

ATTACHMENT #2

TOPIC: BLEND UNIFORMITY

FDA/CDER Review of the PQRI Recommendations on Blend Uniformity Analysis

Review Process

1. FDA's Advisory Committee for Pharmaceutical Science (ACPS)

An overview of the PQRI BU Working Group's activities and emerging recommendations were presented to the ACPS on November 28, 2001. Dr. Garth Boehm (Co-Chair, PQRI BU Working Group) provided the background information related to the working group activities and Dr. Thomas Garcia (Co-Chair, PQRI BU Working Group) presented the draft recommendations. Regulatory perspectives and issues were outlined by Dr. Ajaz Hussain. Transcripts of this meeting are available at:

<http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t1.doc>

The PQRI recommendations were presented and discussed at the May 8, 2002, meeting of the ACPS. The PQRI's BU recommendations were presented to the ACPS by Dr. Thomas Garcia (Co-Chair, PQRI BU Working Group), and the PQRI process explained by Dr. Tobias Massa (Chair, PQRI Steering Committee). Regulatory perspectives and issues were outlined by Dr. Ajaz Hussain. Transcripts of this meeting are available at:

<http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3860T2.pdf>

The following questions were posed to the ACPS.

- Do you consider the PQRI proposal appropriate for inclusion in a planned revised FDA guidance?
 - Supporting simulation studies assume a normal distribution, is this assumption reasonable?
 - Was the retrospective data mining sufficient to conclude that “blend uniformity testing in routine manufacture is not predictive of the uniformity of dosage units?”
 - Is the above conclusion a necessary condition for regulatory application of the PQRI proposal?
- If the proposed stratified sampling and analysis plan is limited only to bioequivalence and validation batches, how should adequacy of mix be ensured for routine production batches?
 - Is the classification (“Readily” /”Marginally” comply) and proposed additional assessment to justify deleting routine BUA justified?
 - In absence of BUA, is stratified sampling plus limited (10/20) product testing sufficient to assure content uniformity of the entire batch?

- Should the planned revised FDA guidance only focus on generic drugs or should it be a general guidance (i.e., for both new and generic drugs)?

2. Internal Peer Review

Following receipt of the PQRI recommendations a group of senior CDER staff representing offices of Pharmaceutical Science, Generic Drugs, New Drug Chemistry, and Compliance reviewed these recommendations. Individuals on this group were not members of the PQRI's BU Working Group. The Office of Biostatistics served as a consultant to the review group on statistical issues. The following comments reflect discussion at CDER and the ACPS meetings referenced above.

FDA/CDER Comments

During routine production of solid dosage forms, the proposed concept of stratified in-process dosage unit analysis can serve as a method to document adequacy of powder blend and to assure drug content uniformity. The PQRI proposal has the potential to improve detection of post-blending particle segregation that can occur with certain powder blends. Such trends (segregation) may not always be apparent during process validation or manifest in every batch. The proposed concept provides data to identify and correct blend sampling error occasionally encountered with "thief" sampling. It reduces the need to collect in-process powder samples and can reduce operator and environmental exposure to (potent) drugs. Some companies routinely utilize similar sampling protocols during process validation.

Prior to any further regulatory policy considerations of the PQRI's recommendations, CDER seeks further clarification and/or scientific justification for the questions identified below along with other comments and suggestions.

Document: "Results of Statistical Analysis of Blend and Dosage Unit Content Uniformity Data Obtained from Product Quality Research Institute Blend Uniformity Working Group Data-Mining Effort"

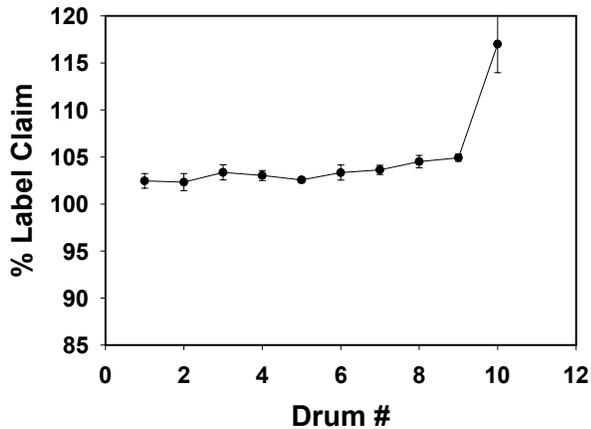
1. It was our understanding that the retrospective data-mining project was intended to provide "supportive" data/information to the scientific arguments and computer simulation studies underpinning the PQRI proposal. However, the report, as written, extended the scope of this (data-mining) effort to hypothesis testing. We feel this extension distracts from the core issue and can potentially be misunderstood without proper context.

The retrospective data collected are not sufficient or appropriate to test the stated hypothesis "Blend Uniformity Testing in Routine Manufacture is Not Predictive of the Uniformity of Dosage Units." If this hypothesis is to be tested the following issues need to be considered:

- (a) A prospective study would be needed to test this hypothesis. Such a study would need to attempt to collect data on batches with high dosage form RSD. Such data were not captured by the data-mining effort despite the efforts of the working group. However, this does not prove that such data do not exist.
 - (b) Observed lack of association between blend and dosage unit data could be, in part, due to a lack of consistency between the two test criteria. The dose content uniformity criterion is intended to address the test units. When it is used for the purpose of defining a pre-specified coverage percentage of an interval (e.g., 90% coverage between 85 -115% of label claim), the current non-parametric based criterion is both lot/batch mean dependent and suffers with high type I and type II error rates. Such weaknesses may contribute to the observed lack of association between pooled (across manufacturers) BU and CU data. Also, issues related to heterogeneity among subpopulations (e.g., manufacturers) are often encountered in retrospective data-mining studies and would need to be addressed.
2. Additional justification is needed to evaluate the assumption that the dose content uniformity data are normally distributed. The percentage of batches failing normality assumption is rather high for certain manufacturers. Additional justification and/or clarification is requested to substantiate the claim that *"using the normal distribution to generate batch location means to perform computer simulations to estimate criteria rejection rates will yield rejection rate estimates that are slightly smaller (more conservative) than criteria rejection rates based on actual data."*
3. On average about 11% of (high 25% for #C2) of batches had at least one location mean that was statistically different from the remaining location means. High deviations were observed either at start-up or final run-out and this observation was described as "dramatically different for other location means." Do such (between-location) deviations not reflect a potential blend and/or dose content uniformity problem?
- (a) From the FDA's perspective, the underlying scientific and engineering principles of powder blending process provide the strongest support for considering the stratified sampling proposal. An important contribution of the PQRI BU Working Group is the publication entitled "A solid Dosage and Blend Content Uniformity Troubleshooting Diagram," published in *Pharm. Tech. March 2001*. This publication provided a mechanistic approach for root cause analysis of observations of content variability (e.g., between-location differences). Mechanistic information contained in this report can, and should, be used along with the statistical simulation work to address the issues raised in this review.

(b) As stated above, the PQRI proposal has the potential to improve detection of post-blending particle segregation that can occur with certain powder blends. Ideally, development and validation efforts would eliminate such blends or correct the problem. In a few cases such problems may not be apparent at the time of process validation. Segregation problems may creep in during routine production due to reasons such as variations in physical attributes of raw materials (that may comply with compendial specifications and other qualification criteria). When particle segregation occurs following blending operation, a stratified sampling of dosage unit may be more effective than conventional blend uniformity analysis plus compendial dose uniformity tests conducted on a few randomly collected samples. An example, discussed at the ACPS meeting (<http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t1.doc> page 170), of such a case is illustrated below. A commercial product that meets blend uniformity (RSD <1%) and USP dose content uniformity Stage I specifications, exhibits a non-random trend (possibly due to segregation) towards the end of the production run that was detected using a stratified sampling protocol.

**Content Uniformity Data
on Tablets (Prod. D, Comp. X)**



4. On page 8 of this document, several different criteria are compared. One of these is referred to as the "FDA Blend Validation Guidance." An FDA staff member presented these criteria at a PDA workshop. No formal FDA guidance with this title exists. Please modify this terminology.

Document: "PQRI Blend Uniformity Working Group Recommendation for the Use of Stratified Sampling to Demonstrate Blend and Dosage Unit Uniformity."

1. These recommendations were written to address the draft ANDA Guidance on Blend Uniformity (August 1999). The PQRI letter to Dr. Woodcock, dated March 28, 2002, expanded the scope of these recommendations to "satisfy the GMP requirements to demonstrate adequacy of mixing to assure uniformity and homogeneity" [21CFR211.110(a)(3)]. FDA/CDER agrees with this change. The PQRI document should be modified to accommodate both NDA and ANDA processes and to address other issues outlined in this review.
2. Please provide additional justification or explanation as to why the proposed dosage unit sample locations and size are independent of:
 - (a) batch size
 - (b) tablet/capsule machine configurations (e.g., two-sided press)
 - (c) differences in blending operation (e.g., tumbling vs. connective and single bin vs. multiple bins)
 - (d) statistical distribution (i.e., normal vs. non-normal distribution)
3. Categorization of product into "Readily Comply" and "Marginally Comply" is based on RSD values obtained for validation and exhibit batches. During routine production of products that "Readily Comply" the number of units to be tested are in accordance with the compendial requirements.
 - (a) Sample RSD calculated from data obtained during routine production (smaller sample size compared to validation batches) may not be a robust estimate of the population RSD. What are the implications of finding RSD values >4% for routine production batches of a product classified as "Readily Comply?"
 - (b) What is the impact of a non-normal distribution?
4. For products categorized as "Marginally Comply"
 - (a) Why "5" consecutive batches? Please provide a statistical and physico-chemical justification.
 - (b) Why was emphasis placed on within-location variance (as opposed to between-location variance) in recommending the sample locations (n=10X3)?
5. A potentially different interpretation of the PQRI recommendation.

At the ACPS meeting on May 8, 2002, during the presentation entitled "PQRI BUWG Recommendation for the Use of Stratified Sampling to Demonstrate Blend and Dosage Unit Content Uniformity," Thomas P. Garcia (Chair, PQRI Blend Uniformity Working Group) stated "Other instances where it [refers to "blend uniformity testing"

per Conclusions slide # 2] is warranted is in validation. The one exception that we highlighted is if you have toxic products where you have contained processes, it may not be in your operator's or safety's best interests to break those containers. We feel that stratified sampling approach is still very discriminating to indirectly measure the uniformity of the mix" (pages 170 and 171 of the May 8, 2002, ACPS meeting transcripts).

The "exception" statement noted by underscore above is not explicit in the PQRI recommendation to the Agency. Please clarify.
