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

Reflection paper on the use of cocrystals of active substances in medicinal products

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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.

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

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1. Introduction

Over the last decade, cocrystals have gained considerable attention as alternative forms in development of medicinal drug products[1]. By making cocrystals of active substances, their solid state properties such as solubility, hygroscopicity and stability may be improved as well as their manufacturing behaviour (compaction, flowability, filterability etc.), which may be of great interest to the pharmaceutical industry[2]. Salt formation is already widely used for this purpose, but cocrystal formation expands the range of potential solid forms for all chemical compounds[3].

Where applicable, this reflection paper should be read in connection with relevant EU directives and CHMP/CVMP guidelines.

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

1.1. Scope

This reflection paper is intended to reflect the current thinking of the CHMP/CVMP regarding different aspects concerning the use of cocrystals of active substances in medicinal products, for either human or veterinary use. These different aspects are also compared for some other solid state forms and 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 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".

Multiple phase materials resulting from e.g. co-precipitation or physical mixing are not cocrystals and are outside the scope of this reflection paper.

2. Cocrystals and other solid state 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]:

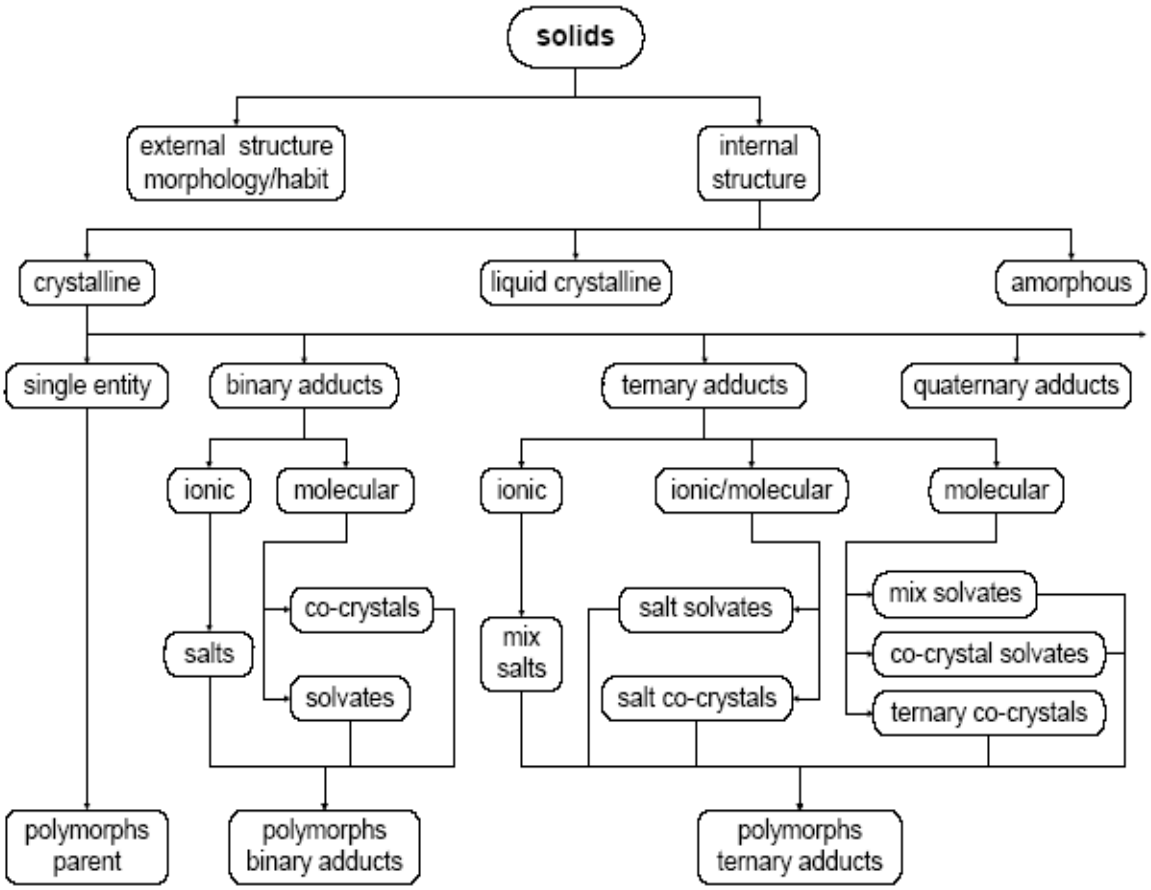

Figure 1: Subdivision of solid state materials.

As evidenced by the large number of marketed crystalline salts of active substances, they are often selected over the free acid or base as pharmaceutical compounds based e.g. on their improved stability, solubility profiles and/or bulk physical properties. Cocrystallisation is a viable alternative to salt formation which can be applied more widely (i.e. also where salts cannot be formed) as well as a versatile tool that can be used to achieve more appropriate solid state properties.

2.2. Cocrystals

Although the detailed definition of cocrystals is still debated in the scientific literature, they are in general defined as homogenous (single phase) 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 ionic bonds (as with salts). The components of a cocrystal may nevertheless be neutral as well as ionized.

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

Homogenous crystalline solids containing variable amounts of co-former (also known as solid solutions) are described in the literature[7,8]. In such not fully stoichiometric solids, the amount of co-former may vary over a given range at a given point in the lattice of a crystal structure. The use of such structure need to be fully justified e.g. from batch to batch consistency and from a quality control point of view.

2.3. Solvates and hydrates

From a scientific point of view, solvates including 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 as well as the active substance itself may be liquids at ambient temperature (e.g. valproic acid[9,10]). It therefore seems to be of 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[11].

2.4. Cocrystals and salts

In salts, the components are arranged in the crystal lattice predominantly based on ion pairing. The components in cocrystals, whether they are neutral, acidic or basic, are assembled via weaker interactions, such as e.g., hydrogen bonding, pi-pi-stacking or van der Waals interactions. Salts are typically formed in an acid–base reaction by proton (H^+) transfer from acid to base.

The extent of this transfer mainly depends on the difference in pKa values of the acid and the conjugate acid of the base. There is no strict borderline between the salt formation in the one end with complete proton transfer and cocrystals formation in the other end with no proton transfer[12].

The extent of proton transfer is often not predictable and spectroscopic tools may be needed to determine the extent of ionization and therefore the location in the cocrystal/salt continuum[12].

Nonetheless, both cocrystals and salts have defined stoichiometries, similar solution speciation characteristics, as well as a solubility product K_{sp}.[2]

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 active substances 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 active substance may exist in mixed ionization states within the same crystal structure (for examples, see reference 9 and the literature cited within); and
- 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 active substances 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 form for the designated purpose, regardless of the molecular bonding involved[13].

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[14]. These different forms are formed as a consequence of different stacking arrangements and/or molecular conformations within the crystal lattice. These different forms may possess different physico-chemical properties[11].

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:

- Cocrystals and abridged applications;
- Cocrystals and New Active Substance (NAS) status for applications with such claims;
- Acceptance of different forms in the same marketing authorisation;
- Acceptance of an ASMF;
- Applicability of Good Manufacturing Practice (GMP) for active substances or finished products;
- Suitability of co-formers; and
- Acceptance of cocrystals containing more than one therapeutic moiety.

3.1.1. Cocrystals 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. Hence, with respect to oral administration, dissolution of such different forms of a drug substance in the stomach or the intestinal canal will lead to the release of the same substance, independent on the form that was taken in. The validity of this assumption is verified by the demonstration of bioequivalence. 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) unless they differ with respect to safety and/or efficacy.

This may also apply to other routes of administration provided that it is possible to show that there is no difference with respect to safety and/or efficacy.

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. Cocrystals 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 active 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 such a form, already authorised as a medicinal product in the EU, is administered orally it will expose a patient to the same therapeutic 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. For other routes of administration (e.g. topical, inhalation) the NAS status will be dependent on what is actually the therapeutic moiety at the site of action in comparison to the authorised product.

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

An active substance exposing patients to a new therapeutic moiety compared to already authorised medicinal products in the EU may be considered as NAS independent of whether it is presented as a molecule, a salt or a cocrystal etc.

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

The directives (Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC Article 13(2)(b)) list the different forms that are regarded as the same active substance in the context of accepting different forms in the applied product in an abridged application and the reference product. As discussed in 3.1.1., this may also apply to cocrystals, hydrates, solvates as well as polymorphic crystal forms. Not all of these different forms will, however be accepted as alternatives in the same medicinal product. For example, within a single marketing authorisation the same salt should always be used. The same applies also to cocrystals, including also solvates.

Under the condition that any difference in, e.g., solubility lacks any clinical significance, it is possible to include forms with different degree of hydration (hydrates, including anhydrous forms) as alternatives in the marketing authorisation for a single medicinal product. 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 expresses 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 marketing authorisation for a single medicinal product provided that any chemical or pharmaceutical difference in properties have no clinical significance.

If alternative forms are applied for in one marketing authorisation, the relevant specifications for each form must be established.

3.1.4. Cocrystals and GMP requirements

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 not a mixture of a chemically defined active substance with other active substances or excipients. The blending of active substances or the blending of an active substance with an excipient is not within the scope of this Reflection Paper.

The formation of cocrystals just like salts is normally subject to compliance with part II of the EU GMP Guide (active substances) and ICH Q7. If however, in more rare cases where a cocrystal is formed in a step during the drug product manufacturing process such as a wet granulation or hot melt extrusion the formation falls under part I of the EU GMP Guide (finished product), while the part II applies to active component(s) forming the cocrystal.

3.1.5. Acceptance of ASMF for cocrystals

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). With reference to the discussion under 3.1.4., regarding GMP, it can be concluded that it is possible to present a single active substance master file for a cocrystal.

3.1.6. Suitability of co-formers

Many active substances are converted to salts for various reasons and even if many counter ions may be used, in practice the number is limited to only relatively few common species. With cocrystals it is generally considered that for a given active substance there are a larger number of possible co-formers available to tailor the solid state properties wanted[6], although simple, well-known molecules such as succinic acid, saccharin and caffeine are often used in the literature[13]. Just as for any other component of a medicinal product, e.g. excipients or counter ions, co-formers must be pharmaceutically acceptable, i.e. their safety and quality must be ensured. If not used previously in medicinal products within the EU/EEA, they should be justified. This may be documented in the same way as for a novel excipient which may, if applicable, include e.g. cross-references to Community provisions based on toxicological data concerning additives in food stuffs.

3.1.7. Acceptance of cocrystals containing more than one therapeutic moiety

It may be possible to form cocrystals containing more than one active substance. A medicinal product containing such a solid state form should be applied for as a fixed dose combination. The cocrystals should be characterised from a chemical and pharmaceutical point of view, being the physical material used in the manufacture of the product. The individual active substances must be documented in line with current guidance on fixed dose combinations. The stoichiometry of the cocrystal does not have to be limited to equimolar amounts. A careful justification of the dose ratio of the individual active substances is required since it is determined and restricted by the relative stoichiometry within the cocrystal. Influence of the co-crystallisation on the bioavailability of the individual active substances should be discussed. Normally, the strength of the medicinal product must be given as for other fixed dose combinations, i.e. stating the amount of each active substance rather than the amount of the cocrystals.

The individual active substances of a cocrystals with more than one therapeutic moiety may qualify for NAS status if it does not expose the patient for the same therapeutic moiety compared to already authorised medicinal products in the EU (see 3.1.2).

3.2. Documentation of cocrystals

As outlined in section 2 (Solid state forms), cocrystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied. All quality-related information should normally 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. The pharmaceutical acceptability of co-formers must be addressed. 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 European Medicines Agency or national competent authorities 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 analytical techniques. Results from more than one technique and an orthogonal approach may be necessary.

The (solid state) form of the active substance should be discussed in Module 3.2.P (or veterinary equivalent) in relation to its fate during manufacture of the drug product. Where relevant for product performance, the preservation of integrity of the cocrystal should be evaluated and if appropriate experimentally confirmed.

4. Conclusion

Cocrystallisation is a viable alternative to salt formation as well as a versatile tool that can be used to achieve more appropriate solid state properties. From a scientific point of view, solvates including hydrates can be considered as a subgroup of cocrystals; nevertheless the regulatory context may sometimes differ. Cocrystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied. In case of a complex co-former additional documentation may be required; a scientific advice procedure is recommended.

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