

Wednesday, 21 January 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"Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [G:\5831dft.doc 10/27/03]."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On 15 November 2003, FAME Systems provided comments based on that review and an in-depth reading of the FDA's "**Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [G:\5831dft.doc 10/27/03].**"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* or *lots* 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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33 Hoffman Avenue Lake Hiawatha, NJ 07034-1922

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

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

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published by the FDA, Facility Automation Engineering (FAME) Systems has rewritten that Draft and offers the "Revised Draft Guidance" that follows to the Agency as a CGMP-compliant scientifically sound alternative that, when followed, provides a confidence level of 95-% or higher that the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

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

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

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

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

Respectfully,

Dr. King

Guidance for Industry

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

REVISED DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

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

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

January 2004
Pharmaceutical CGMP

Guidance for Industry

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

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Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573*

<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)**

**January 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 Content Uniformity

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

I. INTRODUCTION

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

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

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

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

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

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II. BACKGROUND

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

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

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

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

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

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

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

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

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* or *lot*
103 from which they were taken (21 CFR 211.160(b)(2)) nor does it comply with the “**appropriate statistical**
104 **quality assurance criteria**” requirement set forth in 21 CFR 211.165(d). Thus, this guidance must, of
105 necessity, provide a different approach that should, if properly implemented, comply with the
106 aforesaid CGMP requirements. *Where they comply with 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 in-process minimums of
113 21 CFR 211.110. In most cases, traditional powder blend sampling and testing, in conjunction with
114 CGMP-compliant testing for uniformity of content in the finished product, can be used to comply with
115 current good manufacturing practice requirements (CGMPs). Use of at-, in-, or on-line measurement
116 systems may, in some cases, also be appropriate and are described in other guidance documents⁹.

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

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- Conduct *batch- or lot- representative* powder blend sampling and analyses.
- Establish initial criteria for dynamic sampling of in-process dosage units¹⁰ and evaluation of test results.
- Analyze the *dynamically acquired* samples and evaluate data.

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

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

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

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

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- Compare the results found for the dynamically sampled core or capsule content with the powder blend data.
 - Assess final blend and formed tablet core or capsule content uniformity.
 - Correlate the dynamically acquired core and capsule content sample data with the finished dosage unit data and assess uniformity of content for the batch or lot.
 - Test and evaluate exhibit batches or lots and initial performance qualification batches or lots of simple tablets and capsules for uniformity.
 - Test and evaluate routine manufacturing batches for uniformity of their active content.
 - Report the firm's use of dynamic in-process tablet core and capsule inspection plans for content uniformity in the application.

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

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

178 Except where the data triggers an investigation that determines the batch contains valid out of
179 specification (OOS) values that fail to meet: **a)** the USP's post-release lifetime criteria or **b)** predicts
180 that the batch or lot contains such units, the FDA does not intend to inspect such data collected on an
181 existing product for the purpose of evaluating the suitability of proposed methods. Any other FDA
182 decision to such research data would be based on exceptional situations like those outlined in
183 Compliance Policy Guide Sec. 130.300.¹² However, **all** such data acquired in support of, or bearing
184 on, validation or the validity of any regulatory submissions will be subject to inspection in the usual
185 manner.
186

188 ¹¹ In January 2003, the Agency issued “Draft Guidance for Industry—Drug Product Chemistry, Manufacturing,
189 and Controls Information.” Once finalized, it will represent the Agency's perspective on the use of PQIT in
190 the monitoring of a process.

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

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

198

199 IV. ESTABLISHING VALID CONTENT SPECIFICATIONS

200

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

217

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

222

$$223 RSD^2_{\text{Tablet}} = RSD^2_{\text{Tablet Weight}} + RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} + RSD^2_{\text{Error}} \quad (1)$$

224

225 the firm can use the variance values it establishes for Tablet Weight, Tableting, and Error to solve for
226 $RSD^2_{\text{Final Blend}}$. In general, a firm can validly set RSD^2_{Error} to between $0.25 \%^2$ and $2.25 \%^2$ depending
227 upon whether the sampling and testing is performed under ISO 17025 standards or not. For this
228 example, the firm will be presumed to know that, on average, its RSD_{Error} is not more than 1 %.
229 Substituting these estimates of RSD^2_{Tablet} and RSD^2_{Error} into **Equation 1**, the firm should find that:

230

$$231 RSD^2_{\text{Tablet Weight}} + RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} \approx 4.76 \%^2 \quad (2)$$

232

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

238

$$239 RSD^2_{\text{Tableting}} + RSD^2_{\text{Final Blend}} \approx 3.76 \%^2 \quad (3)$$

240

241 When the firm has a formulation program that only develops formulations that are mechanically stable
242 on storage and in the tableting operation, then, the firm can validly set $RSD^2_{\text{Tableting}}$ to be much less
243 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
244 %”), and, solving **Equation 3**, find that:

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~~249~~ $RSD_{\text{Final Blend}}^2 \approx 3.6 \%^2$ (4)

~~250~~
~~251~~ or

252
~~253~~ $RSD_{\text{Final Blend}} \approx 1.9 \%$ (5)
~~254~~

255 Since, for most firms, the variability contribution in storage and tableting is closer to or exceeds “1 %”
256 than the “0.4 %” value used for **Equation 4**, most firms (using an automated tablet press like the one
257 in the example) should set $RSD_{\text{Final Blend}}$ at between “1 %” and “1.7 %.” [**Note:** Practically, even with
258 careful granulation, it is difficult to manufacture final blends with an RSD of less than about 0.9 % (n = 200).
259 Based on the preceding, most firms should set their practical $RSD_{\text{Final Blend}}$ limit to not more than 1.5 %.]
260

261 Reviewing the properties of normal distributions of non-discrete materials with respect to the testing
262 of a small number of samples from a given batch or lot, the firm should note that the most probable
263 range of values should be within ± 3 RSD of the target. Based on that approximation, the firm’s final
264 blend’s *expectation* range should be not more than about $\pm 5.7 \%$ (1.9 % times 3) or, for the example
265 tablet’s target of 100.5 % of label claim, 94.8 % to 106.2 % of label claim. Similarly, the tablets’
266 relative content expectation range should be 100.5 % \pm 7.2 % of label claim or 93.3 % to 107.7 % of
267 label claim.
268

269 Because experience has shown that the distribution of dosage-unit content values is approximately
270 Gaussian (normal), the firm, *not wishing to develop a first-principles approach to the statistical*
271 *treatment of its testing results*, decides that, for statistics-based in-process and release inspection of the
272 dosage units, it will use the recognized 95%-confidence-level consensus standard for inspection by
273 variables for percent nonconforming¹³. *Given it has set its expectations range at the 3 RSD level*
274 *(approximately 99.72 % of the population)*, the firm appropriately selects a 0.4 % level as the limit for
275 the allowable percentage of non-conforming units (units outside of the established specification for
276 tablet samples) in recognition of the possible level of “sample set” variability inherent in the set
277 chosen. However, *recognizing the lifetime post-release limits imposed by the USP on any article in*
278 *the batch*, the firm should set two auxiliary acceptance criteria for the batch. Those criteria are:
279

- 280
- 281 • No valid “unit dose” result or dosage unit value can be outside of the range from 75 % to 125
282 % of the label claim, and
 - 283 • For the dosage units tested, not more than 1.6 % of the samples tested can be outside of 85 %
284 to 115 % of the label claim (for a safety factor of 2+ over USP’s “3.33 %” for any *article*).
285

286 Thus, based on the example and the requirements of CGMP, the blend and tablet specifications can be
287 set for the example presented (e.g., as shown in **Table 1** on the next page). Having established
288 CGMP-compliant specifications for content, the firm now needs to establish an appropriate CGMP-
289 compliant statistics-based sampling plan for both the “Final Blend” and the dosage form (tablet cores
290 and finished tablets in the example presented).
291

292 Though ANSI/ASQC Z 1.9-993 establishes the numbers required for the testing of units, it does not
293 establish the number of units that should be sampled at any stage. Moreover, there are no similar
294 consensus standards that are directly applicable to non-discrete materials such as the final blend.
295

297 ¹³ **ANSI/ASQC Z1.9-1993**, SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY
298 VARIABLES FOR PERCENT NONCONFORMING, American Society for Quality, (ASQ), 611 East
299 Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-
300 414-272-8575 (or its ISO equivalent, ISO 3951:1989).
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Therefore, the next section provides an example that may be used as the basis for the sampling and testing of the “Final Blend,” and the in-process and finished dosage units.

V. ESTABLISHING APPROPRIATE SAMPLING AND SAMPLE EVALUATION PLANS

A. GENERAL CONSIDERATIONS

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

Table 1 – 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 ² 1.6 % Outside Of:
Final Blend	NLT ³ 100	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 ⁴ 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 or lot from which the samples tested were selected.

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

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

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

formulation to the point that:

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

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- 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 not less than 0.7 (e.g., 0.72 to 0.75; n = 3).

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

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

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

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

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

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

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380 the order of 4 g when a 5-mL sample vial is used. When physical properties are to be
381 assessed, 15-g samples should be sampled into appropriate 20-mL containers or 20-g samples
382 should be sampled into appropriate 25-mL containers to ensure that the sample containers are
383 completely filled. In all cases, the vials should be pre-cleaned wide-mouthed vials or bottles
384 that are pre-labeled and stored/contained in an appropriate rack that holds them upright.]
385

386 **2. Establishing The Scientifically Sound And Appropriate “Sampling Size”** 387 **Requirements For Non-Discrete Materials** 388

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

400 **3. Scientifically Sound and Appropriate Test Aliquot Volume (or Weight)** 401 **For Non-Discrete Materials** 402

403 Trained analysts can easily remove minimally biased singlet aliquots that are within 5
404 % of the weight of the targeted unit-dose aliquot for aliquots down to 50 mg (and
405 within 10 % down to 10 mg to 15 mg [a level smaller than most tablets]). Since the
406 goal must be to determine the uniformity at the dosage-unit level, all test aliquots
407 should be taken at a unit-dose or, if justified by the uniformity of the blend, a fraction
408 of the dosage-unit weight. [Note: In general, aliquoting at less than unit-dose weight should
409 be limited to cases where the active content is *NLT* 10 % of the weight of the dose.]
410

411 **4. Representative Sampling Requirements For Non-Discrete Materials** 412

413 Unlike the sampling of discrete materials, the *representative* sampling of non-discrete
414 in-process materials, as required by 21 CFR 211.160(b)(2), can be accomplished with
415 fewer samples. However, the sampling plan used must still “span” the batch and take
416 the samples in a manner that one sampling does not significantly bias the next
417 sampling. In addition, sampling plan must include an appropriate sample for each
418 interface region in the mixer (e.g., the mixer wall/blend boundary layer, the air/blend
419 interface layer, and, when sampled from plastic-bag-lined storage containers, the
420 bag/blend interface layer). In general, at least duplicate aliquots should be evaluated
421 from each location sampled.
422

423 *Using the PQRI’s recommendations concerning the identification of regions of poor*
424 *blending and the CGMP’s requirements for batch- or lot- representative sampling,* the
425 manufacturer should initially choose a sampling pattern, based on developmental
426 studies and at least one confirmatory batch manufactured in the intended type of
427 blender at one-fifth planned production scale or larger, that:
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- Includes more than fifteen (15) sampling locations in the blender with half the sampling locations chosen from the areas where the developmental data found the least homogeneous material (including the blender wall, around the agitator shaft [if any] and in the discharge valve) and the other half in locations where the developmental data found the most homogeneous material – to ensure a *batch-* or *lot-* *representative* sampling.
- In tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from not less than two depths along the axis of the blender (the number of levels should increase as the size of the mixer increases); *based on the PQRI's recommendation for choosing at least 10 locations where the least uniform blend is expected to be found*, the PQRI initially recommends choosing at least 20 locations to adequately assess the blend homogeneity in such tumbling blenders.
- In convective blenders (such as ribbon blenders, screw blenders, plow and paddle mixers, and air jet mixers), a special effort should be made to implement uniform volumetric sampling that, in addition to the general wall and agitator regions, include the corners, the two end “shaft pass through” areas, and discharge area (by analogy, the PQRI initially recommends choosing at least 40 locations to adequately assess the blend homogeneity in convective blenders).

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

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

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

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

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

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

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481
482 component¹⁷. With the preceding as the basis for discussing sampling from the blender, let us
483 proceed to discuss plans for Sampling and Evaluation of a blend in the mixer.
484

1. Sampling Plans

485
486
487 With the preceding as the basis for discussing sampling from the blender, this
488 guidance leaves it up to each firm to establish the appropriate sampling locations in a
489 manner that produces a *representative* sample. Based on the PQRI's input, the
490 industry recommends initially choosing not less than twenty sampling locations when
491 sampling at production scale (implicitly this number is the number recommended for
492 initial "validation" studies where the performance of the blending process is first being
493 assessed at full scale).
494

495 To minimize the risk of sampling bias, the sampling locations at each level should be
496 appropriately offset from the sampling locations at the next level. In general, the
497 samplings should proceed by level from the topmost level to the bottommost level with
498 randomized sampling for the samples taken at each level. To minimize "top biasing,"
499 the sampler probes should be inserted slowly. For example, if a three-level, eight-
500 samples-per-level sampling pattern is selected, then the general setup should offset
501 each level's sampling locations by one-third of the distance between the locations at
502 the top level. As the blend is being sampled, each sample should be transferred into a
503 properly labeled clean sample container that it fills and that container sealed with an
504 appropriate compression-screw cap. When all of the samples have been collected, the
505 sample set should be transferred to the appropriate testing facility for evaluation.
506

2. Evaluation Plans

507
508
509 In general, the firm should adopt a *scientifically sound* hierarchical sample-evaluation
510 plan that initially tests multiple aliquots of all samples and, as the history of the results
511 found dictates, reduces or increases the number of sampled samples tested and the
512 number that are tested in duplicate to estimate the within-sample variability. Initially,
513 *for not less than three (3) consecutive batches (or lots)*, not less than two (2)
514 approximately unit dose aliquots should be taken and tested for active content from
515 each sample sampled. This should be done to establish sound estimates of both the
516 within-sample uniformity and the between-location uniformity of the final blend.
517

518 Based on the results found, the nature of the blend should be assessed¹⁸. From that
519

521 ¹⁷ The use of such blenders not only facilitates the use of the "sampling from the blender" approach but also
522 can increase production throughput. This is the case because one blend can be mixed while the one being
523 sampled is being sampled, the one previously sampled is being transferred into intermediate containers, and
524 another "mix container" is being loaded for mixing (allowing these operations to proceed in parallel).
525

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

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533
534 initial assessment, the number of samples for which duplicates are required should, if
535 indicated, be reduced. *Provided the results found are within the limits established for*
536 *a given final blend and the “within” RSD is consistently less than the “between” RSD,*
537 *the replicates can be appropriately reduced as long as at least two batch-spanning*
538 *samples are tested in duplicate. As the production of final blends continues,* the history
539 observed should permit the firm to similarly adjust the number of sample locations that
540 should be evaluated. The more uniform the history, the fewer locations that should
541 need to be evaluated. However, the minimum number selected in such decisions
542 should be not less than three (3) samples chosen in a way that they “span” the batch.
543 In addition, the minimum number of samples from which duplicate aliquots should be
544 taken and evaluated should not be less than two (2) batch-spanning samples. Thus, the
545 sample evaluation plans hierarchical structure should range from not less than twenty
546 (20) batch spanning (*representative*) samples evaluated in duplicate (not less than 40
547 evaluations) to not less than three (3) batch-spanning samples with duplicate
548 evaluation for the most far apart samples.
549

550 In summary, to address all contingencies, all samples should be sampled and an
551 appropriate justified history-based hierarchical sample-evaluation plan should be used
552 to adjust the number of the sampled samples that should be tested initially. The
553 hierarchical sample-evaluation plan should also provide for increased evaluation
554 whenever an apparent nonconformity (valid OOS) is encountered or the test values
555 observed are significantly outside of the historical norms seen for the final blend.
556

557 **C. INSPECTION PLANS FOR A FINAL BLEND CONTAINED IN “N”** 558 **INTERMEDIATE STORAGE CONTAINERS¹⁹**

559 **1. Sampling Plans²⁰**

560 For blends stored in separately “bagged” 10-kg or smaller identified portions contained
561 in a larger container, sample one appropriately sized multiple-dose sample from each
562 bag into an appropriately labeled and identified sample container. For blends stored in
563 “n,” 25-kg to 35-kg containers, sample one appropriately sized multiple dose sample
564 from the top and the bottom of each container (“2n” samples). For blends stored in
565 “n,” 50-kg to 60-kg containers, sample the appropriately sized multiple-dose sample
566 from the top, middle, and bottom of each container (“3n” samples). In all cases, all
567 sample containers should be sampled at all locations to ensure that all samples needed
568 for any contingency are available without having to resample the containers.
569
570

571
572
573 ¹⁹ This is the sampling plan that should be used when the blender is larger than 30 ft.³ (0.028 m³) or the
574 developmental studies have established that the final formulation is mechanically stable and the
575 manufacturer plans to store the final blend in an identified (numbered) series of labeled intermediate storage
576 containers (commonly, plastic-bag lined 50-kg or 25-kg drums).
577

578 ²⁰ These general sampling plans are based on the requirements stated for components in 21 CFR 211.84(c)(4),
579 “If it is necessary to sample a component from the top, middle, and bottom of its container, such sample
580 subdivisions shall not be composited for testing” that were developed in the 1970’s with the 50-kg container in
581 mind as the most common container size for such materials. The plans in this guidance appropriately reduce
582 the number of levels as the size of the smallest containment unit decreases.
583

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2. Evaluation Plans

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

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

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

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

1. Sampling Plans

For the in-process inspection of a batch or lot, most manufacturers want to dynamically assess the quality of the batch or lot as it is being produced whenever the operation lends itself to such sampling. This is especially true when the process step requires several hours to complete. In general, tablet core formation and capsule filling are process steps that require hours to complete. Thus, this guidance presumes that the manufacturers generally dynamically sample the dosage units as they are being

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633 produced. Beyond the usual strictures for a *representative* sample, dynamic sampling
634 imposes a requirement that each sample taken must be *representative* of the process at
635 the time of that sampling. Because tablet presses and encapsulation systems are a
636 collection of a significant number of individual dosage-forming stations, each
637 sampling should contain some integer multiple of the number of dosage-unit-forming
638 stations. Since, as the discussion will show, a firm needs a sample of not less than
639 1600 to 3200 units for its inspections (attribute [done on the firm's own quality
640 initiative] and variable [required by regulation]), each sampling point should collect
641 "1600 divided by the number of sampling points," or more, *representative* dosage
642 units subject to the constraints that the total number of units collected at each point:

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

646
647 In general, the firm should collect each sampling point's sample in a separate
648 appropriately labeled container (in most cases, a resealable plastic bag may be used
649 and, after sampling, the sampled set of samplings accumulated in an appropriately
650 sized container²¹). Since most firms perform attribute assessment²² using *Military*
651 *Standard 105E* or, more properly, its official replacement ANSI/ASQC Z1.4, and
652 those evaluations are non-destructive, the sample collected for a firm's attribute
653 quality inspections can, *when it passes*, be used as the sample for the required variable
654 assessment studies²³. This is the case because the number of units required for such
655 assessments is on the order of 800 to 1250 units for production-scale batches of tablets
656 and capsules. Moreover, since many firms do double sampling attribute inspection,
657 this sample should contain from 1600 to 2500 or more units. Thus, the number
658 sampled for dosage-unit attribute inspection should, *if preserved*, be more than
659 sufficient for content uniformity assessments as well as for **all** the other appropriate
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663
664
665 ²¹ When the samples from each sampling point are segregated, then, when physical problems are found during
666 attribute inspection, the time sequence of the problem sample set or sets can be identified when the problem
667 does not pervade the batch.

668
669 ²² The current consensus standard, ANSI/ASQC-Z1.4, spells out a set of attribute sampling and
670 evaluation procedures that provide 95-% confidence level assessment of a batch- or- lot
671 *representative* sample of tablet cores for attributes like chipping, capping, cracking, surface pitting,
672 incorrect punching, and broken, or, for capsules, cracked shell, improper closure, incorrect capsule,
673 and shell defects. Simplistically, the manufacturer assigns an allowable projected percentage level
674 for defective dosage units for each attribute and accepts batches when all attributes are found to
675 have defect levels that are less than the allowable number for each attribute assessed.

676
677 ²³ This strategy ensures that the sample submitted for variables assessment is from the physically acceptable
678 batch. In cases where the batch fails the physical properties, at best, the batch of tablet cores is appropriately
679 screened and, after this screening and an appropriate revised in-process sample is generated that represents
680 the screened batch. When this sample passes attribute inspection, the revised *batch-* or *lot-* *representative*
681 core or capsule sample is then submitted for the requisite variables testing under ANSI/ASQC Z1.9. In the
682 worst case, the batch is rejected for failing its physical attributes inspection. When this approach is used, the
683 risk of non-productive sample evaluation is minimized.

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685 variable factor evaluations including, but not limited to, the chemical property
686 evaluations such as rate of active release (using a USP-like “Dissolution” or “Drug
687 Release” test), assay, impurity, water content, and physical property evaluations such
688 as hardness, friability and disintegration.
689

690 In summary, a firm can minimize the number of formed dosage units sampled by
691 appropriately conserving the overall sample collected for attribute inspection and
692 appropriately using it for the requisite assessment of the content uniformity for the
693 formed dosage units in each batch or lot for as well as other variable factors “that may
694 be responsible for causing variability in the characteristics of in-process material and the
695 drug product” (21 CFR 211.110(a)).
696

697 **2. Evaluation Plans** 698

699 Broadly, there are two statistical approaches that one can take to evaluating a
700 *representative* sample from a batch or lot of freshly formed dosage units. Those
701 general approaches are characterized by the distribution assumption made for the units
702 sampled. If no distributional assumption is made, the firm should use a suitable
703 “distribution free” assessment procedure. When the firm can justify classifying the
704 dosage units as belong to a “normal” or “near normal” distribution, the firm should use
705 an appropriate “normal distribution” statistical approach which, in general, requires a
706 significantly smaller number of sample units. This guidance presumes that the
707 manufacturers of tablets and capsules are justified in using “normal distribution”
708 statistical approaches for assessing content uniformity.
709

710 With respect to appropriate “normal distribution” statistical approaches, this guidance
711 presumes that manufacturers should use statistical procedures that provide a 95 % or
712 higher level of confidence that the results for the *representative samples* tested should
713 be predictive of the acceptability of the remaining *batch or lot* of untested units. Given
714 this “confidence level” presumption, this guidance further presumes that each
715 manufacturer should use ANSI/ASQC Z1.9 (or its ISO equivalent, ISO 3951) as the
716 basis for its sample evaluation plans. This presumption is made because ANSI/ASQC
717 Z1.9 and ISO 3951 outline CGMP-compliant sample evaluation plans that test the least
718 number of *representative* sample units that a firm can justify testing for active content
719 whose active content result values can validly be used to predict the acceptability of
720 the entire batch or lot of units at the 95-% confidence level²⁴.
721

722 The cited consensus standards provide evaluation plans for two (2) cases, the “*process*
723
724

725 ²⁴ Firms not wishing to use the recognized applicable statistical consensus standards, ANSI/ASQC Z1.9 (or its
726 ISO equivalent, ISO 3951), should develop, and justify the use of, a suitable *population predictive* evaluation
727 plan that tests the same number or a larger number of *batch- or lot- representative* sample units. This is the
728 case because the consensus standards cited are based on the least number of units required to demonstrate
729 *batch or lot acceptability* at the 95-% confidence level. Firms wishing to have a higher confidence level in
730 the acceptability of the batch or lot tested for its active content should either use a suitable validated
731 statistical program to generate the number of samples required or consult a suitable statistics textbook that
732 discusses designing variables acceptance sampling plans and follow the procedures outlined to determine the
733 appropriate number of *representative* units to evaluate.
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735 *variability known*” case and “*process variability unknown*” case. To justify using the
736 “*process variability known*” case, the manufacturer should be able to establish that its
737 acceptance criteria for all incoming components, including the active, and all in-
738 process materials include appropriately restrictive controls on all the critical variable
739 factors for each component or material. In addition, the firm should have sufficient
740 results data from the intensified testing on final stage developmental and initial
741 production-scale validation batches or lots that demonstrates that the *process mean* and
742 *process variability* for each such batch are, within their respective uncertainties, the
743 same²⁵ for all such batches or lots. When the overall results support the use of an
744 appropriate “*process variability known*” evaluation plan, then that plan, *when it is*
745

747 ²⁵ For the example tablet product, having a targeted mean of 100.5 % of label claim, consider the following
748 scenarios in which all components are presumed to be from *different* lots:

749 Batch evaluation: 200 or more *representative* samples were tested for content uniformity in each case

750 Batches intensively tested: One (1) “technology transfer” and three (3) “initial validation lots

751 Results found:

752 For a **Scenario 1** (process variability known; all critical variable factors well controlled) product:
753

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

754
755 Based on the results observed for the 1000 units tested, the estimated % non-conforming for the process is
756 about 0.1 %, the range of relative means is 0.2 %, and the range of RSD values is 0.2 % (a relative range of
757 about 11 %). The batches are acceptable and, coupled with the process expectations developmental
758 outcomes, the consistency of the data supports setting a process mean of 100.5 % with a process RSD of 1.8
759 %. Provided the facts are as presented in this scenario, the firm would be justified in choosing an
760 appropriate “process variability known” sampling plan.
761

762 For a **Scenario 2** (process variability unknown; all critical component factors not well controlled) product:
763

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

764
765 Based on the results observed for the 1200 units tested, the estimated % non-conforming for the process is
766 about 0.25 %, the range of relative means is 0.6 %, and the range of RSD values is 1 %. While the batches
767 are acceptable, the data does NOT support setting a process mean of 100.5 % (as the formulation is expected
768 to generate). In addition, the relative range for the process RSD values (of about 50 %) does NOT support
769 the premise that the process has a global “process variability”. In this instance, the firm should use the
770 appropriate “process variability unknown” plan.

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771
772 properly established, should be used as the “stage 1” evaluation plan for each batch.
773 When the data does not support the use of a “process variability known” approach to
774 batch assessment (see Footnote 25, Scenario 2), an appropriate “process variability
775 unknown” evaluation plan should be used as the “stage 1” evaluation plan for each
776 batch or lot. In those cases where it is valid to use an appropriate “process variability
777 known” plan for stage 1, the firm’s “stage 2” acceptance evaluation plan, when such is
778 needed, can simply be to switch to the corresponding appropriate “process variability
779 unknown” plan and use it. For an appropriate “stage 2” plan for products that require
780 the “stage 1” plan to be a “process variability unknown” plan, the firm should adopt an
781 appropriate “intensified sample evaluation” plan based on a process capability
782 approach. Thus, the statistical evaluation of an appropriate number of sample units
783 can be globally thought of as a three-tiered plan. The first two tiers of which, “process
784 variability known” and “process variability unknown,” should be based on an
785 appropriate plan from the sets of plans contained in the cited consensus standard
786 documents. The third tier should be based on a “process capability” approach that
787 requires the evaluation of more representative sample units than the “process
788 variability unknown” case. The sections that follow discuss the general requirements
789 for, and limitations on, the use of the approach upon which each tier is based. It is left
790 up to each manufacturer to justify the exact general decision tree that is appropriate for
791 each of their drug products. To simplify this discussion, ANSI/ASQC Z1.9-1993 is
792 the consensus standard used and each batch, or lot, is presumed to contain *NLT*
793 250,000+ tablet cores or filled capsules.
794

795 a. **Tier 1 – Process Variability Known – Evaluation Plans Appropriate**
796 **To Drug Product Manufacture**
797

798 In general, the number of *population-representative* sample unit evaluations
799 required in **Tier 1** for a valid batch inspection plan depends upon the tolerable
800 percentage of nonconforming tablet content values (AQL_{Content}). The
801 relationship between sample number and AQL is inverse. Thus, subject to the
802 design limits and verified outcomes established during product development, a
803 firm wishing to minimize the number of samples that should be tested should
804 choose the smallest “Acceptance Quality Level” (“AQL”) that the design,
805 development, and, where available, historical records factually support.
806 Because the validity of the use of this approach is totally dependent on the
807 validity of the firm’s assertion that the *process variability* is a known value, the
808 use of a “Tier 1” plan” in the firm’s overall evaluation plan should be restricted
809 to products manufactured from components and in-process materials whose
810 critical chemical and physical properties are both identified and well
811 controlled. Moreover, as discussed previously, the determination of the
812 “*process variability*” value should be based on intensified testing on a
813 sufficient number of production-scale related batches or lots manufactured
814 using differing lots of components. [Note: Though a “reduced inspection” option
815 exists, the allowable variability in the chemical and physical properties of the
816 components and in-process materials does not support the use of this option for tablet,
817 capsule, and other solids containing drug products.] Thus, for content uniformity
818 and batches larger than 250,000 units, Row “P” in “Table D-3” of
819 ANSI/ASQC Z1.9 (pages 90 and 91) outlines the number of samples (*n*), the

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820 acceptance criterion (M), and adjustment factor (v) for a given choice of AQL.
821 Those sample numbers range from 42 for an AQL of 0.1 % to 127 for an AQL
822 of 10 %. For the example tablet product (see **Table 1**) used in this guidance
823 where the AQL established is 0.4 %, not less than 54 batch representative
824 sample units should be tested. A “500-unit lot” example showing how the
825 results found for the samples tested are used to determine the acceptability of
826 the batch or lot is shown on page 88 in ANSI/ASQC Z1.9-1993. When the
827 batch or lot results are evaluated and, *in conjunction with the other acceptance*
828 *criteria established for the drug product (see **Table 1**)*, the batch or lot is
829 found to have an acceptable content uniformity, then not only does the batch or
830 lot evaluated have an acceptable content uniformity but the continued use of
831 this “Tier 1” evaluation plan is also validated²⁷. In general, the firm’s use of
832 the “Tier 1” level of inspection should be limited to solid dosage forms for
833 which every variable factor (component, material, process and test) that may
834 adversely affect the uniformity of the content in the formed dosage units is
835
836

838 ²⁶ Should a batch or lot not meet its AQL criteria when evaluated using the firm’s “Tier 1” evaluation plan,
839 then, provided the other critical batch acceptance criteria are met, the firm should switch to their “Tier 2” –
840 Process Variability Unknown – plan. *When the number of sample units already tested is at least the number*
841 *specified in the appropriate “Reduced Inspection” option of this “Tier 2” plan*, the firm should first evaluate
842 the probable acceptability of the population based on the observed sample variability rather than the
843 sample’s projected “process variability.” This decision is appropriate when, for whatever reason, a process
844 operating in control under a “Tier 1” plan indicates that the product may not be acceptable even though the
845 sample units tested meet all of the other acceptance criteria established for content uniformity. If this
846 evaluation finds the product is acceptable, then the **entry point** into the “content uniformity” evaluation
847 decision matrix should be set to the “Tier 2 – Reduced Inspection.” If the samples tested are otherwise
848 acceptable but the batch or lot is still found to be not acceptable, then, the firm should switch to the “Tier 2 –
849 Normal Inspection” plan, evaluate the remaining number of units required to satisfy the 200-unit
850 requirements for batches larger than 150,000 units, and ascertain whether or not the batch or lot is acceptable
851 under this evaluation condition. When it is, then the firm should switch their **entry point** into the “content
852 uniformity” evaluation decision matrix to “Tier 2 – Normal Inspection.” When all of the results are
853 otherwise acceptable but the data do NOT meet the firm’s “Tier 2 – Normal Inspection” criteria, the firm
854 may elect to switch to their “Tier 3 – Process Capability” plan and proceed as it directs²⁶. If the “Tier 3”
855 plan finds the batch acceptable, then the firm should switch their content-uniformity entry point to “Tier 3”
856 and use it for subsequent batches. {Note: the rules for switching from “Tier 3” to “Tier 2 – Normal
857 Inspection,” or “Tier 2 – Normal Inspection” to “Tier 2 – Reduced inspection” or from “Tier 2 – Reduced
858 Inspection” to “Tier 1” are complex and depend upon the:

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

864 Though ANSI/ASQC Z1.4 provides some general guidelines, each firm should appropriately justify the
865 decision tree that they use to control switching among the inspection plans the firm chooses to use.
866

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

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872 well controlled.
873
874

875 **b. Tier 2 – Process Variability Unknown – Evaluation Plans Appropriate**
876 **To Drug Product Manufacture**
877

878 In general, the plans in **Tier 2** are appropriate for manufacturers who identify:
879

- 880 • All critical chemical and physical factors for the components, materials
881 and process steps but do not rigorously control all of them, or
882
- 883 • All of the critical chemical factors but only control some of the critical
884 factors relying instead on one or more process steps (usually granulation
885 related) to minimize or eliminate the non-uniformity that the
886 uncontrolled critical component factors can contribute and choose to use
887 the formed dosage units to define the uniformity of:
888
 - 889 o the formed units, and
 - 890 o the ‘Powder Blend’ from which the dosage units were formed, or
- 891 • All chemical factors but rely on the process steps to minimize or
892 eliminate the non-uniformity that the uncontrolled critical component
893 factors can contribute and use the results for the formed units to
894 determine the content uniformity of both the ‘Powder Blend’ used and
895 the dosage units produced.
896

897 For the tablet example (see **Table 1**) produced in batches larger than 250,000
898 units, the appropriate *batch- or lot- representative* “normal” inspection sample
899 number is 200 units. In cases where the manufacturer can justify the use of a
900 “reduced” inspection plan²⁸, a firm using ANSI/ASQC Z1.9 as the basis for its
901 batch acceptance assessments can choose to test as few as fifty (50) *batch- or lot-*
902 *representative* sample units. However, *on a generalized statistical basis*,
903 evaluating a *representative* set of 75 is a better choice. When the use of this
904 “reduced inspection” option is justified, any “*samples conform but batch or lot*
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908

910 ²⁸ In general, the following conditions should apply before a drug manufacturer can justify switching from the
911 “normal” inspection level to a “reduced” inspection level when **all** of the following conditions have been
912 met:
913

- 914 – The not less than 10 or more lots or batches have been on normal inspection and none has been rejected
- 915 – Production is at a steady rate
- 916 – Reduced inspection has been included as an option in the manufacturer’s filing for the drug product
917 and accepted by the Agency.
918

919 Thus, the choice of this option should be limited to dedicated manufacturing facilities or facilities in which
920 the production campaign or “run” encompasses more than 10 lots or batches. In general, this choice is not
921 appropriate to short-run production unless the firm is justified in using the “*process variability known*”
922 option (Tier 1) and a non-conformance to the requirements for that case contains a provision for switching to
923 the “*process variability unknown – reduced inspection*” option. [Note: Since the ANSI standard’s “tightened”
924 inspection plans: a) do NOT address the acceptability issues associated with the “currently non-acceptable” batch and
925 b) only increase the probability that a subsequent batch or lot will not meet its acceptance criteria, this guidance has
926 elected to switch plans rather than switch to “tightened inspection.”]
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929
930 *is predicted to fail*” assessment should trigger switching to the “*normal*
931 *inspection*” option with the evaluation of the additional *representative* dosage
932 units needed to generate the requisite 200 *batch-* or *lot-* *representative* content
933 results. Should the test results from a batch or lot under “*normal inspection*”
934 meet its sample criteria but fail to meet the acceptance criteria for the batch or
935 lot, the recommended course of action is to switch to a **Tier 3** (based on a
936 process capability approach) plan that the manufacturer has justified and
937 submitted in the appropriate filing that has led the FDA to approve or license
938 that drug product. This is the case because a firm’s switching to the “*tightened*
939 *inspection*” option²⁹ presented in the ANSI/ASQC Z1.9 would lead not only to
940 the rejection of the non-conforming *batch* or *lot* but also to the tightening of
941 the acceptance criteria in a manner that would increase the risk that an
942 acceptable batch would be rejected.
943

1. Process Variability Unknown – Normal Inspection

944
945
946 Though ANSI/ASQC Z1.9 provides two approaches, a range-based
947 procedure and a standard-deviation-based procedure, this guidance
948 recommends that the manufacturers elect to use the standard-deviation-
949 based procedure because: a) it requires the testing of fewer samples
950 than the range-based procedure, and, more importantly, b) it results do
951 not depend upon how the samples being evaluated are grouped. For
952 batches larger than 150,000 dosage units, not less than 200
953 *representative* dosage units³⁰ should be tested when this inspection
954 plan is used. For tablet and capsule batches down to 35,000 units, the
955 firm need only evaluate 150 *representative* dosage units. In general,
956 this, or an appropriate process-capability-based inspection plan, is the
957 *minimum* inspection plan that a manufacturer should use during the
958 development of the manufacturing process for a tablet or capsule
959 product when the developmental batch size exceeds about 500 dosage
960 units. The text and appropriate tables in pages 37 through 53 of
961 ANSI/ASQC Z1.9-1993 contain the information and examples that are
962 needed for a manufacturer to determine the acceptability of a batch or
963 lot based on finding acceptable sample results generated by the testing
964 of any set of “200” or more *representative* units.
965

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

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

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

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

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

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

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

In general, the plans in **Tier 3** are appropriate when the variability of the batches produced is such that use of the consensus standards cited is deemed or found not to be appropriate for a given product. Often, a suitable “Tier 3” inspection plan is the plan of choice for use in the development of a solid dosage form when the controls for the components, in-process materials, and processing steps have not yet been completely developed. Because there a variety of approaches that can be used to evaluate the

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manufacturability of a product using a given set of inputs and operations, this guidance does not propose to address exactly which “*process capability*” approach should be used. This guidance instead focuses on the issues associated with the minimum:

- a) number of *representative* dosage units that a firm should evaluate and
- b) capability result value that a firm should use

to comply with the requirement minimums of CGMP with respect to 21 CFR 211.110.

1. Minimum Number of Units To Inspect

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

2. Minimum “Process Capability” Assessment

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

³¹ For manufacturers who wish to reduce their RSD uncertainty to the point that the error in assigning a process variability from the sample variability observed is less than “5 %,” not less than about 900 *representative* units should be selected when a 95 % confidence level is deemed appropriate. Moreover, at the 99 % confidence level, not less than 1400 units should be tested. In developmental studies, the firms are encouraged to inspect larger numbers and choose a 99 % confidence level for decision making because doing so reduces the risk that the data from the developmental lots does not adequately describe the performance of the projected or observed production-scale batches or lots.

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used by today’s drug product manufacturers. Remembering: a) the general form of the process capability equation for a set of relative values is that a relative range divided by six times the RSD observed is equal to the capability “C” and b) “Six Sigma” quality expects all values to be within a relative range from the “mean minus 6 RSD” to the “mean plus 6 RSD” or a “12 RSD” range, the firm should set a minimum process capability that is not less than “12 RSD”/“6 RSD” or 2.0. [Note: Looking at *process capability*³² in terms of the number of standard deviations from the process target that are tolerated, a *process capability* of “1.33” or “1.34,” a value that most authors consider the minimum acceptability, roughly translates into a targeted quality level of “Four Sigma.”]

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

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

E. INSPECTION PLAN FOR FINISHED TABLETS AND CAPSULES

1. Sampling Plans

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

³² Since “process capability” is a derived value that is essentially the ratio of the allowed range divided by the observed variability, firms should be able to fully justify the range selected where the justified range should be no larger than the projected *population* content range derived from the range observed for the number of samples tested to meet the requirements for the 99-% confidence level.

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1135 Because a finished dosage-unit “appearance” attribute sample for inspection under
1136 ANSI/ASQC Z1.4 is generally collected and examined, that sample should be
1137 conserved and used for the requisite variable factor evaluations required. With this in
1138 mind, let us turn to the evaluation of the finished dosage units sampled for the simple
1139 tablet and capsule products that this guidance directly addresses.
1140

1141 2. Evaluation Plans 1142

1143 When in-process testing establishes the *batch’s* or *lot’s* content uniformity, there
1144 should, in general, be no need to reassess this variable factor for the instances
1145 (addressed by this guidance) in which the post forming operations do not change the
1146 content of the dosage units formed. However, when a firm needs to assess uniformity
1147 at the finished drug product stage, the procedures used for the in-process assessment
1148 can be appropriately adapted for use here. If the drug product assessment for content
1149 uniformity is meant to be a confirmation of the in-process assessment, then, *in cases*
1150 *where the process steps after dosage unit forming cannot change the content of the*
1151 *dosage units*, the firm should be able to justify using an evaluation plan that uses the
1152 RSD established in the in-process testing and a suitable ANSI/ASQC Z1.9-based
1153 “*process variability known*” procedure. In such cases, the firm may be justified in
1154 using the “*process variability known – reduced inspection*” plan because this
1155 inspection is meant to be confirmatory in nature. This guidance leaves it up to the
1156 manufacturer to specify and justify the content evaluation plan, if any, that the firm
1157 should be used.
1158

1159 However, *though outside the scope of this guidance*, one critical process parameter
1160 that should be evaluated at the finished product stage is the release profile of the solid
1161 dosage form. This is the case because the post-dosage-forming processing and
1162 handling steps in the manufacture of tablets (e.g., color coating, inking) and capsules
1163 (e.g., polishing and gel coating) are known to affect the release of the active from the
1164 dosage unit. For example, when a firm’s process adds an “enteric” coating designed to
1165 delay the release of the active until after the dosage unit has passed into the small
1166 intestine, the drug product is designed to delay the release of the active. Since
1167 evaluating the release of the active is outside the scope of this guidance, the
1168 manufacturers should consult other published articles, documents, and texts that
1169 provide general guidance that the firm may use to justify the evaluation plan the firm
1170 establishes for such “active release” evaluations. Because “active release” and “active
1171 content” are correlated variable factors *when the active is being released*, their
1172 correlated nature may be used to justify, *in some cases*, “active release” examination
1173 plans that need only use one of the appropriate “reduced inspection” procedures in
1174 ANSI/ASQC Z1.9.

1175 1176 VI. ESTABLISHING APPROPRIATE TEST PROCEDURES 1177

1178 A. GENERAL CONSIDERATIONS 1179

1180 Since the goal of in-process testing (21 CFR 211.110(a)) is to assess batch uniformity – not
1181 just the uniformity of the samples evaluated, the analytical test procedures chosen should be

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

B. CHOICE OF ANALYTE MEASUREMENT SYSTEM

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

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

Fortunately, progress in instrumentation design and the advent of increasingly powerful microprocessors has made it possible to use rapid scan spectrophotometers and sophisticated component deconvolution software to accurately determine an averaged analyte response that provides the high throughput and response averaging capabilities needed to obtain highly precise and suitably accurate determinations of the content in the dosage units tested. Moreover, robotics has progressed to the point that the entire sample preparation and measurement procedure can be automated. With the Agency's renewed interest in process analytical technology (PAT), manufacturers are encouraged to use such separationless assessment 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 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 or lot 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- or lot- representative* procedure for the assessment of the acceptability of each
1249 final blend for release that the firm’s quality control unit (QCU) can use to release each final blend for
1250 use in the 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 content and other variable
1257 factors directly related to level of the active. In such cases, the generalized set of steps where a
1258 content and/or other uniformity release is required can be labeled as “Powder Blend,” “Formed
1259 Dosage Units,” and “Finished Dosage Units.” To simplify discussion, this section also uses the tablet
1260 product example introduced initially (a 250 mg uncoated tablet containing 0.2 mg of a single stable
1261 active ingredient [“0.08 %” wt./wt] targeted to contain, on average, 100.5 % of its labeled content).
1262

1263 **A. “POWDER BLEND” INSPECTION**
1264

1265 This guidance leaves it up to the manufacturer to justify the sampling and evaluation approach
1266 that it uses during the early stages of the development of a process. However, once a firm has
1267 established the type of dosage form, the components to be used and the general processing
1268 steps that will be used to produce the drug product, the Agency expects to see the
1269 manufacturer use scientifically sound and appropriate *representative-sample-based statistical*
1270 *inspection plans* in the final stages of development as well as in all pre-production-scale
1271 batches or lots. Should a firm elect to pursue a “*process variability known*” approach, the
1272 Agency expects to see proof that the firm has determined the critical physical and chemical
1273 variable factors for each component, process step and processing choice that can affect the in-
1274 process material and drug product content uniformity and has established sufficiently stringent
1275 controls for each.
1276

1277 For those firms who elect to approach the determination of the content uniformity for each
1278 batch or lot of the final “Powder Blend” indirectly (by determining the weight-corrected
1279

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1280 content for the freshly formed dosage units tested and using those values to provide assurance
1281 that the final “Powder Blend” did meet its uniformity criteria), the Agency expects to see an
1282 in-depth justification for choosing that option. That justification should include appropriate
1283 batch- or lot- acceptability for release evaluations ^{34, 35}. With the preceding Agency
1284 expectations in mind, the manufacture should then proceed in the manner that is dictated by
1285 the level of quality that the firm’s controls and process steps have built into the dosage unit
1286 forming operation.

1287
1288 In general, for a developed process, the firm should either have two types of inspection plans
1289 for “Powder Blend” inspection or a single multiple-tier inspection plan. These should address
1290 two (2) general situations, Evaluation Qualification (“EQ”) inspection (commonly referred to
1291 as the Performance Qualification [“PQ”] phase of validation) and Routine Production
1292 Qualification inspection (referred to as the Maintenance Qualification [“MQ”] phase of
1293 validation).

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

1295
1296
1297
1298 The inspection plans for EQI should include an appropriate in-depth assessment of
1299 uniformity of the final “Powder Blend.” Based on the input provided by the PQRI, the
1300 number of sampling locations should be on the order of 20 or more. In general, for “in
1301 the mixer” sampling, the manufacturer should provided a body of evidence that
1302 justifies the amount of sample, the number of sampling locations, and the positions
1303 chosen by a manufacturer for sampling. The manufacturer’s evidence should prove
1304 that the samples sampled are indeed *representative* of the final blend. In general,
1305 increases in blend size and/or the mixer’s design complexity calls for more sampling
1306

1308 ³⁴ For example, a manufacturer has identified and appropriately controlled all of the critical physical and
1309 chemical variables for each component and established in development that the maximum difference in
1310 Assay for unbiased *representative* samples from an in-process blend occurs between the Assay found for the
1311 bulk blend and the Assay for the in-process material remaining in the mixer after it is emptied. For batches
1312 that demonstrated uniformity meeting the criteria established for that “Powder Blend,” this maximum
1313 observed difference could be, for example, 1.4 % of the label claim. Therefore, *when both Assay values are*
1314 *appropriately performed on a sufficient number of appropriately sized aliquots taken from unbiased sample*
1315 *aliquots large enough to be population representative*, the firm may be justified in setting this Assay
1316 difference as a part of its routine-production “Powder Blend” acceptance criteria provided the observed
1317 value for the Assay “Powder Blend” batch or lot is not less than 100 % of the targeted value or, *when that is not the*
1318 *case*, the firm’s dosage forming procedure explicitly requires the formed weight to be adjusted “to provide
1319 not less than 100 percent of the labeled or established amount of active ingredient” (21 CFR 211.101(a)).

1321 ³⁵ For processes like the ones outlined in **Footnote 34** where the “Powder Blend” is mixed in a tote that is
1322 attached to a mixer head for blending and then detached and, after inspection, the tote containing the released
1323 final “Powder Blend” is directly transferred to the feed hopper of the dosage forming system, the firm should
1324 be able to justify relying on the computed Assay for the batch or lot of blended powder provided: a) a valid
1325 *batch- or lot- representative* Assay “Powder Blend” batch or lot value is determined from the sample aliquots tested
1326 and b) that Assay “Powder Blend” batch or lot is not less than 100 % of the level targeted or c), *when the calculated*
1327 *Assay “Powder Blend” batch or lot is less than 100 % of the level targeted*, the production process has explicit
1328 language to require production to adjust the dosage unit slug or fill weight to “to provide not less than 100
1329 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 storage container” point, then an appropriate number of samples should be taken from *NLT* two levels (“Top” and “Bottom”) in each container when the intermediate-storage containers are 25-kg or less and *NLT* three levels (Top, Middle, and Bottom) when these containers contain more than 25 kg each.

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

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

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 samples sampled even in *short-run* situations.
1383

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

1384 In MQI, the EQI history is used to justify the use of an MQI plan which tests less than
1385 all of the samples sampled. By analyzing the EQI results’ history for not less than the
1386 previous ten (10) consecutive acceptable blends, the firm may be able to define a
1387 subset that, on average, provides the same results’ range pattern. In favorable cases,
1388 where the final blend is highly uniform, the firm may be able to justify initially testing
1389 a defined subset of the full set sampled containing as few as one-fourth of the sampled
1390 set. The reduced set may reliably describe an acceptable lot or batch at least 90 % of
1391 the time (with full testing being required about 10 % of the time).
1392

1393 As alluded to previously in **Footnotes 34 and 35**, in well controlled processes, a firm
1394 may be able to justify using a *batch-* or *lot- representative* Assay and Assay Range
1395 approach³⁷ to justify the release of the final “Powder Blend” to the dosage-forming
1396 step provided a post-release conformity content uniformity evaluation on the formed
1397 dosage units (using the weight corrected content data for the tablet cores or capsule
1398 contents at the formed-dosage-unit stage) is used to verify the content uniformity of
1399 the final “Powder Blend” was within its acceptance envelope³⁸. When it is valid to
1400

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~~1402~~
1403
1404 ³⁷ When this approach is used, the Assay and Assay Range must include an evaluation of all of the components
1405 in the blend whose uniformity may affect the overall safety and efficacy of the dosage units formed from the
1406 “Powder Blend;” not just the Assay for the active or actives in the formulation. The variables whose level
1407 should be assessed in the Assay case are the same ones that should also be assessed in when the uniformity
1408 of the final blend is being determined. Those components are, in order of importance, a) stabilizers
1409 (components that stabilize the active or actives in the formulation [e.g., sodium citrate, typically, added in a
1410 “granulating” solution, used to stabilize Penicillin V Potassium]), b) components that facilitate active
1411 adsorption, c) components that regulate (accelerate or retard) the release of the active from the dosage unit
1412 (e.g., cross carmellose sodium, sodium starch glycolate, modified cellulose polymers), d) binders that
1413 increase tablet core or capsule fill cohesion, and e) lubricants that promote the flow of the final blend though
1414 the dosage forming system. Since lubricants are typically added at the end and blended for the least time, the
1415 uniformity of the lubricant directly impacts the uniformity of the final blend. For example, if a blend were
1416 perfectly uniform up to the point that the lubricants are added and the lubricant weight percentage is 2 % of
1417 the tablet weight of 5 mg in the example 250-mg tablet, the lack of uniform dispersion of the lubricant can
1418 easily result in level of lubricant that range from near zero to 20 mg (0 % to 8 % of the unit-dose’s weight).
1419 This translates into a relative active content range impact of from +2 % to – 8 % or a 10 % range. This
1420 problem is particularly severe when a non-rotating-shell blender is used and the material in the discharge
1421 port (which contains no lubricant) is not removed from the port and added back to the blend midway through
1422 the blending of the lubricants and this “discharge port recycling” is not repeated at one minute before the
1423 final blend step is completed. [**Note:** In known cases where no recycling was performed, the level of the active in
1424 discharge-port material has been found to be, on average, up to 10 % higher than it should be. This is one of the
1425 reasons that, absent continual discharge port recycling, such blenders should not be used to produce drug products.]
~~1426~~

1427 ³⁸ The downside of this approach is the problem that such a “retrospective” assessment may generate when the
1428 weight-corrected content values fail to meet the pre-established acceptance criteria for the “Powder Blend.”
1429 At a minimum, the number of *representative* dosage units evaluated will need to be appropriately increased.
1430 Worst case, the much higher “lack of quality” costs associated with rejecting a batch or lot at the formed
1431 dosage stage may outweigh the apparent cost savings afforded by using this approach. Moreover, it is both
1432 more difficult and more costly to validly “rework” the product at the formed dosage unit stage than it is at
1433 the final blend stage.
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1434
1435 use this approach, the inspection plan should include switching to a blend
1436 content-uniformity inspection plan when the requisite Assays do not meet the
1437 manufacturer's relative mean or RSD acceptance criteria.
1438

1439 **B. “FORMED DOSAGE UNIT” INSPECTION**

1440

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

1455 For those firms who elect to approach the determination of the content uniformity for each
1456 batch or lot of the final “Powder Blend” indirectly (by determining the weight corrected
1457 content for the dosage units tested and using those values to provide assurance that the final
1458 “Powder Blend” did meet its uniformity criteria, the Agency expects to see an in-depth
1459 justification for choosing that option
1460

1461 **1. Exhibit, Initial Validation, Initial Production-Scale And Nonconformance** 1462 **Evaluation Qualification Inspection (“EQI”)** 1463

1464 The inspection plans for EQI should include an appropriate in-depth assessment of
1465 uniformity of the dosage units. Minimally, based on either ANSI/ASQC Z1.9 or ISO
1466 3951, initial studies should evaluate no less than 200 *batch- or lot- representative*
1467 dosage units. Firms seeking not only a better understanding of the uniformity of the
1468 formed dosage units in a batch but also to establish a sound value for the *process*
1469 *variability* based on the evaluation of a few initial lots or batches should initially use a
1470 99 % confidence level and test not less than 330 *representative* units. When the firm is
1471 in the process of finalizing their understanding of the post-blending handling impacts
1472 on the uniformity of the dosage units, the average of the differences in an initial set of
1473 not less than three (3) production-scale batches or lots when 330 *representative*
1474 dosage-units are tested from each batch or lot (or not less than five (5) batches or lots
1475 when 200 *representative* dosage units are tested) between the weight-corrected relative
1476 dosage-unit content variance ($RSD^2_{\text{Wt.-Cor. Dosage Unit Content}}$) and the relative blend
1477 content variance ($RSD^2_{\text{Blend Content}}$) can be used to establish the initial post-blending
1478 variance ($RSD^2_{\text{Post-Blend Content}}$). *Provided the dosage-unit content variances observed*
1479 *for each batch are similar* (the range of values observed should be such that the largest
1480 variance is not more than about 20 % larger than the smallest variance), the firm may
1481 be able to justify the use of an appropriate “process variability known” approach to
1482 batch inspection as opposed to a “process variability unknown” approach that initially

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1483 requires testing significantly more *representative* units (about 4 X).

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1485
1486 *When an EQI is conducted using a dynamic sampling plan*, an equal number of dosage
1487 units should be selected at each predefined sampling point (e.g., start, i^{th} interval, and
1488 end). As previously discussed, that number should be some integer number of the
1489 number of dosage forming stations in the equipment used to form the dosage units.
1490 The number of units to be selected from each “added” sampling point should be
1491 determined by the cause (e.g., PQRI, power failure, mechanical breakdown) for the
1492 “added” sampling point. In general, the number of samples selected for evaluation in
1493 EQI should be *NLT 200 representative* dosage units. Therefore, the firm’s EQI plans
1494 should take a suitable random subsample from each interval sample. The subsampling
1495 plan should randomly take an equal number of dosage units from each predetermined
1496 sampling point and the same or a lesser number of dosage units from each “added”
1497 sample point provided the total sampled for evaluation is *NLT* the minimum 200 or
1498 more units required for a statistically valid *batch-* or *lot-* *representative* sample.
1499

1500 When evaluating each dosage unit, a minimum of two determinations should be made
1501 for the response generated by the sample unless the detection/quantitation system
1502 automatically averages the responses measured³⁹.
1503

1504 Thus, in addition to its initial use when the full-scale production of a drug product
1505 commences, EQI should be the initial inspection plan whenever production of a given
1506 drug product is resumed in a facility that campaigns various products or when a
1507 routine production batch does not meet its established MQI acceptance criteria. This is
1508 one reason that a manufacturer who wishes to minimize its inspection overhead is
1509 encouraged to use dedicated production facilities, where possible, and, in any case,
1510 produce drug product batches or lots in campaigns that are as long and as steady as the
1511 firm can support.
1512

1513 For short campaigns (runs), in non-dedicated equipment, it will be hard for a firm to
1514 justify using other than an EQI plan. In such cases, a manufacturer should again do all
1515 that it can to ensure that the drug-product production process has been developed to
1516 the point that the firm has built in rigorous controls on the critical physical and
1517 chemical variables, process steps, and process controls that could, if not so controlled,
1518 adversely impact the content uniformity of the in-process powder “Powder Blend”
1519 from which the dosage units are fabricated. Second, the post-blending handling and
1520 equipment loading procedures and equipment should be optimized to minimize
1521 demixing of the blend being formed into the dosage units. In addition, *to the extent*
1522 *possible*, the manufacturer should minimize the weight control range for the tablet
1523
1524

1526 ³⁹ The reason for requiring duplicate determinations is to provide for an internal check on the validity for a
1527 given response. In general, the firm should set an appropriate “value agreement” limit on the maximum
1528 allowable difference or percentage difference between the first and any subsequent measurement. In cases
1529 where the reported measurements are, in fact, the averages of multiple system assessments (e.g., a direct
1530 UV/Visible spectrophotometric measurement or an automatic averaging of multiple UV/Visible scans by a
1531 diode-array or rapid-scanning spectrophotometer) a firm may be justified in reducing the number of sample
1532 workups that are measured in duplicate to some percentage of the determinations made in order to establish
1533 valid estimates of the measurement uncertainty.
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1535 cores and capsule fills. *Unless the firm develops its production process to the level*
1536 *that its “built in” quality controls ensure that a reduced number of dosage-unit*
1537 *determinations are reliably representative of the batch or lot, a firm may have*
1538 *difficulty justifying testing less than 200 or more representative dosage units in “short*
1539 *run” situations. After sufficient history is accumulated in such cases, a firm may be*
1540 *able, for a well-controlled process, to justify routinely testing a reduced number of*
1541 *representative dosage units even in short-run situations.*

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

1542
1543 In MQI, the EQI history is used to justify the use of an MQI plan that tests less than
1544 the full number of dosage units required by the firm’s CGMP-compliant EQI plan for
1545 evaluating the samples. By analyzing the EQI results’ history for not less than the
1546 previous ten (10) consecutive acceptable blends, the firm may be able to justify using
1547 either a suitable ANSI-based “*process variability unknown*” *reduced-inspection* plan
1548 or, provided the batch or lot variabilities observed are sufficient close to each other,
1549 switching to a suitable “*process variability known*” *normal-inspection* plan. In such
1550 cases, the justifiable number of samples should be between one-fourth and one-half of
1551 the number required for by the firm’s EQI plan.
1552

1553 However, even when the physical and chemical characteristics of the components are
1554 tightly controlled, the limiting ranges for some of the key physical characteristics are
1555 still wide enough that the characteristics of each lot of component do affect the
1556 uniformity of the batch or lot to some degree. Because this is the case, a firm would
1557 be hard pressed to justify a further reduction of the number evaluated from the number
1558 in the “*process variability known*” *normal-inspection* plan to a lesser number. In cases
1559 where the content results are used for confirmation of the adequacy of the uniformity
1560 of the final blend as well as for determining that the dosage units are acceptably
1561 uniform, a firm should not even attempt to justify any further number reduction and,
1562 *even when a “process variability known” normal-inspection plan can be justified,*
1563 *should, in most cases, use a suitable “normal inspection” plan that evaluates between*
1564 *one-third and one-half the number of dosage units that the firm’s CGMP-compliant*
1565 *“process variability unknown” normal-inspection plan requires. In cases, where the*
1566 *uniformity of the final blend is determined directly and the accumulated history (for*
1567 *more than the last 10 batches or lots evaluated) indicates that the final blend samples*
1568 *and dosage units tested are acceptable, highly uniform, and strongly correlated, the*
1569 *firm may be able, for the “process variability known” case to justify starting with a*
1570 *“process variability known” reduced-inspection plan provided that plan tests at least*
1571 *one-third of the number of samples required for the firm’s justified “process*
1572 *variability known” normal-inspection plan. This reduced set can be expected to*
1573 *reliably describe an acceptable lot or batch at least 90 % of the time (with full testing*
1574 *being required about 10 % of the time).*
1575

1576 Thus, a firm’s overall dosage-unit inspection plan should be hierarchical in nature and
1577 consist of the appropriate set of stages and stage controls for evaluating the lot and
1578 switching among the sample numbers required based on the outcomes observed.
1579 Based on the production history, the starting point should be the smallest justifiable set
1580 (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 or lot). In cases where the previous
1585 batch was found to be unacceptable at the formed-dosage-unit stage, the starting point
1586 should be either a) the firm's "process variability unknown" normal-inspection plan
1587 when the investigation finds a proven operator error or mechanical failure as the root
1588 cause of the non-acceptability of the batch or lot tested, or the manufacturer's
1589 scientifically sound process-capability-based inspection plan whenever the firm's
1590 investigation does not definitively find the root cause of the non-acceptability
1591 observed.
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-* or *lot-representative* units as that
1597 required for the "Formed Dosage Unit" stage. In general, the sampling approach should be
1598 simple random sampling and, while recommended, there is no requirement for weighing each
1599 tablet or the contents of each capsule before the unit is tested for content uniformity. In many
1600 cases, *after some justified number of initial production-scale batches or lots*, the firm may be
1601 justified in switching to a plan that initially omits the content uniformity testing of the
1602 "Finished 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* or *lot* at a level of confidence that is
1614 95 % or higher.
1615
- 1616 • A set of *batch-* or *lot-representative* Assay⁴⁰ results on the dosage units finds the mean
1617 Assay is not less than 100 % of the label claim in the case of a stable active or not less
1618 than 100 % 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 or lots. The Agency has this expectation because
1623
1624
1625

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 or lot. In general, at least one or, preferably, two "Assay" evaluations should be
1630 conducted at the "Finished Dosage Unit" stage on a *batch-* or *lot-representative* number of units of
1631 sufficient size (number [not the USP's any 20; nominally, 50 to 200 or more *representative* units]) to ensure
1632 that the "Assay" results obtained are *batch-* or *lot-representative*. In cases where a suitable content
1633 uniformity assessment is made at the "Finished Dosage Unit" stage, the mean of the content values found
1634 may be used in lieu of one "Assay" evaluation provided the analysis procedures used do not introduce a
1635 significant content accuracy bias. To satisfy 21 CFR 211.101(a), the *average* of all of such "Assay" results
1636 on the formed units must have a value that is not less than 100 % of the label claim or targeted level.
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1637
1638 the firm should provide proof that the content uniformity established at the “Formed Dosage
1639 Unit” stage is the same at the uniformity for the content at the “Finished Dosage Unit” stage.
1640

1641 **1. Exhibit, Initial Validation, Initial Production-Scale And Nonconformance** 1642 **Evaluation Qualification Inspection (“EQI”)** 1643

1644 The inspection plans for EQI should include an appropriate in-depth assessment of
1645 uniformity of the dosage units. In general, the plans should be the same as those used
1646 for the “Formed Dosage Unit” case (see VII.B.1).
1647

1648 **2. Routine Manufacturing or Maintenance Qualification Inspection (“MQI”)** 1649

1650 In MQI, the EQI and MQI histories contained in the “Formed Dosage Unit” datasets
1651 coupled with the EQI history for the “Finished Dosage Unit” evaluations should be
1652 used to establish and justify the MQI plan that the manufacturer sets up. *In cases*
1653 *where the content uniformity has been proven to be fixed at the dosage forming stage,*
1654 the firm could simply treat the “MQI” content uniformity test for the “Finished Dosage
1655 Unit” stage as a PQIT whose evaluation frequency should be controlled by, in order of
1656 importance, the:
1657

- 1658 ▪ Acceptability of the previous batch or lot 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 or lots increases).
1662

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 content uniformity assessment.
1666
1667

1668 **VIII. REPORTING THE USE OF THE PROCEDURES OUTLINED IN THIS** 1669 **GUIDANCE** 1670

1671 **A. APPLICATIONS NOT YET APPROVED** 1672

1673 This section refers to the scientific data analysis and other information that should be
1674 submitted to an NDA or ANDA. Information submitted in the application should include
1675 summary reports and scientific analyses or statements about the method being used. The raw
1676 data collected to support using this method should be both submitted and maintained at the
1677 manufacturing site. The Agency recommends that the manufacturer should provide the
1678 following information in the Manufacturing Process and Process Controls section of the
1679 application (CTD⁴¹ 3.2.P.3.3):
1680

1681 ⁴¹ *MAQ: The CTD — Quality*, one in a series of guidances that provide recommendations for applicants
1682 preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD)
1683 for submission to the FDA.
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- A statement that the procedures in this guidance are being used to establish the content uniformity of the final “Powder Blend” and the dosage units, or a description of the alternative *sound* statistical-based methods proving the content uniformity of the blend and the drug product.
- An overview of data analyses used for the uniformity assessment of the final blend, the in-process formed dosage units and the finished dosage units.
- A review of the in-process formed dosage units’ “content result” data that demonstrates that the active content and weight corrected active content results for the formed units indicate that the batches or lots evaluated can validly be considered to be normally distributed with respect to each active ingredient in the drug product.
- A summary of the “Powder Blend” sampling data’s analysis that demonstrating that each final blend is appropriately uniform and meets the minimum qualification criteria established for the level of testing performed.
- Tables showing all of the relevant batch and step identification information, sampling location or time point, assigned test identifier, weight of sample or dosage unit tested, results found, weight corrected result values, and the raw data values used to compute the “results found” values.

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

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

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

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

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B. POSTAPPROVAL CHANGES

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

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

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1790 **GLOSSARY**

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1792 **A. TERMS DEFINED BY REGULATION**

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1794 1. “Acceptance criteria” 21 CFR 210.3(b)(20)

1795 2. “Active ingredient” §§ 210.3(b)(7)

1796 3. “Batch” §§ 210.3(b)(2)

1797 4. “Component” §§ 210.3(b)(3)

1798 5. “Drug product” §§§ (b)(4)

1799 6. “Inactive ingredient” §§§ (b)(8)

1800 7. “In-process material” §§§ (b)(9)

1801 8. “Lot” §§§ (b)(10)

1802 9. “Manufacture, processing, packing, or holding of
1803 a drug product” §§§ (b)(12)

1804 10. “Quality control unit” §§§ (b)(15)

1805 11. “Raw data” 21 CFR 58.3(k)

1806 12. “Representative sample” 21 CFR 210.3(b)(21)

1807 13. “Strength” §§ 210.3(b)(16)

1808

1809 **B. TERMS OR PHRASES DEFINED BY STATUTE**

1810

1811 1. “Abbreviated drug application” 21 U.S.C. 321 (aa)

1812 2. “Adulterated drug”
1813 (contaminated with filth) 21 U.S.C. 321 (a)(1)
1814 (made under filthy conditions) (a)(2)(A)
1815 (CGMP non-compliant) (a)(2)(B)
1816 (in a contaminated container) (a)(3)
1817 (contains “unsafe” color) (a)(4)
1818 (contains “unsafe” animal drug) (a)(5)
1819 (feed containing “unsafe” animal drug) (a)(6)
1820 (strength, quality, or purity differs from official compendium) (b)
1821 (misrepresented strength, quality, or purity) (c)
1822 (mixed with or substituted with another substance) (d)

1823 3. “Counterfeit drugs” 21 U.S.C. 321 (g)(2)

1824 4. “Current good manufacturing practice (CGMP)” 21 U.S.C. 351 (a)(2)(B)
1825 “A drug ... shall be deemed to be adulterated —if it is a drug and the methods used
1826 in, or the facilities or controls used for, its manufacture, processing, packing, or
1827 holding do not conform to or are not operated or administered in conformity with
1828 *current good manufacturing practice* to assure that such drug meets the
1829 requirements of this chapter as to safety and has the identity and strength, and
1830 meets the quality and purity characteristics, which it purports or is represented to
1831 possess; ...”

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1836	5. “Drug”	21 U.S.C. 321 (g)(1)
1837		
1838	6. “Drug Product”	21 U.S.C. 321 (dd)
1839		
1840	7. “New animal drug”	21 U.S.C. 321 (v)
1841		
1842	8. “New drug”	21 U.S.C. 321 (p)
1843		
1844	9. “Official compendium”	21 U.S.C. 321 (j)
1845		
1846	10. “Safe”	21 U.S.C. 321 (u)
1847		

C. TERMS OR PHRASES DEFINED FOR USE IN THIS GUIDANCE

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

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

Characteristic *means* any qualitative or quantitative defining feature.

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

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

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

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

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

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1886
1887 **Dynamic sampling** means the controlled removal of portions of a **population** while the **population** is
1888 being produced. When **dynamic**, interval **sampling** occurs in pharmaceutical manufacturing during
1889 the production of a *batch* of drug product, the **sample** taken at each **sampling point** must, itself, be
1890 **representative** of the possible *variability* in the drug product at that point (see **Example 1**). As a
1891 consequence of this, each **dynamic sample** must encompass the *variability* at the point that said
~~1892~~ **sample** is being taken.

Example 1: Dynamic Sampling During Tablet Manufacture

~~1893~~
~~1894~~
1896 Since a firm's sampling plan is dynamic and specifies taking *samples* from a hypothetical
1897 21-station tablet press at intervals, then the **sample** taken at each **sampling interval** must be
1898 some whole-number multiple of the 21 tablets produced at that interval.

1899 Thus, when the **sampling plan** for this 21-station press requires sampling at start up, "**n**"
1900 intervals during tablet production, and at the end of production, the final *sample* should consist of
1901 at least $([n + 2] \times 21 \times \text{some integer multiple})$ tablets.
1902

1903 **Evaluate** means to consider or examine something in order to judge its value, quality, importance, or
1904 condition.

1905
1906 **Examine**, means to study something in detail – *the drums were opened and their contents examined*
1907 *for the presence of foreign particulate matter*.
1908

1909 **Exhibit batch (or exhibit lot)** refers to any *batch* (or *lot*) submitted in support of an ANDA, NDA,
1910 ANADA, NADA, DMF, or VMF. This includes any submitted bioequivalence, development, start-
1911 up, initial validation, and commercial production *batch* (or *lot*) of a drug product.
1912

1913 **Factor** means something that contributes to or has an influence on the result of something.
1914

1915 **Grab sampling** means **sampling** by choosing any convenient **sample** of some defined or minimum
1916 size (number or amount) from a **population**. The defined **USP sample**, the *article*, is, of necessity, a
1917 **grab sample** as is, of necessity, any "in commerce" sampling from a small portion of a batch.
1918

1919 **Initial validation, performance qualification (PQ), or evaluation qualification (EQ) batch or lot**
1920 is a **batch** or **lot** manufactured and tested to verify the proposed routine manufacturing process
1921 controls are adequate. Because the in-process controls (**21 CFR 211.110(a)**) **require** the
1922 manufacturer to have, and follow for each batch, established control procedures "to monitor the output
1923 and to validate the performance of those manufacturing processes that may be responsible for causing
1924 variability in the characteristics of in-process material and the drug product," each production batch (or
1925 lot) is required to be a one that validates the process – *thus each is a validation batch (or lot)*.
1926

1927 **In-process dosage unit** is a capsule or tablet as it exists at the completion of any in-process step
1928 starting from the time the dosage unit is formed in the manufacturing process and continuing until it is
1929 ready to be packaged. For example, in a process that has processing steps (phases, stages) that: a)
1930 forms the final blend into tablet cores, b) film-coats the cores with a color, c) overcoats the color coat
1931 with a clear coat, d) prints identification on the clear coated units, e) waxes and polishes the printed
1932 units, f) holds the polished units in bulk until the batch is released for packaging, and g) packages the
1933 released polished units for distribution, the outputs of steps "a" through "e" are **all** collections of in-
1934 process dosage units. In the example, the corresponding appropriate "in-process dosage unit" phase-
1935 differentiating identifiers could be: a) "freshly formed," b) "color coated," c) "clear coated," d)
1936 "printed," and e) "polished." At Step "f," the dosage units are **finished dosage units**.
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Inspection is the **sampling** of a **sample** from a **population** coupled with examining or testing that **sample**, or a *subsampling* thereof, for compliance with predetermined **specifications**.

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

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

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

Where X is a given value in the **population**.

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

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

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

Quality means an essential identifying property of something.

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

1. It must be from all portions of the **population** or, *when sampling is performed during the production of the batch or lot*, it must appropriately *span* the production operation that it covers from start to finish.

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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*.

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

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

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

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2038
2039 **Sample variance** or, more accurately, the **sample estimate of variance**, denoted as s^2 , is the estimate
2040 of the variance, the second moment about the **population mean**, μ . Usually, this statistic is computed
2041 using the formula:

$$2042 \quad s^2 = [n \sum_{i=1}^n X_i^2 - (\sum_{i=1}^n X_i)^2] / [n (n-1)] \quad (3)$$

2043
2044 However, the general formula that should be used is:

$$2045 \quad s^2 = [n \sum_{i=1}^n X_i^2 - (\sum_{i=1}^n X_i)^2] / [n (n-f)] \quad (3a)$$

2046
2047 Where f is the degrees of freedom consumed in the computation process.

2048 When the X_i s are “direct” measurements, then f is **1** because one degree of freedom is
2049 consumed in the computation of the “differences.”

2050 However, when the X_i s are ratio measurements, as is often the case in hyphenated
2051 chromatographic/detector measurements using an Internal Standard, then f is **2** and the
2052 proper formula to use is:

$$2053 \quad s^2 = [n \sum_{i=1}^n X_i^2 - (\sum_{i=1}^n X_i)^2] / [n (n-2)] \quad (3b)$$

2054
2055 **Sample variability** or, more accurately, the **sample estimate of variability**, denoted as s , is the
2056 square root of the **sample estimate of variance**. This term is often referred to as the “*sample*
2057 *standard deviation*.” That name is the source of the alternate abbreviation, “SD.” While **variances**
2058 are additive, **variabilities** or *standard deviations* are not additive. Thus, if one needs to add or
2059 average *standard deviations*, one must first convert them into **variances** by squaring them. Then, the
2060 **variances** can be added and the square root of the sum is the *total standard deviation* or, for like
2061 **variances**, dividing the sum by the number of like **variances** added gives the *average variance*, and
2062 the square root of that **variance** is the *average standard deviation*.

2063
2064 **Sample size** has more than one meaning.

- 2065 • For discrete **populations** (tablets, capsules, syringes, *etc.*), it is the number of entities (units) from
2066 a **population** that are either:
 - 2067 ○ Removed by sampling or
 - 2068 ○ Inspected (examined or tested) by some procedure or method.
- 2069 • For *non-discrete* **populations** (blender loads, drums of a component, bulk liquids, *etc.*) it is the
2070 amount of material (by weight or volume) from a **population** that is either:
 - 2071 ○ Removed by **sampling**, or
 - 2072 ○ Inspected (examined or tested [evaluated]) by some procedure or method.

2073
2074 In the USP’s view, **sample size** refers to the minimum number of entities (the **USP article**) for
2075 discrete populations. For non-discrete materials, the **USP article (sample size)** is the stated amount of
2076 material that is required for a given **USP** test or evaluation.

2077
2078 Depending on the context, the **FDA** and the Court (Judge Wolin in **USA v. Barr**) have used the term
2079 **sample size** to connote either:

- 2080 – The physical amount of a non-discrete or discrete material that is to be *sampled* (a defined
2081 number of units in the discrete case or, in the non-discrete materials’ case, nominally, at least
2082 three times the dosage unit weight) or
- 2083 – The amount (number, weight, or volume) to be used in a given test or evaluation to generate a
2084 result.

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2095

2096 **Sampling** means the controlled removal of any portion of a **population** for retention and/or
2097 examination or testing purposes.

2098

2099 **Sampling plan** means the *scientifically sound* and *appropriate* strategy used to take a valid **sample**.

2100

2101 **Significant event** is any event during solid dosage production process that can adversely affect the
2102 integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a
2103 blender to a bin and from the bin to a hopper are two examples of significant events in a blending *or*
2104 dosage-forming process *step*.

2105

2106 **Simple** (Unrestricted) **random sampling** means **sampling** in a manner that each entity in the
2107 **population** has an equal chance of being the first member of the **sample**; each remaining entity has an
2108 equal chance of being the second member of the **sample**; and so on – subject to the constraint that
2109 “each possible **sample** has an equal chance of being selected.”

2110

2111 **Specification** means a detailed description of a component, material, intermediate, product, or control
2112 in terms of the numerical limits, ranges or acceptance criteria that defines what can be accepted for: **a)**
2113 use **or b)**, in the “product” case, for introduction into commerce. For the pharmaceutical industry,
2114 such specifications must be designed to ensure that the each *batch* (or *lot*) of drug product
2115 manufactured by a given firm meets *scientifically sound* and *appropriate* **specifications** that define the
2116 identity, strength, quality and purity of each dose such that, *after the batch (or lot) is released into*
2117 *commerce*, **a)** each dose can validly be represented to be safe and efficacious **and b)** any **USP** (or **NF**)
2118 *article* in said *batch* (or *lot*) will, if tested, meet the explicit and implicit commercial requirements set
2119 forth in the **USP** (or the **NF**) for that product. [**Note:** The term controls includes both the equipment
2120 used to effect the control required and the permissible limits, ranges, and/or acceptance and other
2121 criteria used to establish that a given control is functioning or has functioned as it was designed to
2122 function.] A **specification** is a predefined characteristic, or limit, or range of an attribute or variable
2123 that defines what is an acceptable product outcome for a given process step. Examples of attributes
2124 are:

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

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Examples of attribute characteristics are:

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- Color and
- Shape.

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Examples of limits and ranges for tablet attributes include:

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

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

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- Active level is 100 % to 102 % of the label claim (*LC*),
- After 1 hour, *not less than* 10 % *LC* nor *more than* 30 % *LC* is released and, after 4 hours, *not less than* 70 % *LC* nor *more than* 80 % *LC* is released
- Tablet weights must be between 190 and 210 mg.

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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.

Examples of limits and ranges for acceptable product outcomes include:

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

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

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

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

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

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

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

Test, as a verb, means to examine something in order to ascertain the presence of or the properties of a particular substance – *test for bacteria on a surface* or *test for the level of water in a drug substance*.

Test, as a noun, means a procedure or method used to **evaluate** a **sample** or **sample** aliquot for some **characteristic** or **characteristic** level – *the test for Chloride was negative*.

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

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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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