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November 27, 2000

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

DOCKET NO. 00D-1424 COMMENTS

Dear Sir or Madam:

The Dow Chemical Company has extensive experience in particle size methodologies and appreciates the opportunity to comment on the "Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation" issued for comment on August 30, 2000. The following comments are focused on Section XI.F. "Methodologies Relating to Particle Size Analysis" (Lines 1000-1035). The existing wording regarding "validation" of these methods should be properly discussed. The paragraphs, which follow, are suggested wording that should replace existing wording. Also, many of the particle size methods listed in this draft guidance are particle size related methodologies and not specific for particle size measurement. The comments relating to lines 1011-1026 are proposed wording that deletes particle sized related methodologies.

Particle size analysis can be an important element for quality control and regulatory evaluation of certain drug substances and drug products. The normal concepts of validation will apply to all aspects of particle size methodologies. (Lines 1000-1003)

Particle size evaluation can include characteristics of size, weight percent within a given size range, breadth and/or span of the size distribution, and absolute concentration of particles in a given size range. Every particle size parameter that is being reported must have a separate validation. For instance, if a method reports a volume median diameter and the weight percent within a given size range, a validation must be completed for the volume median diameter measurement and for the weight percent within the size range of interest. Each validation will include the determination of accuracy, precision, linearity, limit of detection, and robustness. (Lines 1005-1007)

There are numerous particle size measurement technologies that are commercially available. Types of particle size measurement technologies include, but are not limited to the following:

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I. Particle Size Measurement Technologies

- 1) Single Particle Measurement
 - a. Microscopy/Image analysis
 - b. Electrozone sensing
 - c. Photozone sensing
- 2) Ensemble Based Technologies
 - a. Combined MIE/laser diffraction
 - b. Acoustic spectroscopy
 - c. Turbidity
- 3) Fractionation Based Technologies
 - a. Sieving
 - b. Sedimentation
 - c. Hydrodynamic chromatography
 - d. Cascade impactor

(Lines 1011-1026)

The method validation for particle size measurement should include details of how the samples are obtained and prepared for analysis, a description of the method of calibration for the instrumentation employed, explicit equations describing the calculation of each size parameter of interest. Sampling procedures can often be the root cause of the variability in the final particle size measurements performed and as a result sampling procedures should be described. A large number of particle size parameters are reported in the open literature and by the manufacturers of particle size measurement instrumentation. Explicit equations that describe how the reported particle size parameters are calculated should be included in the methodology.

Validation can often be performed by confirmation of the particle size parameter of interest via measurement by an independent technique. Because very few NIST-traceable materials are available for particle size, this means that analysts must often create their own standards either via classification of product samples, or via characterization of product samples by an alternate size measurement technique. Also, particle shape can often affect the results that are reported by a particle size analyzer. If there are changes in particle shape and size for the particle matrix of interest, one should determine in the robustness section of the validation how particle shape affects particle size. See additional information in sections V and VII. (Lines 1028-1035)

We appreciate your consideration of these proposed changes and would be willing to discuss these further if that would be helpful.

Sincerely,



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