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

Questions and Answers regarding co-processed excipients used in solid oral dosage forms (H & V)

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Introduction

While co-processed excipients (CoPEs) can offer benefits such as improved functionality and reduced risk of segregation of its individual excipients, they could also introduce additional risks compared to using individual excipients. The use of CoPEs in pharmaceutical formulations can present higher risks due to several factors: e.g. complexity of composition (inherent variability, unpredictable interactions), quality control (challenges for analytical methods, batch to batch consistency), formulation development (complexity of optimisation studies, challenges with scaling up production) and stability issues due to combination of different materials.

These Q&As aim to harmonise and clarify dossier requirements for CoPEs using a risk-based approach; the Q&As are applicable to human and veterinary solid oral dosage forms.

Retrospective application of the Q&As is not intended for marketed products, unless there are changes to the formulation (e.g. introducing a CoPE or changes to the applied CoPE).

1. What is a "co-processed excipient" in the context of these Q&As?

The term "co-processed excipients" (CoPEs) does not appear in the EU Regulation, directives or guidelines. Different definitions of CoPEs exist among regions and stakeholders worldwide, but also the excipient- and/or finished product-manufacturers themselves have been using this term differently from any available definition.

In the context of these Q&As, a CoPE is a combination of two or more Ph. Eur. excipients, typically two, which are processed together using a physical process (e.g. spray-drying) without the formation of covalent bonds. CoPEs have intended functionalities such as improved compaction characteristics which cannot be achieved by e.g. blending during routine manufacturing (low energy). If one or more excipients are added by blending to a CoPE, the resulting blend is not considered a CoPE. The use of excipients such as preservatives, antioxidants, chemical stabilisers etc. in order to prolong the stability of a CoPE is not accepted and is not considered a contribution to the functionality of a CoPE.

A CoPE is not a novel excipient, nor a finished product intermediate without active substance, nor a "ready-to-use mixture" as referenced in EU Guidelines on excipients.

2. How to categorise a co-processed excipient in a finished product using a risk-based approach?

The applicant/MAH needs to demonstrate that they have adequate understanding and control of the finished product and its excipients. The potential impact of the CoPE characteristics on the finished product should be evaluated during pharmaceutical development and an adequate control strategy should be set up to ensure that the finished product is of consistent quality, safety and efficacy. The regulatory expectations in terms of the quality dossier requirements depend on the considered risk of the CoPE. This Q&A identifies three risk categories for the CoPE:

Category A - high risk CoPE

Category B - medium risk CoPE

Category C - low risk CoPE

Risk factors to consider

To assign one of the above-listed risk categories to a CoPE, the following risk factors should, as a minimum, be considered and their impact on the risk level should be identified.

The applicant/MAH should identify which critical quality attributes (CQAs) of the finished product can be impacted by the CoPE material attributes. In line with the principles of ICH Q8, which principles can also be used for veterinary products, CQAs are derived from the Quality Target Product Profile (QTPP) of the product and as such they consider the dosage and target population. The known or potential impact of the CoPE on CQAs, within the context of the finished product, such as appearance, assay, content uniformity, release of the active substance, stability and impurity profile and impact on bioavailability should be considered. Material attributes of the CoPE, such as function, physico-chemical properties, composition of the CoPE in terms of number of excipients and additionally function of other excipients included in the composition of the finished product should be considered. Some general considerations are given below. Specific examples are provided in Annex I.

For example, the function(s) of the CoPE in the finished product should be considered, such as filler, binder, lubricant, stabiliser, surfactant, antioxidant, disintegrant, or release rate controlling agent, taking into account the characteristics of the finished product and the rest of the formulation. A CoPE which function(s) (such as disintegrant, surfactant or release rate controlling agent) has an impact on one or more CQAs will be considered with a higher risk impact than a CoPE which has function(s) (such as filler or binder) with low or no impact on the CQAs. If the formulation includes other excipients with the same function(s), impacting the CQAs, the risk linked to the CoPE may be lower.

The impact on the critical process parameters (CPPs) should also be considered. The physico-chemical characteristics of the CoPE, together with the proportion of the CoPE in the finished product, should all be taken into consideration. For example, the impact of particle size, particle morphology, density and flowability on the CPPs should be determined. The impact on manufacturability is expected to be higher when the CoPE is the main component of the finished product.

When assigning the risk category of the CoPE, it is not sufficient to only consider one risk factor alone, but it is important to consider all risk factors and their relative risk levels, as they are interlinked. When evaluating the impact of the CoPE on the CQA of the finished product, different factors should be considered. It is recommended to start the evaluation by focusing on the function(s) of the CoPE, in relation to the special characteristics of the finished product (QTTPs), taking into consideration the qualitative and quantitative composition of the finished product. The impact ranking table in Annex I gives some examples and considerations on how to evaluate them. Annex II includes an example of a decision tree on risk factors where only high or low impact effects of the CoPE on the CQAs of the finished product are taken into consideration. In addition, the numbers and percentages should be regarded as indicative. Annex I and Annex II are provided for illustrative purposes.

Overall risk evaluation

Once the impact on CQAs (and CPPs if applicable) has been determined, the overall risk category of the CoPE for the specific finished product can be established as outlined in the ICH Q9 guideline on quality risk management, whose principles can also be used for veterinary products.

Any risk mitigation measures related to the impact of the CoPE on the finished product should be described by the applicant/MAH in the risk evaluation.

Once the risk has been established and risk category assigned, the applicant/MAH should consult Q3 to better understand the level of information to be provided in the dossier.

The final decision by the applicant/MAH is a case-by-case judgement, and in cases of doubts, a scientific advice can be requested.

For human finished products the risks related to a CoPE identified through this risk evaluation can be considered when evaluating the risk profile of the excipient (in this case the CoPE) carried out by the manufacturing authorisation holder (MIAH), as part of the formalised risk assessment (FRA) described in the Guidelines of 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use. The applicant/MAH should ensure that they liaise closely with the MIAH so that the risk category and the risk profile for the CoPE are aligned. The manufacturing authorisation holder should then establish and document the elements of EudraLex Volume 4 that it believes are needed to be in place in order to control and maintain the quality of the CoPE. The FRA does not need to be submitted in the dossier but should be available to inspectors during GMP inspections of the MIAH.

For veterinary finished products, the FRA Guidelines do not apply.

3. What are the regulatory dossier requirements to a co-processed excipient?

The dossier should include information in line with Directives, Regulations and Guidelines related to the quality of finished products for human and veterinary use. Some of the relevant Guidelines are listed below:

- EU/ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004).
- EU guideline on development pharmaceutics for veterinary medicinal products (EMA/CVMP/QWP/684556/2022).
- EU Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (R2) (EMEA/CHMP/QWP/396951/2006).
- EU Guideline on excipients in the dossier for application for marketing authorisation for veterinary medicinal products (EMA/CVMP/QWP/307647/2023).
- EU guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015).
- EU guideline on Manufacture of the veterinary finished dosage form (EMA/CVMP/QWP/798401/2015).

The same level of detail is expected for CoPE being described in pharmacopoeias.

Dossier requirements of particular relevance for all categories of CoPEs include:

Description and Composition (3.2.P.1)

The CoPE should be provided in 3.2.P.1 specifying the brand name, grade, the quantity present (mg/unit and %/unit), the function and reference to relevant quality standard (in-house). Each individual excipient included in the CoPE should additionally be listed specifying the grade, quantity (mg/unit and %/unit), function and reference to relevant quality standard (i.e. Ph. Eur.). This also applies to other excipients (e.g. stabilisers, antioxidants etc.) included in single excipients forming the CoPE (allowed as per Ph. Eur.).

It is expected that each individual excipient included in the CoPE complies with Ph. Eur. (general monographs and individual monographs). See also 'Description of the manufacturing process of the CoPE'.

Pharmaceutical Development (3.2.P.2)

Discussion of the CoPE chosen, concentration and characteristics that can influence the finished product performance (e.g. stability, bioavailability) or manufacturability in relation to the respective function of the CoPE and each individual excipient included in the CoPE, should be presented. The intended functionalities of the CoPE - i.e. the unique properties of the CoPE - that are not achievable through blending or by a special grade of *single* excipients should be discussed. It should be addressed what benefits (in manufacturing and/or product quality and performance) are obtained in the finished product. The presence of each individual component and its own specific contribution to the intended functionalities (unique properties) of the CoPE should be explained.

The identification of the risk category of the CoPE based on the risk should be submitted taking the risk factors in Question 2 into account (see Annex I and II). In addition, the risk evaluation of the risk factors mentioned in Q2 should be performed and presented by the applicant in 3.2.P.2.

It should be demonstrated that processing of the individual excipients into the CoPE does not introduce any covalent bonds but only produces a physical interaction, such as hydrogen bonding or Van der Waals forces. Suitable characterisation techniques should be used to demonstrate that the chemical structure of each excipient is preserved. Statements should be supported by data. When such data has been published in scientific literature, a copy would be sufficient. When it is demonstrated that no covalent bonds have been formed, the safety of the CoPE can be assumed to be similar to the safety of the individual excipients.

Description of the manufacturing process of the CoPE (3.2.P.4.):

A general description of the manufacturing process of the CoPE including a flow chart should be provided in 3.2.P.4.1.

In case the single excipients are not isolated during the process (e.g. continuous manufacturing is used), in-process controls should be in place to ensure that the single excipients comply with their respective specification (the individual and general Ph. Eur. monograph and additional tests if any) before inclusion in the CoPE. Such in-process controls should be indicated in the flow-chart.

Specification for the CoPE (3.2.P.4):

An appropriate specification should be established in the dossier in section 3.2.P.4.1 and should include:

- Physical characteristics, especially critical characteristics or material attributes and functionality related characteristics (FRCs).
- Assay and identification of each individual excipient in the final CoPE.
- Test for degradation products (total and individual impurities), unless otherwise justified.
- Purity test may be physical, chemical, biological and where relevant immunological.
- Tests for FRCs to ensure the manufacturing process was complete and did not result in a mixture or incomplete CoPE.
- Where relevant, tests for elemental impurities and residual solvents.

All analytical procedures for testing of the CoPE should be adequately described in section 3.2.P.4.2. For general methods, reference should be made to Ph. Eur. where possible.

The analytical procedures for testing of the CoPE should be duly validated and demonstrated to be suitable for the intended purpose. The documentation should be enclosed in 3.2.P.4.3.

All specification parameters and limits for the CoPE should be justified in section 3.2.P.4.4 (including assay tests, purity tests and omission of tests such as residual solvents, elemental impurities and degradation products and FRCs). The CoPE specification should be justified based on pharmaceutical development of the finished product.

If, after thorough investigation, an assay test of each single excipient or other critical material attributes of the CoPE cannot be performed on the final CoPE, additional detailed information on the control of critical manufacturing steps (in-process controls or critical process parameters) may be needed in the dossier to ensure consistent quality and homogeneity of the CoPE.

Specification for each individual excipient in the CoPE:

- If special grades are needed for the single excipients (before introducing them in the CoPE), related specification parameters (e.g. particle size, viscosity, degree of polymerisation etc.) should be included in addition to the reference to Ph. Eur. specific monographs in the specifications for each individual excipient in 3.2.P.4.1.

SmPC:

For products for human use, the same principles as reflected in the Guideline on Summary of Product Characteristics (SmPC guideline) and EC guideline on "Excipients in the labelling and package leaflet of medicinal products for human use" , are applicable. This means that the CoPEs ingredients should be listed individually.

For products for veterinary use, principles mentioned in the CVMP guideline on excipients and in the QRD templates should be followed.

3.1. The risk assessment concludes a category C (low risk CoPE)

No additional dossier requirements apart from the generally applicable criteria as described above.

3.2. The risk assessment concludes a category B (medium risk CoPE)

The following additional requirements apply:

Additional requirements to Description and Composition for category B CoPE (3.2.P.1)

For excipients which are removed from the CoPE during the process (e.g. solvents, water), the quantity (e.g. a range), function and reference to relevant standard should be listed (a footnote may indicate absence in the final CoPE).

If water is used in the manufacturing process of the CoPE, the quality of the water should also be given in 3.2.P.4, and it should be noted that it is expected that purified water in accordance with Ph. Eur. is applied, unless justified.

Additional requirements to Pharmaceutical Development for category B CoPE (3.2.P.2)

Explanation of the use of a CoPE instead of using special grades of single excipients or routine manufacturing processes e.g. granulation should be provided. This could include development data (e.g. lab scale experiments). The explanation of the specific ratio of single excipients in the CoPE should be provided.

Investigation of impact of changes in the amount of CoPE and each individual excipient on the CQA of the finished product by laboratory trials in accordance with Pharmaceutical Development guidelines requirements is encouraged.

Storage of a CoPE could impact FRCs and/or other specification parameters. This should be considered during finished product development but this consideration and stability studies are not expected to be submitted in the dossier. The container closure system for the CoPE should be suitable for transport and storage.

Additional requirements to Description of the manufacturing process for category B CoPE (3.2.P.4.):

In 3.2.P.4.1 a detailed description of the manufacturing process of the CoPE, including description of process parameters, in-process controls and process evaluation of the manufacturing process of the proposed batch size ranges including:

- A flow-chart should be provided with all unit operations and each individual in-process control listed at each stage.
- Description of the manufacturing process (e.g. critical process parameters) should be given at such a level that the finished product manufacturer is able to make a risk assessment and justify that no new unqualified degradation products are formed under the actual manufacturing conditions.
- The process evaluation should demonstrate that a sufficiently consistent CoPE quality (all relevant quality attributes) is obtained throughout the entire process via appropriate process parameters and in-process controls. A specific assay of each individual excipient should be provided as part of the demonstration. Process validation data is not expected to be provided in the dossier.

Information on the name and address of the manufacturer of the category B CoPE (3.2.P.4.1):

Information on the name and address of the CoPE manufacturer.

3.3. The risk assessment concludes a category A (high risk CoPE)

In addition to the above listed requirements, when a category A CoPE is part of the finished product composition, the requirements described in the European scientific guidelines on the quality of human or veterinary finished products should be considered. Deviations from guidelines should be explained and justified.

Annex I: Risk factors and impact ranking table

Risk factors are interconnected and should not be considered in isolation. The risk factors provided below should all be considered but are not exhaustive.

Numbers and percentages mentioned in the table have been derived from the experience gained so far when reviewing finished product containing CoPEs and should be considered example values only. For simplicity, only examples of high and low impact are presented. However, it is acknowledged that the level of risk is continuum (i.e. not binary and spans between low, medium and high) and the MAH could identify a medium risk level.

	Impact on CQAs of the finished product	
Material attributes of the CoPE	Impact level - High	Impact level - Low
Function(s) of the CoPE		
CoPE function(s) as defined in 3.2.P.1 (e.g. filler, lubricant, stabilisers, antioxidant, disintegrant, surfactant or release rate controlling agent)	Critical functions with high impact on finished product CQAs (e.g. disintegrant, surfactant). The higher the number of critical functions the higher the risk.	Function with low effect on finished product CQA (e.g. filler or binder).
Function of rest of the other excipients included in the composition of the finished product	e.g. finished product contains a CoPE with critical function(s) and other excipients with functions which have low impact the CQAs (e.g. filler), the risk is considered higher.	e.g. risk level is reduced when the finished product contains an excipient with same function as the CoPE and thereby impacting the same CQA.
Physico-chemical characteristics of the CoPE		
Physico-chemical characteristics having an impact on the CQAs of the finished product (e.g. characteristics having an impact on appearance, assay, content uniformity, stability and impurity profile of the finished product and bioavailability, such as particle morphology particle size, amorphous content, solvents, process related impurities, degradation products etc.)	e.g. Particle morphology, surface area, pore size distribution, particle size, amorphous content impacting dissolution have a high risk e.g. a CoPE with impurities that may have an impact on the degradation of the finished product is considered as high risk.	e.g. Particle morphology, Particle size not impacting bioavailability has a low risk with respect to this CQA. e.g. a CoPE that does not have a negative impact on the stability of the finished product is considered to have a low risk with respect to this CQA.
CoPE composition		
Number of excipients in CoPE	≥4 The higher the number of excipients having different functions and/or physico-chemical characteristics, the higher is the risk as it may become increasingly difficult to achieve consistent quality related to the characteristics of each individual excipient	2 The risk linked to the CoPE variability is lower if the number of excipients in the CoPE is low.

	of the CoPE and to control the quality of the CoPE.	
Proportion of CoPE in the formulation: percentage of CoPE in respect to the entire formulation of the finished product.	Impact level - High	Impact level - Low
If the CoPE material attributes have low or medium impact on CQA:	>75% If the CoPE has low or medium impact on CQAs, it is the main component in the formulation and the proportion is high, then the risk is high.	<50% If the CoPE has low or medium impact on CQAs, and other excipients in the formulation have high impact on the CQA, then the risk is low.
If the CoPE material attributes have high impact on CQA:	>30% This risk needs to be taken into consideration with the CoPE impact on CQAs and the rest of the formulation: if the CoPE has an impact on CQAs, its proportion is high and no other excipients impact the same CQAs, then the impact is high.	<15% If the CoPE has an impact on the CQAs but the same CQA is also controlled by other excipients and the proportion of the CoPE is low, then the risk is low.

Example on classification (Category A, High Risk)

Pharmaceutical form: **modified release tablet**

Composition of the finished product:

Function	*Amount*
Active substance	15%
CoPE (retarding agent) Retarding agent/Viscosity modifying agent Pore former/disintegrant Surfactant Glidant	45%
Filler	39%
Glidant	0.25%
Lubricant	0.75%

Risk factor and impact ranking based on Annex I and Annex II.

Has the function of the CoPE excipient a high impact on the FP CQAs? Yes, high risk as the CoPE has multiple functions and is a retarding agent (pore former and viscosity modifying) and disintegrant with impact on the CQA dissolution and bioavailability.	YES →	Have the physico-chemical characteristics of the CoPE a high impact on CQAs of the finished product? Yes, high risk as the physico-chemical characteristics of CoPE such as pore size distribution and particle morphology have impact on CQA dissolution.	YES →	Number of excipients in CoPE Four (4) excipients in CoPE thus high risk as ≥4 .	≥ 4 →	Proportion of CoPE in the finished product The CoPE is 45% of the formulation (high proportion) and thus, high risk as >30%.	>30% →	High Indicates that the Category may end as A. High risk, and CoPE in this finished product is **Category A**.

Example on classification (Category B, Medium Risk)

Pharmaceutical form: **Hard capsules**

Composition of the finished product:

Function	*Amount*
Active substance	45%
CoPE (solubility enhancer) Surfactant Mineral carrier	2%
Diluent	48%
Disintegrant	4%
Lubricant	0.5%
Glidant	0.5%

Risk factor and impact ranking based on Annex I and Annex II.

Has the function of the CoPE excipient a high impact on the FP CQAs? Yes, high risk as the CoPE is a solubility enhancer with impact on the CQA dissolution and bioavailability.	YES →	Have the physico-chemical characteristics of the CoPE a high impact on CQAs of the finished product? Yes, high risk as the physico-chemical characteristics of CoPE (pore size distribution and particle morphology) may have impact on CQA dissolution.	YES →	Number of excipients in CoPE Two (2) excipients in CoPE thus lower risk.	2 →	Proportion of CoPE in the finished product The CoPE is 2% of the formulation and is <15%.	<15% →	Medium, Indicates that the Category may end as B. Medium risk, and CoPE in this finished product is **Category B**.

Example on classification (Category C, Low Risk)

Pharmaceutical form: **film-coated tablet**

Composition of the finished product:

Function	*Amount*
Active substance	15%
CoPE (Filler) Filler Disintegrant	60%
Super disintegrant	5%
Filler	19%
Lubricant	1%

Risk factor and impact ranking based on Annex I and Annex II.

Has the function of the CoPE excipient a high impact on the FP CQAs? No, lower risk. The function of the CoPE is filler/disintegrant and another excipient in the formulation has major impact on same CQA dissolution.	NO →	Have the physico-chemical characteristics of the CoPE a high impact on CQAs of the finished product? No, lower risk.	NO →	Number of excipients in CoPE Two (2) excipients in CoPE thus lower risk.	2 →	Proportion of CoPE in the finished product The CoPE is 60% of the formulation and therefore 50%< %CoPE <75%.	50%< %CoPE <75% →	Low Indicates that the Category may end as C. Lower risk, and CoPE in this finished product is **Category C**.

Annex II: Decision tree on risk factor and impact ranking of CoPE with regard to the CQAs of the finished product

The risk factors in Q2 and risk level described in Risk factors and Impact Ranking table (Annex I) should be considered when deciding on the impact of the CoPE material attributes on the CQAs of the finished product. Numbers and percentages mentioned in the decision tree have been derived from the experience gained so far when reviewing finished product containing CoPEs and should be considered example values only.

For simplicity only impact high and low are considered in the decision tree; however, it is acknowledged that a medium impact can be identified. The final decision will be taken on case by case basis.