

Saturday, 15 May 2004

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

RE: Docket No. 03D-0394

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"Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [G:\5831dft.doc 10/27/03]."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

BACKGROUND

A review of the PQRI 'recommendation' on which this guidance is based was submitted, on 25 September 2003, to CDER's Ombudsman, Warren Rumble, (via e-mail: ombudsman@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).

On 15 November 2003, FAME Systems provided comments based on that review and an in-depth reading of the FDA's "**Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [G:\5831dft.doc 10/27/03]."**

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

INTRODUCTION

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

The procedures outlined in the FDA draft:

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

ⁱ ANSI/ASQC Z1.9-1993, SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING, American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989).

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- *Even when the few tested dosage-unit samples meet the specifications in the FDA's Draft, provide, at best, less than 20-% confidence that the batch is truly acceptable.*

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

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

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

In January 2004, that "revised draft" was submitted to the Agency and posted to the Public Docket 2003D-0493 on 30 January 2004.

Subsequently, this reviewer evaluated the comments submitted by others to said public docket up to 1 April 2004 against the clear requirements of the applicable CGMP regulations and the principles of sound inspection science and generated an in-depth report of his findings.

Using the insights gained from that "comments" review, this reviewer updated the "revised draft" submitted in January 2003 and is submitting the "second revision" that follows based on those insights.

To simplify the language, passages that stated "... batch or lot ..." or had similar language were changed to "... batch ..."

However, this guidance still applies to drug products manufactured as "lots" instead of as "batches" including those where the "lot" is a time-defined segment of production in a "continuous" processing step.

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

Respectfully,

Dr. King

Guidance for Industry

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

DRAFT GUIDANCE – Second Revision

This guidance document is being distributed for comment purposes only.

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

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

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

May 2004
Pharmaceutical CGMP

Guidance for Industry

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

*Additional copies are available from:
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<http://www.fda.gov/cder/guidance/index.htm>

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

**May 2004
Pharmaceutical CGMP**

Contains Nonbinding Recommendations

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Guidance for Industry¹

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

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

I. INTRODUCTION

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

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

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

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

¹ This guidance has been prepared by the Office of Pharmaceutical Science and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration based on the CGMP-conforming input provided in response to the original Draft published by the Agency October 2003 (see footnote 3). This guidance document represents the Agency's current thinking on assessment of the *active uniformity* of final powder blends, and in-process and finished dosage units in the absence of new technology development or implementation.

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39 not required. Similarly, the use of the word *may* indicates an optional course or action and the use of
40 the words *must* or *shall* indicates an action mandated by specific regulatory or statutory requirements.

41

42 II. BACKGROUND

43

44 This guidance is the result of an Agency effort to achieve a *CGMP-conforming* science-based policy
45 for regulatory enforcement. Experts from industry, academia, and the FDA developed the principles
46 underlying this guidance after extensive discussion and docket input. A brief history of the evolution
47 of this guidance is provided in the following paragraphs.

48

49 In response to industry concerns regarding the regulations for demonstrating the uniformity of in-
50 process materials, the FDA published a draft guidance for industry on blend uniformity analysis in
51 August 1999². Comments submitted to the docket resulted in the formation of the Blend Uniformity
52 Working Group (BUWG) by the Product Quality Research Institute (PQRI)³. The PQRI BUWG
53 conducted a meeting open to the public, PQRI Workshop on Blend Uniformity, on September 7 and 8,
54 2000.

55

56 Using the consensus reached by participants in this workshop, the BUWG developed a draft
57 recommendation, "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate
58 Adequacy of Mix for Powder Blends." The draft recommendation received examination and peer
59 review in multiple scientific and other venues open to the public. In addition, the Advisory
60 Committee for Pharmaceutical Science (ACPS) reviewed the draft recommendation and received
61 comment during scheduled meetings of the committee⁴. The draft recommendation was revised to
62 incorporate the results of peer review and comment and was presented to CDER's Center Director in
63 final form on December 30, 2002. The recommendation was subsequently published in the PDA
64 Journal of Pharmaceutical Science and Technology⁵.

65

66 This draft guidance reflects CDER's effort to incorporate the draft recommendation into a CGMP-
67 conforming regulatory policy in a manner that complies with the applicable clear requirement
68 *minimums* (21 CFR 211.1(a)) set forth in 21 CFR Part 211. This approach was used because, as the
69 United States Supreme Court ruled in 1988⁶, the United States Food and Drug Administration cannot
70 legally publish any guidance that contradicts any clear regulation.

71

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

73

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

78

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

81

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

86

87 ⁶ Berkovitz v. US, Supreme Court 1988, **486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**.

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90 III. SCOPE

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

99

100 Unfortunately, *though recommended by the PQRI*, this approach does not meet the clear **current good**
101 **manufacturing practice** (CGMP) **minimum** requirement that all in-process sample sets must be
102 *representative* (as that term *representative* is defined in 21 CFR 210.3(b)(21)⁷) of the *batch* from
103 which they were taken (21 CFR 211.160(b)(2)) nor does it comply with the “appropriate statistical quality
104 assurance criteria” requirement set forth in 21 CFR 211.165(d). Thus, this guidance must, of necessity,
105 provide a different approach that should, *if properly implemented*, comply with the aforesaid CGMP
106 requirements. *Where they agree with the applicable CGMP regulations*, the ideas and concepts
107 proposed by the PQRI have been appropriately incorporated into this guidance.

108

109 The methods described in this guidance are not intended to be the only methods for meeting Agency
110 requirements to demonstrate the “batch uniformity and integrity of drug products” (21 CFR 211.110(a))
111 using statistics-based inspection (21 CFR 211.110(b)⁸) to appropriately establish a multi-tiered
112 sampling plan that can minimize the level of inspection required to satisfy the clear in-process
113 minimums of 21 CFR 211.110. In many cases, traditional powder blend sampling and testing, in
114 conjunction with CGMP-compliant testing for uniformity of the active(s) in the finished product, can
115 be used to comply with current good manufacturing practice requirements (CGMPs). Use of at-, in-,
116 or on-line measurement systems may, in some cases, also be appropriate and are described in other
117 guidance documents⁹.

118

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

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

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

⁹ In August 2003, the Agency issued the draft guidance for industry PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. Once finalized, it will represent the Agency's perspective on this issue.

¹⁰ The in-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.

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- 142 Analyze the *dynamically acquired* samples, evaluate data and confirm acceptability.
- 143
- 144
- 145 Compare the active results found for the dynamically sampled core or capsule content with the
- 146 statically sampled powder blend data for active level.
- 147
- 148 Assess final blend and formed dosage-unit active uniformity for the batch.
- 149
- 150 Correlate the dynamically acquired dosage-unit active sample data with the finished dosage
- 151 unit data and assess in-process and finished dosage unit uniformity for each active in *each*
- 152 *batch*.
- 153
- 154 Test and evaluate initial process conformance batches (exhibit and initial performance
- 155 qualification) of blends and simple tablets and capsules for uniformity of the active(s)
- 156 contained therein.
- 157
- 158 Test and evaluate routine manufacturing batches for uniformity of their active content.
- 159
- 160 Report the manufacturer's in-process static blend and dynamic "dosage units" inspection plans
- 161 for active uniformity in the application or to the Agency's files for an approved drug product.
- 162

163 The methods described in this guidance can be used to monitor active ingredient homogeneity (also
164 commonly known as "Content Uniformity") of powder blends and ensure uniform active content for
165 *each batch* of the finished product for solid oral drug products. These methods are only one way to
166 satisfy the CGMP and application review requirements for in-process testing to demonstrate each
167 batch's in-process blend and product content uniformity for the finished product with respect to active
168 content. The methods presume appropriate monitoring and control of all components, materials, and
169 manufacturing steps as required by the drug CGMP regulations and, where they exceed the CGMP
170 *minimums*, the firm's application commitments.

171 However, this guidance does not discuss the firm's assessment of the other critical variable factors
172 that can and do affect the acceptability of each batch of finished dosage units, or the assessment of
173 the homogeneity of "inactive" ingredients that can adversely affect the acceptability of the batch.
174 Formulations with extremely low dose and/or high potency may call for more rigorous sampling than
175 that described in this guidance to assess the uniformity of powder blends or the uniformity of the
176 active(s) in the finished dosage units. When using the methods described in this guidance as a
177 Periodic Quality Indicator Test (PQIT), described in a recent drug product draft guidance¹¹, for
178 approved products for which other procedures have been accepted, certain data or trends may be
179 observed. We recommend that manufacturers scientifically evaluate such data to determine if they
180 affect the quality of each batch of a drug product and, if so, how.

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182
183 Except where the data triggers an investigation that determines the batch contains valid out of
184 specification (OOS) values that fail to meet: **a)** the USP's post-release lifetime criteria or **b)** predicts
185 that the batch contains such units, the FDA does not intend to inspect such data collected on an
186 existing product for the purpose of evaluating the suitability of proposed methods. Any other FDA
187 decision to review such research data would be based on exceptional situations like those outlined in

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191
192 ¹¹ In January 2003, the Agency issued "Draft Guidance for Industry—Drug Product Chemistry, Manufacturing,
193 and Controls Information." Once finalized, it will represent the Agency's perspective on the use of PQIT in
194 the monitoring of a process.

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195 Compliance Policy Guide Sec. 130.300¹². However, **all** such data acquired in support of, or bearing
196 on, initial validation or the validity of any regulatory submissions will be subject to inspection in the
197 usual manner.

198
199 Because the strength of the foundation limits the strength of the structure built thereon, this guidance
200 will start with the basics, the definition of the “specifications, standards, sampling plans, test procedures,
201 or other ... control mechanisms required ...” (21 CFR 211.160(a)).

202

203 IV. ESTABLISHING VALID SPECIFICATIONS FOR THE ACTIVE(S)

204

205 Since the methods proposed in this guidance are intended for new or improved products that “build
206 in” quality, the first thing that a manufacturer needs to establish is its target specifications. To
207 simplify the discussion, the example drug product is a 250 mg tablet containing 0.2 mg of a single
208 stable active ingredient (“0.08 %” wt./wt.). To further simplify the definition process, the drug
209 product is targeted to contain, on average, 100.5 % of its labeled content (21 CFR 211.101(a)).
210 Though the **USP** allows for a few (“1 in 30”) tablets with contents outside of 85 % to 115 % of the
211 label claim, the **USP**’s expectations is that all should be inside of the range from 85 % to 115 % of the
212 label claim. Since firms want to test the minimum number of tablets that they can and still comply
213 with CGMP, the specification expectation limits must be appropriately inside of the range from “85.0
214 % to 115. %” of the established target. Though there are practical limits to how narrow the range can
215 be, firms that truly “**build quality into**” their products will set these limits as close to the target as the
216 process (process steps, equipment and controls) permits. When the firm uses a “*statistical quality*
217 *control*” approach, today’s CGMP should be a “Six Sigma” approach to active uniformity. When a
218 firm adopts a “Six Sigma” approach, then that firm should set a maximum RSD of $(115 - 85)/12$ or
219 2.5 % RSD for the finished tablets. If the firm corrects for a target of 100.5 % and presumes a
220 symmetrical distribution about the target, the maximum RSD is reduced to about 2.4 %.

221

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

226

$$227 \quad RSD^2_{\text{Tablet}} = RSD^2_{\text{Tablet Weight}} + RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} + RSD^2_{\text{Error}} \quad (1)$$

228

229 the firm can use the variance values it establishes for Tablet Weight, Tableting, and Error to solve for
230 $RSD^2_{\text{Final Blend}}$. In general, a firm can validly set RSD^2_{Error} to between 0.25 %² and 2.25 %² depending
231 upon whether the sampling and testing is performed under ISO 17025 standards or not. For this
232 example, the firm will be presumed to know that, on average, its RSD_{Error} is not more than 1 %.
233 Substituting these estimates of RSD^2_{Tablet} and RSD^2_{Error} into **Equation 1**, the firm should find that:

234

$$235 \quad RSD^2_{\text{Tablet Weight}} + RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} \simeq 4.76 \%^2 \quad (2)$$

236

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

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¹² FDA/ORA Compliance Policy Guide, Sec. 130.300, *FDA Access to Results of Quality Assurance Program Audits and Inspections* (CPG7151.02)

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$$RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} \approx 3.76 \%^2 \quad (3)$$

When the firm has a formulation program that only develops formulations that generate final blends that are mechanically stable on storage and in the tableting operation, then, the firm can validly set $RSD^2_{\text{Tableting}}$ to be much less than $RSD^2_{\text{Final Blend}}$ ($RSD^2_{\text{Tableting}} \ll RSD^2_{\text{Final Blend}}$), for example, 0.16 %² (for an RSD Tableting of “0.4 %”), and, solving **Equation 3**, find that:

$$RSD^2_{\text{Final Blend}} \approx 3.6 \%^2 \quad (4)$$

or

$$RSD_{\text{Final Blend}} \approx 1.9 \% \quad (5)$$

Since, for most firms, the variability contribution in storage and tableting is closer to or exceeds “1 %” than the “0.4 %” value used for **Equation 4**, most firms (using an automated tablet press like the one in the example) should set $RSD_{\text{Final Blend}}$ at between “1 %” and “1.7 %.” [Note: Practically, even with careful granulation, it is difficult to manufacture final blends with an RSD of less than about 0.9 % (n = 200). Based on the preceding, most firms should set their practical $RSD_{\text{Final Blend}}$ limit to not more than 1.5 %.]

Reviewing the properties of normal distributions of non-discrete materials with respect to the testing of a small number of samples from a given batch, the firm should note that the most probable range of values should be within ± 3 RSD of the target. Based on that approximation, the firm’s final blend’s *expectation* range should be not more than about ± 5.7 % (1.9 % times 3) or, for the example tablet’s target of 100.5 % of label claim, 94.8 % to 106.2 % of label claim. Similarly, the tablets’ relative content expectation range should be 100.5 % \pm 7.2 % of label claim or 93.3 % to 107.7 % of label claim.

Because experience has shown that the distribution of dosage-unit active values in uniform batches is approximately Gaussian (normal), the firm, *not wishing to develop a first-principles approach to the statistical treatment of its testing results*, may decide that, *for statistics-based in-process and release inspection of the dosage units*, it will use the recognized 95%-confidence-level consensus standard for inspection by variables for percent nonconforming¹³. *Given it has set its expectations range at the 3 RSD level (approximately 99.72 % of the population)*, the firm should appropriately select a 0.4 % level as the limit for the allowable percentage of non-conforming units (units outside of the established specification for dosage-unit samples) in recognition of the possible level of “sample set” variability inherent in the set chosen. However, *recognizing the lifetime post-release limits imposed by the USP on any article in the batch*, the firm should set two auxiliary acceptance criteria for the batch. Those criteria are:

- No valid “unit dose” result or dosage unit value can be outside of the range from 75 % to 125 % of the label claim, and
- For the dosage units tested, not more than 1.6 % of the samples tested can be outside of 85 % to 115 % of the label claim (for a safety factor of 2+ over USP’s “3.33 %” for any *article*).

¹³ ANSI/ASQC Z1.9-1993, SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING, American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989).

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

Though ANSI/ASQC Z 1.9-993 establishes the numbers required for the testing of units, it does not establish the number of units that should be sampled at any stage. Moreover, there are no similar consensus standards that are directly applicable to non-discrete materials such as the final blend. Therefore, the next section provides an example that may be used as the basis for the sampling and testing of the “Final Blend,” and the in-process and finished dosage units.

Table 1 – Active Content Specifications For Final Blend and Tablets

Specification Stage	Expressed In Terms Of The Percentage Of Label Claim					
	Mean ¹	RSD Limit	Expectation Range (3 RSD)	AQL ²	No Value Can Be Outside Of	NMT ³ 1.6 % Outside Of:
Final Blend	NLT ⁴ 100	1.5	96.0 – 105.	N/A	75 - 125	N/A
Tablet Core	NLT 100	2.4	93.0 – 108.	0.4	75 - 125	85 - 115
Specific ⁵ Tablet Core	NLT 100	1.9	94.8 – 106.2	N/A	N/A	N/A
Finished Tablet	NLT 100	2.4	93.0 – 108.	0.4	75 - 125	85 - 115

1 Required to meet the intent of 21 CFR 211.101(a), “The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.”

2 See ANSI/ASQC Z1.9 for an explanation of the term “AQL” and how to use it and the sample values measured in an appropriately sized representative sample to assess the acceptability of the batch from which the samples tested were selected.

3 “NMT” is an abbreviation for “not more than.”

4 “NLT” is an abbreviation for “not less than.”

5 Specific tablet core values are computed by multiplying each content result by the tablet target weight divided by the weight measured for the unit tested.

V. ESTABLISHING APPROPRIATE SAMPLING AND SAMPLE EVALUATION PLANS

A. GENERAL CONSIDERATIONS

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

- The content for the active in the wall layer is, *on average*, less than 2 % different from the average content in the bulk blend (e.g., 1.4 % to 1.6 %; n = 6) in developmental studies at one-fifth or larger of the planned production scale.

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- The “Final Blend” flow index, as measured by bulk density divided by tapped density for three samples from each development blend, is not less than (*NLT*) 0.75 (e.g., 0.78 to 0.81; n=3) in developmental studies at *NLT* one-fifth planned scale.
- The worst-case uniformity (for the magnesium stearate added to the formulation as a tableting lubricant) has a reproducible RSD that is less than 6 % RSD (e.g., 4.2 % to 5.7 %; n = 4) on developmental studies at *NLT* one-fifth planned scale.
- Post-blend 30-day low-frequency vibration studies on the intermediate containers of the blend shows:
 - o Segregation in the average level of the active between the top and bottom of the container that is less than 2 % (justifying a 15-day [2-week] hold time)
 - o The post-study flow index was *NLT* 0.7 (e.g., 0.72 to 0.75; n = 3).

The other goals are to control the particle size distribution and flow of the components blended such that all intermediate blends and the final blend met their specifications and the one-fifth scale final blends are *NLT* 5 % relative *inside* of the limits established for the planned full scale batches.

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

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

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

In complex mixtures of the type discussed, the size (amount) of the sample sampled must be large enough that the bias in the sampling procedure used is negligible. In addition, *although this guidance only addresses the assessment of the uniformity of the blend with respect to the content of the active*, the final blend should also be evaluated for the uniformity of any release enhancers or retardants added (or their surrogates) to ensure that the release of the active meets the criteria established for it. Finally, in some cases, the firm may need to evaluate the uniformity of the lubricant added (or a surrogate thereof). Each sample should be large enough to permit the withdrawal of at least six (6) unbiased subsamples (aliquots) for each chemical test (such as, content, of

¹⁴ Lee Dudley, “Unlock Better Blending,” *Chemical Processing*, December 2003, Cover and pp. 22 – 28.

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380
381 the active or actives, level of the release-control components, level for impurity or
382 impurities, level of flow agent) for components that may affect the uniformity of the
383 drug product, as well as, *when physical testing is required*, at least one unbiased
384 aliquot for each physical test that must be performed. In general, the preceding are the
385 baseline requirements for *scientifically sound* and *appropriate* sampling of unbiased
386 samples from a batch of a non-discrete material. [Note: In general, for a 250-mg tablet,
387 blend samples in studies where no physical properties are to be assessed should be on the order
388 of 4 g when a 5-mL sample vial is used. When physical properties are to be assessed, 15-g
389 samples should be sampled into appropriate 20-mL containers or 20-g samples should be
390 sampled into appropriate 25-mL containers to ensure that the sample containers are completely
391 filled. In all cases, the vials should be *pre-cleaned* wide-mouthed vials or bottles that are pre-
392 labeled and stored/contained in an appropriate rack that holds them upright.]
393

394 **2. Establishing Scientifically Sound And Appropriate “Sampling Size”** 395 **Requirements For Non-Discrete Materials** 396

397 The lower limits on multiple-dose sample’s size (weight or volume) should be
398 established during product development by comparing the results found for unit-dose
399 samples with the results found for unit-dose aliquots from larger multiple-dose
400 samples taken and handled in a manner that neither additionally mixes nor promotes
401 post-sampling segregation. In general, the closer the results for the mean of the
402 unit-dose samples are to: **a)** the formulation’s targeted mean content level **and b)** the
403 mean of the results from the unit-dose aliquots from the multiple-dose samples, the
404 more uniform the formulation is and/or the less concerns one should have about
405 sampling tool (typically, stainless steel) and container (typically, borosilicate glass)
406 surface-interaction effects.
407

408 **3. Scientifically Sound and Appropriate Test Aliquot Volume (or Weight)** 409 **For Non-Discrete Materials** 410

411 Trained analysts can easily remove minimally biased singlet aliquots that are within 5
412 % of the weight of the targeted unit-dose aliquot for aliquots down to 50 mg (and
413 within 10 % down to 10 mg to 15 mg [a level smaller than most tablets]). Since the
414 goal must be to determine the uniformity at the dosage-unit level, all test aliquots
415 should be taken at a unit-dose or, *if justified by the uniformity of the blend or other*
416 *factors*, a fraction of the dosage-unit weight. [Note: In general, aliquoting at less than
417 unit-dose weight should be limited to cases where the active content is *NLT* 10 % of the weight
418 of the dose.]
419

420 **4. Representative Sampling Requirements For Non-Discrete Materials** 421

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

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429 bag/blend interface layer). In general, at least duplicate aliquots should be evaluated
430 from each location sampled.
431

432 *Using the PQRI's recommendations concerning the identification of regions of poor*
433 *blending and the CGMP's requirements for batch-representative sampling*, the
434 manufacturer should initially choose a sampling pattern, based on developmental
435 studies and at least one confirmatory batch manufactured in the intended type of
436 blender at one-fifth planned production scale or larger, that:
437

- 438 ▪ Includes more than fifteen (15) sampling locations in the blender with half the
439 sampling locations chosen from the areas where the developmental data found the
440 least homogeneous material (including the blender wall, around the agitator shaft
441 [if any] and in the discharge valve) and the other half in locations where the
442 developmental data found the most homogeneous material – to ensure a *batch-*
443 *representative* sampling.
444
- 445 ▪ In tumbling blenders (such as V-blenders, double cones, or drum mixers),
446 samples should be selected from not less than two depths along the axis of the
447 blender (the number of levels should increase as the size of the mixer increases);
448 *based on the PQRI's recommendation for choosing at least 10 locations where*
449 *the least uniform blend is expected to be found*, the PQRI initially recommends
450 choosing at least 20 locations to adequately assess the blend homogeneity in such
451 tumbling blenders.
452
- 453 ▪ In convective blenders (such as ribbon blenders, screw blenders, plow and paddle
454 mixers, and air jet mixers), a special effort should be made to implement uniform
455 volumetric sampling that, in addition to the general wall and agitator regions,
456 include the corners, the two end “shaft pass through” areas, and discharge area
457 (by analogy, the PQRI initially recommends choosing at least 40 locations to
458 adequately assess the blend homogeneity in such convective blenders).
459

460 When the data from such in-depth studies clearly demonstrate that the final blend is
461 acceptably uniform with respect to all of its critical variables, the manufacturer should
462 choose that subset of batch-spanning locations which most consistently provides the
463 same range of uniformity values as the full set. In cases where there are multiple
464 equally *representative* subsets that could be used, the manufacturer should choose that
465 subset that has the least risk of “between sampling location” biasing.
466

467 Having discussed the general considerations for the sampling of non-discrete materials, let us
468 discuss some general sampling plans.
469

469
470 **B. INSPECTION PLANS FOR A FINAL BLEND IN THE MIXER**^{15, 16}
471

472 For the purposes of this discussion, the blender is a tumble mixer from a vendor that makes
473 blenders that permit the “blend container” to be separated from the mixer drive and agitator
474 component¹⁷. With the preceding as the basis for discussing sampling from the blender, let us
475 proceed to discuss plans for Sampling and Evaluation of a blend in the mixer.
476

477 **1. Sampling Plans**
478

479 With the preceding as the basis for discussing sampling from the blender, this
480 guidance leaves it up to each firm to establish the appropriate sampling locations in a
481 manner that produces a *representative* sample. Based on the PQRI’s input, the
482 industry recommends initially choosing not less than twenty sampling locations when
483 sampling at production scale (implicitly this number is the number recommended for
484 initial “validation” studies where the performance of the blending process is first being
485 assessed at full scale).
486

487 To minimize the risk of sampling bias, the sampling locations at each level should be
488 appropriately offset from the sampling locations at the next level. In general, the
489 samplings should proceed by level from the topmost level to the bottommost level with
490 randomized sampling for the samples taken at each level. To minimize “top biasing,”
491 the sampler probes should be inserted slowly. For example, if a three-level, eight-
492 samples-per-level sampling pattern is selected, then the general setup should offset
493 each level’s sampling locations by one-third of the distance between the locations at
494 the top level. As the blend is being sampled, each sample should be transferred into a
495 properly labeled clean sample container that it fills and that container sealed with an
496 appropriate compression-screw cap. When all of the samples have been collected, the
497 sample set should be transferred to the appropriate testing facility for evaluation.
498

499
500
501 ¹⁵ In general, this approach should be limited to blenders having a *nameplate* volume not larger than
502 about 30 ft.³ (0.028 m³).
503

504 ¹⁶ The use of sampling from the blender is an approach that should mostly be used in a process development
505 environment where the true final blend uniformity after blending needs to be assessed along with the
506 uniformity of the blend after transfer into an intermediate storage container. This information is needed to
507 measure “blend” resistance to resegregation after the mixing stops. Coupled with the “post-dosage-forming”
508 uniformity information provided by the formed dosage units, this information is valuable in determining that
509 a given formulation is, or is not, adequately resistant to post-mixing “demixing.” At the production scale,
510 where the mechanical stability of the formulation should have been established before transferring the blend
511 from the developmental stage to the pre-production study stage, the more appropriate sampling point for the
512 “Final Blend” is, in general, shortly before the batch is scheduled to be converted into the dosage form.
513 Thus, even when “sampling from the blender” can validly be accomplished, the better sampling point is from
514 the intermediate sampling containers before dosage-unit forming.
515

516 ¹⁷ The use of such blenders not only facilitates the use of the “sampling from the blender” approach but also
517 can increase production throughput. This is the case because one blend can be mixed while the one being
518 sampled is being sampled, the one previously sampled is being transferred into intermediate containers, and
519 another “mix container” is being loaded for mixing (allowing these operations to proceed in parallel).
520

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2. Evaluation Plans

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

Based on the results found, the nature of the blend should be assessed¹⁸. From that initial assessment, the number of samples for which duplicates are required should, if indicated, be reduced. *Provided the results found are within the limits established for a given final blend and the “within” RSD is consistently less than the “between” RSD*, the replicates can be appropriately reduced as long as at least three (3) batch-spanning samples are tested in duplicate. *As the production of final blends continues*, the history observed should permit the firm to similarly adjust the number of sample locations that should be evaluated. The more uniform the history, the fewer locations that should need to be evaluated. However, the minimum number selected in such decisions should be not less than three (3) samples chosen in a way that they “span” the batch. In addition, the minimum number of samples from which duplicate aliquots should be taken and evaluated should not be less than three (3) batch-spanning samples. Thus, the sample evaluation plans hierarchical structure should range from not less than twenty (20) batch spanning (*representative*) samples evaluated in duplicate (not less than 40 evaluations) to not less than three (3) batch-spanning samples with duplicate evaluation for each sample (not less than 6 evaluations).

In summary, *to address all contingencies*, **all** samples should be sampled and an appropriate justified history-based hierarchical sample-evaluation plan should be used to adjust the number of the sampled samples that should be tested initially. The hierarchical sample-evaluation plan should also provide for increased evaluation whenever:

- a. An apparent nonconformity (valid OOS) is encountered or
- b. The test values observed are significantly outside of the historical norms seen for the final blend.

¹⁸ The test procedures used for evaluating uniformity should be chosen from those analytical evaluation techniques that have inherently high precision and provide integral sample-response averaging (e.g., direct spectrophotometric procedures). Thus, each firm should take this into consideration during the development of the formulation and, to the extent possible, develop a formulation where a pre-separation (e.g., extraction or HPLC) is not required before the test can reliably respond to the level of the active or actives in the formulation. For multiple actives, a firm may be able to use rapid-scan UV/Vis systems equipped with suitable response deconvolution software here.

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C. INSPECTION PLANS FOR A FINAL BLEND CONTAINED IN “N” INTERMEDIATE STORAGE CONTAINERS¹⁹

1. Sampling Plans²⁰

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

2. Evaluation Plans

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

Based on the results found, the nature of the blend should be assessed and, *based on this initial assessment*, the number of samples for which duplicates are required should, if indicated, be reduced or increased. *Provided the results found are within the limits established for a given final blend and the “within” RSD is consistently less than the “between” RSD*, the replicates can be appropriately reduced as long as sample in the bottom of the first and “middle” containers, and the top of the last container are tested in duplicate. As the production of final blends continues, the history observed should permit the number of sample locations that must be evaluated to be similarly adjusted. The more uniform the history, the fewer locations that should need to be evaluated. However, the minimum number selected in such decisions should be not less than the three (3) “*batch-spanning*” samples previously identified. Minimally,

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

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

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620 duplicate aliquots should be taken and evaluated for the limiting three (3) batch-
621 spanning samples discussed previously. Thus, the sample evaluation plan's
622 hierarchical structure should range from not less than "n," "2n" or "3n" batch spanning
623 (*representative*) samples evaluated in duplicate (not less than "2n," "4n," or "6n"
624 evaluations) to not less than the three (3) identified batch-spanning samples with
625 duplicate evaluation on each (or six [6] evaluations).
626
627

628 In summary, *to address all contingencies*, **all** samples should be sampled and an
629 appropriate justified history-based hierarchical sample-evaluation plan should be used
630 to adjust the number of the sampled samples evaluated initially. The firm's
631 hierarchical sample-evaluation plan should also provide for increased evaluation
632 whenever: **a**) an apparent non-conformity (valid OOS) is encountered **or b**) the test
633 values observed are significantly outside of the historical norms seen for those
634 "locations" in the containers in which the final blend is stored.
635

636 **D. INSPECTION PLAN FOR IN-PROCESS TABLET CORES AND FILLED** 637 **CAPSULES**

638 **1. Sampling Plans**

639 For the in-process inspection of a batch, most manufacturers want to dynamically
640 assess the quality of the batch as it is being produced whenever the operation lends
641 itself to such sampling. This is especially true when the process step requires several
642 hours to complete. In general, tablet core formation and capsule filling are process
643 steps that require hours to complete. Thus, this guidance presumes that the
644 manufacturers generally dynamically sample the dosage units as they are being
645 produced. Beyond the usual strictures for a *representative* sample, dynamic sampling
646 imposes a requirement that each sample taken must be *representative* of the process at
647 the time of that sampling. Because tablet presses and encapsulation systems are a
648 collection of a significant number of individual dosage-forming stations, each
649 sampling should contain some integer multiple of the number of dosage-unit-forming
650 stations. Since, *as the discussion will show*, a firm needs a sample of not less than
651 1600 to 3200 units for its inspections (attribute [done on the firm's own quality
652 initiative] and variable [required by regulation]), each sampling point should collect
653 "1600 divided by the number of sampling points," or more, *representative* dosage
654 units subject to the constraints that the total number of units collected at each point:
655
656

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

660 In general, the firm should collect each sampling point's sample in a separate
661 appropriately labeled container (in most cases, a resealable plastic bag may be used
662 and the sampled set of samplings accumulated in an appropriately sized container²¹).
663
664
665
666

668 ²¹ When the samples from each sampling point are segregated, then, when physical problems are found during
669 attribute inspection, the time sequence of the problem sample set or sets can be identified when the problem
670 does not pervade the batch.
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671 Since most firms perform attribute assessment²² using *Military Standard 105E* or,
672 more properly, its official replacement, ANSI/ASQC Z1.4, and those evaluations are
673 non-destructive, the sample collected for a firm's attribute quality inspections can,
674 *when it passes*, be used as the sample for the required variable assessment studies²³.
675 This is the case because the number of units required for such assessments is on the
676 order of 800 to 1250 units for production-scale batches of tablets and capsules.
677 Moreover, since many firms do double sampling attribute inspection, this sample
678 should contain from 1600 to 2500 or more units. Thus, the number sampled for
679 dosage-unit attribute inspection should, *if sampled representatively and their sampling*
680 *points preserved*, be more than sufficient for content uniformity assessments as well as
681 for **all** the other appropriate variable factor evaluations including, but not limited to,
682 the chemical property evaluations such as rate of active release (using a USP-like
683 "Dissolution" or "Drug Release" test), assay, impurity, water content, and physical
684 property evaluations such as hardness, friability and disintegration.
685

686
687 In summary, a firm can minimize the number of formed dosage units sampled by
688 appropriately sampling and conserving an overall *representative sample* collected for
689 attribute inspection and appropriately using it for the requisite assessment of the active
690 content uniformity for the formed dosage units in each batch for as well as other
691 variable factors "that may be responsible for causing variability in the characteristics of in-
692 process material and the drug product" (21 CFR 211.110(a)).
693

2. Evaluation Plans

694
695 Broadly, there are two statistical approaches that one can take to evaluating a
696 *representative* sample from a batch of freshly formed dosage units. Those general
697 approaches are characterized by the distribution assumption made for the units
698 sampled. If no distributional assumption is made, the firm should use a suitable
699 "distribution free" assessment procedure. When the firm can justify classifying the
700 dosage units as belong to a "normal" or "near normal" distribution, the firm should use
701 an appropriate "normal distribution" statistical approach which, in general, requires a
702 significantly smaller number of sample units. This guidance presumes that the
703

704
705
706 ²² The current consensus standard, ANSI/ASQC-Z1.4, spells out a set of attribute sampling and
707 evaluation procedures that provide 95-% confidence level assessment of a *batch-representative*
708 sample of tablet cores for attributes like chipping, capping, cracking, surface pitting, incorrect
709 punching, and broken, or, for capsules, cracked shell, improper closure, incorrect capsule, and shell
710 defects. Simplistically, the manufacturer assigns an allowable projected percentage level for
711 defective dosage units for each attribute and accepts batches when all attributes are found to have
712 defect levels that are less than the allowable number for each attribute assessed.

713
714 ²³ This strategy ensures that the sample submitted for variables assessment is from the physically acceptable
715 batch. In cases where the batch fails the physical properties, at best, the batch of tablet cores is appropriately
716 screened and, after this screening and an appropriate revised in-process sample is generated that represents
717 the screened batch. When this sample passes attribute inspection, the revised *batch-representative* core or
718 capsule sample is then submitted for the requisite variables testing under ANSI/ASQC Z1.9. In the worst
719 case, the batch is rejected for failing its physical attributes inspection. When this approach is used, the risk
720 of non-productive sample evaluation is minimized.
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721
722 manufacturers of tablets and capsules are justified in using “normal distribution”
723 statistical approaches for assessing content uniformity.

724
725 *With respect to appropriate “normal distribution” statistical approaches, this*
726 *guidance presumes that manufacturers should use statistical procedures that provide a*
727 *95 %, or higher, level of confidence that the results for the representative samples*
728 *tested should be predictive of the acceptability of the remaining batch of untested*
729 *units. Given this “confidence level” presumption, this guidance further presumes that*
730 *each manufacturer should use ANSI/ASQC Z1.9 (or its ISO equivalent, ISO 3951) as*
731 *the basis for its sample evaluation plans. This presumption is made because*
732 *ANSI/ASQC Z1.9 and ISO 3951 outline CGMP-compliant sample evaluation plans*
733 *that test the least number of representative sample units that a firm can justify testing*
734 *for active content whose active content result values can validly be used to predict the*
735 *acceptability of the entire batch of units at the 95-% confidence level²⁴.*

736
737 The cited consensus standards provide evaluation plans for two (2) cases, the “*process*
738 *variability known*” case and “*process variability unknown*” case. To justify using the
739 “*process variability known*” case, the manufacturer should be able to establish that its
740 acceptance criteria for all incoming components, including the active, and all in-
741 process materials include appropriately restrictive controls on all the critical variable
742 factors for each component or material. In addition, the firm should have sufficient
743 results data from the intensified testing on final stage developmental and initial
744 production-scale “validation” or process conformance batches that demonstrates that
745 the *process mean* and *process variability* for each such batch are, *within their*
746 *respective uncertainties*, the same²⁵ for all such batches. When the overall results
747 support the use of an appropriate “*process variability known*” evaluation plan, then
748 that plan, *when it is properly established*, should be used as the “stage 1” evaluation
749 plan for each batch. *When the data does not support the use of a “process variability*
750 *known” approach to batch assessment (see Scenario 2)*, an appropriate “*process*
751 *variability unknown*” evaluation plan should be used as the “stage 1” evaluation plan
752 for each batch. In those cases where it is valid to use an appropriate “*process*
753 *variability known*” plan for stage 1, the firm’s “stage 2” acceptance evaluation plan,
754 *when such plans are needed*, can be simply to switch to the corresponding appropriate
755

757 ²⁴ Firms not wishing to use the recognized applicable statistical consensus standards, ANSI/ASQC Z1.9 (or its
758 ISO equivalent, ISO 3951), should develop, and justify the use of, a suitable *population predictive* evaluation
759 plan that tests the same number or a larger number of *batch-representative* sample units. This is the case
760 because the consensus standards cited are based on the least number of units required to demonstrate *batch*
761 *acceptability* at the 95-% confidence level. Firms wishing to have a higher confidence level in the
762 acceptability of the batch tested for its active content should either use a suitable validated statistical
763 program to generate the number of samples required or consult a suitable statistics textbook that discusses
764 designing variables acceptance sampling plans and follow the procedures outlined to determine the
765 appropriate number of *representative* units to evaluate.

767 ²⁵ For the example tablet product, having a targeted mean of 100.5 % of label claim, consider the two (2)
768 scenarios on the next page in which all components are presumed to be from *different* lots. Each batch’s
769 results consist of the evaluation of 200 or more *representative* samples tested for active uniformity in each
770 scenario. The batches intensively tested consist of one (1) “technology transfer” and three (3) “initial
771 validation” batches. The scenarios on the next page then provide example results.

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Scenarios

Scenario 1^A

[Process variability known; all critical variable factors well controlled]

Process Identifier	Content Uniformity Data			
	Relative Mean	Relative RSD	Number Tested	Relative Value Range
Technology transfer	100.4	1.8	200	93.2 – 104.8
Initial Val-1	100.6	1.9	200	94.2 – 107.7
Initial Val-2	100.4	1.8	200	95.1 – 107.1
Initial Val-3	100.6	1.7	400	92.4 – 108.0
Weighted Process	100.5	1.8	1000	92.4 – 108.0

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

Scenario 2^B

[Process variability unknown; all critical component factors not well controlled]

Process Identifier	Content Uniformity Data			
	Relative Mean	Relative RSD	Number Tested	Relative Value Range
Technology transfer	100.3	2.1	200	93.2 – 105.8
Initial Val-1	100.0	1.3	200	94.2 – 104.1
Initial Val-2	100.3	2.3	400	92.1 – 108.0
Initial Val-3	100.6	1.9	400	93.0 – 108.6
Weighted Process	100.2	2.0	1200	92.1 – 108.6

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

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“*process variability unknown*” plan and use it. For an appropriate “stage 2” plan for products that require the “stage 1” plan to be a “*process variability unknown*” plan, the firm should adopt an appropriate “*expanded sample evaluation*” plan based on a process capability approach. Thus, the statistical evaluation of an appropriate number of sample units can be globally thought of as a three-tiered plan. The first two tiers of which, “*process variability known*” and “*process variability unknown*,” should be

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782 based on an appropriate plan from the sets of plans contained in the cited consensus
783 standard documents. The third tier should be based on a “*process capability*”
784 approach that requires the evaluation of more *representative* sample units than the
785 “*process variability unknown*” case. The sections that follow discuss the general
786 requirements for, and limitations on, the use of the approach upon which each tier is
787 based. It is left up to each manufacturer to justify the exact general decision tree that
788 is appropriate for each of their drug products. To simplify this discussion,
789 ANSI/ASQC Z1.9-1993 is the consensus standard used and each batch is presumed to
790 contain *NLT* 250,000+ tablet cores or filled capsules.

791
792 **a. Tier 1 – Process Variability Known – Evaluation Plans Appropriate**
793 **To Drug Product Manufacture²⁶**
794

795 In general, the number of *population-representative* sample unit evaluations
796 required in **Tier 1** for a valid batch inspection plan depends upon the tolerable
797 percentage of nonconforming tablet **active** content values (AQL_{Active content}).

800 ²⁶ Should a batch not meet its AQL criteria when evaluated using the firm’s “Tier 1” evaluation plan, then,
801 provided the other critical batch acceptance criteria are met, the firm should switch to their “Tier 2” –
802 Process Variability Unknown – plan. *When the number of sample units already tested is at least the number*
803 *specified in the appropriate “Reduced Inspection” option of this “Tier 2” plan*, the firm should first evaluate
804 the probable acceptability of the population based on the observed sample variability rather than the
805 sample’s projected “process variability.” This decision is appropriate when, for whatever reason, a process
806 operating in control under a “Tier 1” plan indicates that the product may not be acceptable even though the
807 sample units tested meet all of the other acceptance criteria established for content uniformity. If this
808 evaluation finds the product is acceptable, then the **entry point** into the “content uniformity” evaluation
809 decision matrix should be set to the “Tier 2 – Reduced Inspection.” If the samples tested are otherwise
810 acceptable but the batch is still found to be not acceptable, then, the firm should switch to the “Tier 2 –
811 Normal Inspection” plan, evaluate the remaining number of units required to satisfy the 200-unit
812 requirements for batches larger than 150,000 units, and ascertain whether or not the batch is acceptable
813 under this evaluation condition. When it is, then the firm should switch their **entry point** into the “content
814 uniformity” evaluation decision matrix to “Tier 2 – Normal Inspection.” When all of the results are
815 otherwise acceptable but the data do NOT meet the firm’s “Tier 2 – Normal Inspection” criteria, the firm
816 may elect to switch to their “Tier 3 – Process Capability” plan and proceed as it directs²⁷. If the “Tier 3”
817 plan finds the batch acceptable, then the firm should switch their content-uniformity entry point to “Tier 3”
818 and use it for subsequent batches. {Note: the rules for switching from “Tier 3” to “Tier 2 – Normal
819 Inspection,” or “Tier 2 – Normal Inspection” to “Tier 2 – Reduced inspection” or from “Tier 2 – Reduced
820 Inspection” to “Tier 1” are complex and depend upon the:

- 821
- 822 • General past production history,
 - 823 • Proximity of changes in the source of or acceptance criteria for a component or in-process material, or
824 processing to the current inspection entry point,
 - 825 • Steadiness of the production of consecutive batches, and
 - 826 • Whether or not the dosage units are produced on a dedicated production line.

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

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

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The relationship between sample number and AQL is inverse. Thus, *subject to the design limits and verified outcomes established during product development*, a firm wishing to minimize the number of samples that should be tested should choose the smallest “Acceptance Quality Level” (“AQL”) that the design, development, and, *where available*, historical records factually support. Because the validity of the use of this approach is totally dependent on the validity of the firm’s assertion that the *process variability* is a known value, the use of a “Tier 1” plan” in the firm’s overall evaluation plan should be restricted to products manufactured from components and in-process materials whose critical chemical and physical properties are both identified and well controlled. Moreover, *as discussed previously*, the determination of the “*process variability*” value should be based on intensified testing on a sufficient number of production-scale related batches manufactured using differing lots of components. [Note: Though a “reduced inspection” option exists, the allowable variability in the chemical and physical properties of the components and in-process materials does not support the use of this option for tablet, capsule, and other solids containing drug products.] Thus, for content uniformity and batches larger than 250,000 units, Row “P” in “Table D-3” of ANSI/ASQC Z1.9 (pages 90 and 91) outlines the number of samples (n), the acceptance criterion (M), and adjustment factor (v) for a given choice of AQL. Those sample numbers range from 42 for an AQL of 0.1 % to 127 for an AQL of 10 %. For the example tablet product (**see Table 1**) used in this guidance where the AQL established is 0.4 %, not less than 54 batch representative sample units should be tested. A “500-unit batch” example showing how the results found for the samples tested are used to determine the acceptability of the batch is shown on page 88 in ANSI/ASQC Z1.9-1993. When the batch results are evaluated and, *in conjunction with the other acceptance criteria established for the drug product (see Table 1)*, the batch is found to have an acceptable active content uniformity, then not only does the batch evaluated have an acceptable active content uniformity but the continued use of this “Tier 1” evaluation plan is also validated²⁷. In general, the firm’s use of the “Tier 1” level of inspection should be limited to solid dosage forms for which every variable factor (component, material, process and test) that may adversely affect the uniformity of the content in the formed dosage units is well controlled.

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

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

- All critical chemical and physical factors for the components, materials and process steps but do not rigorously control all of them, or
- All of the critical chemical factors but only control some of the critical factors relying instead on one or more process steps (usually granulation related) to minimize or eliminate the non-uniformity that the uncontrolled critical component factors can contribute and choose to use the formed dosage units to define the uniformity of:
 - o the formed units, and

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

For the tablet example (see **Table 1**) produced in batches larger than 250,000 units, the appropriate *batch-representative* ‘normal’ inspection sample number is 200 units. In cases where the manufacturer can justify the use of a ‘reduced’ inspection plan²⁸, a firm using ANSI/ASQC Z1.9 as the basis for its batch acceptance assessments can chose to test as few as fifty (50) *batch-representative* sample units. However, on a *generalized statistical basis*, evaluating a *representative* set of 75 is a better choice. When the use of this ‘reduced inspection’ option is justified, any ‘*samples conform but batch is predicted to fail*’ assessment should trigger switching to the ‘*normal inspection*’ option with the evaluation of the additional *representative* dosage units needed to generate the requisite 200 *batch-representative* content results. Should the test results from a batch under ‘*normal inspection*’ meet its sample criteria but fail to meet the acceptance criteria for the batch, the recommended course of action is to switch to a **Tier 3** (based on a process capability approach) plan that the manufacturer has justified and submitted in the appropriate filing that has led the FDA to approve or license that drug product. This is the case because a firm’s switching to the ‘*tightened inspection*’ option²⁹ as outlined in ANSI/ASQC Z1.9 would lead not only to the rejection of the non-conforming *batch* but also to tightening of the acceptance criteria

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

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

Thus, the choice of this option should be limited to dedicated manufacturing facilities or facilities in which the production campaign or ‘run’ encompasses more than 10 lots or batches. In general, this choice is not appropriate to short-run production unless the firm is justified in using the ‘*process variability known*’ option (Tier 1) and a non-conformance to the requirements for that case contains a provision for switching to the ‘*process variability unknown – reduced inspection*’ option. [Note: Since the ANSI standard’s ‘tightened’ inspection plans: a) do NOT address the acceptability issues associated with the ‘currently non-acceptable’ batch and b) only increase the probability that a subsequent batch will not meet its acceptance criteria, this guidance has elected to switch plans rather than switch to ‘tightened inspection.’]

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

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942 in a manner that would increase the risk that an acceptable batch would be
943 rejected.
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1. Process Variability Unknown – Normal Inspection

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Though ANSI/ASQC Z1.9 provides two approaches, a range-based procedure and a standard-deviation-based procedure, this guidance recommends that the manufacturers elect to use the standard-deviation-based procedure because: **a)** it requires the testing of fewer samples than the range-based procedure, **and**, more importantly, **b)** it results do not depend upon how the samples being evaluated are grouped. For batches larger than 150,000 dosage units, not less than 200 *representative* dosage units³⁰ should be tested when this inspection plan is used. For tablet and capsule batches down to 35,000 units, the firm need only evaluate 150 *representative* dosage units. In general, this, or an appropriate process-capability-based inspection plan, is the *minimum* inspection plan that a manufacturer should use during the development of the manufacturing process for a tablet or capsule product when the developmental batch size exceeds about 500 dosage units. The text and appropriate tables in pages 37 through 53 of ANSI/ASQC Z1.9-1993 contain the information and examples that are needed for a manufacturer to determine the acceptability of a batch based on finding acceptable sample results generated by the testing of any set of “200” or more *representative* units.

2. Process Variability Unknown – Reduced Inspection

Provided the manufacture can justify the use of a “reduced inspection” plan, the manufacturer should again, where possible, elect to use the standard-deviation-based procedure described in the text and the appropriate tables in pages 37 through 53 of ANSI/ASQC Z1.9-1993 to assess the acceptability of a batch when the valid content results found from the evaluation of the requisite number of *representative* sample units meet their acceptance criteria (sample specifications). In general, a firm using this ANSI/ASQC Z1.9 procedure is justified in evaluating as few as 50 *representative* units and using the results obtained to ascertain whether or not the batch is acceptable. When the firm is justified in using this inspection plan to evaluate the content uniformity of the batch based on the sample units tested, the firm’s inspection plan should provide an explicit provision for switching to “*normal inspection*” option when batches are found to be nonconforming (not

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

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991 meeting the acceptance criteria for reduced inspection). Firms wishing
992 a higher level of confidence may elect, where this option exists, to use
993 the next larger sample size as its “*reduced inspection*” number. In the
994 tablet example that this guidance uses, this would translate into testing
995 75 dosage units instead of the 50-unit minimum that the consensus
996 standard requires.
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998

999 In summary, the preceding “Tier 2” inspection plans are those that most of
1000 today’s manufacturers should be using for routine production-scale batch
1001 acceptability assessments. This is the case because:
1002

- 1003 • The goal of this CGMP-based in-process content assessment is to ensure
1004 that each batch produced has acceptable content uniformity (21 CFR
1005 211.110(a), “To assure batch uniformity ...”), and
1006
- 1007 • Most of today’s firms do not identify and rigorously control all of the
1008 critical physical property characteristics of the components and in-
1009 process materials used in the manufacture of a solid dosage form
1010 product.
1011

1012 Thus, *contrary to the assertions of some*, the appropriate **minimum** goal cannot
1013 simply be to find that the content results are acceptable for the few tested units.
1014 *Provided a confidence level of 95 % is acceptable*, the plans in ANSI/ASQC
1015 Z1.9 provide the minimum plans that a firm can use and meet the drug-product
1016 CGMP regulation’s **minimums**.
1017

1018 **c. Tier 3 – Process-Capability-Based – Evaluation Plans Appropriate To Drug**
1019 **Product Manufacture**
1020

1021 In general, the plans in **Tier 3** are appropriate when the variability of the batches
1022 produced is such that use of the consensus standards cited is deemed or found not to be
1023 appropriate for a given product. Often, a suitable “Tier 3” inspection plan is the plan
1024 of choice for use in the development of a solid dosage form when the controls for the
1025 components, in-process materials, and processing steps have not yet been completely
1026 developed. Because there a variety of approaches that can be used to evaluate the
1027 manufacturability of a product using a given set of inputs and operations, this guidance
1028 does not propose to address exactly which “*process capability*” approach should be
1029 used. This guidance instead focuses on the issues associated with the minimum:
1030

- 1031 **a.** Number of *representative* dosage units that a firm should evaluate and
1032
- 1033 **b.** Capability result value that a firm should use
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1035 to comply with the requirement minimums of CGMP with respect to 21 CFR 211.110.
1036

1037 **1. Minimum Number of Units To Inspect**
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1039 Since capsule content and tablet-core content values are close to being
1040 normally distributed in a well-controlled process, this guidance will presume
1041 this is the case for the content values in each batch. Because the general form
1042 of all capability assessment approaches is based on a specification range
1043 divided by some standard deviation (“s”) or, *using this guidance’s relative*
1044 *approach*, a relative range divided by some relative standard deviation (RSD),

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1045 the validity of that “s” or “RSD” depends upon how close it is to the true value
1046 for the population. Consulting appropriate statistical texts (e.g., Chapter 2 in
1047 *EXPERIMENTAL STATISTICS, Handbook 91* [see Other References: 18]), that
1048 discuss the analysis of measurement data from normal populations, a firm
1049 should find that a significant number of units must be tested when, *for*
1050 *confidence levels that are 95 % or higher*, the estimate of the RSD derived
1051 from the samples tested must be close to the true population relative variability
1052 “ $R\sigma_{Batch}$ ”. Practically, not less than about 400 *population representative* units
1053 should be tested ensure that the RSD computed (RSD_{Sample}) is definitely within
1054 10 % of the true relative variability of the batch (“ $R\sigma_{Batch}$ ”). Though this
1055 number is a suggested *minimum* number for those firms who choose to use this
1056 approach to determining the acceptability of a batch, a firm may be able to
1057 justify using a smaller number when their production history indicates that
1058 testing a smaller subset provides adequate assurance of batch acceptability at a
1059 confidence level that is not less than 95 % provided the RSD_{Sample} uncertainty
1060 vis-à-vis the true value for the batch is estimated to be within “8 %” or less of
1061 the true population value (when a firm can justify using a 95 % confidence
1062 level) and within “9 %” of the true population variability (when a 99 %
1063 confidence level is determined to be appropriate)³¹.
1064

2. Minimum “Process Capability” Assessment

1065 Since the current recognized state of “good” quality in today’s industrial
1066 America is “Six Sigma,” CGMP dictates that that standard should be the one
1067 used by today’s drug product manufacturers. Remembering: **a)** the general
1068 form of the process capability equation for a set of relative values is that a
1069 relative range divided by six times the RSD observed is equal to the capability
1070 “C” **and b)** “Six Sigma” quality expects all values to be within a relative range
1071 from the “mean minus 6 RSD” to the “mean plus 6 RSD” or a “12 RSD”
1072 range, the firm should set a minimum process capability that is not less than
1073 “12 RSD”/”6 RSD” or 2.0. [Note: Looking at *process capability*³² in terms of the
1074 number of standard deviations from the process target that are tolerated, a *process*
1075 *capability* of “1.33” or “1.34,” a value that most authors consider the minimum
1076 acceptability, roughly translates into a into a targeted quality level of “Four Sigma.”]
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1082 ³¹ For manufacturers who wish to reduce their RSD uncertainty to the point that the error in assigning a process
1083 variability from the sample variability observed is less than “5 %,” not less than about 900 *representative*
1084 units should be selected when a 95 % confidence level is deemed appropriate. Moreover, at the 99 %
~~1085~~
1086 confidence level, not less than 1400 units should be tested.

1087 In developmental studies, the firms are encouraged to inspect larger numbers and choose a 99 % confidence
1088 level for decision making because doing so reduces the risk that the data from the developmental lots does
~~1089~~
~~1090~~ not adequately describe the performance of the projected or observed production-scale batches.

1091 ³² Since “process capability” is a derived value that is essentially the ratio of the allowed range divided by the
1092 observed variability, firms should be able to fully justify the range selected where the justified range should
1093 be no larger than the projected *population* content range derived from the range observed for the number of
1094 samples tested to meet the requirements for the 99-% confidence level.
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In summary, inspection based on a “capability” approach and today’s “Six Sigma” expectations for “good” quality require the manufacturer to evaluate more *representative* sample units than the procedures outlined in ANSI/ASQC Z1.9. In general, this is the approach that a firm should use in developing a drug product. This is the case because the specifications developed from the testing of more units are more likely to provide the firm with solid evidence as to what the true population limits are and properly drive process improvement to the point that the developed process probably should, *when implemented*, consistently produce batches that meet or exceed the established specifications that the firm’s data clearly justify.

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

E. INSPECTION PLAN FOR FINISHED TABLETS AND CAPSULES

1. Sampling Plans

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

Because a *batch-representative* finished dosage-unit “appearance” attribute sample for inspection under ANSI/ASQC Z1.4 is collected and examined, that sample should be appropriately conserved and used for the requisite variable factor evaluations required. With this in mind, let us turn to the evaluation of the finished dosage units sampled for the simple tablet and capsule products that this guidance directly addresses.

2. Evaluation Plans

When in-process testing establishes the *batch’s* active uniformity, there should, in general, be no need to reassess this variable factor for the instances (addressed by this guidance) in which the post forming operations do not change the content of the dosage units formed. However, when a firm needs to assess uniformity at the finished drug product stage, the procedures used for the in-process assessment can be appropriately adapted for use here. If the drug product assessment for active uniformity is meant to be a confirmation of the in-process assessment, then, *in cases*

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1144 *where the process steps after dosage unit forming cannot change the content of the*
1145 *dosage units, the firm should be able to justify using an evaluation plan that uses the*
1146 *RSD established in the in-process testing and a suitable ANSI/ASQC Z1.9-based*
1147 *“process variability known” procedure. In such cases, the firm may be justified in*
1148 *using the “process variability known – reduced inspection” plan because this*
1149 *inspection is meant to be confirmatory in nature. This guidance leaves it up to the*
1150 *manufacturer to specify and justify the content evaluation plan, if any, that the firm*
1151 *should use.*

1152
1153 However, *though outside the scope of this guidance, one critical process parameter*
1154 *that should or, in many cases, must (21 CFR 211.167(c)) be evaluated at the finished*
1155 *product stage is the release profile of the solid dosage form. This is the case because*
1156 *the post-dosage-forming processing and handling steps in the manufacture of tablets*
1157 *(e.g., color coating, inking) and capsules (e.g., polishing and gel coating) are known to*
1158 *affect the release of the active from the dosage unit. For example, when a firm’s*
1159 *process adds an “enteric” coating designed to delay the release of the active until after*
1160 *the dosage unit has passed into the small intestine, the drug product is designed to*
1161 *delay the release of the active. Since evaluating the release of the active is outside the*
1162 *scope of this guidance, the manufacturers should consult other published articles,*
1163 *documents, and texts that provide general guidance that the firm may use to justify the*
1164 *evaluation plan the firm establishes for such “active release” evaluations. Because*
1165 *“active release” and “active content” are correlated variable factors when the active is*
1166 *being released, their correlated nature may be used to justify, in some cases, “active*
1167 *release” examination plans that need only use one of the appropriate “reduced*
1168 *inspection” procedures in ANSI/ASQC Z1.9.*

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1170 VI. ESTABLISHING APPROPRIATE TEST PROCEDURES

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1172 A. GENERAL CONSIDERATIONS

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1174 Since the goal of in-process testing (21 CFR 211.110(a)) is to assess batch uniformity – not
1175 just the uniformity of the active level in the samples evaluated, the analytical test procedures
1176 chosen should be those that have the minimum imprecision subject to the constraint that the
1177 procedure’s verified inaccuracy is on the order of 1 % or less. Further, *because a firm may*
1178 *need to test on the order of 50 to 500 dosage units in order to make a CGMP-compliant*
1179 *determination of the acceptability of a batch with respect to its active content uniformity, the*
1180 *test procedures chosen should maximize sample throughput and, where possible, choose or*
1181 *develop procedures that inherently provide instrument averaged assessments of the response or*
1182 *responses used to compute the content for each dosage unit tested. In cases where the results*
1183 *from the testing of the dosage units evaluated for content indicate that the batch is acceptable*
1184 *and downstream processing has been verified not to affect the content level, the average of the*
1185 *active content values found may, in many cases, be validly used as the firm’s “Assay” for the*
1186 *batch being tested.*

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B. CHOICE OF ANALYTE MEASUREMENT SYSTEM

Historically, the tendency has been to develop and use procedures based on the use of high-performance liquid chromatographic (HPLC) separation of the chemical components in the dosage unit coupled with single-wavelength quantitation of the response produced by the active at some suitable wavelength using a compact spectrophotometer with a limited linear range and a wide (20-nm) bandwidth or similarly inexact diode-array systems as the analyte measurement system.

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

Fortunately, progress in instrumentation design and the advent of increasingly powerful microprocessors has made it possible to use rapid scan spectrophotometers and sophisticated component deconvolution software to accurately determine an averaged analyte response that provides the high throughput and response averaging capabilities needed to obtain highly precise and suitably accurate determinations of the content in the dosage units tested. Moreover, robotics has progressed to the point that the entire sample preparation and measurement procedure can be automated. With the Agency’s renewed interest in process analytical technology (PAT), manufacturers are encouraged to use such separationless assessment procedures³³ to speed the testing of the requisite number of sample units that CGMP requires a firm to test.

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

³³ Since these test procedures are only intended to assess the acceptability of the in-process batch for release to further processing (21 CFR 211.110(c)), the manufacturer should not feel compelled to use a test procedure based on, or derived from, the **USP**’s “in commerce” test procedure whenever that procedure includes HPLC. Instead, *wherever possible*, rapid-scan computerized spectrophotometric procedures using spectral deconvolution should be used to assess the uniformity of content for the batch being tested.

1232
1233 **VII. ESTABLISHING A CGMP-COMPLIANT INSPECTION PLAN FOR THE**
1234 **ACTIVE CONTENT IN A DRUG-PRODUCT PROCESS**
1235

1236 One of the fundamental tenets of quality system is that requisite level of quality required by the
1237 customer must be designed into all aspects of the process that produces the product. A second tenet is
1238 that all process inputs and processing steps must be properly controlled before one can ensure that the
1239 product will reliably meet its established quality criteria. A third tenet is that the costs associated with
1240 a quality failure are reduced when the failure is detected as soon as possible in the process. This
1241 guidance presumes that the manufacturer understands and develops the firm’s drug product processes
1242 for solid dosage units in a manner that fully complies with the first two of these quality tenets.
1243

1244 Further, to minimize the complexity of this discussion by including explicit discussions for the known
1245 variety of steps leading up the final blend, this guidance begins its discussion at the end of the process
1246 step that generates the final blend. Unless a manufacturer can justify combining the generation of the
1247 final blend and the dosage forming operation into a single process step, a firm is required to develop
1248 and use some *batch-representative* procedure for the assessment of the acceptability of each final
1249 blend that the firm’s quality control unit (QCU) can use to release each final blend for use in the
1250 dosage forming step (21 CFR 211.110(c)). By performing in-depth studies during process
1251 development, a firm can determine the *material-representative* sample number assessment minimums
1252 that should be used to meet the requirements minimums of the CGMP regulations for each dosage-unit
1253 processing stage that can adversely impact the uniformity of the in-process material or the drug
1254 product with respect to any of its critical variable factors (21 CFR 211.110(a)). For the simple tablet
1255 and capsule products covered by this guidance, a firm can, in general, justify excluding packaging
1256 operations from the set of process steps that can affect the uniformity of the active content and other
1257 variable factors directly related to level of the active. In such cases, the generalized set of steps where
1258 an active content and/or other uniformity assessment for release is required can be labeled as “Powder
1259 Blend,” “Formed Dosage Units,” and “Finished Dosage Units.” To simplify discussion, this section
1260 also uses the tablet product example introduced initially (a 250 mg uncoated tablet containing 0.2 mg
1261 of a single stable active ingredient [“0.08 %” wt./wt] targeted to contain, on average, 100.5 % of its
1262 labeled content).
1263

1264 **A. “POWDER BLEND” INSPECTION**
1265

1266 This guidance leaves it up to the manufacturer to justify the sampling and evaluation approach
1267 that it uses during the early stages of the development of a process. However, once a firm has
1268 established the type of dosage form, the components to be used and the general processing
1269 steps that will be used to produce the drug product, the Agency expects to see the
1270 manufacturer use *scientifically sound* and *appropriate representative-sample-based statistical*
1271 *inspection plans* in the final stages of development as well as in all pre-production-scale
1272 batches. Should a firm elect to pursue a “*process variability known*” approach, the Agency
1273 expects to see proof that the firm has determined the critical physical and chemical variable
1274 factors for each component, process step and processing choice that can affect the in-process
1275 material and drug product content uniformity and has established sufficiently stringent
1276 controls for each.
1277

1278 For those firms who elect to approach the determination of the content uniformity for each
1279 batch of the final “Powder Blend” indirectly (by determining the weight-corrected active
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1281 content for the freshly formed dosage units tested and using those values to provide assurance
1282 that the final “Powder Blend” did meet its uniformity criteria), the Agency expects to see an
1283 in-depth justification for choosing that option. That justification should include appropriate
1284 batch-acceptability for release evaluations^{34,35}. With the preceding Agency expectations in
1285 mind, the manufacture should then proceed in the manner that is dictated by the level of
1286 quality that the firm’s controls and process steps have built into the dosage unit forming
1287 operation.

1288
1289 In general, for a developed process, the firm should either have two types of inspection plans
1290 for “Powder Blend” inspection or a single multiple-tier inspection plan. These should address
1291 two (2) general situations, Evaluation Qualification (“EQ”) inspection (commonly referred to
1292 as the Performance Qualification [“PQ”] phase of validation) and Routine Production
1293 Qualification inspection (referred to as the Maintenance Qualification [“MQ”] phase of
1294 validation).

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

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1298
1299 The inspection plans for EQI should include an appropriate in-depth assessment of
1300 uniformity of the final “Powder Blend.” *Based on the input provided by the PQRI*, the
1301 number of sampling locations should be on the order of 20 or more. In general, for “in
1302 the mixer” sampling, the manufacturer should provided a body of evidence that
1303 justifies the amount of sample, the number of sampling locations, and the positions
1304 chosen by a manufacturer for sampling. The manufacturer’s evidence should prove
1305 that the samples sampled are indeed *representative* of the final blend. In general,
1306 increases in blend size and/or the mixer’s design complexity calls for more sampling
1307

1309 ³⁴ For example, a manufacturer has identified and appropriately controlled all of the critical physical and
1310 chemical variables for each component and established in development that the maximum difference in
1311 Assay for unbiased *representative* samples from an in-process blend occurs between the Assay found for the
1312 bulk blend and the Assay for the in-process material remaining in the mixer after it is emptied. For batches
1313 that demonstrated uniformity meeting the criteria established for that “Powder Blend,” this maximum
1314 observed difference could be, for example, 1.4 % of the label claim. Therefore, *when both Assay values are*
1315 *appropriately performed on a sufficient number of appropriately sized aliquots taken from unbiased sample*
1316 *aliquots large enough to be population representative*, the firm may be justified in setting this Assay
1317 difference as a part of its routine-production “Powder Blend” acceptance criteria provided the observed
1318 value for the Assay “Powder Blend” batch is not less than 100 % of the targeted value or, *when that is not the case*,
1319 the firm’s dosage forming procedure explicitly requires the formed weight to be adjusted “to provide not less
1320 than 100 percent of the labeled or established amount of active ingredient” (21 CFR 211.101(a)).

1322 ³⁵ For processes like the ones outlined in **Footnote 34** where the “Powder Blend” is mixed in a tote that is
1323 attached to a mixer head for blending and then detached and, after inspection, the tote containing the released
1324 final “Powder Blend” is directly transferred to the feed hopper of the dosage forming system, the firm should
1325 be able to justify relying on the computed Assay for the batch of blended powder provided: a) a valid *batch-*
1326 *representative* Assay “Powder Blend” batch value is determined from the sample aliquots tested and b) that Assay
1327 “Powder Blend” batch is not less than 100 % of the level targeted or c), *when the calculated Assay “Powder Blend”*
1328 *batch is less than 100 % of the level targeted*, the production process has explicit language to require
1329 production personnel or computerized systems to adjust the dosage unit slug or fill weight to “to provide not
1330 less than 100 percent of the labeled or established amount of active ingredient” (21 CFR 211.101(a)).
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locations when the samples are taken directly from the blender. When the firm elects to locate the completion of the final “Powder Blend” step at the “post-mixing filled intermediate blend-storage container” (IBC) point, an appropriate number of samples should be taken from *NLT* two levels (“Top” and “Bottom”) in each container when the intermediate-storage containers are about 25-kg and *NLT* three levels (Top, Middle, and Bottom) when these containers contain about 50 kg each.

Whenever an EQI is being conducted, an appropriate number of unit-dose (or smaller) aliquots should be evaluated from each sample location. This is the case because the firm needs valid estimates of the local (within-sample), global (across the sample locations) and residual error variability values in order to properly use the valid results to ascertain whether or not a batch of non-discrete material is or is not acceptably uniform with respect to its active content. Since the active content level and active content level variability found for all valid results for the sample aliquots evaluated from a given location can validly be projected to adjacent locations, in addition to the observed active content range, other indicators of built-in quality can be found in the reproducibility of: **a)** the extreme and mean values; and **b)** the locations of the sample containing the lowest content and the sample containing the highest content level. [Note: For moderately uniform blends, the range of values found in the blend is significantly larger than the within-sample location range and the location of the historical least and highest content levels tend to be reproducibly localized. For a “perfectly uniform” blend, the within-location ranges and between-location ranges are not significantly larger than the test procedure uncertainty³⁶ and the location of the least and highest levels should be approximately random.]

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

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

³⁶ Since these test procedures used have overall limiting relative accuracy of a given content value is on the order of 1% or larger, a highly uniform blend cannot be expected to exhibit a measured RSD that is significantly less than 1 % unless a large number of aliquots are prepared for each sample location.

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1382 fraction of the samples sampled even in *short-run* situations.
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2. Routine Manufacturing or Maintenance Qualification Inspection (“MQI”)

1385 In MQI, the EQI history is used to justify the use of an MQI plan which tests less than
1386 all of the samples sampled. By analyzing the EQI results’ history for not less than the
1387 previous ten (10) consecutive acceptable blends, the firm may be able to define a
1388 subset that, on average, provides the same results’ range pattern. In favorable cases,
1389 where the final blend is highly uniform, the firm may be able to justify initially testing
1390 a defined subset of the full set sampled containing as few as one-fourth of the sampled
1391 set. The reduced set may reliably describe an acceptable batch at least 90 % of the
1392 time (with full testing being required about 10 % of the time).
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1395

1396 As alluded to previously in **Footnotes 34 and 35**, *in well controlled processes*, a firm
1397 may be able to justify using a *batch-representative* Assay and Assay Range approach³⁷
1398 to justify the release of the final “Powder Blend” to the dosage-forming step provided
1399 a post-release conformity active uniformity evaluation on the formed dosage units
1400 (using the weight corrected content data for the tablet cores or capsule contents at the
1401 formed-dosage-unit stage) is used to verify the active uniformity of the final “Powder
1402 Blend” was within its acceptance envelope³⁸. When it is valid to use this approach,
1403

1405 ³⁷ When this approach is used, the Assay and Assay Range must include an evaluation of all of the components
1406 in the blend whose uniformity may affect the overall safety and efficacy of the dosage units formed from the
1407 “Powder Blend;” not just the Assay for the active or actives in the formulation. The variables whose level
1408 should be assessed in the Assay case are the same ones that should also be assessed in when the uniformity
1409 of the final blend is being determined. Those components are, in order of importance, a) stabilizers
1410 (components that stabilize the active or actives in the formulation [e.g., sodium citrate, typically, added in a
1411 “granulating” solution, used to stabilize Penicillin V Potassium]), b) components that facilitate active
1412 adsorption, c) components that regulate (accelerate or retard) the release of the active from the dosage unit
1413 (e.g., cross carmellose sodium, sodium starch glycolate, modified cellulose polymers), d) binders that
1414 increase tablet core or capsule fill cohesion, and e) lubricants that promote the flow of the final blend through
1415 the dosage forming system. Since lubricants are typically added at the end and blended for the least time, the
1416 uniformity of the lubricant directly impacts the uniformity of the final blend. For example, if a blend were
1417 perfectly uniform up to the point that the lubricants are added and the lubricant weight percentage is 2 % of
1418 the tablet weight of 5 mg in the example 250-mg tablet, the lack of uniform dispersion of the lubricant can
1419 easily result in level of lubricant that range from near zero to 20 mg (0 % to 8 % of the unit-dose’s weight).
1420 This translates into a relative active content range impact of from +2 % to – 8 % or a 10 % range. This
1421 problem is particularly severe when a non-rotating-shell blender is used and the material in the discharge
1422 port (which contains no lubricant) is not removed from the port and added back to the blend midway through
1423 the blending of the lubricants and this “discharge port recycling” is not repeated at one minute before the
1424 final blend step is completed. [**Note:** In known cases where no recycling was performed, the level of the active in
1425 discharge-port material has been found to be, on average, up to 10 % higher than it should be. This is one of the
1426 reasons that, absent continual discharge port recycling, such blenders should not be used to produce drug products.]
1427

1428 ³⁸ The downside of this approach is the problem that such a “retrospective” assessment may generate when the
1429 weight-corrected content values fail to meet the pre-established acceptance criteria for the “Powder Blend.”
1430 At a minimum, the number of *representative* dosage units evaluated will need to be appropriately increased.
1431 Worst case, the much higher “lack of quality” costs associated with rejecting a batch at the formed dosage
1432 stage may outweigh the apparent cost savings afforded by using this approach. Moreover, it is both more
1433 difficult and more costly to validly “rework” the product at the formed dosage unit stage than it is at the final
1434 blend stage.
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1435
1436 the inspection plan should include switching to a blend content-uniformity inspection
1437 plan when the requisite Assays do not meet the manufacturer’s relative mean or RSD
1438 acceptance criteria.
1439

B. “FORMED DOSAGE UNIT” INSPECTION

1440 This guidance again leaves it up to the manufacturer to justify the sampling and evaluation
1441 approach that it uses during the early stages of the development of a process. However, once a
1442 firm has established the type of dosage form, the components to be used and the general
1443 processing steps that will be used to produce the drug product, the Agency expects to see the
1444 manufacturer use *scientifically sound* and *appropriate representative-sample-based statistical*
1445 *inspection plans* in the final stages of development as well as in all pre-production-scale
1446 batches. Should a firm elect to pursue a “*process variability known*” approach, the Agency
1447 expects to see proof that the firm has determined the critical physical and chemical variable
1448 factors for each component, process step and processing choice that can affect the in-process
1449 material and drug product content uniformity and has established sufficiently stringent
1450 controls for each. With respect to the dosage units evaluated, the firm should weigh each
1451 tablet core or the contents of each capsule as a part of the evaluation process and maintain the
1452 link between that weight and the content level found in all cases.
1453
1454
1455

1456 For those firms who elect to approach the determination of the active content uniformity for
1457 each batch of the final “Powder Blend” indirectly (by determining the weight corrected
1458 content for the dosage units tested and using those values to provide assurance that the final
1459 “Powder Blend” did meet its uniformity criteria, the Agency expects to see an in-depth
1460 justification for choosing that option.
1461

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

1462 The inspection plans for EQI should include an appropriate in-depth assessment of
1463 uniformity of the dosage units. Minimally, based on either ANSI/ASQC Z1.9 or ISO
1464 3951, initial studies should evaluate no less than 200 *batch-representative* dosage
1465 units. Firms seeking not only a better understanding of the uniformity of the formed
1466 dosage units in *each batch* but also to establish a sound value for the *process*
1467 *variability* based on the evaluation of a few initial lots or batches should initially use a
1468 99 % confidence level and test not less than 330 *representative* units. When the firm is
1469 in the process of finalizing their understanding of the post-blending handling impacts
1470 on the uniformity of the dosage units, the average of the differences in an initial set of
1471 not less than three (3) production-scale *batches* when 330 *representative* dosage-units
1472 are tested from each *batch* (or not less than five (5) *batches* when 200 *representative*
1473 dosage units are tested) between the weight-corrected relative dosage-unit content
1474 variance ($RSD^2_{\text{Wt.-Cor. Dosage Unit Content}}$) and the relative blend content variance
1475 ($RSD^2_{\text{Blend Content}}$) can be used to establish the initial post-blending variance ($RSD^2_{\text{Post-}}$
1476 $RSD^2_{\text{Blend Content}}$). *Provided the dosage-unit content variances observed for each batch are*
1477 *similar* (the range of values observed should be such that the largest variance is not
1478 more than about 20 % larger than the smallest variance), the firm may be able to
1479 justify the use of an appropriate “*process variability known*” approach to batch
1480 inspection as opposed to the “*process variability unknown*” approaches that initially
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1484 require testing significantly more *representative* units (about 4 X).
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1486

1487 *When an EQI is conducted using a dynamic sampling plan*, an equal number of dosage
1488 units should be selected at each predefined sampling point (e.g., start, *i*th time point,
1489 and end). As previously discussed, that number should be some integer number of the
1490 number of dosage forming stations in the equipment used to form the dosage units.
1491 The number of units to be selected from each “added” sampling point should be
1492 determined by the cause (e.g., PQRI, power failure, mechanical breakdown) for the
1493 “added” sampling point. In general, the number of samples selected for evaluation in
1494 EQI should be *NLT 200 representative* dosage units. Therefore, the firm’s EQI plans
1495 should take a suitable random subsample from each point sample. The subsampling
1496 plan should randomly take an equal number of dosage units from each predetermined
1497 sampling point and the **same** number of dosage units from each “added” sample point
1498 provided the total sampled for evaluation is *NLT* the minimum 200 or more units
1499 required for a statistically valid *batch-representative* sample.
1500

1501 When evaluating each dosage unit, a minimum of two determinations should be made
1502 for the response generated by the sample unless the detection/quantitation system
1503 automatically averages the responses measured³⁹.
1504

1505 Thus, in addition to its initial use when the full-scale production of a drug product
1506 commences, EQI should be the initial inspection plan whenever production of a given
1507 drug product is resumed in a facility that campaigns various products or when a
1508 routine production batch does not meet its established MQI acceptance criteria. This is
1509 one reason that a manufacturer who wishes to minimize its inspection overhead is
1510 encouraged to use dedicated production facilities, *where possible*, and, *in any case*,
1511 produce drug product batches in campaigns that are as long and as steady as the firm
1512 can support.
1513

1514 For short campaigns (runs), in non-dedicated equipment, it will be harder for a firm to
1515 justify using other than an EQI plan. In such cases, a manufacturer should again do all
1516 that it can to ensure that the drug-product production process has been developed to
1517 the point that the firm has built in rigorous controls on the components’ critical
1518 physical and chemical variables, process steps, and process controls that could, if not
1519 so controlled, adversely impact the content uniformity of the in-process powder
1520 “Powder Blend” from which the dosage units are fabricated. Second, the post-
1521 blending handling and equipment loading procedures and equipment should be
1522 optimized to minimize demixing of the blend being formed into the dosage units. In
1523 addition, *to the extent possible*, the manufacturer should minimize the weight control
1524
1525

1527 ³⁹ The reason for requiring duplicate determinations is to provide for an internal check on the validity for a
1528 given response. In general, the firm should set an appropriate “value agreement” limit on the maximum
1529 allowable difference or percentage difference between the first and any subsequent measurement. In cases
1530 where the reported measurements are, in fact, the averages of multiple system assessments (e.g., a direct
1531 UV/Visible spectrophotometric measurement or an automatic averaging of multiple UV/Visible scans by a
1532 diode-array or rapid-scanning spectrophotometer) a firm may be justified in reducing the number of sample
1533 workups that are measured in duplicate to some percentage of the determinations made in order to establish
1534 valid estimates of the measurement uncertainty.
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1535
1536 range for the tablet cores and capsule fills. *Unless the firm develops its production*
1537 *process to the level that its “built in” quality controls ensure that a reduced number of*
1538 *dosage-unit determinations are reliably representative of the batch,* a firm may have
1539 difficulty justifying testing less than 200 or more *representative* dosage units in “*short*
1540 *run*” situations. *After sufficient history is accumulated in such cases,* a firm may be
1541 able, *for a well-controlled process,* to justify routinely testing a reduced number of
1542 *representative* dosage units even in *short-run* situations.
1543

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

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1545
1546 In MQI, the EQI history is used to justify the use of an MQI plan that tests less than
1547 the full number of dosage units required by the firm’s CGMP-compliant EQI plan for
1548 evaluating the samples. By analyzing the EQI results’ history for not less than the
1549 previous ten (10) consecutive acceptable blends, the firm may be able to justify using
1550 either a suitable ANSI-based “*process variability unknown*” *reduced-inspection* plan
1551 or, *provided the batch variabilities observed are sufficient close to each other,*
1552 switching to a suitable “*process variability known*” *normal-inspection* plan. In such
1553 cases, the justifiable number of samples should be between one-fourth and one-half of
1554 the number required for by the firm’s EQI plan.
1555

1556 However, *even when the physical and chemical characteristics of the components are*
1557 *tightly controlled,* the limiting ranges for some of the key physical characteristics are
1558 still wide enough that the characteristics of each lot of component do affect the active
1559 uniformity of the batch to some degree. Because this is the case, a firm would be hard
1560 pressed to justify a further reduction of the number evaluated from the number in the
1561 “*process variability known*” *normal-inspection* plan to a lesser number. In cases
1562 where the active content results are used for confirmation of the adequacy of the
1563 active uniformity of the final blend as well as for determining that the dosage units are
1564 acceptably uniform, a firm should not even attempt to justify any further number
1565 reduction and, *even when a “process variability known” normal-inspection plan can*
1566 *be justified,* should, in most cases, use a suitable “*normal inspection*” plan that
1567 evaluates between one-third and one-half the number of dosage units that the firm’s
1568 CGMP-compliant “*process variability unknown*” *normal-inspection* plan requires. In
1569 cases, where the uniformity of the final blend is determined directly and the
1570 accumulated history (for more than the last 10 batches evaluated) indicates that the
1571 final blend samples and dosage units tested are acceptable, highly uniform, and
1572 strongly correlated, the firm may be able, for the “*process variability known*” case to
1573 justify starting with a “*process variability known*” *reduced-inspection* plan provided
1574 that plan tests at least one-fourth of the number of samples required for the firm’s
1575 justified “*process variability known*” *normal-inspection* plan. This reduced set can be
1576 expected to reliably describe an acceptable batch at least 90 % of the time (with full
1577 testing being required about 10 % of the time).
1578

1579 Thus, a firm’s overall dosage-unit inspection plan should be hierarchical in nature and
1580 consist of the appropriate set of stages and stage controls for evaluating the batch and
1581 switching among the sample numbers required based on the outcomes observed.
1582 Based on the production history, the starting point should be the smallest justifiable set
1583 (governed by the historical outcomes observed and controlled by the outcomes [blend

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1584 and dosage unit] observed for the previous batch). In cases where the previous batch
1585 was found to be unacceptable at the formed-dosage-unit stage, the starting point should
1586 be either: **a)** the firm’s “*process variability unknown*” normal-inspection plan when the
1587 investigation finds a proven operator error or mechanical failure as the root cause of
1588 the non-acceptability of the batch tested, **or b)** the manufacturer’s *scientifically sound*
1589 *process-capability-based* inspection plan whenever the firm’s investigation does not
1590 definitively find and correct the root cause of the non-acceptability observed.
1591
1592

1593 **C. “FINISHED DOSAGE UNIT” INSPECTION**

1594

1595 Here, this guidance suggests that the initial inspection plans suitable for use at the “Finished
1596 Dosage Unit” stage should test the same number of *batch-representative* units as that required
1597 for the “Formed Dosage Unit” stage. In general, the sampling approach should be simple
1598 random sampling and, while recommended, there is no requirement for weighing each tablet
1599 or the contents of each capsule before the unit is tested for content uniformity. In many cases,
1600 *after some justified number of initial production-scale batches*, the firm may be justified in
1601 switching to a plan that initially omits the active content uniformity testing of the “Finished
1602 Dosage” units provided:

- 1603 • A suitable content uniformity evaluation is conducted whenever the uniformity of the
1604 content at the “Formed Dosage Unit” stage, while acceptable, is outside of its established
1605 expectations.
1606
- 1607 • A PQIT test is used to periodically confirm the agreement between the uniformity at the
1608 “Formed Dosage Unit” stage and that at the “Finished Dosage Unit” stage.
1609
- 1610 • The manufacturer’s quality plan includes the appropriate CGMP-compliant, statistically
1611 sound and appropriate evaluation of the “Dissolution” or “Drug release” variable and,
1612 where required, “Impurity level” that tests a scientifically sound number of units that is
1613 sufficient to establish the acceptability of each *batch* at a level of confidence that is 95 %
1614 or higher.
1615
- 1616 • A set of *batch-representative* Assay⁴⁰ results on the dosage units finds the mean Assay
1617 is not less than 100 % of the label claim in the case of a stable active or not less than 100
1618 % of the filed target level when a small percentage of degradation is permitted.
1619

1620 However, the Agency expects to see the manufacturer use *scientifically sound* and *appropriate*
1621 *representative-sample-based statistical inspection plans* in the final stages of development as
1622 well as in all pre-production-scale batches. The Agency has this expectation because the firm
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1627 ⁴⁰ Provided the analysis procedures used do not introduce a significant content accuracy bias, the average of the
1628 content uniformity results found at the “Formed Dosage Unit” stage can be used as one estimate of the
1629 “Assay” of the batch. In general, at least one or, preferably, two “Assay” evaluations should be conducted at
1630 the “Finished Dosage Unit” stage on a *batch-representative* number of units of sufficient size (number [not
1631 the USP’s any 20; nominally, 50 to 200 or more *representative* units]) to ensure that the “Assay” results
1632 obtained are *batch-representative*. In cases where a suitable content uniformity assessment is made at the
1633 “Finished Dosage Unit” stage, the mean of the content values found may be used in lieu of one “Assay”
1634 evaluation provided the analysis procedures used do not introduce a significant content accuracy bias. To
1635 satisfy 21 CFR 211.101(a), the *average* of all of such “Assay” results on the formed units must have a value
1636 that is not less than 100 % of the label claim or targeted level.
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1638 should provide proof that the active content uniformity established at the “Formed Dosage
1639 Unit” stage is the same at the uniformity for the active at the “Finished Dosage Unit” stage.
1640

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

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1642 The inspection plans for EQI should include an appropriate in-depth assessment of
1643 active uniformity of the dosage units. In general, the plans should be the same as those
1644 used for the “Formed Dosage Unit” case (see VII.B.1).
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2. Routine Manufacturing or Maintenance Qualification Inspection (“MQI”)

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1649 In MQI, the EQI and MQI histories contained in the “Formed Dosage Unit” data sets
1650 coupled with the EQI history for the “Finished Dosage Unit” evaluations should be
1651 used to establish and justify the MQI plan that the manufacturer sets up. *In cases*
1652 *where the active content uniformity has been proven to be fixed at the dosage forming*
1653 *stage*, the firm could simply treat the “MQI” content uniformity test for the “Finished
1654 Dosage Unit” stage as a PQIT whose evaluation frequency should be controlled by, in
1655 order of importance, the:
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- 1658 ▪ Acceptability of the previous batch manufactured
- 1659 ▪ Number of previous acceptable batches in the current campaign
- 1660 ▪ Length of the production history for the drug product (appropriately increase the
1661 separation interval as the unbroken number of accepted batches increases).
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1663 The switching rules in ANSI/ASQC Z1.9 may be used to justify the firm’s decision
1664 tree for switching among the manufacturer’s inspection plans (“normal inspection,”
1665 “reduced inspection” and “PQIT inspection”) for active uniformity assessment.
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1669 Section D which follows presents one fairly detailed example of an integrated
1670 Inspection Plan for a hypothetical drug product and process that addresses the
1671 inspection of that process’ final blend and formed dosage units for a single active.
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D. AN “EXAMPLE” IN-PROCESS INSPECTION PLAN

1. BACKGROUND, BASIS SCENARIO, AND AN IN-PROCESS INSPECTION OF A HYPOTHETICAL DRUG PRODUCT

Background

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1676 To address the clear CGMP requirement *minimums* for the assessment of the
1677 uniformity of the active or actives in the final blend and the dosage units formed
1678 therefrom, this reviewer offers the following scenario. [Note: The plans proposed here do
1679 not explicitly address the generally inapplicable “process variability known” situation because
1680 most firms either do not control or do not adequately control all of the critical physical and/or
1681 chemical properties of all of the components they use in the manufacture of drug products that
1682 they currently produce.]
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Basis Scenario

Before any comprehensive inspection plan can be proposed, the manufacturing scenario must be clearly delineated because the appropriateness of the inspection plan proposed depends upon the manufacturing scenario under which the drug product is produced.

This guidance uses the following “Example Inspection Plan” for active uniformity in the “final blend” and the “formed dosage units” (both capsules and tablets) to illustrate a comprehensive approach to the inspection of such materials:

Hypothetical In-Process Inspection Plan For A Drug Product

XYZ Pharmaceutical is in the process of starting up a **dedicated** manufacturing unit for the continual production of 2-million-dosage-unit batches of a new fast-tracked drug product, YZWU, which contains a single active, Zwut, which is produced in both tablet and capsule form from the same blends.

The process development has proceeded to the point that one (1) scale up batch, one near-full-scale demonstration conformance batch, and three (3) initial full-scale process “evaluation qualification” (EQ) conformance batches have been intensively studied and found to be acceptable and easily meet the *scientifically sound* and *appropriate statistics-based sample specifications* and *batch acceptance criteria* established by the manufacturer, and the firm has produced an additional seven (7) production-scale batches to build inventory.

Based on the body of knowledge accumulated, the validity of the batch sampling plans and sample-testing procedures have been established in development and their validity has been confirmed by the results found for the initial process conformance batches.

Using those findings, the basis decision variables for active uniformity were defined as follows:

- ❖ Campaign Manufacture Interruption Switch (“CMI”) variable was set to “zero” because there had not yet been any manufacturing interruption or campaign termination. [Decision Points: If CMI = 0, take no action. If CMI = 1, set all switches as follows: (CAB = 0, IBS= “value at last batch produced,” IDUS = “value at last batch produced,” NAB = “value at last batch produced.”]
- ❖ Consecutively Acceptable Batches (“CAB”) variable was set to “10” initially for the ten (10) successful “EQ” conformance and inventory building batches – the Non-Acceptable Batches (“NAB”) variable was set to “zero.” [Decision Points: If NAB > 3, STOP manufacture. If CAB < 5, make no decision; when CAB = 5, check to see if a reduction in inspection is supportable. When CAB = 30, consider switch to a “process variability known” (“PVK”) plan.]
- ❖ Blend Inspection Level (“IBS”) set to “1” (reduced set) because the data from full-set sampling on all previous batches established that XYZ’s reduced sampling plan adequately characterized the final blends.

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- ❖ Dosage-Unit Inspection Level (“IDUS”) was set to “2” (normal inspection) since an insufficient body of knowledge had been accumulated to reduce the level of inspection (“IDUS” = 1) and no need had been found to switch to the distribution acceptance set (“IDUS” = 3).
- ❖ Blend Uniformity Exception (“IBUE”) was set to “0” (all previous had met expectations). [Decision Points: “IBUE” > 3, “increase” IDUS; otherwise leave where it is – IDUS reduced one level when NAB =0 and CAB 5 or more.]
- ❖ Drug-Unit Exception (“IDUE”) was set to “0” (all previous had met expectations). [Decision Points: “IDUE” >3, “increase” IDUS if less than 3; otherwise leave alone – if IDUS >1 reduced each time NAB =0 and CAB found to be 5 or more.]

2. THE IN-PROCESS INSPECTION PLAN

a. Inspection of Final Blends for Active Uniformity (Follow “IBS”)

1. Sample, collect, transport, and control the *full batch-representative* set (*established in process development and scale up, and confirmed in at least one near-full-scale conformance batch produced in the “same” [blender configuration and mixer manufacturer’s model] blender as will be used in routine production*) of samples using your established batch-spanning plan that has been proven to collect non-biased samples (each consisting of more than enough material in amount for all possible evaluations for all critical variable factors that must be evaluated for uniformity) in a manner that preserves the link between the sample and the location from which it was sampled. PROCEED as directed by your current value for “IBS.”
2. **BLEND SAGE 1** (“IBS = 1”): Select the *minimum batch-representative* subset set (*established based on your analysis of the outcomes from your scale up conformance batches and near-full-scale batches*) and, *using aliquot-removal techniques that have been proven to be capable of sampling unbiased aliquots from your samples*, remove, transfer, weigh, prepare, and test the appropriate number of aliquots from each sample in the sub set in a manner that preserves the link between the location, weight, aliquot ID, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 3**. [Note: In general, not less than 30 % of the samples should be evaluated in duplicate.]
3. **BLEND EVALUATION 1: EVALUATE** valid results found and PROCEED as follows:
 - a. IF any result is less than 75.0 % or more than 125. % of the targeted level for that blend (“75.0 to 125.”), **REJECT** Final Blend, SET “CAB” to “0” (zero), INCREMENT “NAB” and “IBUE,” NOTIFY your quality unit, AND PROCEED to **Step b**; ELSE GO to **Step d**.
 - b. SET “IBS” to “2” AND PROCEED to **Step c**.

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- c. IF “NAB” is greater than 2, SET “CAB” = “0” and “NAB” = “0” AND **STOP** manufacturing Blends until notified to restart production. ELSE sample and test the next Final Blend (“A”).
 - d. IF the Mean found is within 1 % of the Targeted Mean, PROCEED to **Step e**; ELSE GO to **BLEND STAGE 2 (Step 4)**.
 - e. IF one (for tablet products) is, or two (for capsule products) are, outside of the range from 87.0 % to 113. % of the targeted level for the Blend, *WHEN* “NAB” > 0 AND “IBS” = “1”, SET “IBS” to “2” and “IBUE” to “0”, AND PROCEED to **BLEND STAGE 2 (Step 4)**. ELSE GO to **Step f**.
 - f. IF all results are inside of the range from “87.0 to 113. %” of the target BUT not inside of the range from “90.0 % to 110. %” of the target, EITHER, *WHEN* “NAB” = “0” (zero), INCREMENT “IBUE” (Blend Uniformity Exception) twice, INCREMENT “CAB,” **ACCEPT** the blend for further processing, AND GO to **Step i**, OR, *WHEN* NAB > “0” (zero), SET “IBS” to 2 AND GO to **BLEND STAGE 2 (Step 4)**. ELSE GO to **Step g**.
 - g. IF all of the results are inside of the range from “90.0 to 110. %” of the target BUT not appropriately inside of the range from “95.0% to 105. %” of the target, EITHER, *WHEN* “NAB” = “0” (zero), INCREMENT “IBUE” and “CAB” once, **ACCEPT** the blend for further processing, AND GO to **Step i**, OR, *WHEN* NAB > “0” (zero), SET “IBS” to 2, AND PROCEED to **BLEND STAGE 2 (Step 4)**. ELSE GO to **Step h**
 - h. IF all of the results are *appropriately* inside of the range from “95.0 to 105. %” of the target, INCREMENT “CAB,” AND **ACCEPT** the blend for further processing. PROCEED to **Step i**.
 - i. IF “IBUE” > “3,” UNLESS “IDUS” = “3”, INCREMENT “IDUS,” SET “IBUE” to “0” (zero), AND GO to **Step j**. ELSE just GO to **Step j**.
 - j. IF “CAB” ≥ “5,” SET “NAB” to “0” (zero), PROCEED to sample and test the next Final Blend (“a. Step 1”). ELSE just GO to “a. Step 1”
4. **BLEND STAGE 2 (“IBS” = 2):** *For the samples not previously sampled*, using aliquot-removal techniques that have been proven to be capable of sampling unbiased aliquots from your samples, remove, transfer, weigh, prepare, and test duplicate aliquots from each sample in the sub set in a manner that preserves the link between the location, weight, aliquot ID, and valid results found for the active(s). *For the previously tested samples*, collect a single additional aliquot from each of these both to obtain within-location estimates of active level where the previous location samples were only sampled and evaluated in singlicate and, where the location samples were previously evaluated in duplicate, provide some estimate of the bias, if any, between the test sets (the original and the current one). Conduct this Step in the same manner as discussed for **BLEND STAGE 1**. PROCEED to **Step 5**.

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5. BLEND EVALUATION 2: EVALUATE valid results and PROCEED as follows:

- a. IF any result is less than 75.0 % or more than 125. % of the targeted level for that blend OR the mean observed is not within 1 % of the targeted mean, REJECT the blend, SET “CAB” = 0, INCREMENT “NAB” once and “IBUE” 3 times, NOTIFY your quality unit, AND GO to **Step b.** ELSE GO to **Step c.**
- b. IF “NAB” is greater than 2, SET “CAB” = “0” and “NAB” = “0” AND STOP manufacturing Blends until notified to restart production. ELSE sample and test the next Final Blend (“A”).
- c. IF none are less than 80.0 % of the target, BUT more than 1 (for tablet products) result is, or more than 2 (for capsules), results are outside of the range from 85.0 % to 115. % of the targeted level for the Final Blend, REJECT the Blend, NOTIFY your quality unit, AND GO to **Step b.** ELSE GO to **Step d.**
- d. IF all results are in the range from “85.0 to 115. %” of the target, BUT 2 (for tablet products) [or 3 (for capsule products)] are outside of the range from “87.0 % to 113. %” of the target, INCREMENT “IBUE” twice, INCREMENT “CAB,” ACCEPT the blend for further processing, AND PROCEED to **Step g.** ELSE GO to **Step e.**
- e. IF all results are inside of the range from “87.0 to 113. %” of the target BUT not inside of the range from “92.0 % to 108. %” of the target, THEN, INCREMENT “CAB” and “IBUE” once, ACCEPT the blend for further processing, AND GO to **Step g;** ELSE PROCEED to **Step f.**
- f. IF all of the results are inside of the range from “92.0 to 108. %” of the target, INCREMENT “CAB,” ACCEPT the blend for further processing, AND GO to **Step g.**
- g. IF “IBUE” > “3,” UNLESS “IDUS” = “3,” INCREMENT “IDUS,” SET “IBUE” to “0” (zero), AND GO to **Step h.** ELSE GO to **Step h.**
- h. IF “NAB = 0, “CAB” ≥ 5, “IBUE” = 0 and “IBS” = 2, SET “IBS” to “1,” AND GO to **Step i.** ELSE, just GO to **Step i.**
- i. IF “CAB” ≥ “5,” SET “NAB” to “0” (zero), AND PROCEED to sample and test next Final Blend (“a. **Step 1.**”). ELSE just GO to “a. **Step 1.**”

b. Inspection of Dosage Units for Active Uniformity

(Follow “IDUS”)

1. Sample, collect, transport, and control the *full batch-representative* set (*established in process development and scale up, and confirmed in at least one near-full-scale conformance batch produced in the “same” [equipment operating conditions and configuration, and manufacturer] dosage-forming equipment as will be used in routine production*) of samples using your established batch-spanning plan that has been proven to collect non-biased *sampling-point-representative samples* (each consisting of some integer multiple of the number of dosage-forming stations in the equipment being used [to ensure each sample is

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representative of the “local” production environment at the time of the sampling]) at each sampling point subject to the constraint that the total number collected is batch-representative and more than enough dosage units in number for all possible evaluations for all critical variable factors that must be evaluated for uniformity) in a manner that preserves the link between the sample and the sampling point from which it was sampled. THEN, *based on the Dosage Unit Stage established when the final blend was accepted*, PROCEED to the Appropriate DOSAGE UNIT STAGE (controlled by current “IDUS” value).

2. **DOSAGE-UNIT STAGE 1** (“IDUS = 1): For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, SELECT ***not less than 50 dosage units at random*** from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each “routine” sampling point. The sample collection should be done in a manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit “ID,” acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 3**. [Note: In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such “test-equipment averaged” cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.]
3. **DOSAGE UNIT EVALUATION 1: EVALUATE valid results found and proceed as follows:**
 - a. **IF** any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units (“75.0 to 125. %”), **REJECT** the dosage unit batch, **SET** “CAB” to “0,” **INCREMENT** “NAB” once and “IDUE” 3 times, **NOTIFY** your quality unit AND **GO** to **Step b**. **ELSE** GO to **Step c**.
 - b. **IF** “NAB” is greater than 2, **STOP** manufacturing dosage-form batches until notified to restart production. **ELSE** sample and test the next Final Blend (“a. Step 1”).
 - c. **IF** the Mean found is within 1 % of the Targeted Mean, **PROCEED** to **Step d**; **ELSE**, **GO** to **DOSAGE-UNIT STAGE 2 (Step 4)**
 - d. **IF** all are inside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, **GO** to **Step h**.
 - e. **IF** 1 or 2 (for tablets) is/are, or 2 to 6 (for capsules) are, outside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, **EITHER**, **WHEN** “NAB” = “0” (zero), **PROCEED** to **DOSAGE-UNIT STAGE 2 (Step 4)** **OR**, **WHEN** NAB > “0” (zero), **REFER** the batch to your quality unit for their decision [NOTE: IF ACCEPT, SET “IDUS” to “2” AND GO to **DOSAGE-UNIT STAGE 2**

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- 1932 (Step 4). IF REJECT, SET “CAB” to “0,” INCREMENT “NAB,” AND GO
1933 to Step b.] ELSE, GO to Step f.
- 1934 f. IF 3 to 6 (for tablets) are, or 7 to 12 (for capsules) are, outside of the
1935 range from 85.0 % to 115. % of the targeted level for the formed
1936 dosage units, EITHER, WHEN ‘NAB’ = “0” (zero), PROCEED to
1937 DOSAGE-UNIT STAGE 3 (Step 6) OR, WHEN NAB > “0” (zero),
1938 REFER the batch to your quality unit for their decision [NOTE: IF
1939 ACCEPT, SET “IDUS” to “3” AND GO to DOSAGE-UNIT STAGE 3
1940 (Step 6). IF REJECT, SET “CAB” to “0,” INCREMENT “NAB,” AND GO
1941 to Step b.]
1942 ELSE, GO to Step g.
- 1943 g. IF “NAB” > 2, STOP manufacturing dosage-form batches until
1944 notified to restart production, AND SET “IDUE” = “0.” ELSE,
1945 INSPECT next “Dosage Units” Batch [“b. Step 1.”]).
- 1946 h. IF all of the results are inside of the range from “95.0 to 105.” of the
1947 target, GO to Step l. ELSE, GO to Step i.
- 1948 i. IF all of the results are inside of the range from “92.0 to 108.” of the
1949 target, GO to Step k. ELSE, GO to Step j.
- 1950 j. EVALUATE results using your proven AQL (% Nonconforming),
1951 your ISO/ANSI reduced-inspection “process variability unknown—
1952 SD” plan,
1953 AND ACCEPT the batch when the data meets the ISO/ANSI
1954 acceptance criteria, INCREMENT “CAB” once and “IDUE” twice,
1955 AND GO to Step m.
1956 OR, WHEN data does NOT MEET ISO/ANSI criteria, DO NOT
1957 INCREMENT any counters AND
1958 PROCEED to DOSAGE STAGE 2 (Step 4) when not more than 1
1959 (for tablets) or 2 (for capsules) is outside of “90.0 % to 110. % of
1960 target
1961 OR, when not more than 4 (for tablets) or 6 (for capsules) are
1962 outside of “92.0 to 108. %” of the target, PROCEED to
1963 DOSAGE-UNIT STAGE 3 (Step 6).
1964 OR ELSE INCREMENT “NAB” AND, GO to Step g.
- 1965 k. EVALUATE the results using your proven AQL (% Nonconforming),
1966 your ISO/ANSI reduced-inspection “process variability unknown—
1967 SD” plan, AND EITHER ACCEPT the batch when the data meets the
1968 ISO/ANSI acceptance criteria, INCREMENT “CAB” and “IDUE,”
1969 AND GO to Step m.
1970 OR, WHEN data does NOT MEET ISO/ANSI criteria, DO NOT
1971 INCREMENT any counters AND:
1972 IF “NAB” = “0” (zero), PROCEED to DOSAGE STAGE 2 (Step
1973 4), OR,
1974 IF “NAB” > 0, PROCEED to DOSAGE STAGE 3 (Step 6).
- 1975 l. EVALUATE the results using your proven AQL (% Nonconforming)
1976 and your ISO/ANSI reduced-inspection “process variability
1977 unknown—SD” plan, ACCEPT the batch when the data meets the
1978 ISO/ANSI acceptance criteria, INCREMENT “CAB” AND GO to
1979 Step m.

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OR, WHEN data does not meet criteria, PROCEED to **DOSAGE STAGE 2 (Step 4)**.

- m. IF “IDUE” > “3,” UNLESS “IDUS” > “2,” INCREMENT “IDUS,” SET “IDUE” to “0” (zero), AND GO to **Step n**. ELSE GO to **Step n**.
- n. IF “NAB” = 0, “CAB” ≥ 5, “IBUE” = 0 and “IDUS” = 2, SET “IDUS” to “1,” AND GO to **Step o**. ELSE, just GO to **Step o**.
- o. IF “CAB” ≥ “5,” SET “NAB” to “0” (zero), AND PROCEED to sample and test next dosage-unit batch (“**b. Step 1**”). ELSE GO to “**b. Step 1**.”
4. **DOSAGE-UNIT STAGE 2** (“IDUS” = 2): For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, **SELECT not less than “200”^{E1} dosage units at random**

^{E1} In cases where 50 representative units have already been evaluated, you need only select an additional 150 batch-representative dosage-unit samples.

from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each “routine” sampling point. The sample collection should be done in a manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit “ID,” acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. **PROCEED to Step 5.** [Note: In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such “test-equipment averaged” cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.]

5. **DOSAGE-UNIT EVALUATION 2:** EVALUATE the valid results found and proceed as follows:
- a. IF any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units, REJECT the dosage-unit batch, SET CAB to “0,” INCREMENT “NAB” once and “IDUE” 3 times, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step c**.
- b. IF “NAB” is greater than 2, **STOP** manufacturing Blends until notified to restart production; ELSE sample and test the next batch of dosage units (“**b. Step 1**”).
- c. IF the Mean found is within 0.5 % of the Targeted Mean, PROCEED to **Step d**; ELSE, GO to **DOSAGE-UNIT STAGE 3**.
- d. IF all are inside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, GO to **Step h**.
- e. IF 1 or 2 (for tablets) is/are, or 2 to 6 (for capsules) are, outside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, EITHER, WHEN “NAB” = “0” (zero), GO to **Step h**, OR, WHEN NAB > “0” (zero), REFER the batch to your quality unit

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- 2031 for their decision [**NOTE:** IF ACCEPT, SET “IDUS” to “2” AND GO to
2032 **Step h**). IF REJECT, SET “CAB” to “0,” INCREMENT “NAB,” AND GO
2033 to **Step b**.] ELSE, GO to **Step f**.
- 2034 f. IF 3 to 6 (for tablets) are, or 7 to 12 (for capsules) are, outside of the
2035 range from 85.0 % to 115. % of the targeted level for the formed
2036 dosage units, EITHER, WHEN “NAB” = “0” (zero), PROCEED to
2037 **DOSAGE-UNIT STAGE 3 (Step 6)** OR, WHEN NAB > “0” (zero),
2038 REFER the batch to your quality unit for their decision [**NOTE:** IF
2039 ACCEPT, SET “IDUS” to “3” AND GO to **DOSAGE-UNIT STAGE 3**
2040 **(Step 6)**. IF REJECT, SET “CAB” to “0,” INCREMENT “NAB,” AND GO
2041 to **Step b**.]
2042 ELSE, GO to **Step g**.
- 2043 g. IF “NAB” > 2, STOP manufacturing dosage-form batches until
2044 notified to restart production, AND SET “IDUE” = “0.” ELSE,
2045 INSPECT next “Dosage Units” Batch [**“b. Step 1.”**]).
- 2046 h. IF all of the results are inside of the range from “95.0 to 105.” of the
2047 target, GO to **Step i**. ELSE, GO to **Step i**.
- 2048 i. IF all of the results are inside of the range from “92.0 to 108.” of the
2049 target, GO to **Step k**. ELSE, GO to **Step j**.
- 2050 j. EVALUATE results using your proven AQL (% Nonconforming),
2051 your ISO/ANSI *reduced-inspection* “process variability unknown—
2052 SD” plan,
2053 AND ACCEPT the batch when the data meets the ISO/ANSI
2054 acceptance criteria, INCREMENT “CAB” once and “IDUE” twice,
2055 AND GO to **Step m**.
2056 OR, WHEN data does NOT MEET ISO/ANSI criteria, DO NOT
2057 INCREMENT any counters AND
2058 PROCEED to **DOSAGE STAGE 3 (Step 6)** *when not more than 6*
2059 *(for tablets) or 12 (for capsules) is outside of “90.0 % to 110. % of*
2060 *target*
2061 OR, *when not more than 4 (for tablets) or 6 (for capsules) are*
2062 *outside of “92.0 to 108. %” of the target*, PROCEED to
2063 **DOSAGE-UNIT STAGE 3 (Step 6)**.
2064 OR ELSE INCREMENT “NAB” AND, GO to **Step g**.
- 2065 k. EVALUATE the results using your proven AQL (% Nonconforming),
2066 your ISO/ANSI *reduced-inspection* “process variability unknown—
2067 SD” plan, AND EITHER ACCEPT the batch when the data meets the
2068 ISO/ANSI acceptance criteria, INCREMENT “CAB” and “IDUE,”
2069 AND GO to **Step m**.
2070 OR, WHEN data does NOT MEET ISO/ANSI criteria, DO NOT
2071 INCREMENT any counters, AND PROCEED to **DOSAGE STAGE 3**
2072 **(Step 6)**.
- 2073 l. EVALUATE the results using your proven AQL (% Nonconforming)
2074 and your ISO/ANSI *reduced-inspection* “process variability
2075 unknown—SD” plan, ACCEPT the batch when the data meets the
2076 ISO/ANSI acceptance criteria, INCREMENT “CAB” AND GO to
2077 **Step m**.

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OR, WHEN data does not meet criteria, PROCEED to **DOSAGE STAGE 3 (Step 6)**.

- m. IF “IDUE” > “3,” UNLESS “IDUS” > “2”, INCREMENT “IDUS,” SET “IDUE” to “0” (zero), AND GO to **Step n**. ELSE GO to **Step n**.
- n. IF “NAB =0, “CAB” ≥ 5, “IBUE” = 0 and “IDUS” = 2, SET “IDUS” to “1,” AND GO to **Step o**. ELSE, just GO to **Step o**.
- o. IF “CAB” ≥ “5,” SET “NAB” to “0” (zero), AND PROCEED to sample and test next dosage-unit batch (“**b. Step 1**”). ELSE GO to “**b. Step 1**.”

6. **DOSAGE-UNIT STAGE 3 (“IDUS” = 3):** For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, **SELECT not less than “400”^{E2} dosage units at random** from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each “routine” sampling point. The sample collection should be done in a

^{E2} In cases where 200 representative units have already been evaluated, you need only select an additional 200 batch-representative dosage-unit samples.

manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit “ID,” acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 7**. [**Note:** In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such “test-equipment averaged” cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.]

7. **DOSAGE-UNIT EVALUATION 3:** EVALUATE the valid results found and proceed as follows:
- a. IF any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units (“75.0 to 125. %”) OR more than 12 (for tablets) or 21 (for capsules) are outside of the range from “85.0 to 115. %” of the target, REJECT the dosage unit batch, SET CAB to “0,” INCREMENT “NAB” once and “IDUE” 3 times, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step c**.
 - b. IF “NAB” is greater than 2, STOP manufacturing Blends until notified to restart production; ELSE sample and test the next batch of dosage units (“**b. Step 1**.”).
 - c. IF the Mean found is within 0.3 % of the Targeted Mean, PROCEED to **Step d**; ELSE, REFER the formed dosage-units batch to your quality unit.
 - d. IF all are inside of the range from 95.0 % to 105. % of the target, GO to **Step k**. ELSE, GO to **Step e**.

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- e. IF all are inside of the range from 92.0 % to 108. % of the target, GO to **Step j**. ELSE, GO to **Step f**.
- f. IF all are inside of the range from 85.0 % to 115. % of the target, GO to **Step i**. ELSE, GO to **Step g**.
- g. EVALUATE the results using the criterion:
{The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is ≥ 1.5 ,
AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT “CAB,” AND GO to **Step l**.
OR, *WHEN* the data does not meet this criterion,
EITHER REJECT the dosage-units batch, SET “CAB” = “0,” INCREMENT “NAB” once AND “IDUE” twice, START an investigation AND PROCEED to **Step h**.
OR REFER the batch to your quality unit for handling. [Note: Your choice here should be based on the previous history (“NAB”) for the formed dosage units of this drug product.]
- h. IF “NAB” > 2, STOP manufacturing dosage-form batches until notified to restart production, AND SET “IDUE” = “0.” ELSE, INSPECT next “Dosage Units” Batch [**“b. Step 1”**].
- i. EVALUATE the results using the criterion:
{The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is ≥ 1.5 },
AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT “CAB,” AND GO to **Step l**.
OR, *WHEN* the data does not meet this criterion,
EITHER REJECT the dosage-units batch, SET “CAB” = “0,” INCREMENT “NAB” once AND “IDUE” twice, START an investigation AND PROCEED to **Step h**.
OR REFER the batch to your quality unit for handling. [Note: Your choice here should be based on the previous history (“NAB”) for the formed dosage units of this drug product.]
- j. EVALUATE the results using the criterion:
{The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is ≥ 1.8 },
AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT “CAB,” AND GO to **Step l**.
OR, *WHEN* it does not, EVALUATE using the previous criterion:
{The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is ≥ 1.5 },
AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT “CAB” and “IDUE,” AND, GO to **Step l**.
OR, *WHEN* it dose not meet this relaxed criterion, REFER the batch to your quality unit for exception handling.
- k. EVALUATE the results using the criterion:

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2176 {The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is
2177 ≥ 2.0 },
2178 AND ACCEPT the batch as having an acceptable active uniformity
2179 when the data meets that criterion, INCREMENT “CAB,” AND GO to
2180 Step 1.
2181 OR, WHEN it does not, EVALUATE using the previous criterion:
2182 {The lesser of $|115. - \bar{x}|$ or $|\bar{x} - 85.0|$ } divided by $(3.27 \times \text{RSD}_{n=400})$ is
2183 ≥ 1.8 },
2184 AND ACCEPT the batch as having an acceptable active uniformity
2185 when the data meets that criterion, INCREMENT “CAB” and “IDUE,”
2186 AND, GO to Step 1.
2187 OR, *WHEN it dose not meet this relaxed criterion*, REFER the batch to
2188 your quality unit for exception handling.
2189 **l.** IF “NAB” = 0, “CAB” ≥ 5 , “IDUE” = 0 and “IDUS” = 3, SET “IDUS”
2190 to “2,” AND GO to Step m. ELSE, just GO to Step m.
2191 **m.** IF “CAB” ≥ 5 ,” SET “NAB” to “0” (zero), AND PROCEED to
2192 sample and test next dosage-unit batch (“**b. Step 1.**”). ELSE GO to “**b.**
2193 Step 1.”
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3. IMPORTANT NOTES

2195 **A.** The dosage-unit inspection plans proposed are based on those applicable
2196 consensus (ISO, ANSI) standard’s “process variability unknown—standard
2197 deviation” plans for Stage I and Stage 2 and a distribution statistics
2198 “capability” criterion for the Stage 3. The consensus standard’s “process
2199 variability unknown” plans must be used until:
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2201 **1.** The drug product’s history encompasses a sufficient number (typically, not
2202 less than 15+) of consecutive acceptable batches indicates that the process
2203 is capable of operating in control for significant periods of time and, if any,
2204 the root causes of any non-complying batches have been conclusively
2205 identified,
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2207 **2.** The observed mean and variability for the accepted batches both fall in a
2208 narrow range, and
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2210 **3.** The controls on the acceptance of all components
2211 **Fully comply with all** the applicable **CGMP** requirement *minimums*.
2212 **Have been proven to include sufficiently rigorously controls on all**
2213 critical physical and chemical characteristics for all components.
2214 **Historically indicate that**, *when any non-conformance of an in-process*
2215 *material has been traced to or implicated the controls on a component*, the
2216 **controls** on that component **have been appropriately strengthened**.
2217 **Retrospective treatment of the results data using** the current apparent
2218 **RSD_{Process}** for all batches, *including those that were not released*, as an
2219 approximation for the process variability σ_{Process} and the *applicable* ISO or
2220 ANSI consensus **standard’s “process variability known” plans does**
2221 **NOT change the release status of any released or rejected batch**.
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4. Production is at a steady rate, the production campaigns routinely exceed 50 batches, and there have been no batch rejections in the previous campaign per campaign

- B.** When all of the preceding condition have been met, you may consider for the dosage units augmenting your inspection plan to include the appropriate “process variability known” ISO or ANSI consensus standards’ “REDUCED” (“**Stage A**”) and “NORMAL” (**Stage B**) inspection plans in front of your “Stage 1” plan and modify in the “Blend Outcomes” rules to include a set of criteria that will permit the selection of “**Stage A**” or “**Stage B**” as the starting point for the assessment of the uniformity of the active in the dosage units. Of course, you would need a more complex set of “switching” control rules to manage what would now be a “5-Stage” Inspection plan for the Dosage Units (**Stage A, Stage B, Stage 1, Stage 2, and Stage 3**). In general terms, the “**Stage A**” plan provides a “Process Variability Known—REDUCED” inspection plan that decrease the requisite number of batch-representative dosage units from “50” (**Stage 1**) representative dosage units to on the order of “12 – 22” for AQL’s not greater than 1.5 % and, the “**Stage B**” plan provides “Process Variability—“NORMAL” inspection plan that changes the requisite number from “50” (Stage 1) to on the order of “40 to 70” for AQL’s not greater than 1.5 %. In most cases, where the number required for the **Stage B** plan equals or exceeds the number required for the **Stage 1** plan, you can omit the **Stage 1** plan and end up with a “4 Stage” Inspection plan (**Stage A, Stage B, Stage 2, and Stage 3**) with “12 – 22” units, “40 to 70” units, “200” units, and “400” units as the total number tested for each stage. In cases where the **Stage B** plan tests less than the **Stage 1** plan, you may elect to use the 5-stage plan or a “4 Stage” Inspection plan that consists of **Stage A, Stage 1, Stage 2, and Stage 3** with “12 – 22” units, “50” units, “200” units, and “400” units as the total number tested for each stage. [Note: Given the USP’s post-release expectations, a firm would have a hard time justifying an AQL greater than 1.5 % (and should probably, *if supportable*, choose an AQL that is 1 % or less) for tablets or, for capsules an AQL greater than 2.5 % (and should probably, *if supportable*, choose an AQL that is 1.5 % or less).]

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

A. APPLICATIONS NOT YET APPROVED

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

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application (CTD⁴¹ 3.2.P.3.3):

- A statement that the procedures in this guidance are being used to establish the content uniformity of the final “Powder Blend” and the dosage units, or a description of the alternative *sound* statistical-based methods proving the content uniformity of the blend and the drug product.
- An overview of data analyses used for the uniformity assessment of the final blend, the in-process formed dosage units and the finished dosage units.
- A review of the in-process formed dosage units’ “content result” data that demonstrates that the active content and weight corrected active content results for the formed units indicate that the batches evaluated can validly be considered to be normally distributed with respect to each active ingredient in the drug product.
- A summary of the “Powder Blend” sampling data’s analysis that demonstrating that each final blend is appropriately uniform and meets the minimum qualification criteria established for the level of testing performed.
- Tables showing all of the relevant batch and step identification information, sampling location or time point, assigned test identifier, weight of sample or dosage unit tested, results found, weight corrected result values, and the raw data values used to compute the “results found” values.

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

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

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

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

⁴¹ *MAQ: The CTD — Quality*, one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the FDA.

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

B. POSTAPPROVAL CHANGES

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If you plan on changing the firm’s existing controls for blend content uniformity and dosage-unit content uniformity to the methods described in this guidance, the change may be considered a minor change as described in the postapproval changes guidance⁴². When this change results in an increase in the level of confidence in the content uniformity of each batch deemed acceptable, the Agency recommends the sponsor provide a notice of the change in the next annual report along with the information indicated in the preceding section (VIII. A.). The raw data collected to support changes and all other contingent records and notes should also be maintained at the manufacturing site. However, when this change results in a decrease in the level of confidence in the content uniformity of each batch deemed acceptable, the Agency recommends the sponsor provide a notice of the change in a CBE-30 supplement along with all of the information indicated in the preceding section (VIII. A.).

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⁴² FDA's guidance for industry on Changes to an Approved NDA or ANDA.

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GLOSSARY

A. TERMS DEFINED BY REGULATION

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

B. TERMS OR PHRASES DEFINED BY STATUTE

- 1. “Abbreviated drug application” 21 U.S.C. 321 (aa)
- 2. “Adulterated drug”
 - (contaminated with filth) 21 U.S.C. 321 (a)(1)
 - (made under filthy conditions) (a)(2)(A)
 - (CGMP non-compliant) (a)(2)(B)
 - (in a contaminated container) (a)(3)
 - (contains “unsafe” color) (a)(4)
 - (contains “unsafe” animal drug) (a)(5)
 - (feed containing “unsafe” animal drug) (a)(6)
 - (strength, quality, or purity differs from official compendium) (b)
 - (misrepresented strength, quality, or purity) (c)
 - (mixed with or substituted with another substance) (d)
- 3. “Counterfeit drugs” 21 U.S.C. 321 (g)(2)
- 4. “Current good manufacturing practice (CGMP)” 21 U.S.C. 351 (a)(2)(B)
“A drug ... shall be deemed to be adulterated —if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with *current good manufacturing practice* to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; ...”

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2408	5. “Drug”	21 U.S.C. 321 (g)(1)
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2410	6. “Drug Product”	21 U.S.C. 321 (dd)
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2412	7. “New animal drug”	21 U.S.C. 321 (v)
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2414	8. “New drug”	21 U.S.C. 321 (p)
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2416	9. “Official compendium”	21 U.S.C. 321 (j)
2417	10. “Safe”	21 U.S.C. 321 (u)
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C. TERMS OR PHRASES DEFINED FOR USE IN THIS GUIDANCE

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

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

Characteristic *means* any qualitative or quantitative defining feature.

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

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

Conformance batch (sometimes referred to as a “validation” batch or “demonstration” batch) *refers to* any batch prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. [**Note:** Prior to the manufacture of a conformance batch, the manufacturer should have identified and controlled all critical sources of variability.]

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

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

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

Dynamic sampling means the controlled removal of portions of a **population** while the **population** is being produced. When **dynamic**, interval **sampling** occurs in pharmaceutical manufacturing during the production of a *batch* of drug product, the **sample** taken at each **sampling point** must, itself, be **representative** of the possible *variability* in the drug product at that point (see **Example 1**). As a consequence of this, each **dynamic sample** must encompass the *variability* at the point that said **sample** is being taken.

Example 1: Dynamic Sampling During Tablet Manufacture

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

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

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

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

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

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

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

Initial process conformance, initial validation, performance qualification (PQ), or evaluation qualification (EQ) 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 required to be a one that validates the process – *thus each is a validation batch*.

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2505 **In-process dosage unit** is a capsule or tablet as it exists at the completion of any in-process step
2506 starting from the time the dosage unit is formed in the manufacturing process and continuing until it is
2507 ready to be packaged. For example, in a process that has processing steps (phases, stages) that: **a)**
2508 forms the final blend into tablet cores, **b)** film-coats the cores with a color, **c)** overcoats the color coat
2509 with a clear coat, **d)** prints identification on the clear coated units, **e)** waxes and polishes the printed
2510 units, **f)** holds the polished units in bulk until the batch is released for packaging, and **g)** packages the
2511 released polished units for distribution, the outputs of Steps “**a)**” through “**e)**” are **all** collections of in-
2512 process dosage units. In the example, the corresponding appropriate “in-process dosage unit” phase-
2513 differentiating identifiers could be: **a)** “freshly formed,” **b)** “color coated,” **c)** “clear coated,” **d)**
2514 “printed,” and **e)** “polished.” At Step “**f)**,” the dosage units are **finished dosage units**. At end of
2515 Step “**g)**,” the dosage units are **finished packaged dosage units**.
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2517 **Inspection** is the **sampling** of a **sample** from a **population** coupled with examining or testing that
2518 **sample**, or a *subsample* thereof, for compliance with predetermined **specifications**.
2519

2520 **Measure** means to find out the size, length, quantity, or rate of something using a suitable instrument
2521 or device, or to assess the quality of something by quantitatively comparing it to some standard.
2522

2523 The **normal, or Gaussian, distribution** is a unimodal symmetrical **distribution** having a **population**
2524 **mean**, μ , and **population standard deviation**, σ . The *variance* of this **distribution** is σ^2 . Its *mean* or
2525 average value, μ , is also its *mode* (the most frequent value) and *median* (the value that divides the
2526 distribution in half). This is the case because a **normal distribution** is both *unimodal* and
2527 *symmetrical*. Moreover, σ is the distance from the mean, μ , to the two inflection points on the curve
2528 that encompasses the **population** values. Thus, μ is the location parameter for a normal distribution
2529 and σ describes the spread, scatter or dispersion of the **population** about the *mean*. Defining z as the
2530 distance from the mean in units of standard deviation, the values of z can be computed using the
2531 formula:
2532

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

2533
2534 Where \mathbf{X} is a given value in the **population**.
2535
2536

2537 Using z , we can ascertain the proportion, **P**, of entities in the **population** that have values of z smaller
2538 than any given z . The proportions found are such that 34.13 % of the **population** is between 0 and 1
2539 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
2540 0.14 % is outside of 3 or $-3 z$. Based on this, 68.26 % of the **population** is between -1 and $+1 z$,
2541 95.44% is between -2 and $+2 z$, and 99.72% is between -3 and $+3 z$.
2542

2543 **Population** means any finite or infinite collection of individual entities. For control purposes, a
2544 **population** is also a collection governed by some property that differentiates between things that do
2545 and things that do not belong. The term **population** carries with it the connotation of completeness.
2546 Depending upon the setting, the drug-product CGMP regulations treat a *lot*, a *batch*, a small group of
2547 *batches*, or all of the *lots* or *batches* produced in a given time interval as the **population** being
2548 evaluated. *Batch* quality evaluations must be designed to predict whether, or not, the *samples* tested
2549 (or examined) from a *batch* being inspected not only meet their specifications but also predict that the
2550 *batch* does, or does not, belong to the universe of releasable drug product.
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2552 **Purity** means the absence, or degree of absence, of anything of a different type – *tests to establish the*
2553 *purity of the water in the holding tank*.
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Quality means an essential identifying property of something.

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

1. It must be from all portions of the **population** or, *when sampling is performed during the production of the batch*, it must appropriately *span* the production operation that it covers from start to finish.
2. Its *size (number)* must be large enough that the results obtained from testing or evaluating that number of entities or amounts can validly predict the **population's** distribution with respect to the parameter or parameters evaluated.
3. Each removal of entities or an amount in the set of removals that define the complete **sample** must be done so that its removal does not bias or affect the selection of the next removal in the set.

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

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

1. The **sample** set must *span* the population – be from all parts of the *batch* or, in the dynamic case, cover the production period from start to finish.
2. Relevant characteristics of the **population** sampled must bear an established or proven relation to the corresponding characteristics of the **population** of all possible **samples** associated with the sampling scheme used. [**Note:** In dynamic sampling, the number of **samplings** must be sufficient to reflect the variability in the production step that is being sampled, and each **sampling** must be *representative* of the local variability present at the time of **sampling**.]
3. The **population sample** must be of sufficient *size* that valid generalizations about properties of the **population** may be inferred from the results obtained from the evaluation of those properties in the **samples**. The inferences from the results must be made using a recognized, proven “book of rules” whose validity rests on statistics, the mathematical theory of probability.
4. The sampling of any given **sample** in the **sampling** set that defines the complete **sample** must be done in a manner that ensures it does not bias the next **sample**.

RSD is an acronym for the term relative standard deviation; $RSD = [(standard\ deviation)/(mean)] \times 100\%$.

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

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2610 **Sample mean** is the average of the measured values for the **samples** evaluated. Usually, the mean is
2611 computed using the formula:

$$\bar{X} = 1/n \sum_{i=1}^n X_i \quad (2)$$

2616 Where the X_i are the values observed for the n samples evaluated.

2618 **Sample variance** or, more accurately, the **sample estimate of variance**, denoted as s^2 , is the estimate
2619 of the variance, the second moment about the **population mean**, μ . Usually, this statistic is computed
2620 using the formula:

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

2624 However, the general formula that should be used is:

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

2629 Where f is the degrees of freedom consumed in the computation process.

2630 When the X_i s are “direct” measurements, then f is 1 because one degree of freedom is
2631 consumed in the computation of the “differences.”

2632 However, when the X_i s are ratio measurements, as is often the case in hyphenated
2633 chromatographic/detector measurements using an Internal Standard, then f is 2 and the
2634 proper formula to use is:

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

2638 **Sample variability** or, more accurately, the **sample estimate of variability**, denoted as s , is the
2639 square root of the **sample estimate of variance**. This term is often referred to as the “*sample*
2640 *standard deviation*.” That name is the source of the alternate abbreviation, “SD.” While **variances**
2641 are additive, **variabilities** or *standard deviations* are not additive. Thus, if one needs to add or
2642 average *standard deviations*, one must first convert them into **variances** by squaring them. Then, the
2643 **variances** can be added and the square root of the sum is the *total standard deviation* or, for like
2644 **variances**, dividing the sum by the number of like **variances** added gives the **average variance**, and
2645 the square root of that **variance** is the *average standard deviation*.

2647 **Sample size** has more than one meaning.

- 2649 • For discrete **populations** (tablets, capsules, syringes, *etc.*), it is the number of entities (units) from
2650 a **population** that are either:
 - 2651 ○ Removed by sampling or
 - 2652 ○ Inspected (examined or tested) by some procedure or method.
- 2654 • For *non-discrete populations* (blender loads, drums of a component, bulk liquids, *etc.*) it is the
2655 amount of material (by weight or volume) from a **population** that is either:
 - 2656 ○ Removed by **sampling**, or
 - 2657 ○ Inspected (examined or tested [evaluated]) by some procedure or method.

2659 In the USP’s view, **sample size** refers to the minimum number of entities (the **USP article**) for
2660 discrete populations. For non-discrete materials, the **USP article (sample size)** is the stated amount of
2661 material that is required for a given **USP test** or evaluation.

2663 Depending on the context, the **FDA** and the Court (Judge Wolin in **USA v. Barr**) have used the term
2664 **sample size** to connote either:

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2666 – The physical amount of a non-discrete or discrete material that is to be *sampled* (a defined
2667 number of units in the discrete case or, in the non-discrete materials' case, nominally, at least
~~2668~~
~~2669~~ three times the dosage unit weight) or

2670 – The amount (number, weight, or volume) to be used in a given test or evaluation to generate a
2671 result.
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2673 **Sampling** *means* the controlled removal of any portion of a **population** for retention and/or
2674 examination or testing purposes.
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2676 **Sampling plan** *means* the *scientifically sound* and *appropriate strategy* used to take a valid **sample**.
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2678 **Significant event** *is* any event during solid dosage production process that can adversely affect the
2679 integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a
2680 blender to a bin and from the bin to a hopper are two examples of significant events in a blending *or*
2681 dosage-forming process *step*.
2682

2683 **Simple** (Unrestricted) **random sampling** *means sampling* in a manner that each entity in the
2684 **population** has an equal chance of being the first member of the **sample**; each remaining entity has an
2685 equal chance of being the second member of the **sample**; and so on – subject to the constraint that
2686 “each possible **sample** has an equal chance of being selected.”
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2688 **Specification** *means* a detailed description of a component, material, intermediate, product, or control
2689 in terms of the numerical limits, ranges or acceptance criteria that defines what can be accepted for: **a)**
2690 use **or b)**, in the “product” case, for introduction into commerce. For the pharmaceutical industry,
2691 such specifications must be designed to ensure that the each *batch* of drug product manufactured by a
2692 given firm meets *scientifically sound* and *appropriate specifications* that define the identity, strength,
2693 quality and purity of each dose such that, *after the batch is released into commerce, a)* each dose can
2694 validly be represented to be safe and efficacious **and b)** any **USP** (or **NF**) *article* in said *batch* will, if
2695 tested, meet the explicit and implicit commercial requirements set forth in the **USP** (or the **NF**) for
2696 that product. [**Note:** The term controls includes both the equipment used to effect the control required
2697 and the permissible limits, ranges, and/or acceptance and other criteria used to establish that a given
2698 control is functioning or has functioned as it was designed to function.] A **specification** *is* a
2699 predefined characteristic, or limit, or range of an attribute or variable that defines what is an
~~2700~~ acceptable product outcome for a given process step. Examples of attributes are:

- 2702 • Comparative degree of whiteness against some set of “white” standards, and
- 2703 • Degree of perfection (for tablets, un-chipped, chipped, scratched, marked, spotted, specked,
~~2704~~ miss-punched, cracked, de-laminating, and broken).

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~~2706~~ Examples of attribute characteristics are:

- 2708 • Color and
- ~~2709~~ • Shape.

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~~2711~~ Examples of limits and ranges for tablet attributes include:

- 2713 • No blue or broken tablets in any *representative* 1250 examined, and
- ~~2714~~ • NMT 3 chipped or cracked tablets in any *representative* 800 examined.

2716 Examples of variables are: content, active release rate, and weight. Examples of limits and ranges for
~~2717~~ variable factors include:

- 2719 • Active level is 100 % to 102 % of the label claim (*LC*),
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- 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

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- Tablet weights must be between 190 and 210 mg.

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Specification Limit is a predefined upper limit, lower limit, or range that, *for a given characteristic (attribute or variable) factor*, defines what is an acceptable product outcome for a given process step.

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Examples of limits and ranges for acceptable product outcomes include:

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

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

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

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

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

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

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

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Variable means something that is capable of changing or varying and, in the pharmaceutical industry, the **variables** are those control and material **factors** that are known to control or contribute to the *variability* in the product produced by a given process.

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Weight correction is a mathematical correction to validly normalize the content result obtained for the level of active in a “freshly formed” dosage unit to what that active content result would **probably** have been had that dosage unit been formed at the manufacturer’s established target weight. *For example, a tablet with a measured strength of 19.4 mg and weight of 98 mg has a weight fraction active content of $0.197959184 \text{ mg}_{\text{Active}}/\text{mg}_{\text{Tablet}}$ ($\text{mg}_{\text{Active}}/\text{mg}_{\text{Tablet}} = 19.4 \div 98 = 0.197959184 \text{ mg/mg}$). If the drug-product’s label claim is 20 mg per each 100 mg tablet, the weight-corrected result percent of active in the dosage unit tested is $0.197959184 \text{ mg}_{\text{Active}}/\text{mg}_{\text{Tablet}} \div 0.20 \text{ mg}_{\text{Active}}/\text{mg}_{\text{Tablet}} * 100 \% = 98.9795918 \%$ of the label claim. Rounding that result to two decimal places and using the result to estimate the content of active in the blend that went into that tablet, you find that the blend content was probably 99% of the blend’s target content level for the active.*

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2825 have **no** authority to issue any communication that is at odds with any clear regulation and **b)**
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