



March 28, 2002

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Dear Dr. Woodcock:

On behalf of the Scientific Steering Committee and the Board of Directors of the Product Quality Research Institute, I am pleased to submit the enclosed recommendation to you for FDA's consideration. This paper, "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends" was prepared to address concerns raised following issuance of the FDA draft *Guidance for Industry, ANDA's: Blend Uniformity Analysis* (August 3, 1999).

As you are aware, the Product Quality Research Institute is a unique organization that for the first time brings together the innovator and generic pharmaceutical industry, academia and the FDA (specifically the Center for Drug Evaluation and Research) to address issues related to pharmaceutical product quality. In addition to academic and industry members, the Blend Uniformity Working Group of PQRI included FDA representatives from CDER's Office New Drug Chemistry, Office of Generic Drugs and Office of Compliance. The enclosed recommendation represents a 2-year effort by the group to address the gap between scientific principles and regulatory policy related to blend uniformity analysis and content uniformity of solid oral dosage forms. The group process included identification of the issues associated with blend uniformity analysis as currently performed, i.e., direct sampling of powder blends prior to manufacture of the final oral dosage form, evaluation of the scientific literature on the topic of blend uniformity and careful evaluation of various alternatives to direct sampling.

After extensive evaluation, the group concluded that in-process dosage unit analysis (of tablet cores, hard gelatin capsules or other solid dose forms) should be considered as an alternative to routine blend sampling

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Janet Woodcock, M.D., Director
March 28, 2002
Page 2

analysis to satisfy the GMP requirement to demonstrate “adequacy of mixing to assure uniformity and homogeneity” [21CFR211.110(a)(3)].

Our analysis of data obtained from pharmaceutical companies confirms that the blend analysis is not always predictive of blend uniformity. There may be a lack of correlation between blend testing RSD values and uniformity of dosage units, indicating that blend uniformity testing as proposed by FDA is not always predictive of final product quality. Therefore we recommend that FDA should allow stratified sampling and testing of in-process dosage units to demonstrate the uniformity of all production batches in lieu of sampling and testing of the blend, and that it should revise its guidances, and policies or GMP interpretations to reflect the proposed changes.

Information reviewed by the PQRI expert working group indicates that uniformity of dosage units can be affected by a number of factors and elements in the manufacturing process, besides mixing. Furthermore, sampling of bulk powders from mixers can introduce sampling errors. Our working group believes that a stratified sampling approach, as described in the recommendation, is scientifically valid and is one acceptable alternative approach to assuring uniformity of solid dosage forms. The PQRI analysis of data confirms the validity of the stratified sampling approach. We recommend that FDA utilize these principles in any guidance regarding GMP compliance or application submissions.

As noted in the recommendation, stratified in-process dosage unit analysis has many positive aspects:

- It is an accurate and reflective measure of homogeneity of the product.
- It eliminates blend sampling error issues related to thief sampling.
- It applies resources where they produce reliable, accurate information about the quality of the product given to the patient.
- Weighing errors when trying to assay blend samples are eliminated.
- It removes the safety issues surrounding blend sampling of toxic or potent drugs manufactured in isolated environments.
- It accounts for segregation after blending.

This recommendation is being submitted to FDA for consideration in modifying the draft guidance on BUA to include stratified in-process

Janet Woodcock, M.D., Director
March 28, 2002
Page 3

sampling and analysis of dosage units as an alternative to direct blend sampling to demonstrate uniformity and homogeneity. As stated in the PQRI By-Laws and agreed by FDA, the expectation of the Institute is that FDA will evaluate the recommendation and either adopt it as part of the ANDA guidance or, if it chooses not to adopt it, to provide a scientific explanation to PQRI where the recommendation is lacking.

We look forward to FDA's assessment of the recommendation. Please feel free to contact me at 317-276-0368 if you have any questions regarding our proposal.

Respectfully submitted,

A handwritten signature in cursive script that reads "Tobias Massa".

Tobias Massa, PhD
Chair
PQRI Scientific Steering Committee

CC: Ajaz Hussain
Helen Winkle