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Saturday, 15 November 2003

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 03D-0493

FORMAL COMMENTS ON:

"**Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment** [*G:\5831dft.doc 10/27/03*]."

Pursuant to a "request for comment" in ***FEDERAL REGISTER*, Vol. 68, No. 216**, pp 63109 – 63110.

A review of the PQRI 'recommendation' on which this guidance is based (that embodies many of these comments) was submitted, on 25 September 2003, to CDER's Ombudsman, Warren Rumble, (via e-mail: **ombudsman@cder.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@cder.fda.gov**).

The comments being provided are based on that review and an intermediate-level review of the "**Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment** [*G:\5831dft.doc 10/27/03*]."

This commentary adds 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to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations pertinent to this Draft guidance.

The comments begin at Line 16 of the Draft.

In general, the comments are in the current font, "News Gothic MT."

When a wording change within existing wording is suggested, the comment text is entered in an *italicized News Gothic MT* font.

When text additions are presented, they are placed within quotation marks (" ") in the "News Gothic MT" font.

Explanatory remarks and notes are indented on both margins.

The original text is presented in a "Times New Roman" font and quoted references to CGMP are presented in a "Lydian" font.

Should anyone in the Agency who reviews said comments need clarification on a given suggestion, then, they should e-mail **drking@dr-king.com** their questions and, where appropriate, this commenter will provide additional clarifying remarks.

Respectfully,

Dr. Paul G. King

2003D-0493

EMC 1

Formal Review of Guidance for Industry[1]: Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

"I. INTRODUCTION"

This draft guidance begins with an "**Introduction**" that in the first paragraph states (Lines 18-23), " This guidance is intended to assist manufacturers of human drug products in meeting the requirements of 21 CFR 211.110 for demonstrating the ~~adequacy of mixing to ensure~~ uniformity of in-process powder blends, *and in-process* and finished dosage units. This guidance describes the procedures for assessing powder mix adequacy, correlating in-process dosage unit test results with powder mix test results, and establishing the initial criteria for control procedures used in routine manufacturing. *This guidance applies only to drug products that are a) 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 b) capsules filled with a uniform mixture of solids."*

Reviewing **21 CFR 211.110**, this commenter finds no ***requirement*** *per se* "for demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished dosage units."

The clear requirements of **21 CFR 211.110** are (with underlining emphasis added):

"(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established 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."

"Adequacy of mixing to assure uniformity and homogeneity" is but one of the suggested list of control procedures that, where appropriate, must be used ("Such control procedures shall include, but are not limited to, the following, where appropriate: (1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; (5) Clarity, completeness, or pH of solutions")."

"Adequacy of mixing to assure uniformity and homogeneity" is therefore simply one of the in-process control procedures that are applicable to tablets and capsules.

The requirements set forth in **21 CFR 211.110(a)** are for the development and use of written control procedures for each batch to monitor the output and validate the performances of ALL those manufacturing processes that may be responsible for causing variability in the in-process material and the drug product.

"(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 where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications."

The requirements here are for valid in-process specifications that are consistent with the drug product final specifications.

Today, given the general acceptance of statistics in all US industries, such specifications must be:

a. Derived "from previous (including developmental) acceptable process average and process variability estimates" for the ***batch*** – NOT just for the samples tested.

b. Determined "by the application of suitable statistical procedures." [**Note:** To be ***suitable*** under CGMP,

i. The samples tested must span the batch output at the phase where the sampling is being performed and be sufficient to be ***batch-representative*** (**21 CFR 211.160(b)(2)**), and

ii. The statistical procedures used must predict, at a confidence level of not less than 95 % (the recognized {since the 1960's} consensus level of confidence required to meet the statistical quality control criteria established for the drug product in **21 CFR 211.165(d)**), that the batch is acceptable.]

"(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods."

Here the requirements are for the testing of in-process materials "at the commencement or completion of significant" production "phases" (not just the final blend and the initially formed dosage unit stage) "or after storage for long periods."

"(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Here the requirement is for a "quarantine system designed to prevent" the use of rejected in-process materials "in manufacturing or processing operations for which they are unsuitable"

With these clear regulatory requirement minimums in mind, let us now examine the extent to which the guidance complies with these requirement minimums.

"II. BACKGROUND"

In presenting the "**Background**" (Lines 32 through 55), those that prepared it have left out the repeated failure of those generating the various documents cited to respond to, much less address, the science-supported dissenting views of this commenter (and perhaps other commenters).

For example, until recently, Lee Kirsch, the editor of the PDA's Journal of Pharmaceutical Science and Technology, has refused to publish (even as a "Letter to Editor") this commenter's dissenting views on the article referenced in Footnote 5 ("The Use of Stratefied Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends, *PDA J. Pharm. Sci Technol.*, 57:59-74, 2003").

Before proceeding further, this commenter suggests that some of the key terminology used needs to define, in terms consistent with CGMP and statistics, the underlying science upon which inspection (sampling and sample evaluation) is based.

To that end, this commenter offers the following definitions that have previously been shared with the Agency:

Population — 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.

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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.

Sample — 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.

Representative Sample — Any subset of a *population* whose measured characteristics can be validly 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, if sampling is performed during the production of a *batch*, it must appropriately *span* the production operation it covers from start to finish.
2. Its *size* 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 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.

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) 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* 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— The controlled removal of any portion of a *population* for retention and/or examination or testing purposes.

Representative Sampling— 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.
   [**Notice:** 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*.

Simple *(Unrestricted)* ***Random Sampling***— 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."

Grab Sampling— 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, of necessity, any "in commerce" sampling from a small portion of a batch.

Dynamic Sampling— 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 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] x 21 x** some **integer** multiple) tablets.

Static Sampling— 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.

Sampling Plan — The *scientifically sound* and *appropriate* strategy used to take a *sample*.

Statistical Inference — 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.

Statistical inferences involve reaching conclusions about *population* characteristics from a study of *samples* that are known, or can validly be presumed, to be *representative* portions of the *population*.

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.

Distribution— A value ordered frequency table or figure depicting the range of values in the *population* and the number of entities having each value.

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*). [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 pseudo-*normal distribution*.

Normal, or Gaussian, Distribution— A unimodal symmetrical distribution having a *population mean*, μ, and *population standard deviation*, σ.

The variance of its distribution is σ^2.

Its mean or average, μ, is also its mode (the most frequent value) and median (the value that divides the distribution in half).

This is the case since a *normal distribution* is both unimodal and symmetrical

Moreover, σ is the distance from the mean, μ, to the two inflection points on the curve that encompasses the *population* values.

Thus, μ is the location parameter for a normal distribution and σ 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:

$$z = (X - \mu) / \sigma \quad (1)$$

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 *z*, 13.59 % between 1 and 2 or –1 and –2 *z*, 2.14 % is between 2 and 3 or –2 and –3 *z* and 0.14 % is outside of 3 or –3 *z*.

Based on this, 68.26 % of the *population* is between –1 and +1 *z*, 95.44% is between –2 and +2 *z*, and 99.72% is between –3 and +3 *z*.

Sample Mean — The average of the measured values for the *samples* evaluated.

Usually, the mean is computed using the formula:

$$\overline{X} = {}^{1}/_{n} \Sigma^{n}_{i=1} X_i \quad (2)$$

Where the X_i are the values observed for the *n samples* evaluated.

Sample Estimate of Variance — Denoted as s^2, is the estimate of the variance, the second moment about the *population* mean, μ.

Usually, this statistic is computed using the formula:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n(n\text{-}1)] \quad (3)$$

However, the general formula that should be used is:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n(n\text{-}f)] \quad (3a)$$

Where *f* is the degrees of freedom consumed in the computation process.

When the X_is are "direct" measurements, then **f** is **1** because one degree of freedom is consumed in the computation of the "differences."

However, if the X_is are ratio measurements, as is often the case in hyphenated chromatographic/detector measurements using an Internal Standard, then **f** is **2** and the proper formula to use is:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n(n\text{-}2)] \quad (3b)$$

Sample Estimate of Variability — Denoted as **s**, is the square root of the 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, 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: **a)** sum or, dividing by the number added, **b)** the average variance, one can compute **a)** the total standard deviation or **b)** the average standard deviation.

Confidence — 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 set of observations made on a *population-representative sample*.

Confidence Interval— The predicted range of values or states obtained from applying a statistical estimation procedure to the results obtained from a *population-representative* set of observations made on a *sample*.

Specification — 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:

- Whiteness, 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 98 % 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— A predefined upper limit, lower limit, or range that, for a given characteristic 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 800-unit *sample*,
- The acceptable *purity* for a *batch* of Primidone is 99 % to 100 % by weight.

Inspection— The *sampling* of a *sample* from a *population* coupled with examining or testing that *sample*, or a sub-*sample* thereof, for compliance with predetermined *specifications*.

Representative Inspection — The *sampling* of a *representative sample* from a *population* coupled with examining or testing that *representative sample*, or a *representative* sub*sample* thereof, for compliance with predetermined *specifications*.

"III. SCOPE"

With these definitions in mind, let us consider what the guidance proposes.

First, the Draft's definition of "*Stratified sampling*" (Lines 60 through 65) seems to be problematic because, by targeting "locations in the compression/filling operation that have the greatest potential to yield extreme highs and lows in test results" (Lines 61 and 62), the sampling plan defined:

- Is not a ***batch representative sampling plan***
- Cannot ensure that the samples sampled are, as **21 CFR 211.160(b)(2)** requires, ***representative*** of the ***batch***.

At least it claims to be a sampling plan for dosage units that samples at "predefined intervals" and collects "representative samples from" those "specifically targeted" areas

However, as we shall see, as described in the Draft, the procedures proffered do not sample interval *representative samples*.

Next, the Draft states (Lines 62 through 65), "These test results are used to monitor the manufacturing process output that is most responsible for causing finished product variability. The test results can be used to develop a single control procedure to ensure adequate powder mix and uniform content in finished products."

Since the samples taken and tested are not even batch representative, how can the test results from the testing of a small number of non-representative dosage units validly "be used to develop a single control procedure to ensure adequate powder mix and uniform content in finished products?"

The Draft continues (Lines 67 through 70) with "The methods described in this guidance are not intended to be the only methods for meeting Agency requirements to demonstrate the adequacy of powder mix. Traditional powder blend sampling and testing, in conjunction with testing for uniformity of content in the finished product, can be used to comply with current good manufacturing practice requirements."

Given the 1988 Supreme Court case, Berkovitz v. USA, **this commenter was unaware that the Agency could legally have or promulgate any** "Agency requirements to demonstrate adequacy of mixing" **that were at odds with the clear regulatory requirement *minimums* established in the CGMP regulations.**

Yet the preceding seems to assert that the FDA has administrative authority to ignore clear regulatory requirements and substitute its own however sound requirements in their place without amending said regulations.

Moreover, this Draft continues (Lines 71, 72 and Footnote 6) with "Use of at-, in-, or on-line measurement systems can also be appropriate and are described in other guidance documents.[6]

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[6] 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."

As others have when commenting on similar Draft guidance documents, this commenter objects to references to other Draft Guidance documents that may, or may not, be finalized and issued.

Next the Draft states (Lines 74 through 86 and Footnote 7), "This guidance provides recommendations on how to:

- Conduct powder blend sampling and analyses.
- Establish initial criteria for stratified sampling of in-process dosage units[7] and evaluation of test results.
- Analyze the stratified samples and evaluate data.
- Correlate the stratified sample data with the powder blend data.
- Assess powder mix uniformity.
- Correlate the stratified sample data with the finished dosage unit data and assess uniformity of content.
- Test exhibit and validation batches for adequacy of powder mix.
- Test and evaluate routine manufacturing batches.
- Report the use of stratified sampling in the application.

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

Then, the Draft states (Lines 88 through 92), "The methods described in this guidance can be used to monitor active ingredient homogeneity of powder blends and to ensure uniform content 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 adequacy of powder mix and uniform content of the finished product."

Since these methods are based on a sampling plan that does <u>not</u> meet the clear requirements of the CGMP regulations for the taking and testing of *batch-representative samples*, these "*stratified sampling*" methods cannot validly be used to satisfy any CGMP requirement.

Therefore, these methods are, contrary to what the draft asserts, clearly <u>not</u> "one way to satisfy the CGMP" regulations governing drug products.

Properly, the next sentence (Lines 92 and 93) should be revised to read, "The method assumes appropriate monitoring of all manufacturing steps as required by the regulations ~~or~~ *and, where they exceed the CGMP* ***minimums****, the firm's* application commitments."

Since all drug product manufacturers must meet all of the applicable CGMP minimums, a firm's application commitments should only be an issue when they clearly exceed the CGMP ***minimums***.

Though those that drafted this guidance clearly recognized the need to assess "potency and other attributes that can affect the drug product," the Draft continues with (Lines 93 through 97) "This guidance does not discuss the assessment of the potency and other attributes that can affect the finished dosage units, or the homogeneity of inactive ingredients. 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."

The guidance then adds a paragraph (Lines 99 through 105 and Footnote 8), "When using the methods described in this guidance, certain data or trends may be observed. We recommend that manufacturers scientifically evaluate these types of research data to determine if they affect the quality of a product and, if so, how. The FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of proposed methods. Any FDA decision to inspect research data would be based on exceptional situations similar to those

outlined in Compliance Policy Guide Sec. 130.300.[8] Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner.

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

a paragraph that seems to be out of place in a "**SCOPE**" section.

Moreover, this "out of place" paragraph seems to have been lifted from the Draft "PAT" guidance and inserted in the scope of a Draft guidance that purports and is represented to addresses CGMP compliance issues.

Factually, if the results clearly indicate a batch failure that requires an investigation (and all such failures do require an investigation), the paragraph is seemingly at odds with the Agency's policy of reviewing all of a firm's investigations.

"IV. CORRELATION OF IN-PROCESS STRATIFIED SAMPLING WITH POWDER MIX AND FINISHED PRODUCT"

This section begins by stating (Lines 111 through 119) "If you plan to follow the procedures described in this guidance document, we recommend that you first complete the process development procedures described in this section before using the methods described in sections V, VI, VII. The subsections below describe how to assess the adequacy of powder mix, uniformity of content of the in-process and finished dosage units through correlation and assessment of data from development, validation and manufacturing batches. These procedures can reveal deficiencies in the blending operation that may not have been previously detected. We recommend that manufacturers correct deficiencies in the blending operation before implementing the routine manufacturing control methods described in this guidance."

Given the section's title and the Draft's "*Stratified sampling*" definition, how can a CGMP-compliant drug-product manufacturer follow this section's "guidance" and still remain CGMP compliant?

"A. Assessment of Powder Mix Uniformity"

This subsection states (Lines 123 through 141): "We recommend the assessment of powder mix uniformity using the following procedures:

- Conduct blend analysis on batches by extensively sampling the mix in the blender and/or intermediate bulk containers (IBCs).

This commenter has no problems with what is said here provided the sampling plan:

a. Samples unbiased samples of sufficient size,
b. The samples sampled are batch representative,
c. Test-sample-aliquot size is unit dose or smaller,
d. Sufficient sample aliquots are tested for each key variable factor, and
e. Scientifically sound and appropriate batch spanning specifications are set for each critical variable factor (typically, the evaluation of the content of each active ingredient, disintegrant (or its surrogate), lubricant (or its surrogate), and, for "sustained release" dosage forms, each release regulator (or its surrogate).

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- Identify appropriate blending time and speed ranges, dead spots in blenders, and locations of segregation in IBCs. Determine sampling errors.

  While such research may be laudable, it would be better to focus on develop blends that are uniform and mechanically stable rather than to focus on "finding" those "spots" in a given set of experiments that appear to be "dead spots in blenders" or "locations of segregation in IBCs."

  This commenter would cast the second bullet in positive terms as follows:

  - "Develop controls on component specifications, blender loading and blending regimens that eliminate 'dead spots' in the blender and 'segregation' on storage in the IBCs."

- Define the effects of sample size (e.g., 1-10X dosage unit range) while developing a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3X can be used with adequate scientific justification. Appropriate blend sampling techniques and procedures should be developed for each product with consideration to various designs of blend powder sampling and the physical and chemical properties of the blend components.

  This commenter also disagrees with the tenor of this bullet point.

  The positive needs to be stated.

  This commenter recommends the following alternative:

  - "Develop a sampling plan that: a) samples aliquots of sufficient size that they are not significantly biased by the sampling procedure used and, at a minimum, are at least five (5) times the amount needed for all testing when physical characteristic tests are performed or, when no physical characteristic tests are required, ten (10) times that needed for all testing, b) takes a batch-representative set of samples from each batch, c) subsamples unbiased unit-does or smaller aliquots from each sample for all chemical tests, d) tests sufficient subsample aliquots from each sample to provide sufficient data to characterize the batch, and e) evaluates the results obtained against scientifically sound and appropriate specifications that, at the last step, must be appropriately inside of the batch specifications for the dosage units by at least the amount of variability allowed for the weight of the dosage unit."

  In this commenter's experience, at full scale, for non-V blenders that are 30-cu-ft or smaller, sampling from 12 to 15 appropriately sampling locations in the blender (V's require a few more points because of their geometry) or, if the sampling point is IBC oriented, the material in the blender valve wall area after the last container is filled and "T/M/B" when 50-kg IBCs (or "T/B" from 25-kg IBCs) are used.

  However, the preceding numbers are only valid "rules of thumb" for blends that are a) uniform and b) mechanically stable.

- Design blend-sampling plans and evaluate them using appropriate statistical analyses.

  In general, this commenter agrees with what this bullet states, but would revise it slightly to read as follows:

- Design blend-sampling plans and evaluate them using ~~appropriate~~ *scientifically sound* statistical analyses *that are appropriate for non-discrete materials*.

When modified in this manner, the wide spread misuse of statistical procedures that are appropriate for discrete materials but not for non-discrete materials should be eliminated.

For example, when the materials are non-discrete, the values found from a given location are not totally independent of those in "adjacent locations.

If one is testing drum samples from drums filled in a known sequence, the values found for a factor for material in the top of drum "n-1" should be about the same as that in the bottom of drum "n."

The statistical tests used for discrete units, in general, presume that the values found for each unit are independent of each other.

- ~~Quantitatively measure any variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. Significant within-location variance in the blend data can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error[9] or agglomeration.[10, 11] Significant between-location variance in the blend data can indicate that the blending operation is inadequate.~~

~~[9] If blend sampling error is detected, more sophisticated, statistical analyses should be applied to assess the situation, such as the use of methods described in J Berman, DE Elinski, CR Gonzales, JD Hofer, PJ Jimenez, JA Planchard, RJ Tlachac, PF Vogel, "Blend Uniformity Analysis: Validation and In-Process Testing." *Technical Report No. 25, PDA J Pharm. Sci. Technol.*, 51(Suppl 3i iii), S1-99, 1997.~~

~~[10] OS Sudah, PE Arratia, D. Coffin-Beach, FJ Muzzio, "Mixing of Cohesive Pharmaceutical Formulations in Tote (Bin) Blenders," *Drug Dev. Ind. Pharm*, 28(8): 905-918, *2002.*~~

~~[11] V Swaminathan, DO Kildsig, "Polydisperse powder mixtures: effect of particle size and shape on mixture stability," *Drug Dev. Ind. Pharm.*, 28(1):41-48, 2002.~~

This commenter cannot agree with this bullet because it is at odds with the fundamental precepts of statistics.

While one can compute "standard deviations" from the results obtained, one cannot "measure variability."

Properly, one can only **estimate** the ***sample variability*** and/or the ***population variability***.

Further, to estimate these variabilities and properly apportion them with any level of confidence, many more aliquots and replicate determinations are needed than this Draft indicates.

Moreover, to extrapolate from the results for a given batch to the process, the manufacturer needs to have rigorous controls on the physical properties of each of the components used – something that most manufacturers lack.

Finally, as this commenter has clearly established in a review of the PDA's *Technical Report No. 25*, *provided to all in the industry who wrote it*, the statistical procedures contained therein are <u>neither</u> *scientifically sound* <u>nor</u> *appropriate* for use in evaluating the properties of the batch.

Based on the preceding, this reviewer recommends deleting this bullet and, <u>provided</u> the other changes suggested are made and sufficient test replications are made for each sample aliquot work-up tested, replacing it with the following:

- "Provided all of the observed average values for the multiple measurements made on each aliquot tested are within the scientifically sound and appropriate predetermined limits specified, at the 95% confidence level or higher, **estimate** the following parameters: batch mean, batch variance, the test variance, the within-location variability, the between-location variability, and the "random" error component for each factor evaluated. Use these values to estimate the true batch mean and limit values and the minimum "process" capability for the batch. Use that data to develop the appropriate control charts for that process. When there is significant between-location variance in the blend data, the manufacture needs to ascertain what combination of improved controls (on the physical properties of the components, formulation, blender loading, blending regimen, and, where the blender is unloaded into IBCs, blender unloading, IBC storage and IBC sampling) are needed to render the blend uniform."

"B. Correlation of Powder Mix Uniformity with ~~Stratified~~ *Dynamically Sampled* In-Process Dosage Unit Data"

This subsection states (Lines 146 through 170): "We recommend the following steps for correlation:

- Conduct periodic sampling and testing of the in-process dosage units by sampling them at defined intervals ~~and locations~~ throughout the compression or filling process. Use a minimum of 20 appropriately spaced in-process dosage unit sampling points. ~~There should be at~~ *At* least ~~7 samples~~ *one sample unit from each dosage-forming station in the dosage-forming system being used should be* taken from each of these locations for a total minimum of at least ~~140 samples~~ *three times the number of sample units needed to do all the in-process testing required by the CGMP regulations for drug products.*"

This commenter finds that the Draft's proposal does not ensure that the samples are representative of the batch.

As an alternative, this commenter would propose that the *dynamic sampling* defined by this commenter should be used.

In dynamic sampling, the number of intervals needed depends upon the uniformity of the blend – the more uniform the batch, the fewer intervals need to be sampled.

However, rather than being rigorously fixed, some jitter in the interval should be built in to guard against a periodic variation.

In addition, to ensure that the sample is "representative" of the batch at the sampling point some multiple of the number of compression stations in the tablet press or the encapsulation stations in the encapsulator must be collected at each sampling time point.

Even when the dosage-unit-forming system has only seven stations, the sampling plan proposed does not collect the minimum number of samples needed for three times the testing that needs to be preformed.

For today's 250,000+ unit batches, the minimum number of tablet cores or filled capsules that can be tested for a single variable in the "true process

variability unknown" normal inspection case is 200 units when the distribution can be approximated as a normal distribution and 300 units when a distribution-free approach is needed.

When the minimum is 200 units for a single variable factor ("the content of a single active), then, a valid sampling plan would need to sample no less than 600 dosage units.

Moreover, if not less than 200 units need to be tested and, for a 42-station press, 84 units were collected at each of 20 intervals (for a total of 1660 units), at least 10 units would need to be sampled at RANDOM from each of the 20 defined intervals, weighed, worked up, and properly tested.

Those that review these comments will need to address these issues and ensure that, whatever is suggested, the suggestions must conform to all of the clear requirement ***minimums*** of CGMP including scientifically sound representative-sample sampling and testing plans that provide some significant level of confidence (95 % or higher) that the population estimates for the batch probably do encompass all of the units in the batch. [**Note:** In contrast, the confidence level from the testing sets of 30 truly random units or 30 units "chosen at random from representative samples units collected at each interval" is ***less than 20 %***. Moreover, factually, there is no way to take 10 valid random samples that are truly batch representative from the 20 representative interval samples. At a minimum, one must take 20 units at random (one at random from each interval sample) to span the batch. Thus, if the Agency truly believes that at least 20 intervals must be sampled to properly span the batch, the random samples tested must be integer multiples of 20 units. When one must be confident (at a confidence level of at least 95 % {a level that is adequate for batches of up to 500,000 units}) concerning the acceptability of a batch, between 200 and 300 "random" units (10 to 15 from each representative interval sample) need to be weighed, worked up and appropriately tested {with multiple measurements to identify the testing uncertainty}). If a 99% level of confidence is required (a level that becomes more and more necessary when the size of the batch exceeds 3,000,000 units), then the number of representative units that need to be tested is on the order of 900 to 1200 units. Lest anyone think that either of these numbers is significant, these numbers translate into the testing of not more than 0.1% of today's typical full-scale batch (today, a typical tablet batch nominally produces between 250,000 and 5,000,000 dosage units).]

- Take ~~7~~ *a location-representative number of* samples from each additional location to further assess each significant event,[12] such as filling or emptying of hoppers and IBCs, start and end of the compression or filling process and equipment shutdown. This may be accomplished by using process development batches, validation batches, or by using routine manufacturing batches for approved products.

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

This commenter agrees with the need for points to cover "significant events" and would add, start of compression of capsule filling and tooling or other maintenance disruptions.

Again, the taking of seven-unit samples is scientifically unsupportable.

For start up, successive "all station" sample sets should be taken until the production equipment appears to the operator to be meeting its set-up criteria.

At that point, the first interval sample should be taken and, based on the nominal unit production speed and batch size, the sampling times for the intervals should be estimated.

The preceding procedure should also be used whenever an interruption requires a maintenance step that changes the nature of the dosage forming system (such as a tooling replacement.

After the normal "end of compression" or "end of filling" sample units are taken, a hopper run-down study similar to the start up one should be conducted until the unit-forming system looses weight control.

While the testing of appropriate units from a) the starting up to "start" point, b) restarting up to "restart" point, and c) the "end of processing" sample to the loss of weight control should be used to verify the validity of the controls established to define the "in control" points in the dosage-forming step, the "significant event" "restart" sample sets must be included in and augment the number of samples required to be tested to establish the uniformity of the batch.

Thus, a firm would need to test not less than 200 batch-representative units (10 from each of the 20 interval samples) plus 10 randomly selected units from each "restart" sampling or 10 times the number of interval plus the number of restarts.

~~• Significant events may also include observations or changes from one batch to another (e.g., batch scale-up and observations of undesirable trends in previous batch data).~~

This commenter strikes this bullet point because it is not pertinent to the case at hand where the tablet data are to be compared with the previous final blend data for the same batch.

This must be the case because, *given the lack of rigorous controls on the physical properties of the components used,* the blend results from one batch cannot be validly compared to the tablet results from some other batch.

• Prepare a summary of the data *including the specific content values (content values corrected to the target unit or unit-fill weight) for each tablet tested and the corresponding statistical estimates derived therefrom minimally at the 95-% confidence level* ~~and analysis used to correlate the stratified sampling locations with significant events in the blending process. We recommend you submit this summary with the application as described in section VIII of this guidance.~~

For reasons similar to those stated for the previous bullet, this commenter does not understand the rationale for including "discrete event" issues in a section providing guidance for a comparison of the blend data from one batch to the dosage-unit data from that same batch.

Also, since the individual results cannot be directly compared, the comparison must be made on a population statistics inferential basis.

• Compare the powder mix uniformity *statistics-derived results obtained using the approaches outlined in Subsection A* with the *corresponding* in-process dosage-unit *statistical population*

inferential values derived from the specific response result values obtained. ~~data described above~~.

Since there is no valid way to directly compare an individual result for a given blend sample to a given individual specific result from a given dosage unit, statistics must be used to compare the aggregate properties of the two process steps (final blend and dosage-unit formation).

The Draft should address this reality.

Also, to make the comparison an "apples to apples" comparison, the specific content values (not the observed content values) for the dosage unit values must be compared to the blend data

- Investigate any discrepancies observed between powder mix and dosage-unit data and establish root causes. At least one trouble-shooting guide is available that may be helpful with this task.[13] Possible corrections may range from going back to formulation development to improve powder characteristics to process optimization. Sampling problems may also be negated by use of alternate state-of-the-art methods of *in situ* real-time sampling and analysis.

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

"C. Correlation of ~~Stratified~~ *Dynamically Sampled* In-Process *Dosage-Unit* Samples with the Finished Product"

This subsection states (Lines 174 through 185): "We recommend the following steps:

- "Conduct testing for uniform content of the finished product using an appropriate *CGMP-compliant* procedure *(21 CFR 211.160(b)(3), 21 CFR 211.165(d), and, for controlled-release dosage forms, 21 CFR 211.167(c))* or, *when the manufacturer's approved application or license specifies a larger batch-representative number is required to be tested,* ~~as~~ *the larger number* specified in the Abbreviated New Drug Application (ANDA) or the New Drug Application (NDA) for approved products."

The CGMP regulations ***minimums*** clearly require that batch representative samples be sampled and tested since doing less renders the batch adulterated.

Given the CGMP requirement minimums and the 1988 Supreme Court decision, Berkovitz v. USA, the Agency's guidance cannot legally do less than what the CGMP regulations clearly require.

- "Compare the *statistical inferences derived from the* results ~~of stratified~~ *observed for the dynamically sampled* in-process dosage unit analysis *from the previous step* with ~~uniform content~~ *the corresponding statistical inferences derived from the representative sample results from* of the finished dosage units from ~~the previous~~ *this* step. This analysis ~~should~~ *must* be done without weight correction.[14]

[14] Weight correction is a mathematical correction to ~~eliminate~~ *correct for* the effect of ~~potentially variable~~ *the* tablet weight on ~~measurement of mix adequacy~~ *measured tablet content values* — see Glossary, Section IX."

By definition, a "correction" does not eliminate anything; it corrects an observed factor (in this case the observed active content value) for the effect on

that factor of some partially correlated confounding factor (in this case, tablet weight).

The correction presumes that a) the content level depends upon the weight of the dosage-unit core or, in the case of capsules, the dosage-unit fill and b) this weight dependency can be removed by multiplying each active level by the target unit weight divided the observed weight.

Practically, this is obviously much easier to do for tablet cores than it is for the fill weight in the case of capsules.

This commenter would prefer that the Draft used the term "specific content."

- "Prepare a summary of the data and analysis used to conclude that the ~~stratified~~ *dynamic* in-process sampling provides assurance of uniform content of the finished product. We *recommend* you submit this summary with the application as described in section VIII of this guidance."

As these terms are defined, *dynamic sampling* takes batch-*representative samples* and complies with this CGMP requirement for the in-process (**21 CFR 211.160(b)(2)**) and drug product (**21 CFR 211.160(b)(3)**) samples while "*stratified sampling*" neither takes *batch-representative samples* nor complies with said CGMP requirement.

"V. EXHIBIT/*INITIAL FULL-SCALE* VALIDATION BATCH POWDER MIX HOMOGENEITY"

This section states (Lines 188 through 234): "This section describes sampling and testing the powder mix of exhibit and process validation batches used to support implementing the ~~stratified~~ sampling ~~method~~ *plans* described in this guidance."

Since, according to 21 CFR 211.110(a), the in-process controls for each batch must be designed 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," every batch is a process validation batch.

Thus, even in the 1970's, the CGMP regulations recognized that validation is a journey and not a destination.

Given the preceding, this section must be addressing the initial validation batches for which the FDA generally has a higher expectation for the manufacturer to conduct intensified study to confirm that full-scale process does indeed produce batches that meet their scientifically sound and appropriate pre-established batch specifications.

Based on the preceding, this commenter has changed the title by inserting the word "*INITIAL FULL-SCALE*" before "**VALIDATION**" in this section's title.

Turning to the text, as the Draft defines the term "*stratified sampling*," it does not comply with the CGMP minimums for drug products.

Moreover, this guidance does not describe the sampling method; it describes a general sampling plan.

Therefore, this commenter has appropriately corrected the text to reflect both of these realities.

"We recommend that during the manufacture of exhibit and process validation batches, you assess the uniformity of the powder blend, the in-process dosage units, and the finished product independently.

Formal Review of Guidance for Industry[1]: Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

We recommend you use the following steps to identify sampling locations and acceptance criteria prior to the manufacture of the exhibit and/or validation batches.[15]

[15] This is described in Section IV of this guidance."

In general, the steps and acceptance criteria proposed are not scientifically sound and appropriate and, therefore, do not comply with the CGMP minimums set forth in **21 CFR 211.110** and **21 CFR 211.160**.

Based on the preceding this Draft should be withdrawn and replaced by a Draft that a) is scientifically sound (including statistically sound) and b) does comply with the requirements set forth in the CGMP regulations for drug products, **21 CFR 211**.

"1. Carefully identify at least 10 sampling locations in the blender ~~to represent~~ *that have been established to be* potential areas of poor blending. *Also carefully identify at least 10 sampling corresponding locations in the blender that have been established to be areas of excellent blending.* For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least two depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling to include the corners and discharge area (at least 20 locations are recommended to adequately validate convective blenders). *The 'poor blending' locations should include at least one sample from all 'boundary layer' locations."*

Though this commenter finds a few problems with the approach *per se* even when it is being applied to 'exhibit' and 'initial full-scale validation batches.'

First, as written, the first sentence literally suggests that the manufacturer can arbitrarily choose locations 'to represent' not 'that are... potential problem areas of poor blending.'

Literally, the careful selection process suggested encourages the manufacturer to 'carefully' choose areas of good blending and designate them as the 'poor blending' locations as much as it encourages them to properly select areas where the risk of "poor blending" is known to be highest.

Moreover, it does not suggest that the areas chosen should have some justification (proof) that establishes the validity of the locations that have been selected

Second, as originally written, the Draft fails to direct, as it should, the manufacturer to sample an equal number of the same number of carefully identified 'potential areas of excellent blending.'

This is required because an equal number of 'potential non-problem areas' need to be included to permit the validation to ascertain the validity of the hypothesized 'potential poor blending' and 'potential excellent blending' location selection process as well as to determine: a) the degree of contrast, if any, between the 'potential poor blending' and the 'potential excellent blending' locations and b) valid estimates of the variability of the batch vis-à-vis the target values established for the variable factors evaluated.

Third, it fails to suggest that the appropriate 'boundary layer' locations should be explicitly included in the 'poor blending locations' set.

Since most engineers know the boundary layer materials (such as, the wall/blend interface, the final upper surface, the final material in the blender's discharge valve) have the greatest intrinsic risk for the materials to have properties that are significantly different from the bulk material, it seems odd that the guidance does not even suggest that sampling these materials should be included in any "worst area" directed portion of a sampling plan.

"2. ~~Collect at least 3 replicate samples from each location~~. *At each sample location defined in Step 1, collect a single unbiased sample of sufficient size so that it is: a) equal to or larger than the threshold size established for an 'unbiased' sample from that blend and b) contains sufficient mass to provide at least five (5) times the material needed for all the possible tests when multiple variable factors are being evaluated or, when a single factor, like active content, is being evaluated, at least ten (10) times the unit-dose amount required for a single test aliquot. In addition, for one of the "poor" and one of the "excellent" locations selected at random, sample a single replicate aliquot of the same size as the first aliquot. Take care to ensure that the sampling pattern sequence used minimizes the risk of the current sample's sampling being biased by the previous sample's sampling. Then, for each variable factor test required to evaluate all of the key variable factors in the blend, subsample unbiased duplicate unit-dose (or smaller) aliquots from each of the samples collected, work each aliquot up separately, test each aliquot preparation with at least a duplicate measurements (or the equivalent) for each response being evaluated, appropriately compute the result values for each aliquot evaluated, and tabulate the results obtained by variable evaluated and location.* ~~Samples should meet the following criteria~~ *For each factor evaluated, all of the results found should:*

a. *Fall appropriately within the USP's limits (for variables such as active content and impurity level) or*
b. *For variables (like, disintegrant content or level of release-control agent) that are surrogates or partial surrogates for a USP variable (like Dissolution or Drug Release for the directly evaluated blend variable 'disintegrant content' and/or 'level of release control agent), derived USP limits for variability.*

For the factor active content, for example, the results found should meet the following criteria:"

The fundamentals of scientifically sound sampling first and foremost require the samples sampled to be 'unbiased' by the sampling process.

For powder blends, the general rule of thumb is that, for a suitable sampling device, the risk of sampling bias increases as the size of the sample sampled decreases.

In this commenter's experience, *for single-factor studies of active content using properly handled samples*, sampling with sample sizes at about 10X the unit-dose weight have permitted the unbiased aliquoting of multiple (up to about 5) unit-dose (or smaller) aliquots without introducing any significant "sampling" bias or variability into the result values for the test aliquots.

Similar multiple factor studies have shown that a lower multiple can be used because, in general, there is no need, on average, to test more than two aliquots for each factor from each sample aliquot.

After unbiased aliquots are sampled, the next hurdle is to develop a procedure for removing "unbiased" aliquots from such samples and quantitatively evaluating each such aliquot.

This commenter has found that, with training, a trained Analyst can reliably remove unbiased aliquots that are typically within 5 % of the target weight for aliquots down to between 50 and 75 mg and within 10 % of the target weight aliquot weights down 25 mg.

Since only a small number of unbiased unit-dose aliquots are tested and the drug product batch must, if released meet the USP's expectations, all must be within the range from 85 % to 115 % of the USP's mid-range or, for drug products not listed in the USP, its equivalent FDA-approved or FDA-licensed target value.

For the final blend, how far each must be inside of this range depends upon the relative variability contributions allowed after the final blend is sampled.

For example, if a total post-final-blend variability allowed is "± 1%" for post-blend handling and "± 2 %" for the permitted tableting weight range, the permissible range for the result values is reduced to "88 % to 112 % of said target.

Using the preceding information, the properties of distributions, and presuming that the distribution of the active in the blend is at least pseudo Gaussian, the process is said to be minimally capable when the permitted range divided by 6 times the standard deviation observed is 1.34 or larger.

Solving the preceding for the maximum permissible "standard deviation," you should find that, for this example:

(112 – 88) = (6 x 1.34) "relative s" or "relative s" ≤ 2.98[5]

Moreover, since the limiting relative uncertainty for tablet weights is about 1 % and the limiting overall relative uncertainty for the post-blend handling operations is also on the order of 1 %, the limiting "RSD" in this case is < 3.23[3].

Thus, the maximum permissible "relative s" or "RSD":

a. Cannot be a fixed number and
b. Depends upon the allowable range and the post-final-blend variability contributions to the drug product variability.

Thus, rather than setting any number limit, the guidance should establish the USP's expectation range as the basis and show the appropriate correction process that the manufacture must use to establish the maximum permissible RSD for the batch's final blend to be sufficiently uniform.

For capsules, where the limiting fill-weight RSD is typically 2 % or higher and the post-handling blend operations typically also have higher RSD, their limiting "RSD" is typically < 2.73[6].

Abbreviating the "relative post-blend variability contributions" discussed as "RPBVC" and generalizing from the preceding discussions, one gets the equation:

$$RSD_{\text{Observed for Active Content}} \leq (30 - RPBVC_{\text{Established for the process}})/8.04 \qquad (1')$$

In addition, because unbiased samples are taken and unbiased aliquots are evaluated, the observed mean of all of the aliquots tested should be statistically the same as the formulation target active content level.

Since a 95 % confidence level is the minimum that a firm could justify using under CGMP, the observed relative mean level should, in general, be within "$\{(t_{[0.975,n]} \times RSD_{Observed})/\sqrt{n-1}\}$" of the relative target level.

Thus, the observed relative distance of the mean from the target should be such that the absolute value of that difference ($|\bar{x}_{Observed} - Target|$) is not greater than $\{(t_{[0.975,n]} \times RSD_{Observed})/\sqrt{n-1}\}$ (where "N" is the number of aliquots tested) or:

$$(|\bar{x}_{Observed} - Target|) \leq \{(t_{[0.975,n]} \times RSD)/\sqrt{n-1}\} \qquad (2')$$

Using the preceding, the following can be set as the active content expectations for the unbiased sample aliquots tested from an acceptable batch:

- "~~Assay one sample per location (number of samples (n) ≥ 10)~~ *Determine the active content level for not less than duplicate aliquots from the sample or samples sampled from each sampling location (number of sample aliquots [n] ≥ 22;* (n = ~~20~~ *42* for a ribbon blender)."
- "RSD *(relative standard deviation)* ~~of~~ *computed from* all individual results ≤ [(30 – $RPBVC_{Established\ for\ the\ process}$)/8.04] where RPBVC is twice the sum of the relative percentage magnitudes of the post-blend relative variability contributions."
- "All individual *aliquot relative* `results` *for the active content* are within ~~10.0 percent (absolute) of the mean of the results~~ ∓ *[(30 – RPBVC)/2] % of the process target mean."*

"If samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. We also recommend that you not proceed any further with implementation of the methods described in this guidance until the criteria are met."

Provided Attachment 1 is revised to reflect the changes introduced by this commenter, this commenter has no problem with this paragraph.

"~~Sampling errors may occur in some powder blends, sampling devices, and techniques that make it impractical to evaluate adequacy of mix using only the blend data. In such cases, we recommend that you use in-process dosage unit data in conjunction with blend sample data to evaluate blend uniformity~~."

This commenter does NOT agree with this paragraph because, as the commenter's remarks on the taking and testing of unbiased samples indicate, it is possible to take and test unbiased sample aliquots in most every instance.

When the blender size or configuration precludes directly sampling from it and/or introduces sample-level biases that cannot be overcome by increasing sample size, a valid IBC-container-sampling plan can be developed and used to overcome such problems.

Because this is increasingly the case, this commenter recommends that the Agency include and establish the validity of a sampling plan that the Agency would recommend to the industry.

If the root cause of observed non-uniformity problems is related to the sampling device used and/or the sample techniques used, sound science requires that the manufacturer change either or both in a manner that eliminates such biases.

"Some powder blends may present *an* unacceptable safety risk when directly sampled. The safety risk, once described, may justify an alternate procedure. In such cases, process knowledge and data from indirect *blend uniformity assessment* ~~sampling~~ combined with ~~additional in-process dosage unit data~~ *the specific (weight corrected) result values and the predicted batch characteristics derived from the testing of* ***not less than*** *200 batch representative tablet-core or capsule content samples (the minimum number required for a 95-% confidence-level prediction of the acceptability of the batch)* may be adequate to demonstrate the ~~adequacy of the powder mix~~ *the requisite level of blend uniformity* . ~~Data analysis~~ *The supporting data, hazard evidence used to rule out direct sampling and the results analysis* used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility."

When the health hazard is so high that directly sampling the blend samples is too risky, the manufacturer should document the facts of their claim and proceed to use other means (including the use of isolators for all sampling, handling, and evaluation operations that involve the active) to work with such materials.

~~As an alternative, you can substitute the procedures described in the PDA Technical Report No. 25, (see reference in footnote 8) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above~~.

Because the procedures in ***PDA Technical Report No. 25*** do <u>not</u> meet the clear requirement minimums established in the CGMP regulations for drug products, such procedures cannot lawfully be used.

Moreover, based on the 1988 Supreme Court decision cited previously, it is not legal for any person in the Agency to recommend the use of any procedure that does not at least meet the applicable CGMP regulations.

For both of the preceding reasons, this paragraph should be removed from the Draft.

"VI. VERIFICATION OF MANUFACTURING CRITERIA"

This section begins by stating (Lines 237 through 246): "You should complete the assessment of powder mix uniformity and correlation of stratified in-process dosage unit sampling development procedures before establishing the criteria and controls for routine manufacturing. We also recommend that you assess the normality and determine RSD ~~from~~ *of* the results ~~of stratified~~ *found for the GMP-compliant dynamic* in-process dosage ~~unit sampling and~~ *units'* testing that ~~were developed~~ *was conducted on an appropriate representative sample units subset from the representative samples sampled.* The RSD value *from the in-process results* should be used to classify the ~~testing results~~ *in-process core or capsule fill batch material* as either *readily ~~pass~~ passing* (RSD ≤ ~~4.0%~~ *2.5%*) , *marginally ~~pass~~ passing* (RSD ≤ ~~6.0%~~ *3.7%*) or *inappropriate* for demonstration of batch ~~homogeneity~~ uniformity (RSD > ~~6.0%~~ *3.7 %*). The procedures are discussed in the following sections:

The first sentence was revised to a) remove the non-CGMP-compliant "*stratified sampling*" approach and b) substitute the CGMP-compliant "*dynamic sampling*" approach.

The sentence was then modified to make it more technically correct.

Then, using a distribution resilient "process capability" approach, the RSD values in the Draft were revised to be congruent with an expectation range of from 85 % to 115 % of the targeted level with a C_P of 1.34 for the *marginally passing* level and C_P of 2.0 for a *readily passing* level.

"A. In-Process Dosage Unit Sampling and Analysis"

This subsection states (Lines 249 through 270): "We recommend the following steps:

- "Carefully identify ~~locations~~ *points* throughout the compression or filling operation to sample in-process dosage units. *Your selection should be done in a manner that ensures the points selected encompass the dosage-forming phase of the manufacture of the batch.* The sampling locations should also include significant process events (such as, hopper changeover~~,~~ *and hopper*–filling, ~~or~~ *mechanical-failure-triggered* machine shutdown and *restart, and* the beginning and end of the compression or filling operation~~.~~[16]*) that are outside of the dosage-forming machinery's normal operating envelope.* There should be at least 20 locations ~~with 7 samples each for a minimum total of 140 samples~~ *at which you sequentially sample a number of dosage units that is some integer multiple of the dosage-unit forming stations in the system being studied for a minimum total of not less than 600 units for each variable factor that needs to be evaluated for to comply with the representative sample sampling requirements of the drug CGMP regulations (21 CFR211.160(b)(2). In general, the samples at each sampling point should be placed in a suitable separate labeled container.* These include periodic sampling locations and significant event locations.

[16] The beginning and end samples are taken from dosage units that would normally be included in the batch."

In the planning process for the dynamic sampling of a production phase, the sampling needs to be defined in terms of "*points*" rather than "locations."

This is the case because the ***location*** of the sampling (the discharge chute from the dosage forming equipment) remains fixed and the sampling points are separated by time rather than location.

While this commenter has no problem with the total number of points level, valid unbiased "process representative" dynamic sampling requires the sampling of not less than one dosage unit from each dosage-forming unit station at each sampling point.

Typically, because the samples collected are used for both variable factor testing and attribute factor examination, some integer multiple of that number of dosage units is sampled at each sampling point.

Because the manufacturer needs to be highly confident (a confidence level of 95% or higher) that their findings are truly predictive of the results that would be found if the entire batch were tested, not less than 200 batch-representative units (made up of an equal number of randomly selected units from the process-representative sample units collected at each sampling point) need to be tested for the single variable factor, active content, being addressed in this guidance.

The need for testing such a 200-unit sample is dictated by

a. The lack of rigorous controls on each of the physical properties that affect the uniformity achieved each time a defined processing step set is performed using components whose properties vary in a complex undefined manner.
b. The need for a confidence level of 95 % or higher in the validity of the estimation of the acceptability or non-acceptability of the batch at the end of this process phase.
c. The numbers required by the applicable recognized statistical consensus standards ("**ISO 3951**" or "**ANSI/ASQC Z 1.9**") for evaluating batches of discrete units for the normal inspection, "process variability unknown" case, and
d. A lack of sufficient production history to justify the use of a hierarchical sampling plan that initially tests a consensus-standard-recognized defined subset (75 representative units in this case) and then proceeds in different pre-established manners depending upon the outcome observed for the initial subset tested.

- "~~Sample~~ *For each sampling point, sample* at least ~~7~~ *one in-process unit for each dosage forming station in the dosage-forming system being used to form the* in-process dosage units ~~from each sampling location~~. *Generally, some sequential integer multiple of the minimum number is collected so that the samples collected can be used for the manufacturer's pre-determined physical attribute examinations for problems (such as picking, capping, chipping, breakage, and proper embossing and/or debossing. In general, the sample collected at each sampling point is between 50 and 200 units. Thus, for a 20 sampling-point plan, the total sample collected is typically between 1000 and 4000 units."*

  Because ***21 CFR 211.160(b)(2)*** requires that each sample be *representative* of the batch, the number taken at each sampling point in a *dynamic sampling* plan must be some integer multiple of the number of dosage-forming stations to ensure that the local (sampling point) variability is "captured" in each sample sampled.

- "~~Assay at least 3 of the 7~~ *For a 20-point sampling, select, at random, 10 units from each sample point, weigh each, work up each unit in a manner that preserves the link between each unit's identity and its weight, appropriately test the each worked up sample, determine the results for each sample,* ~~and~~ weight correct each result *and appropriately tabulate the results found.* (The number of samples should be specified and justified for a given product and process.)

- "Conduct an analysis of the dosage–unit ~~stratified~~ *dynamic* sampling ~~data~~ weight-corrected *results* to demonstrate that the *results obtained for the batch-representative samples tested indicate that the dosage units in the* batch *probably* ~~has~~ *have* a *near* normal *active-content* distribution ~~of active ingredient~~. *At the simplest level, one can determine the mean, median and mode values for the data set – when they are, within the observed result uncertainty, the same, the level of active in the batch of tablets can be considered to be normally distributed. If this simple test is inconclusive, then you should a frequency bar graph of depicting the frequency of values in a given narrow value range interval on its "Y=axis" against the intervals on the "X-axis" and examine this chart and the tabulation of the results versus time point.* Indications of trends, bimodal distributions, or other forms of a distribution other than

normal should be investigated. If *any of* these ~~occurrences~~ *conditions* significantly affect your ability to ensure batch ~~homogeneity~~ *uniformity*, ~~they should be corrected~~ *the root cause or causes for the non-uniformity of the results should be identified, appropriate corrective actions implemented, and the studies repeated until the results indicate that the batch is sufficiently uniform with respect to the level of active in the dosage units.*"

The critical caveats are: a) the samples tested must be *representative* of the batch and b) the number tested must be sufficient to provide a high level of confidence (typically, at the 95 % confidence level or higher) that the outcomes observed for the samples tested do, in fact, reflect the untested units in the batch.

- "Prepare a summary of this analysis. Potential investigation results along with a description of batch normality should be included in the summary. ~~Submit~~ *For drug product applications presented to the Agency for review, you should submit* this summary with the application as described in section VIII of this guidance."

"In addition to this analysis of batch normality, we recommend that you classify the test results as *readily ~~pass~~ passing* or *marginally ~~pass~~ passing* according to the following procedure:"

"B. Criteria to Meet the *Readily ~~Pass~~ Passing* Classification"

This subsection states (Lines 274 through 286): "For each ~~separate~~ *individual* batch, compare the test results to the following criteria:"

- "For all individual results (for each batch, $n \geq$ ~~60~~ *200*), the overall RSD $\leq$ ~~4.0~~ 2.5 percent."

To be confident (at the 95 % confidence level) that the "normally distributed" results obtained for the samples tested apply to the batch, one must test not less than 200 representative units.

Testing a smaller number reduces the level of confidence that one can have that the results found for the samples tested match those of the untested portion of the batch.

Levels of confidence below "95 %" are not consistent with either CGMP or today's expectations for batch quality.

Similarly, since the post-release expectation (based on the USP's any article requirements) is that all units must be between 85 % and 115 % and the level of capability (C_P) for a process that corresponds to a "readily passing" batch is 2.0, the upper limit on the overall RSD for the results from the testing of not less than 200 batch-representative units should be 2.5 percent – NOT the Draft's 4.0 (which roughly translates into a "process capability" of "1.25," a value that does not meet the recognized minimum value for even a marginally capable process.

In today's "six sigma" quality world, a normally distributed product having its mean at 100 % of the target and an RSD of 2.5 % still translates into an expectation that the batch contains units that are outside of the USP's expectation range.

- *"For all individual results (for each batch, $n \geq 200$), the overall mean percent of the target value should be not less than the target value percent. In practical terms, $[\bar{x}_n + (t_{(0.975,n)} \times RSD / \sqrt{n-1})] \% \geq Target_{Process} \%$."*

  A critical CGMP-compliance issue is whether or not the overall mean is sufficiently close to the target level to ensure that the CGMP formulation requirement set forth in **21 CFR 211.101(a)**

- "Each ~~location~~ *sampling-point* mean is within 90.0 percent to110.0 percent of target strength."

  As stated previously, the samples are from different points in time not from different locations.

  Based on this, the Draft's text should be changed in the manner indicated.

- "All *of the* individual results are within the range of ~~75.0~~ *85.0* percent to ~~125.0~~ *115.* percent of *the* target strength."

  For a batch to be characterized as "readily passing," all of the results found must be within the USP's "any article" *expectation range* and not its lifetime "no units can be outside of" range.

  This is the case because the percentage of samples tested is typically less than 0.1% of the batch.

  In such cases, all results must be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 will fail the USP's uniformity of dosage units by content uniformity criteria for the active content and, if such articles are tested, the batch will fail.

  Therefore, the "readily pass" range must be "85 % to 115 %" or narrower.

If your test results meet these criteria, ~~they are~~ *the batch can be* classified as *readily ~~pass~~ passing* and, *provided you have adequate controls on all of the physical properties of the components in your formulation, all of the data for the development and other initial validation batches supports the batch-to-batch reproducibility of the results obtained,* you ~~can~~ *may be able to* start routine batch testing using the Standard Verification Method (SVM) described in section VII. If your test results fail to meet these criteria, we recommend that you compare the results with the *marginally ~~pass~~ passing* criteria described below."

"C. Criteria to Meet the *Marginally ~~Pass~~ Passing* Classification"

This subsection states (Lines 290 through 306): "If your dosage unit test results fail to meet the criteria for the *readily pass* classification, you should *first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with "significant events," (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from "after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the '25 %' full mark" to "after ...into the hopper, continue running until the level ... reaches the '50 %' full mark) to*

reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to the formulation development stage as the current process does not reliably produce in-process units that meet the CGMP minimums. ***In some cases****, you may be able to justify evaluating* ~~assay the remaining dosage units (all 7 units per location)~~ *another set of dosage units* and ~~compare~~ *comparing* the test results to the following criteria:"

When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure.

For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing.

However, unlike the USP's "grab sample" approach where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a) closer to the target level and b) smaller or certainly not larger than the value found for the smaller number of batch-representative samples.

Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are "admitting" that the sampling and testing plans they propose do <u>not</u> reflect the CGMP minimum requirement for that both must be representative of the batch.

- For all individual results (for each batch, $n \geq$ ~~140~~ *400*), *the overall* RSD $\leq$ ~~6.0~~ *2.5* percent."

- *"For all individual results (for each batch, $n \geq 400$), the overall mean percent of the target value should be not less than the target value percent. In practical terms:*

  $[\bar{x}_n + (t_{(0.975,n)} \times RSD / \sqrt{n-1})]\ \% \geq Target_{Process}\ \%.$ (3´)"

  A critical CGMP-compliance issue is still whether or not the overall mean is sufficiently close to the target level to ensure that the CGMP formulation requirement set forth in **21 CFR 211.101(a)**

- Each ~~location~~ *sampling-point* mean *(of 20 units chosen at random from the number collected at each sampling point)* is within 90.0 percent to 110.0 percent of target strength.

- All individual results are within the range of 75.0 percent to 125.0 percent of target strength *and not more than one (1) unit in 100 units tested is outside of the range from 85 % to 115 % of the target strength and no test point of 20 contains more than one (1) unit that is outside of the 85 % to 115 % range.*

  The only area where testing more *batch-representative units* can validly tolerate a widening of the control expectations is in the expectation for the limiting values observed.

Since to be using these criteria, the distribution of units has been found to be "normal," testing more units increases the probability that one or more units from the extreme limits of the population's distribution will be selected and tested.

However, any allowance for this risk must be tempered by the USP's clear post-release, "any article" requirements for active content.

The revision of the last criterion proposed properly reflects that reality.

"If your test results meet these criteria, ~~results~~ *the batch* can be classified as *marginally ~~pass~~ passing.* If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and repeat the powder mix homogeneity assessment, in-process dosage unit sampling correlation, and initial criteria establishment procedures. The disposition of batches that have failed the m*arginally pass* criteria is outside the scope of this guidance. 306

"D. Sample Locations for Routine Manufacturing"

We recommend that you prepare a *scientifically sound and justified* summary of ~~the~~ *your in-process* data analysis from the powder mix assessment and ~~stratified~~ *dynamically sampled, batch-representative formed- dosage-unit* sample testing *studies that you have performed.* From the data analysis, you should establish the ~~stratified~~ *dynamically formed dosage-units'* sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. You should identify *and designate* ~~at least 10~~ *not less than 11 "routine production"* sampling ~~locations~~ *time points (the start point, the end point, and not less than 9 approximately evenly spaced intermediate points)* during capsule filling or tablet compression ~~to represent~~ *that your studies have established to be representative of* the entire routine manufacturing *of the formed units that comprise the* batch *while making provision for the inclusion of any 'significant events' that may occur during this production step. In addition, the number sampled at each point should be appropriately adjusted to be that integer multiple of all of the dosage forming stations in the forming system that is required to satisfy all of the firm's pre-established sampling and sample evaluation (examination and testing) for the said formed units."*

Apparently, those that drafted this portion of the guidance are again attempting to turn a CGMP requirement (**21 CFR 211.160(b)(2)**) that the in-process sampling be *representative* of the batch into an explicit guidance "suggestion" that choosing a number of points "to represent" the batch somehow satisfies this CGMP requirement when it does not necessarily do so.

The reality is that this juxtaposition of terms, "to represent the entire routine manufacturing" for the clear regulatory requirement of **21 CFR 211.160(b)(2)**, "Such samples shall be representative and properly identified," is neither scientifically sound nor CGMP-compliant.

This is the case because the samples from any set of points, including those from sets that are not batch representative, can be validly held "to represent" the properties of the batch.

However, only those samples from point sets that meet the requirements for a dynamically sampled batch-representative set meet the CGMP requirements set forth in **21 CFR 211.160(b)(2)**.

Thus, the guidance should specifically require the selection to include the start point (just after the manufacturer begins to collect the formed units as a part of the batch) and the end point (the last units included in the batch) because, for a *dynamically sampled sample* must span the batch to be " batch representative", as required by the CGMP regulations.

Therefore, this commenter has altered the Draft text to reflect the preceding factual scientific and regulatory realities.

"VII. ROUTINE MANUFACTURING BATCH TESTING *AND BATCH VERIFICATION* METHODS *FOR THE FINISHED DRUG-PRODUCT*"

This section begins by stating (Lines 320 through 322): "~~We~~ *After completing the in-process procedures described above as well as any others required to comply with the in-process CGMP requirements set forth in 21 CFR211 Subparts F, I and J, we* recommend that you evaluate the routine manufacturing batches against the following criteria ~~after completing the procedures described above~~ to assess the adequacy of the powder mix and ~~uniform~~ *uniformity of the active* content in *the* finished dosage form."

Since this section seems to address the testing of the finished drug product and applying methods to evaluate the results to "verify" the acceptability of the batch, its title (Line 318) needs to be changed as shown.

Though this guidance only addresses active content uniformity of the final blend, the in-process dosage form and the finished drug product, the in-process and drug-product CGMP requirements cover uniformity with respect to other variable factors as well as, in the case of the drug product, other criteria.

These must be met along with the scientifically sound and regulatory-compliant recommendations set forth in this Draft.

To recognize the preceding realities, this commenter has modified the Draft in the manner shown.

In addition to revisions required to make the text CGMP compliant, those modifications include:

a. Rewording of the phrase "uniform content" to make it more grammatically and technically correct, *"uniformity of the active* content ..." and
b. Adding the appropriate article modifier, *"the,"* to the phrase "in drug product."

The text of this section continues with (Lines 324 through 331):

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

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

First, the grammar needs to be corrected in the last sentence in the first paragraph to change "SCM" to *"SCM's criteria"* since that is what is the difference to which the sentence alludes

This must be the difference that needs to be stated because the obvious difference in the two methods their titles, "SCM" and "MCM," does not need to be stated.

Second, in order to ensure that a batch representative sample is taken and to minimize the time costs and other risks that the proposed text engenders when it talks of different samplings, this commenter has rewritten this text to reflect that the sampling should be a one-time event and the various schema for evaluating the acceptability of the batch for release should test the appropriate batch representative subsample from the batch at each stage.

The basis for the revisions proposed are the criteria established in the relevant applicable consensus standards (**ISO 3951:1989**, "Sampling procedures and charts for inspection by variables for percent nonconforming," and its American counterpart, **ANSI Z 1.9-1993**, "Sampling Procedures and Tables for Inspection by Variables for Percent Nonconforming") because these are recognized minimum consensus statistical quality control standards that are suitable for demonstrating compliance with the clear explicit requirements set forth in **21 CFR 211.165(d)**, "Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels."

Moreover, the least test-intensive "cases" of the "cases" outlined in these standards that can validly be used are the appropriate "process variability unknown" cases.

This is the scientifically sound limiting situation because the drug products that are covered by this guidance are made from components whose key physical properties are either uncontrolled (the usual situation for one or more of the key physical properties for almost all components) or not rigorously controlled to a level that the permitted variability has been demonstrated to have no effect on variability in the active content (the situation that exists in all the cases of which this commenter is aware). [**Note:** Even in situations where the process is adaptive, the key properties that can affect the process output need to be at least adequately characterized. In most cases, today's manufacturers neither adequately characterize nor control key physical properties that are known to affect final blend, in-process core and drug product uniformity with respect to not only active content but also the critical factor of active availability (as measured by Dissolution or Drug Release).]

Finally, one of the precepts introduced in FDAMA (the 1997 Food and Drug Administration Modernization Act) when addressing medical devices was the recognition of applicable national and international standards where such are appropriate.

This commenter understands that it would be in the best interests of public health and public health safety if the Agency were to do likewise when it comes to the scientifically sound inspection of drug product samples.

Based on the preceding, the text should be revised to read as follows:

"These routine manufacturing batch-testing methods are the Standard Criteria Method (SCM) and the Marginal Criteria Method (MCM). In both methods, the samples sampled should consist of at least that number of randomly

distributed, batch representative dosage units required to satisfy the testing (**21 CFR 211.165(d)**) and sample retention criteria (**21 CFR 211.170(b)**) established in the CGMP regulations. In general, this mean that the sample should consist of not less than three times the number of finished dosage units required to perform all of the CGMP-mandated testing plus the number needed to conduct any and all finished dosage unit examinations required by the manufacturer.

The first method, ***SCM***, consists of three stages, each with the *accept/reject* criteria appropriately derived from the criteria set forth in the recognized consensus standards, "**ISO 3951**" and "**ANSI/ASQC Z 1.9**," for the "process variability unknown, standard deviation" case [16A] for batches larger than 150,000 dosage units [16B]. The second stage provides for the testing of a reduced number of samples as compared to the numbers required for the first and third stages. In each case, this guidance recommends testing an appropriate number of batch-representative samples and using the results from both each test group and the aggregate samples tested to evaluate the batch's conformance to each stage's criteria. The second method, ***MCM***, tests a large number of samples and uses *accept/reject* criteria that are different from the criteria established in the ***SCM***.

[16A] Because the current state of the pharmaceutical industry is such that the critical physical properties of the components are not rigorously controlled, there can be no expected process variability. This is the case simply because there is no valid way to define the process when the inputs are allowed to vary in unknown ways without any effective means for the process controls and steps to adapt to the unknown variations and unknown variation interactions. Until such time as that changes, the manufacture of dosage forms that can be affected by these variations, especially the tablet and solids in capsules dosage forms that this guidance addresses must use a scientifically sound model that is based on the 'process variability unknown' reality.

[16B] Since most of today's routine production tablet and dry-filled capsule batches produce more than 150,000 dosage units, this is the sample testing level that should be selected for routine testing.

If the batch-representative results meet the USP's lifetime criteria but fail to conform to the ***SCM*** criteria, we recommend testing additional samples and using the criteria in the ***MCM*** to assess whether or not the batch is acceptable for release with respect to the uniformity of its active content. Both verification methods and the procedures for switching from one to the other are detailed below and in the flow chart in Attachment 2."

This reviewer leaves it up to the Agency personnel to appropriately revise "Attachment 2."

This commenter recommends deleting Lines 333 through 371 as shown, and replacing it with a) the text that follows the justification for deleting the Draft text or b) some similarly *scientifically sound* and *appropriate* method that can determine the acceptability (or lack thereof) of the **batch**.

~~"A. Standard Criteria Method (SCM)~~

~~"We recommend using the SCM verification method when either of the following conditions is met:~~

- ~~Results of establishing initial criteria are classified as *readily pass*.~~
- ~~Results of testing to the MCM pass the criteria for switching to the SCM (see section C below).~~

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

~~*1. Stage 1 Test*~~

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

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

~~If the results pass these criteria and the adequacy of mix and uniformity of dosage unit content for the batch are adequate, you can use the SCM for the next batch. If test results fail stage 1 criteria, you should conduct extended testing to stage 2 acceptance criteria.~~

~~*2. Stage 2 Test*~~

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

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

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

Justification for the Deletion

The preceding section is **not** based on the applicable sound statistical science and it does **not** meet the statistical quality control criteria established in **21 CFR 211.165(d)**.

This is the situation because:

1. The sampling plan does **not** collect enough samples to meet the inherent sample-size sufficiency component of the requirement that the sample be batch representative.
2. The correction of the results for unit weight is not scientifically sound because
   a. Especially in the case of sugar-coated and multiply film-coated and waxed tablets and finished capsules that are difficult to weigh, empty, and reweigh the "shell" to determine the weight of fill (post-fill banded and gel-coated capsules), the weight variability observed is not provably attributable to the variation in the weight, and

   b. In general, it introduces an unwarranted artificial bias into the final results.

3. **Even at the 30-unit level, the results found can only be extrapolated to the batch at a confidence level that is less than 20 %.**
4. **The proposed method fails to address the issues of: a) the "built in quality" with respect to the critical physical properties of the components used or b) the continuity of production (*ideally*, dedicated equipment and processing or, *less ideally*, long runs the produce multiple (10's or 100's) lots of a single drug product at a steady rate).** [***Note:*** In general the only the ***SCM, Stage 2*** and ***MCM*** procedures can validly be used for short runs. Moreover, when the tablet or hard-gelatin solid-fill capsule manufacturer fails to adequately control the key physical properties of the components used to manufacture the "final blends" and formed dosage units, the ***MCM*** procedure is the only procedure that validly be used *even when* the initial validation batches happen to give results for the initial validation batches' final blend samples and formed dosage units that are *readily passing*.]
5. The acceptance criteria fail to properly consider, much less address, more than one possible 'batch failing' situation including, but not limited, to:
   a. Valid content test result values may be found that are outside of the USP's post-release expectation that all content values must be inside of the range from "85 % to 115 %" of the target level,
   b. Valid content values may be found that are outside of the USP's lifetime acceptance range of "75 % to 125 %" of the target level,
   c. A mean for the samples tested that is not close enough to the target mean to support the release of the batch.
6. The sampling plan and the result acceptance criteria for the finished drug product units do **not** comply with the *statistical quality control* mandates, including scientifically sound, "appropriate acceptance levels and/or appropriate rejection levels" set forth in **21 CFR 211.165(d)**.

Moreover, as written, some of the statements in this section are blatantly at odds with not only CGMP and sound science, but also with common sense.

How can anyone believe that the active content test results from as few as 10 units in batches of hundreds of thousands or millions of units can confidently predict that uniformity of the blend and the final drug product batch not only with respect to the measured active content but also with respect to the other critical batch post-release requirements established by the USP including, but not limited to, active availability (as measured by *Dissolution* and *Drug Release*), impurity level, and water content.

Factually, ***even if the 30 units tested are somehow batch representative,*** one can only be less than 20 % confident that those values reflect the distribution of the active content in the batch of dosage units.

Moreover, with respect to the untested variable factors that are required to meet other uniformity criteria, one can have little, "≪ 20 %," (unless there is proof of some absolute correlation between active content and the unmeasured variable) or close to "zero" (when the variables [e.g., water content] are not correlated with the active level) confidence in the uniformity of the batch with respect to variables other than active content.

For example, the Draft falsely asserts, "If your results pass these criteria, the adequacy of mix and uniformity of content for the batch are adequate and you can use stage 1 of SCM for the next batch." [**Note:** At the 95 % confidence level, the calculated RSD is an approximately 25 % uncertain estimate of the batch RSD for sets 30 representative units and a 45 % uncertain estimate of the batch RSD for sets of 10 representative units. For the 10-unit case, this means that a 'passing RSD' of "5.0%" can easily be found for batches that have a true batch RSD *larger than* 7.2 % and, for the 30-unit case, the true batch RSD can be *larger than* 6.2 %.]

The preceding underscores the non-validity of the RSD acceptance criteria set for the sample results and the lack of any supportable science for setting *sample-based acceptance criteria*, for whatever reason, that are the same for different numbers of samples. [**Note:** In contrast, the United States Pharmacopeia (USP) seems to have gotten it about right for their grab-sample-based any-article-in-commerce *sample-based acceptance criteria*. They properly specified a limit (range) for the individual units (something that this Draft fails to do) that was narrower (85 % to 115 %) and set a smaller RSD (6.0 [with an upper uncertainty limit of about 9]) for sets of 10 than the corresponding limit (75 % to 125 %) and RSD (7.8 with an upper uncertainty limit of about 10) for sets of 30 units. In contrast, the Draft's obviously **sample-based** acceptance criteria: a) fail to set any limits on the individual result values and b) improperly sets the same RSD for the 10-unit and the 30-unit sample results.]

The CGMP regulations clearly and plainly require scientifically sound and appropriate batch-based acceptance criteria – not the sample-based acceptance criteria set forth in this Draft.

Based on all of the preceding, this commenter suggests an alternative is needed that, at a minimum:

a. Tests batch-representative samples sets having sizes appropriate to today's state of control over the inputs and processes that affect the uniformity of the drug product,

b. Ensures that the batch has the mean strength that it purports or is represented to have

c. Does ensure that the process produces drug-product dosage units that are evaluated in a manner that complies with **21 CFR 211.165(d)**, and

d. Utilizes "**ANSI/ASQC Z 1.9**," a recognized applicable consensus American National Standard that is equivalent to the recognized international standard ('**ISO 3951:**1989') as the basis for the sampling, testing, and result evaluation plan proposed for representative dosage units sampled and tested at any stage. "**ANSI/ASQC Z1.9**" can validly be, and has been used, to derive statistical quality control acceptance specifications appropriate to the ***batch*** that comply with the clear mandates for such set forth in the drug product CGMP regulations at **21 CFR 211.165(d)**.

The commenter's detailed alternative is as follows:

"A. A Standard Criteria Method (*SCM*) That ONLY Addresses Active Uniformity

We recommend using the ***SCM*** verification method for assessing batch active content uniformity when the following conditions have been met:

- The initial process validation studies have determined that the initial batches meet the criteria established for the *readily passing* case.
- The mean, mode and median values for all initial full-scale validation batches and all previous batches have demonstrated that it is valid to treat the distribution of the active content values in the 'final blend' and 'dosage units' as being normally distributed about the observed mean for each batch. [**Note:** *For this to be the case*, $mean_n \simeq mode_n \simeq median_n$ for $n \geq 200$ for the initial validation batches and the first ten (10) batches in the previous and current campaigns, and, for all other batches, $n \geq 75$.]
- You have established (proven):
  - **a.** You have suitable:
    - **i.** ***Direct controls*** on the key physical properties of *each and every* component that you use in the formulation of the "final blend" from which you form the dosage units

    or

    - **ii.** (***Indirect controls***) Established granulation steps that adequately mitigate the variability in the physical properties of components used to manufacture the "final blend" used to manufacture the formed dosage units,

    and

  - **b.** These controls are adequate to control the variability to an extent that ensures the "final blends" produced are adequately uniform.

  [**Note:** Manufacturers and the Agency often talk the talk of 'building quality into their products.' Unless the manufacturer builds in appropriately narrow control limits on the physical properties of the components used and/or granulates the component materials appropriately to overcome physical property incompatibilities, then not only are they not only are they not walking the walk of 'building quality into their products' but also, more importantly, the findings from the previous cases cannot properly be used to predict the probable uniformity of the next batch produced. In spite of the preceding realities, this commenter continues to hear manufacturers openly stating that they cannot control the physical properties of their component, they must take whatever their suppliers supply. Does anyone doubt that such positions do not build quality into dry-solids-based dosage forms?]
- The production must be either in dedicated systems with strong preventive maintenance programs or the production campaigns must have long runs (>> 10 batches) with strong preventive maintenance programs, and the blending equipment must be free from patterned wear that may adversely affect the blending of the components. [**Note:** The SCM approach cannot be validly applied to mixers (like, of example, non-rotating shell blenders) that are subject to non-uniform wear that introduces ever-changing wear patterns into the blender. Nor is this approach viable in "short run systems" or systems whose blending patterns are not controlled.]
- Production must be at a 'steady' rate, and at least the 10 previous batches must have met the '***SCM***' acceptance criteria.

- The testing on the previous batch demonstrated that the previous batch met the ***SCM*** method-selection and batch-acceptance criteria. [**Note:** Use ***SCM, Stage 0 Examination*** when, overall, the previous batch was tested by and met all of the '***SCM, Stage 0*** criteria; use ***SCM, Stage 1 Examination*** when, on initial testing, the previous batch met all of the '***SCM, Stage 1***' criteria; and use ***SCM, Stage 2 Examination*** in all other instances: **a)** where, overall, the previous batch was required to be tested to meet and met all of the '***SCM, Stage 2*** criteria, **b)** where you are starting up a new campaign (non-'steady state' batch production), or **c)** where: **i)** the results from the five previous consecutive ***MCM*** batches meet the '***SCM, Stage 2*** criteria, **ii)** the controls on the physical properties of the components used are sufficient to support the switch from ***MCM*** to ***SCM, Stage 2***, and **iii)** quality management elects to switch from ***MCM*** to ***SCM, Stage 2 Examination***.]
- The CGMP-compliant, batch-representative in-process blend (or, if safety or other considerations have led the Agency to authorize batch-representative formed dosage-unit testing in lieu of blend testing) met the scientifically sound, in-process, batch, content-uniformity, acceptance criteria established for this drug product blend.

In cases where: a) the authorized in-process test for active content is tablet cores or capsule fill in lieu of blend testing, b) it has been established that none of the post-dosage-forming steps change the active content in the dosage units, c) not less than 200 batch-representative cores were tested, and d) the results from the testing of the 200 batch-representative cores met their acceptance criteria, you can use the ***Stage 0 Evaluation*** option to evaluate both the uniformity of the 'final blend' with respect the active content as well as uniformity of the active content for the 'freshly formed' dosage units.

In cases where the process development studies have shown that none of the post-dosage forming steps have any significant adverse impact on the variability of the active content, the manufacturer can dynamically sample a batch representative sample and appropriately test a suitably sized batch-representative subsample from the in-process dosage-forming step. If you can validly use the ***Stage 1 Evaluation*** option, can validly use the *Sampling Choice A* alternative, and have elected to use this alternative, proceed to ***Stage 1 Evaluation***, *Sampling Choice A;* otherwise (elected sampling at a later point or mandated sampling at a later point), proceed to ***Stage 1 Evaluation***, *Sampling Choice B.* [**Note:** Even if you can validly collect the sample at a later post processing point where, the time-related dosage-unit forming effects, if any, have been only partially randomized because of the mixing that occurs in the subsequent processing steps, this guidance only discusses two options (the in-process dynamic sampling and the completely randomized options). This choice was made to minimize the complexity of the guidance. Should you choose to sample at some step where the dosage units are only partially randomized, you will need to devise and justify a sampling plan that is appropriate to your sampling point.]

In all other cases, the samples to be tested should be taken at random from the batch-representative finished drug-product 'Attribute Evaluation and Reserve' sample collected from the output of the last processing step that the

drug-product units undergo prior to their being packaged for distribution. In such cases, you should proceed to ***Stage 1 Evaluation***, *Sampling Choice B.* [**Note:** Typically, at this point the intermediate processing steps have randomized the units to the extent that any sample 'of sufficient size' selected from the batch can validly be considered to be representative of the batch. Moreover, provided that sample in its aggregate initially contains sufficient sample for twice the number needed for all attribute examinations, it should also contain sufficient samples for all variable tests and the sample units required for the 'Reserve,' if any, (**21 CFR 211.170(b)**). In general, such an aggregate sample should initially contain more than three times the number of samples required to do all variable testing for ***SCM, Stage 2 Evaluation***.]

When it is valid to use ***SCM***, the manufacturer should start up using the ***Stage 2 Evaluation*** (**see Note**) option until, for at least 10 consecutive '***SCM, Stage 2 Evaluation***' batches in any production campaign or "run," the batches meet the following criteria:

a. All valid relative active-content results have met the '***SCM, Stage 2***' acceptance criteria,
b. All valid relative active content test result values are in the range '85.0 % to 115. %' of the target level,
c. The relative content mean for each batch is *not less than* 99.0 % and *not more than* 101.5 % of the validated target level,
d. The mean, mode and median relative content values are approximately equal (to within some small (< 3 %) relative percent) [a normal distribution test] to each other, and
e. The mean of the relative mean values for this and the previous 9 batches is *not less than* 99.5 % and *not more than* 100.7 % of the target value [a "running average"].

[**Note:** The ***SCM, Stage 0*** option is a special case of the **SCM, Stage 2** case that can be used in instances where, for valid personnel safety reasons, the manufacturer is justified in (and the Agency has accepted the manufacturer's) using the freshly formed dosage units both to:

a. Establish ex-post-facto the uniformity of the blend by 'weight correcting' the relative content values to approximate the uniformity of the blend that went into their manufacture, and
b. Use the *uncorrected* content result values to establish the batch uniformity at the 'formed dosage units' stage.

Because the preceding is uses a single set of measured content result values for the formed units in lieu of establishing the uniformity of the blend before initiating the dosage-unit forming phase of the drug-product manufacturing process, the minimum number of representative samples must be the number required for the 'normal inspection, batch-variability-unknown case.' Lacking any knowledge of the uniformity of the 'final blend,' you cannot validly presume that the current 'final blend' meets the prior uniformity criteria established by the previous batches. This is the only time when the weight corrected data should be used for making a decision. For all other situations, it is not a valid to use the weight-corrected results to ascertain whether or not the in-process dosage units meet their pre-established acceptance criteria. **This is the case because making such corrections obscures what can be and, in many cases, is the significant variability in the amount of active in the dosage unit because of the**

variability in its core weight (for tablets) or its fill weight (for capsules). Factually, a batch is <u>not</u> in control when the dosage unit active levels range from 70 % to 140 % of the target level even if their weight-corrected values are in the range from 95 % to 105 % of the target.]

When the preceding conditions ('a.' through 'e.') are **<u>all</u>** met, you may validly switch to the ***SCM, Stage 1 Evaluation*** option and use it as long as:

1. Production of the batches proceeds at a 'steady' rate and
2. There are no failures of any batch to meet **<u>any</u>** of its '***SCM, Stage 1***' acceptance criteria.

Based on the preceding, the **SCM** inspection plans and their acceptance criteria are as follows:

1. Stage 0 Evaluation

Using the dynamically sampled relative active content results found for the in-process freshly formed dosage units and American National Standard, '**ANSI/ASQC Z1.9**-1993,' follow that standard's applicable instructions, examples and tables (pages 37 through 52) in conjunction with the firms pre-established Acceptable Quality Level (AQL) for the allowable percentage of units outside of the expectation range to determine whether or not the batch is acceptable. [**Note:** Because the USP's "any thirty" limit is an aggregate of not more than 3.333333 % (1 in 30) outside of the range 85 % to 115 %, the maximum tabulated AQL that can be permitted for a tablet product is 1.5 % (corresponding to an M_{200} of 2.86 %). Typically, the results of the process development and initial process validation studies can be used to select the appropriate value for a tablet or capsule drug product. Given the higher variabilities inherent in the filling of capsules than in the forming of tablets in the 1970's when the USP established these uniformity criteria, the USP waffled by stating that no more than "1 or 2 in 30" can be outside of "85 % to 115 %." Even though today's equipment has reduced the limiting uncertainties in both the forming of tablets and the filling of capsules, the USP has not changed its expectations. In most cases a firm can justify using the "1.5 %" AQL although quality-based manufacturers routinely produce drug products having an AQL of 0.65 or less. "Six sigma" producers should easily be able to establish and support an AQL of 0.1 (corresponding to an M_{200} of 0.294 %). Because of the CGMP batch target conformity requirement set forth in **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**'), it is often the case that the firm may be justified in setting a larger upper-limit AQL and a smaller lower AQL because the manufacturer has elected to add a justified slight overage to: **a)** ensure that **21 CFR 211.101(a)** is met and **b)** reduce the number of units that must be composited (either physically or, where possible, by averaging the content data to determine the batch's mean content level is not less than the nominal 'overageless' *minimum* target level. The procedure in this guidance will presume: **a)** different AQL values for the upper and lower limits and **b)** the AQL for the upper limit (AQL_U) is not less than the AQL for the lower limit (AQL_L).]

When it is appropriate to use this option and you elect to use it, you should proceed as follows:

1. Weight correct the results found for the "freshly formed" dosage units in the in-process dosage forming step, and check to see that the weight-corrected

meet the batch acceptance criteria established for the in-process "final blend" (**see "Section V"**) and, when they do, proceed to **Step 2**; else proceed to **Step 12**.

2. Write down the pre-determined AQL_U and AQL_L values (for example, 1.0 and 0.65).
3. Using ***Table B-3*** (on page 41 of the standard), look up [by reading down from the '(normal inspection)' header] and write down the 'M_{200}' values that correspond to the AQL levels justified for the process (for the example, $M_{U,200}$ is '2.04' % and $M_{L,200}$ is '1.42' %).
4. Using the "as is" relative content results, compute and/or write down from the previous in-process studies, the relative mean ($\bar{X}_{200}$ %) and the relative standard deviation (RSD_{200} %).
5. If the relative mean is less than 99 %, the batch fails the batch's mean acceptance criterion and you should proceed to **Step 11**; otherwise proceed to **Step 6**.
6. Compute the following relative quality indices:
   a. $Q_U = [115\ \% - (\bar{X}_{200}\ \%)]/(RSD_{200}\ \%)$
   b. $QL = [(\bar{X}_{200}\ \%) - 85\%]/(RSD_{200}\ \%)$
7. Look up in ***Table B-5*** the estimated batch percentage above U (p_U) and the estimated batch percentage below L (p_L) and compute p by adding p_U and p_L)
8. Compare p_U with M_U, p_L with M_L, and p with the higher of M_U or M_L. [**Note:** Given that the manufacturer must strive to comply with **21 CFR 211.101(a)**, AQL_U should almost always be higher than or, at the least, *not less than* AQL_L. Hence, p should almost always be compared to M_U.]
9. The batch is acceptable if each 'p' value is less than the 'M' value to which it is compared.
10. If the batch is acceptable, appropriately note that the active content met its AQL acceptance criteria in your records and then proceed with the evaluation of the next variable factor (typically, Dissolution or Drug Release) that needs to be evaluated for the batch's acceptability; otherwise proceed to **Step 11**.
11. Report the problem to the proper quality manager and with this official's assistance, initiate the appropriate investigation, and, If the statistical quality results, though outside of the statistical quality criteria, the mean and/or the standard deviation, indicate that testing additional samples may find the batch to be acceptable and the investigation indicates that additional testing is warranted, you should set the Examination method to '***SCM, Stage 2***' and proceed to the ***Stage 2 Evaluation*** section.
12. If the specific relative content results fail to meet their valid 'final blend' acceptance criteria and, after a thorough investigation, quality-unit management decides that, in spite of this failure, the processing of the batch should continue and the results of the evaluation of the drug product be used to determine the acceptability of the batch, then set the Examination method to '***MCM***' and proceed to the ***MCM*** section.

2. Stage 1 Evaluation

***Sampling Choice A**: Dynamic Sampling As The Dosage Units Are Formed*

When it is valid to use this option, we recommend that you proceed as follows:

1. Choose a 'routine production' sampling point plan that calls for taking a start sample, an end sample, and not less than some appropriate odd number of approximately evenly spaced intervals during-routine-production sample points as well as provides for an additional 'restart' sampling point each time there is an interruption in the routine production. [**Note:** The number of intervals should be inversely proportional to the uniformity of the blend. In general, that number should be not less than three (3). For the examples shown, that number will be nine (9), a number for blends that are moderately uniform across the batch. The reason for using an odd number is to ensure that the routine sets include a mid-point set. If any are collected, each "restart" sample should be treated as a "special condition" sample and appropriately "positioned" between the preceding and the subsequent routine sampling point.]
2. At each sampling point, into a separate suitable pre-labeled container collect in sequence not less than four (4) times the number of dosage units as there are active dosage-forming stations in the production equipment. Collect each in an appropriate pre-labeled intermediate storage container. [**Note:** To ensure that adequate samples are collected for all tests and examinations, including physical examinations, collect not less than 1600 to 2500 samples in all (typically, *less than* 1 % of today's *minimum* full-scale production batch). Ideally, the samples collected are first used for the non-destructive physical attribute examinations (which typically require the visual examination of 800 or 1250 dosage units {'**ANSI/ASQ Z 1.4**'}) and then returned to their original labeled intermediate-storage containers for use in the requisite variables testing program.]
3. After all of the requisite samples have been collected, conduct the requisite physical examinations and proceed to **Step 4**,
4. If the requisite physical examinations show that the samples collected meet the drug product batch's pre-set "physical properties" acceptance criteria, proceed to **Step 5**; otherwise, proceed as directed by the appropriate quality unit management person with executive authority [**➔ Physical Properties Failure**]
5. From each intermediate-storage container, select twenty (20) units at random and place then in a suitable pre-labeled test-sample container that contains a separate compartment for each dosage unit and has a lid so that, after the units are selected, the sample container can be sealed, and, after the twentieth unit is selected, close the container. When the requisite test samples have been collected from all the intermediate containers, proceed to the ***Initial Testing Decision*** section.

Sampling Choice B: *Static Sampling After The Finished Dosage Units Have Been Completely Intermingled*

When it is appropriate to use this option, we recommend that you proceed as follows:

Formal Review of Guidance for Industry[1]: Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

1. If all the finished dosage units are in a single bulk-storage container proceed to **Step 2**; if they are in two to five (5) bulk-storage containers, proceed to **Step 3**; otherwise, proceed to **Step 4**.
2. Have the units transferred from that bulk container into another bulk container. During the transfer process, at not less than 10 random intervals across the transfer, collect not less than 180 randomly selected units for from each interval during the transfer of the batch (not less than 1800 units in all). When the requisite sample has been collected, proceed to **Step 5**.
3. Prepare a set of appropriately numbered and labeled intermediate-storage sample containers (one for each bulk container). Then, in sequence, randomly select 200 units from each bulk container and place it in its intermediate storage containers. Repeat the container sampling sequence until at least 1800 samples have been selected. When the sampling has been completed, proceed to **Step 5**.
4. Prepare a set of appropriately numbered and labeled intermediate-storage sample containers (one for each bulk container) divide 2000 by the number of containers and round the result up to the near higher integer value. At random, collect that integer number of finished dosage units from each bulk container taking care to maintain the container link between the intermediate sample and the bulk container from which it was taken. When the sampling has been completed, proceed to **Step 5**.
5. After all of the requisite samples have been collected, conduct the requisite physical examinations and proceed to **Step 6**.
6. If the requisite physical examinations show that the samples collected meet the drug product batch's pre-set "physical properties" acceptance criteria, proceed to **Step 7**; otherwise, proceed as directed by the appropriate quality unit management person with executive authority [**➔ Physical Properties Failure**]
7. Divide 200 by the number of intermediate-storage samples generated by the preceding steps. Round that number up to the nearest whole integer. Randomly collect that integer number of dosage units from each intermediate-storage sample container and, as the dosage units are being collected place the sampled dosage units into a properly numbered and labeled test-sample storage container. When the requisite subsample set has been collected proceed to the ***Initial Testing Decision*** section.

Initial Testing Decision

We recommend that you proceed as follows:

1. If you have arrived at this point from ***Sampling Choice A***, proceed with the test-sample containers to **Step 2**; if you have arrived here from ***Sampling Choice B***, proceed with the test-sample containers to **Step 5**.
2. Sequentially, open a given test-sample container, remove, weigh, record the weight, and return each test dosage unit in a manner that preserves the link between the dosage unit's weight and the dosage unit weighed. When the 20th unit has been returned to the opened test-sample container, close that test-sample container. Proceed to **Step 3**.

3. Repeat **Step 2** until the weights of all of the dosage units in the test-sample containers have been measured and recorded and proceed to **Step 4**.
4. Then, verify that the weights of the dosage units meet the batch's pre-set "weight uniformity" criteria. When they do, proceed to **Step 7**; otherwise, proceed as directed by the appropriate quality unit management person with executive authority (➔ **Weight Uniformity Failure**).
5. Weigh 200 units, chosen at random, from the sample containers, appropriately distribute them into a set of ten (10) labeled test-sample containers, and proceed to **Step 6**.
6. If the weights obtained meet the pre-determined weight range, weight average, and distribution criteria, proceed to **Step 7**, otherwise, proceed as directed by the appropriate quality unit management person with executive authority [➔ **Weight Uniformity Failure**].
7. If the previous batch met the acceptance criteria for a ***Stage 1 Examination***, proceed to **Step 8**; otherwise proceed to ***Stage 2 Examination***.
8. From the sample-test containers select a 75-unit batch representative sample as follows:
   a. Divide 75 by the number of test-sample containers, round the result to the next lower integer, and use that as your test-container-basis sampling number. [**Note:** For example, when dynamic sampling is used for an uneventful routine production batch and your "routine batch" sampling interval plan is "Start," 9 interval samples, and "End," you will have 11 containers. Since 75/11 is 6.8181, your basis sampling number is 6.]
   b. Appropriately remove and track your basis number of units from each test-container and properly transfer each into a suitable, appropriately labeled, sample-preparation container [**Note:** In the example, in doing this you will collect 66 dosage units 6 each in 11 trays. This will leave you needing to collect 9 additional units in a 12^{th} tray.]
   c. Then, if necessary, randomly select one unit from one of a pre-determined reduced subset of the test-sample containers, and appropriately transfer that unit into a suitable, appropriately labeled, sample-preparation container. [**Note:** In the example case, you might elect to sample the additional unit needed from each of the 9 intermediate point test-sample containers.]
   d. Repeat **Step c** until a total of 75 units have been properly transferred into your suitable sample-preparation containers. [**Note:** In the dynamically sampled case, you will need to use a set of suitable, point-labeled preparation-sample trays that maintain the links between the point, the unit and the unit's weight. In all other cases, you need only use at most one 'intermediate-unit-collection-container (IUCC),'-labeled preparation-sample container more than the original number of IUCCs.]
   e. When the requisite 75-unit sample has been properly collected, proceed to **Step 9**.
9. Taking into account the stability of the sample preparations, the processing capability of the laboratory, the maximum test-unit groupings that can be handled, and the laboratory's SOPs, select an appropriate preparation work-up plan to use for preparing and analyzing the 75 units. After selecting the

proper work up plan, proceed to **Step 10**. [**Note:** If the sample preparations have limited stability, it may be necessary to use a 'sequential sample prep/test/evaluate/decide' plan. If the sample preparation solutions are moderately stable, a 'groups of five' plan may be appropriate. If the sample preparation solutions are very stable, then a 'groups of 15' or a 'groups of 25' plan may be appropriate. Generally, the design, staffing and/or operation of most labs do not permit groups larger than about 25 to be prepared at about the same time.]

10. Verify that the preparation-sample containers or trays that contain the base number of units are sequentially numbered and that the next higher number has been assigned to the container that contains the 'make up' units. When you have finished, proceed to **Step 11**. [**Note**: When, for example, the number of IUCCs is six (6) and the number of sample-preparation containers is therefore seven (7) (with six containing 12 units each and the seventh containing 3 units), you should have assigned the number tags '1' through '6' to the six containing 12 each and the tag '7' to the last container.]

11. Using the 'test grouping' plan selected in **Step 10**, proceed to select and work up the test samples in the first group using the assigned random numbers to populate each group derived from the weight/unit linked dynamically sampled units and the container numbers to populate each group derived from statically sampled units. If you need assistance in deciding how to accomplish, you may use the guidance provided in the following note. [**Note:** For example, when you are evaluating a dynamically sampled batch and the 'preparation' plan specifies groups of fifteen (15), you could start by randomly selecting one (1) dosage unit from each of the 12 trays (one from trays '1' through '11' and then trays '1' through '3') for the first group of 15, followed by one from trays '4' through '12' and one from trays '1' though '6' for the second group of 15, followed by one from trays '7' through '12' and one from trays '1' through '9' for the third group of fifteen, followed by one from trays '10' through '12' and the trays '1' through '12' for the fourth group of 15, and finish by working up by the 11 remaining units in trays '1' trough '11' and the 4 units remaining in tray '12' for the fifth group. When you are evaluating a statically sampled batch, like the one discussed in **Step 9** (six original basis set preparation containers and a 7th container to hold the three additional units to make the total 75), and the preparation set size is 15, for the first set, 'Set 1,' select any 2 from each of containers '1' through '6' to get 12 and then one from the odd containers ('1,' '3' and '5') to get the 15 needed. For the second set, 'Set 2,' select 2 from each of the containers '1' through '6' and then one from the even containers ('2,' '4' and '6') to get the second set. Repeat the preceding test-sample selection plan for Sets '3' and '4.' For the last set, Set '5,' select 2 from each of the containers '1' through '6' and use the three (3) in container '7' to complete the 15.]

12. Test each group prepared and evaluate the results obtained as follows:

- **a.** Verify that the measurement system was in control (suitable) during the entire testing interval.
- **b.** Verify that the result values obtained are valid.
- **c.** If all of the results are valid and between 85 % and 115 %, proceed to **Step 13**; otherwise, notify your supervisor and the appropriate quality manager of the problem and proceed as the quality unit directs. [**Note:** If the unexpected results are confirmed to be valid and only one value of all of the

values collected is outside of the range from 85 % to 115 % but still inside the range from 75 5 to 125 %, the '***SCM, Stage 1***' testing should be allowed to continue until, subject to the *OOB* conditions stated later in this Note, all 75 units have been evaluated with the proviso that the other 125 units required to satisfy the testing requirements for ***Stage 2*** will need to be appropriately evaluated, and the Examination **method set to '*SCM, Stage 2.*'** In addition, there is no need to evaluate the results against the *Stage 1 Evaluation* criteria because its first criterion that the ***SCM*** results must meet is "all valid content result values mist be within the relative range from "85.0 % to 115. %." ***Out-of-Bounds (OOB) Limits On SCM Testing:*** If the number of valid result values outside of the range from 85 % to 115 % exceeds 3 and you elect to continue testing, after completing the testing of the 75 units and finding 6 or fewer *OOB* content results, you will need to switch to ***MCM***, test its number of samples, and set the Examination *method to* '***MCM.***' When the number of valid *OOB* result values outside of 85 % to 115 % exceeds 12 or any one is found to be outside of 75 5 to 125 %, the batch should be considered a failure and the testing terminated.]

13. When all of the groups have been tested and their results found to be acceptable, proceed to **Step 15**; otherwise proceed to **Step 14**.
14. Select and prepare the next group to be tested and proceed to **Step 12**.
15. If the links (between weight, original location point of production, and result) have been preserved (the *dynamic sampling* case) for the units, proceed to **Step 16**; otherwise proceed to **Step 17**.
16. Compute the weight-corrected relative result values (the relative specific active content) and use that discrete-units data, the comparable non-discrete blend data obtained when the final blend was tested and the appropriate scientifically sound statistical assessment procedures to estimate the average variability introduced by the blend manipulation steps between the blend sampling point and the formation of the dosage units, and proceed to **Step 17**.
17. Using the measured relative results' data obtained for the 75 units tested, evaluate the statistical quality of the batch using '**ANSI/ASQC Z 1.9**' for the 'variability unknown, reduced inspection, 75-representative dosage units' case ('**ANSI/ASQC Z 1.9**,' ***Table B-4***, page 42) as follows:
    a. Write down the pre-established AQL_U and AQL_L values (for example, 1.0 and 0.65).
    b. Using ***Table B-4*** (on page 42 of the standard), look and write down the "M_{75}" values that correspond to the pre-established AQL levels (for the example, $M_{U,75}$ is '3.17' % and $M_{L,75}$ is '2.27' %).
    c. Compute the 75-sample relative mean ($\bar{X}_{75}$ %) and the relative standard deviation (RSD_{75} %).
    d. If the relative mean is less than 98 % proceed to **Step 18**; otherwise proceed to **Step e**.
    e. Compute the following relative quality indices:
        i. $Q_U = [115 - (\bar{X}_{75}\,\%)]/(RSD_{75}\,\%)$
        ii. $QL = [(\bar{X}_{75}\,\%) - 85]/(RSD_{75}\,\%)$

f. Using ***Table B-5,*** look up the estimated batch percentage above U (p_U) and the estimated batch percentage below L (p_L) and compute p by adding p_U and p_L)

g. Compare p_U with M_U, p_L with M_L, and p with the higher of M_U or M_L. [**Note:** Given that the manufacturer must strive to comply with **21 CFR 211.101(a)**, AQL_U should almost always be higher than or, at least, not less than AQL_L. Hence, p should almost always be compared to M_U.]

h. The batch is acceptable if each 'p' value is less than the 'M' value to which it is compared.

i. If the batch is acceptable, appropriately note that the active content met its AQL acceptance criteria in your records and then proceed with the evaluation of the next variable factor (typically, ***Dissolution*** or ***Drug Release***) that needs to be evaluated for the batch's acceptability (➔ **EXIT**); otherwise proceed to **Step 18.**

18. If the statistical quality results, though outside of the statistical quality criteria, the mean and/or the standard deviation, indicate that testing additional samples may find the batch to be acceptable, set the Examination method to ***Stage 2 Examination*** and proceed as that section directs; otherwise proceed to **Step 19.** [**Note:** For the RSD, a comparison of the observed RSD to the Maximum Standard Deviation (MSD) (computed using the Table B-6 and the instructions beneath it) can be used as a guide in this decision making process. In general, if the observed RSD is less than the MSD, a *Stage 2 Evaluation* should be conducted. When the RSD is greater than MSD, but not significantly greater than MSD, you should set the Examination method to the *Marginal Criteria Method (MCM)* and proceed to the *MCM* section. Similarly, if the mean is within the range from 96 % to 104 % of the target, additional testing may be warranted especially, given **21 CFR 211.101(a)**, when the mean is on the high side and it or the p_U that fails to meet the acceptance criteria established.]

19. Report the problem to the proper quality manager and with this official's assistance, initiate the appropriate investigation, and, if that investigation indicates that additional testing is warranted, you should set the Examination method to '***SCM, Stage 2***' and proceed to the ***Stage 2 Evaluation*** section.

In general, when the results pass these criteria, you can use the ***SCM*** for the next batch. If test results fail to meet the ***Stage 1*** criteria, you may be able to validly conduct the full-AQL sample testing provided in ***Stage 2*** and accept the batch when it meets the ***Stage 2*** acceptance criteria or you may need to switch to the ***MCM*** method. In the worst cases, a valid result outside of the relative range of 75 % to 125 % or a significant number of units outside of the relative range of 85 % to 115 %, you should reject the batch and, if possible rework it.

3. Stage 2 Evaluation

For this choice, how you proceed depends upon how you arrived at this point in the evaluation of the acceptability of a batch for release. In general, there are three ways that you can get to this point, (1) the '***SCM, Stage 0***' active-content results can meet their batch 'final blend' acceptance criteria but, for whatever

reason, fail to meet their 'dosage unit' acceptance criteria; (2) the previous batch was required to be tested using the ***SCM, Stage 2 Evaluation***, and (3) the valid results from an initial ***SCM, Stage 1 Evaluation*** failed to meet the batch acceptance criteria but no valid results were outside of the relative range, '75 % to 125 % of the target,' and not more than a few units were outside of the relative range '85 % to 115 % of the target.'. [**Note:** In situations '(1)' and '(2),' 200 batch-representative samples will need to be collected and tested. In '(3),' the requisite 200 sample units will have already been collected and up to 75 of them will have been tested leaving a balance of about 125 units to be tested. In ***SCM, Stage 1 Evaluation*** situations where the finding of an excess number of out of specification units has terminated the ***SCM, Stage 1 Evaluation***, a quality-unit decision to authorize switching to the ***SCM, Stage 2 Evaluation*** procedure will also trigger the testing of the balance of the 75 units selected for the ***SCM, Stage 1 Evaluation*** set before the ***SCM, Stage 2 Evaluation*** is started. Thus, this '***SCM, Stage 2 Evaluation***' entry option only needs to address those issues associated with evaluating the remaining 125 units. In all cases, where the test goes to completion, a total of 200 units will be tested and their relative content values used to determine whether or not the batch meets its specifications and AQL criteria.]

With the preceding introduction in mind, you should proceed as follows:

1. If the samples needed have already been selected (***SCM, Stage 2 Evaluation*** triggered by a non-conformity to the active content acceptance criteria in the ***SCM, Stage 1 Evaluation***), proceed to **Step 18**; otherwise proceed to **Step 2**.
2. If you are justified in choosing, and have elected to perform, dynamic sampling, proceed to **Step 3**; otherwise, proceed to **Step 7.**
3. Choose a 'routine production' sampling point plan that calls for taking a start sample, an end sample, and not less than some appropriate odd number of approximately evenly spaced intervals during-routine-production sample points as well as provides for an additional 'restart' sampling point each time there is an interruption in the routine production. [**Note:** The number of intervals should be inversely proportional to the uniformity of the blend. In general, that number should be not less than three (3). For the examples shown, that number will be nine (9), a number for blends that are moderately uniform across the batch. The reason for using an odd number is to ensure that the routine sets include a mid-point set. If any are collected, each "restart" sample should be treated as a "special condition" sample and appropriately "positioned" between the preceding and the subsequent routine sampling point.]
4. At each sampling point, collect in sequence *not less than* four (4) times the number of dosage units as there are dosage-forming stations in the production equipment. Collect each in an appropriate pre-labeled intermediate storage container. [**Note:** To ensure that adequate samples are collected for all tests and examinations, including physical examinations, collect not less than 1800 to 2500 sample units in all (typically, *less than* 1 % of today's full-scale production batch). Ideally, the samples collected are first used for the non-destructive physical attribute examinations (which typically require the visual examination of 800 or 1250 dosage units {'**ANSI/ASQ Z 1.4**' a recognized American attribute standard that is the successor to ***Mil Spec 105***}) and then, if they examined units meet their visual acceptance criteria, returned to their original

labeled intermediate-storage containers for use in the requisite variables testing program.]

5. After all of the requisite samples have been collected, perform the requisite physical properties examinations on the samples collected and, when the samples examined meet their "physical properties" acceptance criteria, proceed to **Step 6**; otherwise, proceed as directed by an appropriate quality unit management person with executive authority (➔ **A Physical Properties Failure**).
6. From each intermediate-storage container, select twenty (20) units at random and place then in a suitable pre-labeled test-sample container that contains a separate compartment for each dosage unit and has a lid so that, after the units are selected, the sample container can be sealed, and, after the twentieth unit is selected, close the container. When the requisite 200+ batch-representative test samples (20 units from each interval sample) have been collected from all the intermediate containers, proceed to the **Step 12**.
7. If all the finished dosage units are in a single bulk-storage container proceed to **Step 8**; if they are in two to five (5) bulk-storage containers, proceed to **Step 9**; otherwise, proceed to **Step 10**.
8. Have the units transferred from that bulk container into another bulk container. During the transfer process, at not less than 10 random intervals across the transfer, collect not less than 200 randomly selected units from each interval during the transfer of the batch. When the requisite sample has been collected, proceed to **Step 11**.
9. Prepare a set of appropriately numbered and labeled intermediate-storage sample containers (one for each bulk container). Then, in sequence, randomly select 200 units from each bulk container and place it in its intermediate storage containers. Repeat the container sampling sequence until at least 2000 samples have been selected. When the sampling is complete, proceed to **Step 11**.
10. Prepare a set of appropriately numbered and labeled intermediate-storage sample containers (one for each bulk container) divide 2000 by the number of containers and round the result up to the near higher integer value. At random, collect that integer number of finished dosage units from each bulk container taking care to maintain the container link between the intermediate sample and the bulk container from which it was taken. When the sampling has been completed, proceed to **Step 11**.
11. After all the required batch-representative units have been collected, perform the requisite physical examinations, and when the samples meet their pre-set "physical properties" acceptance criteria, proceed to **Step 12**; otherwise, proceed as directed by an appropriate quality unit management person with executive authority (➔ **A Physical Properties Failure**).
12. Divide 200 by the number of intermediate-storage samples generated by the preceding steps. Round that number up to the nearest whole integer. Randomly collect that integer number of dosage units from each intermediate-storage sample container and, as the dosage units are being

collected place the sampled dosage units into a properly numbered and labeled test-sample storage container. When the requisite subsample set has been collected proceed to the **Step 13**.

13. Weigh the not less than 200 batch-representative sample dosage sampled, and, provided the weighed units meet the weight acceptance criteria (range, mean, and distributional) for the drug-product, proceed to **Step 14**; otherwise, proceed as directed by the appropriate quality unit management person with executive authority (➔ **Weight Uniformity Failure**).
14. If you have arrived at this point from **Step 6**, proceed with the test-sample containers to **Step 15**; if you have arrived here from **Step 13**, proceed with the test-sample containers to **Step 17**.
15. Sequentially, open a given test-sample container, remove, weigh, record the weight, and return each test dosage unit in a manner that preserves the link between the dosage unit's weight and the dosage unit weighed. When the 20th unit has been returned to the opened test-sample container, close that test-sample container. Proceed to **Step 16**.
16. Repeat **Step 15** until the weights of all of the dosage units in the test-sample containers have been measured and recorded. Then, proceed to **Step 17**
17. From the sample-test containers select 200 batch-representative dosage units as follows:
    a. Divide 200 by the number of test-sample containers, round the result to the next lower integer, and use that as your test-container-basis sampling number. [**Note:** For example, when dynamic sampling is used for an uneventful routine production batch using a sampling plan that takes samples at 11 routine interval points, you will have 11 containers. Since 200/11 is 18.1818, your basis sampling number is 18.]
    b. Appropriately remove and track your basis number of units from each test-container and properly transfer each into a suitable, appropriately labeled, sample-preparation container [**Note:** In the example, in doing this you will collect 198 dosage units {18 each in 11 trays}. This will leave you needing to collect 2 additional units in a 12th tray.]
    c. Then, if necessary, randomly select one unit from one of a pre-determined reduced subset of the test-sample containers, and appropriately transfer that unit into a suitable, appropriately labeled, sample-preparation container. [**Note:** In the example case, you might elect to sample the additional unit needed from the 'Start' and 'End' test-sample containers.]
    d. Repeat **Step c** until a total of 200 units have been properly transferred into your suitable sample-preparation containers. [**Note:** In the dynamically sampled case, you will need to use a set of suitable, point-labeled preparation-sample trays that maintain the links between the point, the unit and the unit's weight. In all other cases, you need only use at most one 'intermediate-unit-collection-container (IUCC),'-labeled preparation-sample container more than the original number of IUCCs.]
    e. When the requisite 200-unit sample has been properly collected, proceed to **Step 19**.

18. When 75 units have already been tested in a non-conforming ***SCM, Stage 1 Evaluation***, select 125 batch-representative dosage units as follows:

- **a.** Divide 125 by the number of test-sample containers, round the result to the next lower integer, and use that as your test-container-basis sampling number. [**Note:** For the example we have been using, when dynamic sampling was used for an uneventful routine production batch, you will have 11 containers. Since 125/11 is 11.3636, your basis sampling number is 11.]
- **b.** Appropriately remove and track your basis number of units from each test-container and properly transfer each into a suitable, appropriately labeled, sample-preparation container [**Note:** In the example we have been using, in doing this you will collect 121 dosage units {11 each in 11 trays}. This will leave you needing to collect 4 additional units in a 12th tray.]
- **c.** Then, if necessary, randomly select one unit from one of a pre-determined reduced subset of the test-sample containers, and appropriately transfer that unit into a suitable, appropriately labeled, sample-preparation container. [**Note:** In the example case, you might elect to sample the additional unit needed from the 'Start,' 'End,' 'Interval 5' and 'Interval 7' test-sample containers.]
- **d.** Repeat **Step c** until a total of 200 units have been properly transferred into your suitable sample-preparation containers. [**Note:** In the dynamically sampled case, you will need to use a set of suitable, point-labeled preparation-sample trays that maintain the links between the point, the unit and the unit's weight. In all other cases, you need only use at most one "intermediate-unit-collection-container (IUCC),"-labeled preparation-sample container more than the original number of IUCCs.]
- **e.** When the requisite 125-unit sample has been properly collected, proceed to **Step 19**.

19. Taking into account the stability of the sample preparations, the processing capability of the laboratory, the maximum test-unit groupings that can be handled, and the laboratory's SOPs, select an appropriate preparation work-up plan to use for preparing and analyzing the 200 or 125 units. After selecting the proper work up plan, proceed to **Step 20**. [**Note:** If the sample preparations have limited stability, it may be necessary to use a 'sequential sample prep/test/evaluate/decide' plan. If the sample preparation solutions are moderately stable, a 'groups of five' plan may be appropriate. If the sample preparation solutions are very stable, then a 'groups of 15' or a 'groups of 25' plan may be appropriate. Generally, the design, staffing and/or operation of most labs do not permit groups larger than about 25 to be prepared at about the same time.]

20. Verify that the preparation-sample containers that contain the base number of units are sequentially numbered and that the next higher number has been assigned to the container that contains the 'make up' units. When you have finished, proceed to **Step 21**. [**Note**: When, for example, the number of IUCCs is six (6) and the number of sample-preparation containers is therefore seven (7) (with six containing 33 {or, for the125-unit sample case, 20} units each and the seventh containing 2 units {or, for the125-unit sample case, 5}), you should have assigned the number tags '1' through '6' to the six containing 12 each and the tag '7' to the last container.]

21. Using the "test grouping" plan selected in **Step 19**, proceed to select and work up the test samples groups by randomly selecting samples from each container or, for dynamic-sampling-case, tray in a manner similar to that explicitly shown in the ***SCM, Stage 1*** case. If you need assistance in deciding how to accomplish, you may use the guidance provided in the following note. Then, proceed to **Step 22**. [**Note:** *For the '75/125-unit case' from a* ***SCM, Stage 1*** *non-conformity or a '200-unit at once' case*, where: **a)** you are evaluating a dynamically sampled batch and **b)** the "preparation" plan specifies groups of 25, you could first work up two individual units randomly selected from trays '1' through '12' (exhausting the 'overflow' tray) and one from tray '1' for the first group of 25, followed by two from trays '1' through '11' and one each from trays '2' through '4' for the second group of 25, followed by 2 units from trays '1' through '11' and '1' from trays '5' through '7' for group the third group of 25 [the last group for a successful ***Stage 1*** *Evaluation*, 75-unit case], followed by 2 units at random from trays '1' through '11' and one from trays '8' through '10' for the fourth group of 25, ,..., and finish by working up by the set remaining units for the eighth, and final, group of 25 units . When you are evaluating a statically sampled batch, like the one discussed in the **Note** in **Step 20**, the preparation set size is 25, and the sample size is 200, for the first set, 'Set 1,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '1' to get the 25 needed. For the second set, 'Set 2,' select 4 from each of the containers '1' through '6' and then one from the container '2' to get the second set. For the third set, 'Set 3,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '3.' For the fourth set, 'Set 4,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '4.' For the fifth set, 'Set 5,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '5.' For the sixth set, 'Set 6,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '6.' For the seventh set, 'Set 7,' select any 4 from each of containers '1' through '6' to get 24 and then one from container '7.' For the last set, 'Set 8,' select 4 from each of the containers '1' through '6' and the last one in container '7' to complete the 25. {When the sample size is 125 and preparation set size is 25 (where the containers '1' through '6' contain 20 units each and the seventh container contains 5 units), for each preparation set, take 4 from each of the containers '1' through '6' and one from the seventh container to get 25 samples in each preparation set.]

22. Prepare each preparation group, test the resulting solutions and evaluate the results obtained as follows:

- **a.** Verify that the measurement system was in control (suitable) during the entire testing interval.
- **b.** Verify that the result values obtained are valid.
- **c.** If all of the results are valid and between 85 % and 115 %, proceed to **Step 23**; otherwise, notify your supervisor and the appropriate quality manager of the problem and proceed as the quality unit directs. [**Note:** If the unexpected results are confirmed to be valid and only one value of all of the values collected is outside of the range from 85 % to 115 % but not outside of 75 % to 125 %, the "**SCM, Stage 1**" testing should be allowed to continue until, subject to the *OOB* conditions stated later in this Note, all 75 units have been evaluated with the proviso that the other 125 units required to satisfy the testing requirements for ***SCM, Stage 2*** will need to be appropriately evaluated,

and the Examination **method set to '*SCM, Stage 2.*'** In addition, there is no need to evaluate the results against the '***Stage 1 Evaluation***' criteria because its first criterion the '***SCM, Stage 1***' results must meet is 'all valid content result values mist be within the relative range from 85.0 % to 115. %.' ***Out-of-Bounds (OOB) Limits On SCM Testing:*** If the number of valid result values outside of the range from 85 % to 115 % exceeds 4 and you elect to continue testing, after completing the testing of the 75 units and finding 12 or fewer *OOB* content results, you will need to switch to ***MCM***, test its number of samples, and set the Examination *method to* '***MCM***.' If the number of valid *OOB* result values outside of 85 % to 115 % exceeds 12 or any apparently valid result is outside of 75 % to 125 % of the established target value (an out-of-specification [OOS] result, the batch should be considered a non-conforming and the testing terminated.]

23. When all of the groups have been tested and their results found to be acceptable, proceed to **Step 25**; otherwise proceed to **Step 24**.
24. Select the next group to be tested and proceed to **Step 22**.
25. If the links (between weight, original location point of production, and result) have been preserved (the *dynamic sampling* case) for the units, proceed to **Step 26**; otherwise proceed to **Step 27**.
26. Compute the weight-corrected relative result values (the relative specific active content) and use that discrete-units data, the comparable non-discrete blend data obtained when the final blend was tested and the appropriate scientifically sound statistical assessment procedures to *estimate the average variability introduced by the blend manipulation steps between the blend sampling point and the formation of the dosage units*, and proceed to **Step 27**.
27. Using the measured relative results data obtained for the 200 units tested, evaluate the statistical quality of the batch using '**ANSI/ASQC Z 1.9**' for the 'variability unknown, reduced inspection, 200-representative dosage units' case ('**ANSI/ASQC Z 1.9**,' ***Table B-3***, page 41) as follows:
    a. Write down the pre-established AQL_U and AQL_L values (for example, 1.0 and 0.65).
    b. Using ***Table B-3*** (on page 41 of the standard), look (down from the top ['normal inspection']) and write down the 'M_{75}' values that correspond to the pre-established AQL levels (for the example, $M_{U,200}$ is '2.04' % and $M_{L,200}$ is '1.42' %).
    c. Compute the 200-sample relative mean ($\bar{X}_{200}$ %) and the relative standard deviation (RSD_{200} %).
    d. If the relative mean for the 200 units is outside of the range from "99 % to 102 % of the target" proceed to **Step 28**; otherwise proceed to **Step e**.
    e. Compute the following relative quality indices:
        i. $Q_U = [115 - (\bar{X}_{200}\ \%)]/(RSD_{200}\ \%)$
        ii. $QL = [(\bar{X}_{200}\ \%) - 85]/(RSD_{200}\ \%)$
    f. Using ***Table B-5,*** look up the estimated batch percentage above U (p_U) and the estimated batch percentage below L (p_L) and compute p by adding p_U and p_L)

g. Compare p_U with M_U, p_L with M_L, and p with the higher of M_U or M_L. [**Note:** Given that the manufacturer must strive to comply with **21 CFR 211.101(a)**, AQL_U should almost always be higher than or, at least, not less than AQL_L. Hence, p should almost always be compared to M_U.]

h. The batch is acceptable if each 'p' value is less than the 'M' value to which it is compared.

i. If the batch is acceptable, appropriately note that the active content met its AQL acceptance criteria in your records and then proceed with the evaluation of the next variable factor (typically, ***Dissolution*** or ***Drug Release***) that needs to be evaluated for the batch's acceptability (➔ **EXIT**); otherwise proceed to **Step 26**.

26. If, though outside of the statistical quality acceptance criteria established for ***SCM, Stage 2***, the statistical quality results for the mean and the standard deviation indicate that testing additional samples may find the batch to be acceptable, set the Examination method to ***MCM*** and proceed as that section directs; otherwise proceed to **Step 27**. [**Note:** In general, when the observed RSD_{200} is not greater than 3 %, you may be justified in proceeding to the ***MSM*** stage. Similarly, if the relative mean for the 200 results is within the range from 98 % to 103 % of the target, additional testing may be warranted especially, given **21 CFR 211.101(a)**, when the mean is on the high side and it or the p_U is the parameter that fails to meet the acceptance criteria established.]

27. Report the problem to the proper quality manager and with this official's assistance, initiate the appropriate investigation, and, if that investigation indicates that additional testing is warranted, you should set the Examination method to '***MCM***' and proceed to the ***MCM*** section.

In general, when the results pass these criteria, you can use the ***SCM*** for the next batch. When the test results fail to meet the ***Stage 2*** criteria, you should switch to the ***MCM*** method *even when* proven equipment malfunction (indicative of a failure to have an adequate preventive maintenance program) other than a power outage or operator error (indicative of an inadequate operator control and/or deficient operator training program) have caused the non-uniformity observed. [**Note:** If you have a quality-built-in approach, that approach must be 'self evident' not only in the drug product but also in the equipment, personnel, and procedures at all levels.]

In the worst cases (a valid active content result outside of the relative range of 75 % to 125 % or a significant number [for example, > 6 in 200 units tested] of the content results outside of the relative range of 85 % to 115 %), you should reject the batch and, if possible rework it.

In instances where a ***SCM, Stage 2*** non-conformance is observed and the ***SCM, Stage 2 Evaluation*** was triggered by a ***SCM, Stage 0*** non-conformance, you may be able to directly use data generated from both those stages and validly proceed to ***MCM*** provided: **a)** no valid content value in the combined 400 batch-representative relative active content result values is outside of the range from 75 % to 125 % and b) not more than 12 of those relative active content values are outside of the range from 85 % to 115 %."

Returning to the Draft, this commenter recommends deleting Lines 373 through 399 as shown, and replacing it with a) the text that follows the justification for deleting the Draft text or b) some similarly *scientifically sound* and *appropriate* method that can determine the acceptability (or lack thereof) of the **batch**.

~~**"B. Marginal Criteria Method (MCM)**~~

~~After powder mix assessment, in-process dosage unit stratified sampling correlation and initial criteria establishment, we recommend that you use the MCM when either of the following conditions is met:~~

- ~~Results of initial criteria establishment qualified as *marginally pass*.~~
- ~~Results of initial criteria establishment qualified as *readily pass* or a batch was tested according to SCM and the test results failed both stage 1 and stage 2 criteria.~~

~~Then, we recommend you use the weight-corrected results from the stage 2 SCM analysis and compare this with the MVM criteria:~~

- ~~For all individual results ($n \geq 30$) the RSD ≤ 6.0 percent.~~
- ~~Mean of all results is 90.0 percent to 110.0 percent of target assay.~~

~~We recommend that all results from analysis of any remaining location samples be computed with the stage 2 SCM data. No test results should be removed from the analysis. If the test results pass these criteria, the adequacy of mix and uniformity of content for the batch are adequate. We recommend that you continue to test routine manufacturing batches with MCM criteria. If the test results fail the criteria, you should no longer use the verification testing methods to ensure adequacy of mixing or uniformity of content until you investigate the failure (per 21 CFR 211.192) to establish justified assignable cause(s), take necessary corrective actions and repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures.~~"

Justification for the Deletion

The preceding section is **not** based on the applicable sound statistical science and it does **not** even attempt to address much less meet the statistical quality control criteria established in **21 CFR 211.165(d)**.

This is the situation because:

1. The sampling plan does **not** collect enough samples to meet the inherent sample-size sufficiency component of the requirement that the sample be batch representative.
2. The correction of the results for unit weight is not scientifically sound here because
   a. Especially in the case of sugar-coated and multiply film-coated and waxed tablets and finished capsules that are difficult to weigh, empty, and reweigh the "shell" to determine the weight of fill (post-fill banded and gel-coated capsules), ***the weight variability observed is not provably attributable to the variation in the weight***, and
   b. In general, it introduces an unwarranted artificial bias into the final results.
3. **Even at the "30-unit" level, the results found can only be extrapolated to the batch at a confidence level that is less than 20 %.**

4. The acceptance criteria fail to properly consider, much less address, more than one possible "batch failing" situation including, but not limited, to:
   a. Valid content test result values may be found that are outside of the USP's post-release expectation that all content values must be inside of the range from 85 % to 115 % of the target level,
   b. Valid content values may be found that are outside of the USP's lifetime acceptance range of 75 % to 125 % of the target level,
   c. A mean for the samples tested that is not close enough to the target mean to support the release of the batch.
5. The sampling plan and the result acceptance criteria do **not** comply with the *statistical quality control* mandates, including scientifically sound, "appropriate acceptance levels and/or appropriate rejection levels" set forth in **21 CFR 211.165(d)**.

Moreover, as written, some of the statements in this section are blatantly at odds with not only CGMP and sound science, but also with common sense.

How can anyone believe that the active content test results from as few as 30 units in batches of hundreds of thousands or millions of units can confidently predict that uniformity of the blend and the final drug product batch not only with respect to the measured active content but also with respect to the other critical batch post-release requirements established by the USP including, but not limited to, active availability (as measured by *Dissolution* and *Drug Release*), impurity level, and water content.

Factually, ***even if the 30 units tested are somehow batch representative,*** one can only be less than 20 % confident that those values reflect the distribution of the active content in the batch of dosage units.

Moreover, with respect to the untested variable factors that are required to meet other uniformity criteria, one can have little, "≪ 20 %," (if there is proof of some very strong correlation between active content and the unmeasured variable) or close to zero (when the variables [e.g., water content] are not correlated with the active level) confidence in the uniformity of the batch.

For example, the Draft falsely asserts, "If the test results pass these criteria, the adequacy of mix and uniformity of content for the batch are adequate." [**Note:** At the 95 % confidence level, the calculated RSD is an approximately 25 % uncertain estimate of the batch RSD for sets 30 representative units. For the 30-unit case, the true batch RSD can easily be larger than 6.2 %.]

The CGMP regulations clearly and plainly require scientifically sound and appropriate batch-based acceptance criteria – not the sample-based acceptance criteria set forth in this Draft.

Based on all of the preceding, this commenter suggests an alternative that:

a. Tests batch-representative samples sets having sizes appropriate to today's state of control over the inputs and processes that affect the uniformity of the drug product when the initial validation results indicate that the process' control of the uniformity of the content of the "final blend" and/or the "formed dosage units" is marginal. ,
b. Ensures that the batch has the mean strength that it purports or is represented to have

c. Does comply with **21 CFR 211.165(d)**, and

d. Utilizes a suitable normal-distribution, process-capability-based approach to ensuring that the **batch**, and not just the samples tested, is acceptable and meets the AQL-related criteria established in the method in a manner that complies with the clear mandates for such set forth in the drug product CGMP regulations at **21 CFR 211.165(d)**.

That detailed alternative is as follows:

"B. A Marginal Criteria Method (*MCM*) That ONLY Addresses Active Uniformity

We recommend using the ***MCM*** verification method for assessing batch active content uniformity when the following conditions have been met:

- The initial process validation studies have determined that the initial full-scale batches meet the criteria established for the *marginally passing* case or, if the if the initial full-scale criteria met the *readily passing* criteria but, for whatever reason, the physical properties of the components are not adequately controlled, and/or the production is produced in short campaigns, and/or the mixer shell on the mixers used is subject to wear patterning that continually alters the blending pattern within the blender.
- The mean, mode and median values for all initial full-scale validation batches and all previous batches have demonstrated that it is valid to treat the distribution of the active content values in the "final blend" and "dosage units" as being normally distributed about the observed mean for each batch. [**Note:** For this to be the case, $mean_n \simeq mode_n \simeq median_n$ for $n \geq 400$ dosage units.]
- None of the units tested in the validation batches yielded in valid results that were outside the relative range of 75 % to 125 % of the approved target and less than 12 in 400 were outside of the range from 85 5 to 115 % of that target, and the observed batch "relative mean" value for the not less than 400 batch-representative dosage units was not less than 99.5 % nor more than 100.5 %. [**Note:** As more batch-representative units are tested from a normal distribution, the mean value should converges on the established target mean and the sample RSD even though the range of values observed may increase.]
- The testing on the previous acceptable batch demonstrated that that batch met the ***MCM*** batch-acceptance criteria.
- The CGMP-compliant, batch-representative in-process blend (or, if safety or other considerations have led the Agency to authorize batch-representative formed dosage-unit testing in lieu of blend testing) met the scientifically sound, in-process, batch, content-uniformity, acceptance criteria established for this drug product blend.

In cases where: a) the Agency-authorized in-process 'final blend' test for active content uniformity is the evaluation of the tablet cores or capsule fill in lieu of blend testing, b) it has been established that none of the post-dosage-forming

steps change the active content in the dosage units, c) not less than 400 batch-representative cores were tested, and d) the weight-corrected relative content results from the testing of the 400 batch-representative 'freshly formed' dosage met the acceptance criteria for the 'final blend,' you can use the uncorrected relative result values and the procedures for relative result assessment in the ***Sampling Choice A*** option to also evaluate the uniformity of the active content for the 'freshly formed' dosage units.

In cases where the process development studies have shown that none of the post-dosage forming steps have any significant adverse impact on the variability of the active content, the manufacturer can also dynamically sample a batch representative sample at the dosage forming stage and appropriately test a suitably sized batch-representative subsample from that in-process dosage-forming step. If you can validly use the ***Sampling Choice A*** option, and have elected to use this alternative, proceed to the ***Sampling Choice A*** section; otherwise (elected sampling at a later point or process-mandated sampling at a later point), proceed ***Sampling Choice B*** section. [**Note:** When you elect to or must (because post-dosage-forming operations have been shown to significantly affect the uniformity of the dosage units) collect the sample at a later post-dosage-unit-forming stage where the time-related dosage-unit forming effects, if any, have been only partially randomized because of the mixing that occurs in the subsequent processing steps, this guidance only discusses two choices (the in-process 'dynamic sampling' and the 'completely randomized static sampling' options). Limiting the discussion to these two options minimizes the complexity of a guidance that is already complex. Should you choose to sample at some step where the dosage units are only partially randomized, you may need to devise and justify a sampling plan that is appropriate to your particular situation.]

In all other cases, the samples to be tested should be taken at random from the batch-representative finished drug-product 'Attribute Evaluation and Reserve' sample collected from the output of the last processing step that the drug-product units undergo prior to their being packaged for distribution. In such situations, you should use the ***Sampling Choice B*** option. [**Note:** Typically, at this point the intermediate processing steps have randomized the units to the extent that any sample 'of sufficient size' selected from the batch can validly be considered to be representative of the batch. Moreover, provided that sample in its aggregate initially contain sufficient sample for three (3) times the number needed for all attribute examinations, it should also contain sufficient samples for all variable tests and the sample units, if any, required for a 'Reserve" (**21 CFR 211.170(b)**). In general, such an aggregate sample initially should contain more than three times the number of samples required to do all variable testing for the ***MCM*** approach.]

You should use the '***MCM*** approach:

1. When the development and initial validation results indicate the product is a ***marginally passing*** product **or**
2. *When the initial validation results are* ***readily passing***, you:
   a. Have changed the source of a component,
   b. Do not have controls on all the key physical properties of all the components or the *direct* and *indirect* controls you have set have not

been proven during the development to be sufficient to ensure (at a confidence level of at least 90 %) that the 'worst case' combinations of components produce 'final blend' results that meet the ***readily passing*** criteria,

c. Manufacture the drug product in short (< 20-batch) runs) and the between run history of the drug product indicates that there is a *significant between-run effect* on the uniformity of the batches produced,

d. Manufacture the drug product in blending equipment whose mixing patterns are ***non-reversibly*** affected by wear patterning, and/or

e. The previous batch has failed to meet the ***readily passing*** criteria you have established for the drug product at any stage.

In such cases, the manufacturer should start up using the appropriate '***Sampling Choice***' option for at least 5 consecutive '***MCM*** batches.

In general each batch should be such that:

a. All valid relative active content test result values should be in the range '75.0 to 125. % of the target,'

c. The relative content mean for each batch is *not less than* 98.5 % and *not more than* 102 % of the validated target level,

d. The mean, mode and median relative content values are approximately equal (to within 1.5 % relative), and

e. The mean of the relative mean values for this and the previous nine (9) batches is *not less than* 99. % and *not more than* 101. % of the target value.

f. The RSD for the 400-unit representative sample tested for the uniformity of the active content (without weight correction) should be not more than 2.5 % for tablet drug products or not more than 3 % for powder- and solid-slug-filled capsules.

When the preceding conditions ('a.' through 'f.') are **all** met for at least five (5) consecutive batches, you may be able to validly switch to the appropriate ***SCM, Stage 2 Evaluation*** option and use it provided:

1. Production of the batches proceeds at a steady rate,

2. The mixing equipment used is not subject to wear patterning that can affect the uniformity of the final blend,

3. The controls on the physical properties of the components used have been established as being adequate,

4. There has been no change for the source of any component in the current and the previous five (5) acceptable batches, and

5. Except for instances of equipment failure and proven operator error, there are no failures of any batch to meet **any** of its '***MCM*** acceptance criteria for the active content or any other key variable (such as, Drug Release or Dissolution, Water Content, impurity) established by the USP or the FDA.

Based on the preceding, the ***MCM Sample Stage*** procedures and ***MCM*** acceptance criteria are as follows:

Formal Review of Guidance for Industry[1]: Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

1. Sampling Choice A – Dynamic Sampling and Evaluation Of The 'Freshly Formed' Dosage Units

We recommend that you should proceed as follows:

1. When" **a)** it is valid to use this option, **b)** you have elected to use it, and **c)** no dosage units have yet been produced for the lot that is to be evaluated, proceed to **Step 2**; else proceed to **Step 21**.
2. Choose a "routine production" sampling point plan that:
   a. Calls for taking a start sample, an end sample, and *not less than* 9 approximately evenly spaced during-routine-production sample points and
   b. Provides for an additional "restart" sampling point each time there is an interruption in the routine production.
3. At each sampling point, *into a separate suitable pre-labeled container for each point*, collect, in sequence, not less than four (4) times the number of dosage units as there are active dosage-forming stations in the production equipment. Collect each in an appropriate pre-labeled intermediate storage container. [**Note:** To ensure that adequate samples are collected for all tests and examinations, including physical examinations, collect not less than 2500 samples in all (typically, *less than* 1 % of today's *minimum* full-scale production batch). Ideally, the samples collected are first used for the non-destructive physical attribute examinations (which typically require the visual examination of 800 or 1250 dosage units {"**ANSI/ASQ Z 1.4**"}) and then returned to their original labeled intermediate-storage containers for use in the requisite variables testing program.]
4. After: **a)** all of the requisite samples have been collected **and b)** the requisite physical examinations successfully completed, proceed to **Step 5**; otherwise proceed as directed by the appropriate quality unit management person with executive authority. [**Physical Attributes Failure**]
5. From each intermediate-interval 'sampled sample' container, select forty (40) units at random and place then into suitable pre-labeled test-sample containers that contains a separate compartment for each dosage unit and has a lid so that, after the units are selected, the sample container can be sealed, and, after the fortieth unit is selected, close the last labeled test-sample container. When the requisite 400+ batch-representative test samples (40 units from each interval sample) have been collected from all the intermediate containers, proceed to the **Step 6**. [**Note:** In this guidance, the maximum size of a suitable individually compartmentalized test-sample container with closure is presumed to be one that can hold twenty (20) dosage units. Further, the procedural steps presented are written for use in a suitable assembly-line-like or robotic environment.]
6. Weigh all of the samples collected and, provided the weights found meet all of their "weight" acceptance criteria (range, mean, and distribution, proceed to Step 7; otherwise, proceed as directed by the appropriate quality unit management person with executive authority (➔ **Weight Uniformity Failure**).

7. Since the test-sample trays for each interval should be labeled with the batch identifier, a point identifier suffix (typically, -SRT, -IPi [-IP1, -IP2, ..., and -IPn], and -END for the routine samples, and RSi [RS1, RS2, ..., RSn] for the restart samples), the tray-set identifier suffix (typically, -A, -B, -C, ...) and the 20 positions are numbered from "1" to "20," separate the interval samples into their tray sets (-A. -B, -C, ...) and proceed as follows, for each set (-A, -B, -C, ...):
   a. Divide the number of samples sampled by the number of tray sets to get the number of samples in a given tray set. [**Note:** In this guidance, that "tray sets" number is presumed to be 2 to get the number of samples in each tray set. Moreover, this and all other examples will presume the batch is formed without interruption ("a routine production batch") and, therefore, that each test-sample tray set consists of 11 trays of 20 units/tray or 220 dosage units.]
   b. Divide 200 by the number of test-sample trays and round the result down to the next smaller integer to get your basis number for each set. [**Note:** For the example 11-point sampling plan used, you should get 200/11 = 18.1818 or 18 as your basis number for each set of test-sample trays.]
   c. For each test-sample tray, appropriately remove and track your basis number of units from each test-container and properly transfer each into a suitable, appropriately labeled (one tray for each sampling point), sample-preparation container [**Note:** In the example, in doing this you will collect 198 dosage units (18 each in 11 trays). This will leave you needing to collect 2 additional units in a 12th tray.]
   d. Repeat **Step c** until you have collected the basis number of units from each test-sample tray and properly transferred it into the corresponding preparation-sample tray. When finished, proceed to **Step e**.
   e. Then, when necessary, randomly select one unit from one of a pre-determined reduced subset of the test-sample containers, and appropriately transfer that unit into a suitable, appropriately labeled, sample-preparation container. [**Note:** In the example case, needing two addition al units, you might elect to sample the additional unit needed from the 'Start' and 'End' test-sample containers.]
   f. Repeat **Steps d** until a total of 200 units have been properly transferred into your suitable sample-preparation containers. [**Note:** In the dynamically sampled case, you will need to use a set of suitable, point-labeled preparation-sample trays that is no more than one tray larger than the number of trays in each tray set of test-sample containers and transfer the individual dosage units in a manner that maintains the link between the point, the unit and the unit's weight for each sample in the test-set.]
   g. If the requisite 200-unit sample has been properly collected for each set, proceed to **Step 8;** else select the next test-sample set and repeat this step.
8. Taking into account the stability of the sample preparations, the processing capability of the laboratory, the maximum test-unit groupings that can be handled, and the laboratory's SOPs, select an appropriate

preparation work-up plan to use for preparing and analyzing the 200 units in each preparation-sample set. After selecting the proper work up plan, proceed to **Step 9**. [**Note:** If the sample preparations have limited stability, it may be necessary to use a sequential sample prep/test/evaluate/decide" plan. If the sample preparation solutions are moderately stable, a 'groups of five' plan may be appropriate. If the sample preparation solutions are very stable, then a 'groups of 15' or a 'groups of 25' plan may be appropriate. Generally, the design, staffing and/or operation of most labs do not permit groups larger than about 25 to be prepared at about the same time. In this guidance, we will presume that it is valid to prepare 25-dosage units at a time.]

9. Appropriately select (in a pseudo-random manner such that the group spans the dynamically sampled production interval), work up a suitably sized group of preparation samples from the preparation-sample trays (**consult** the applicable **Steps** and **Notes** in the ***SCM, Stage 1 Examination*** and **SCM, Stage 2 Examination** sections [**VII. A**]), and proceed to **Step 10**.
10. Appropriately test the worked group of the preparation-sample dosage units, determine the valid result values for each sample prepared in this group, and proceed to **Step 11**.
11. Evaluate the dosage-unit results obtained as follows:
    a. Verify that the measurement system was in control (suitable) during the entire testing interval.
    b. Verify that the result values obtained are valid.
    c. If all of the valid results are between 75 % and 125 % of your target level, proceed to **Step 12**, otherwise,
        i. **Immediately notify** your laboratory supervisor,
        ii. **Make certain** the appropriate quality manager in the manufacturer's organizational structure is notified of the problem and
        iii. Proceed as the quality unit or units involved direct you to in writing.

        [**Note:** The preceding is written to include what should be done when the testing laboratory is a contract laboratory.]
12. If all valid result values are within the relative range from 85.0 % to 115. %, proceed to **Step 14**; otherwise proceed to **Step 13**.
13. If the number of valid result values outside of the range from 85 % to 115 % (the 'in bounds' or 'expected' range) exceeds one (1) for this group, or the cumulative number of results outside of 85 % to 115 % of the established target value exceeds six (6), notify your supervisor and the appropriate quality management personnel that the batch:
    a. In the case of the first one found with an 'out of bounds' (OOB) result value, contains an apparently valid OOB result, or
    b. In the case where the total of OOB exceeds six (6), contains a significant number of apparently valid OOB result values.

    [**Note:** If the cumulative valid results at the completion of any test group contain more than 12 valid OOB values, the batch should be considered a

failure, the testing terminated, and the appropriate supervisory and quality unit personnel notified in writing of the problem.]

14. Select and appropriately prepare the next group to be tested, and proceed to **Step 10** until: **a)** all groups of preparation samples in all sets have been tested or **b)** an apparently valid out-of-specification (OOS) result has been found or too many OOB result values have caused the quality unit to terminate the testing of this batch.
15. When all of the groups have been tested and their results found to be acceptable, proceed to **Step 17**; otherwise proceed to **Step 16**.
16. Proceed as directed in writing by the appropriate quality-unit personnel.
17. Compute the weight-corrected relative result values (the relative specific active content) and use that discrete-units data, the comparable non-discrete blend data obtained when the final blend was tested and the appropriate scientifically sound statistical assessment procedures to estimate the average variability introduced by the blend manipulation steps between the blend sampling point and the formation of the dosage units, and proceed to **Step 18**.
18. Compute the relative mean ($\bar{x}_{400}$ %), mode, median, and RSD (RSD_{400} %) for the 400 valid batch-representative dosage-unit active content results obtained and verify that the results meet following acceptance criteria:
    - **c.** No valid result has a relative value that is outside of the range from 75.0 % to 125.0 % of the target level of the active content.
    - **d.** Not more than 12 active content values in 400 (3 % of the values) are outside of the relative range '85 % to 115 % of the target drug-product level.'
    - **e.** The relative mean has about the same value as the relative median (to within 1.5 %)
    - **f.** The relative mean has about the same value as the relative mode (to within 2 %
    - **g.** The observed batch 'relative mean' value for the not less than 400 batch-representative dosage units tested is not less than 99.5 % nor more than 100.5 %.
    - **h.** For the relative range 85 % (L) to 115 % (U) of the target level of the active, the relative RSD for the valid relative result values satisfies the following requirements:
        - **i.** For capsule drug products, **[(U – L) / (6 RSD)] ≥ 1.67**
        - **ii.** For tablet drug products, **[(U – L) / (6 RSD)] ≥ 2.00**
19. When the batch is acceptable, appropriately note that the active content met its specification and AQL acceptance criteria in your records and then proceed with the evaluation of the next variable factor (typically, ***Dissolution*** or ***Drug Release***) that needs to be evaluated for the batch's acceptability (➔ **EXIT**); otherwise proceed to **Step 20**.
20. Report in writing the problematic OOB or OOS results and other findings that indicate that this batch is not acceptable for release at the 'freshly formed' dosage-unit stage to your supervisor and to the proper quality

unit management personnel. [**Note:** The quality unit management of the quality unit or units involved (testing and acceptance for release) should initiate the appropriate investigation and decide how to proceed in all such situations.]

21. When, the dosage units have already been formed and dynamic sampling used to gather the appropriate dynamically sampled batch-step-spanning representative samples needed to as certain the acceptability of the batch, proceed as follows:

i. If you have arrived at this point as a result of an ***SCM, Stage 2*** non-conformity in situations where 200 'freshly formed' batch-representative dosage units were tested as an approved surrogate for the uniformity of the 'final blend' and, because of a non-conformity to the dosage-unit acceptance specifications for the dosage units, another 200 batch representative samples were tested under the ***SCM, Stage 2 Examination*** acceptance criteria, take all of the existing valid data and proceed to **Step 17**, otherwise proceed to **Step b**.

j. If you have arrived at this point because you started with a ***SCM, Stage 2 Examination*** but the valid results obtained for the 200 batch-representative dosage units did not meet all of the ***SCM, Stage 2 Examination*** criteria, proceed to **Step 22**; else proceed to **Step c**.

k. If you have arrived at this point, because a valid ***SCM, Stage 1 Examination*** has given valid result values for the batch-representative samples tested that not only did not meet the batch acceptance criteria of ***SCM, Stage 1 Examination*** but also triggered the need for you to undertake the ***MCM***, proceed to **Step 23**.

22. Take the original set of in-process labeled point sample containers, and from each intermediate-interval 'sampled sample' container, select twenty (20) units at random and place then into suitable pre-labeled test-sample containers that contains a separate compartment for each dosage unit and has a lid so that, after the units are selected, the sample container can be sealed, and, after the twentieth unit is selected, close the last labeled test-sample container. When the requisite 200+ batch-representative test samples (20 units from each interval sample) have been collected from all the intermediate containers, proceed to **Step 6**.

23. As directed by your supervisor complete the testing of the first batch-representative 200-unit sample as directed in ***SCM*** **(VII.A)**, determine and evaluate the valid active content results for the 200-unit representative sample using only the limits criteria and proceed to **Step 24**

24. When all of the results observed for the 200 batch-representative dosage units are within the range from 75 % to 125 % of the target active content level and not more than six (6) are outside of the range from 85 % to 115 5% of the active content level, proceed to **Step 22**, otherwise proceed to **Step 25**.

25. Report in writing your OOB and/or OOS findings to your supervisor and to the appropriate managerial personnel in the quality unit or units involved in deciding the course of action to take, and, if directed to

proceed, proceed as the quality unit having release authority and responsibility directs.

2. Sampling Choice B – Static Sampling And Evaluation Of The "Finished" Dosage Units

We recommend that you should proceed as follows:

1. When you should, or have elected to, use the 'finished, unpackaged' drug-product dosage units as the in-process control for the drug product is the option required and no 'finished' dosage units have yet been produced for the batch that is to be evaluated, proceed to **Step 2**; else proceed to **Step 18**.
2. Choose a given end-of-step sampling spot (such as, after the coated, inked, waxed tablets have been polished) as the 'routine production' sampling place and devise a sampling plan that takes a batch-representative sample from the batch that is large enough for all physical attribute examinations as well as large enough that it contains at least four (4) times the amount to perform all variable-factor testing and results examinations [**Note:** To ensure that adequate samples are collected for all tests and examinations, including physical examinations, collect not less than 2500 samples in all (typically, *less than* 1 % of today's *minimum* full-scale production batch). Ideally, the samples collected are first used for the non-destructive physical attribute examinations (which typically require the visual examination of 800 or 1250 dosage units {"**ANSI/ASQ Z 1.4**"}) and then returned to their original labeled intermediate-storage container or containers for use in the requisite variables testing program. To support investigations into the extent and location of a 'non-compliance' should one be found to occur, it is recommended that you take a number of units at random from each container in which the output of the phase you are sampling from is stored. Moreover, the amount of units taken form each such container should be approximately proportional to the fraction of the batch in that container.]
3. After: **a)** all of the requisite samples have been collected in the specified number of sampling containers **and b)** the requisite physical examinations successfully completed, proceed to **Step 4**; otherwise proceed as directed by the appropriate quality unit management person with executive authority (➔ **Physical Properties Failure**).
4. From each 'sampled sample' container, select the appropriate number (**see** the **Note** in **Step 2**) of units at random and place then into a corresponding suitable pre-labeled test-sample container that has a lid so that, after the units are selected, the sample container can be sealed, and, after the last unit is selected for that container, close the last labeled test-sample container. When the requisite 400+ batch-representative test samples have been collected from all the 'sampled sample' containers, proceed to the **Step 5**.
5. Weigh all of the samples collected and, provided the weights found meet all of their "weight" acceptance criteria (range, mean, and distribution, proceed to **Step 6**; otherwise, proceed as directed by the appropriate

quality unit management person with executive authority (→ **Weight Uniformity Failure**).

6. Taking into account the stability of the sample preparations, the processing capability of the laboratory, the maximum test-unit groupings that can be handled, and the laboratory's SOPs, select an appropriate preparation work-up plan to use for preparing and analyzing the 400 units in the-sample set. After selecting the proper work up plan, proceed to **Step 7**. [**Note:** If the sample preparations have limited stability, it may be necessary to use a 'sequential sample prep/test/evaluate/decide' plan. If the sample preparation solutions are moderately stable, a 'groups of five' plan may be appropriate. If the sample preparation solutions are very stable, then a 'groups of 15' or a 'groups of 25' plan may be appropriate. Generally, the design, staffing and/or operation of most labs do not permit groups larger than about 25 to be prepared at about the same time. In this guidance, we will presume that it is valid to prepare 25-dosage units at a time.]
7. Appropriately select (in a pseudo-random manner such that the group spans the sample container (or containers when the sampled samples are stored in more than one container) and work up a suitably sized group of preparation samples (**consult** the applicable **Steps** and **Notes** in the ***SCM, Stage 1 Examination*** and **SCM, Stage 2 Examination** sections [**VII. A.**]).
8. Appropriately test the worked group of the preparation-sample dosage units and determine the valid result values for each sample prepared in this group.
9. Evaluate the dosage-unit results obtained as follows:
   a. Verify that the measurement system was in control (suitable) during the entire testing interval.
   b. Verify that the result values obtained are valid.
   c. If all of the results are valid and between 75 % and 125 % of their target level, proceed to **Step 10**; otherwise,
      i. **Immediately notify** your laboratory supervisor,
      ii. **Make certain** the appropriate quality manager in the manufacturer's organizational structure is notified of the problem and
      iii. Proceed as the quality unit or units involved direct you to in writing.

      [**Note:** The preceding is written to provide an example of what should be done when the testing laboratory is a contract laboratory.]
10. If all valid result values are within the relative range from '85.0 % to 115. %,' proceed to **Step 12**; otherwise proceed to **Step 11**.
11. If the number of valid result values outside of the range from 85 % to 115 % (the 'in bounds' or 'expected' range) exceeds one (1) *for this group*, or the cumulative number of results outside of 85 % to 115 % of the established target value exceeds six (6), notify your supervisor and the appropriate quality management personnel that the batch:
    a. In the case of the first one found with an 'out of bounds' (OOB) result value, contains an apparently valid OOB result, or

b. In the case where the total exceeds six (6), contains a significant number of apparently valid OOB result values.
[**Note:** If the cumulative valid results at the completion of any test group contain more than 12 valid OOB values, the batch should be considered a failure, the testing terminated, and the appropriate supervisory and quality unit personnel notified in writing of the problem.]

12. Select and appropriately prepare the next group to be tested, and proceed to **Step 8** until: **a)** all groups of preparation samples in all sets have been tested (proceed to **Step 13**) or **b)** an apparently valid out-of-specification (OOS) result has been found or too many OOB result values have caused the quality unit to terminate the testing of this batch (proceed as directed by the appropriate quality unit management person with executive authority [➔ **Content Uniformity Failure**]).

13. When all of the groups have been tested and their results found to be acceptable, proceed to **Step 15**; otherwise proceed to **Step 14**.

14. Proceed as directed in writing by the appropriate quality-unit personnel (➔ **Content Uniformity Failure**).

15. Compute the relative mean ($\bar{x}_{400}$ %), mode, median, and RSD (RSD_{400} %) for the 400 valid batch-representative dosage-unit active content results obtained and verify that the results meet following acceptance criteria:

a. No valid result has a relative value that is outside of the range from 75.0 % to 125.0 % of the target level of the active content.

b. Not more than 12 active content values in 400 (3 % of the values) are outside of the relative range '85 % to 115 % of the target drug-product level.'

c. The relative mean has about the same value as the relative median (to within 1.5 %)

d. The relative mean has about the same value as the relative mode (to within 2 %)

e. The observed batch "relative mean" value for the *not less than* 400 batch-representative dosage units tested is *not less than* 99.5 % or *not more than* 100.5 %.

f. For the relative range 85 % (L) to 115 % (U) of the target level of the active, the relative RSD for the valid relative result values satisfies the following requirements:

i. For capsule drug products, **[(U – L) / (6 RSD)]** ≥ 1.67

ii. For tablet drug products, **[(U – L) / (6 RSD)]** ≥ 2.00

16. When the batch is acceptable, appropriately note that the active content met its specification and AQL acceptance criteria in your records and then proceed with the evaluation of the next variable factor (typically, ***Dissolution*** or ***Drug Release***) that needs to be evaluated for the batch's acceptability (➔ **EXIT**); otherwise proceed to **Step 17**.

17. Report in writing the problematic OOB or OOS results and other findings that indicate that this batch is not acceptable for release at the 'freshly formed' dosage-unit stage to your supervisor and to the proper quality

unit management personnel (➔ **Content Uniformity Failure**). [**Note:** The quality unit management of the quality unit or units involved (testing and acceptance for release) should initiate the appropriate investigation and decide how to proceed in all such situations.]

18. When, the dosage units have already been formed and dynamic sampling used to gather the appropriate dynamically sampled batch-step-spanning representative samples needed to as certain the acceptability of the batch, proceed as follows:
    a. If you have arrived at this point because you started with a ***SCM, Stage 2 Examination*** but the valid results obtained for the 200 batch-representative dosage units did not meet all of the ***SCM, Stage 2 Examination*** criteria, proceed to **Step 19**; else proceed to **Step b**.
    b. If you have arrived at this point, because a valid ***SCM, Stage 1 Examination*** has given valid result values for the batch-representative samples tested that not only did not meet the batch acceptance criteria of ***SCM, Stage 1 Examination*** but also triggered the need for you to undertake the ***MCM***, proceed to **Step 20**.
19. Take the original set of in-process labeled point sample containers, and another 200 batch-representative dosage units, at random, in the same manner as you did for the **SCM, Stage 2 Examination**. When the requisite 200+ batch-representative test samples have been properly collected, proceed to **Step 5**.
20. As directed by your supervisor, complete the testing of the first batch-representative 200-unit sample as directed in ***SCM*** **(VII. A)**, determine and evaluate the valid active content results for the 200-unit representative sample using only the limits criteria and proceed to **Step 21**
21. When all of the results observed for the 200 batch-representative dosage units are within the range from 75 % to 125 % of the target active content level and not more than six (6) are outside of the range from 85 % to 115 % of the active content level, take this set of 200 results and the previous 200-result set an proceed to **Step 15**, otherwise proceed to **Step 22**.
22. Report in writing your OOB and/or OOS findings to your supervisor and to the appropriate managerial personnel in the quality unit or units involved in deciding the course of action to take, and, if directed to proceed, proceed as the quality unit having release authority and responsibility directs.

Returning to the Draft's text, this commenter recommends deleting Lines 401 through 405 and not replacing them as follows:

~~"C. Switching to Standard Test Method from Marginal Test Method~~

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

~~• Five consecutive batches pass the MCM criteria and result in RSD $\leq$ 5.0 percent~~"

The justification for the preceding deletion is two-fold.

First, the criteria as proposed: **a)** are not scientifically sound, **b)** are not batch specifications (they are sample specifications), **c)** do not meet the clear CGMP ***minimum*** requirements of ***21 CFR 211.160(b)(2)*** that the in-process samples must be representative of the batch, and **d)** improperly attempt to equate the purported uniformity of the batch with respect to the active content in the dosage units to the uniformity of the batch of dosage units with respect to other key constrained variables such as Dissolution or Drug Release, impurity level and total water content that may have varying levels of correlation with the uniformity of the active.

Second, the commenter's alternatives incorporate the "method" switching rules into the two methods.

Returning to the Draft, the title for the next section ("**VIII.**"), Line 408, needs to be modified to REMOVE the obviously non-CGMP-compliant "stratified sampling" approach and replace it with a CGMP-compliant approach to the in-process sampling and testing of the blends, the formed dosage units, and finished dosage units that complies with the clear requirements of **21 CFR 211.110,** "Sampling and testing of in-process materials (blends and formed dosage units) and drug products (finished, unpackaged dosage units)" as follows:

"**VIII. REPORTING *RESULTS FOUND FROM* THE USE OF ~~STRATIFIED~~ *CGMP-COMPLIANT DYNAMIC AND STATIC IN-PROCESS* ~~SAMPLING~~ *INSPECTION*"**

Considering the text, the commenter offers the following the changes to Lines 410 through 451,

"**A. ~~Applications~~ *Submissions For Drug Products That Are* Not Yet Approved *Or Licensed***

This section refers to the scientific data analysis and other information that should be submitted ~~to an NDA or ANDA~~ *in the appropriate portions of the Chemistry, Manufacturing, and Controls section of any submission (ANDA, NDA, AADA, NADA) of a drug product for approval or licensing.* ~~Information~~ *The information* submitted in the ~~application~~ *submission* should include *the intermediate data and result values, investigations, justifications, rationales,* summary reports and scientific analyses or statements about the *in-process inspection* method being used *to ensure that the batch and not just the samples tested is acceptable for release under the applicable CGMP regulations.* The *truly* raw data collected *for all the samples evaluated* and *the supporting standards' raw data* to support using ~~this~~ *the* method *used* should be maintained**,*** *and be readily available for inspection,* at the manufacturing site.

We recommend that you provide the following information in the Manufacturing Process and Process Controls section of the application (CTD[17] 3.2.P.3.3).

[17] *Draft M4Q: The CTD – Quality*, one in a series of *draft* 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.

- Statement that the methods in this guidance are *only* being used *and can only be* to demonstrate the ~~adequacy~~ *uniformity* of *the final* powder mix *the freshly formed dosage units, and the "finished, unpackaged" drug product units with respect to the active content* or a

description of *the* alternative methods that *the manufacturer has used to* demonstrate the ~~adequacy~~ *uniformity* of the powder mix, *the in-process formed dosage units and the in-process finished dosage forms with respect to the active content and the other key variable factors such as disintegrants, release retardants, and lubricants that are clearly required to be adequately controlled under* ***21 CFR 211.110****. [****Note:*** *Other methods and procedures are required to demonstrate compliance of the processing stages prior to the final blend to* ***21 CFR 211.110*** *as well as to demonstrate the adequacy of the uniformity values for other critical variables such as disintegrants, release retardants and lubricants that directly can and do affect the efficacy and safety of the dosage units in the* ***batch****].*

- Summary of *the* data *and data* analysis from the powder mix assessment ~~and~~ as well as from ~~stratified sample testing~~ *the dynamic and static batch-representative sampling, examination, testing, and evaluation of the in-process "freshly formed" dosage units or the "finished' dosage units to demonstrates compliance with* ***21 CFR 211.110****, and for the finished drug product, the statistical quality control requirements of* ***21 CFR 211.165(d)*** *with respect to the active content, and any other variable factor(such as Dissolution, Drug Release, impurity, water content, residual solvents) that may adversely impact the safety and efficacy of the dosages units in the batch.*

- ~~Summary of the stratified~~ *An informative tabulation of the valid results obtained from the* in-process *batch-representative* dosage ~~unit~~ *units dynamically or statically sampled and tested to support the uniformity of the of the drug product batches with respect to the active and an analysis of that data that demonstrates:* ~~sampling data analysis demonstrating a~~ a) *the degree to which the data approximate a* normal distribution of active ingredient *and the other components that govern the availability of the active* in the batch, *b) the validity of the batch release specifications set for the in-process final blend, the "freshly formed" dosage units and the "finished" drug product, c) the compliance of the sampling and testing of the output of the various in-process manufacturing steps and the finished drug product with the CGMP requirements, and the validity of the controls on the incoming components, in-process materials and the drug product.*

- Summary of the powder mix, *in-process formed dosage units and drug product* sampling data *and a supporting scientifically sound and appropriate batch-statistics-based* analysis demonstrating that ~~it~~ *each* met the minimum *CGMP-compliant in-process statistics-based* criteria for *the initial process* validation and *for* establishing *the validity of the* initial criteria *used to establish the uniformity of the various materials with respect to the active content as well as the other variables that can adversely impact the safety and efficacy of the drug product batch.*

We recommend that you provide the following information in the Drug Product Specification section of ~~the application~~ *your submission* (CTD 3.2.P.4.1):

- ~~Statement~~ *A declaration* in the *drug* product specification stating that the methods in this guidance are being used to demonstrate finished product uniformity of content *for each active* or a description of *the scientifically sound and appropriate batch-statistics-based CGMP-compliant* alternative methods used to demonstrate finished product uniformity of content *for each active*

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

- Summary of *the results'* data *and the scientifically sound* analysis ~~for~~ *thereof that establishes the* correlation of *the batch-representative* in-process dosage unit *uniformity results for each active* ~~stratified sampling~~ with *the batch-representative* finished product uniformity of content *results for each active ingredient*
- Summary of *the results'* data *and the scientifically sound* analysis ~~for~~ *thereof that establishes the degree of* correlation of *the batch-representatively-sampled* powder mix uniformity *results for each active ingredient* with *the batch-representative* in-process dosage unit ~~stratified sampling~~ *results for each active ingredient*

B. Postapproval Change

If you plan on changing *any of* ~~the~~ *your* existing controls for ~~adequacy~~ *the active-content uniformity* of ~~mix~~ *final blend* and/*or* the uniformity of content *for each active in the in-process dosage units and/or the drug product* to the methods described in this guidance, the change should be considered ~~a minor change as described~~ *according to the criteria set forth* in the *Agency's guidance* ~~postapproval changes guidance.~~[18] *for postapproval changes.* ~~We~~ *When the change can properly be classified as a minor change, we* recommend you provide a notice of the change in the next annual report along with the information indicated in section A, above. ~~The~~ *While the intermediate results, standards, and statistically derived data should be tabulated and submitted, the* raw data collected to support changes can be maintained at the manufacturing site. 451

[18] FDA's guidance for industry on *Changes to an Approved NDA or ANDA."*

Considering the definitions provided in the "**GLOSSARY**," this commenter recommends adding the definitions that the commenter has provided in this commentary (in pages 2 through 7) to the "**GLOSSARY.**"

In addition, this commenter recommends making the following changes to the definitions in the "**GLOSSARY**" contained in Lines 453 through 486 of the Draft's text.

"GLOSSARY

Absolute as used to define the *limits for a variable means the maximum bounded range for that variable. For example, an* ~~acceptable~~ *absolute content* range ~~(+/- 10%) in~~ *a) is a content range which is independent of the value of the mean value observed for any set of samples and within* which *all* individual sample values must fall ~~and which is independent of the value of the mean~~. *For example, if ~~the mean of all blend samples is 95.0%,~~ the manufacturer's established requirement is that all blend samples must fall within 95.0 % to 105 % of the target value, the* ***absolute*** *range is ~~85.0% to105.0%, not (95.0% +/- 9.5%)~~ 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 %, not 99.5 % - 3.5%/+5.5 %).*

Formal Review of Guidance for Industry[1]: Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

Exhibit Batches refer to any batch of drug product submitted in support of an ~~NDA or ANDA~~ IND, ANDA, NDA, ANADA, or NADA. This includes bioequivalence, ~~test~~ *development, start-up, initial validation*, and commercial production batches of a drug product.

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 ~~before it is coated or~~ *and continuing until it is* 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."*

RSD is relative standard deviation; *RSD = [(standard deviation)/(mean)] x 100%.*

Significant event is any operation 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 or from the bin to a hopper are two examples of significant events in ~~the~~ *a* blending ~~and~~ *or* compression process *step*. 470

Stratified sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process 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****). Stratified sampling does not provide samples that meet this CGMP minimum requirement.*

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

~~**Validation**~~ ***Initial validation*** **batch** is a batch 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 is a required to be a batch that validates the process.*

Weight correct is a mathematical correction to ~~eliminate the effect of potentially variable tablet weight on measurement of mix adequacy~~ *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} *(*$mg_{Active}/mg_{Tablet} = 19.4 \div 98 = 0.197959184$ ~~*mg/mg*~~*). ~~Label~~ If the drug-product's label claim is 20 mg per each 100 mg tablet, ~~so~~ the weight—corrected result percent of active in the dosage unit tested is ~~0.198~~0.197959184* $\sim\!\!\sout{mg}_{Active}/\sim\!\!\sout{mg}_{Tablet} \div 0.20\ \sim\!\!\sout{mg}_{Active}/\sim\!\!\sout{mg}_{Tablet} * 100$ ~~*%*~~ *= 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 ~~or~~ 99% of ~~target~~ the blend ~~assay~~ target content level for the active. In general, this use of weight corrected results in determining batch acceptability should be limited to: a) cases where the results from the testing of the freshly formed dosage units has been justified on "personnel safety" grounds in lieu of "final blend" testing, or b) where they may contribute to understanding the root cause of the failure of a batch to meet any of its uniformity criteria.

As stated in the text, though this commenter has attempted to flag the exit points to assist the Agency, this commenter leaves it up to the Agency to appropriately revise the two flow diagrams presented as **Attachments 1** and **2** after they have revised the Draft's text: **a)** as this commenter has suggested or **b)** in any manner that is scientifically sound and complies with ***all*** of the clear applicable CGMP requirement ***minimums*** set forth in **21 CFR 211**.

This Commenter's Concluding Remarks

Based on the obvious, documented, numerous divergences of the Draft from the clear requirement ***minimums*** set forth in the CGMP regulations for drug products, this Draft needs serious review and revision by the Agency.

Further, the Agency needs to be concerned about issuing guidance such as this (even in draft form) that so blatantly ignores any clear CGMP regulation.

This is the case because, in 1988, the US Supreme Court held that to the extent that such publications are clearly at odds with any statute or clear regulation governing the industry, publishing such is outside of the Agency's administrative discretion.

In addition, this commenter was surprised that the Agency would issue, even in Draft form, a guidance containing text that is obviously at odds with sound science.

Finally, *in a separate submission*, this commenter is again submitting the commenter's review of the PQRI document ("The Use of Stratefied Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends, *PDA J. Pharm. Sci Technol.*, 57:59-74, 2003") used as the basis for this guidance, and, as appendices, reviews of documents used to support that PQRI document.

End of E-Docket Submission