What Is the "Correct" Method to Use for Particle-Size Determination?

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Advances in analytical methodology have given pharmaceutical researchers a number of tools for determining particle size and particle-size distribution, including microscopy, sieving, and laser diffraction. But which technique is "correct"?

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These days, I get to visit a variety of institutions and have the privilege of being exposed to a large number of situations that can be classified as interesting. Very often I am shown a volume of data and asked to produce a theory (usually on the spot) that explains what is going on. Some of the questions relate to the crystal form of a given substance, others to its interaction with the environment, and still more relate to transformations that have taken place because of pharmaceutical processing.

Some of the most interesting questions are associated with the bulk properties of powders. These questions might relate to flowability, compressibility, or moisture sorption properties of the powder. During the initial stages of my data gathering, I try to profile the substance in question. One of the first questions I ask is, "What is the average particle size of the particles making up the powder, and what do you know about the particles' distribution?" Usually I am told that the average size is so many micrometers and that the distribution is not very wide. Sometimes I inquire about the extent of method development or validation that certified the result, but the response to this question is often too embarrassing to discuss further.

Even more interesting are the situations in which I am conducting a study of excipient materials as supplied by different manufacturers, and I attempt to use their certificates of analysis to deduce what grades of a particular substance correspond to them. In my possession are numerous microcrystalline cellulose samples of various particle-size grades. Unfortunately for me, some of these have been sized by using full analytical sieving, others by air-jet sieving, and still others by laser diffraction. What I would like is a compendial map as to which method and technology is required, but in the absence of that how can one method be adjudged more "correct" than another?

It is well known that if one performs particle-size distribution studies on a given sample using microscopy, sieving, light scattering (or any of the other available techniques), one usually will obtain different values for the mean particle size and the overall distribution. However, no one standard definition exists for *particle size.* The various statistical diameters that have been defined yield measures that have meaning, but these measurements only have value when averaged over a large ensemble of measurements. All measurements require one to as-

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sume that the particles making up the sample are not biased in any sense and that their measurement in a monitoring mode is entirely random. If all the particles in a sample were spherical, then it would be anticipated that all methods would yield equivalent results (and they usually do). When applying any technique that reduces some experimental observable obtained on an irregular particle shape to that of an equivalent spherical particle, one must expect the introduction of error.

Assuming the instrument of measurement was properly working and calibrated (if necessary), three important questions must be addressed when determining how correct a particle-size distribution is:

- Was the sample obtained using appropriate sampling procedures?
- Was the sample properly prepared and introduced into the instrument?
- Were all instrumental parameters correctly used for the analysis?

If all of the answers to the preceding questions are in the affirmative, then I would assert that the particle-size distribution is correct. The correct (but differing) particle-size results obtained using various instruments are all equally correct, but each simply may be expressing its correct results in different terms.

The decision as to which particle-size methodology is most appropriate for a given situation becomes largely a matter of accuracy versus precision. If absolute accuracy is most important, then one must conduct rigorous research to verify that the method finally adopted does indeed yield particle-size results that are absolutely indicative of the characteristics of the bulk lot from which the sample was drawn. If, however, one is more interested in developing profiles of lot-to-lot variability, then use of any of the available methods that yields correct results is appropriate. It is crucial that a rigorous test procedure be developed and followed for each assay determination and that the procedure be validated as fully as possible. **PT**