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October 19, 1999

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

Subject: **Comments on Draft Guidance "ANDA's: Blend Uniformity Analysis"**

Gentlemen:

The following are G.D. Searle and Co.'s comments regarding the draft guidance to industry entitled "ANDA's: Blend Uniformity Analysis."

One of the regulatory requirements for manufacture of a drug product is that the manufacturing process must be validated. If the manufacturer demonstrates through validation that the process consistently yields finished product meeting the registered release specification, we do not believe that a blend uniformity specification is necessary.

Also, if the company demonstrates satisfactory blend uniformity during development and validation with a parallel history of satisfactory content uniformity (CU) of finished dosage forms, then BUA ought not be necessary after commercialization as uniformity and homogeneity can be monitored via CU analysis.

We find it curious that the recommended BUA specification is tighter (90.0-110.0% with an RSD of <5%) than content uniformity (85.0-115.0% with an RSD <6.0%). If the company has failures based on the suggested BUA criteria, we wonder what recourse the company has? Should the batch be rejected before tablets are produced and tested? If there is no second tier analysis available, what can the company do? The relevant literature contains many examples in which firms experience questionable BUA results while the corresponding CU data are immaculate.

Finally, under section II of the guidance (on page 3), it reads: "Under current good manufacturing practices (CGMPs), an applicant is required to perform a test or examination on each commercial batch of all products to monitor the output and validate the performance of processes that could be responsible for causing variability, which

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includes the adequacy of mixing to insure uniformity and homogeneity (21 CFR 211.110(a)(3)). A BUA test for commercial batches in an approved application meets this requirement." We agree that BUA, if it is utilized as the sole test for uniformity assessment, would indeed meet the requirement. However, as standard practice in the industry, content uniformity is the test that is performed upon the final dosage form for the assessment of homogeneity. Content uniformity, since it is performed upon the finished product, is therefore considered to be more significant and representative of the batch as compared to an in-process type of test such as BUA. As described above, adding BUA testing to each batch of product that has been previously validated, where it is performed in addition to content uniformity, appears to be redundant and only adds an incremental amount to the support of GMP's. We wonder if the concept of BUA testing can be further explained as to how this concept, when done on a routine basis in addition to content uniformity, supports the GMP's to any added significant extent.

Sincerely,

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