



**GUIDELINE FOR
SUBMITTING SUPPORTING
DOCUMENTATION IN DRUG
APPLICATIONS FOR THE MANUFACTURE
OF DRUG SUBSTANCES**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

314.50(e)(2)(i)). Since reference standards are essential to testing the bulk substance, their integrity should be safeguarded by proper storage and their stability monitored by periodic examination.

G. Solid-State Drug Substance Forms: Relationship to Bioavailability

The regulations require, where appropriate, specifications characterizing the drug substance so as to assure the bioavailability of the drug product (see 21 CFR 314.50(3)(ii), and 320.52(e)[4-1-85 edition]). Certain solid-state properties of the drug substance (e.g., polymorphic form or amorphism, solvation or hydration, various types of inclusion complexes, and particle size or surface area) may profoundly affect dissolution and bioavailability from solid dosage forms or suspension drug products. These properties are less important for solution dosage forms and for drug substances which are highly water soluble.

For drug substances with limited aqueous solubility (e.g., griseofulvin, nitrofurantoin), particle size can have a large effect on the behavior of the drug product, and significant differences in particle size may also affect toxicity. Identifying, characterizing, and controlling the differences in

solid-state forms is especially important when a bioavailability problem exists and/or the drug substance is obtained from multiple sources.

By the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms, whether these affect the dissolution and bioavailability of the drug product, and whether particle size is important for dissolution and bioavailability of the drug product. It is not necessary to 'create' additional solid-state forms by techniques or conditions irrelevant to the synthetic process.

The applicant should provide information describing how and why it has been concluded that (a) a change in solid-state form does not occur when the drug substance is manufactured and stored according to the NDA directions; or (b) different forms occur but do not result in a bioavailability problem; or (c) polymorphism, solvation, or particle size has an important effect on bioavailability. The test methods used should be briefly described and be shown to be suitable. In cases (a) and (b), suitability means that the procedure(s) can, with reasonable certainty, detect and distinguish between polymorphs (or solvates) should they occur. For case (c), suitability

means that the procedure(s) can detect and quantitate polymorphs and/or solvates in admixtures of such forms, or measure particle size.

Appropriate manufacturing and control procedures (including in-process testing when needed) should be established for the production of the desired solid-state form(s). It should be emphasized that the manufacturing process (or storage condition) is responsible for producing particular polymorphs or solvates; the control methods merely determine the outcome.

While specific kinds of differences in solid-state forms are considered separately below, there is some interdependence; thus comparisons should, if possible, be performed on samples of similar particle size.

1. Polymorphism

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. One of the critical

factors affecting polymorphism (or solvation) is the choice of final solvent and isolation conditions in the synthesis. As noted previously (II.D.2.d.), when a change is made in the final crystallization solvent, evidence must be provided that no transformation in solid-state form has occurred. Routine storage conditions, as well as some conditions of product manufacture (e.g., tablet compression, or use of an organic solvent during granulation) may also cause transformations. The question is: Is the crystalline (or amorphous) form stable, or is it time and/or process dependent?

Appropriate analytical procedures should be used to determine whether (or not) polymorphism occurs. Some examples of physico-chemical measurements and techniques are (1) melting point (including hot-stage microscopy); (2) infrared spectra (not in solution); (3) X-ray powder diffraction; (4) thermal analysis methods (e.g., differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA)); (5) Raman spectroscopy; (6) comparative intrinsic dissolution rate; (7) scanning electron microscopy (SEM). These methods are not ranked in order of their discriminating or quantitating ability. It is the

applicant's responsibility to select the method(s) used to provide evidence concerning polymorphism, and if bioavailability is affected, to provide and demonstrate the suitability of the specifications and tests (including preparation and provision of reference standards) for the control of the solid-state form of the drug substance.

2. Solvation (including hydration)

Conditions used in manufacture and/or storage of the drug substance may result in the isolation or formation of a solvated or hydrated drug substance. This is most directly assessed by testing for loss on drying (LOD) or by Karl Fischer titration (for hydrates). Information from other methods (e.g., TGA) may be necessary, because some solvates are known to be stable at temperatures above the boiling point of the solvent. When solvation or hydration affects bioavailability, appropriate manufacturing and control procedures should be established.

3. Particle Size (and surface area)

Particle size distribution and surface area of the drug substance may affect the dissolution and bioavailability of the drug product. Therefore, an applicant may conduct