great detail about qualifying impurities and developing specifications for the impurities in APIs. Finally, the FDA advises in the Guidance (see Section L3b) that one should compare the impurity profile of the generic drug substance with the process impurity profiles found in the innovator's marketed drug product (looking at three or more different lots of the innovator's product). A final comment about this point is that today's innovator product may be made with the drug substance synthesized by a different process than the originally launched innovator product. The generic API may be synthesized with an expired patented process of the innovator resulting in an impurity profile, which may be different from that found in today's innovator drug product. There is no benchmark "fingerprint" of the original innovator drug substance to make any comparisons of the original impurity profile with the current impurity profile of the innovator. An interesting issue is that if there was a USP monograph for the "innovator drug in place, prior to the point in time of submitting an ANDA for the drug product, a public standard would be available to establish 'objective' boundaries for critical quality attributes for the drug substance" [?]. Subsequent changes in the pioneer impurity profile might require update of the USP monograph. However, the initial impurity profile testing requirements were presumably part of the original USP monograph testing requirements and as such would still be available for comparative testing. Today's newer analytical technologies such as near infrared will permit more incisive analysis of the innovator drug product so that, even in the absence of a USP monograph, the ability to carry out a fingerprint of the innovator product (search for the impurity profile of the drug substance therein) is within technical boundaries for getting reliable information.

Physical Form

Another critical aspect of the API comparability to the innovator API is the physical form. This generally falls in the domain of the "morphic form," including particle size distribution. The term "morphic form" includes variances in crystal form (amorphous versus crystalline), polymorphism, solvates, and hydrates. Current precedents indicate that variants of the morphic form of the pioneer NCE can be incorporated into ANDAs, if the ultimate test for demonstration of the bioequivalence of the ANDA drug product to the pioneer listed drug product is successful.

Related aspects of the physical form of the API, such as particle size distribution, are important with respect to the in vitro dissolution performance of the finished dosage form. As noted above, the final dosage form developed by the ANDA sponsor must meet the FDA Office of Generic Drugs benchmark of "bioequivalence," which frequently is related to the in vitro dissolution performance of the dosage form. Thus, the physical form characteristics of the API need to be controlled such that, once bioequivalence is demonstrated versus the innovator product, subsequent batches of the API will provide the same performance characteristics to the final dosage form.

Developing final specifications for the API is based on establishing the desired chemical and physical profile of the API. The API suppliers frequently develop particle size "grades" for individual customers of the same API. It is very important to have similar, preferably identical, test methods at the API source and the API user