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3 Committee for Medicinal Products for Human Use (CHMP)
4 Committee for Medicinal Products for Veterinary Use (CVMP)

5 **Reflection paper on the use of cocrystals and other solid**
6 **state forms of active substances in medicinal products**
7 **Draft**

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8 The present document reflects the current thinking of the CHMP and CVMP. The principles spelled out
9 in this reflection paper will be reviewed in light of experience gained with regulatory submissions and
10 contributions from stakeholders.

9
10 Comments should be provided using this [template](#). The completed comments form should be sent to
qwp@ema.europa.eu

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Keywords	Cocrystals, salts, hydrates, solvates, polymorphic forms, solid state, active substance.
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33 **Executive Summary**

34 The content of this reflection paper represents the current thinking of the CHMP/CVMP Quality Working
35 Party concerning recent scientific developments on solid state forms, in particular cocrystals. The
36 reflection paper provides guidance concerning the legal basis and submission requirements for
37 cocrystals.

38 Comments from stakeholders would be welcomed.

39 **1. Introduction**

40 This reflection paper discusses solid state forms as active ingredients in medicinal products with special
41 attention to cocrystals.

42 Over the last decade, cocrystals have gained considerable attention as alternative solid-state forms in
43 drug development.¹ By making cocrystals of pharmaceutically interesting substances, their solid state
44 properties such as solubility, hygroscopicity and stability may be improved as well as their
45 manufacturing behaviour (compaction, flowability, filterability etc.).² Salt formation is already widely
46 used for this purpose, but with cocrystal formation this can now be achieved also for substances that
47 lack the possibility of salt formation.³

48 Where applicable, this reflection paper should be read in connection with the principles of relevant
49 guidelines such as:

- 50 • ICH Q11 Guideline on development and manufacture of drug substances (chemical entities and
51 biotechnological / biological entities) (CHMP/ICH/425213/2011)
- 52 • Reflection paper on considerations given to designation of a single stereo isomeric form
53 (enantiomer) as new active substance in relation to a reference active substance which is a
54 racemic mixture of enantiomers (EMA/651649/2010)

55 It should be noted that while elaborating this reflection paper, the FDA has published Guidance for
56 Industry which classify cocrystals differently from what is expressed here.⁴

57 **1.1. Scope**

58 This reflection paper is intended to give the current thinking of the European Regulators regarding
59 different aspects concerning the use of different solid state forms of active ingredients in medicinal
60 products, for either human or veterinary use. These aspects include, for example, the applicability of
61 Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC, the
62 acceptability of the Active Substance Master File (ASMF) procedure and the possibility to include
63 different solid state forms within the same marketing authorisation.

64 Directives 2001/83/EC and 2001/82/EC address only different forms of an active substance in
65 Articles 10(2)(b) and 13(2)(b) respectively where, for example, different salts are concluded to be the
66 same active substance for the purpose of an abridged application unless they are different with regard
67 to efficacy or safety:

68 *“The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active*
69 *substance shall be considered to be the same active substance, unless they differ significantly in*
70 *properties with regard to safety and/or efficacy”.*

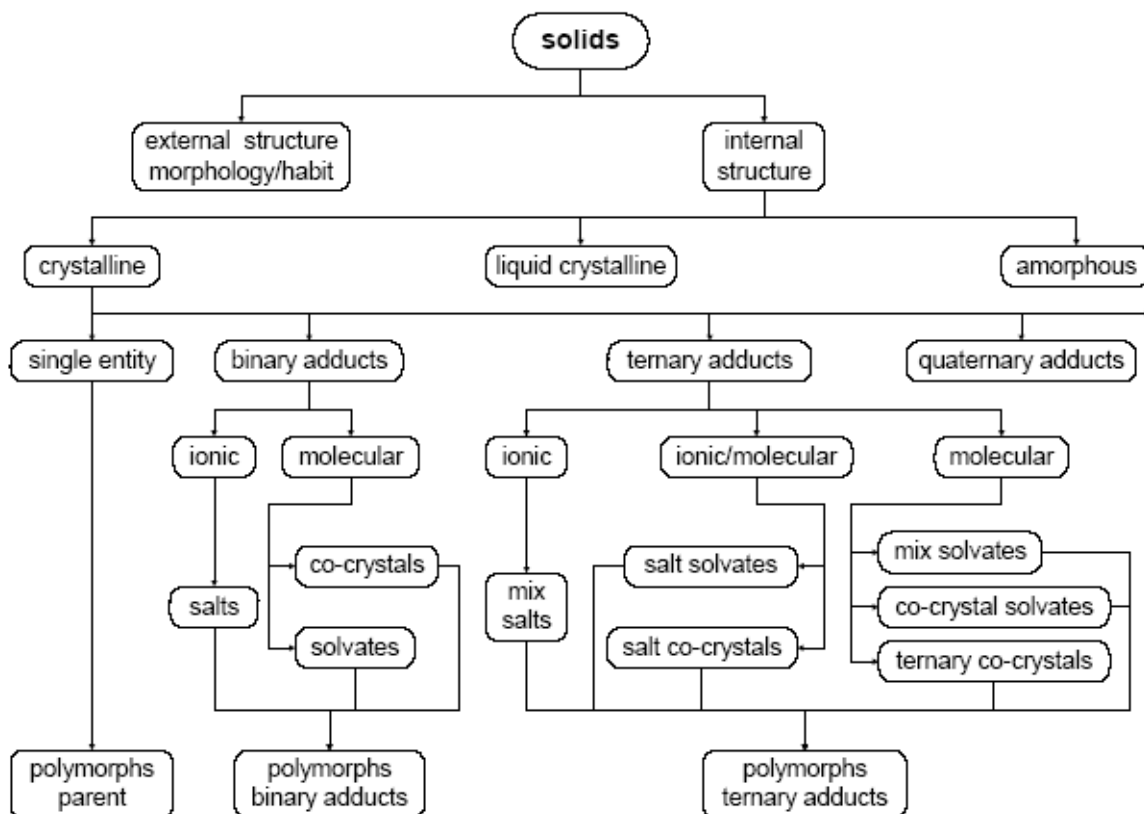
71 This reflection paper is further focusing on solid state forms not mentioned in the Directives, e.g.,
72 cocrystals.

73 **2. Definitions of cocrystals and their comparison to other**
74 **known solid forms**

75 **2.1. Diversity of solid state forms**

76 A general subdivision of solid state materials (treating solvates separately from other cocrystals) is
77 summarized in the following figure⁵:

78
79
80



81
82
83 *Figure 1: Subdivision of solid state material of an active moiety.*
84

85 As evidenced by the large number of marketed crystalline active pharmaceutical ingredient (API) salts,
86 they are often selected over the free acid or base as pharmaceutical compounds based e.g. on their
87 improved stability and/or solubility profiles. Cocrystallisation is considered as a viable alternative to
88 salt formation in cases where salts do not have the appropriate solid state properties or where salts
89 cannot be formed.

90 **2.2. Cocrystals**

91 Although the detailed definition of cocrystals is still debated in the scientific literature, they are in
92 general defined as homogenous crystalline structures made up of two or more components in a definite
93 stoichiometric ratio where the arrangement in the crystal lattice is not based on ion pairing (as with
94 salts). Co-precipitation or physical mixing resulting in variable stoichiometry is excluded.

95 In the field of pharmaceutical sciences, where at least one of the components in the crystal lattice is a
96 designated API, these structures are also referred to as pharmaceutical cocrystals.⁶ The other
97 components in a pharmaceutical cocrystal are called co-formers.

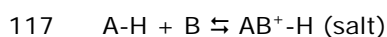
98 **2.3. Solvates and hydrates**

99 From a scientific point of view, solvates and hydrates can be considered as a subgroup of cocrystals.
100 The solvent, or the water, acts as a co-former in the same way as other co-formers. Such forms may
101 be the result of a design to achieve crystals with certain properties, but they may also be the result of
102 a selection of a final solvent based on other criteria. To be able to distinguish hydrates and solvates
103 from (other) cocrystals it has been suggested to limit the definition of cocrystals by stating that the
104 components of a cocrystal should exist as individual solids at ambient conditions. This has been
105 criticized since not only solvents, but also other potential co-formers may be liquids at ambient
106 temperature. It therefore seems to have little scientific value to limit the definition of cocrystals in this
107 way. However, the terms 'hydrates' and 'solvates' are descriptive and widely used, and they should
108 therefore be retained while keeping in mind that they are part of, rather than separate from, the
109 general concept of cocrystals.⁷

110 **2.4. Cocrystals and salts**

111 In contrast to salts, where the components are arranged in the crystal lattice predominantly based on
112 ion pairing, the components in cocrystals are assembled via weaker interactions, such as e.g.,
113 hydrogen bonding, π - π -stacking or van der Waals interactions. Salts are formed in an acid–base
114 reaction between the API and an acidic or basic substance by proton (H^+) transfer from acid (A) to
115 base (B).

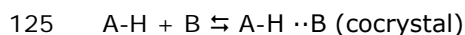
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119 Proton transfer mainly depends on the difference in pKa values of the components. Usually, a
120 difference of about 3 pKa units between the conjugate base and the conjugate acid is considered to
121 result in salt formation. For systems with $\Delta \text{pKa} < 0$, where no proton transfer occurred and the
122 components are instead present in the crystal as neutral entities, the product is generally considered
123 as a cocrystal.⁸

124



126

127 In instances where the difference in pKa values is between 0 and 3, the extent of proton transfer is
128 usually not predictable and spectroscopic tools may be needed to probe the extent of ionization and
129 therefore the location in the cocrystal/salt continuum.⁹

130 Nonetheless, both cocrystals and salts have defined stoichiometries, similar solution speciation
131 characteristics, as well as a solubility product K_{sp} .

132 However, crystalline forms are neither cleanly divided nor differentiated from one another by the
133 ionization state(s) of the individual components, as ionization is possible in both pure component APIs
134 and cocrystals, as well as in salts. Examples include:

- 135 • Amphoteric compounds, which possess acidic and basic functional groups, may experience
136 proton transfer in the solid state, resulting in pure component zwitterionic forms. (For
137 examples, see reference 9 and the literature cited within)
- 138 • A pure component API may exist in mixed ionization states within the same crystal structure.
139 (For examples, see reference 9 and the literature cited within)
- 140 • Multi-component salt cocrystals (or cocrystalline salts) will by definition have ionized
141 components. (For examples, see reference 3 and the literature cited within)

142 From a material point of view, the classification of solid state APIs into salts or cocrystals is considered
143 only of theoretical nature. Ultimately, the resulting material properties are the critical factors that
144 determine the suitability of a developed solid state API form for the designated purpose, regardless of
145 the molecular bonding involved.¹⁰

146 **2.5. Polymorphism**

147 In the solid state, single as well as multiple entities, such as salts, hydrates, cocrystals, etc., may
148 exhibit polymorphism, which is the ability of a compound in the solid state to exist in different
149 crystalline forms having the same chemical composition.¹¹ These different forms are formed by the
150 weak interactions between the components present in the solid state. The energy necessary for
151 melting, vaporization or dissolution are sufficient to disrupt these weak bonds.¹² These different forms
152 may possess different physico-chemical properties.¹³

153 **3. Discussion**

154 **3.1. Regulatory implications of solid state forms**

155 The understanding of cocrystals and other solid state forms of active substances from a regulatory
156 point of view may be of importance for:

- 157 • acceptance of abridged applications
- 158 • granting of New Active Substance (NAS) status for applications with such claims
- 159 • acceptance of different forms in the same marketing authorisation
- 160 • acceptance of an Active Substance Master File
- 161 • applicability of Good Manufacturing Practice (GMP) for active substances or finished products

162 **3.1.1. Solid state forms and abridged applications**

163 An abridged application makes reference to the safety and efficacy documentation of an approved
164 reference product containing the same active substance. Directives 2001/83/EC Article 10(2)(b) and
165 2001/82/EC 13(2)(b) define what can be considered as the same active substance in the context of
166 accepting an abridged application.

167 Cocrystals, hydrates and solvates are held together by weak interactions that are in most cases broken
168 upon dissolution. This is the same situation as with salts. This means that when a drug substance in
169 such different forms is dissolved in the stomach or the intestinal canal, the likelihood is very high that
170 these different forms will expose the patient to the same active moiety. Cocrystals, hydrates and
171 solvates will therefore be considered eligible for generic applications in the same way as salts are
172 (Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC).

173 Polymorphic forms of a single entity active substance, or of salts, cocrystals, hydrates or solvates, will
174 also be considered eligible for generic applications in the same way.

175 **3.1.2. Solid state forms and New Active Substance (NAS) status**

176 To avoid misuse of the benefits of data protection given to new active substances when first receiving
177 a marketing authorisation, an assessment is done by the competent authorities to ensure that when an
178 applied substance is claimed to be new, it is indeed new.

179 Since cocrystals, hydrates and solvates are held together by weak interactions that are in most cases
180 broken upon dissolution, when administered they will expose a patient to the same moiety. Just as for
181 salts, they will therefore not be considered as NASs in themselves unless they are demonstrated to be
182 different with respect to efficacy and/or safety.

183 Polymorphic forms of a single entity active substance, or of salts, cocrystals, hydrates or solvates, will
184 also not be considered as NASs in themselves.

185 **3.1.3. Acceptance of different solid state forms in the same marketing** 186 **authorisation.**

187 Given that cocrystals and other solid state forms of active substances can be considered as the same
188 active substance according to the Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC Article
189 13(2)(b), would that imply that such different forms can be used as alternatives in a single marketing
190 authorisation?

191 In the directives it is clearly stated that the possibility to regard the listed forms as the same substance
192 is limited to the purpose of the Article, namely to accept abridged applications where the different
193 forms are present in the applied product and the reference product. It must therefore not be
194 understood that the different forms listed in the directive could be accepted as alternatives in the same
195 product. The same is also true for cocrystals in general, including also solvates. For a given product, it
196 should be unambiguous what the active moiety is accompanied with, whether it is a counter-ion of a
197 salt or a co-former of a cocrystal.

198 An exemption from this principle is hydrates. Under the condition that any difference in, e.g., solubility
199 lacks any clinical significance, it is possible to include different hydrates (also anhydrous forms) as
200 alternatives in the same marketing authorisation. The different amounts of water administered to the
201 patient lack all significance after dissolving the drug in the aqueous environment such as e.g. the
202 stomach or the intestinal canal. Any such proposal must be justified and the lack of clinical significance
203 demonstrated, e.g., by comparison of the intrinsic solubility, etc. The relevant sections of the dossier
204 such as manufacturing description and formula, specifications, etc., must take into account the actual
205 forms used. The SmPC may use wording under section 2 that express the content without defining the
206 hydrated state.

207 Different crystal forms of the same composition (polymorphic forms; see figure 1) may be accepted as
208 alternatives in the same marketing authorisation provided that any difference in properties have no
209 clinical significance. If alternative forms are applied for, the relevant specifications for each form must
210 be established.

211 **3.1.4. Acceptance of GMP**

212 According to part II of the European Union (EU) good manufacturing practice (GMP) guide, an active
213 pharmaceutical ingredient (API) is defined as any substance or mixture of substances intended to be
214 used in the manufacture of a drug (medicinal) product and that, when used in the production of a

215 drug, becomes an active ingredient of the drug product. In this context, the term 'mixture' refers to
216 cases where the active substance is not a single chemically defined substance (e.g., herbal extracts)
217 and it is not meant to allow a mixture of a chemically defined active substance with other active
218 substances or excipients to be considered as a single API. The blending of active substances, or the
219 blending of an API with an excipient, are considered as the first step in the manufacture of the
220 medicinal product, and therefore do not fall under the definition of an active substance. In the same
221 context, co-precipitates, formed by either random inclusion or occlusion of a co-solute into a growing
222 crystal lattice, as well as purely adsorptive processes, are not considered to be covered by this
223 definition.

224 In contrast to these purely physical mixtures of different chemical compounds, cocrystals, like salts,
225 are formed based on electrostatic or other non-covalent interactions and show well defined
226 stoichiometries and a regular spatial distribution of the individual components, resulting in defined
227 crystal structures and physico-chemical properties (see 2.4).

228 As a consequence of these differences between physical mixtures and cocrystals, the formation of
229 cocrystals is subject to compliance with part II of the EU GMP Guide (active substances) while the
230 formation of physical mixtures fall under part I of the EU GMP Guide (finished product).

231 **3.1.5. Acceptance of ASMF for solid state forms**

232 In accordance with Directives 2001/83/EC and 2001/82/EC, the quality documentation of an active
233 substance may under certain conditions be submitted directly from a manufacturer of the active
234 substance to the competent authority in the form of an Active Substance Master File (ASMF). This is
235 further elaborated in the Guideline on Active Master File Procedure (CHMP/QWP/227/02 Rev 3/Corr;
236 EMEA/CVMP/134/02 Rev 3/Corr). This procedure may only be applied for discrete active substances,
237 and not for mixtures of substances (QWP Q&A). With reference to the discussion under 3.1.4.
238 regarding GMP, it can be concluded that as a consequence of the differences between physical
239 mixtures and cocrystals, it is possible to present a single active substance master file for a cocrystal,
240 but for a physical mixture it is not possible.

241 **3.2. Documentation of cocrystals**

242 As outlined in section 3 (Discussion), cocrystals and salts share many conceptual similarities and
243 therefore also similar principles for documentation should be applied. As pharmaceutical cocrystals are
244 considered as alternative solid state forms of an API, all quality-related information should be provided
245 in part 3.2.S of the dossier (for veterinary applications in part 2.C) . This includes general information,
246 as well as information regarding the manufacture, characterisation, and control of the drug substance,
247 reference standards or materials, container-closure system and stability. If desired, and if the
248 prerequisites mentioned in section 3.1.5 are met, the applicant may employ the ASMF procedure. In
249 line with ICH Q11, commonly available chemicals employed as co-formers in the cocrystal manufacture
250 would be considered as reagents. However, for more complex or novel co-formers, details of the
251 manufacture, characterisation and controls, with cross references to supporting safety data, should be
252 provided for them, according to the drug substance format. In these cases, the applicant is encouraged
253 to seek scientific advice on the classification of the co-former from the Agency prior to submission.

254 If a cocrystal is claimed, and to rule out the possibility of the formation of a purely physical mixture of
255 two or more crystalline compounds, the formation of a cocrystal should be unambiguously
256 demonstrated by means of adequate state of the art analytical techniques. Results from more than one
257 technique and an orthogonal approach may be necessary.

258 The integrity of the cocrystal during the entire manufacturing process should be experimentally
259 confirmed.
260

4. References

- ¹ Qiao, N.; Schlindwein, W.; Malek, N.; Davies, A.; Trappitt, G.; Pharmaceutical cocrystals: An overview, *Int. J. Pharm.* **2011**, *419*, 1-11
- ² Aitipamula, S. et al.; Polymorphs, Salts, and Cocrystals: What's in a Name? *Cryst. Growth Des.* **2012**, *12*, 2147-2157
- ³ Schultheiss, N.; Newman, A. Pharmaceutical Cocrystals and Their Physicochemical Properties, *Cryst. Growth Des.* **2009**, *9*, 2950-2967
- ⁴ *Regulatory Classification of Pharmaceutical Co-Crystals*, Guidance for Industry, FDA (CDER), **2013**
- ⁵ Zhang GGZ, Zhou D. Crystalline and amorphous solids. In: Qui Y, Chen Y, Zhang GGZ, Liu L, Porter W editors, *Developing Solid Oral Dosage Forms: Pharmaceutical Theory & Practice*. Burlington, MA: Academic Press; **2009**. p. 26
- ⁶ Shan, N.; Zaworotko, M.J.; The role of cocrystals in pharmaceutical science, *Drug Disc. Today*, **2008**, *13*, 440 – 446
- ⁷ Stahly, G.P.; Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals; *Cryst. Growth Des.* **2007**, *7*, 1007-1026
- ⁸ Childs, S.L.; Stahly, G.P.; Park, A.; The Salt-Cocrystal Continuum: The influence of Crystal Structure on Ionization State, *Mol. Pharm.* **2007**, *4*, 323-338
- ⁹ Childs, S.L.; Stahly, G.P.; Park, A.; The Salt-Cocrystal Continuum: The influence of Crystal Structure on Ionization State, *Mol. Pharm.* **2007**, *4*, 323-338
- ¹⁰ Kim, S.; Li, Z.; Tseng, Y.-C.; Nar, H.; Spinelli, E.; Varsolona, R.; Reeves, J.T.; Lee, H.; Song, J.J.; Smoliga, J.; Yee, N.; Senanayake, C. Development and Characterization of a Cocrystal as a Viable Solid Form for an Active Pharmaceutical Ingredient. *Org. Process Res. Dev.* **2013**, *17*, 540 – 548
- ¹¹ European Pharmacopoeia: 5.09 **2011** 7.
- ¹² Stahly, G.P.; Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals; *Cryst. Growth Des.* **2007**, *7*, 1007-1026
- ¹³ Guidelines on the Chemistry of New Active Substances, CPMP/QWP/130/96. Rev 1 (human) and EMEA/CVMP/541/03 (veterinary)