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Overview of comments received on "Q&A regarding co-processed excipients used in solid oral dosage forms H and V" (EMA/CHMP/CVMP/QWP/422493/2024)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
Pfizer	General	0	0	As a proposal, instead of the categorization of risk could we request from the excipient supplier the full composition and assay for all components in the CoA (where possible)? Where assay for all components is not possible information on the control of critical manufacturing steps (in-process controls or critical process parameters) could be provided to ensure consistent quality and homogeneity of the CoPE.		Not accepted. The concept of risk categorisation should be seen as a means of making sure that an appropriate level of information is available to both the product manufacturer and the agencies. As most examples of use of CoPEs are expected to fall under low risk, the risk categorisation is essential to the proposed QA.
Pfizer	General	0	0	The requirements for a co-processed excipient are far superior to that of a single component excipient and suppliers are unlikely to be able to provide all of the testing and documentation specified within this guideline.		Comment not accepted. Requirements defined for the documentation are proportioned to the risk level assigned to the CoPE. The Applicant/MAH should demonstrate to have adequate knowledge and control of CoPE considering the impact it could have on its FP. Information should be available when a confidentiality agreement is in place.
Pfizer	Specific	239		It is not clear from a scientific perspective how the percentages were calculated to determine the impact level.		The comment is acknowledged. The percentages should be seen as a help to categorise the impact level. The percentages are based on current knowledge and should be considered example values only. It is of importance that guidance is presented so the same procedure is adopted by all parties. The text is proposed to be left unaltered.
Pfizer	Specific	117-117		Why is the brand name of the CoPE required? Any CoPE that meets the specification included should be acceptable.		No change. In line with EU Guideline *on excipients in the dossier for application for marketing authorisation of a medicinal product* . Since the common name is not sufficient to indicate functional properties.

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Pfizer	Specific	118-121		Please clarify what qualifies as a "relevant standard"?Is this the vendors responsibility or the DP developers responsibility?		Clarification added. “quality” added to relevant standard. It is the finished product manufacturer/MAH responsibility. “in-house” and “Ph. Eur” included in relevant places.
Pfizer	Specific	122-123		Compliance with individual monograph - can the CoA from the vendor satisfy this requirement?		No change. Further guidance regarding individual excipients is provided in subsections of the Q&A. A CoA from CoPE manufacturer can be provided if appropriate. For P.1 it is the same requirement as for excipients, in general. When a specific Ph. Eur. monograph exist for individual excipients, compliance is expected.
Pfizer	Specific	125-132		This is a significant burden on drug product development applicants to demonstrate the benefits of CoPE vs individual excipients. Extra development work has to be undertaken to develops such a data package for filing. Typically, the vendor information comparing such property may be available. Would the agency accept such information from the vendor or from the literature?		Not agreed. The benefits of CoPE on the finished product performance or manufacturability is typically the reason for choosing CoPE instead of individual excipients and is therefore the requirement is already addressed in e.g. ICH Q8 “discussion of the excipients chosen”. It is not considered extra development work but part of the usual development and evolution of the formulation. Information from the CoPE manufacturer and literature can be submitted to support the discussion, where relevant for the specific applied finished product.
Pfizer	Specific	137-140		Would the agency accept such information from the vendor or from the literature? An MAH/FPM should not be regenerating data particularly if it is supported by vendor data.		No change. It is not expected that FPM/MAH regenerates data on preservation of the excipient structure when data is submitted from the CoPE manufacturer in the dossier. The Q&A under 3.2.P.2 already describes the acceptance of a copy of literature.
Pfizer	Specific	145-146		Please confirm if information from vendor will meet this requirement? Also, where in 3.2.P.4 is the ‘description of the manufacturing process’ for the CoPE expected?		Clarification added. Information is expected from CoPE manufacturer to be included in the MAA dossier. Section 3.2.P.4.1 is the preferred section. Corrected in various places.

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Pfizer	Specific	151-160		All of this information listed here seems more appropriate for 3.2.P.2 rather than 3.2.P.4. Also, where FRCs for individual excipients do not exist then what is required for this CoPE and what is the likelihood that individual excipient FRC's will translate to FRC's for CoPE's?		Comment not accepted. The text refers to the establishment of a specification for the CoPE, information expected in the 3.2.P.4 section of the dossier. FRCs for CoPE should be established since CoPE has, by definition, intended functionalities which cannot be achieved by using the individual excipients. The specifications are related to the CoPE and not to the individual excipients. Therefore, the characteristics related to the CoPE functionalities should be defined and tested.
Pfizer	Specific	162-163		____	Can we use "other country pharmacopoeias" rather than third country pharmacopoeia?	Comment not accepted. The wording “third country pharmacopoeia” is already used in the Directive 2001/83, Regulation 2019/06 and in the *Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product.*
Pfizer	Specific	199-203		This incurs a significant burden on the FPM to develop data on single excipient vs CoPE's and demonstrate the superiority of the CoPE's in the DP, which is not justified. As long as the CoPE is demonstrated to be suitable for its intended use and has no impact on the quality of the product then this should be sufficient.		Not accepted. For Category B, the increased risk is identified when e.g. the function or physico-chemical characteristics has high impact on FP CQA. In addition, when numbers of single excipients and proportion increases the likelihood of impact on FP CQA increases. Therefore, additional explanation is requested in P.2. Often these experiments are already performed by FPM during formulation development as described in ICH Q8. However, clarification added.
Pfizer	Specific	212-224		A FPM/MAH will not have access to such detailed information as this is proprietary information.		No accepted. Information is available when a confidentiality agreement is in place. The bullet points are defining the level of detail (not as detailed as finished product manufacturing). Based on experience such information has been shared.
Pfizer	Specific	36-37		If a ready to use mixture provides functional benefits, they should be classified as co-processed excipients. This is because it is likely some physical interaction is changing the functionality of excipients and therefore a classification as co-processed excipients should be considered		Comment noted but out of scope.

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Pfizer	Specific	38-48		Given that the categorization of risk (A, B or C) depends on the specific finished product, the same CoPE can therefore end up with different risk categories. Practically this means that an excipient supplier will have to be ready with documentation for the highest risk category which will be a considerable burden for them.		Comment is not agreed. Based on the type of CoPE and finished product for which they are used, such situation will happen in rare cases. In fact, any type of excipient needs to be assessed for potential risks on a case-by-case basis, CoPE is no exception
IPEC Europe on behalf of IPEC Federation	General comments	0	0	IPEC Europe appreciates the opportunity to provide comments on the European Medicines Agency's "Questions and Answers regarding co-processed excipients used in oral dosage forms (H & V)" document, hereafter referred to as "Q&A". We furthermore appreciate the clarification that a "CoPE is not a novel excipient, nor a finished product intermediate without active substance." IPEC believes that the existing regulatory framework is adequate. However, we noted that there several statements and perceptions about CoPE that shall be corrected or addressed more precisely to align with the existing regulatory framework.		To be addressed under each specific case below.
IPEC Europe on behalf of IPEC Federation	Specific	151		Insert header to mirror the CTD structure more comprehensively	3.2.P.4 Control of Excipients 3.2.P.4.1 Specification for the CoPE.	Partly accepted.
IPEC Europe on behalf of IPEC Federation	Specific	100-101		Reword line 100 to emphasize the importance of the FRA documentation in context with GMP inspections. Delete line 101 as It is stated above that the FRA is applicable to human drugs while for veterinary products the principles of ICH Q8 could be applied.	The FRA documentation does not need to be submitted in the dossier but should be readily available to inspectors during on-site GMP inspections of the finished drug manufacturer.	Comments are acknowledged. Sentence about submission of FRA in the dossier has been modified accordingly. Reference to FRA Guidelines is kept for better transparency.

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IPEC Europe on behalf of IPEC Federation	Specific	104-115		The type, amount and location of the CoPE information should not differ to the relevant requirements of EMEA /CHMP/QWP/396951/2006, EMA/CVMP/QWP/307647 /2023, and the ICH M4 guideline on the Common Technical Document. Regardless of the potential risk level, the risk mitigation and -control can be fully addressed in the relevant CTD sections of the above-mentioned guidelines. Any additional supportive information related to CoPE manufacturing may be provided in 3.2.A.3 - Excipients in line with the ICH M4 Implementation Working Group Q&A document.	The dossier should include information to an extent as required for excipients in line with: -EMEA/CHMP/QWP/396951/2006 Guideline on excipients in the dossier for application for marketing authorization of a medicinal product (R2) -EMEA/CHMP/QWP/307647/2023 Guideline on excipients in the dossier for application for marketing authorization of a veterinary medicinal product -ICH M4 Guideline on The Common Technical Document for the registration of pharmaceuticals for human use – ICH M4 Implementation working group – Q&A The following CoPE information should be provided in the CTD sections assigned by the aforementioned guidelines	Comment not accepted. The guidelines mentioned in the proposed re-wording are already referenced in the lines 104-115. Also the other guidelines mentioned in the lines 104-115 are relevant for the scope of Q&A. The proposed re-wording "include information to an extent…" is not applicable considering that the main goal of the proposed Q&A is to clarify requirements for CoPE not covered by the existing guidelines.
IPEC Europe on behalf of IPEC Federation	Specific	116-123		The relevant standard may be an in-house specification, in case the raw material used in the CoPE production is an intermediate of a compendial excipient in form of a slurry or dispersion that is taken out of the process prior to the finishing to the finished compendial excipient. Stabiliizers, antioxidants, surfactants etc. may not act as excipient in the drug formulation. In case of compendial CoPE ingredients, their use / presence in the ingredients may be described in the monograph. In case of non-compendial excipients the use of such substances should be justified. As explained above, the use of non-compendial excipients and excipients described in third country pharmacopoeias is acceptable in line with EMEA/CHMP /QWP/396951/2006 and EMA/CVMP/QWP/798401 /2015.	3.2.P.1 Description and Composition of the drug product The brand name of the CoPE and if applicable, the monograph title of the CoPE should be stated. The CoPE ingredients should be listed with a reference to the applicable standard (compendial monograph or "in-house specification"). The quantity of the CoPE ingredients present in the drug product (mg/unit and % /unit) and the function(s) should be stated. This also applies to stabilisers, antioxidants, surfactants etc. included in the individual components forming the CoPE, if they are present in the drug product in relevant amounts. In case finished compendial excipients are used as raw material in the production of the CoPE, the excipient shall comply with the relevant monograph.	Not agreed. Only CoPE manufactured using Ph. Eur. excipients are in scope of these Q&As. Clarification: Line 120 updated with "(i.e. Ph. Eur.)". There is not a lower level (or "relevant amount") for other excipients (e.g. stabilisers etc.) in included in single excipients forming the CoPE. If included it should be described in P.1. For issues related to excipients not isolated in the process; When it is dried, it should comply the Ph. Eur. Clarification added in the Q&A.
IPEC Europe on behalf of IPEC Federation	Specific	124-132		The scope of pharmaceutical development should not differ to other types of excipients. The rationale for co-processing should be justified by the CoPE manufacturer and is not subject of drug development	3.2.P.2 Pharmaceutical Development The choice of the CoPE should be discussed taking into consideration the compatibility of the CoPE (ingredients) with active substances and, where relevant, with other excipients. The amount of CoPE used, the concentration of the CoPE ingredients, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed in relation to the respective function of each CoPE ingredient.	Not agreed. The rationale for co-processing is part of the discussion of the choice of CoPE. The choice of CoPE should be discussed by FPM/MAH. This is not different from what is required for other excipients.
IPEC Europe on behalf of IPEC Federation	Specific	13-20		The introduction implies that the use of CoPE -by default- introduces additional risk compared to using individual excipients, which is inaccurate. Rather, CoPE can reduce the risk as described in the proposed revised text. In fact, any type of excipient needs to be assessed for potential risks on a case-by-case basis, but an additional risk should not be presented as a given in the introduction section. The Q&A should not introduce new requirements (dossier content, water quality) beyond existing guidelines. It should reflect that the formalized risk assessment is applicable and refer to the correct (!) CTD sections in the dossier. The dossier requirements are defined in existing guidelines. Risk mitigation and -control as part of the FRA is not part of the dossier as correctly stated in line 100 of the draft Q&A.	Compared to a mere physical mixture of excipients (mixed excipients), co-processed excipients (CoPE) offer several benefits, such as improved flowability, compressibility, reduced dust formation etc. At the same time, the use of CoPEs reduces the risk of segregation of its individual ingredients during drug manufacturing, which is a common problem associated with mixed excipients. As is required for any individual excipient and mixed excipients, CoPEs need to be assessed for potential risks to conclude appropriate risk mitigation and -control measures. These Q&As aim to foster a mutual understanding amongst CoPE excipient manufacturers, -users and competent health authorities about the applicability of the existing regulatory framework, including the formalized risk assessment, and the excipient information in the dossier for marketing authorization (type of data and correct location /CTD section).	Partly accepted. Further benefits are added. Q&A requirements follow requirements for non-compendial excipients but clarified specifically for CoPE for which no guidance exists. The Introduction should not include the FRA.

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IPEC Europe on behalf of IPEC Federation	Specific	133-136		Delete, as the formalized risk assessment and conclusion is not part of the dossier.		Not agreed. Justification of risk category for dossier requirements is not the formalised risk assessment for ascertaining GMP for excipients.
IPEC Europe on behalf of IPEC Federation	Specific	137-150		Delete 137-143, as this belongs to the characterization of the excipient. This information should be provided as supportive information in 3.2..A.3. Also the information related to CoPE manufacturing should be provided in 3.2.A.3- Excipients. Insert the proposed text to mirror the CTD structure more comprehensively	3.2.P.2.1 Components of the Drug Product 3.2.P.2.1.2 Excipients The choice of the CoPE listed in 3.2.P.1 and the characteristics that can influence the drug product performance should be discussed relative to the CoPE functions. 3.2.P.3.2 Batch Formula The batch formula of the finished drug product should include the amount of the CoPE to be used in the manufacturing process on a per batch basis.	Not agreed. Demonstrating lack of covalent bonds can be provided via copy of literature, data from FPM or CoPE manufacturer. The FPM should know what the CoPE is (i.e. no covalent bonds) and include this in P.2. A section on 3.2.P.3.2 batch formula is not considered an issue that would need to be clarified in this Q&A.
IPEC Europe on behalf of IPEC Federation	Specific	152-160		Reword	The specification for a CoPE should include: •Physical characteristics, especially critical characteristics or material attributes and functionality related characteristics (FRCs). •Assay and identification of each individual excipient in the finished CoPE. If, after thorough investigation, an assay test for each single excipient cannot be performed on the CoPE, the assay may be controlled via suitable in-process controls of the CoPE manufacturing process. In this case an appropriate justification should be provided in 3.2.P.4.4. •Impurities should be controlled in line with ICH Q3 guidelines as applicable. Impurities that are controlled in the CoPE ingredients may be omitted from the CoPE specifications, provided the impurity is not a degradation product and/or the co-processing does not lead to higher concentrations of the impurity.	Comment partially accepted. Suggestions accepted with slight rewording in bold: First part of the second bullet re-worded as: *"Assay and identification of each individual excipient in the **final** CoPE".* Not to move text from line 171 to second bullet and keep wording as is. The last bullet on impurities is not accepted. ICH Q3 is not applicable for excipients. In any case all parameters in the specification should be justified as described in line 168-169.
IPEC Europe on behalf of IPEC Federation	Specific	162-170		Reword and insert CTD titles to mirror the CTD structure more comprehensively. Reword.	3.2.P.4.2 Analytical procedures All analytical in-house procedures and test methods of third country pharmacopoeias should be described. If Ph. Eur general methods are used, the reference to the Ph. Eur should be sufficient. 3.2.P.4.3 Validation of analytical procedures The analytical procedures for testing of the CoPE should be duly validated and demonstrated to be suitable for the intended purpose. 3.2.P.4.4 Justification of specifications The drug product manufacturer should justify why the CoPE specification is found to be appropriate for the use in the specific drug formulation. All specification parameters and limits for the CoPE as well as the omission of tests should be justified. Tests performed on individual ingredients may not need to be repeated on the CoPE.	Comment partially accepted. Subheadings clarified in various places. The rewording for the section 3.2.P.4.2 is not accepted. Keep the sentence that the documentation should be enclosed in the dossier P.4.3. as this is a general requirement from the Directive. 3.2.P.4.4 not accepted as proposed. The responsibilities don't need to be mentioned (finished product manufacturer). It always is. The last sentence is already covered by the possible justification of the omission (line 168-169)

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IPEC Europe on behalf of IPEC Federation	Specific	171-174		Delete 171-174 as this is addressed already in the proposed text above. If an in-process control is applied instead of an assay test on the finished CoPE, the relevant information should be provided in 3.2.A.3 (see following proposals). Insert the proposed text.	Any supplemental information on the CoPE not addressed in the 3.2.P sections should be provided in 3.2.A.3-Excipients. This applies particularly to the information related to the CoPE manufacturing: 3.2.A.3 Excipients Manufacturer of the CoPE: The name and address of the CoPE manufacturer should be provided. Description of the manufacturing process of the CoPE: A flow-chart with all unit operations and in-process control controls listed at each stage. To demonstrate that a sufficiently homogenous CoPE quality is obtained, analytical batch data should be presented. It should further be demonstrated that processing of the individual excipients into the CoPE does not produce a novel excipient via formation of new covalent bonds between the CoPE ingredients. Suitable characterization 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. Control of materials: Materials used in the manufacture of the CoPE such as process water, raw materials, solvents and process aids should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. If water is used in the manufacturing process of the CoPE, its quality should be appropriate for the intended use. For the manufacture of CoPE to be used in non-sterile oral dosage forms potable water is considered acceptable.	Comment not accepted. Lines 171-174 is not already addressed. The use of a different section 3.2.A.3 could create confusion. Keep information in P.4 for life cycle management. Not accept adding dossier requirements for all categories of CoPE. Some requirements are already included in the Q&A.
IPEC Europe on behalf of IPEC Federation	Specific	181-184		Reword to avoid confusion of CoPEs with excipient mixtures.	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.	Comment accepted.
IPEC Europe on behalf of IPEC Federation	Specific	187-188		Delete as the dossier content is not linked to the risk category.		Comment not accepted. Different dossier requirements have been defined depending on the risk category assigned. These lines clarify what it is expected for category C CoPE.
IPEC Europe on behalf of IPEC Federation	Specific	189-191		Delete as the dossier content is not linked to the risk category		Not accepted.

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IPEC Europe on behalf of IPEC Federation	Specific	192-197		Delete. Solvents and water used during the process and removed during the finishing of the CoPE do not represent excipients in the CoPE. It seems contradictory to list solvents as a component of the drug product and to explain in a footer that they are not a drug component. Residual water in single monographed excipients would not be handled this way either. The expectation for the use of purified water as process water in the manufacture of medium to high-risk CoPEs is scientifically not appropriate. The need for purified water cannot be linked to the number of CoPE ingredients or the total amount and functionality of CoPE in the drug product. The process water is removed for the most part during the finishing of the CoPE. Potable water should be acceptable as it is for the production of individual excipients		Not accepted. The water quality for a category B CoPE may be critical considering the proximity to the final FP. Therefore, purified water is mentioned. However, a different quality (e.g. potable water) can be justified cf. Line 197 also for category B CoPEs. Several CoPE are using purified water already.
IPEC Europe on behalf of IPEC Federation	Specific	198-206		Delete. The principles of pharmaceutical development apply to each excipient regardless of its risk profile. It is considered out of scope of pharmaceutical development to discuss various other theoretical formulation options. Furthermore, the dossier content is not linked to the risk category. Changes in the CoPE composition are subject of regular change management.		Not accepted. For Category B, the increased risk is identified when e.g. the function or physico-chemical characteristics has high impact on FP CQA. In addition, when numbers of single excipients and proportion increases the likelihood of impact on FP CQA increases. Therefore, additional explanation is requested in P.2. Often these experiments are already performed by FPM during formulation development as described in ICH Q8. It is encouraged to gain knowledge on impact of changes in CoPE composition on FP CQAs.
IPEC Europe on behalf of IPEC Federation	Specific	207-209		Stability information for the CoPE may be provided in 3.2.A.3. As for any type of excipients the container closure system should be suitable for transport and storage.		Not accepted. Stability data from the excipient manufacturer is not requested for category B CoPE. Instead the FPM/MAH should know if storage could impact the FRC's of the CoPE and it should be considered during finished product development but this consideration is not expected to be included in the dossier in P.2. In addition, the FPM/MAH should make sure that suitable Container Closure System (CCS) for the CoPE, but information on CCS should not be included in the dossier. Clarification added.
IPEC Europe on behalf of IPEC Federation	Specific	210-224		Delete as the dossier content is not linked to the risk category. As addressed earlier in the comments, the relevant CoPE manufacturing information should be provided in 3.2.A.3		Not agreed. Less information is requested in the dossier when the CoPE has lower risk. Information is expected from CoPE manufacturer to be included in the MAA dossier. Section 3.2.P.4.1 is the preferred section. Corrected in various places.
IPEC Europe on behalf of IPEC Federation	Specific	225-227		As stated earlier in the comments, any information related to CoPE manufacturing / manufacturer should be filed in 3.2.A.3		Not agreed. Information is expected from CoPE manufacturer to be included in the MAA dossier. Section 3.2.P.4.1 is the preferred section. Corrected in various places.

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IPEC Europe on behalf of IPEC Federation	Specific	228-232		Delete as the dossier content is not linked to the risk category.		Comment not accepted. Different dossier requirements have been defined depending on the risk category assigned
IPEC Europe on behalf of IPEC Federation	Specific	233-264		Reword header as suggested and replace the table in Annex I by the Table 1 submitted by IPEC separately due to formatting restrictions of the electronic submission form	Annex: Potential risk factors, risk mitigation/-control and measures and relevant CTD sections	Not accepted. The proposed Table 1 is not supported and the concept of risk factors is essential to the QA.
IPEC Europe on behalf of IPEC Federation	Specific	25-28		Delete, to focus on the definition.		Not accepted. It is of importance to specify the use of the term CoPEs for the following discussion as different parties may use different terminology.
IPEC Europe on behalf of IPEC Federation	Specific	264-265		For the same reasons provided for the replacement of Annex I, we suggest deleting Annex II (text and decision tree)		Not accepted.
IPEC Europe on behalf of IPEC Federation	Specific	29-32		Very often, excipients slurries or -dispersions are used as raw material for CoPE manufacturing, before they are dried separately to a finished compendial excipient. Accordingly, these raw materials cannot be tested according to the corresponding monograph, and are characterized by appropriately justified in-house specifications, instead. Furthermore, the use of excipients described in third country pharmacopoeias and non-compendial excipients is acceptable according to EMEA/CHMP/QWP/396951/2006 and EMA/CVMP/QWP/307647/2023 To that end, the restriction to Ph.Eur. excipients in the definition is considered neither appropriate nor practicable. Remove the remark “typically two” as there are plenty of CoPE containing more than 2 ingredients.	In the context of these Q&As, a CoPE is a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing. Co-processing is performed using physical processes, excluding elements of chemical synthesis and hence, significant chemical change. However, in some instances, formation of necessary components may occur, such as in situ salt formation. CoPE does not contain active pharmaceutical ingredients and comply with the definition of “excipients” of Directive 2001/83/EC, Article 1(3b).	Not accepted. The proposal would widen the scope of the QA significantly. It is expected that the individual excipients in a CoPE are described in the Ph. Eur. to ensure that the quality of the material is in line with EU legislation. The statement “typically” is kept, it does not restrict the number of excipients.
IPEC Europe on behalf of IPEC Federation	Specific	32-35		CoPE have a retest period, not a shelf-life.	If one or more excipients are added by blending to a finished CoPE, the resulting blend is not considered a CoPE. The addition of preservatives, antioxidants or chemical stabilisers to the finished CoPE. solely to prolong the retest period of a CoPE is not accepted as is not considered a contribution to the functionality of a CoPE.	The comment is acknowledged. Retest period or shelf life can apply. Slight change of wording.

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IPEC Europe on behalf of IPEC Federation	Specific	36-37		CoPEs can be ready-to-use preparations to be used in direct compression or film coating similar to excipient mixtures, referenced in Annex I, 4. of EMEA/CHMP /QWP/396951/2006.	A CoPE is not a novel excipient, nor a finished product intermediate without active substance. CoPEss can be ready-to-use preparations to be used in direct compression or film coating similar to excipient mixtures, referenced in Annex I, 4. of EMEA/CHMP /QWP/396951/2006.	Proposed wording is not accepted. Mixtures are not considered CoPE.
IPEC Europe on behalf of IPEC Federation	Specific	44-48		The FRA already addresses the risk categories low, medium & high risk, which may apply to any type of excipient. However, there is no link of the risk category to new requirements such as the use of purified water and the provision of CoPE manufacturing information as part of the drug product manufacturing process (3.2. P. sections). The Q&A is not considered the appropriate way to introduce new requirements.	As with any excipient intended for use in human finished drug products, the manufacturing authorization holder (MAH) needs to evaluate the risks related to a CoPE according to 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 quality risk management principles should be used to evaluate the risks related to the quality, safety and function of the CoPE (including each ingredient) and to classify the CoPE as low risk, medium risk or high risk. The MAH 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 needed for the specific intended use.	Comments are not accepted. Risk categories are provided during product development, and that is beginning of lifecycle management. To provide FRA related to the appropriate GMP is the next step based on the proposed manufacturing strategy.
IPEC Europe on behalf of IPEC Federation	Specific	50-51		Editorial, due to previous edits.	To assign the risk category to a CoPE, the following risk factors should, as a minimum, be considered and their impact on the risk level should be identified.	Comment not accepted.
IPEC Europe on behalf of IPEC Federation	Specific	52-55		Editorial	In line with the principles of ICH Q8, which can also be applied 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.	Not Accepted. It is the principles of ICH Q8 and not the guideline that can be applied for veterinary products.
IPEC Europe on behalf of IPEC Federation	Specific	56-68		The risk factors provided as examples (e.g. the number of excipients and the “thresholds” for the amount of the CoPE in the finished drug) appear to some extent arbitrary. Furthermore, as stated in Annex I, the MAH may conclude a different risk category than described in the examples. We suggest to replace the examples as well as Annex I by the Table 1 that we have submitted separately by email, due to format constraints in the electronic feed-back form. The table provides an overview of typical risk factors, corresponding risk mitigation and -control measures as well as the appropriate CTD sections in the dossier.	Material attributes of the CoPE, such as function, physico-chemical properties, composition of the CoPE and additionally, the function of other excipients included in the finished product should be considered.	Not accepted. The concept of risk categorisation should be seen as a means of making sure that an appropriate level of information is available to both the product manufacturer and the agencies. As most examples of use of CoPEs are expected to fall under low risk, the risk categorisation is essential to the proposed QA. For this reason, the submitted Table 1 is not accepted.

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IPEC Europe on behalf of IPEC Federation	Specific	72-80		Delete. Rationale: Typically, the combination of excipients (regardless, if added individually or as a mixed or co-processed excipient) represent the main component of the finished drug product. The impact on manufacturability will be higher…" should be deleted, as it represents a default conclusion. The impact should rather be determined as part of the FRA. The formalised risk assessment represents a holistic assessment of different risk factors. Like Annex I, the decision tree in Annex II is based on arbitrary figures for the number of ingredients and amount of CoPE in the drug product. As correctly stated in Annex I and II, the MAH may conclude a different risk than suggested by the annexes.		Comment is not agreed, only slight modification of the sentence about impact of manufacturability.
IPEC Europe on behalf of IPEC Federation	Specific	82-84		Replace by proposed wording to improve readability in context with the changes proposed above.	Once the impact on CQAs (and CPPs if applicable) has been determined, the appropriate risk mitigation measures should be established by the applicant/MAH in line with ICH Q9 guideline on quality risk management, whose principles can also be used for veterinary products.	Not accepted. As discussed previously, it is of importance to retain the concept of risk categories.
IPEC Europe on behalf of IPEC Federation	Specific	85-86		Editorial	Any risk mitigation measures related to the impact of the CoPE on the finished product should be described by the applicant/MAH in the formalised risk assessment documentation.	Comment is not agreed. The risk evaluation provided within this Q&A goes first, FRA is related to the next step of evaluation of the product. Risk mitigation measures should be described in dossier.
IPEC Europe on behalf of IPEC Federation	Specific	87-88		Delete, as the risk category is not linked to the dossier content.		Not accepted. The concept of risk categorisation should be seen as a means of making sure that an appropriate level of information is available to both the product manufacturer and the agencies. As most examples of use of CoPEs are expected to fall under low risk, the risk categorisation is essential to the proposed QA.
IPEC Europe on behalf of IPEC Federation	Specific	91-97		Delete, as the applicability of the FRA for human products is already addressed above. The execution of the FRA generally requires a close collaboration between the excipient- and the finished drug manufacturer. The dossier content is specified in the relevant EU guidelines mentioned before. As outlined in Table 1 (submitted by IPEC separately by email) the risk mitigation and control measures can be addressed in line with the aforementioned guideline, regardless of the risk category.		Comment is not agreed. Risk categories are provided during product development, and that is beginning of lifecycle management. To provide FRA related to the appropriate GMP is the next step based on the proposed manufacturing strategy, not the beginning of the CoPE life. Thus the collaboration of the finished product manufacturer and CoPE manufacturer should be close earlier than proposed by the stakeholders.
Giovanni Siciliani	General	0	0	The clarifications provided by EMA in this Q&A document for co-processed excipients in solid oral dosage forms are welcomed. Similar clarifications for other dosage forms (e.g. parenteral) or route of administration (e.g. inhalation) would be considered beneficial as well in the future.		Noted.
Giovanni Siciliani	Specific	29-30		Clarification should be added that the CoPE is only non-novel, when the individual components are also non-novel for the proposed route of administration.	In the context of the Q&A, a CoPE is a combination of two or more Ph.Eur. excipients and already established for oral use, typically two, which are processed…	Not accepted, it is already clear that novel CoPE is out of scope of the QA.

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Giovanni Siciliani	Specific	137-139		Clarification should be added about the creation of ionic bonds upon co-processing of excipients. Specifically, are two or more co-processed ions which are held together by charge differences considered a CoPE?		Not agreed. Ionic bonds are not mentioned specifically, since it would be a case by case decision if creation of ionic bonds will result in a different excipient, novel excipient or not and thereby if it will result in a CoPE or not.
Giovanni Siciliani	Specific	139-140		Clarification or examples should be added in terms of expectation to demonstrate that the chemical structure of excipients is preserved, more specifically when polymers are used.		Not accepted. It is up to the FPM/MAH to include data from CoPE manufacturer or literature. It is preferable to be not too prescriptive in favour of flexibility
Giovanni Siciliani	Specific	140-141		Clarification should be added that supportive data may not be published / publicly available and thus should be made available to the sponsor by the CoPE manufacturer. If on the other hand data was published a reference (no copy) should be deemed sufficient	When such data has been published in scientific literature a reference would be sufficient. If such data was generated by the CoPE manufacturer but not published, a copy should be provided.	Not accepted. The current text does not exclude providing supportive data from the CoPE manufacturer. Copies of literature should be submitted.
Giovanni Siciliani	Specific	145-146		Clarification should be added for CoPEs that a high-level description can be deemed sufficient as long as the key manufacturing principle is provided. The current term 'general' used in the sentence is not clear. Of note, based on the Q&A structure this basic requirement only applies to category C (low risk) CoPEs.	A high-level description of the manufacturing process encompassing the key manufacturing principle (e.g. spray-drying, solvent evaporation, melt extrusion, crystallization, etc.) of the CoPE including a flow chart should be provided.	Not accepted. A general description is considered a high-level description
Giovanni Siciliani	Specific	169-170		Only specifications for CoPE CQA's that are relevant to the performance of the finished product (FP) should be justified based on development data of the FP. This is in line with EMEA/CHMP/QWP/396951/2006	For CoPE quality attributes that are critical to the performance of the medicinal product, the relevant CoPE specifications should be justified based on pharmaceutical development of the finished product.	Not accepted. All the specifications should be justified based on pharmaceutical development of the finished product.
Giovanni Siciliani	Specific	229-232		It is not clear, which additional requirements should be provided for category A (high risk) CoPEs, since the referenced European scientific guidelines on the quality of the human or veterinary finished products should be considered also for category C and B CoPEs. Examples of additional requirements for Category A CoPEs would be helpful.		Not accepted. The CoPE category A dossier requirements mimics the requirements for finished products. However, no change is proposed to avoid to be too prescriptive.
Giovanni Siciliani	Specific	254-255		Example on classification (Category B, Medium Risk): The response to the below referenced question seems to be incomplete / does not read well and could lead to confusion. See clarification proposal on the right. 'Have the physico-chemical characteristics of the CoPE a high impact on CQA's of the finished	Yes, high risk as the physico-chemical characteristics of CoPE (pore size distribution and particle morphology) have impact on CQA dissolution.	Accepted. The text is clearer as proposed.
CSL Vifor	General	0		Flavours should not be in scope of the document, even if they are co-processed, e.g. flavouring substances on carrier		Comment noted. Flavours are not intended to be in scope of the Q&A.
CSL Vifor	General	0		Hard capsules may also be exempted from the documentary requirement		Comment noted. Hard capsules are not intended to be in scope of the Q&A.
CSL Vifor	Specific	30-31		the definition includes also hard capsules	add sentence to clarify if hard capsules are in scope of the document	Comment noted. Hard capsules are not intended to be in scope of the Q&A.

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CSL Vifor	Specific	36-37		Flavours to be added	add "nor a flavour"	Comment noted. Flavours are not intended to be in scope of the Q&A.
CSL Vifor	Specific	137		"demonstrated" implies creation of data by the marketing authorisation holder This might nor be necessary, example: hard capsules	replace "demonstrated" by "demonstrated or justified"	Not accepted. Lines 140-141 state that published data (e.g. by the CoPE manufacturer or literature) are acceptable
CSL Vifor	Specific	139		demonstrate" implies creation of data by the marketing authorisation holder This might nor be necessary, example: hard capsules	replace "demonstrate" by "demonstrated or it should be justified"	Not accepted. Lines 140-141 state that published data (e.g. by the CoPE manufacturer or literature) are acceptable
CSL Vifor	Specific	155		In case of CoPE with two excipients it is not necessary to have assay values for both; Assay of second excipient can be derived from that of the first one; i.e. assay(2nd) = 100% - assay(1st)	add "unless otherwise justified"	Not accepted. Based on this comment it is assumed that assay of each excipient (if tested separately) is exactly 100%
CSL Vifor	Specific	165		in case of general monographs no validation needed, e. g. bulk and tapped density	add "or general compendial methods should be used"	Not accepted. “Duly validated” is a general requirement from the Directive and cover all situations. General guidance on validation requirements are covered by other Guidelines and Ph. Eur.
CSL Vifor	Specific	169		For CoPE the specifications are usually defined by the supplier	add "or on batch data of the supplier"	Not accepted. All the specifications should be defined and justified based on pharmaceutical development of the finished product.
CSL Vifor	Specific	171		see comment to line 155		Not accepted. Based on this comment it is assumed that assay of each excipient (if tested separately) is exactly 100%
CSL Vifor	Specific	223		see comment to line 155		Not accepted. Based on this comment it is assumed that assay of each excipient (if tested separately) is exactly 100%
AnimalhealthEurope	General	0	0	AnimalhealthEurope would like to thank the QWP for this Q&A and is grateful for the opportunity to comment. Please find some comments below. Should you have further questions, AnimalhealthEurope is happy to provide any clarification needed.		Thanks from Animalhealth Europe are appreciated
AnimalhealthEurope	General	0	0	The scope of this Q&A is not fully clear as only some categories of excipients are mentioned in the document. Therefore, for the sake of clarity, it is suggested to further detail what are the categories qualifying as CoPE. E.g. “ready-to-use mixture” are excluded. Please refer to comments in the specific comments section.		Noted.
AnimalhealthEurope	Specific	23-37		The concerned CoPE seems mainly to be those that have a function in regard to the manufacturing process (filler, disintegrant…) and the exclusion of “ready-to-use mixture” (is this referring to purchased on the shelf?) as referenced in EU Guidelines on excipients is clearly indicated. It is not clear enough if some other mixtures such as flavouring agents or colouring matters for instance, which purpose is not link to the manufacturing process, are considered as CoPE in the scope of the Q&A.	Proposal is to list the EU Guidelines on excipients mentioned in the Q&A and detail, where relevant, the list of mixtures that are not considered as CoPE. The list could be based on the annex from Guideline EMA /CVMP/QWP/307647/2023 and EMEA/CHMP/QWP /396951/2006 for instance.	Not agreed. Flavours and colouring matters are not intended to be in scope of the Q&A. Mixtures are excluded in line 32-33 of the Q&A.

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AnimalhealthEurope	Specific	2to29		Draft Ph. Eur. monograph states "the individual components may be pharmacopeial excipients or non-pharmacopeial excipients that have previously been evaluated for safety". In case a non-compendial is used is this considered a novel? Also, when it was already used in another finished product. Please clarify.		Not accepted. It is foreseen that it is understood that a non-compendial excipient is not the same as a novel excipient. We are of the opinion that both these terminologies are widely used.
AnimalhealthEurope	Specific	2to36		Suggest defining and differentiate CoPEs a bit more clearly (from e.g. ready to use granulation without active ingredient) in terms of manufacturing process, material characterization and quality attributes		Not agreed, as it is not possible to include the manufacturing process, material characterization and quality attributes in a definition.
AnimalhealthEurope	Specific	0		According to draft EP should comply as well with general requirement for substances for pharmaceutical use.		Noted. The CoPE should comply with the general monograph "substances for pharmaceutical use". This is already addressed in Q3 since Directives, Regulations and Guidelines are mentioned which is considered sufficient.
AnimalhealthEurope	Specific	5/155		In the case of finished product manufacturers, manufacturing the co-processed excipients, this requirement is excessive as the product manufacturer are already testing the individual component against the compendia. It would be useful to bring this granularity in the text between "ready-to-use" on one hand and manufactured CoPEs on the other hand.		Not accepted. Testing of individual components cannot be used as replacement of control of final CoPE in the case when CoPE is manufactured by FP manufacturer. Requirements should be the same irrespectively from the manufacturer. In any case the control strategy can be justified.
AnimalhealthEurope	Specific	5/156		In the case of finished product manufacturers, manufacturing the co-processed excipients, this requirement is excessive as in case there would be any impurity of concern, it would be monitoring at the finished product level. It would be useful to bring this granularity in the text between "ready-to-use" on one hand and manufactured CoPEs on the other hand.		Not accepted. Testing of individual components cannot be used as replacement of control of final CoPE in the case when CoPE is manufactured by FP manufacturer. Requirements should be the same irrespectively from the manufacturer. In any case the control strategy can be
AnimalhealthEurope	Specific	6to186		QRD is mentioned. A reference to the QRD document would be useful.		Not accepted. QRD templates can be easily found on EMA website.
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	29-35		The EXP WP was pleased to read that the definition of a CoPE provided in the context of the draft Q&As is broadly in line with the draft Ph. Eur. text on CoPEs.		Noted
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	62-63		It is recommended to add binders, which are commonly used in CoPEs for oral solid dosage forms, to the examples. If adding binders makes the list too long, we would propose removing antioxidants.	"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, […]"	Accepted, the list states that examples are given "such as" and should not be seen as definitive. It is acknowledged that binders can be of importance.

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European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	109-110		The EXP WP suggests considering a future revision of the guidance on excipients in the marketing authorisation application (MAA) dossier (EMEA/CHMP /QWP/396951/2006), in particular to clarify the current common expectations of regulators on co-processed excipients in relation to MAAs. As many of these are already in use, there may now be sufficient experience among European regulators to warrant such a revision.		Noted. The excipients Guideline revision is already on the QWP workplan.
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	116-123		This paragraph seems to be based on the assumption that CoPE manufacturing starts from finished excipients, which can be individually tested for Ph. Eur. compliance. This is not necessarily the case because it is not uncommon to blend components before the final drying step (not just in the case of continuous manufacturing).	"The routine manufacturing process may be such that there is no isolation of an individual component. However, that component would still have to meet pharmacopoeial requirements if isolated."	Comment partly accepted. Text is amended and a reference to 'Description of the manufacturing process of the CoPE' is added.
European Directorate for the Quality of Medecines and	Specific	118		It might be preferrable to refer to "relevant quality standards" –as per ICH M4Q.	[…] reference to relevant quality standards.	Accepted
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur.	Specific	120		It might be preferrable to refer to "relevant quality standards" –as per ICH M4Q.	[…] reference to relevant quality standards.	Accepted
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	163		According to directive 2001/83/EC, compliance with the monograph of a third country pharmacopoeia can be accepted in cases where a starting material is described neither in the Ph. Eur. nor in the pharmacopoeia of a member state. It is suggested to add this clarification.	[…] including third country pharmacopoeia (e.g. USP-NF) methods, where these are not described in either the Ph. Eur. or a pharmacopoeia of a member state.	Partly accepted. The issue is clear from the Directive. Q3 mentions the Directive, therefore no need to explicitly state this. However, the text has been amended for clarity.
European Directorate for the Quality of Medecines and HealthCare - Ph. Eur. Excipient performance working party (EXP WP)	Specific	192		The Ph. Eur. (as well as other regulatory texts such as the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use') defines an excipient as any constituents of a medicinal product other than the active substance and the packaging material. Substances removed during the process are therefore not considered to be excipients.	For excipients substances which are removed from the CoPE during the process (e.g. solvents, water), […]	Not accepted. Even solvents and residues after removing are considered excipients and they should comply with the general monograph <2034>
ECA/EQPA	General	0	0	These Q&As are laying dossier requirements down so Q&As are not a suitable way of doing this . The content should be published as a formal guideline. Alternatively, a Reflection Paper might be considered if the topic is still in a state of flux.		Noted. The excipients Guideline revision is already on the QWP workplan.
ECA/EQPA	General	0	0	In relation to lines 91-100, we now have a situation where the MAH/MA applicant has to carry out a risk assessment to determine the impact of the co-processed excipient on CQAs or CPPs and the MIAH has a legal obligation to carry out a risk assessment of all excipients to determine an appropriate level of GMP to be applied. To avoid duplication and confusion the risk assessment elements identified in the Q&As should be incorporated into the existing GMP formalised risk assessment guideline, amended as appropriate. The content will then be limited to the dossier requirements.		Not accepted. The comment is acknowledged and could be taken into consideration if the guideline is to be updated.

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ECA/EQPA	Specific	93		The term "Finished Product Manufacturer" is not fully interchangeable with the term "Manufacturing Authorisation Holder". The latter has a legal obligation to carry out a risk assessment of all excipients to determine an appropriate level of GMP to be applied by the excipient manufacturer. The former may be (often is) located in a third country so cannot be a Manufacturing Authorisation Holder and cannot be held accountable for the obligations of the same. In this case responsibility rests with the importer, who must hold a MIAH, The task of, but not responsibility for, risk assessment could be delegated to the "Finished Product Manufacturer" by the "Manufacturing Authorisation Holder" under GMP rules relating to outsourcing.	The term "Finished Product Manufacturer" should not be used and the term "Manufacturing Authorisation Holder" should always be used in this context.	Accepted.
Teva Pharmaceuticals	General	0	0	In general, this guideline imposes a significant burden on submission documentation when a co-processed excipient is purchased from third parties. Obtaining the information on the manufacturing process description, flow chart, and analytical methods and validations for co-processed excipients can be very challenging. The development of the co-processed excipient is also expected to be included in the dossier. Excipient suppliers often keep this information confidential as it is their competitive advantage.		Comment not accepted. Requirements defined for the documentation are proportioned to the risk level assigned to the CoPE. The Applicant/MAH should demonstrate to have adequate knowledge and control of CoPE considering the impact it could have on its FP. Information should be available when a confidentiality agreement is in place
Teva Pharmaceuticals	General	0	0	It is unclear from the guideline if excipients that are pharmacopoeial substances are exempted or if the same level of detail is expected. We would expect that these substances are out of scope for this Q&A.		Not accepted. The same level of detail is expected for CoPE being described in pharmacopoeias. Clarification added.
Teva Pharmaceuticals	29-35			It should be clarified that excipients with their own Ph. Eur. monograph are not in the scope of this Q&A.		Not accepted. The same level of detail is expected for CoPE being described in pharmacopoeias. Clarification added.
Teva Pharmaceuticals	30			co-processing should be more clearly defined, simple mixing is also a physical process	which are processed together using a physical process other than simple mixing/blending (e.g. spray drying)	Not accepted. The comment is acknowledged, but as “physical process” is followed by “without the formation of covalent bonds” in the same sentence, the text is considered clear.
Teva Pharmaceuticals	30-31			It is noted that the wording implies that change in ionic bonds is fine, that would not be considered a CoEP		Not agreed. The comment is not fully understood. Ionic bonds are not mentioned specifically, since it would be a case by case decision if creation of ionic bonds will result in a different excipient, novel excipient or not and thereby if it will result in a CoPE or not.
Teva Pharmaceuticals	34-35			“The use of excipients such as preservatives, antioxidants, chemical stabilisers etc. in order to prolong the shelf-life or stabilise a CoPE is not accepted and is not considered a contribution to the functionality of a CoPE.” The wording implies that the stability/shelf-life of the excipient should be somehow tested and		Yes, stability would need to be considered in the cat B (line 198 for more details) and described in cat A. However, stability would not be expected in low risk CPEs (cat C).

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Teva Pharmaceuticals	129-131			The proposed wording suggest that there must be some benefit of using CoPEs. While there is a need to discuss and justify the use, function and level of excipients, there is currently no requirement to use “better/the best possible” type of excipient in a finished product. Therefore It should be clearly stated that CoPEs can also be used if there is no further benefit.		Not accepted. There will always be some benefits e.g. manufacturability.
Teva Pharmaceuticals	144			A more specific location within 3.2.P.4 should be specified for providingthe Description of the manufacturing process of the CoPE		Agree. Section 3.2.P.4.1 is the preferred section. Corrected in various places.
Teva Pharmaceuticals	151			Clarify eCTD section for excipient specification	Specification for the CoPE (3.2.P.4.1)	Accepted
Teva Pharmaceuticals	155			A specific assay for all components is not justified when the composition determines the amount of one of components (e.g. in case there are two components, one component is measured as x%, the other is than 100-x%).		Not accepted. Based on this comment it is assumed that assay of each excipient (if tested separately) is exactly 100%
Teva Pharmaceuticals	156			The term "degradation product" suggest that the impurity method should be stability indicating for the CoPE. Please clarify if this is indeed a requirement.		Noted. It is already clarified in line 156 that it is possible to justify absence of including degradation products in the specification and therefore also no need for stability indicating method.
Teva Pharmaceuticals	165			If the single excipient Ph. Eur. monograph method is used for a CoPE, is a full validation required, or partial validation is sufficient (e.g. specificity and accuracy)		Noted. “Duly validated” is a general requirement from the Directive and cover all situations. General guidance on validation requirements are covered by other Guidelines and Ph. Eur.
Teva Pharmaceuticals	199-203			Unless the CoPE is custom made, this can be problematic, as the specific ratio of single excipients will not be tailored to the specific drug product, only some general supporting data will be available from the CoPE manufacturer (if any).		Not accepted. Explanations should be included in the dossier. Absence of data can be justified.
Teva Pharmaceuticals	204-206			This may require asking for custom CoPE composition from the supplier, which may not be practical (needs more time, add cost and complexity to the development)		Not accepted. The investigation is encouraged as stated but not a strict requirement. If critical to the quality of the finished product the ratio/assay of the excipients in the CoPE should be challenged within acceptable specification range.

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Teva Pharmaceuticals	207-208			This suggests that some stability data for the CoPE should be available, and/or trials should be made using CoPE of different age. This is again adding complexity (time, cost) to new developments.		Not accepted. Stability data from the excipient manufacturer is not requested for category B CoPE. Instead the FPM/MAH should know if storage could impact the quality and FRC's of the CoPE and it should be considered during finished product development but this consideration is not expected to be included in the dossier in P.2.
Teva Pharmaceuticals	212-213			Detailed description of the CoPE manufacturing process and controls may bring about confidentiality questions with suppliers and finished product manufacturers.		Not accepted. Information is available when a confidentiality agreement is in place. The bullet points are defining the level of detail (not as detailed as finished product manufacturing). Based on experience such information has been shared.
Teva Pharmaceuticals	219-220			It is noted that degradation products from excipients are not covered by ICH Q3B, so the meaning of "unqualified" is to be defined here (e.g. what level of impurities in a CoPE is acceptable without further justification?)		Not agreed. This is not different from non-compendial excipients when setting specification limits.
Teva Pharmaceuticals	221			The requirement to demonstrate "a sufficiently homogenous CoPE quality (all relevant quality attributes)" sounds like "process validation" data, including tests like blend uniformity, plus uniformity of other relevant CMAs/FRCs. This may bring about confidentiality questions with suppliers and finished product manufacturers, and requires an unjustified amount of extra work to produce.		Partly accepted. Process validation is not requested. The demonstration is focused on few critical parameters such as homogenous CoPE quality (ratio/assay). Clarification has been added.
Teva Pharmaceuticals	223-224			An indirect assay should be sufficient for the other component where the qualitative composition is well-defined (cf. comment #8).		An assay of each individual excipient should be provided as part of the demonstration. Assay by calculation is not considered acceptable.
Teva Pharmaceuticals	229-232			The extent of information required would require close and full co-operation between the Finished Product Manufacturer an the CoPE supplier, i.e. co-development. This This may bring about confidentiality questions and may not be practical.		Comment not accepted. Requirements defined for the documentation are proportioned to the risk level assigned to the CoPE. The Applicant/MAH should demonstrate to have adequate knowledge and control of CoPE considering the impact it could have on its FP. Information should be available when a confidentiality agreement is in place.

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