Guidance for Industry

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2004
OGD

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Guidance for Industry[1]

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

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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]

[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] This guidance addresses polymorphic forms in the context of ANDA approvals, however, these issues also may be relevant for new drug applications (NDA) including the submission of patent information for polymorphic forms of the active ingredient pursuant to 21 CFR 314.53(b).
[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 use interchangeably.
[5] The terms *polymorphic forms* and *polymorphs* are synonymous and are used interchangeably in this draft guidance.
[6] Refer to Section IV for more information.

If you plan to submit an application in the Common Technical Document (CTD) format, you may refer to the International Conference on Harmonisation (ICH) guidance, *Common Technical Document — Quality: Questions and Answers/Location Issues,*[8] which is available on the Internet at www.fda.gov/cder/guidance/index.htm. You may refer to Section III.A.3.1, *Polymorphism*, of that guidance to find the suggested placement of information related to polymorphism that is important to include when submitting applications in the CTD-Q format.

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 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.[9]

- 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.[10] 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.

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[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.

[8] This guidance is intended to clarify location issues for information submitted to FDA in the CTD format as described in the guidance for industry, M4Q *CTD-Quality (CTD-Q)*, August 2001. The *CTD-Q* provides recommendations for applicants preparing the *Common Technical Document for the Registration of Pharmaceuticals for Human Use* for submission to FDA.

[9] 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.

[10] SR Byrn, RR Pfeiffer, and JG Stowell. *Solid-State Chemistry of Drugs*. 2nd Edition, SSCI, Inc., West Lafayette, Indiana, 1999.

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,[11] 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.[12] Demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to support the existence of polymorphs. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are helpful to further characterize polymorphic forms.

C. Influence of Polymorphism On Drug Substance And Drug Product

1. Influence on Solubility, Dissolution, and Bioavailability (BA) and Bioequivalence (BE)

The solid-state properties of a drug substance can have a significant influence on the solubility of the drug substance. Since polymorphic forms differ in their internal solid-state structure, a drug substance that exists in various polymorphic forms can have different aqueous solubilities and dissolution rates.[13] When there are differences in the solubilities of the various polymorphic forms, we recommend that you focus on the potential effect such differences can have on drug product bioavailability (BA) and bioequivalence (BE).[14]

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[11] 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.

[12] 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.

[13] HG Brittain and DJW Grant. "Effect of polymorphism and solid-state solvation on solubility and dissolution rate." In HG Brittain (ed.) *Polymorphism in Pharmaceutical Solids.* Marcel Dekker, Inc., New York, 1999, pp. 279-330.

[14] Bioavailability (BA) is defined in 21 CFR 320.1(a) as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action." Bioequivalence (BE) is defined in 21 CFR 320.1(e) as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

Whether drug product BA/BE can be affected by the differences in solubilities of the various polymorphic forms depends on the various physiological factors that govern the rate and extent of drug absorption including gastrointestinal motility, drug dissolution, and intestinal permeability. In this context, the Biopharmaceutics Classification System (BCS)[15, 16] provides a useful scientific framework for regulatory decisions regarding drug substance polymorphism.

For a drug whose absorption is only limited by its dissolution, large differences in the solubilities of the various polymorphic forms are likely to affect BA/BE. On the other hand, for a drug whose absorption is only limited by its intestinal permeability, differences in the solubilities of the various polymorphic forms are less likely to affect BA/BE. Furthermore, when the solubilities of the polymorphic forms are sufficiently high and drug dissolution is rapid in relation to gastric emptying, differences in the solubilities of the polymorphic forms are unlikely to affect BA/BE.

Upon demonstration of in-vivo bioequivalence between the generic drug product[17] and the reference listed drug (RLD),[18] in-vitro dissolution testing is then used to assess the lot-to-lot quality of the generic drug product. Drug product dissolution testing frequently provides a suitable means to identify and control the quality of the product from both the bioavailability and physical (stability) perspectives. In particular, inadvertent changes to the polymorphic form that may affect drug product BA/BE can often be detected by drug product dissolution testing.

2. Influence on Manufacturing of the Drug Product

Drug substance polymorphic forms can also exhibit different physical and mechanical properties, including hygroscopicity, particle shape, density, flowability, and compactibility, which in turn may affect processing of the drug substance and/or manufacturing of the drug product. Since an ANDA applicant should demonstrate that the generic drug product can be manufactured reliably using a validated process, we recommend that you pay close attention to polymorphism and crystalline habit as they relate to pharmaceutical processing.[19]

The effect of polymorphism on pharmaceutical processing also depends on the formulation and the manufacturing process.[20] For a drug product manufactured by direct compression, the solid-

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[15] GL Amidon, H Lennernas, VP Shah, and JR Crison. "A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability," *Pharm. Res.* 12:413-420, 1995.

[16] LX Yu, GL Amidon, JE Polli, H Zhao, M Mehta, DP Conner, VP Shah, LJ Lesko, M-L Chen, VHL Lee, and AS Hussain. "Biopharmaceutics Classification System: The scientific basis for biowaiver extension." *Pharm. Res.* 19:921-925, 2002.

[17] The term *generic drug product* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[18] See 21 CFR 314.3 (b) (providing that *reference listed drug* means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application).

[19] Section 505(j)(4)(A) provides that FDA must approve an ANDA if, among other things, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.

[20] DA Wadke, ATM Serajuddin, and H Jacobson. "Preformulation testing." In HA Lieberman, L Lachman, and JB Schwartz (eds.) *Pharmaceutical Dosage Forms: Tablets* (Vol. 1). Marcel Dekker, Inc., New York, 1989, pp. 1-73.

state properties of the active ingredient will likely be critical to the manufacture of the drug product, particularly when it constitutes the bulk of the tablet mass. On the other hand, for a drug product manufactured by wet granulation, the solid-state properties of the active ingredient are often masked by the resultant granulation, therefore, such properties of the active ingredient are less likely to affect the manufacture of the drug product. In the context of the effect of polymorphism on pharmaceutical processing, what is most relevant is the ability to consistently manufacture a drug product that conforms to applicable in-process controls and release specifications.

Polymorphic forms of the drug substance can undergo phase conversion when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray-drying, and compaction. Exposure to environmental conditions such as humidity and temperature can also induce polymorph conversion. The extent of conversion generally depends on the relative stability of the polymorphs, kinetic barriers for phase conversion, and applied stress.[21] Nonetheless, phase conversion generally is not of serious concern, provided that the conversion occurs consistently, as a part of a validated manufacturing process where critical manufacturing process variables are well understood and controlled and where drug product BA/BE has been demonstrated.

3. Influence on Stability

Polymorphs can have different physical and chemical (reactivity) properties. The most stable polymorphic form of a drug substance is often chosen during development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability. However, a metastable form can be chosen for various reasons, including bioavailability enhancement. Since an ANDA applicant must demonstrate that the generic drug product exhibits adequate stability[22] we recommend that you focus on the potential effect that a polymorphic form can have on drug product stability. Nonetheless, because drug product stability is affected by a multitude of other factors, including formulation, manufacturing process, and packaging, it is the stability of the drug product, and not stability of the drug substance polymorphic form that should be the most relevant measure of drug quality.

IV. POLYMORPHISM AND *SAMENESS* IN ANDAs

Section 505(j)(2) of the Act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the RLD. Under section 505(j)(4) of the Act, FDA must approve an ANDA unless the agency finds, among other things, that the ANDA contains insufficient information to show that the active ingredient is the same as that in the RLD. FDA regulations implementing section 505(j) of the Act provide that an ANDA is suitable for consideration and approval if the generic drug product is the "same as" the RLD. Specifically, 21 CFR 314.92(a)(1) provides that the term "same as" means, among other things, "identical in active ingredient(s)." The drug substance in

[21] SR Vippagunta, HG Brittain, DJW Grant. "Crystalline solids," *Adv. Drug Del. Rev.* 48:3-26, 2001.
[22] See footnote 19.

a generic drug product is considered to be the same as the drug substance in the RLD if it meets the same standards for identity.[23]

When a United States Pharmacopeia (USP) monograph exists for a particular drug substance, standards for identity generally refer to the definition (i.e. chemical name, empirical formula, molecular structure, description) at the beginning of the monograph. However, FDA may prescribe additional standards that are material to the *sameness* of a drug substance.[24]

Polymorphic forms of a drug substance differ in internal solid-state structure, but not in chemical structure. In the context of *sameness* of active ingredient(s) in the preamble to the 1992 final rule, FDA specifically rejected a proposal that would have required an ANDA applicant to show that the active ingredient in its generic drug product and the active ingredient in the RLD "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process and that the stereochemistry characteristics and solid state forms of the drug have not been altered."[25] Therefore, differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Act and FDA regulations.

In addition to meeting the standards for identity, each ANDA applicant is required to demonstrate that, among other things, the drug product exhibits sufficient stability and is bioequivalent to the RLD.[26] While the polymorphic form can affect drug product stability and bioequivalence, these performance characteristics are also dependent on the formulation, the manufacturing process, and other physicochemical properties (e.g., particle size, moisture) of both the drug substance and formulation excipients. Thus, using a drug substance polymorphic form that is different from that of the RLD may not preclude an ANDA applicant from formulating a generic drug product that exhibits bioequivalence and stability. Therefore, the drug substance in the generic drug product need not have the same polymorphic form as the drug substance in the RLD.

Over the years, FDA has approved a number of ANDAs in which the drug substance in the generic drug product had a different polymorphic form from the drug substance in the respective RLD (e.g., warfarin sodium, famotidine, and ranitidine). Also, FDA has approved some ANDAs in which the drug substance in the generic drug product differed in solvate or hydrate forms from the drug substance in the corresponding RLD (e.g., terazosin hydrochloride, ampicillin, and cefadroxil).

V. CONSIDERATIONS FOR POLYMORPHISM IN ANDAs

The decision trees shown in Attachments 1 to 3 provide ANDA applicants with a suggested process for evaluating the importance of and approaches to setting specifications for polymorphic forms in solid oral drug products and oral suspensions. Although the conceptual framework adopted by these decision trees is based primarily on the potential for polymorphic

[23] See preamble to the 1992 final rule (57 FR 17958; April 28, 1992).
[24] See footnote 23.
[25] See footnote 23.
[26] See 505(j)(4) of the Act and 21 CFR 314.127.

forms to affect drug product BA/BE, we recommend that you still consider the influence polymorphic forms may have on the ability to manufacture the drug product and on the stability of the drug product.

The following sections describe each of the decision trees.

A. Investigating the Importance of Setting Specifications for Polymorphs

Decision Tree 1 provides recommendations on when specifications for polymorphic form(s)[27] for the drug substance and/or the drug product may be appropriate. Polymorphs are unlikely to have a significant effect on BA/BE when all forms have the same solubilities or all forms are highly soluble.

ANDA applicants are expected to have adequate knowledge on drug substance polymorphs. Information on polymorphism can come from the scientific literature, patents, compendia, other references, or in some cases, polymorph screening.

B. Setting Specifications for Polymorphs in Drug Substances

Decision Tree 2 provides an approach for setting specifications for polymorphs in the drug substance when at least one form is known to have low solubility based on the BCS. If relevant and adequate specifications for polymorphs are included in the USP, ANDA applicants may adopt these specifications for the drug substance polymorphic form. Otherwise, we recommend that a new specification for the drug substance polymorphic form be established.

C. Investigating the Importance of Setting Specifications for Polymorphs in Drug Products

Decision Tree 3 provides an approach when considering the importance for setting specifications for polymorphs in the drug product. Generally, specifications for polymorphs in drug products are not necessary if the most stable polymorphic form is used or if the same form is used in an approved product of the same dosage form. However, since manufacturing processes can affect the polymorphic form, we recommend that you use caution if a metastable form is used.

Drug product performance testing (e.g., dissolution testing) can also generally provide adequate control of polymorph ratio changes that can influence drug product BA/BE for poorly soluble drugs. In such instances, setting specifications for polymorphs in the drug product would generally not be considered important for ensuring adequate product performance. Only in rare cases would we recommend setting specifications for polymorphic forms in drug products.

[27] See footnote 7.

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ATTACHMENT 1 – DECISION TREE 1

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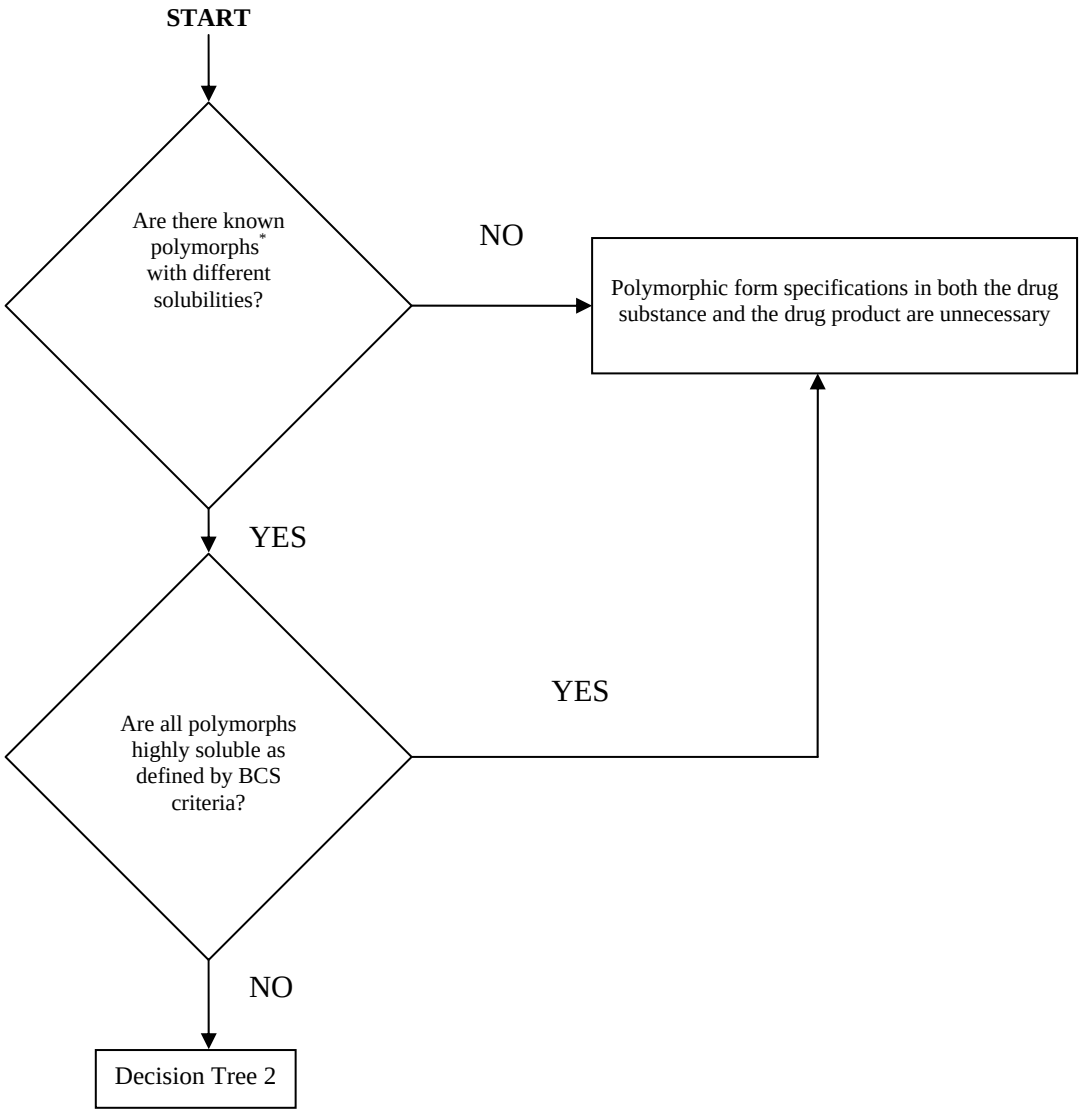
260 *Decision Tree 1* Investigating the importance of setting specifications for polymorphs for
261 solid oral and suspension dosage form products.



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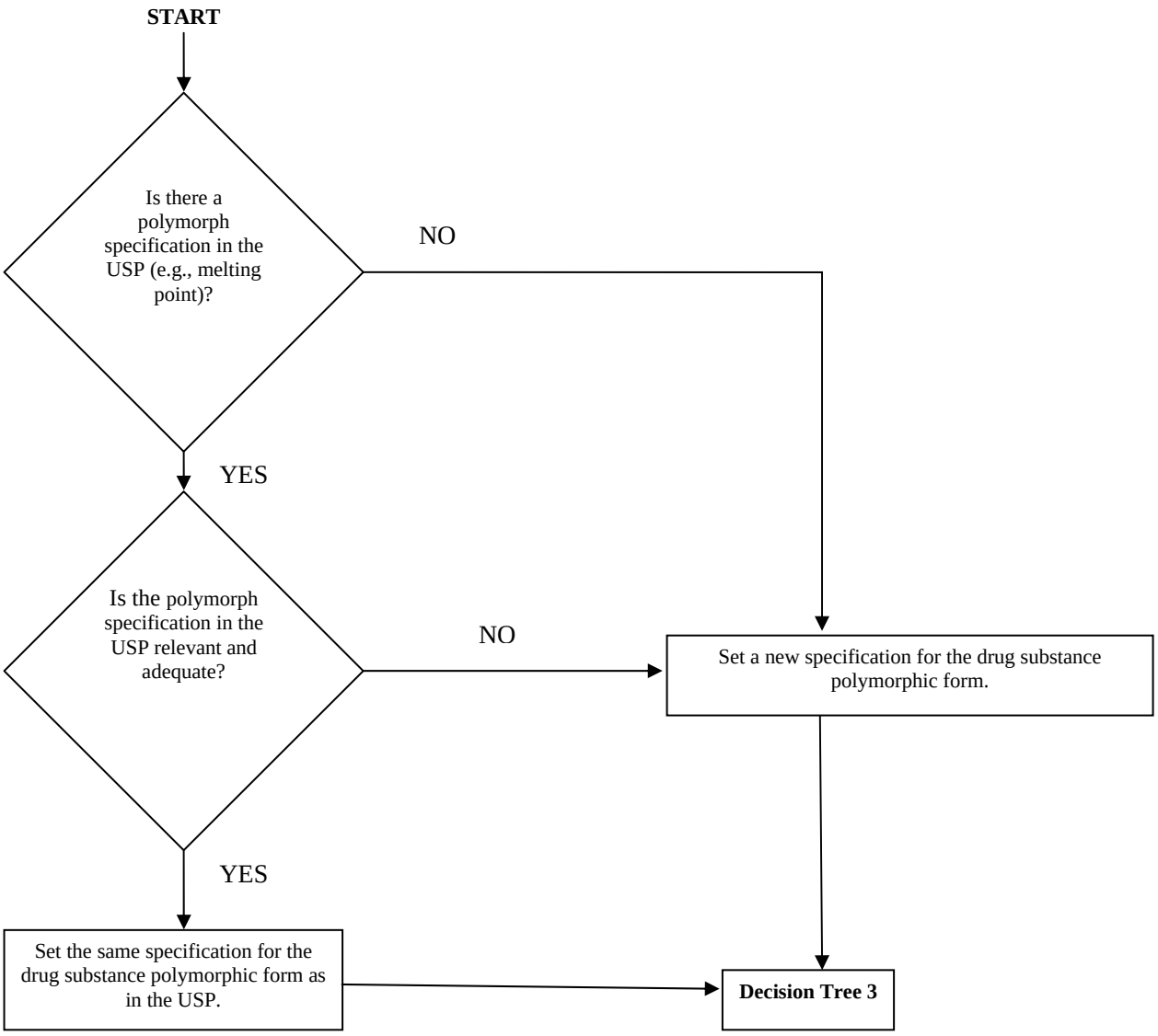
263 *We recommend that you consider only those polymorphs that are likely to form during manufacture of the drug
264 substance, manufacture of the drug product, or while the drug substance or drug product is in storage. See footnote
265 7 in this guidance document.

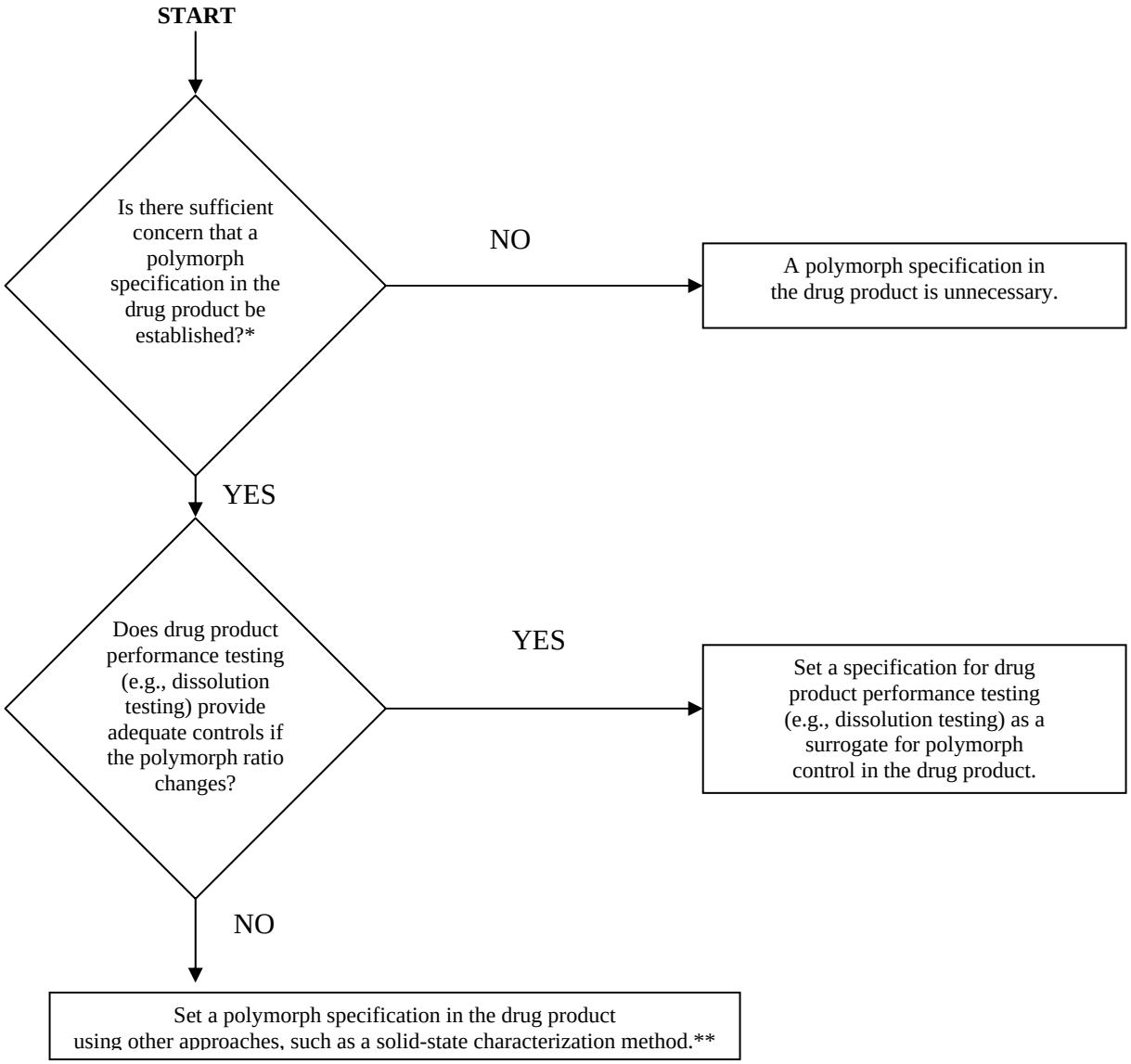
ATTACHMENT 2 – DECISION TREE 2

Decision Tree 2 Setting specifications for polymorphs in drug substances for solid oral and suspension dosage form products.



ATTACHMENT 3 – DECISION TREE 3

Decision Tree 3 Investigating the importance of setting specifications for polymorphs in drug products for solid oral and suspension dosage form products.



*In general, there may not be a concern if the most stable polymorphic form is used or the same form is used in a previously approved product of the same dosage form.

**Drug product performance testing (e.g., dissolution testing) can generally provide adequate control of polymorph ratio changes for poorly soluble drugs, which may influence drug product BA/BE. Only in rare cases would polymorphic form characterization in the drug product be recommended.