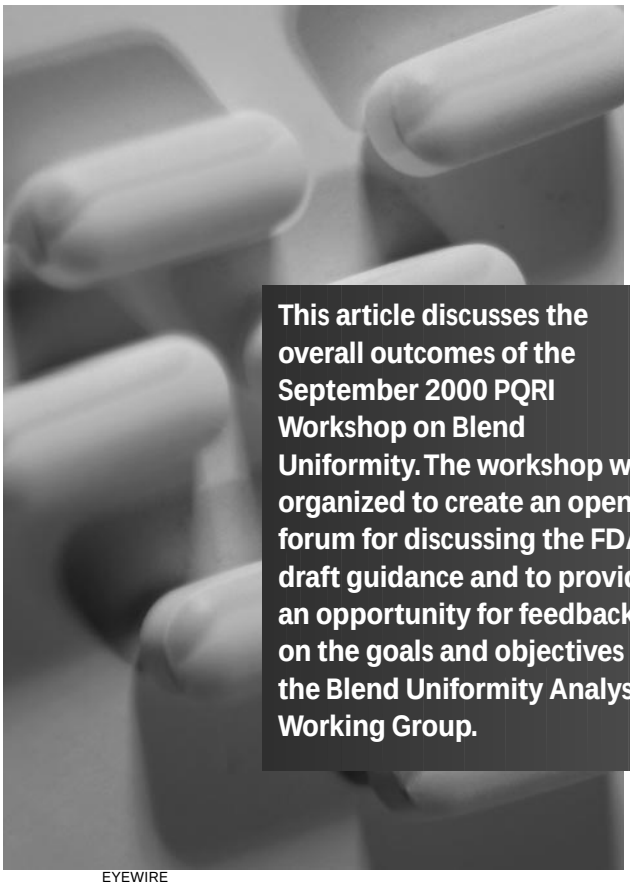
A Report of the PQRI Workshop on Blend Uniformity

Jozef H. Timmermans



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This article discusses the overall outcomes of the September 2000 PQRI Workshop on Blend Uniformity. The workshop was organized to create an open forum for discussing the FDA draft guidance and to provide an opportunity for feedback on the goals and objectives of the Blend Uniformity Analysis Working Group.

Jozef H. Timmermans is Manager of Pharmaceutical Technical Operations at Merck and Company, Inc., Summeytown Pike WP62M-1, West Point, PA 19486.

The Blend Uniformity Analysis Working Group (BUAWG) of the Product Quality Research Institute (PQRI) held a workshop about blend uniformity on 7–8 September 2000. Approximately 250 representatives from the pharmaceutical industry, FDA, and academia attended the workshop. The main purpose of the meeting was to create an open forum to discuss the August 1999 FDA draft guideline for routine blend uniformity testing on abbreviated new drug application (ANDA) products. Presentation topics included a review of current regulatory practices of blend uniformity (Buhay, FDA), a discussion of the FDA BUA draft guidance (Holcombe, FDA), powder blending (Muzzio, Rutgers University), handling of powder blends (Prescott, Jenike and Johanson), blend sampling and assessment (Berman, Bayer), acceptance criteria and data analysis (Planchard, Aventis), near-infrared (NIR) spectroscopy (Sekulic, Pfizer), new devices for physical sampling (Muzzio, Rutgers University), validation requirements for novel analytical techniques (Takiar, FDA), and a discussion of the BUAWG research (Garcia, Glaxo Wellcome). In addition, breakout discussion sessions were organized to obtain answers to the following questions: Is blend uniformity testing on every batch a value-added test? How does one validate the process when a sampling problem exists? What new technologies are available to assess blend uniformity?

The following describe the overall outcome of the workshop:

- With currently available technology, blend uniformity testing is not value-added during routine manufacturing. If required, most workshop participants favored a reasonable amount of extended finished product and core testing.
- Appropriate and meaningful blend uniformity testing not only should be conducted during development but should be confirmed during validation.
- No universal new technology is available for blend uniformity testing. NIR spectroscopy is being used by several companies during development, but it has significant limitations.
- The PQRI BUAWG should focus its efforts on investigating enhanced testing of in-process cores or capsules in lieu of blend uniformity analysis; identifying high-risk practices; and confirming the hypothesis that routine blend uniformity analysis does not add any value (data mining).
- Although blend uniformity testing is not value-added, FDA representatives insisted on having it conducted rather than

challenge the Barr ruling, which was published in the early 1990s. The Barr ruling is used as the legal foundation to enforce the blend uniformity issue.
- It was obvious that several companies are investing significant resources in the area of new technology development and implementation (e.g., NIR spectroscopy).

Background

PQRI was formed as a collaboration of seven pharmaceutical organizations (including FDA Center for Drug Evaluation and Research) with a mission to generate scientific information to support regulatory policy. Since the foundation was established, three other organizations, USP among them, have joined PQRI. The Blend Uniformity Working Group was formed within PQRI to evaluate issues regarding blend uniformity in general as well as the draft guidance on this subject as published by FDA–Office of Generic Drugs in 1999. The working group consists of members from industry, academia, and FDA.

Since the early 1990s the generics industry has performed routine blend uniformity testing on every batch in response to inspector expectations to demonstrate adequacy of mix (good manufacturing practice [GMP] specification). More recently, on an inconsistent basis, blend uniformity test data have been submitted as part of their ANDAs. To unify filings and expectations, FDA published a draft guidance on blend uniformity testing during routine manufacturing for ANDA products in August 1999. The guidance also was drafted as a result of increased content uniformity failures observed by FDA. Industry response to this proposal embodied both the concerns of routine testing as a GMP requirement and the limitations of current blend uniformity testing, sampling methodologies, and criteria. These concerns were consistent across both generic and innovator drug manufacturers. Also, the draft *CFR* that was published three years ago stated that drug manufacturers will test blend uniformity on every scalable batch. The Parenteral Drug Association addressed the issue of blend uniformity in a technical bulletin that was published two years ago. However, the recommendations in that bulletin are rarely used because they are based on a complicated and cumbersome statistical approach.

After the publication of the draft guidance, PQRI formed the BUAWG, which is charged with the investigation of this issue and the generation of potential solutions, alternatives, counterpoints, etc. Even though the draft guidance currently covers only generic products, there is a general expectation that it also may become applicable to innovator products sometime in the future. The workshop, the subject of this article, was organized to create an open forum for discussing the draft guidance and to provide an opportunity to give feedback on the goals and objectives of the BUAWG.

Workshop presentations

Review of current regulatory practice of blend uniformity. Presented by Nicholas Buhay (FDA), this session reviewed the current regulatory practices and regulations pertaining to blend uniformity. The subject is covered under GMP and drug approval programs. The regulation specifies that "control procedures shall include … the following, where appropriate: … adequacy of mixing to assure uniformity and homogeneity …." Mr. Buhay explained that "where appropriate" does not allow exception of certain products of a dosage form but rather refers to those control procedures that are not necessarily appropriate to all dosage forms (i.e., there is no freedom for interpretation). The requirement applies whenever mixing is performed for the manufacturing process. The regulations do not specify blend uniformity. Blend uniformity is a specific testing approach for the evaluation of "batch uniformity" of a powder mix. The GMP is open to other testing approaches. In addition, the regulations do not specify particulars (e.g., equipment, amount, and locations), acceptance criteria, limits, and significance of testing results. This has led to the generation of the draft guidance on blend uniformity for ANDAs.

Discussion of the BUA draft guidance. Presenter Frank Holcombe Jr., PhD (FDA), indicated that currently limited information about BUA is being submitted in ANDAs; however, the amount of information has been increasing since the early 1990s. Moreover, significant variation exists in the information that is being submitted. On the basis of reviewers' complaints and the significant variation in expectations of reviewers and inspectors, the Office of Generic Drugs (OGD) decided to generate the draft guidance. Some of the highlights of the guidance include the following:
- The guidance is intended for ANDAs.
- The guidance refers to 21 *CFR* Part 211 and Part 314 (process controls).
- Coverage includes both application and routine production batches.
- The guidance is based in part on the chapter on content uniformity in *USP*.
- Sample size should be no more than three times the dose unit weight; however, if a bias is observed one may increase sample size as much as ten times the dose unit weight.
- Sampling locations are not restricted.
- Six to 10 locations should be sampled.
- Chemical analysis should be performed on unit dose size.

After the release of its publication, the OGD received a large number of comments and is working on revisions. Comments pertained to both concept (e.g., use beyond ANDAs) and technical areas (e.g., sampling problems, sample size, analytical sample preparation, treatment of out-of-specification [OOS] data, basis for acceptance criteria). The PQRI Drug Product Technical Committee (DPTC, drug product project oversight committee) and BUAWG are involved in these revisions, which may include a provision for the deletion of the routine testing requirement. Some areas that still must be addressed are problems inherent in powder sampling, multitier testing procedures, basis for acceptance criteria, sample size for both field retrieval and analytical preparation, and the question of whether this is an inappropriate test for a validated process. The revised document also will explain the difference between NDA and ANDA requirements for BUA and the potential use of alternate methods when dealing with OOS results.

Powder blending. Presenter Fernando Muzzio, PhD (Rutgers University), reviewed current blending equipment and its effi-

ciencies (tumbling, convective, airflow, gravity flow, attrition, etc.). In general, blending equipment is poorly characterized and is primarily selected on the basis of company experience, manufacturers' claims, ease of emptying and cleaning, safety, and cost. However, questions and issues that are often ignored include dead spots; scale-up; ease of sampling; speed control; and products' tendency to segregate, agglomerate, or break. Dr. Muzzio described the three mechanisms for mixing: convection, dispersion, and shear. Three main tumbling lessons exist for free-flowing materials: slow axial mixing (Are there dead spots at axial extremes?); speed is not very important (time or number of revolutions is); and the fill level is extremely important. He then presented data that demonstrated the importance of how the blender is charged (order and direction compared with rotation axis). He also showed data that indicated the effect of baffles as well as changes in chemical composition of the blend (e.g., sorption of water). Last, he proposed an approach for scale-up of mixing processes, which is based on the following similarity criteria: use of vertically layered systems, matching of blender geometry, fill level, material, Froude number, and number of revolutions (dimensionless mixing time). Dr. Muzzio emphasized that the understanding of sampling capabilities must first begin with an understanding of powder blending.

Handling of powder blends. Presenter James Prescott (Jenike and Johanson, Inc.) discussed the challenges to product uniformity, including how to achieve an adequate blend, prove the state of the blend, and maintain the blend quality through subsequent handling. He provided examples of observed failures with the current validation approach and the effect of blend handling subsequent to the blending process, demonstrating that it may not be possible to correlate tablet content uniformity with blend uniformity. He also reviewed the possible flow patterns in hoppers, funnel flow, and mass flow, and their characteristics. Subsequently, he discussed the three main segregation mechanisms: particle entrainment, air entrainment, and sifting. For each of these mechanisms, Mr. Prescott provided conditions and examples and then presented some suggestions regarding what to do about segregation. These include change material (cohesion, size distribution, granulate, ordered blend), minimize initial occurrence of segregation (mix when needed, prevent airflow, use proper chute hopper design), and provide remixing (use mass flow, use an insert, control velocity profiles).

Blend sampling and assessment. In his presentation, Jonathan Berman, PhD (Bayer Consumer Care), discussed various aspects of blend sampling and assessment. He reviewed the unit dose sampling (UDS) requirement and its drawbacks, as well as potential causes for BUA variability (actual blending process, analytical error, sampling error). A specific example of a process yielding good product but failing BUA was provided. Dr. Berman also presented more detail about the various sampling devices and techniques and their potential effect on the BUA results. On the basis of his experience, Dr. Berman stated that BUA is a poor in-process control for various reasons, including the fact that one cannot steer the process in the right direction, it is a pass–fail test, there are sampling errors and safety issues, it requires a waiting period, and powders are labile. He went on to propose a better approach: eliminate the UDS requirement and analyze periodic core tablet samples collected during compression (i.e., the compressing machine can be viewed as a sampling device).

Acceptance criteria and data analysis. Presenter Jerome Planchard, PhD (Aventis Pharmaceuticals), discussed the various sampling-plan elements, including sample location, number of samples, target weight, sampling device and procedure, data analysis, and acceptance criteria. He then reviewed how an operating characteristic curve (OCC) — a numerical simulation of a process — is developed. Various OCCs were presented for three sets of criteria applicable to BUA: FDA validation ($n = 10$, relative standard deviation [RSD] $<5\%$, all between 90 and 110%), FDA routine ($n = 6$–10, RSD $<5\%$, average between 90 and 110%), and those listed in the PDA technical report No. 25. Dr. Planchard presented a conclusion for each of three criteria.

- FDA validation: easy data analysis, not suitable with substantial bias, not suitable with substantial thief error, becomes more difficult to meet as sample number increases.
- FDA routine: easy data analysis, not affected by sample bias, increases in power as *n* increases, suitable for routine or validation batches with small thief error.
- PDA: difficult data analysis, requires relatively large sample number (72 blend samples, 72 tablet samples), only suitable for validation batches, increases in power as *n* increases, not affected by bias, suitable in presence of large sample error, rejects processes with significant segregation.

Near-infrared spectroscopy (NIRS). Sonja Sekulic, PhD (Pfizer), began her presentation by introducing NIRS, including a brief review of the theory as well as some of the technology's advantages (speed, high signal-to-noise ratio, chemometric advances, remote operation using fiber optics). She then discussed the use of NIRS for the prediction of tablet or slug potency and compared the results with those from high-performance liquid chromatography (HPLC), demonstrating that NIRS can be used for uniformity testing of tablets and slugs (not universal). Subsequently, Dr. Sekulic presented the fully automated NIRS-based blend unit, developed in-house; potential ways of analyzing the NIRS data (qualitative and quantitative); and some of the drawbacks of the on-line analysis (e.g., only outside of blender being sampled, limited sensitivity, instrument transfer, chemometric complexity). She also discussed the regulatory status (USP chapter) and some of the miniaturization possibilities provided by small spectrometers attached to the blending vessel. She then presented a prototype of an NIRS-based instrument for at-line capsule analysis and some of the data obtained on this system. Dr. Sekulic concluded her presentation with the review of other techniques and technologies, including acoustic sensors, miniature spectrophotometers, vision and imaging systems, and sensor thieves.

New devices for physical sampling. Dr. Fernando Muzzio began his presentation with a review of the hidden assumptions about assessment of mixture quality (e.g., small number of samples is sufficient, sample obtained by standard techniques is representative of the composition of a system at a given location,

the state of the blend at a given stage of the process predicts the final state of the blend at the end of the process). He then provided specific examples that demonstrated the invalidity of these assumptions. Subsequently, Dr. Muzzio reviewed the various sampling devices that have been developed and used (e.g., side sampling, end sampling, core sampling), their insertion impact on a powder bed, and experimental data. Last, he elaborated on core sampling, developed in his lab, and some of its advantages over other sampling techniques (e.g., improved accuracy, uniform sample weight, 20 or more samples per stab, easy to retain samples that are spatially correlated, and concentration profiles gained across the entire system for small blenders).

Validation requirements for new analytical techniques. Presenter Neeru Takiar (FDA) discussed the following requirements for validation: Methods must meet proper standards of accuracy and reliability; USP and NF methods do not need to be validated; and noncompendial methods do require validation. She then reviewed the USP elements for method validation (e.g., accuracy, precision, limit of detection, limit of quantitation, linearity, range, ruggedness, and robustness) and the requirements for the various categories (i.e., assay categories I, II, and III). She also presented an NIRS-based case study conducted by the FDA–Division of Drug Analysis office in St. Louis. NIRS was used for analysis of acetaminophen tablets and the results were compared with those from HPLC. The data showed that the NIRS and HPLC results were comparable. Ms. Takiar also mentioned the *USP* chapter on NIRS and indicated that FDA and industry training was needed on the subject. Finally, she indicated that there is a wider interest in evaluating novel techniques.

Break-out sessions

Is blend uniformity testing on every batch a value-added test? In this session, moderated by John Clark (FDA) and Michael Kopp (Teva), the following conclusions were presented:

- Blend uniformity is not a good in-process control.
- Blend uniformity analysis can provide in-process information during the development and validation stages.
- No one generally has been able to demonstrate a statistical correlation between powder blends and content uniformity.
- Most session participants favor extended finished-product testing versus mandatory routine blend sampling (a reasonable amount of finished product testing).
- Higher costs are acceptable to obtain meaningful data.
- Many variations on this theme exist (e.g., extended content uniformity testing and extended testing during validation).
- The following must be determined: number of units to be sampled, sampling frequency, and statistical techniques to be applied.
- An extensive database to support a change to the guidance is needed.
- Criteria to discontinue blend uniformity analysis postapproval must be developed (e.g., number of batches and historical variation).
- Opting for older technologies to meet BUA requirements must be avoided.

How do you validate the process when you have a sampling problem? This session was moderated by Muralidhara Gavini, PhD (FDA), and Jean-Marie Geoffroy, PhD (Abbott).

Participants reached the following general agreements:

- Appropriate development work is necessary (Can PQRI define what is appropriate?).
- Appropriate and meaningful blend uniformity testing should not only be conducted during development but also be confirmed during validation.
- Routine blend uniformity testing is not value-added.
- Most everyone has had to deal with blend uniformity failures.

The following responses to the question, "What is your most common action if you encounter a blend uniformity failure?" were provided:

- Almost all companies conduct investigations into the cause.
- Some companies execute something similar to the PDA recommendation.
- Reserve samples are tested to help decipher the underlying problem (proactive protocols).
- One recommendation called for looking at mg/g of product and mg/tab.

The following are comments related to the PDA recommendation:

- Complexity can be intimidating, but it's doable.
- Some companies execute methodology similar to the PDA recommendation to help decipher the issue.

The following are comments related to adequacy of mix:

- The final product is consistently acceptable and independent of the blend results.
- The blend is consistently manufactured (e.g., RSD) and produces a good final product.

Other comments included the following:

- *Acceptance criteria* is a good term for PQRI to help define.
- Is the tablet press an appropriate sampling device?
- Compression–encapsulation process should be profiled not only for content uniformity but also for dissolution.

What are the new technologies available to assess blend uniformity? This session was moderated by Neeru Takiar (FDA) and Jozef Timmermans (Merck).

The following desirable characteristics of new technologies were discussed:

- product friendly (i.e., noninvasive, no contamination potential, nondestructive, not affected by the process)
- process friendly (i.e., versatile — same process for multiple products, practical minimal effect on final product cost, provides blending completeness/endpoint, provides comfort level to only monitor dosage form)
- effortless (i.e., continuous, automated, fast — on-line and in real time, easy calibration, easy maintenance, eliminate physical sampling, eliminate operator-to-operator variability)
- meaningful (i.e., accurate, precise, repeatable, "validation-capable" by another analytical method, overall results are equivalent or better than current methods, has regulatory acceptance).

Additional "thinking out of the box" comments were made regarding the following:

- process equipment: identify and eliminate dead spots, make "sampling friendly"
- sampling: sample from hopper–chute–feedframe, use a tablet press as a sampling device
- surrogate tests: dosage form weight, particle size, tracer material
- procedures: return a portion of non-uniform blend to mixer, miniaturize the process to minimize scaling issues, apply parametric release concept, superdevelop or "validate" the process.

Research should focus on the following:

- Fill "lack of basic understanding" holes for all solids unit operations.
- To support basic research and validation, improve powder sampling evaluation methods.
- To support routine product-release testing, strive for technology of final solid dosage forms (assume this will replace the need for routine blend uniformity testing) with a rejection system.

Although NIRS is the most mature of new technologies, other technologies include the following:

- laser-induced fluorescence
- photon migration
- magnetic resonance imaging
- acoustics. **PT**

FYI

Pharmacopeial courses

The U.S. Pharmacopeia (USP, Rockville, MD) has announced it will offer courses through its Pharmacopeial Education (PE) Program. The courses are designed to increase *USP–National Formulary* (*USP–NF*) users' understanding of pharmacopeial processes, tests, methods, and acceptance criteria. Course topics include fundamentals of dissolution and standards development. Customized courses also are available.

For more information, contact USP, 12601 Twinbrook Parkway, Rockville, MD 20852, tel. 800.822.8772, fax 301.816.8148, e-mail pharmacopeialeducation@usp.org, www.usp.org/pe.