21 May 2015
EMA/CHMP/CVMP/QWP/284007/2015
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on the use of cocrystals and other solid state forms of active substances in medicinal products' (EMA/CHMP/CVMP/QWP/136250/2014)

Comments from:

No	Name of organisation or individual
1	EFPIA
2	APIC (Pieter van der Hoeven, pvd@cefic.be)
3	AESGP
4	IFAH-Europe
5	Jyoti Tiwari
6	Novartis
7	Vertex Pharmaceuticals Inc.
8	ENANTIA, S.L.
9	Innovation and Quality Consortium
10	Dada Consultancy BV
11	European Generic medicines Association (EGA), Brussels, Belgium
12	Dipharma Francis Srl
13	MEB

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	The content of this Reflection Paper is considered to have dealt with many regulatory and scientific aspects of the potential utilisation of cocrystals in a well-considered, logical and appropriate manner. Cocrystals can be considered in the same way as any other drug substance. We agree that salts and cocrystals can equally be accepted as drug substances.	Comment noted.
1	We note little comment on conformer safety beyond that in lines 250-253 and would consider this a potential topic for further reflection.	Comment noted. A new section 3.1.6 is added on “Suitability of co-formers”.
1	It is important that regional regulators adopt similar positions on the scientific, regulatory and legal aspects of cocrystal use and manufacture. Therefore, it would be important for some discussions to take place between EMA QWP and FDA (or the ICH regions) to clarify and / or contextualise any significant differences between the regulatory perspectives. We believe that the EMA approach is both appropriate and scientifically justified.	Comment noted.
1	We note the following potential challenge in the reflection paper: “For a given product, it should be unambiguous what the active moiety is accompanied with, whether it a counter-ion of a salt or a co-former of a cocrystal”. This statement implies mutual exclusivity, whereas, as cited in the reflection paper, the proton position in some materials can lie anywhere on a continuum and therefore cannot always be unambiguously defined as co-crystal or salt (reference 8 in reflection paper). Indeed, this statement is in conflict with the classification of forms based on their material properties rather than molecular bonding (lines 142-5). Thus, the Reflection Paper (or any following guidance)	Agreed. Contradictory text deleted.

	could make it clearer that in such cases some ambiguity can be accepted.	
1	The statement “The integrity of the cocrystal during the entire manufacturing process should be experimentally confirmed” is concerning (and commented on in detail in line 258 below).	Comment noted.
2	The Reflection paper on the use of cocrystals and other solid state forms of active substances in medicinal products contains at page 8 a definition about the term “mixture”. In addition it is outlined that for mixture of substances the ASMF procedure does not apply but they would fall under part I of the EU GMP Guide (finished product). The topic “API-Mixtures” (API-MIX = API mixed with one or more auxiliary substance(s) for stability, safety and any other reasons duly justified by the applicant as for instance workability/handling reasons) is currently in discussion within the European Member States, the European Commission and EMA. Please also refer to the APIC position paper on the definition of an API. In APIC’s point of view API-Mixtures for the reasons as described above should be considered to be APIs with all relevant regulatory and quality aspects. APIC suggests: Amendment of the question and answer 2007 (EMA QWP Quality of Medicines part 1 Q&A) **“on Active Substance - Active-substance-master-file procedure”** to allow certain API-MIX, according to additional clearly defined exemptions, such that the Q&A would read as follows: “...Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing into the finished dosage form for reasons of safety, stability and/or workability and/or any other reasons duly justified by the applicant such that it needs to be mixed with one or more	Comment noted. All discussion on this kind of mixtures is deleted except for a statement that it is out of scope of this Reflection paper.

	auxiliary substances or, in the case of herbal dry extracts, if it is not possible to produce a solid extract without auxiliary ingredients. Such mixtures (API-MIX) shall fall under the definition of API…"	
3	The draft reflection paper provides an interpretation of the term "mixtures" which is enshrined in the definition of active pharmaceutical substance (API) in the Community Code. "*Any substance or **mixture of substances** intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis*." It also defines a mixture of an API with an auxiliary substance as the first step towards the finished product hence subject to GMP Part I and not GMP Part II. The EMA Q&A "can a mixture of an active substance with an excipient be submitted through an active substance master file (ASMF) procedure" (August 2007) states that exceptions are permitted when the active substance cannot exist on its own, for example, due to insufficient stability without a stabilising agent. **The reflection paper should reference this Q&A and the fact that on some basis exceptions are permitted**. AESGP believes that when the API cannot exist on its own for stability but also safety reasons or for other scientific reasons dully justified by the applicant, APIX should be permitted and considered API and thus subject to GMP Part II. We understand that these aspects are currently being discussed by the EMA QWP and GMDP inspectors group and the Commission with the view to possibly revise this Q&A.	Comment noted. All discussion on this kind of mixtures is deleted except for a statement that it is out of scope of this Reflection paper.
4	IFAH-Europe welcomes the opportunity to comment on this draft Reflection Paper. IFAH-Europe receives favourably the publication of this document which reflects the industry point of view i.e. stating the scientific thinking of having co-	Comment noted.

	crystals and salts at the same level and considering co-crystals as APIs. This Reflection Paper is scientifically sound and well prepared, explaining the topic in clear words.	
5	Submission requirements have not been dealt in detail in the concept paper and need to be elaborated with respect to agency's expectations.	Comment noted. A new section 3.2 is added on "Documentation of cocrystals".
5	If possible, co crystals may be explained with the help of any suitable examples which have already been registered in EU or are in existence. It would help in better understanding of the concept.	Comment noted, but no suitable examples found.
5	Details need to be provided on the control of solvents if present as co-formers. In case class I and II solvents are present in the co-crystal then the monitoring and acceptable levels need to be discussed.	Not agreed. Residual solvents should comply with ICH Q3C guideline.
7	We believe this was a well-conceived reflection paper. We would like to offer some additional thoughts on the regulatory classification of co-crystals. We would prefer the flexibility to treat a co-crystal as either API or drug product intermediate depending on the route of co-crystal manufacture. For example it would seem appropriate for the following scenario to be classified as a drug product intermediate: when the co-crystal is formed in one step of a drug product manufacturing process such as a wet granulation or hot melt extrusion. During this process the co-crystal can also be embedded into an excipient matrix. This situation is particularly germane in a continuous manufacturing process. Following the above example, it would be preferred if there would be clear guidelines for the definition of the co-crystal as API or DPI for regulatory purposes.	Comment noted. In section 3.1.4 "Cocrystals and GMP requirements", a sentence mentioning the case of cocrystals formation during the manufacture of the drug product.
8	In general Enantia agrees with the text proposed in the refection paper.	Comment noted.
9	Co-crystals do provide opportunities for improved pharmaceutical products and we are aware of a number of co-crystals in development. We support the EMA	Comment noted.

	approach to co-crystals and regard the Reflection Paper logical and pragmatic; its content has dealt with many regulatory and scientific aspects of the potential utilisation of co-crystals in an appropriate manner. We agree that the definition is still being debated, but Figure 1 in the reflection paper is useful in setting context and clarity. We also agree that classifying solid state forms based on their resulting material properties, irrespective of the molecular bonding involved, is key to their success towards the designed purpose.	
9	We note the following potential challenges in following any guidance resulting from the reflection paper:	
9	1: Lines 92-94: Co-crystal definition rules out non-stoichiometric (yet crystalline) adducts. We are aware of literature examples that fall under these non-stoichiometric crystalline adducts. Crystalline non-stoichiometric adducts offer the same advantages as co-crystals and share many of the properties of the co-crystals. Sometimes, they may offer additional advantages in terms of fine-tuning a particular physicochemical property. It is our view that the non-stoichiometric crystalline adducts should be added to this reflection paper. This document can make clear that the distinction between co-crystals (stoichiometric adducts) and crystalline non-stoichiometric adducts exists only in the stoichiometry but that the non-stoichiometric crystalline adducts provide similar general advantages as co-crystals. Here are some examples from literature regarding non-stoichiometric crystalline adducts. Homogenous crystalline solids containing variable amounts of co-former (also known as solid solutions) are not uncommon (references 1-3). In such solids, amount of co-former may vary over a given range. One co-former can by replaced by another co-former (or solvent molecules) at the equivalent lattice points in a crystal structure. Exchangeable molecules usually exhibit similar size, shape and often offer comparable directional interactions. In particular, APIs forming channel crystal structures can be prone to form adducts with variable	Comment noted. A paragraph is added under Section 2.2 as well as a couple of the references given: “Homogenous crystalline solids containing variable amounts of co-former (also known as solid solutions) are described in the literature.i,ii 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 a consistency and a quality control point of view.” i M. Peterson et al. ii M Dabros et al. (although the page numbers are corrected to 4132-4135)

	stoichiometry. They can accommodate greater changes in the composition of the guest molecules since the modifications in size and shape of exchangeable guest components are less restricted by directional interactions with API (references 4, 5). M. Peterson et al, Cryst. Growth & Design, 2008, 9, 4487-4493 M. L. Brader et al, Nat. Biotechnol., 2002, 20, 800-804 M. Dabros et al, Angew. Chem. Int. Ed. 2007, 46, 4123-4735 S. Childs et al, Cryst. Growth & Desgin, 2009, 9, 1869-1999, N. Variankaval et al, Cryst. Growth & Design, 2006, 6, 690-700 S. Childs et al, Mol. Pharm., 2007, 4, 3, 323–338	
9	2. For a given product, it should be unambiguous what the active moiety is accompanied with, whether it a counter-ion of a salt or a co-former of a co-crystal". This statement implies mutual exclusivity, whereas as cited in the reflection paper, the proton position can lie anywhere on a continuum and therefore cannot always be unambiguously defined as co-crystal or salt (reference 6). Indeed, this statement is in conflict with the classification of forms based on their material properties rather than molecular bonding (lines 142-5). An improved guidance would be that sponsors should make every effort to characterize the extent of ionization of the components, and name the drug substance appropriately. More specifically we recommend a change to the wording in the guidance as follows: "For a given product, every reasonable effort should be taken to characterize the co-former state, recognizing that in some cases it may be challenging to unambiguously identify whether the second component exists as a co-former or a counter-ion".	Agreed. Contradictory text deleted.

9	3. We fully agree that 'since co-crystals are held together by weak interactions that are in the most case broken upon dissolution' then when administered by e.g. the oral route they will expose a patient to the same moiety (like salts). Thus, we agree co-crystals would not be considered to be different in terms of efficacy by e.g. the oral route and thus would not qualify for NAS status. However, by some routes (e.g. topical or inhaled) the similarity of efficacy and safety (and hence the regulatory equivalence to a prior product) should perhaps not be assumed, as the active substance may be liberated differently from a co-crystal under such administration conditions. In addition, even by the oral route, it could be that the liberated co-former has to be considered as an additional risk to patient safety, especially when the co-former is not typically also a counter-ion typically used in salt formation, with respect to the same active moiety delivered without the co-former. (The reflection paper may want to consider further what should be said regarding safety of the co-former material as an additional topic).	Comment noted. Section 3.1.2 has been reworded to clarify the importance of the actual therapeutic moiety. The acceptability of the co-former is addressed in a new section 3.1.6.
9	4. The concept of Essential Similarity, in which all solid state forms are interchangeable and assumed to give equivalent PK, appears to underpin the reflection paper (lines 68-70, 167-170, 179-182 and 193-195). Given this, we do not understand the position to then exempt hydrates. It is our understanding that hydrates are not dissimilar to polymorphs or solvates in that any solubility decrease compared to a reference anhydrous form in aqueous media is analogous to the same decrease, for example, that could result from a more stable anhydrous form. So we recommend that hydrates not be separated from other phases for the purposes of this reflection paper and request removal of hydrates from special consideration.	Comment noted. Cumbersome text in 3.1.3 is changed to clarify that alternative hydrated forms of an active substance can be accepted in one marketing authorisation, while e.g. different salts or cocrystals cannot.
11	The European Generic medicines Association (EGA), welcomes what it considers a comprehensive reflection paper on the topic of cocystals.	Comment noted.
11	The EGA takes notes of the EMA acknowledgement that US FDA guidance and EMA reflection paper were developed concomitantly however not in concentration	Comment noted.

	and contain divergent approaches to cocrystals. This is certainly not a satisfactory situation and we call on EMA to pursue all possible efforts to seek convergence on key scientific, regulatory and legal aspects using existing collaboration platforms (bilateral and / or international such as ICH).	
11	Regarding the issue of mixtures of substances, we would like the EMA Reflection paper on cocrystals to cross-refer to the EMA Q&A 'can a mixture of an active substance with an excipient be submitted through an active substance master file (ASMF) procedure?' (August 2007) in order to ensure consistency and acknowledgment that exceptions are foreseen in certain circumstances. The EGA believes that when an API cannot exist on its own for stability, but also safety or other scientific reasons (duly justified by the applicant), API mixtures should be permitted and subject to GMP Part II. These considerations are currently under discussion among regulators (EMA QWP, EMA GMDP IWG and European Commission) in order to allow for a consistent interpretation and implementation throughout the EU.	Comment noted. All discussion on this kind of mixtures is deleted except for a statement that it is out of scope of this Reflection paper.
12	The reflection paper in object reports a very detailed analysis of the possible solid forms (salts, solvates, cocrystals, etc.) and of the differences between the different cases, but no mention is made as to the acceptable identity of the coformer in a cocrystal. The addition of a description like "pharmaceutically acceptable coformer" somewhere in the text might be useful. There are several cases reported in patent and scientific literature of API-API cocrystals, i.e. crystal structures where the two coformers are both Active Pharmaceutical Ingredients. Cases such as these are not contemplated in the reflection paper in object. A minor change to a specific scheme (line 117) is suggested below.	Comment noted. New sections 3.1.6 "Suitability of co-formers" and 3.1.7 "Acceptance of cocrystals containing more than one therapeutic moiety", are added. Line 117 is deleted. All discussion on this kind of mixtures is deleted except for a statement that it is out of scope of this Reflection paper.

	Although we fully agree that a cocrystal is not a purely physical mixture of an API and a coformer and should therefore not be treated as such, we feel that the definitions given of physical mixtures might involuntarily involve (and therefore cause problems for) cases in which the active ingredients cannot, for documented safety or stability reasons, be handled on their own. We therefore suggest the addition of a clarification in this sense in paragraphs 3.1.4 and 3.1.5, as detailed below.	
13	The Medicines Evaluation Board in the Netherlands (MEB) highly appreciates the development of a reflection paper on the use of co-crystals and other solid state forms of active substances. The MEB agrees that the document is needed to favour a consistent approach in the European Union on the data to be provided in Module 3 of the Marketing Authorisation Dossier and the relevant assessment policies.	Comment noted.
13	The scope of the Reflection Paper is not clear as it varies among the different parts of the document. For example, the title indicates that the document has a focus on co-crystals and other solid state forms, whereas: • Line 34 & 35 indicates that the reflection paper represents the current thinking on solid state forms, in particular co-crystals. • Line 36 & 37 indicate that the guidance relates to co-crystals i.e. apparently not to other solid state forms? • Line 71 indicates that the document has a focus on solid state forms and that co-crystals are just an example.	Agreed. It has been clarified and consistently implemented that the scope is cocrystals and other forms are just discussed for comparison.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
5-6	5	Comment: The title of the paper is not suitable. Proposed change (if any):As the concept paper basically deals with the co crystals and all other solid state forms of the active substances have not been described adequately, the term “Other solid state forms” may be removed from the title.	Agreed. The title is changed accordingly.
5-7	13	The title should be consistent with the scope of the document, see general comment. The title may be revised as follows: “Reflection Paper on the use of solid state forms of active substances in medicinal product with a particular focus on co-crystals”.	Agreed. The title is changed in accordance with the previous comment. This is believed to address the concern.
35	13	To the best of our knowledge, there are no recent scientific developments on solid state forms as the information provided is already known for many years. Therefore, please revise the word scientific into regulatory.	Agreed. However, the Executive Summary is deleted.
43-45	1	Comment: Minor adjustment to the text, for clarity. Proposed change: “By making cocrystals of pharmaceutically interesting substances, their solid state properties such as solubility, hygroscopicity and stability may be improved as well as **other physical properties relating to** their manufacturing behaviour (compaction, flowability, filterability etc.)”.	Partially agreed. Text changed to ”By making cocrystals of active substances of interest to the pharmaceutical industry, 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 great of interest to the pharmaceutical industry".
45-47	1	Comment: the following statement should be clarified: "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." Cocrystallisation is not limited to only those substances that lack ionizable functional groups amenable to salt formation. In fact cocrystallisation expands the range of solid forms of all compounds, ionizable molecules included. Proposed Change: "Salt formation is already widely used for this purpose for ionisable compounds, ~~but with cocrystal formation this can now be achieved also for substances that lack the possibility of salt formation~~ **but cocrystal formation expands the range of potential solid forms for all chemical compounds."**	Agreed. Proposed change implemented.
71-72	5	Comment: This statement should be changed. Proposed change (if any): As this reflection paper is not describing any other solid state form which is not mentioned in the Directives e.g. liquid crystalline materials, the reference to solid state forms not mentioned in the Directives should be removed.	Agreed. Sentence deleted.
73	13	The heading is causing confusion in view of the scope of the document and the following heading would be preferred "2 Solid state forms".	Not accepted. However, title changed to "2 Cocrystals and other solid state forms"
75	13	The heading of this chapter would benefit from rewording. The following heading is proposed "2.1 Definitions: solid state forms".	Not accepted. However title changed to "2.1 Diversity of solid state forms"
80	9	To be consistent with the rest of the document, replace "cocrystal" with "co-	Not agreed. This is the only place

		crystal".	where "co-crystal" appears and that is because it is a reproduction of the graph from a given source.
86-87	1	Proposed Change: "... based e.g. on their improved stability and/or solubility profiles **and bulk physical properties**."	Agreed. The proposed change is implemented.
87-89	1	Comment: regarding the statement, "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": as written, this statement implies that cocrystallisation should be employed only after salts are fully explored, when in the pursuit of a solid form with acceptable properties (material property based solid state design), the ionization state really should not matter. Proposed Change: "Cocrystallisation is ~~considered as~~ a viable alternative to salt formation **and can be applied more widely (i.e. where salts cannot be formed) and can have more appropriate solid state properties."**	Partially agreed. Text changed to "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."
88	1	Replace "…in cases where salts…" with "inco cases where free acids, bases or salts…".	Not applicable. Sentence changed as cited in the previous comment from the same stakeholder.
88	9	Replace "…in cases where salts…" with "in cases where free acids, bases or salts…".	See previous comment.
90	13	This heading of this chapter would benefit from rewording. The following heading is proposed "2.2 Definitions: co-crystals".	Not accepted. This heading is kept since the proposal for the heading of section 2 was not accepted.
91-94	1	Comment: minor change to text suggested. Proposed Change: "Although the detailed definition of cocrystals is still debated in the scientific literature, they are in general defined as homogenous (single	Accepted.

		phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal structure is not based on ionic bonds ~~ion pairing~~ (as with salts)".	
95-97	8	Comment: Reference to API-API cocrystals. Despite in lines 95-96 is hinted (the text mentions that "at least one component is an API"), some specific reference to API-API compounds should be included. There are instances of API-API cocrystals in clinical development and therefore those examples, as category, should be reflected in the document. Therefore, different pharmaceutical cocrystals could be considered: in addition to API· (Non active co-former) also $API_1 \cdot API_2$ or API· (API salt). Proposed change (if any):	Agreed. A new section 3.1.7 "Acceptance of cocrystals containing more than one therapeutic moiety" has been added to address this issue.
98	13	The heading of this chapter would benefit from rewording. The following heading is proposed "2.3 Definitions: solvates and hydrates".	Not accepted. This heading is kept since the proposal for the heading of section 2 was not accepted.
105-106	1	Comment: both APIs and potential cocrystal formers may be liquids at ambient temperature. Proposed Change: "This has been criticized since not only solvents, but also APIs and ~~other~~ potential co-formers may be liquids at ambient temperature."	Agreed. Sentence reformulated to "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)."
109, 151	4	Comment: References 7 and 12 are identical. Proposed change: The citations in the text and the reference list should be revised accordingly.	Accepted. Duplicate references will be removed in the final version.
110-145	1	Comment: we consider this section (2.4 Cocrystals and Salts) could be simplified. The most important comment from our perspective is that "From a	Agreed. The section is simplified while

		material point of view, the classification of solid state APIs into salts or co-crystals is considered only of theoretical value. Ultimately, the resulting material properties are the critical factors that determine the suitability of a developed solid state API form, regardless of the molecular bonding involved." It would not be useful if there was an expectation generated that the actual form of cocrystal assembly needed to be determined, and we recommend this section be simplified. It is important to note however that we agree that both cocrystals and salts should have defined stoichiometries (line 130) as well as ruled out as a physical mixture (lines 254-257).	keeping the cited paragraph.
113	1	MINOR: Typographic - n-n stacking intends 'pi-pi'?	Accepted. Greek letter pi became difficult to recognize in the final font.
117	1	Comment: The formula needs to be corrected as follows. Proposed Change: "A-H + B ⇆ A^- + BH^+"	Agreed. However, the section is simplified and the formula deleted.
117	8	Comment: The formula leads to confusion. Proposed change (if any): AH + B ⇆ A^- +BH^+	Agreed. However, the section is simplified and the formula deleted.
117	9	Replace equation "A-H + B ⇆ AB+-H (salt)" with "A-H +B ⇆A^-B^+-H (salt)" that is add negative charge to "A" in the salt.	Agreed. However, the section is simplified and the formula deleted.
117	12	Comment: The formula as is written is confusing. It could be written in a more comprehensible form. Proposed change (if any): A-H + B → A^- BH^+ (salt)	Agreed. However, the section is simplified and the formula deleted.
120	9	Replace "the conjugate base and the conjugate acid" with "acid and the conjugate acid of the base".	Accepted.

125	9	A-H + B ⇆ A-H ··B (co-crystal). This discussion is "salt centric" considering the extensive use of salts in pharmaceutical industry, this may be understandable but this reflection paper is about co-crystals. By thinking about co-crystals in the context of salts, this paper limits itself to one category of co-crystals but not all possible co-crystals. A simple example would be a co-crystal between acidic API and an acidic co-former. Many other examples are known in literature where co-crystals are formed between components that are neither acids nor bases.	Agreed. Section is modified in order to simplify and make it less “salt centric”.
123, 129	4	Comment: References 8 and 9 are identical. Proposed change: The citations in the text and the reference list should be revised accordingly.	Accepted. Duplicate references will be removed in the final version.
130	1	Comment: it is unclear what ‘cocrystals and salts have … similar solution speciation” means. Proposed Change: this text should be clarified or omitted.	Partially agreed. A reference to published literature is added to this sentence.
146	13	The heading of this chapter would benefit from rewording. The following heading is proposed “2.4 Definitions: polymorphism”.	Not accepted. This heading is kept since the proposal for the heading of section 2 was not accepted.
149-151	1	Comment: it is not clear what the point is here. The energy necessary for melting, vaporization & dissolution is also sufficient to disrupt stronger ionic bonds as in salts? Proposed change: suggest a more relevant supporting statement: “These different forms are ~~formed by the weak interactions between the components present in the solid state. The energy necessary for 150 melting, vaporization or dissolution are sufficient to disrupt these weak bonds.~~ **formed as a consequence of different stacking arrangements and/or molecular confirmations within the crystal lattice.** These different forms may possess	Accepted.

		different physico-chemical properties”	
169	13	The words the likelihood is very high result in the question “and what if it is not”. Therefore it is recommend to either delete this part of the sentence or to add a sentence indicating if, and if so, how it can be controlled whether this assumption is correct.	Agreed. Sentence changed to “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.”
179-182	1	Comment: we agree that ‘since cocrystals… are held together by weak interactions that are in the most case broken upon dissolution’ then when administered by e.g. the oral route they will expose a patient to the same moiety. When this is the case, and the cocrystal does not impart ENHANCED dissolution properties to the active substance which are key to bioperformance, we agree such cocrystals would not be considered to be different in terms of efficacy by e.g. the oral route and thus many cocrystals would not qualify for NAS status. We note that cocrystals are like salts in this respect (as both provide the same moiety in solution) and either salts or cocrystals can be similar to the active moiety in solution after oral administration or can impart different dissolution properties. However, by some routes (e.g. topical or inhaled) the similarity of efficacy and safety (and hence the regulatory equivalence to a prior product) should perhaps not be assumed, as the active substance may be liberated differently from a cocrystal under such administration conditions.	Agreed. Text modified to “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

		In addition, even by the oral route, it could be that the liberated co-former has to be considered as an additional risk to patient safety with regard to the same active moiety delivered without the co-former. (The reflection paper may want to consider further what should be said regarding safety of the conformer material as an additional topic).	site of action in comparison to the authorised product." A new section 3.1.6 "Suitability of co-formers" is added to address the issue in the last paragraph of the comment.
191-197	1	Comment: we agree with the content of the sentence but consider the language used ("it must therefore not be understood") could confuse non-English speakers. Proposed Change: simpler text could be used for this important point (on the interpretation of "essential similarity") e.g. "The different forms listed in the directive will not be accepted as alternatives in the same product." And sponsors should make every effort to characterize the extent of ionization of the components, and name the drug substance appropriately").	Agree to simplify the language used to "Not all of these different forms listed in the directive will, however not 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."
191-206	11	Comment: We agree that it is appropriate to draw a parallel between acidic and basic co-formers (as found in co-crystals) to acidic and basic counter ions (as observed in salts). Both represent a fundamental component of the identity of the drug substance which must be declared in the summary of product characteristics and elsewhere. As such, in this instance, inclusion of two or more salts/co-polymers in the same Marketing Authorisation would not be possible. However, we disagree that this should be extended to hydrates and solvates. • Provided that an applicant demonstrates that a difference in solvate does not result in any difference in quality/safety/efficacy there is no scientific (or regulatory) reason to proactively prevent inclusion of different solvates in the same Marketing Authorisation. The safety profiles of commonly used solvents are also extremely well established and understood.	Comment noted. However, current wording accept different hydrated versions as well as different polymorphic forms of an active substance in one Marketing Authorisation but not different salts, cocrystals or solvates.

		• At the very least, the same exemption proposed for differences in the degree of hydration should also apply to differences in the degree of solvation. If two APIs are included in a dossier and the solvate is the same but the degree of solvation is different, the Health Authority assessment should focus on the worst case (i.e. greatest degree of solvation). An alternative API with a lower degree of solvation would always therefore be acceptable from a safety/efficacy perspective provided that the Applicant can preclude any detrimental impact on quality. Whilst we would fully agree that different solvates should be considered to represent different physical forms (with the onus on the applicant to demonstrate that there is no implication on the quality of the resulting finished product) it seems unnecessarily restrictive to completely preclude the use of different solvates and/or APIs with different degrees of solvation within the same Marketing Authorisation. Proposed change (if any): Please amend this section accordingly.	
211-230	2	Comment: Please see general comment Proposed change (if any): To add the following exemption at the end of chapter 3.1.4 on Acceptance of GMP: Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing into the finished dosage form for reasons of safety, stability and/or workability and/or any other reasons duly justified by the applicant such that it needs to be mixed with one or more auxiliary substances or, in the case of herbal dry extracts, if it is not possible to produce a solid extract without auxiliary ingredients. Such mixtures (API-MIX) shall fall under the definition of API and therefore their formation fall under part II of the EU GMP Guide (active substances).	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.

211-230	11	Comment: The specific case where an active substance cannot exist on its own is not acknowledged here. Proposed change (if any): Refer to exceptional circumstances in line with the EMA Q&A (including a cross-reference to the Q&A).	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
211-230	12	Comment: Please see general comment Proposed change (if any): To add the following exemption at the end of chapter 3.1.4 on Acceptance of GMP: Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing for reasons of safety, stability and/or workability and/or any other reasons duly justified by the applicant such that it needs to be mixed with one or more auxiliary substances. Such mixtures (API-MIX) shall fall under the definition of API and therefore their formation fall under part II of the EU GMP Guide (active substances).	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
215-218	3	Comment: This does not reflect the exceptional situation under which the API cannot exist on its own. Proposed change (if any): 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 **as a general rule** to allow a mixture of a chemically defined active substance with other active substances or excipients to be considered as a single API. **Exceptions can however exist when the API cannot exist on its own e.g. for stability reasons as reflected in the EMA Q&A(1)** [and please add reference to the Q&A in the Reflection paper].	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
222	1	Proposed Change: Insert "also: "adsorptive processes, are **also** not considered…".	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and

			therefore all discussion on them is deleted except for a statement that they are out of scope.
222	9	Insert “also: “adsorptive processes, are <u>also</u> not considered.	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
228-230	3	Comment: idem as above. Proposed change (if any): As a consequence of these differences between physical mixtures and cocrystals, the formation of cocrystals is subject to compliance with Part II of the GMP guide (active substances) while the formation of physical mixtures fall**, <u>as a general rule,</u>** under part I of the EU GMP Guide.	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
229	1	Proposed Change: consider adding a reference to ICH Q7 – i.e. “the formation of cocrystals is subject to compliance with part 11 of the EU GMP guidance (and ICH Q7).”	Agreed. A reference to ICH Q7 is added.
231-240	2	Comment: Please see general comment. Proposed change (if any): To add the following exemption at the end of chapter 3.1.5 on Acceptance of ASMF for solid state forms: Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing into the finished dosage form for reasons of safety, stability and/or workability and/or any other reasons duly justified by the applicant such that it needs to be mixed with one or more auxiliary substances or, in the case of herbal dry extracts, if it is not possible to	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.

		produce a solid extract without auxiliary ingredients. Such mixtures (API-MIX) shall fall under the definition of API and therefore the acceptance of ASMF applies.	
231-240	11	Comment: Same as above (211-230). Proposed change (if any): Same as above.	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
234-240	12	Comment: Please see general comment. Proposed change (if any): To add the following exemption at the end of chapter 3.1.5 on Acceptance of ASMF for solid state forms: Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing for reasons of safety, stability and/or workability and/or any other reasons duly justified by the applicant such that it needs to be mixed with one or more auxiliary substances. Such mixtures (API-MIX) shall fall under the definition of API and therefore the acceptance of ASMF applies.	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.
236-237	3	Comment: This statement again does not reflect the full Q&A which mentions the possibility of making exceptions in cases where the API cannot exist on its own e.g. for stability reasons. Proposed change (if any): This procedure may only be applied for discrete active substances and not for mixtures of substances **as a general rule**. **The QWP Q&A however also refers to exceptions for which the use of an ASMF is acceptable.**	Comment noted. Physical mixtures of active substances are not within the scope of this Reflection Paper and therefore all discussion on them is deleted except for a statement that they are out of scope.

240	13	The phrase “but for a physical mixture it is not possible” should be deleted as this guidance is not related to the scope of this document and subject to debate.	
245-247	5	Comment: The terms characterisation and control of drug substance should be elaborated. Proposed change (if any): Details on the proposed techniques for characterisation of the co crystals should at least be provided for demonstrations of the crystal structure.	Not agreed. It is more appropriate to leave to the applicant with the greater knowledge on his material to choose methodology, since each case may need its particular considerations and since science may evolve, leaving detailed prescriptions more or less obsolete.
247-250		Comment: There is no mention of the co-formers having to be pharmaceutically acceptable. We think it should be specified that the co-formers have to be pharmaceutically acceptable. Criteria of pharmaceutical acceptance would be appreciated. Proposed change (if any):	Agreed. A new section 3.1.6 on “Suitability of co-formers” has been added.
250-253	5	Comment: This statement needs to be elaborated with respect to complex co-formers. Proposed change (if any): The basis on which complexity of the co-formers would be decided should be included. At least a brief overview of the characteristics of complex co-formers should be included.	Not agreed. It is not considered feasible to elaborate more on this, and therefore applicants are encouraged to seek scientific advice on the classification in these cases.
254-257	1	Comment: the text states that the possibility of the formation of a purely physical mixture of two or more compounds should be unambiguously demonstrated. This is agreed.	Accepted.

		However the text continues 'by means of adequate state-of-the-art analytical techniques. We note that a cocrystal can sometimes be determined in as simple a manner as e.g. by its melting point and high tech analytics may not be required. Proposed Change: remove need for state-of-the art analytical techniques.	
255-257	9	It should be acknowledged that '*the formation of a co-crystal should be unambiguously demonstrated by means of adequate state of the art analytical techniques*' can be analytically challenging for low dose formulations in particular.	Comment noted.
258	1	Comment: the text reads: "The integrity of the co-crystal during the entire manufacturing process should be experimentally confirmed." This text is considered potentially confusing (even incorrect) for the following reasons. We assume that it is the integrity through drug product manufacture that should be shown. Firstly, this integrity would NOT be expected for manufacture of a liquid product (though a cocrystal could still be needed to stabilise the ingoing API). In addition, there may not be any need for the cocrystal to remain intact through the manufacture of an oral product, as the pharmacokinetics of the free form and the cocrystal may be the same. Thus provided the product is suitably stable, there may be no need to expect integrity, or even understand if the product continues to contain 100% cocrystal at manufacture, release or on stability of the drug product. Proposed Change: remove this sentence or modify to: "The integrity of the cocrystal during the entire drug product manufacturing process may be	Agreed. Paragraph changed to "The (solid state) form of the active substance should be discussed in Module 3.2.P 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."

		important in some case and should be evaluated."	
258	6	Comment: The statement in line 258 "The integrity of the cocrystal during the entire manufacturing process should be experimentally confirmed" can be technically challenging for drug products with low drug load, e.g. inhalation products. It is further assumed that this confirmation could be carried out a single time during the product development phase. Proposed change (if any): Add "*if technically feasible".*	Comment noted. Paragraph changed to "The (solid state) form of the active substance should be discussed in Module 3.2.P 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.
258	9	"*The integrity of the co-crystal during the entire manufacturing process should be experimentally confirmed*" is a little bit concerning, considering the possible partial dissociation to the primary components. This should not be any different than disproportionation of salts or amorphization, so the requirements for integrity of the co-crystal should not differ from those applied to other crystalline forms.	Agreed. Paragraph changed to "The (solid state) form of the active substance should be discussed in Module 3.2.P 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.
258-259	10	Comment: It is indicated that the integrity of the cocrystal during the entire manufacturing process should be experimentally confirmed. Does "the entire manufacturing process" only refer to the manufacturing process of the cocrystal or does it also refer to the manufacturing process of a drug product containing that cocrystal? In the latter case this requirement for	Comment noted. Paragraph changed to "The (solid state) form of the active substance should be discussed in Module 3.2.P in relation to its fate during manufacture of the drug product. Where relevant for product

		cocrystals would be different from the requirements for salts and hydrates. For example, if salts or hydrates are dissolved during the manufacturing process of a drug product (e.g. to manufacture an aqueous, liquid dosage form or where the drug substance is dissolved in a granulating liquid during wet granulation), salts will dissociate and hydrate water will be lost. Would it be acceptable to use a cocrystal for the preparation of a solution for injection (e.g. because it dissolves easier or faster), knowing that the cocrystal will not stay intact during the manufacturing process of the drug product? Proposed change (if any): ~~The integrity of the cocrystal during the entire manufacturing process should be experimentally confirmed.~~	performance, the preservation of integrity of the cocrystal should be evaluated and if appropriate experimentally confirmed.
261	1	Comment: duplicate entries from the reference list should be removed. Proposed Change: “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” should be removed.	Accepted. Duplicate references will be removed in the final version.