Current FDA requirements regarding the filing of an ANDA for a single-component listed drug product include that the API must be the same chemical entity, which is contained, in the approved NDA listed drug product. The critical aspects of sameness or comparability for the "generic" API versus the innovator API include three realms: chemical structure, impurity profile, and physical form.

Chemical Structure

Same chemical entity, including

- Salt or free base/acid form
- Isomeric composition
- Hydrate, solvate, or polymorphic form (see "Physical Form" for more details about the allowed latitude for variances)

Impurity Profile

- Establish the total impurity profile for replicate batches of the final process material (specified as well as unspecified impurities)
- Determine if there are impurities in the generic API, which are not present in the innovator API, and the relative level of such impurities
- List the total impurity profile for the generic API

The FDA Guidance "ANDAs: Impurities in Drug Substances," issued June 2009, is the current benchmark for categorizing, quantifying, specifying, qualifying, and reporting on impurities in generic APIs [6]. Part of the impurity assessment is reporting, identification, and qualification threshold. There is a very detailed "Impurities Decision Tree" in the guidance, which needs to be reviewed in depth when an issue arises about unknown impurities, or impurities whose safety profile cannot be gleaned from the literature and, more importantly, that impurity does not appear to be present in the innovator drug substance. Based on the guidance above, the critical aspect of dealing with "impurities," which includes organic impurities (process and drug related), inorganic impurities, and residual solvents, appears to focus on the issue of relating the levels found in the API to established pharmacopoeial standards or known safety data. A critical cutoff point for the organic impurities appears to be a level of 0.1%. The API manufacturer is encouraged to try to reduce the level of detected, individual impurities to levels of less than 0.10%. As far as impurity specifications are concerned, the issue is to have in place validated assay procedures than can assure a level of detection and a level of quantitation for all impurities. Maintaining individual impurities below 0.10% and assuring that the total of all specified and unspecified, identified and unidentified impurities at a level of 1% is likely to satisfy FDA concerns about the impurity profile for an API. On an individual basis, levels can be specified for individual impurities based on the process chemistry and stability history for the drug substance. The specification level has to meet benchmark standards of safety for use in the finished dosage form. The "ANDAs: Impurities in Drug Substances" guidance noted above goes into