EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2014
EMA/CHMP/CVMP/QWP/136250/2014
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of cocrystals and other solid state forms of active substances in medicinal products

Draft

Draft agreed by CHMP/ CVMP Quality working party	25 February 2014
Adoption by CHMP for release for consultation	20 March 2014
Adoption by CVMP for release for consultation	8 May 2014
Start of consultation	31 July 2014
End of consultation (deadline for comments)	31 October 2014

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

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

Keywords	Cocrystals, salts, hydrates, solvates, polymorphic forms, solid state, active substance.

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Executive Summary

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

Comments from stakeholders would be welcomed.

1. Introduction

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

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

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

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

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

1.1. Scope

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

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

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

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

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

2.1. Diversity of solid state forms

A general subdivision of solid state materials (treating solvates separately from other cocrystals) is summarized in the following figure[5]:

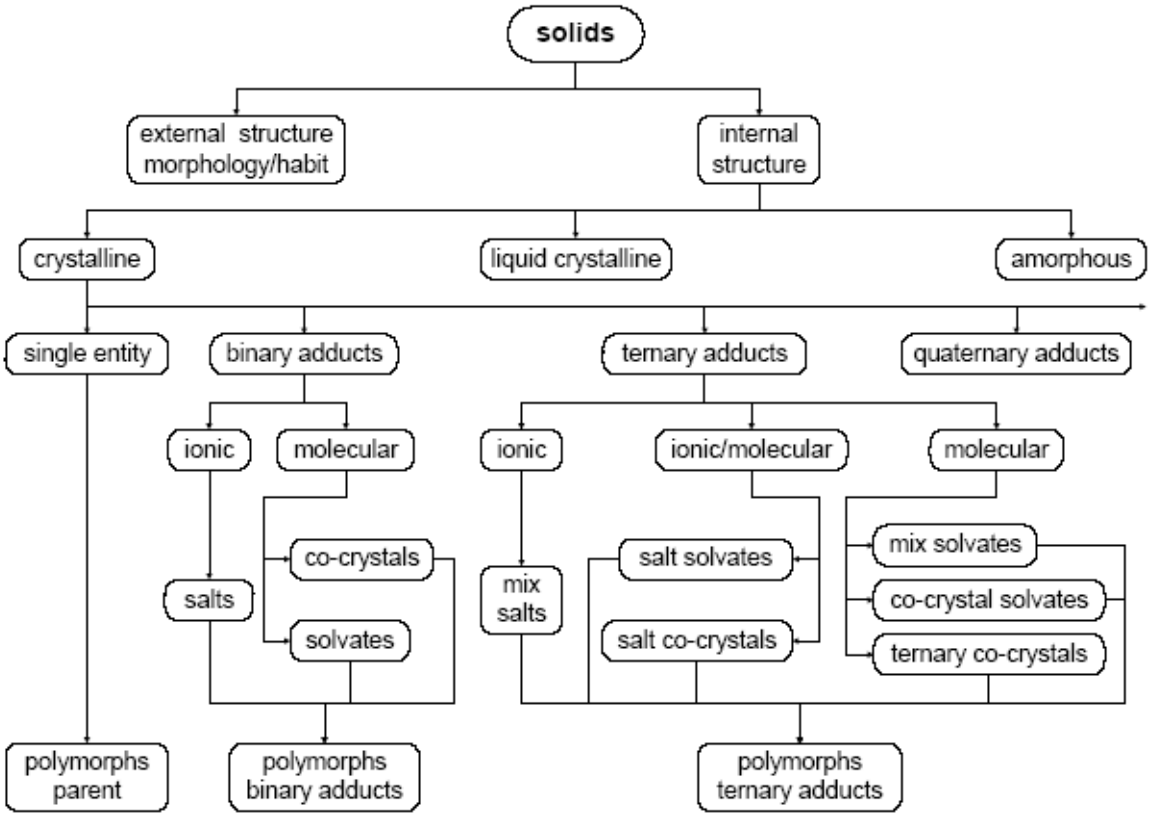

Figure 1: Subdivision of solid state material of an active moiety.

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

2.2. Cocrystals

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

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

2.3. Solvates and hydrates

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

2.4. Cocrystals and salts

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

$A\text{-}H + B \leftrightarrows AB^+\text{-}H$ (salt)

Proton transfer mainly depends on the difference in pKa values of the components. Usually, a difference of about 3 pKa units between the conjugate base and the conjugate acid is considered to result in salt formation. For systems with Δ pKa < 0, where no proton transfer occurred and the components are instead present in the crystal as neutral entities, the product is generally considered as a cocrystal.[8]

$A\text{-}H + B \leftrightarrows A\text{-}H \cdot\cdot B$ (cocrystal)

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

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

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

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

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

2.5. Polymorphism

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

3. Discussion

3.1. Regulatory implications of solid state forms

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

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

3.1.1. Solid state forms and abridged applications

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

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

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

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

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

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

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

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

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

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

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

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

3.1.4. Acceptance of GMP

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

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

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

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

3.1.5. Acceptance of ASMF for solid state forms

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

3.2. Documentation of cocrystals

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

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

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

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