

# Current Events in Blend and Content Uniformity

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This article presents a summary of the stratified sampling session held at the 2013 ISPE Annual Meeting.

In 1999, the Product Quality Research Institute (PQRI) established the Blend Uniformity Working Group. The purpose of this group was to make scientifically based recommendations on suitable procedures to ensure blend and content uniformity of a batch. The recommendation had to comply with 21 CFR 211.110 *Sampling and Testing of In-Process Materials and Drug Products*,<sup>1</sup> which require in-process testing for adequacy of mix. The recommendation provided an alternative approach to assess blend uniformity from that described in the former FDA guidance document, “Blend Uniformity” issued by the Office of Generic Drugs.<sup>2</sup> On 31 December 2002, PQRI submitted the group’s final recommendation to the FDA,<sup>3</sup> which formed the basis for the FDA draft guidance for industry, “*Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment*,” issued October, 2003<sup>4</sup> hereafter referred to as the draft guidance document. Although the draft guidance document was never finalized, it was extensively used throughout the pharmaceutical industry. On 7 August 2013 the FDA withdrew the draft guidance document because it was no longer consistent with current Agency thinking.<sup>5,6</sup>

A group of individuals from the FDA, academia, and industry (sponsored by the International Society for Pharmaceutical Engineering (ISPE)) formed to discuss alternative approaches to assess Blend and Content Uniformity (BUCU) Group. This group sponsored a session at the ISPE Annual Meeting on 6 November 2013<sup>7</sup> to discuss the concerns that lead to the withdrawal of the draft guidance document. The session also included presentations for potential alternative approaches for the assessment of blend and content uniformity of solid dosage forms. The purpose of this article is to

provide a summary of that session. Note that some presentations are not summarized here, in cases where permissions for publication were not granted.

## Basis for the Withdrawal of the Draft Guidance Document

The primary reason for the withdrawal of the draft guidance document was that Sections V and VII no longer represent of the Agency’s current thinking. Section V recommended taking at least three replicate samples from at least 10 locations within the blender. However, the guidance only required that one sample from each location be evaluated to assess blend uniformity as part of first stage testing. The FDA’s current preference is to analyze all three replicates from each location.<sup>6</sup> The use of nested sampling plans and testing of replicate samples from each location allows the data to be subjected to Variance Component Analysis. This statistical technique divides the total variance into “between location” (the amount of variability across the sampling locations in a blender, or during a compression, encapsulation or filling process), and “within location” (the amount of variability between samples within a given sampling location). High between location variances often indicate poor mixing and non-uniformity within the blender, and also can imply non-uniformity or segregation during dosage form manufacture. High within location variances can be indicative of sampling bias (for blends) or incomplete mixing on a unit dose scale. Both variances are indicative of the quality of the batch.

The number of samples and the acceptance criteria contained in Section VII (Routine Manufacturing Batch Testing Methods) were based upon the limits published in the United States Pharmacopeia (USP) General Chapter

<905> *Uniformity of Dosage Units*.<sup>8</sup> This was intentional to avoid any changes to the existing quality standard or an increase in the number of dosage units to be tested. The use of stratified sampling plans resulted in increased confidence for the uniformity of the batch, because sample locations target problematic areas prone to segregation or incomplete mixing. USP <905> *Uniformity of Dosage Forms* does not include a statistical sampling plan and is only intended to determine conformance of a defined sample. FDA's position is the results from USP <905> *Uniformity of Dosage Units* provide limited assurance that the batch meets specifications and statistical quality control criteria. [CGMP also requires sampling plans to be scientifically sound and representative of the entire batch (21 CFR 211.160(b)).] The FDA cited more statistically sound sampling plans and acceptance criteria that can be used to ensure the batch complies with current CGMPs, including 21 CFR 211.110, *Sampling and Testing of In-Process Materials and Drug Products*, 21 CFR 211.160 *General Requirements* [Subpart I, Laboratory Controls] and 21 CFR 211.165 *Testing and Release* [of the finished drug product] for Distribution.<sup>1</sup>

A science- and risk-based approach should be used to assess blend and content uniformity. Although powder thief sampling has known limitations, the FDA encourages industry to continue using the technique to assess blend uniformity (and identify errors when they exist), as well as more innovative approaches such as NIR<sup>9</sup> and Statistical Process Control (SPC) to assess blend uniformity. The technique(s) that companies choose to assess blend or content uniformity should be justified, including the number and size of samples, the position of probes, and the amount of sample measured.

The FDA recommends the use of stratified sampling plans when the batch contains locations that may have different results for a measured quality characteristic. The expectation is for the product quality to be consistent throughout the entire batch with no significant differences existing between locations. ASTM E2709<sup>10</sup> and ASTM E2810<sup>11</sup> can be referenced for establishing acceptance criteria for a stratified sampling plan.

## Sampling Plans and Statistical Methods for Process Validation (Jim Bergum)

### Sampling Plans

A sampling plan describes where (locations) and how the samples are taken from the blend or batch, and the number of samples (blend amount or dosage units) taken from each location. The most common plans are given below:

- **Simple Random Sampling:** each dosage unit has an equal probability of being chosen as a member of the units to be tested and are picked completely at random.
- **Stratified Sampling:** partitions the batch into "strata"

(for example, first 1/3, middle 1/3, and final 1/3). The combination of all strata covers the entire batch. Then random sampling is performed within each stratum.

- **Systematic Sampling:** samples are taken at equal intervals throughout the batch. The first sample location is determined at random in the first interval then the remaining samples are taken at equal intervals from that point.

Typically for both simple random and stratified sampling, only one dosage unit is tested at each location which is called Sampling Plan 1. If greater than one dosage unit is taken at each location, the plan is referred to as Sampling Plan 2. Suppose 12 dosage units are taken from a batch and tested based on a systematic sampling plan using Sampling Plan 1. The variability in the results could be due to different locations or just the natural variability had all units been taken from the same location.

Figure 1 shows what the data would look like in the case where there is location to location variation (top half) and where there is no location to location variation (bottom half).

In the upper portion of the plot where there is location to location variation, the results at each location are similar, but there is variation between the locations. In the lower portion of the plot where there is no statistically discernible location to location variability, the within location variability is as variable as the variability between the locations.

### ASTM E2709/E2810

The USP Uniformity of Dosage Units (UDU) given in General Chapter <905> Uniformity of Dosage Units of the USP UDU test is a market standard and is not intended for inspecting uniformity of finished product for lot/batch release or as a lot inspection procedure. Passing the UDU test once does not provide statistical assurance that a batch of drug product will meet specified statistical quality criteria.

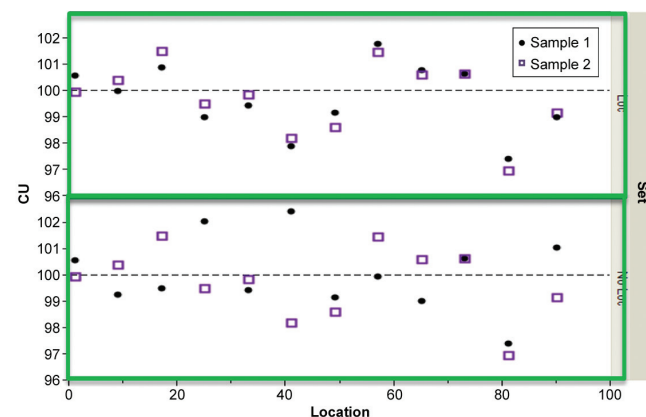


Figure 1. Batch data with and without location variability (CU vs. Location).

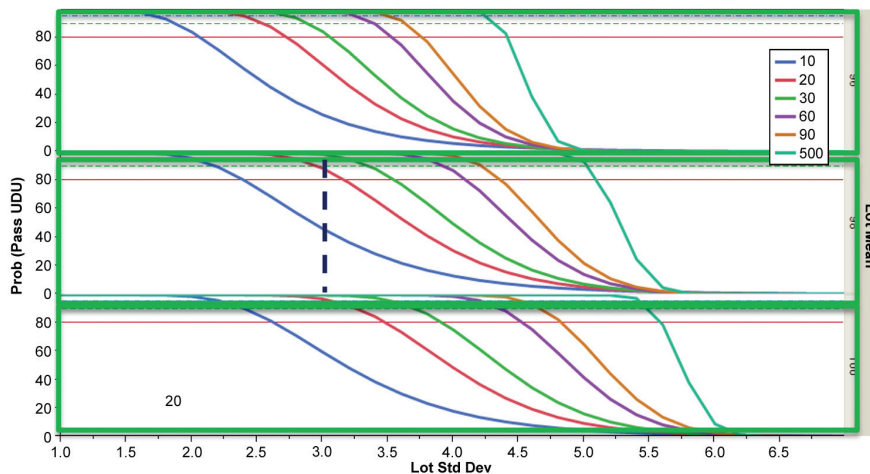


Figure 2. OC curves for Sampling Plan 1 (OC Curve = Prob (Passing Acceptance Limit Table for Specific Lot Mean and Standard Deviation)).

A methodology was developed by James Bergum<sup>12</sup> and updated by Bergum and Li<sup>13</sup> to provide this assurance that resulted in the following standards: ASTM E2709, “Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure” and E2810, “Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units.” ASTM E2709 provides the general methodology and E2810 applies the methodology specifically to the UDU test. The goal is to develop limits based on the process validation sample results that would provide confidence that the testing standard samples would pass the testing standard. The method assumes that the content uniformity results can be approximated by a normal distribution. A summary of the methodology with examples is given in the Encyclopedia of Bio-Pharmaceutical Statistics.<sup>14</sup>

As an example, suppose that a sample of 20 dosage units were taken from a batch using Sampling Plan 1 with a sample mean and standard deviation of 99% and 2.46% label claim, respectively. The ASTM E2810 acceptance limit table associated with this plan using a 95% confidence level and ensuring at least a 95% probability of passing the USP UDU test has an upper limit on the sample standard deviation for a sample mean of 99% of 3.52%. Therefore, this sample meets the criterion ensuring, with 95% confidence, that a sample taken for testing against the USP UDU test has at least a 95% chance of passing the UDU test.

Operating Characteristic (OC) curves show the probability of passing the acceptance limit table for various sample sizes. They are used to select a sample size. Figure 2 shows the OC curves based on 95% confidence intervals for batch means of 96, 98, and 100%LC and various sample sizes from 10 to 500 using Sampling Plan 1. Suppose based on lab data and current knowledge of the product that the expected ‘true’ batch mean would be above 98%LC and the standard deviation is less than 3%. The dashed vertical line is for

a lot mean of 98% with a lot standard deviation of 3%. The dashed horizontal reference line is at 95% in the figure. So if we want a good chance of passing the acceptance limit table, a sample size of 30 would be reasonable.

Sampling Plan 2 is generally a systematic sample where more than one dosage unit is tested from each location. Suppose that a batch is sampled at 15 locations evenly distributed throughout the batch and four tablets are tested at each location.

The statistics required to use the acceptance limit table for Sampling Plan 2 are the overall mean, the within-location standard deviation and the standard deviation of the location means. Suppose these values are 98.93%, 1.07%, and 1.06%, respectively.

The acceptance limit table for Sampling Plan 2 contains limits for the overall mean for various combinations of the within-location and location mean standard deviation. If the acceptance limit table in this example was constructed using 90% Confidence with 95% coverage, the lower and upper limits on the overall mean are 89.1 to 110.9%LC. Since the overall mean in our sample is 98.93%LC, the sample passes the limits.

### What Level of Variation is Acceptable (James Prescott)

As discussed in other presentations, different drug products could have different maximum and minimum potency values before the patient is affected by either an unsafe or ineffective dose. Note also that the patients themselves are variable one-to-another, in terms of body weight and how they respond to a given drug. If these limits were understood for a population of patients, one could then determine what the acceptable levels of uniformity could be for the product itself. This knowledge could be used to answer questions such as:

- What is the upper and lower acceptable limit for the potency of any single dosage unit a patient could receive (i.e., within the entire population/batch that is released)? Note this is different than limits on values for a single dose that is *tested* from a smaller subset of a population. For example, a batch with a mean of 100%, an RSD of 6.0% and a normal distribution would theoretically have 31 of 1,000,000 tablets outside of 75 to 125%. In this case, 31 consumers may receive tablets that could be unsafe or ineffective. There would be a low probability of directly measuring these specific tablets via most sampling plans, but these nonetheless would be released as part of the

batch (if a 6% RSD were acceptable).

- Does the variation matter solely from tablet-to-tablet or could it matter bottle-to-bottle (of tablets)? For example, a single tablet being low might not matter if the overall course of treatment is at the target value. On the other hand, if the bottle overall is sub-potent, this might have more of an effect than if a single dosage unit is low. In some manufacturing processes, the dosage units are packaged in a sequence closely aligned with when they were created. Other processes (such as film coating an entire batch) randomize the dosage units such that there is no connection between packaging and dosage unit creation, in terms of the sequence. This could have an effect on the sampling plan and acceptance criteria.

If the acceptable level of uniformity is understood for the patient, in terms of either single dosage limits or overall treatment limits, this could be translated to specific sampling plans designed to detect these limits.

### *What Could Effect Uniformity*

Sampling and testing is done to challenge the assumption that the product is sufficiently uniform. If no special causes that can create non-uniformities are present, and all variation throughout the entire population is by random variation, one would expect a normal distribution. In this case, the population's uniformity could be reasonably estimated with a limited number of samples to determine, within a range of certainty, an estimate of what the population mean and standard deviation would be. The sole question would then be what an acceptable range would be for a population mean and population standard deviation.

However, the assumption that no special causes are present is not valid when non-uniformities arise. Reasons for non-uniformity include: poor blending, segregation from the blender to the creation of a dose, poor particle dispersion (e.g., agglomerates), losses of components or dispensing errors, and product weight variations. Non-uniformities also can *seem* to be present due to sampling problems (e.g., thief sampling errors) or due to analytical errors. Each of these root causes can result in different forms of variability or signals. These signals, if correctly captured and interpreted, can point back to the likely root causes.<sup>15</sup>

Since these signals are not occurring randomly, but as a function of when and where the problems arise in the manufacturing process, sampling must include samples produced during these points. Therefore, in defining an appropriate sampling plan, some fundamental knowledge of what to look for, and where/when to look for it, is required; otherwise, a very large number of samples may be needed to cover all the bases. For example, it is generally recognized that segregation can lead to non-uniformities particularly at the very beginning or very end of discharge of a bin. Focusing sample

collection in these areas can be a better use of resources to challenge whether segregation occurred, rather than simple random sampling. This was the rationale for targeting "significant events" in the draft guidance document.<sup>4</sup>

Separating out within-location vs. between-location variations is one critical aspect in understanding uniformity, as these variations are attributed to different root causes. For example, within-location variations are usually attributable to poor dispersion of the active drug due to poor micro blending or agglomeration, sampling/analytical errors, or just random noise in the process. Between-location variations are usually attributable to poor macro blending or segregation. Having a single sample from a given location might show an unacceptable result, but does not allow for distinction of the possible source(s) of the problem. Further, if there is high within-location variation, there is a risk that a single sample from a given location might be non-representative of the location as a whole, e.g., the location is superpotent overall, but the one sample analyzed is close to target. Note that for a location to provide relevance in this sort of analysis, the samples that represent the location must have been collected from essentially the same time point or position. Factors that could negatively influence this approach include sub-sampling from a larger sample, sampling error (in the case of thief samples), and physical differences during the dose creation (multiple stations or lanes on the forming machine).

Not all non-uniformities are equal. A batch which has normally-distributed data, shows mostly within-location variation, with all locations being statistically identical, would suggest a process where random variation alone is occurring, without any special or assignable root causes. This gives a higher degree of assurance that all dosage units would have the same random variation, and thereby less concern that there are undetected dosage units that would be worse than that estimated by statistical inference. On the other hand, data which shows tails, non-normality, and/or locations that are different than others (high between-location variations), imply that a special cause may be occurring, which might lead to intervals during manufacturing which are even worse than those that were sampled.

A question that must be addressed with any sampling plan and acceptance criteria is whether any or all specific problems (blend non-uniformities, segregation, agglomeration) must be targeted with specific, customized sampling plans, or whether the approach can allow these potential problems to be uncovered by other means.

### *Holistic Considerations*

Understanding the uniformity of a particular batch is never done in the vacuum of just looking at uniformity of the dosage units. There is prior knowledge of many factors that could give rise to or prevent uniformity issues, such as the

drug loading, whether the blend is a dry blend (e.g., direct compression) or granulated (e.g., wet granulated, roller compacted, spray dried), the particle size and shape of the components (which may give some insight on dispersability, agglomeration, and segregation potential), cohesiveness/stickiness of the blend and/or its components, the scale of handling (e.g., development vs. manufacturing) and the process/equipment being employed (e.g., in-bin blending, scoop vs. automated feed of the press, isolation features for press feeding). Long before the first sample is pulled, one can already have one or more hypotheses that should be tested to demonstrate that sufficient uniformity is likely to be achieved and maintained.

Once multiple batches have been made, comparison between the current batch under consideration and all prior batches also could come into play. A change in behavior can be as telling as the actual values themselves. For example, a process which has a long history of <2% RSD could be looked into when a 5% RSD is noted, even if 5% is otherwise acceptable. Another example is if all batches had mean values between 99 and 101%, a result of 97% could be a warning indicator.

### *Comparison of Blend Data to Product Data*

Product (dosage unit) uniformity is the sole area of concern for the patient, as they are only consuming dosage units and not samples from the blender. However, blend uniformity data can provide additional insight to batch uniformity, provided that one can rely on the samples collected from the blender as being unbiased/without error, which is often not the case. "Adequacy of mixing" is also required per CGMPs although demonstration of an adequate mix can be achieved without using samples from the blender itself.

If one has reasonable assurance that blend sampling errors are not occurring, comparing blend uniformity data to product uniformity data can provide further insight as to possible manufacturing issues. For example:

- A decrease in overall potency from the blender to the dosage units could be an indication of losses of active during manufacturing.
- An increase in between-location variations could be an indication of segregation during transfer.

Blend data and content uniformity data should be compared, but they may not be correlated. If both have variations solely due to random noise, they will not be correlated. If correlated (high BU RSD translates consistently to high dosage unit RSD), special causes for variations are present, such as incomplete mixing of certain batches or variations in raw materials that create non-uniformities that translate from blending through to the dosage units.

### *Some Common, Specific Questions that are not Well-Addressed Currently*

Common sampling strategies and acceptance criteria have not addressed the following questions, which seem to arise regularly:

- Does one need to consider the uniformity/quality of the blend at the very beginning or very end of compression, if these portions of the batch are waste? If not, could the tails be extended intentionally, e.g., longer start-up period, earlier shut-down, so as to avoid having a uniformity problem?
- Should normality of the data be considered, and if so, what deviation from normality should cause concern? What test(s) should be used for normality? Should normality tests be restricted to each single batch or the process as a whole?
- If a process has consistently shown excellent uniformity (e.g. >10,000 dosage units tested over many years, with an average batch RSD of 2.3%, normally distributed), and one day a single dosage result of 136% is found without any assignable cause after extensive investigations (no manufacturing or laboratory errors found, no deviations from normal), should this *require* any process improvements or new controls, or is this just the tail of normal, random variations that were occurring all along? Does this result call into question the process or product?

### **Relationship of Blend Uniformity to the Finished Drug Product Uniformity and Performance Variability (Ravi Tejwani)**

#### *Typical Sources of Variation*

In a given powder blending based manufacturing process, several possible sources of variation exist. Broad classes of these include those arising from the material properties, manufacturing process, and from the measurement systems. While not always feasible, material properties can be mitigated to some extent to minimize the dosage form variability. The constraints resulting from material properties (e.g., particle size, choice of process, type of blend formed by a given material), unless mitigated, tend to be limiting in the sense that they cannot be overcome by making changes to the manufacturing process. The manufacturing process related variations could arise from either the process design (e.g., insufficiency of blending time, too fast a filling process to allow sufficient time for filling or a dispensing system) or the errors in the execution of an established process that is known to produce uniform product (also referred to as control system variability, e.g., RPM calibration of the blending equipment or weight control on a dispensing system such as a dosator or a fill cam). Typical product development activity should include a systematic study of all applicable sources of variation and ensure that their contributions

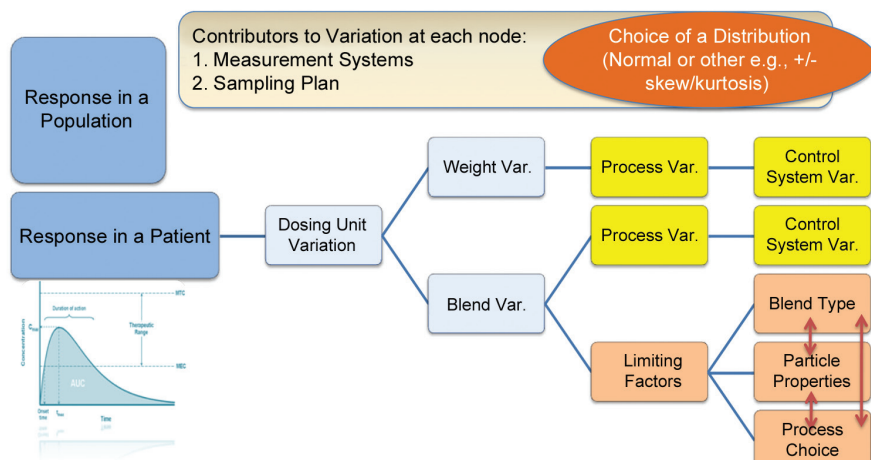


Figure 3. Relationship among the typical sources of variation in a drug product.

remain under control. The relationship among the typical sources of variation is shown in Figure 3. During the product development as well as during routine manufacture an additional source of variability is often realized, and that is the variability of the measurement system (errors of sampling as well as the error of measurement). Most frequently cited examples of sampling are the design of thief during powder sampling, and inadequate protocol employed in sampling of the finished dosage units. The error of measurement is usually easily accessible through the validation of the analytical methods.

### Considerations for the Limiting Factors

Factors such as particle size of the active ingredient and the type of blend are usually decided earlier in product development and determine the best possible dosing unit precision that a manufacturing process can deliver. For example, uniformity of a random blend increases to a limiting value in a blending operation; however, it never approaches as high as that of a structured blend. This is one of the reasons for adding a granulation unit operation in a manufacturing process. Reader is referred to literature for more detailed discussion on the blend types<sup>16</sup> and the effect of particle size of active<sup>17</sup> on the uniformity of blends and dosing units.

### Accountability for Multiple Sources of Variation – It is all about Bookkeeping

Often reported thief related errors (one of the two components of the blend measurement system) sometimes make blend variability appear higher than it is, leading to an abandonment of the

BU approach altogether because the dosing unit variability is shown to be much lower than that of the blend. If a reasonable effort is made to decrease (or accounted for properly) the sources of error in the measurement systems, this anomaly usually disappears. After all, the dosing units are prepared from the blend by some sampling method (a dosator, a screw feeder, or a tablet press die with a fill cam). In a possible scenario of lack of any feasible blend analysis method, at the very least, a good correlation between the dosing unit weights (W) and the potency (D) can be demonstrated as an indirect evidence of blend uniformity. In the following equation, the residual term in the

regression between D and W should contain the information about the blend uniformity:

$$D = WB \tag{Equation 1}$$

Where D = dosing unit potency, W = weight of the dosing unit, and B = concentration of the active in the batch of blend that was used for weighing the dosing units. Absence of such a correlation may signal the need for further investigation. Finally, the quantitative amount of the “unaccounted variance” allowed for a given product depends on the specific risk benefit profile of the product (discussed further under the Biorelevance topic below).

It also should be noted that the uncertainty of the estimates of variability depends on sampling related factors: 1) the aliquot size (or dosing unit size) and 2) the number of aliquots (in case of blends) or the number of dosing units. It should be noted that the most relevant size of powder blend aliquots is the same as the target weight of the blend in the

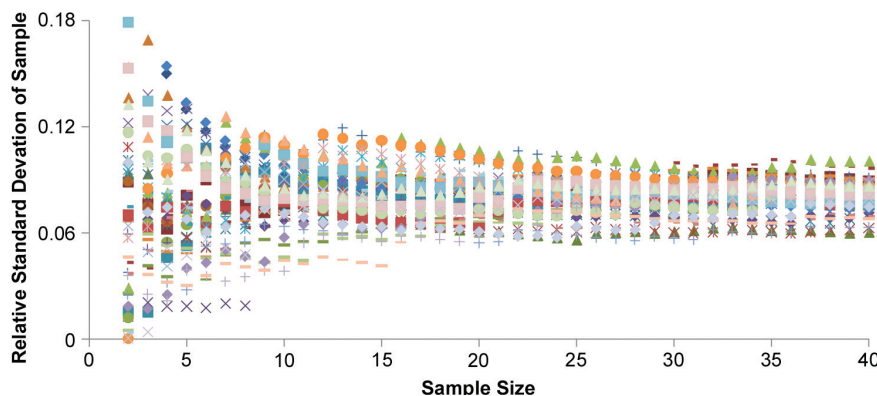


Figure 4. Relative Standard Deviation as a Function of Sample Size. The Samples are drawn randomly from a Batch of 100,000 units simulated with an underlying mean of 1 and Relative Standard Deviation of 0.08. Symbols indicate different samples drawn from the same batch.

dosing unit. Any larger aliquot size would lead to a more liberal estimate and a smaller aliquot size would lead to a more conservative estimate.

During the product development phase, only a reasonable estimate of the variability is desired (e.g., to guide next steps in product or process design) as opposed to adjudicating the release of a batch. Determining the number of aliquots or dosing units needed to estimate variability in absence of an acceptance criterion can be difficult. In this situation, a point of diminishing returns exists near 30 to 40 units as shown in Figure 4. Data interpretation (as to the true variance of the batch) should take into consideration that significant uncertainty still remains in the estimate of the variability. For example, approximately one third of samples (at  $n = 10$ ) will show a RSD less than 0.06 despite the batch RSD at 0.08 (i.e. 1/3 odds of erroneous acceptance).

The exercise in Figure 4 was repeated for various batches with differing RSD values. This type of simulations suggest that a sampling spread of approximately 50% to 150% exists around the batch RSD values at a sample size of 10 (target RSD of 8 has a spread from approximately 4 to 12). This spread remains the same irrespective of the batch size simulated or its RSD. Based on this, one would not expect multiple samples of 10 dosing units each (or powder aliquots each) conform with each other, let alone the blend samples relating to the dosing units.

The manufacturing process related sources of variation (e.g., number of blender revolution) can only be studied after assuring that the measurement system (sampling and analytical) variability is lower than the former.

### Biorelevance of the Uniformity Specification: A Separate Specification for Each Product

For a given drug, the favorable and unfavorable responses are considered to be related to the quantity of the active drug administered.<sup>18</sup> Both types of responses are generally correlated to the concentration in the central tissues such as blood or plasma. Since most dosing regimens involve some type of periodicity in multiple dosing, it is reasonable to conclude that the preceding statements relate to the steady state concentrations as opposed to the concentrations obtained from single doses. Further, if the dose response (favorable or unfavorable effect) of a given drug is driven by the area under the concentration time profile (AUC), the AUC obtained at the steady state of multiple dosing is relevant. Following is a set of simulation studies undertaken<sup>19</sup> to evaluate the effect of variation in the dosing unit content on the *in vivo* concentrations.

In each of the simulations below, the pharmacokinetic parameters for each drug candidate, (amoxicillin<sup>20</sup> and levothyroxine<sup>21</sup>) were obtained from the respective published studies in the literature. Relative standard deviation values of 6.5%, 13%, and 20% were simulated for 500 mg amoxicil-

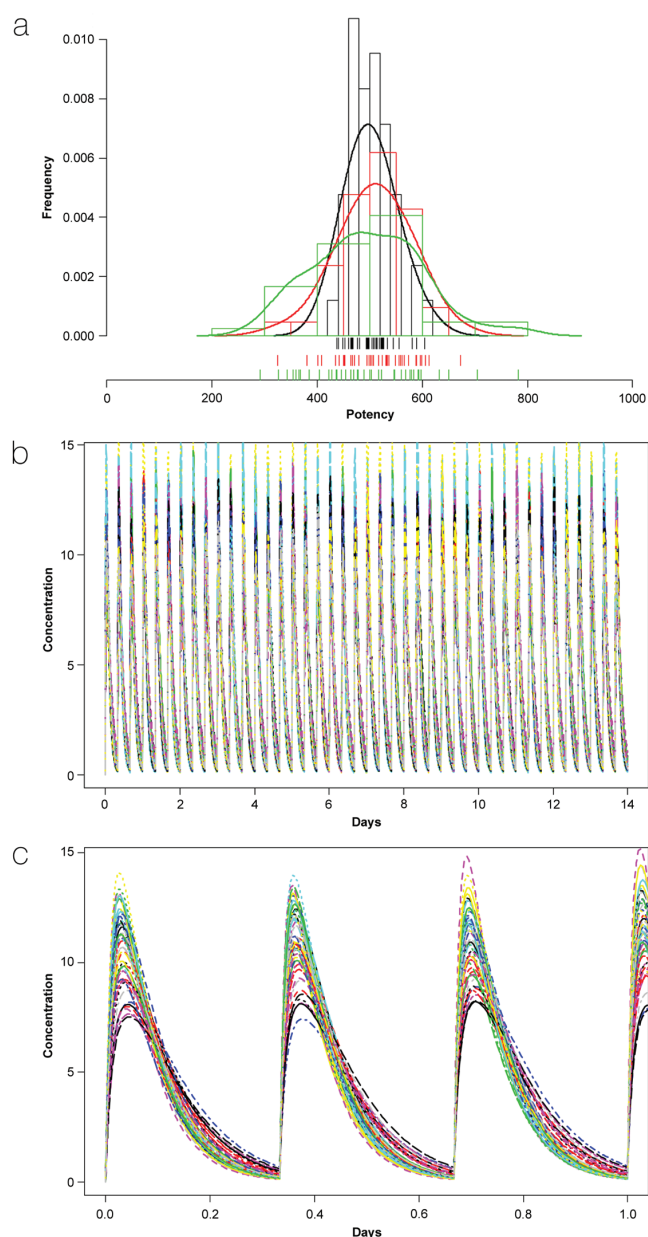


Figure 5. Simulated Potency Distribution and PK profiles for Amoxicillin 500 mg. Panel A: Potency distributions of the tablets used as input for pharmacokinetic simulation, Panel B: Plasma concentration vs. time profile after multiple dosing for 13% RSD tablets in a clinical trial with 48 subjects, Panel C: Magnification of Panel B. Color codes for Panel A: Black = 6.5% RSD, Green = 13% RSD, Red = 20% RSD. Each color in Panel B and C represents a simulated subject.

lin, and values of 1%, 2%, and 6.5% were simulated for 150-mcg levothyroxine.

It is known that multiple dosing of an active leads to a “loading” phase and a “maintenance” phase to the dosing regimen. The two phases are clearly apparent in cases where the steady state  $C_{max}$  is a multiple of the  $C_{max}$  levels observed

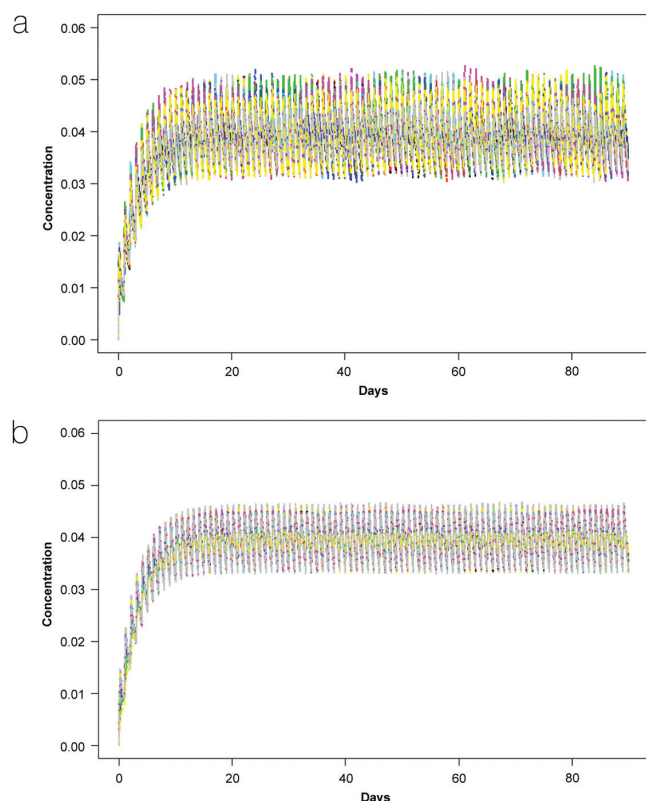


Figure 6. Simulated PK profiles for levothyroxine, 150 mcg. Panel A: Plasma concentration vs. time profile after multiple dosing for 6.5% RSD tablets in a clinical trial with 48 subjects Panel B: Pharmacokinetic simulation of 1% RSD tablets in a clinical trial with 48 subjects, each color in Panel A and B represents a simulated subject.

after a single dose (e.g., levothyroxine, Figure 6); and not so apparent in cases where the steady state  $C_{max}$  is close to the  $C_{max}$  observed after a single dose (e.g., amoxicillin, Figure 5).

In the case of amoxicillin, where usually time spent above a certain minimum concentration relates to the biological efficacy; variations of as high as 13% RSD in the tablet potencies lead to relatively small perturbations in the time spent above a given concentration in the simulations. Further, the simulations show that the  $C_{max}$  may change from dosing unit to dosing unit (a parameter correlated to the potency of each unit). Since typical safety margins are larger than a few multiples (assumed), the variation in  $C_{max}$  observed for amoxicillin is not likely to traverse the thresholds.

In case of levothyroxine, the pharmacologic activity depends on the maintenance of the levels of the hormone within a narrow concentration window. The width of the  $C_{max}$  to  $C_{min}$  window at the steady state becomes a concern given the fact that a dose level of 137 mcg is considered clinically different from 150 mcg. The simulations show that the dosing unit variations of 6.5% would exceed the lower threshold, and a 1% or 2% RSD standard may be more appropriate.

The limits specified in USP <905> allow for approxi-

mately 6.5% RSD for dosing units, irrespective of the specific drug properties. The simulations above demonstrate that significantly different limits could be applicable for each drug depending on its pharmacologic profile. Sufficient information regarding the dose response and manufacturability of a given drug candidate may be available to allow for establishing such a requirement for dosing unit precision.

## Going Forward

The BUCU Group intends to publish a paper (Spring 2014) which defines alternate approaches for the assessment of blend and content uniformity. The intent is to identify a number of techniques to assess blend and content uniformity, rather than rely on a single approach.

In addition, discussions have occurred within the group since the November session regarding the potential impact that the group's output will have on USP General Chapter <905> Uniformity of Dosage Units. USP recognizes that the USP <905> is specific to compliance testing of finished drug product and is not intended to evaluate the acceptability of whole batches of units that were not subjected to the test. The emergence of consensus standards such as those cited in this text provides an opportunity to strengthen the USP standard by inclusion of these concepts. This could provide a readily available source for these standards and unambiguously apply them to USP articles. In addition, the process of developing a USP chapter will include oversight by the USP Council of Experts, as well as providing an additional round of public comment for those who may not be focused on other sources of product standards. The pharmaceutical community could engage in a public discussion to determine how well a USP chapter such as this would be accepted. That said, the withdrawal of the draft guidance document serves this purpose in that it is the removal of a batch release recommendation, a portion of which was inappropriately based on the compliance testing chapter USP <905>. The full impact of this new approach can be explored in additional publications that can focus on the ability to advertise product quality through compliance with a public quality standard.

The group's recommendations and the impact they will have on USP <905> will be discussed at the 3rd Annual ISPE – FDA GMP Conference (Baltimore, Maryland; 2-5 June 2014).

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## About the Authors



**James S. Bergum, PhD** received his PhD in statistics from Montana State University (1981). Bergum worked in nonclinical biostatistics for Wyeth from 1981 to 1988 and Bristol Myers Squibb from 1981 to 2012. His primary job responsibility was

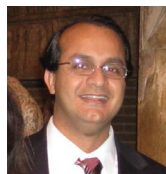
to provide statistical support to research and development, including design and analyses of experiments, analytical assay development and method validation, process validation, stability, drug safety evaluation, and teaching short courses to scientists. He developed a statistical method that resulted in two ASTM methods (ASTM E2709 referenced in the FDA guidance for Process Validation and E2810) that can be used to evaluate development, process validation, or release data. After retiring in 2012, Bergum started BergumSTATS, a statistical consulting company specializing in statistics related to Chemistry, Manufacturing, and Control (CMC) issues. His current interests are statistical methodologies that can be applied to product development, process validation, and manufacturing.



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**Ravindra W. Tejwani** was trained as a pharmacist and has worked in the pharmaceutical industry for more than two decades. He has earned his MS in pharmaceutical sciences from the University of Mississippi and his PhD in pharmaceutical sciences from the University of Kentucky. He has been author or co-author of many publications, conference symposia, and patents. Tejwani maintains interest in computational modeling and simulation of the phenomena in pharmaceutical sciences. In this area, his recent works include molecular dynamics simulations of the lipid bilayer membranes, prediction of content uniformity, and biorelevance of content uniformity. In his role at BMS since 1997, he has been involved in several positions of increasing responsibility and has led development, scale up and technology transfer, and commercialization of new drug products.

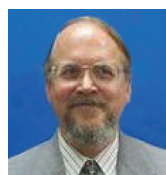


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**Jon Clark** brings many years of experience in the global pharmaceutical industry and more than 20 years of experience with the US Food and Drug Administration (FDA). For the last 10 years at FDA, Clark has held the title of Associate Director for Program Policy, Office of Pharmaceutical Science, in FDA's Center for Drug Evaluation and Research. As Vice President, Clark will lead the development of new monographs in both the United States Pharmacopeia-National Formulary (USP-NF) and the USP Medicines Compendium (MC), focusing on the possibility of comprehensive monographs that are potentially suitable for all three compendia. Clark will work closely with Todd Cecil, PhD, Vice President of Chemical Medicines – Monograph Modernization to advance a full cohort of monographs. He holds an MS in chemistry from Rutgers University and a BS in chemistry from University of Michigan Ann Arbor.



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