
Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry

DRAFT GUIDANCE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)**

**August 2016
Pharmaceutical Quality/CMC**

Revision 1

Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry

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Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 drug and co-crystal formers ("coformers"), in the same crystal lattice. Pharmaceutical co-crystals have opened up opportunities for engineering solid-state forms beyond conventional solid-state forms of an active pharmaceutical ingredient (API), such as salts and polymorphs.³ Co-crystals can be

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 revises the April 2013 guidance for industry *Regulatory Classification of Pharmaceutical Co-Crystals*, which classified co-crystals as a drug product intermediate (or as an in-process material). After it has been finalized, this guidance will replace the 2013 guidance.

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).

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39 tailored to enhance drug product bioavailability and stability and to enhance the processability of
40 APIs during drug product manufacture.⁴ Another advantage of co-crystals is that they generate a
41 diverse array of solid-state forms for APIs that lack ionizable functional groups, which is a
42 prerequisite for salt formation.

43

III. DISCUSSION

44

45
46 Co-crystals are readily distinguished from salts because unlike salts, their components are in a
47 neutral state and interact nonionically. In addition, co-crystals differ from polymorphs, which are
48 defined as including only single-component crystalline forms that have different arrangements or
49 conformations of the molecules in the crystal lattice, amorphous forms, and multicomponent
50 phases such as solvate and hydrate forms. Instead co-crystals are more similar to solvates, in that
51 both contain more than one component in the lattice. From a physical chemistry perspective, co-
52 crystals can be viewed as a special case of solvates and hydrates, wherein the second component,
53 the coformer, is nonvolatile. Therefore, co-crystals are classified as a special case of solvates in
54 which the second component is nonvolatile.⁵

55

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

58

- 59 • If both drug and coformer have ionizable functional groups, a conclusion that the component
60 drug and coformer exist in their neutral states in the co-crystal and interact nonionically.

61 Consider the following to guide your decision:

62

- 63 ○ Generally speaking, if the API and its coformer have a ΔpK_a (pK_a (base) - pK_a (acid)) \geq
64 1, there will be substantial proton transfer resulting in ionization and potential formation
65 of a salt as opposed to a co-crystal. On the other hand, if the API and its coformer have a
66 ΔpK_a (pK_a (base) - pK_a (acid)) $<$ 1, there will be less than substantial proton transfer. If
67 this criterion is met, the API-coformer entity should be classified as a co-crystal.

68

- 69 ○ If, however, you believe that the classification of the pharmaceutical solid as a salt or co-
70 crystal is not predicated on these relative pK_a values, use spectroscopic tools and other
71 orthogonal approaches to provide evidence to the contrary.⁶

72

- 73 • Assurance that substantial dissociation of the API from its co-crystal form occurs before
74 reaching the site of pharmacological activity. Given that the interaction of the API with its
75 coformer is of similar magnitude to the interaction of the API with solvents in solvates, an in
76 vitro evaluation based on dissolution and/or solubility is generally considered sufficient to

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

⁶ If the asymmetric unit of the crystalline phase contains both co-crystal and salt components, i.e., ionic and nonionic interactions, the API will be treated as a salt.

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77 demonstrate that the active API dissociates from its coformer before reaching the site of
78 pharmacological activity.

79
80 A co-crystal with a pharmaceutically acceptable coformer that meets the above conditions can be
81 considered to be a pharmaceutical co-crystal and has a regulatory classification similar to that of
82 a polymorph of the API.⁷ Specifically, it is not regarded as a new API.⁸ From a regulatory
83 perspective, drug products that are designed to contain a new co-crystal are considered analogous
84 to a new polymorph of the API. A co-crystal that is composed of two or more APIs (with or
85 without additional inactive cofomers) will be treated as a fixed-dose combination product and
86 not a new API.

87
88 If you are using a material that the Agency previously considered to be a co-crystal, you may
89 continue to do so. In new applications formatted as common technical documents, provide
90 evidence of the previous co-crystal designation in section 3.2.S.1 (Components of the Drug
91 Substance).⁹

92
93 The type and extent of characterization and release testing performed on the co-crystal should be
94 sufficient to ensure the identity, strength, quality, and purity of the API(s).

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

⁸ Different co-crystals of a salt API will be treated as a polymorph of that salt. As applicable, the pKa rule and/or orthogonal characterization data can be used to provide supporting evidence for each case.

⁹ For information on common technical documents, see <http://www.fda.gov/drugs/developmentapprovalprocess/formsubmissionrequirements/electronic submissions/ucm153574.htm>.

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95 **GLOSSARY**

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97 **Co-crystals:** Crystalline materials composed of two or more different molecules within the same
98 crystal lattice that are associated by nonionic and noncovalent bonds.

99

100 **Polymorphs:** Different crystalline forms of the same API. This may include solvation or
101 hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current
102 regulatory scheme, different polymorphic forms are considered the same APIs. (See guidance for
103 industry ANDAs: *Pharmaceutical Solid Polymorphism*.)

104

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