acceptable, the Agency recommends the sponsor provide a notice of the change in the next annual report along with the information indicated in the preceding section (VIII. A.). The raw data collected to support changes and all other contingent records and notes should also be maintained at the manufacturing site. However, when this change results in a decrease in the level of confidence in the content uniformity of each batch or lot deemed acceptable, the Agency recommends the sponsor provide a notice of the change in a CBE-30 supplement along with all of the information indicated in the preceding section (VIII. A.).

\[42\] FDA’s guidance for industry on Changes to an Approved NDA or ANDA.
GLOSSARY

A. TERMS DEFINED BY REGULATION

1. "Acceptance criteria" 21 CFR 210.3(b)(20)
2. "Active ingredient" §§ 210.3(b)(7)
3. "Batch" §§ 210.3(b)(2)
4. "Component" §§ 210.3(b)(3)
5. "Drug product" §§ (b)(4)
6. "Inactive ingredient" §§ (b)(8)
7. "In-process material" §§ (b)(9)
8. "Lot" §§ (b)(10)
9. "Manufacture, processing, packing, or holding of a drug product" §§ (b)(12)
10. "Quality control unit" §§ (b)(15)
11. "Raw data" 21 CFR 58.3(k)
12. "Representative sample" 21 CFR 210.3(b)(21)
13. "Strength" §§ 210.3(b)(16)

B. TERMS OR PHRASES DEFINED BY STATUTE

   (contaminated with filth) (a)(2)(A)
   (made under filthy conditions) (a)(2)(B)
   (CGMP non-compliant) (a)(3)
   (in a contaminated container) (a)(4)
   (contains “unsafe” color) (a)(5)
   (contains “unsafe” animal drug) (a)(6)
   (feed containing “unsafe” animal drug) (b)
   (strength, quality, or purity differs from official compendium) (c)
   (misrepresented strength, quality, or purity) (d)
   (mixed with or substituted with another substance)
3. "Counterfeit drugs" 21 U.S.C. 321 (g)(2)
   “A drug … shall be deemed to be adulterated —if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess: …"
C. TERMS OR PHRASES DEFINED FOR USE IN THIS GUIDANCE

Absolute Range, as used to define the limits for a variable, means the bounded range for that variable. For example, an absolute content range is a content range: a) which is independent of the value of the mean value observed for any set of samples and b) within which all individual sample values are expected to fall. If the manufacturer’s established requirement is that all blend samples must fall within 95.0% to 105% of the target value, the absolute range is 95.0% to 105% and not a) 100±5% or b) when the sample tested ranges from 96.0% to 105% and the mean is 99.5%, the absolute range is from 96 to 105% – not the apparent dispersion about the mean (99.5% -3.5%/+5.5%).

Attribute, as used in the sciences, including statistics, means a quality of something and, accordingly assessments of an attribute are qualitative in nature; antonym: variable

Characteristic means any qualitative or quantitative defining feature.

Confidence means how certain one can be about the validity of the predicted characteristics of a population. Confidence depends on the valid application of a given statistical procedure to a sufficient set of observations made on a population-representative sample. In general, the larger the number of population-representative units tested the higher the level of confidence that the values observed for the units tested accurately predict the true population distribution of unit values.

Confidence interval is the predicted range of values or states obtained from applying a scientifically sound and appropriate statistical estimation procedure to the results obtained from a population-representative set of observations made on a sample.

Correlation, as used in statistics, means the degree to which two or more variables are related and change together. “Correlation coefficient” means a number or function (having a value of between –1 and +1) that indicates the probable degree of correlation between two variables.

Critical, as that term applies to pharmaceutical products and processes, is an adjective that applies to any process or product characteristic that is required to be controlled in a manner that complies with, or pertaining to any applicable requirement defined in, the drug CGMP as set forth in 21 CFR 210 through 21 CFR 226. Non-critical, in the same context, is an adjective that applies to any process or product characteristic that is above or in addition to the minimums established in the drug CGMP – for example, the uniformity of the color of the finished tablets.

Distribution is a value ordered frequency table or figure depicting the range of values in the population and the number of entities having each value.
**Dynamic sampling** means the controlled removal of portions of a **population** while the **population** is being produced. When **dynamic**, **interval sampling** occurs in pharmaceutical manufacturing during the production of a **batch** of drug product, the **sample** taken at each **sampling point** must, itself, be **representative** of the possible **variability** in the drug product at that point (see Example 1). As a consequence of this, each **dynamic sample** must encompass the **variability** at the point that said **sample** is being taken.

**Example 1: Dynamic Sampling During Tablet Manufacture**

Since a firm’s sampling plan is dynamic and specifies taking **samples** from a hypothetical 21-station tablet press at intervals, then the **sample** taken at each **sampling interval** must be some whole-number multiple of the 21 tablets produced at that interval.

Thus, when the **sampling plan** for this 21-station press requires sampling at start up, “n” intervals during tablet production, and at the end of production, the final **sample** should consist of at least \((n + 2) \times 21 \times \text{some integer multiple}\) tablets.

Evaluate **means** to consider or examine something in order to judge its value, quality, importance, or condition.

Examine, **means** to study something in detail – the drums were opened and their contents examined for the presence of foreign particulate matter.

**Exhibit batch (or exhibit lot)** refers to any **batch** (or **lot**) submitted in support of an ANDA, NDA, ANADA, NADA, DMF, or VMF. This includes any submitted bioequivalence, development, start-up, initial validation, and commercial production **batch** (or **lot**) of a drug product.

**Factor** **means** something that contributes to or has an influence on the result of something.

**Grab sampling** **means** **sampling** by choosing any convenient **sample** of some defined or minimum size (number or amount) from a **population**. The defined **USP sample**, the **article**, is, of necessity, a **grab sample** as is, of necessity, any “in commerce” **sampling** from a small portion of a batch.

**Initial validation, performance qualification (PQ), or evaluation qualification (EQ) batch or lot** is a **batch** or **lot** manufactured and tested to verify the proposed routine manufacturing process controls are adequate. Because the in-process controls (21 CFR 211.110(a)) require the manufacturer to have, and follow for each batch, established control procedures “to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product,” each production batch (or lot) is required to be a one that validates the process – thus each is a **validation batch** (or **lot**).

**In-process dosage unit** is a capsule or tablet as it exists at the completion of any in-process step starting from the time the dosage unit is formed in the manufacturing process and continuing until it is ready to be packaged. For example, in a process that has processing steps (phases, stages) that: a) forms the final blend into tablet cores, b) film-coats the cores with a color, c) overcoats the color coat with a clear coat, d) prints identification on the clear coated units, e) waxes and polishes the printed units, f) holds the polished units in bulk until the batch is released for packaging, and g) packages the released polished units for distribution, the outputs of steps “a)” through “e)” are **all** collections of in-process dosage units. In the example, the corresponding appropriate “in-process dosage unit” phase-differentiating identifiers could be: a) “freshly formed,” b) “color coated,” c) “clear coated,” d) “printed,” and e) “polished.” At Step “f,” the dosage units are **finished dosage units**.
**Inspection** is the **sampling** of a **sample** from a **population** coupled with examining or testing that sample, or a **subsample** thereof, for compliance with predetermined **specifications**.

**Measure** means to find out the size, length, quantity, or rate of something using a suitable instrument or device, or to assess the quality of something by quantitatively comparing it to some standard.

The **normal**, or **Gaussian**, distribution is a unimodal symmetrical **distribution** having a **population mean**, \( \mu \), and **population standard deviation**, \( \sigma \). The variance of this distribution is \( \sigma^2 \). Its mean or average value, \( \mu \), is also its **mode** (the most frequent value) and **median** (the value that divides the distribution in half). This is the case because a normal distribution is both **unimodal** and **symmetrical**. Moreover, \( \sigma \) is the distance from the mean, \( \mu \), to the two inflection points on the curve that encompasses the **population** values. Thus, \( \mu \) is the location parameter for a normal distribution and \( \sigma \) describes the spread, scatter or dispersion of the **population** about the mean. Defining \( z \) as the distance from the mean in units of standard deviation, the values of \( z \) can be computed using the formula:

\[
z = \frac{X - \mu}{\sigma}
\]

(1)

Where \( X \) is a given value in the **population**.

Using \( z \), we can ascertain the proportion, \( P \), of entities in the **population** that have values of \( z \) smaller than any given \( z \). The proportions found are such that 34.13% of the **population** is between 0 and 1 or 0 and \(-1 \), 13.59% between 1 and 2 or \(-1\) and \(-2 \), 2.14% is between 2 and 3 or \(-2\) and \(-3 \) and 0.14% is outside of 3 or \(-3 \). Based on this, 68.26% of the **population** is between \(-1\) and \(+1 \), 95.44% is between \(-2\) and \(+2 \), and 99.72% is between \(-3\) and \(+3 \).

**Population** means any finite or infinite collection of individual entities. For control purposes, a **population** is also a collection governed by some property that differentiates between things that do and things that do not belong. The term **population** carries with it the connotation of completeness. Depending upon the setting, the drug-product CGMP regulations treat a **lot**, a **batch**, a small group of **batches**, or all of the **lots** or **batches** produced in a given time interval as the **population** being evaluated. **Lot** or **batch** quality evaluations must be designed to predict whether, or not, the **samples** tested (or examined) from a **lot** or **batch** being inspected not only meet their specifications but also predict that the **lot** or **batch** does, or does **not**, belong to the universe of releasable drug product.

**Purity** means the absence, or degree of absence, of anything of a different type -- **tests to establish the purity of the water in the holding tank**.

**Quality** means an essential identifying property of something.

**Representative Sample** means any subset of a **population** whose measured characteristics can validly be used to predict the characteristics of the **population**. When a CGMP regulation requires a **representative sample**, that sample must be **representative** of the **lot** or **batch** addressed by said regulation. For a **sample** to be **representative**, it must satisfy three criteria:

1. It must be from all portions of the **population** or, when sampling is performed during the **production of the batch or lot**, it must appropriately span the production operation that it covers from start to finish.
2. Its size (number) must be large enough that the results obtained from testing or evaluating that number of entities or amounts can validly predict the population’s distribution with respect to the parameter or parameters evaluated.

3. Each removal of entities or an amount in the set of removals that define the complete sample must be done so that its removal does not bias or affect the selection of the next removal in the set.

Representative Inspection is the sampling of a representative sample from a population coupled with examining or evaluating (testing) that representative sample, or a representative subsample thereof, for compliance with predetermined specifications.

Representative sampling means sampling in a manner that is designed to assure that the sample taken is representative of the population from which it is taken. In order to make valid nontrivial generalizations about the population from the results obtained by evaluating a sample from said population, the sample must have been obtained by a sampling scheme that ensures four (4) conditions:

1. The sample set must span the population – be from all parts of the batch or, in the dynamic case, cover the production period from start to finish.

2. Relevant characteristics of the population sampled must bear an established or proven relation to the corresponding characteristics of the population of all possible samples associated with the sampling scheme used. [Note: In dynamic sampling, the number of samplings must be sufficient to reflect the variability in the production step that is being sampled, and each sampling must be representative of the local variability present at the time of sampling.]

3. The population sample must be of sufficient size that valid generalizations about properties of the population may be inferred from the results obtained from the evaluation of those properties in the samples. The inferences from the results must be made using a recognized, proven “book of rules” whose validity rests on statistics, the mathematical theory of probability.

4. The sampling of any given sample in the sampling set that defines the complete sample must be done in a manner that ensures it does not bias the next sample.

RSD is an acronym for the term relative standard deviation; \( RSD = \left( \frac{\text{standard deviation}}{\text{mean}} \right) \times 100\% \).

Sample means any portion of a population. A sample is any subset of the population. It can be a single entity, a group of entities, or a portion removed from another sample. It carries the connotation of incompleteness.

Sample mean is the average of the measured values for the samples evaluated. Usually, the mean is computed using the formula:

\[
\bar{X} = \frac{1}{n} \sum_{i=1}^{n} X_i
\]  \hspace{1cm} (2)

Where the \( X_i \) are the values observed for the \( n \) samples evaluated.
Sample variance or, more accurately, the sample estimate of variance, denoted as $s^2$, is the estimate of the variance, the second moment about the population mean, $\mu$. Usually, this statistic is computed using the formula:

$$s^2 = \left[ n \sum_{i=1}^{n} X_i^2 - (\sum_{i=1}^{n} X_i)^2 \right] / [n (n-1)] \quad (3)$$

However, the general formula that should be used is:

$$s^2 = \left[ n \sum_{i=1}^{n} X_i^2 - (\sum_{i=1}^{n} X_i)^2 \right] / [n (n-f)] \quad (3a)$$

Where $f$ is the degrees of freedom consumed in the computation process. When the $X_i$s are “direct” measurements, then $f = 1$ because one degree of freedom is consumed in the computation of the “differences.” However, when the $X_i$s are ratio measurements, as is often the case in hyphenated chromatographic/detector measurements using an Internal Standard, then $f = 2$ and the proper formula to use is:

$$s^2 = \left[ n \sum_{i=1}^{n} X_i^2 - (\sum_{i=1}^{n} X_i)^2 \right] / [n (n-2)] \quad (3b)$$

Sample variability or, more accurately, the sample estimate of variability, denoted as $s$, is the square root of the sample estimate of variance. This term is often referred to as the “sample standard deviation.” That name is the source of the alternate abbreviation, “SD.” While variances are additive, variabilities or standard deviations are not additive. Thus, if one needs to add or average standard deviations, one must first convert them into variances by squaring them. Then, the variances can be added and the square root of the sum is the total standard deviation or, for like variances, dividing the sum by the number of like variances added gives the average variance, and the square root of that variance is the average standard deviation.

Sample size has more than one meaning.

- For discrete populations (tablets, capsules, syringes, etc.), it is the number of entities (units) from a population that are either:
  - Removed by sampling or
  - Inspected (examined or tested) by some procedure or method.

- For non-discrete populations (blender loads, drums of a component, bulk liquids, etc.) it is the amount of material (by weight or volume) from a population that is either:
  - Removed by sampling, or
  - Inspected (examined or tested [evaluated]) by some procedure or method.

In the USP’s view, sample size refers to the minimum number of entities (the USP article) for discrete populations. For non-discrete materials, the USP article (sample size) is the stated amount of material that is required for a given USP test or evaluation.

Depending on the context, the FDA and the Court (Judge Wolin in USA v. Barr) have used the term sample size to connote either:

- The physical amount of a non-discrete or discrete material that is to be sampled (a defined number of units in the discrete case or, in the non-discrete materials’ case, nominally, at least three times the dosage unit weight) or
- The amount (number, weight, or volume) to be used in a given test or evaluation to generate a result.
Sampling means the controlled removal of any portion of a population for retention and/or examination or testing purposes.

Sampling plan means the scientifically sound and appropriate strategy used to take a valid sample.

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

Simple (Unrestricted) random sampling means sampling in a manner that each entity in the population has an equal chance of being the first member of the sample; each remaining entity has an equal chance of being the second member of the sample; and so on – subject to the constraint that “each possible sample has an equal chance of being selected.”

Specification means a detailed description of a component, material, intermediate, product, or control in terms of the numerical limits, ranges or acceptance criteria that defines what can be accepted for: a) use or b), in the “product” case, for introduction into commerce. For the pharmaceutical industry, such specifications must be designed to ensure that the each batch (or lot) of drug product manufactured by a given firm meets scientifically sound and appropriate specifications that define the identity, strength, quality and purity of each dose such that, after the batch (or lot) is released into commerce, a) each dose can validly be represented to be safe and efficacious and b) any USP (or NF) article in said batch (or lot) will, if tested, meet the explicit and implicit commercial requirements set forth in the USP (or the NF) for that product. [Note: The term controls includes both the equipment used to effect the control required and the permissible limits, ranges, and/or acceptance and other criteria used to establish that a given control is functioning or has functioned as it was designed to function.] A specification is a predefined characteristic, or limit, or range of an attribute or variable that defines what is an acceptable product outcome for a given process step. Examples of attributes are:

- Comparative degree of whiteness against some set of “white” standards, and
- Degree of perfection (for tablets, un-chipped, chipped, scratched, marked, spotted, specked, miss-punched, cracked, de-laminating, and broken).

Examples of attribute characteristics are:

- Color and
- Shape.

Examples of limits and ranges for tablet attributes include:

- No blue or broken tablets in any representative 1250 examined, and
- NMT 3 chipped or cracked tablets in any representative 800 examined.

Examples of variables are: content, active release rate, and weight. Examples of limits and ranges for variable factors include:

- Active level is 100 % to 102 % of the label claim (LC),
- After 1 hour, not less than 10 % LC nor more than 30 % LC is released and, after 4 hours, not less than 70 % LC nor more than 80 % LC is released
- Tablet weights must be between 190 and 210 mg.
Specification Limit is a predefined upper limit, lower limit, or range that, for a given characteristic (attribute or variable) factor, defines what is an acceptable product outcome for a given process step. Examples of limits and ranges for acceptable product outcomes include:

- Acceptable batches contain NMT 3 chipped tablets in any 2500-unit sample,
- The acceptable purity for a batch of Primidone is 99% to 100% by weight.

Static sampling means the controlled removal of any portion of a population for retention and/or testing purposes from the entire population after a given production step has been completed.

Statistical inference means making generalizations about the characteristics of a population derived from the study of one or more representative samples from the population. Statistical inference takes two forms:

- Estimates of the magnitudes of population characteristics and
- Tests of hypotheses regarding population characteristics.

Thus, statistical inferences are predictions of what would be the case if the parent population were fully analyzed with respect to the characteristic or characteristics evaluated. In the world of drug products, the most common distributions found are the normal or Gaussian, the skewed Gaussian, the Poisson and, in multi-station production equipment, multi-modal (usually bimodal). [Note: The bimodal distribution is typically caused by tooling and setup differences or operational problems during the production of a given batch.] To simplify discussion, this discussion will presume that the distribution of an in-control pharmaceutical component, material or process product can validly be approximated as a normal or pseudo-normal distribution.

Stratified sampling is the process of collecting a sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process to obtain a sample dosage unit that specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content. Stratified sampling is therefore, by definition, a non-CGMP-compliant form of sampling because the drug product CGMP regulations require the samples to be representative (21 CFR 211.160(b)) of the lot or batch (as that term is defined in 21 CFR 210.3(b)(21) – not of the higher risk portions of the lot or batch. By definition, stratified sampling does not provide samples that meet this CGMP minimum requirement that the samples must be batch or lot representative.

Target assay, target content or target refers to the intended strength or intended amount of active ingredient in the dosage unit that meets the requirements set forth in 21 CFR 211.101(a).

Test, as a verb, means to examine something in order to ascertain the presence of or the properties of a particular substance – test for bacteria on a surface or test for the level of water in a drug substance. Test, as a noun, means a procedure or method used to evaluate a sample or sample aliquot for some characteristic or characteristic level – the test for Chloride was negative.

Variable means something that is capable of changing or varying and, in the pharmaceutical industry, the variables are those control and material factors that are known to control or contribute to the variability in the product produced by a given process.
**Weight correction** is a mathematical correction to validly normalize the content result obtained for the level of active in a “freshly formed” dosage unit to what that active content result would probably have been had that dosage unit been formed at the manufacturer’s established target weight. For example, a tablet with a measured strength of 19.4 mg and weight of 98 mg has a weight fraction active content of 0.197959184 mg Active/mg Tablet (mg Active/mg Tablet = 19.4 / 98 = 0.197959184 mg/mg). If the drug-product’s label claim is 20 mg per each 100 mg tablet, the weight-corrected result percent of active in the dosage unit tested is 0.197959184 mg Active/mg Tablet / 0.20 mg Active/mg Tablet * 100 % = 98.9795918 % of the label claim. Rounding that result to two decimal places and using the result to estimate the content of active in the blend that went into that tablet, you find that the blend content was probably 99% of the blend’s target content level for the active.
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1 “Federal Food, Drug, And Cosmetic Act,” UNITED STATES CODE, TITLE 21—FOOD AND DRUGS, CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT, SUBCHAPTER I—SHORT TITLE provides “This chapter may be cited as the ‘Federal Food, Drug, and Cosmetic Act’” (June 25, 1938, ch. 675, Sec. 1, 52 Stat. 1040.) This “short title” is commonly abbreviated as “FDC Act.”


5 In 1988, the United States Supreme Court in Berkovitz v. US (486 US 531, 100 L Ed 2d 531, 108 S Ct 1954) overturned a US Appeals Court decision and ruled that: a) FDA administrators have no authority to issue any communication that is at odds with any clear regulation and b) no firm can use any such communication as a defense for the firm’s failure to comply with any such regulation.

6 “Generic Drug Enforcement Act of 1992” – Pubic Law 102-282, Sec. 1(a), May 13, 1992, 106 Stat. 149, provided that: “This Act [enacting sections 335a to 335c of this title {FDC Act}, amending sections 321, 336, 337, and 355 of the title {FDC Act}, and enacting provisions set out as notes under section 335a of this title {FDC Act}] may be cited as the ‘Generic Drug Enforcement Act of 1992’.” This “title” is commonly abbreviated as “GDEA.”


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