
Guidance for Industry

Regulatory Classification of Pharmaceutical Co-Crystals

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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CMC

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I. INTRODUCTION

This guidance provides applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) with the Center for Drug Evaluation and Research's current thinking on the appropriate regulatory classification of pharmaceutical co-crystal solid-state forms. This guidance also provides information about the data that you, the applicant, should submit to support the appropriate classification of a co-crystal, as well as the regulatory implications of the classification.

The recommendations in this guidance apply to materials that the Agency has not previously evaluated and determined to be pharmaceutical co-crystals. The recommendations do not apply to materials that the Agency has previously designated as salts, complexes, or other non-co-crystalline forms.

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. BACKGROUND

Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Given the association of two or more molecules in the co-crystal lattice, it is useful to consider the association of components more generally. A drug product is a finished dosage form (e.g., tablet; capsule; or solution that contains an active pharmaceutical ingredient² (API) generally, but not necessarily, in association with inactive ingredients (excipients)).³ This

¹ This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this guidance, the term "active pharmaceutical ingredient" is synonymous with the term "drug substance" (as defined in 21 CFR 314.3).

³ See 21 CFR 210.3(b)(4).

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association of the API with its excipient(s) is designed to achieve performance characteristics to ensure drug product stability, bioavailability, patient acceptance, and other quality characteristics. However, this association of the API with its excipient(s) in the dosage form may vary considerably. At one extreme, this association of the API with its excipient(s) may be at a macromolecular level typical of a physical mixture, as in a tablet manufactured by dry compression of the API with various excipients. At another extreme, this association of the API with its excipient(s) may be at a molecular level, such as an API incorporated into a β – cyclodextrin excipient, in formulations designed for the purposes of enhancing drug bioavailability, enhancing stability, or masking taste. Another example where this association of the API with its excipient(s) exists at a molecular level may occur in the case of amorphous API-excipient dispersion, in formulations designed to enhance drug product bioavailability.

Traditionally, solid-state polymorphic forms of an API are classified as either crystalline, amorphous, or solvate and hydrate forms, and applicable regulatory schemes for these solid-state polymorphic forms are well-defined (see Glossary). Co-crystals, however, are distinguishable from these traditional pharmaceutical solid-state forms. Unlike polymorphs, which generally speaking contain only the API within the crystal lattice,⁴ co-crystals are composed of an API with a neutral guest compound (also referred to as a conformer) in the crystal lattice. Similarly, unlike salts (see Glossary), where the components in the crystal lattice are in an ionized state, a co-crystal's components are in a neutral state and interact via nonionic interactions.

Pharmaceutical co-crystals have opened the opportunity for engineering solid-state forms designed to have tailored properties to enhance drug product bioavailability⁵ and stability, as well as enhance processability of the solid material inputs in drug product manufacture.⁶ Pharmaceutical co-crystals are of interest because they offer the advantage of generating a diverse array of solid-state forms from APIs that lack ionizable functional groups needed for salt formation.

At present no formal regulatory policy exists governing the classification of pharmaceutical co-crystals. In response to the need for regulatory guidance, this guidance provides our current thinking on the appropriate classification of co-crystal solid-state forms, the data that should be submitted to support the classification, and the regulatory implications of such a classification.

III. DISCUSSION

In a co-crystal, the molecular association between an API and its excipient(s) occurs within the same crystal lattice and is governed by nonionic interactions, unlike the ionic interactions required for salt formation of an API. Therefore, within the Agency's current regulatory framework, co-crystals are classified as dissociable "API—excipient" molecular complexes (with the neutral guest compound being the excipient). Co-crystals within this broader category are

⁴ Polymorphic forms also may include solvate (or hydrate) forms that contain—in addition to the active ingredient either stoichiometric or nonstoichiometric amounts of a solvent (or water) in the crystal lattice.

⁵ See for example, McNamara et al., "Use of a Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API," *Pharmaceutical Research*, 23(8), 2006, pp. 1888-1897.

⁶ See for example, Trask et al., "Physical Stability Enhancement of Theophylline via Cocrystallization," *International Journal of Pharmaceutics*, 320, 2006, pp. 114-123.

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uniquely defined by the fact that the molecular association of API and its excipient(s) occurs within the crystal lattice. In this manner, an API that has been processed with a co-crystallizing excipient to generate an “API—excipient” co-crystal should be treated as a drug product intermediate.⁷

For NDAs and ANDAs containing or claiming to contain a co-crystal form, you should submit appropriate data that support the following:

- A conclusion that the component API with the excipient compounds in the co-crystal exist in their neutral states and interact via nonionic (versus ionic) interactions. You should consider the following to guide your decision:
 - Generally speaking, if the API and its excipient(s) have a ΔpK_a (pK_a (base) - pK_a (acid)) ≥ 1 , there will be substantial proton transfer resulting in ionization and formation of a salt as opposed to a co-crystal. On the other hand, if the API and its excipient(s) have a ΔpK_a (pK_a (base) - pK_a (acid)) < 1 , there will be less than substantial proton transfer. If this criterion is met, the active ingredient-excipient complex should be classified as a co-crystal.
 - If, however, you believe that the classification of the pharmaceutical solid as a salt or co-crystal is not predicated on these relative pK_a values, then spectroscopic tools using various orthogonal approaches should be used to prove otherwise.
- Assurance that complete dissociation of the API from its excipient occurs prior to reaching the site of action for pharmacological activity.⁸

An “API—excipient” co-crystal that meets these conditions is a “pharmaceutical co-crystal” and has a regulatory classification of a drug product intermediate. Specifically, it is not regarded as a new API. Drug products that contain “API—excipient” co-crystals are not considered to contain new API, but rather a specifically designed component called a “co-crystal drug product intermediate.”

If you are using a material that the Agency previously considered to be a co-crystal, you may continue to do so. New applications should provide evidence of the previous co-crystal designation in the 3.2.P.2.1 (Components of the Drug Product) section of a [common technical document \(CTD\) formatted application](#).

The type and extent of characterization and release testing performed on the active pharmaceutical ingredient, the co-crystal intermediate, or both should be sufficient to ensure the identity, strength, quality, and purity of the active ingredient, critical process intermediates, and drug product. Regardless of whether the co-crystal is manufactured in an API manufacturing facility or in one typically used to manufacture drug product (dosage

⁷ For the purposes of this guidance, the term “drug product intermediate” is synonymous with the term “in process material” (as defined in 21 CFR 210.3(b)(9)).

⁸ Analogous approaches can be used to demonstrate that for an active moiety’s given salt form, the active moiety dissociates from its corresponding counterion prior to reaching the site of pharmacological action.

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form), the co-crystal should be manufactured in a facility that operates in accordance with current good manufacturing practice (CGMP).

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GLOSSARY

Co-crystals: Crystalline materials composed of two or more molecules within the same crystal lattice.

Polymorphs: Different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients. (See Guidance for Industry: *ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information*, July 2007.)

Salts: Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound. Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients. (See 21 CFR 314.108 and 21 CFR 320.1(c).)