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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Re: Docket 2003D-0493 (*Draft Guidance on the Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessments*)

To whom it may concern

Upon review of the ***Draft Guidance on the Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessments***, Upsher Smith Laboratories, Inc. (USL) would like to submit several comments and suggestions for your consideration. Although we applaud the movement toward a more scientific and/or statistical approach to blend assessment, the proposed draft guidance appears lacking in an understanding of the difficulty to apply the proposed rules to a manufacturing and testing organization.

1. In the guidance, there is no mention of the USP requirements on the Uniformity of Dosage Units <905>, in which Weight Variation may be used in some cases. If a product contains 50 mg or more of an active ingredient comprising 50% or more, by weight, of the dosage unit, special consideration could be made and the products in this category excluded from this guidance. At a minimum, criteria could be established during development and validation work through the recommended correlation of in-process stratified sampling with powder mix and finished product. Would it be possible to incorporate the Weight Variation instead of the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) testing for routine testing based on the amount of active ingredient of the dosage unit?
2. During the verification of the Manufacturing Criteria (Section VI), there is a requirement to sample "at least 20 locations". This requirement does not seem to account for short tableting runs. For instance, if you were tableting for 10 hours...you would sample every 30 minutes, but if you were tableting for only one hour...you would be sampling every 3 minutes. For a short run, the 20 periodic locations do not seem to add any value to the data collected as you would anticipate very little difference between individual samples taken that closely together. Some consideration for the size of the run (either length of time or total number of tablets produced) would appear to be warranted to ensure appropriate statistical coverage.
3. Once we begin routine manufacturing batch testing, it appears the management of the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) testing would be somewhat difficult to track. In order to implement this guidance, a company will need to

UPSHER-SMITH LABORATORIES, INC.

6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upshe-smith.com

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create new systems to track the manufacture and release of product. The implementation of new systems can be a huge burden and very costly, especially if a company's products have already been demonstrated to be well in control. The following are some scenarios that are likely to occur in a typical manufacturing/testing organization:

- a. In general, a company will test first in-first out (FIFO), but on occasion business requirements may require a company to test out of sequence. For example, it is not atypical for a company to produce both a branded and a private label product (having the same formulation). The order of manufacturing may be to produce the brand first, followed by a campaign of the private label product. Due to a change in the Sales/Marketing Department's forecast, a company may need to release the private label product first. Based on the product requirements, the laboratory will test the private label product before continuing testing on the branded product in order to get it released. The products are the same formulation and the only difference would be tooling used in compression. According to the guidance, we would be required to (or due to the switching rules requirements, it becomes more important to) test the branded product before we could test and release the private label to ensure the SCM requirements were met. If the requirements were not met, we would need to switch to the MCM requirements for the next 5 consecutive batches, which could include the private label batches we are trying to release. This would put an unnecessary strain on a company and how the company does business. A company would not be allowed to respond to any changes in the forecast. This has a potential negative impact on consumers if the company is unable to supply to meet customer needs and an organization may lose some of their competitive edge. I am certain the intent of this guidance was not to put some companies at a disadvantage, to limit an organization's flexibility or to minimize an organization's ability to respond to market demands.
- b. At times, product may be held due to a pending investigation, which does not impact any other lots and has nothing to do with the blend process at the point in time that it is held. Depending on the type of investigation, the analytical laboratory may not receive samples of that lot at that time. The manufacturing team continues to produce additional lots and the testing is completed on those lots. According to this guidance, we would not be able to release those later lots until the lot under investigation was tested and released. Once again, there is an impact on how we release products.
- c. The guidance does not address dosage-proportional drugs. If the drugs are made from the same blend and a problem is seen in one dose and not the other...are both drug products suspect? For instance, a company may manufacture an 80 mg tablet and a 120 mg tablet from the same blend. A company would test the 80 mg tablets, that were compressed first, and, if the results were acceptable, would release the 80 mg strength. After the release of the 80 mg tablets, the company finds that they fail the SCM requirements with the 120 mg strength. What implications are there to the strength (80 mg) that was released previously? It is very typical for products to be prioritized by need in the laboratory and released based upon this priority. It is not uncommon, then, to release different dosage-proportional strengths of a product weeks apart.

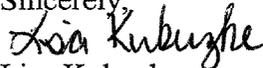
4. The guidance document fails to consider the importance of performing a solid investigation and the role that the results of that investigation might have on whether or not switching to a tightened inspection process is appropriate. Many investigations are quite lengthy and take some time to determine root cause and appropriate corrective action. I think it is onerous to assume that a company should automatically switch to tightened inspection based upon the test results irrespective of completing their investigation. The investigation, once complete, may identify a root cause that has no impact on subsequent batches of product. Any additional testing on subsequent batches would be costly, would be of no added value, and would simply be considered "waste". Also, while the investigation is ongoing, the company is continuing to produce product. A company certainly can't stop testing that additional product while it waits for the investigation to be completed.

It would appear to make more sense to apply the switching rules once the investigation is complete and has identified a systemic problem that may impact future product. Any product that is already produced and been tested and shown to pass would need to be considered "good" (after all it did pass fairly rigorous testing). The switch would take place on product manufactured after the investigation was completed to ensure that any corrective action was effective. Again, I believe that the investigation into a blend issue is absolutely crucial but I think it is premature to jump to the conclusion that all subsequent batches are suspect without having completed that investigation.

5. It is our understanding that if we adopt this guidance, the Agency would expect us to establish verification of manufacturing criteria for our currently approved products. This would be an overwhelming task to complete all the required sampling/testing to show control of a process that we have considerable history on. Would it be acceptable to grandfather in currently approved products and only incorporate the required testing to support any changes to the process? Certainly, grandfathering of products that have higher proportions of active ingredient makes scientific sense as you would not anticipate a product that is substantially all active to display blend anomalies. Similarly, products that have demonstrated a long history of acceptable results, and where manufacturing issues and customer complaints have been minimal, would not seem to be good candidates for further levels of control. The application of this guidance to currently approved and marketed products requires further discussion to ensure that the benefits of any additional work outweigh the significant burden to the organization required to adopt these controls.

If you have any questions, please feel free to call me. My phone number is (763) 315-2087. Thank you for the opportunity to comment on the guidance.

Sincerely,



Lisa Kukuzke

Associate Director, Quality Control/Marketed Product Support
Upsher Smith Laboratories, Inc.
6701 Evenstad Dr.
Maple Grove, MN 55369