European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON FIXED COMBINATIONS – REV 1

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	
2	Gilead	
3	Lundbeck	
4	Roche	
5	Merck	
6	Schering-Plough	
7	Les Laboratoires Servier	
8	AESGP	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
(1) The revision of the current guideline was welcomed and full support was given to a guideline that could be harmonised with the FDA guideline and integrate consideration of non-clinical requirements for a combination program. **(outcome: out of scope)** Although the current guideline provides general guidance on the safety, efficacy and pharmacodynamic/pharmacokinetic data requirements for FDCs, it would be valuable to provide reference(s) to other CHMP guideline(s) that are relevant to the quality aspects of FDCs. **(outcome: out of scope)** The FDA Guidance for Industry (Nonclinical Safety Evaluation of Drug or Biologic Combinations - http://www.fda.gov/cder/guidance/6714fnl.htm) provides a decision tree helping the applicant to define very clearly the non-clinical requirements for a combination program. In the EMEA guideline describing the nonclinical considerations (EMEA/CHMP/SWP/258498/2005 - http://www.emea.europa.eu/pdfs/human/swp/25849805enfin.pdf) for developing a fixed combination, which will come into effect on 1st August 2008, there is not such a decision tree where nonclinical requirements and in particular duration of studies could be discussed. Given the nonclinical data are discussed, it would be very helpful to include such a decision tree in the upcoming revised guideline (CPMP/EWP/240/95) together with standard dossier requirements for the different types of indications/claims. **(outcome: out of scope)** The opportunity of this revision should be taken to introduce, define or clarify some key concepts and their related requirements: - The concept of fixed dose combination (FDC) treating 2 closely related diseases (dual target FDC), **(outcome: accepted)** - The concept of a substitution indication for FDC (meaning a FDC indicated for patients already treated by the 2 components but as separate tablets)' **(outcome: accepted)** - The booster concept that mainly strengthens the effect of one active substance by combination with e.g. an enzyme inhibitor, although the focus of the current guideline is on the added effects of 2 or more active substances. **(outcome: to discuss)** To harmonise with the EMEA guideline on nonclinical considerations (EMEA/CHMP/SWP/258498/2005), more specific differentiation/guidance on the following scenarios would also be appreciated: - Approved products at approved dosages in an approved regimen, - Approved products at novel dosages or in a novel regimen, - One or more approved products at approved dosages in an approved regimen and one or more unapproved products, - One or more approved products at novel doses or in a novel regimen and one or more unapproved products, - Or unapproved products. **(outcome partly accepted)** Some recommendations in terms of paediatric development would be very helpful if this were detailed in the guidance. **(outcome: not accepted)**
(2) The draft Guideline currently includes a stringent requirement for "confirmatory clinical trials that are considered necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances". The basis for the requirement for a comparison of the efficacy and safety of the individual components versus the actual fixed combination is currently unclear for fixed combinations of active substances that have previously been authorised for use in combination with the same Posology/Method of Administration and for which bioequivalence has been demonstrated. The requirement for confirmatory clinical studies as currently written will likely impede the development and timelines for the introduction of new fixed combinations that represent a simplification of therapy, improve patient satisfaction and/or adherence, and thereby maximize the possibility of long-term therapeutic success (e.g. for the treatment of HIV-1 infection). (substitution indication) **(outcome: accepted, see later)**

(3) The scope of the guideline is to provide scientific requirements for applications according to Article 10b of Directive 2001/83/EC, as amended, the so-called fixed combination medicinal products. The guideline also mentions fixed combination medicinal products containing one or more substances, which have not yet been authorised in the EEA. These medicinal products should be applied for according to Article 8.3 of Directive 2001/83/EC, as amended, and are therefore *not* included in the scope of the guideline. **(not accepted)** In our opinion the scope of the guideline should be extended to also cover this type of fixed combination products, and the guideline should also provide scientific requirements for these products. The requirements for these products are identical to neither the "pure" Article 8.3 nor Article 10b applications, and hence a need for further elaboration is needed. **(outcome: legal basis will be clarified)** Also it could be considered to include scientific requirements for medicinal products that are aimed as "add-on" treatment. These products cannot be considered as fixed combination medicinal products, but there is a strong resemblance. The guideline should provide information on the *differences* in requirements for fixed combination medicinal products and medicinal products aimed as "add-on" treatment. **(outcome: out of scope)**		
(4) More specific differentiation/guidance on the following scenarios would be appreciated: • Approved products at approved dosages in an approved regimen • Approved products at novel dosages or in a novel regimen • One or more approved products at approved dosages in an approved regimen and one or more unapproved products • One or more approved products at novel doses or in a novel regimen and one or more unapproved products • Unapproved products **(outcome: legal basis will be clarified)**		
(5) This guideline is intended to provide guidance on fixed-combination medicinal products containing two or more active substances. As a general comment, the guidance needs to provide more detail in the section on Safety Aspects (Sec 4.4.3) to be in alignment with guidance on Combination Safety Testing in the draft ICH M3 guidance. **(outcome: to discuss)**		
(5) At present the guideline does not cover co-administration although we know from experience that Agencies consider the guideline when approving medicines for co-administration. Some language on co-administration may increase predictability of the regulatory standards (e.g. human safety requirements). This is worth some further discussion. **(outcome: out of scope)**		
(7) Our main comments relate to combination packs which may not have the disadvantages of fixed combinations. Consider that some National Health systems promote a "Transport box" to be used by the pharmacists (eg antiosteoporotic medicinal product + calcium supplement medicinal product): when dispensing, both products are delivered to the patients who are prescribed the antiosteoporotic drug allowing a better compliance and therefore a public health benefit. **(see later)** Consider the case of fixed combinations aiming at covering a substitution indication. **(outcome: accepted)**		
EXECUTIVE SUMMARY		
	(5) Use of 1st line and 2nd line terminology is somewhat misleading. We believe the intent of the guideline is to ask sponsors to state if their development program is to use the combo product as initial therapy or only after the individual components have failed (or patient becomes intolerant). It needs to be clarified if this also implies the use of the combo only after ANY standard therapy has failed or the patient is intolerant. We assume that this guidance will also apply to 1 or 2 investigational compounds (NCEs) in development as combination therapy (FDCs) when either or both have limited data or experience. Please provide more detail related to the timing of Safety Assessment, phase I,II, III studies.	Partly accepted. The text will read: "The development of fixed-combination medicinal products will reflect the intended use (first or second line indication in patients inadequately controlled with individual component(s) of the combination) and the intended indication (treatment of one disease or e.g. two closely related diseases like hyperlipidemia and hypertension, or substitution indication). See legal basis.

1 INTRODUCTION		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
1st & 2nd paragraphs	(1) Only 2 reasons are mentioned for the combination of medicinal products, i.e. "to improve compliance and to benefit from the added effects of the two products" while in the 2nd paragraph two others are mentioned, viz. the counteracting by one substance of an adverse reaction by another substance, and simplification of the therapy (the latter resulting in improvement of patient compliance). The boosting concept is not mentioned, and besides, it seems more logical to mention the improvement of compliance as the last of the various reasons as it seems the least frequent and even challenging to achieve with the regulators It is suggested for clarification, to combine these 2 paragraphs to address the various reasons for fixed combinations of medicinal products.	Accepted. The text will read: Fixed-combination medicinal products have been increasingly used to benefit from the added effects of medicinal products given together. In addition, it is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product. Potential advantages of fixed combination products may also include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy (improved compliance).
3rd Paragraph Line 9	(1) Editorial: Please remove "s" after developments. "Clinical developments should correspond…"	Accepted
3rd Paragraph Line 11	(1, 4) The sentence between bracket seems very specific and rather obvious: "(e.g. in cases when each component of the fixed combination has several possible dosages, dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only)" The reasons why "*dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only*" are not scientifically justified, especially when surrogate endpoints are validated and recognised by regulators. Fixed combinations applying to this situation have been approved recently. It is suggested to remove the statement: "Clinical developments should correspond to each situation/intended claim. In addition, particular attention should be drawn to the doses of each active substance in the fixed combination product. Each dose combination should be carefully justified and clinically relevant ~~(e.g. in cases when each component of the fixed combination has several possible dosages, dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination~~	Not accepted. The text does not state that dosages based on surrogate endpoints will not be approved; however, dosages that have shown benefit on hard clinical outcomes (if any) may be preferable.

[1] Where applicable

	~~than the dosages effective on surrogate endpoints only).~~"	
	(4) We should add: In the case, that the doses used in the FDC are identical to the doses used in the broad clinical setting and safety data generated with this dose are available, demonstration of comparability in the PK properties might be sufficient.	Accepted. Belongs to the section 4.4.1
	(4) The reasons why "*dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only*" are not scientifically justified, especially when surrogate end-points are validated and recognised by regulators (fixed combinations applying to this situation have been approved recently).	Not accepted. The text does not state that dosages based on surrogate endpoints will not be approved; however, dosages that have shown benefit on hard clinical outcomes may be preferable.
	(5) Paragraph 3: "…(e.g., in cases when each component of the fixed combination has several possible dosages, dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only)." The interpretation here is that in the development program of each of the components, some doses may have been studied against hard clinical outcomes and others only against surrogates. While that is correct, it's important to note that, sponsors may have selected doses for confirmatory studies based on doses targeting surrogate outcomes in earlier trials and only took one or two promising (and usually higher) doses forward. This latter scenario will appear to make the section quoted above inconsistent with section 4.1.2(a) (i). The dose appropriate (and perhaps lower) for use in the combo may have shown activity based on surrogate outcome rather than hard clinical outcomes. It is unclear what type of additional data/study (if any) the competent authority will request under such a scenario. First paragraph, line 4: patient compliance should be added to this list.	Not accepted. The text does not state that dosages based on surrogate endpoints will not be approved; however, dosages that have shown benefit on hard clinical outcomes may be preferable. Accepted.
2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**

	(8) With regard to combination pack, there should be consistency with the CMD (h) guidance stating that "combination packages should be distinguished from a fixed combination…." We would suggest rephrasing, taking a similar wording than the one adopted by the CMD(h) in its Q&A # 14 on combination packages[2] as the current wording is unjustifiably too restrictive. Combination packs should be allowed on basis of justified benefit to public health or increased user-friendliness for patients/consumers.	Not accepted.
2nd Paragraph Line 5	(1, 7) The acceptability of combination packs is defined through "clear public health benefit". It is not necessary to restrict the definition with additional criteria. It is suggested to reword the sentence as proposed: "Combination packs would ~~only~~ be acceptable ~~in very exceptional cases,~~ when there would be clear public health benefits for the treatment regimen…"	Partly accepted. The text will read: "Combination packs would only be acceptable in exceptional cases, when there would be clear public health benefits for the treatment regimen and/or compliance, taking into account the required justifications set-out in section 4.1 of this guideline. Applicants are therefore advised to consult with the relevant National Competent Authority/EMEA prior to submission, on the acceptability of the proposed combination pack."
3rd Paragraph Line 10	(1) To clarify the statement, it is suggested to provide an example to support "a new chemical substance which dissociates *in vivo* into two well known substances".	Not accepted. The sentence seems clear enough.
	(5) Paragraph 3: The guideline applies to an NCE that dissociates in vivo into "two well known active substances." I believe this should read "two or more..." But this sentence also begs the question, what does the guideline consider a "well known active substance"? the criticism of combination packs is in direct contrast to US guidance, example includes one for development of co-packaged marketed HIV products	"Two or more…" accepted.
3 LEGAL BASIS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1st paragraph, last line on page 3	(1) Clarification on the legal basis for this type of combination (i.e. a potential FDC of an NCE with an established substance) is welcome. However it would be useful to add clarification to the effect that such an application under Article 8.3 may, like any application, be based solely on the applicants' own tests and trials or be 'mixed' in the sense of also including cross-references to the literature or available 3rd party data.	The text will read: "In accordance with Article 10b of Directive 2001/83/EC: "In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3) (i),

[2] http://www.hma.eu/20.html#irfaq_19_9d311

	A suggested addition is thus proposed to clarify the situation: "…that combination shall be provided in accordance with Article 8(3) (i), but it shall not be necessary to provide scientific references relating to each individual active substance. ***Such an application under Article 8.3 may, like any application, be based solely on the applicants' own tests and trials or be 'mixed' in the sense of also including cross-references to the literature or available 3rd party data***".	but it shall not be necessary to provide scientific references relating to each individual active substance". … "In case of fixed-combination medicinal products containing one or more substances which have not been authorised in the EEA, an application according to art 8.3 of Directive 2001/83/EC should be made. In this case, results of non-clinical tests and clinical trials relating to the individual substances as well as on the combination should be provided, justified in the non-clinical and clinical overviews, and supported by scientific advice if appropriate".
3rd Paragraph	(1) Clarification is requested for the following statement: "*Applications for fixed-combination medicinal products submitted under Art 10b of Directive 2001/83/EC, should concern individual substances which have been authorised in the EEA via a Community or national procedure. In case of fixed-combination medicinal products containing one or more substances which have not been authorised in the EEA, an application according to art 8.3 of Directive 2001/83/EC should be made."* One interest of a FDC can be the possibility to decrease the amount of one/both active substance(s) in the FDC due to synergic effects between both active substances. Thus it should be reinforced that Art. 10b applications are based on active substances authorised and not on strengths of corresponding medicinal products. In addition, there should be the need to mention the data protection period – as full data will be needed if the innovator still has data protection. (1, 8)	The text will read: "In accordance with Article 10b of Directive 2001/83/EC: "In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3) (i), but it shall not be necessary to provide scientific references relating to each individual active substance". … "In case of fixed-combination medicinal products containing one or more substances which have not been authorised in the EEA, an application according to art 8.3 of Directive 2001/83/EC should be made. In this case, results of non-clinical tests and clinical trials relating to the individual substances as well as on the combination should be provided, justified in the non-clinical and clinical overviews, and supported by scientific advice if appropriate".
	(5) Paragraph 1: Cites Article 10b of Directive 2001/83/EC on the need for preclinical and clinical trials for only the combo where its components are authorized medicinal products. It is possible that this section of the guideline is clarified in the subsequently referenced document (Notice to Applicants); however, We are not sure if all competent authorities apply this provision of the Directive consistently. Moreover, there could be minor changes to the active moiety of the component. It's unclear from the guideline how the competent authorities would handle such potentially minor changes and if such compounds would be classified as NCE's.	The "minor changes" should always be fully justified. The revised text applies.
	(2) ***"In case of fixed-combination medicinal products containing one or more substances which have not been authorized in the EEA, an application according to art 8.3 of Directive 2001/83/EEC should be made".*** In cases where a new fixed dose combination product is comprised of one or more new chemical entities in combination with one or more previously authorised medicinal product(s), the guidance should be modified to indicate that full information would only be required for the new chemical	The text will read: "In accordance with Article 10b of Directive 2001/83/EC: "In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3) (i), but it shall not be necessary to provide scientific references relating to each

	entity/entities components and that it is not necessary to provide scientific references in Modules 4 & 5 or individual study summaries Modules 2.6 & 2.7 relating to previously approved active substances, where the applicant can provide a Letter of Authorisation to cross-refer to the previously submitted data. This will avoid a situation whereby applicants are otherwise required to re-submit full copies of all reports and individual study summaries in support of the previously authorised components. It is proposed that only new study reports and summaries related to the proposed fixed combination should be included in modules 2 to 5 of the MAA submission.	individual active substance". … "In case of fixed-combination medicinal products containing one or more substances which have not been authorised in the EEA, an application according to art 8.3 of Directive 2001/83/EC should be made. In this case, results of non-clinical tests and clinical trials relating to the individual substances as well as on the combination should be provided, justified in the non-clinical and clinical overviews, and supported by scientific advice if appropriate".
Page 4, 1st paragraph	(5) In situations where one of the active substances have been registered locally please confirm if is required to have a registration in all EU member states or will it be sufficient to have the active ingredient registered in some countries only	The judgement will be on the case by case basis. No general recommendation can be given.
4 MAIN GUIDELINE TEXT		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	(8) We propose to clarify that combination products, by decreasing the number of individual dose units are more patient friendly and simplify therapy which have for result to improve compliance (decreased likelihood to miss a dose, etc.).	Accepted.The text will read: "by decreasing the number of individual dose units, which simplifies therapy and improves patient compliance."
Section 4	(5) 4.1.1: This may be the correct place to recommend that a sponsor seek scientific advice early in development to map out a protocol design strategy 4.1.2b.: i. this "disadvantage" can apply to all pharmaceuticals and thus has little value here. Selection of dose for patients of different physical size may need to be considered. 4.2: Another occasion where the sponsor could be directed to seek scientific advice.	Accepted. The text will read: "A scientific advice from National Competent Authorities or the EMEA may be helpful in this respect"
Section 4.1.2.	(1) The section "justification" is unchanged whereas the executive summary (page 1) introduces a new concept i.e. FDCs for an intended indication defined as "*two closely related diseases like hyperlipidemia and hypertension*". Thus, the section justification should include this new concept.	Accepted.

	Editorial/Formatting of this section is not consistent as sub-bullets under "disadvantages" are not at the same level as those under "potential advantages". Please consider revision (either i. or •) Proposed change: ***c) <u>An identifiable patient group for which the combination of actives and doses is suitable therapy</u>.***	Accepted Text flue. Not accepted.
Section 4.1.2 Subsection a)	(1) The subsection a) describes potential advantages of FDCs with 2 possible options to improving the benefit/risk assessment. It is our opinion that another case can be taken into account, especially for antimicrobials, the reduced incidence of resistance. Thus we propose to add an additional item. Add: ***(iii) <u>reduced incidence of resistance</u>***	Additional item not accepted. The text will be modified as follows: "**a simplification of therapy** by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and improves patient compliance. This is also referred to as a "substitution indication". The improvement of patient compliance is considered especially important in situations where it may contribute reducing the incidence of resistance (e.g. HIV products, tuberculosis)"
Section 4.1.2 Subsection a) i	(1) In the section "addition or potentiation of therapeutic activities of their substances, which results in "a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile", in our view, " at higher dose" should be removed given there is still a benefit if doses are identical with a better safety profile. An addition to the existing text is thus proposed: - a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile Or - a level of efficacy above the one achievable by a single substance with an acceptable safety profile. ***<u>Or</u>*** - ***<u>a level of efficacy similar to the one achievable by each active substance used alone, but associated with a better safety profile"</u>***	Not accepted. This would mean that fixed combination is as effective as monotherapy (same doses as in combination), with less side effects (this is hard to believe)
Section 4.1.2 Subsection b)	(1) In this subsection entitled "a simplification of therapy" it is not clear what is expected. In addition, this subsection should mention the FDC intended for a substitution indication (meaning in patients already under stable dose of both components but as separate tablets). This kind of FDC is fully covering the	Accepted. The text will read: "**a simplification of therapy** by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and improves patient compliance. This is also referred to as a "substitution indication". The

	objective of simplification of therapy. Please consider addition of the proposed statement: iii. a substitution indication, a FDC indicated for patients already treated by the 2 components but as separate tablets and stabilised (a switch from separate tablets to a FDC)	improvement of patient compliance is considered especially important in situations where it may contribute reducing the incidence of resistance (e.g. HIV products, tuberculosis)"
Section 4.1.2 b)	(7) Disadvantages of fixed combination include: Proposal: Add: **Combination packs may not display all the disadvantages of fixed combinations.**	Not accepted. Unclear.
Section 4.1.3 General rules	(5) The inclusion of a substance to counteract an adverse reaction of another substance may be considered justified, but only if the adverse reaction is a serious or a commonly occurring one. This may require further explanation. The inclusion of a substance to counteract an AE of another substance may be considered justified, but only if the AE reaction is a serious or commonly occurring or compliance limiting one.	Accepted
4.1.3 **Justification** **General rules**	(2) ***"Each substance of the fixed combination must have documented contribution within the combination."*** This statement implies that each component of the fixed dose combination would need to be studied individually as part of the Phase 3 development programme for the fixed dose combination. This statement should be amended to accommodate scenarios where a fixed dose combination can be developed without the need for studying the individual components separately. This is of particular relevance in fixed dose combinations for the treatment of HIV infection where the combination can comprise of three or more active components. In such a case, data would not necessarily be available demonstrating the safety and efficacy of each individual component to the overall fixed dose combination product (e.g. for adjunctive therapies intended for use in combination). Based on this, the term "documented contribution" should be clarified to state what type of data is required.	Not accepted.
Section 4.1.3 1st paragraph 1	(1, 4) To improve the reading, we are suggesting an alternative wording: "***In principle the duration of action of the substances in the combination product should not differ significantly unless strong justification is provided. Examples where this would be required would be for substances intended to enhance absorption of co-formulated drugs or where the substances are intended to exert their effects successively***."	The text was revised as follows: "As a general rule, the choice of each substance in the fixed combination as well as the whole concept on which the rational for the fixed combination is based have to be fully justified; this can be achieved by taking into account mode(s) of action, pharmacokinetics, and treatment recommendations for a given clinical setting. Combinations, in principle, may not be considered rational if the duration of action of the substances differs significantly. This may not necessarily apply

		where it can be shown that the combination is clinically valid despite differences in this respect, e.g. if one substance is intended to enhance absorption of the other or where the substances are intended to exert their effects successively."
Section 4.1.3 4th paragraph	(1, 4) "The inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse ~~in undesirable~~ ***is not an appropriate reason for the combination***."	Accepted. The text will read: "The inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse is not an acceptable reason to develop a fixed combination".
Section 4.1.3 Last point	(6) Point reads that "Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations." This is a very general statement with a wide array of potential exceptions. As such, it does not provide useful guidance to readers. Proposal: Suggest either deleting this point or elaborating with examples of some of the potential situations that are being generalized here Last sentence page 4: this should be read as "is undesirable"	Not accepted. The statement seems clear enough.
Section 4.2 1st paragraph 1st sentence	(1, 4) We suggest rewording the text, as the statement is not correct if the intention is to mitigate a side effect: "The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect ***or improves the overall benefit risk in that indication (e.g. if intention is to mitigate a side effect)***"	Accepted The text will read: The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect or improves the overall benefit risk ratio by mitigating side effects.
4.2 **Indications**	***(2) The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect.*** The statement as written applies to fixed dose combinations where each individual active component in the fixed dose combination targets the disease condition. The statement should be extended to include fixed dose combinations where one component enhances the activity or decreases the risk of cumulative toxicity of the principle active component.	Accepted. The text will read: The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect or improves the overall benefit risk ratio by mitigating side effects.
Section 4.2 2nd Paragraph	(1) The dual target FDC, e.g. a FDC acting on 2 disease states frequently co-existing in patients or 2 closely related diseases, should be also introduced here.	Accepted

Section 4.2	(3) In the guideline it is stated that "An indication must be a well-recognised disease state….". This sentence seems to set limitations rather than making way for development of medicinal products for novel disease states. Proposal: It is proposed to delete the word "well-recognised".	Not accepted
Section 4.2 Last Paragraph Line 13 and 14	(1) This sentence (relating to first/second line treatment) will not apply to all therapeutic settings e.g. treatment of osteoporosis. Moreover, together with first-line and second-line, a third case may be added: substitution indication, in patients adequately controlled with the individual substances, given concurrently, at the same dose level as in the combination, but as separate tablets. This case is discussed in the Q&A document on the clinical development of fixed combination belonging to different therapeutic classes in the field of cardiovascular treatment and prevention. Thus, we propose to add this indication as an additional option: "Fixed combination medicinal products may be indicated in different situations: - In first line therapy, for patients receiving previously neither of the substances - In second line therapy, when monotherapy has not demonstrated a satisfactory benefit/risk ratio. ***<u>As substitution indication, in patients adequately controlled with the individual substances, given concurrently, at the same dose level as in the combination, but as separate tablets</u>"***	Accepted. The text will read: "Fixed combination medicinal products may be indicated in different situations: • in first line therapy, for patients receiving previously neither of the substances • in second line therapy, when monotherapy with either component has not demonstrated a satisfactory benefit/risk ratio • as a substitution indication, in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets".
Section 4.2 3rd §	(7) Fixed combination medicinal product may be indicated in different situations: - in first line therapy, for patients receiving previously neither of the substances in second line therapy, when monotherapy has not demonstrated a satisfactory benefit/risk ratio **or when compliance can be improved**.	Accepted. The text will read: "Fixed combination medicinal products may be indicated in different situations: • in first line therapy, for patients receiving previously neither of the substances • in second line therapy, when monotherapy with either component has not demonstrated a satisfactory benefit/risk ratio • as a substitution indication, in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets".
section 4.3 PK and PD studies	(5) **4.3 Pharmacodynamic and Pharmacokinetic studies** The possibility of interactions between the substances should always be considered. The applicant should submit data either to establish that such interactions do not occur or that they are clearly recognized and defined.	

	It would be helpful to suggest appropriate timing of such studies. e.g. at filing, prior to PhIII etc.	To discuss
Section 4.3.1	(1) As potential synergies between treatments can also be leveraged by separate administration, safety and efficacy information generated with separate substances can be used for filing a FDC to leverage the additional benefit of increased compliance and easier administration. Therefore for PD as well as safety similar requirements as getting a label for use in combination should be applied	
Section 4.3.2 1st paragraph	(1) The 1st paragraph states "*In general, the applicant must demonstrate that the various substances do not affect each others respective pharmacokinetic patterns"*, but in some instances the substances will affect each others PK patterns – e.g. in case of a combination with a booster -, and then it should rather be investigated to what extent the various substances affect each others PK patterns.	
Section 4.3.2 (Sentences 1 and 2) Pharmacokinetic studies	(6) The first 2 sentences are repetitive and could be condensed and clarified. "These interactions should be studied in healthy volunteers but also in patients if the disease modifies the pharmacokinetic of one substance and in high risk subgroups (elderly, patients with renal failure or hepatic impairment" Pharmacokinetic characterization of individual components of the combination could not have been well characterized in special population such as elderly or renal impairment etc. Therefore, if lack of clinically significant PK interaction is demonstrated in healthy volunteers between the individual drug entities, characterization of pharmacokinetic interaction in patients with hepatic or renal impairment would not be necessary. Also, considering the intrinsic nature of diseases and concomitant medications used for treatment these underlying condition, results from interaction studies performed in these patient populations would be confounded and would not be able to detect any subtle interaction. Suggest revising as follow: In general, the applicant must demonstrate that the various substances do not adversely impact each others respective pharmacokinetic patterns. We recommend replacing the existing text with: "demonstrate lack of	The text has been revised as follows: "This section covers the pharmacokinetic aspects of fixed dose combinations for immediate or modified release where applicable. The need for pharmacokinetic documentation depends on the type of fixed dose combination, as follows i) The new fixed dose combination (FDC) is a generic of an existing product. In this case the pharmacokinetic bioequivalence following the "NfG on the Investigation of Bioavailability and Bioequivalence" and the "NfG on Modified Release Oral and Transdermal Dosage Forms" is adequate. A BCS-based biowaiver is applicable here for immediate release formulations where all individual components of the FDC are considered eligible. ii) The combination contains known active substances and it is a substitution indication (i.e. use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) or the new FDC contains known active ingredients

	interactions in healthy subjects to assure lack of clinically significant interaction of individual components in these special patient population."	that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual mono-components and the marketing formulation (fixed combination). iii) One of the active substances is an NCE. This case should be treated as a New Drug Application and the full characterisation of the pharmacokinetic profile (including interaction studies and studies in special populations and patients) is recommended to be made using the combination (and not only with just the new mono-component). This may be especially important if the rationale of the fixed combination is based on an interaction (such as for ritonavir boosted protease inhibitors). For the latter two cases (ii and iii), the applicant should in general evaluate to what extent the various substances affect each others respective pharmacokinetic patterns (interaction) based either on previous knowledge or on experimental evidence. In some cases, a pharmacokinetic interaction (i.e. combination with a metabolism inhibitor) constitutes the rationale of the fixed combination. These interactions should normally be studied in healthy volunteers. If the application covers several strengths, then demonstration of bioequivalence study with only one strength may be acceptable. Biowaiver for an additional strength may be applicable when the conditions for this as detailed in the guideline on bioequivalence are fulfilled for all individual active substances. If the SPC recommends taking each component in fasting or fed states then one bioequivalence study is adequate according to SPC recommended condition. But comparative studies in the fasted and fed state are necessary for fixed dose modified release drugs following the recommendations in the NfG on Bioequivalence and NfG on Modified Release Drugs."
Section 4.3.2 Last paragraph	(1, 4) In general, it shall be clearly stated when the writer refers to a fixed dose combination where any of the substances has been approved. With respect to "interactions should be studied in healthy volunteers but also in patients…" the non-specification of the approval status of the substances intended for fixed dose combination leads to different interpretations ~~"These interactions~~ ***If none of the substances intended for a fixed dose combination is approved or these interactions are not clearly recognized and defined, interactions*** should be studied in healthy volunteers but also in	See revised text on PK.

	patients if the disease modifies the pharmacokinetics of one substance and in high-risk subgroups (elderly, patients with renal failure or hepatic impairment)."	
Section 4.4 (First sentence)	(6) Section states that fixed-combination product should concern individual substances which have been authorized in EEA. A potential scenario exists in which one component of the proposed combination product was judged to not provide sufficient efficacy or safety advantages over currently approved products and therefore was deemed not approvable in EU. However, in combination there could be synergistic efficacy which might justify the promise of the combination as a beneficial therapeutic product. Suggest revising as follow: Applications for fixed-combination medicinal products submitted under Art 10b of Directive 2001/83/EC, should in general concern individual substances which have been authorized in the EEA via a Community or national procedure.	This section has been moved to Legal basis.
Section 4.4 a)	(8) When the fixed combination corresponds closely to combinations that are already in widespread use **or when the fixed combination contains substances that are well-known and are used commonly together**, a well founded bibliographical data analysis could be submitted. Provided that the respective data from the simultaneous use are thoroughly and reliably documented, this analysis **may be sufficient for the justification of the efficacy and safety of the fixed combination** (instead of :"may be helpful in reducing the amount of clinical trials to be performed) and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination	Accepted Not accepted. What is suggested is that an approval of FDC may be based on bibliographical data only, without any PK study.
Section 4.4. b)	(3) It is suggested to add that it is advised to have a discussion and negotiation with the national competent authorities or the EMEA on how many safety and efficacy studies are to be provided.	Accepted. The sentence: "A scientific advice from National Competent Authorities or the EMEA may be helpful in this respect." has been added in the 4.1 Justification
	(4) In the event that one of the substances intended to be registered as component of a fixed-combination pharmaceutical form is being under examination as stand alone MAA, full safety and efficacy data in relation to the fixed-combination should be provided. Inclusion of data on the individual substances, including that one being currently assessed, is not required.	Not accepted. Either the substance is known (authorised) or not. See legal basis.
Section 4.4.1, *The proposed dosage regimen must be*	(4) The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant ~~*population subgroup*~~ and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone.	

justified- paragraph 1 paragraph 2	Comment: Delete the word significant population subgroup – change to <u>target population</u>. *("The multilevel factorial design …..…".)*: Not clear what the purpose of this paragraph is as it is located under the heading composition and dosage regimen. Is it related to study design or statistical analysis tools.	Accepted The factorial design is a tool for choosing the doses appropriate for the requested claim.
Section 4.4 Subsections a) & b)	(1) They are cases (e.g. Type 2 Diabetes) where the approval of the NCE is based upon clinical studies of this NCE as add-on to the standard treatment. In this case, it does not correspond to a "widespread use". The 2 compounds can frequently be co-prescribed and a FDC is usually welcomed in this population. However, the dossier usually required in this case is limited to the studies already performed with the free combination and a bioequivalence. This section should clarify the possibility of using existing trials of the co-administration of a NCE as add-on to standard/background therapy and a bioequivalence and without a dossier similar to a NCE	Accepted for a substitution indication
Section 4.4 Subsection b)	(1) Clarification Requested: We note for an "essentially new" FDC, the example when one of the active substances is a new chemical entity (NCE)/new active substance has been removed. Although this scenario is not very common, there have been recent examples where a NCE is only being commercialised in a FDC product. It is recommended to include this scenario in the examples as it was provided in the previous version. This would also be within the scope of Article 8.3 of Directive 2001/83/EC. Please change as follows: "When the fixed combination is essentially new (active substances ***<u>whose administrations are</u>*** not usually combined, unusual quantitative compositions of usually combined substances, or ***<u>one active substance is a new chemical entity</u>***), the data needed..…"	The revised text will read: "When the fixed combination is essentially new (active substances not usually combined or unusual quantitative composition of usually combined substances or one active substance is a new chemical entity), the data needed are similar to a new chemical entity in the situation where the fixed combination is to be proposed (first line or second line therapy). A full dossier will be needed for a new chemical entity in the fixed combination, and on the individual substances as appropriate. Existing experience with the substances will also be taken into account." Accepted
4.4.1 **Efficacy and Safety** Composition and dosage regimen	(2) ***"The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone."*** This statement requires further clarification as it again implies that each of the components in the fixed dose combination must have been studied individually in Phase 3. As commented above under section 4.1.3 for fixed dose combinations for the treatment of HIV, the safety and efficacy should	Not accepted. The general statement remains.

	be supported by clinical data on the fixed dose combination in the absence of complete (i.e. phase 3) safety and efficacy information on the individual components.	
Section 4.4.1	Clarification Requested: Please consider modifying the term "Composition" in the title. This section deals with dosage of individual active substances and the justification of the proposed dosing regimen; the use of the term "composition" may imply qualitative or quantitative compositions and may be confusing. Please consider changing the header as proposed: **"**4.4.1 ~~Composition~~ ***Dosage strengths*** and ~~dosage~~ ***treatment*** regimen**"**	Accepted.
Section 4.4.1 Paragraph 1 Paragraph 2	(1) It is proposed to revise the 1st paragraph for clarification: "The dosage of each substance within the fixed combination must be such that the combination is safe and effective for a significant ~~population subgroup~~ ***target population*** and the benefit/risk assessment of the fixed ***dose*** combination is equal or exceeds the one of each of its substances taken alone." It is not clear what the purpose of this paragraph is as located under 4.4.1 heading. Is it related to study design or statistical analysis tools? Please clarify.	Accepted
Section 4.4.2	(1) General comments for this section: **It would be valuable to include in this section the standard dossier requirements for each type of FDC (first line, second line, substitution or others). For example:** - Confirmatory clinical trials versus individual treatment (or reference therapy) are not necessary when the indication is only second line in patients inadequately controlled on one component - When the indication sought is only substitution (in patient adequately controlled on a stable dose of the components), a bridging bioequivalence study is sufficient especially when there is no change in the dose regimen A rewording is thus proposed: Remove	Proposal accepted. The text will read: "For the first line therapy indication (in patients previously receiving neither of the substances), the acceptance of such an indication (and corresponding development) for a fixed combination product will depend on recommendations for treatment and clinical practice in each therapeutic field. For the second line therapy indication, a trial in non-responders or patients insufficiently controlled with optimally dosed monotherapy, is recommended; patients should be randomized to a fixed combination versus optimal monotherapy and active comparator. In both cases, the development of a fixed combination should follow specific disease-related guidelines in the choice study design (severity of the disease at baseline, primary and secondary efficacy endpoints, study duration,

	~~Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible.~~ Add ***When the fixed-combination contains the same actives in the same doses as an established (registered) regimen of single entity products, a bridging bioequivalence and or PK study may be sufficient.*** ***When the fixed combination is intended for a substitution indication pharmacokinetic and (occasionally) pharmacodynamic data would generally suffice for this type of application.***	comparators). For a substitution indication (for patients adequately controlled with a stable doses of monocomponents), comparative pharmacokinetic data and (in some cases) pharmacodynamic data (e.g. different administration time) are generally considered sufficient."
Section 4.4.2 1st paragraph 1st line	(1) In specific situations, one singleton may be inactive in the targeted indication. In this situation, for ethical reasons, the combination may not need to be compared to its individual substances. It is thus suggested to amend the current statement: "Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible. ***In specific situations, one entity may be inactive in the targeted indication. This should be justified by pre-clinical, clinical or historical data. Nevertheless, in this situation and for ethical reasons, the combination may not need to be compared to each of its individual substances***."	This is a particular situation. General statement remains.
Section 4.4.2	(5) **4.4.2 Therapeutic Trials** Paragraph 1 and 2: "confirmatory clinical trials" - Doing parallel group comparisons of two or more components versus combo versus placebo versus reference treatment could be really daunting. The guideline should provide potential alternative designs to make such studies feasible, e.g., factorial designs.	Factorial design is recommended for the choice of dose(s).
Section 4.4.2	(3) In this section it is stated "Inclusion of a placebo group is recommended when feasible". This formulation is rather unclear and it is suggested to add more information on when and how to include placebo groups.	Not accepted. The statement seems clear enough.
4.4.2 **Efficacy and Safety**	(2) ***"Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible."***	

Therapeutic trials	It is unclear as to why confirmatory clinical trials are considered necessary for a new fixed combination that contains active substances that have been developed and/or approved for use in combination as separate agents and where the new fixed combination has been shown to be bioequivalent to the individual components (unless the fixed combination differs in Posology or Method of Administration). In addition to the comments above on the requirement to establish efficacy of each individual component prior to Phase 3 studies of a fixed dose combination (see Sections 4.1.1 and 4.4.1), this study design is also difficult and often infeasible. Demonstrating non-inferior safety and efficacy of a fixed dose combination to a regimen comprised of the individual components in most cases would require a very large number of subjects to meet a tight non-inferiority delta. If the study is conducted in a blinded manner, the reduction in pills afforded by a fixed dose combination is not captured in the study. The guideline currently offers no provision for scientific justification to be provided to support the absence of comparative data on the individual components versus the fixed dose combination on the grounds of safety and efficacy e.g. risk of resistance, sub-therapeutic dose of treating with an individual component alone. Proposal: "Clinical trials are required to confirm the efficacy and safety of all components of the fixed combination when used in combination for the proposed indication. A fixed combination may be supported by results of a bioequivalence study alone where clinical efficacy and safety studies have previously been conducted with the individual components in combination therapy and there is no change to the proposed Posology or Method of Administration. However, in cases where there is an absence of such data appropriate justification should be provided."	Accepted for a substitution indication. Not accepted;
Section 4.4.2, last sentence	(4) We do not consider it justifiable to require comparative clinical trials versus reference treatment for fixed combinations if this is not required for the individual substances.	Comparison to reference treatment may be necessary in order to put into the perspective the improvement obtained with the new combination treatment.
Section 4.4.3 1st paragraph	(1) A reference to the recently adopted CHMP Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005) should be added in this section. Besides, it would be helpful to mention whether an approach is acceptable as the one presented in the FDA Guidance for Industry on Nonclinical Safety Evaluation of Drug or Biologic Combinations of March 2006, with a 90-day bridging study in the more relevant species and a bridging embryo-foetal developmental study in the more relevant species.	Out of scope

	Regarding dose proportioning in the safety studies, it is stated that the studies have to be performed with the FDC in the proportion present in the product, but this does not take into account species differences (animal versus man) in e.g. sensitivity to particular toxicities or exposure ratios between the substances. This guidance would also improve if it would mention well-known exceptions, such as contraceptive pills with a fixed estrogen/progestogen ratio; if the optimal human ratio is used in a rat toxicity study, virtually only the estrogen component can exert an effect.	
Section 4.4.3 (first paragraph)	(6) This guidance calls for the combination to be administered to animals in the same dose ratio as used in the clinic. This is fine if the kinetics of each compound in animals is similar to that in humans, which is often not the case. If the kinetics are different, the result can be a large safety margin for one drug and a small safety margin for the other drug. In addition, this design does not allow for evaluation of additive or synergistic toxicities. Proposal: Please consider allowing as an option a more scientifically valid (although potentially technically challenging) approach, which would be to administer the drugs at doses that are intended to approximate the exposure ratio (not dose ratio) as that anticipated/achieved in the clinic. In order to detect synergistic or additive toxicities the study design may need to include each of the active substances at doses where minimal toxicity of each individual component as a monotherapy is evident, irrespective of whether those doses result in the ratio of the actives that is present in the intended commercial drug products. Nonclinical toxicity studies may be conducted prior to the availability of clinical data to determine a suitable clinical dose ratio for a combination. If this is the case, suggest that a study design in which scientifically justified dose ratios based on data available at the time should be considered as a reasonable approach.	Out of scope
4.4.3 **Efficacy and Safety**	***(2) "Safety studies in animals should, as a general rule, have been performed with the active substances of the fixed combination in the proportion present in the product. Such studies may not be required where all the substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented."*** The statement as written suggests a full non-clinical development programme is required for some FDC products. Reference should be made to	Out of scope

	the CHMP guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005) due to come into effect in August 2008. The statement should be aligned with this guideline which allows for bridging studies when appropriate.	
Section 4.4.3 (second paragraph)	(6) The second paragraph of this section indicates: "…. safety data on 300-600 patients for six months or longer will be required. The absence of such data should be justified by the applicant." Proposal: If there is not evidence of additive or synergistic toxicity, or evidence of new toxicity, PK or metabolic interactions in shorter term studies in animals or patients (less than or equal to 3 months), it is not clear why longer term safety studies would be required. It would be better to make this point rather than indicating "The absence of such data should be justified by the applicant."	The revised text will read: "In the case of fixed combinations intended for long term use, the amount of safety data to provide should follow recommendations given in specific disease-related guidelines. The absence of such data should be justified by the applicant". The revised text will read: "To what extent such safety information should be provided "ex novo" for the submitted dossier will depend on the available information for each of the components at the proposed doses given as either monotherapy or as a free combination. For pure substitution indications in case of FDC containing active substances with a wide therapeutic experience in the claimed indication at the proposed dosing schedule an abridged safety database from available experience may be considered. Otherwise, a self-standing database tailored to the claimed indication should be provided. In any case, the rationale supporting abridging available safety data to the final formulation should be adequately justified on the basis of the following considerations (see also under pharmacokinetics and efficacy sections): 1. Degree of knowledge of the active substances in the indication claimed. As stated above, any FDC containing a NCE should be considered as a NCE itself, and therefore be supported by a full dossier. 2. Proposed dosing schedule. Changes in dosage and/or posology regimen of any of the components that may lead to tolerability differences, specially linked to the switch from individual tablets to a FDC, should be adequately addressed. 3. Potential for PK and/or PD interactions leading to safety concerns. 4. Existing recommendations on specific safety issues (e.g. special populations, cardiac repolarisation and need for a TQT study) "
	(5) **4.4.3 Safety Aspects** Paragraph 1: The guideline states that animal studies may not be required where all components of the combo have been "extensively and safely used in humans in identical or very similar combinations for a long period…" While one seeks to avoid a prescriptive recommendation in a guideline such	Out of scope

	as this, we believe it would be helpful if the guideline provided a bit more clarity as to what constitutes extensive and safe use and for how long a period. To avoid any ambiguity we would prefer a statement/clarity about duration of chronic tox recommended as well as clarity about what time point combo studies for SA are needed for different phases of clinical development Page 6, section 4.3.3 Safety aspects, 1st paragraph It is stated that as a general rule no additional safety studies in animals will be required for the fixed dose combination. Please clarify whether this implies that information on the individual substances then will be required included in the application.	
4.4. Efficacy	(8) Point a) states that "*when the fixed combination corresponds closely to combinations that are already in widespread use, a well founded bibliographical data analysis could be submitted*". We agree with this statement and believe it should be clarified that this also encompass medicines which are commonly taken simultaneously in a given short-term pathology (e.g. combination to treat a common cold may include an analgesic with a decongestant which are commonly used together if not available in combination). Evidence of the simultaneous use should be provided by the applicant to complement the data on individual substances. This should also apply to the safety aspect in order to avoid unnecessary studies to be performed on animals.	The judgement will be on the case by case basis. General statement applies.
Section 4.4.3	(5) The term "combination" needs to be defined in this section as the nonclinical safety studies needed to characterize the combination will depend on the existing data and experience with the individual components of the combination Original Text: Safety studies in animal should, as a general, have been performed with the active substances of the fixed combination in the proportion present in the product. Proposed Addition: Combinations may involve: (1) two or more late stage entities (defined as compounds with significant late stage i.e. Phase 3 or greater clinical	Out of scope.

	experience; (2) one or more late stage entity(ies) and one or more early stage entities (defined as compounds with limited clinical experience, i.e. Phase 2 or less); or (3) more than one early stage entity. Depending on the situation, combination studies in animals may or may not be necessary to support clinical studies.	
Section 4.4.3	(5) The guidance regarding the timing and the scope of combination testing needs to be elaborated in greater detail. Original Text: Such studies may not be required where all substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented. Proposed Revision: ~~Such studies may not be required where all substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented.~~ The nonclinical studies required (type and number) to characterize the combination will depend on the toxicologic and pharmacokinetic profiles of the individual entities, treatment indication or indications, the intended populations of combination drug products in humans, and, in general, their timing would follow the timing of ICHM3 for the analogous studies. It is anticipated that for most combinations involving late stage entities, very minimal additional nonclinical studies will be required unless mandated by data gaps such as the possibility of a PK/PD interaction, toxicologic interaction, narrow margins of safety etc. Where there is adequate experience for the products having been co-administered in patients , such non-clinical studies may not be of value in support of initial fixed dose combinations, but may provide value for the overall safety assessment in support of large clinical trials or prior to marketing For combinations of a late stage entity(ies) with an early stage entity(ies), or two or more early stage entities, repeat-dose studies in animals may be recommended at the same time in drug development that such studies would be recommended to support clinical studies for products of one new active ingredient. If chronic studies per ICH had already been conducted for each individual component of a combination containing an unmarketed component, then a bridging combination study of 90 days only in the most appropriate species should be conducted to support long-term clinical studies or marketing, provided new, significant toxicological findings are not	Out of scope

	observed. (5) The guidance does not articulate a position on the aspects of genotoxicity, safety pharmacology, reproductive toxicity, or carcinogenicity studies. <u>Proposed Text:</u> Assessment of combination genotoxicity, safety pharmacology, reproductive toxicity or carcinogenicity studies are not considered of scientific value if the individual agents have been tested with current standards and are not generally useful in support of clinical trials or marketing. In those cases where the patient population includes WOCBP, and where there is evidence of mechanistic interaction of the agents, combination embryofetal studies should be considered. Provided the individual agents have been tested, the timing of such studies, if conducted, should be prior to marketing, otherwise it should be consistent with the timing of single agents.	
DEFINITIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	(1) For clarification, it is suggested covering in this definition the situation where a combination pack contains e.g. product "A" in tablet form and product "B" in a powder form. In addition, for clarification, please consider standardizing the terminology to "Fixed dose combination" rather than "Fixed combination" throughout the document. Finally, it is suggested to move the whole section at the beginning of the guideline to make clear what a fixed dose combination means: A 'combination pack' ~~consist of more than one medicinal product, or more than one pharmaceutical form of the same medicinal product,~~ ***<u>is</u>*** presented under a single (invented) name, where the individual products/forms are intended for simultaneous or sequential administration. ***<u>It can consist of more than one medicinal product or form containing the same or different actives.</u>***	Accepted. Definition were put after the introduction. The text will read: "A 'combination pack' consists if more than one medicinal product, or more than one pharmaceutical form of the same product, presented under a single (invented) name and in a single product package (e.g. box, blister pack), where the individual products/forms are intended for the simultaneous or sequential administration."
	(5) second paragraph: at the end of the sentence "…' presented under a single (invented) name,…" add after "name" the following {and in a single product	Accepted. The text will read: "A 'combination pack' consists if more than one medicinal product, or more than one pharmaceutical form of the same product, presented under a single

	package, e.g., box, blister pack}. This addition will better define physical packaging of the fixed combination when more than one component is involved.	(invented) name and in a single product package (e.g. box, blister pack), where the individual products/forms are intended for the simultaneous or sequential administration."
	(4) Suggestion for clarification only: We suggest to cover in this definition the situation where a combination pack contains e.g. product "A" in tablet form and product "B" in a powder form. Proposal: A combination pack is presented under a single (invented) name, where the individual products/forms are intended for simultaneous or sequential administration. It can consist of more than one medicinal product or form containing the same or different actives.	The text will read: "A 'combination pack' consists if more than one medicinal product, or more than one pharmaceutical form of the same product, presented under a single (invented) name and in a single product package (e.g. box, blister pack), where the individual products/forms are intended for the simultaneous or sequential administration."
REFERENCES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	It would be useful to complete reference list by adding the CHMP guideline on the non-clinical development of FDC EMEA/CHMP/SWP/258498/2005/ ***CHMP Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005)*** http://www.emea.europa.eu/pdfs/human/swp/25849805enfin.pdf	A non-clinical development is out of scope.