Background Information for the October 2002 ACPS Meeting

Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications

INTRODUCTION

Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (1). Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystalline solid adducts containing either stoichiometric or nonstoichiometric amounts of a solvent incorporated within the crystal structure. If the incorporated solvent is water, the solvates are also commonly known as hydrates. Polymorphism refers to the occurrence of different crystalline forms of the same drug substance. Polymorphism in this commentary is defined as in the International Conference on Harmonization (ICH) Guideline Q6A (2), to include solvation products and amorphous forms.

Polymorphs and/or solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapor pressure, and density. These properties can a direct impact on the process-ability of drug substances and the quality/performance of drug products, such as stability, dissolution, and bioavailability. A metastable pharmaceutical solid form can change crystalline structure or solvate/desolvate in response to changes in environmental conditions, processing, or over time.

Several regulatory documents and literature reports (2-4) address issues relevant to the regulation of polymorphism. The concepts and principles outlined in these are applicable for an ANDA. However, certain additional considerations may be applicable in case of ANDAs. Often at the time FDA receives an ANDA a monograph defining certain key attributes of the drug substance and drug product may be available in the Unites States Pharmacopoeia (USP). These public standards play a significant role in the ANDA regulatory review process and in case of polymorphism, when some differences are noted, lead to additional

requirements and considerations. This commentary is intended to provide a perspective on polymorphism in pharmaceutical solid in the context of ANDAs. It highlights major considerations for monitoring and controlling drug substance polymorphs and describes a framework for regulatory decisions regarding drug substance "sameness" considering the role and impact of polymorphism in pharmaceutical solids.

POLYMORPHISM IN PHARMACEUITCAL SOLID DRUG SUBSTANCE AND THE ISSUE OF "SAMENESS"

FDA may refuse to approve an ANDA referencing a listed drug if the application contains insufficient information to show that the drug substance is the "same" as that of the reference listed drug. A drug substance in a generic drug product is generally considered to be the same as the drug substance in the reference listed drug if it meets the same standards for identity. In most cases, the standards for identity are described in the USP although FDA may prescribe additional standards when necessary. Because drug product performance depends on the product formulation, the drug substance in a proposed generic drug product need not have the same physical form (particle size, shape, or polymorph form) as the drug substance in the reference listed drug. An ANDA applicant is required to demonstrate that the proposed product meets the standards for identity, exhibits sufficient stability and is bioequivalent to the reference listed drug.

Over the years FDA has approved many generic drug products based upon a drug substance with different physical form from that of the drug substance in the respective reference listed drug (e.g., warfarin sodium, famotidine, and ranitidine). Also many ANDAs have been approved in which the drug substances differed from those in the corresponding reference listed drugs with respect to solvation or hydration state (e.g., terazosin hydrochloride, ampicillin, and cefadroxil).

Since polymorphs exhibit certain differences in physical (e.g., powder flow and compactability, apparent solubility and dissolution rate) and solid state chemistry (reactivity) attributes that relate to stability and bioavailability it is essential that the product development and the FDA review process pay close attention to this issue. This scrutiny is essential to ensure that polymorphic differences (when present) are addressed via design and control of formulation and process conditions to physical and chemical stability of the product over the intended shelf-life, and bioavailability/bioequivalence.

CHARACTERIZATION OF POLYMORPHS

A number of methods have been employed for characterizing polymorphs in pharmaceutical solids (5). Polarizing optical microscopy and thermomicroscopy have proven to be useful tools. Thermal analysis procedures, such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), can be used to obtain additional information, including phase changes, and to deduce whether each isolated form is a solvate or anhydrate. These thermal methodologies are employed to distinguish between enantiotropic and monotropic systems. For an enantiotropic system, the relative stability of a pair of solid forms inverts at some transition temperature beneath the melting point while a single form is always more stable beneath the melting point in a monotropic system (5).

The utility of solid-state spectroscopy for characterization of polymorphic systems is becoming exceedingly important. Nuclear magnetic resonance (NMR), infrared absorption, and Raman spectroscopy are used to study crystal structures. These methods require that either the nuclei of the pair of substances being examined exist in magnetically inequivalent environments or the vibrational modes are sufficiently different between the structural forms to permit differentiation.

It should be emphasized that the definitive criterion for the existence of polymorphism is via demonstration of a nonequivalent crystal structure, usually by comparison of the x-ray diffraction patterns. Microscopy, thermal analysis methodology, and solid state NMR are generally considered as sources of supporting information.

PROPERTIES OF POLYMORPHS

Solubility and Dissolution

The solid state characteristics of drugs are known to potentially exert a significant influence on the *solubility parameter*. Polymorphs of a drug substance can have different apparent aqueous solubility and dissolution rate, when such differences are sufficiently large bioavailability is altered and it is often difficult to formulate a bioequivalent drug product using a different polymorph.

Solubility at a defined temperature and pressure is the saturation concentration of the dissolved drug in equilibrium with the solid drug. Aqueous solubility of drugs is traditionally determined using the equilibrium solubility method that involved suspending an excess amount of a solid drug in a selected aqueous medium. The equilibrium solubility method may not be suitable to determine the solubility of a

metastable form, since the metastable form may convert to the stable form during the experiment.

When the solubility of metastable forms of a drug substance can not be determined by the equilibrium method, the intrinsic dissolution method may be useful to deduce the relative solubilities of metastable forms (6). Use of the intrinsic dissolution method assumes that the intrinsic dissolution rate is proportional to the solubility - the proportionality constant being the transport rate constant, which is constant under the same hydrodynamic conditions in a transport-controlled dissolution process.

Polymorphic differences and transformation that result in different apparent solubility and dissolution rate are generally detected by dissolution testing. This test provides a suitable means to identify and control the quality of a product from both bioavailability and (physical) stability perspectives. When solubility and dissolution rate of the relevant polymorph forms are sufficiently high and controlled via dissolution regulatory concerns with respect to bioavailability and stability are minimum. The Biopharmaceutics Classification (7,8) criteria of high solubility and rapid dissolution should be considered in regulatory decisions.

Stability and Manufacture-ability

Polymorphs of a pharmaceutical solid may have different physical and solid state chemical (reactivity) properties (9). The most stable polymorphic form of a drug substance is often used because it has the lowest potential for conversion from one polymorphic form to another while the metastable form may be used to enhance the bioavailability. Gibbs free energy, thermodynamic activity, and solubility provide the definitive measures of relative polymorphic stability under defined conditions of temperature and pressure. The relative polymorphic stability may be determined by an iterative examination of the relative apparent solubility of supersaturated solutions of polymorphic pairs. Since the rate of conversion to the more stable form is often rapid when mediated by the solution phase, the less stable polymorph with the greater apparent solubility dissolves, while the more stable polymorph with the lower apparent solubility crystallizes out upon standing.

Solid-state reactions include solid-state phase transformations, dehydration/desolvation processes, and chemical reactions. One polymorph may convert to another during manufacturing and storage, particularly when a metastable form is used. Since an amorphous form is thermodynamically less stable than any crystalline form, inadvertent crystallization from an amorphous drug substance may occur. As a consequence of the higher mobility and ability to

interact with moisture, amorphous drug substances are also more likely to undergo solid-state reactions.

In addition, phase conversions of some drug substances are possible when exposed to a range of manufacturing processes (10). Milling/micronization operations may result in polymorphic form conversion of a drug substance. In the case of wet granulation processes, where the usual solvents are aqueous, one may encounter a variety of interconversions between anhydrates and hydrates, or between different hydrates. Spray-drying processes have been shown to produce amorphous drug substances. However, phase conversions should not be of concern if they occur consistently.

CONSIDERATIONS OF POLYMORPHISM IN ANDAs

Decision Trees #1 - #3, as shown in Figure 1, provide a process for evaluating when and how polymorphs of drug substances in ANDAs should be monitored and controlled. These decision trees were developed based on the ICH Guideline Q6A decision trees on polymorphism (2) and adopt the concepts from the Biopharmaceutics Classification System (7, 8).

Decision Tree #1 considers whether there is a need to set polymorphic acceptance criteria in drug substances and drug products. If no known polymorphs exist or all known polymorphs are highly soluble and sufficiently stable, it is expected that polymorphism is unlikely to have an effect on bioavailability and stability. This approach assumes that adequate knowledge of drug substance polymorphs is available by the time an ANDA is filed.

Decision Tree #2 discusses how to set a polymorph specification for a drug substance, given the fact that at least one polymorph is known to have low solubility based on the BCS. If an ANDA has the same polymorph specification as the U. S. Pharmacopoeia (USP), and the USP specification is adequate, no further polymorphic test or acceptance criteria for the drug substance beyond the existing USP methodology would be necessary. Otherwise, an ANDA applicant should set a new polymorphic acceptance criterion for the drug substance.

Decision Tree #3 discusses if there is a need to set a polymorph specification for a drug product. It is not necessary to have a polymorph specification for a drug product if the most stable polymorphic form is used or the form is used in a previously approved product(s) that was developed *without extraordinary formulation or manufacturing process development effort*. Furthermore, drug

product dissolution testing can frequently detect polymorphic conversions. In rare cases, solid state characterization may have to be employed.

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LEGEND

Figure 1(a): Decision Tree #1. Investigating the need to set acceptance criteria for polymorphs in drug substances and drug products in ANDAs for solid dosage forms or liquids containing undissolved drug substance

Figure 1(b): Decision Tree #2. Investigating how to set acceptance criteria for polymorphs in drug substances in ANDAs for solid dosage forms or liquids containing undissolved drug substance

Figure 1(c): Decision Tree #3. Investigating the need to set acceptance criteria for polymorphs in drug product in ANDAs for solid dosage forms or liquids containing undissolved drug substance

Figure 1(a): Decision Tree # 1

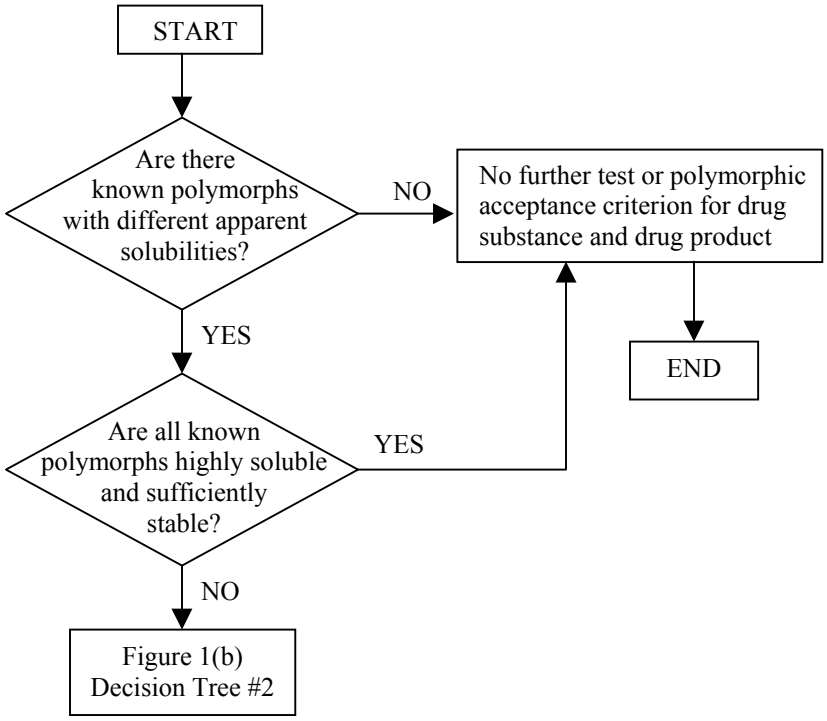


Figure 1(b): Decision Tree # 2

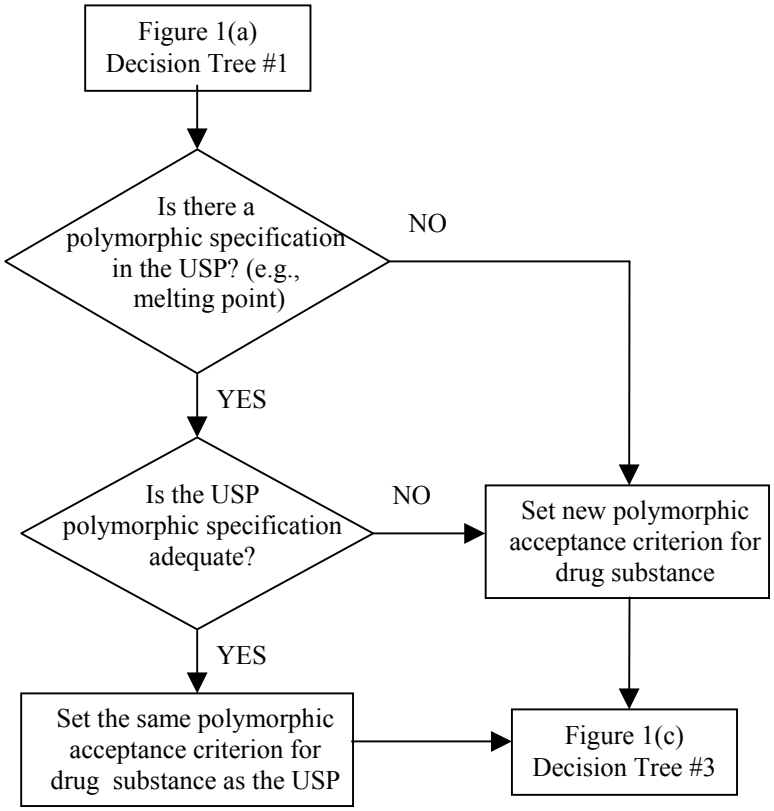
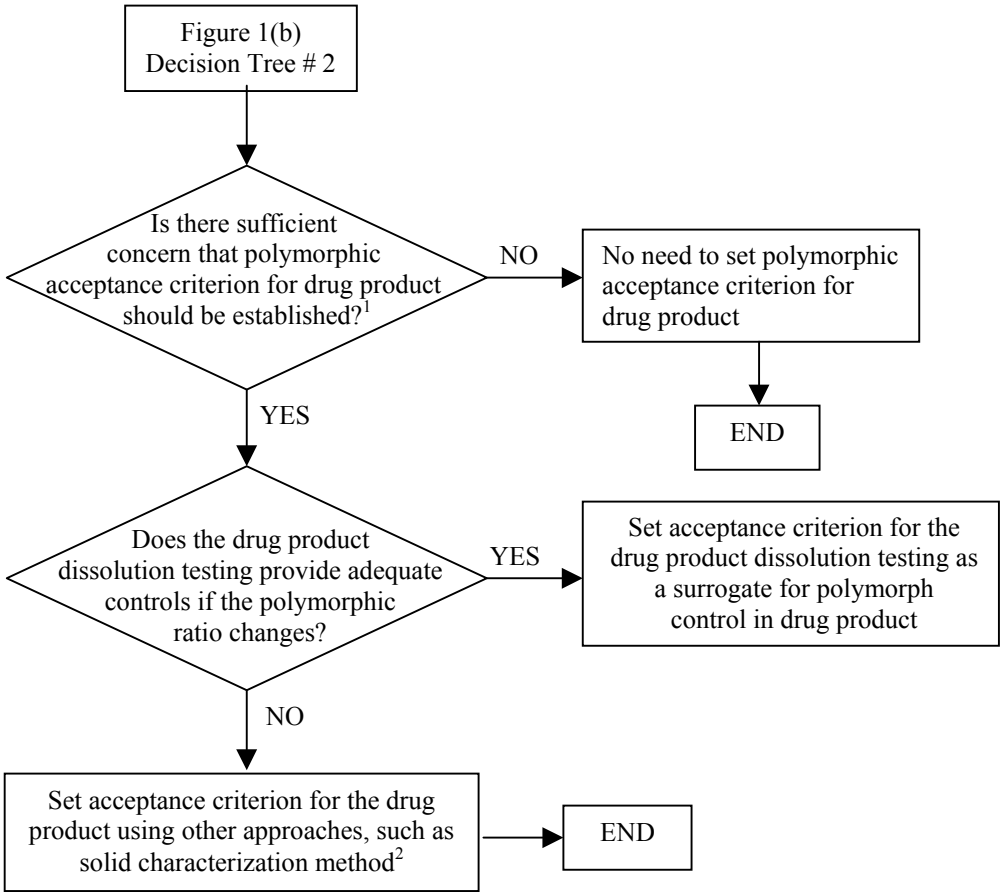


Figure 1(c): Decision Tree # 3



[1] In general, there should not be a concern if the most stable polymorphic form is used or the form is used in a previously commercialized product

[2] Dissolution testing with appropriate dissolution medium can frequently detect potential conversion of polymorphs during storage. In rare cases, the dissolution testing is not able to detect the polymorph ratio change