Guidance for Industry

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2007
OGD

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Contains nonbinding recommendations

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I. INTRODUCTION[2]

Chemistry, manufacturing, and controls (CMC) information must be submitted to support the approval of an abbreviated new drug application (ANDA).[3] This guidance is intended to assist applicants with the submission of ANDAs when a drug substance[4] exists in polymorphic forms.[5] Specifically, this guidance provides:

- FDA recommendations on assessing *sameness*[6] when the drug substance exists in polymorphic forms.
- Decision trees that provide recommendations on monitoring and controlling polymorphs in drug substances and/or drug products.[7]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

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[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Office of Pharmaceutical Science (OPS), Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).
[2] Although issues relating to polymorphic forms may be relevant to new drug applications (NDAs), this guidance only addresses polymorphic forms in the context of ANDA approvals.
[3] See 21 CFR 314.94 (a)(9); see also section 505(j)(4)(A) of the Federal Food, Drug, and Cosmetic Act (the Act).
[4] For the purposes of this guidance the terms *drug substance* and *active ingredient* are used interchangeably.
[5] The terms *polymorphic forms* and *polymorphs* are synonymous and are used interchangeably in this guidance.
[6] Refer to Section IV for more information.
[7] This guidance is intended to help industry with the most common types of polymorphs. A drug substance may exist in many polymorphic forms, but some forms may be rare and not likely to form. For example, in one approved drug product, the drug substance can exist in at least twenty polymorphic forms, but in reality only a subset of polymorphic forms has the potential to develop under the process conditions used to manufacture the drug substance and drug product. Therefore, we recommend that you consider only those polymorphs that are likely to form during manufacture of the drug substance, manufacture of the drug product, or while the drug substance or drug product is in storage.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEFINITION OF TERMS: POLYMORPHIC FORMS AND POLYMORPHISM

We recommend that ANDA applicants investigate whether the drug substance in question can exist in polymorphic forms. Polymorphic forms in the context of this guidance refer to crystalline and amorphous forms as well as solvate and hydrate forms, which are described below.[8]

- Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice.
- Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice.
- Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent.[9] If the incorporated solvent is water, the solvate is commonly known as a hydrate.

When a drug substance exists in polymorphic forms, it is said to exhibit polymorphism.

III. GENERAL PRINCIPLES OF PHARMACEUTICAL SOLID POLYMORPHISM

A. Importance of Pharmaceutical Solid Polymorphism

Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility,[10] dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product.

B. Characterization of Polymorphs

There are a number of methods that can be used to characterize polymorphs of a drug substance.[11] Demonstration of a nonequivalent structure by single crystal X-ray diffraction is

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[8] Guidance for industry, Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,* International Conference on Harmonisation (ICH), December 2000.
[9] SR Byrn, RR Pfeiffer, and JG Stowell. *Solid-State Chemistry of Drugs*. 2nd Edition, SSCI, Inc., West Lafayette, Indiana, 1999.
[10] Apparent solubility refers to the concentration of material at apparent equilibrium (supersaturation). Apparent solubility is distinct from true thermodynamic solubility, which is reached at infinite equilibrium time.
[11] H Brittain. "Methods for the characterization of polymorphs and solvates." In HG Brittain (ed.) *Polymorphism in Pharmaceutical Solids*. Marcel Dekker, Inc., New York, 1999, pp. 227-278.

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