

Agency Position on Polymorphism and Abbreviated New Drug Applications

For a generic drug product to be regarded as having the same active ingredient under section 314.92(a)(1), the drug substance in a proposed generic drug product need not have the same physical form as the drug substance in the reference listed drug. FDA states in its *Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book)* that the Agency considers drug products containing different polymorphs of the same drug substance to be pharmaceutically equivalent. The *Orange Book* describes pharmaceutical equivalents as, among other things, containing the same active ingredient(s). Therefore, FDA regards different polymorphs of a drug substance as the same active ingredient.

Also, the *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, issued February 1987, in discussion of the relationship of solid-state drug substance forms to bioavailability, notes the following:

Some drug substances exist in several different crystalline forms (“polymorphs”), due to a different arrangement of molecules in the crystal lattice, which thus show distinct differences in their physical properties. The same drug substance may also exist in a noncrystalline (amorphous) form. These various forms differ in their thermodynamic energy content, *but not in composition.*

As the Guideline points out, the polymorphic form of a drug substance can affect the dissolution and bioavailability of drug products. Thus, it is possible that a difference in physical form of the active ingredients might prevent a proposed generic drug from being bioequivalent to the reference listed drug (thus barring approval of the ANDA). However, this difference in bioequivalence would not mean that the generic and reference listed drug products contained different active ingredients; it would mean that the *drug products* would *not* be the “same.” If however, the drug product had been shown to be bioequivalent to the reference listed drug, in addition to meeting other requirements, the drug product would be considered to be the same, and could be approved.

Reprints from the Orange Book, USP, and CDER Drug Substance Guideline providing additional information are attached.

F. Holcombe, Jr. / 4/8/02