
Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry

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

**February 2018
Pharmaceutical Quality/CMC
Revision 1**

Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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I. INTRODUCTION

This guidance provides applicants planning to submit new drug applications (NDAs) and abbreviated new drug applications (ANDAs) with information on the appropriate regulatory classification of pharmaceutical co-crystal solid-state forms.² This guidance also provides information about the data that applicants 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.

In general, FDA's guidance documents 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 crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers"), in the same crystal lattice. Pharmaceutical co-crystals have provided opportunities for engineering solid-state

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

² This guidance finalizes the August 2016 revised draft guidance for industry *Regulatory Classification of Pharmaceutical Co-Crystals*, which classified co-crystals as a drug product intermediate (or as an in-process material), and replaces the 2013 guidance of the same name.

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forms beyond conventional solid-state forms of an API, such as salts and polymorphs.³ Co-crystals can be tailored to enhance drug product bioavailability and stability and to enhance the processability of APIs during drug product manufacture.⁴ Another advantage of co-crystals is that they generate a diverse array of solid-state forms for APIs that lack ionizable functional groups, which is a prerequisite for salt formation.

III. DISCUSSION

Co-crystals are distinguished from salts because unlike salts, the components that co-exist in the co-crystal lattice with a defined stoichiometry interact nonionically. In addition, co-crystals differ from polymorphs, which are defined as including 1) single-component crystalline forms that have different arrangements or conformations of the molecules in the crystal lattice, 2) amorphous forms, and 3) multicomponent phases such as solvate and hydrate forms.⁵ Instead, co-crystals are more similar to solvates, in that both contain more than one component in the lattice. From a physical chemistry and regulatory perspective, co-crystals can be viewed as a special case of solvates and hydrates, wherein the second component, the cofomer, is not a solvent (including water), and is typically nonvolatile.⁶

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

- Provide evidence to demonstrate that both the API and cofomers are present in the unit cell.
- If both API and cofomer have ionizable functional groups, a conclusion that the component API and cofomer co-exist in the co-crystal which interact nonionically. Consider the following to guide your decision:
 - Generally speaking, if the API and its cofomer have a ΔpK_a (pK_a (conjugate acid of base) - pK_a (acid)) ≥ 1 , there will be substantial proton transfer resulting in ionization and potential formation of a salt as opposed to a co-crystal. On the other hand, if the API and its cofomer have a ΔpK_a (pK_a (conjugate acid of base) - pK_a (acid)) < 1 , there will be less than substantial proton transfer. If this criterion is met, the API-cofomer entity should be classified as a co-crystal.

³ 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).

⁴ Schultheiss, N and A Newman, 2009, Pharmaceutical Cocrystals and Their Physicochemical Properties, *Crystal Growth & Design*, 9(6):2950–2967; Shan, N and MJ Zaworotko, 2008, The Role of Cocrystals in Pharmaceutical Science, *Drug Discovery Today*, 13(9–10):440–446.

⁵ See the guidance for industry ICH Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ Note that USP infrared identity test <197> may not be applicable when comparing co-crystals with different cofomers.

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- If, however, it is determined that the classification of the pharmaceutical solid as a salt or co-crystal is not predicated on these relative pKa values, use spectroscopic tools and other orthogonal approaches to provide evidence to the contrary.
- Assurance that substantial dissociation of the API from its co-crystal form occurs before reaching the site of pharmacological activity. Given that the interaction of the API with its coformer is of similar magnitude to the interaction of the API with solvents in solvates, an in vitro evaluation based on dissolution and/or solubility is generally considered sufficient to demonstrate that the API dissociates from its coformer before reaching the site of pharmacological activity.

A co-crystal with a pharmaceutically acceptable coformer that meets the above conditions can be considered to be a pharmaceutical co-crystal and has a regulatory classification similar to that of a polymorph of the API.⁷ Specifically, it is not regarded as a new API.⁸ From a regulatory perspective, drug products that are designed to contain a new co-crystal are considered analogous to a new polymorph of the API. A co-crystal that is composed of two or more APIs (with or without additional inactive cofomers) will be treated as a fixed-dose combination product and not a new single API.

If you are using a material that the Agency previously considered to be a co-crystal, you may continue to do so. In new applications formatted as common technical documents, provide evidence of the previous co-crystal designation in section 3.2.S.1 (Components of the Drug Substance).⁹

The type and extent of characterization and release testing performed on the co-crystal should be sufficient to ensure the identity, strength, quality, and purity of the API(s).

⁷ See the guidance for industry *ANDAs: Pharmaceutical Solid Polymorphism*.

⁸ Different co-crystals of a salt API will be treated as a polymorph of that salt.

⁹ For information on common technical documents, see

<http://www.fda.gov/drugs/developmentapprovalprocess/formsubmissionrequirements/electronic submissions/ucm153574.htm>.

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GLOSSARY

Co-crystals: Crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds.

Coformer: A component that interacts nonionically with the API in the crystal lattice, that is not a solvent (including water), and is typically nonvolatile.

Polymorphs: Different crystalline forms of the same API. 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 APIs. (See guidance for industry *ANDAs: Pharmaceutical Solid Polymorphism*.)

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 APIs. (See 21 CFR 314.108 and 21 CFR 320.1(c).)