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SCIENCE MEDICINES HEALTH

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Submission of comments on 'Guideline on Clinical Development of Fixed Combination Medicinal Products' (EMA/CHMP/281825/2015)

Comments from:

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1. General comments

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1	The section on the **scope** of the guideline needs to specify: - the type of products exempted: Fixed combination products of vitamins, oligoelements and minerals should be accepted as being effective and safe considering that such active ingredients have a well-established medicinal use with recognised efficacy and an acceptable level of safety. This exemption shall be applicable to fixed combination products containing solely vitamins, oligoelements and/or minerals. - the type of products not covered but addressed by other existing EMA guidelines: Fixed combination of herbal substances / herbal preparations containing or not vitamins and/or minerals are covered by the existing “Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations” (EMEA/HMPC/166326/05).	Accepted. It is agreed that clinical development of fixed dose combinations composed of herbal products, vitamins, oligoelements and minerals is not covered in this guideline. The scope is updated with the addition of the following text: “ The clinical development of herbal fixed dose combinations as well as those composed of vitamins, oligoelements and minerals, are outside of the scope of this guideline. For information on herbal combination products, refer to Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations” (EMEA/HMPC/166326/05).”
1	Please note that for Global development programs, efficacy of FDC is usually demonstrated against the same	Partially accepted. The guideline clarifies that these are the patients who after being treated with an optimal dose for a sufficiently long period of

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	dose of the monotherapy component as that contained within the FDC. Clarification is requested that the term 'optimal' dose in regards to the monotherapy comparator arms refers to the same principles.	time do not respond satisfactorily. Moreover, the clinical data should demonstrate a favourable benefit-risk balance for the combination of active substances across all dose and strength combinations available in the fixed combination medicinal product.
1	In the last iteration of the guidelines (CHMP/EWP/240/95), guidance was provided for combination pack products (consisting of one or more medicinal products or forms of the same product presented under a single name and in a single product package and intended for simultaneous or sequential use). There is, however, no provision for combination packs in the proposed revision. Would it be possible to please provide some clarity as to what guidance documents should be consulted for combination packs in the future?	Accepted. Indeed, the current guideline under revision does not cover combination packs as these are not considered fixed dose combination medicinal products, as per the concept paper: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139482.pdf These do not fall within the scope of this guideline. Reference to combination packs is made in the Notice to Applicant, Vol. 2A, Chapter 1, section 5.5.
1	The proposed text provides considerable detail for prescription product development; however, it does not provide as much guidance for non-prescription products containing well-established actives. Given the extension of the proposed guideline to stretch across all legal bases, would it be possible to please provide more detailed guidance? Particularly, guidance would be helpful in the case of Article 10(a) "Literature"	Accepted. The guideline is applicable to products irrespective of the proposed legal status for prescription. The guideline does not make reference to any legal basis since this is the choice of the applicant and depends on the type of product and its development. The Guideline is structured depending on the different therapeutic scenarios (initial therapy, substitution, add-on, etc). The evidence base

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	or 10(3) “Hybrid” applications containing well-established combinations with considerable Post-Marketing Surveillance safety data on the single components or combinations (e.g. for new products containing combinations already covered by a Global Marketing Authorisation).	for each scenario can be substantiated either with own clinical trials, literature references of a mix of these. Evidence of combined use only will not suffice to establish the positive benefit/risk of a combination. In view of this, the scenarios foreseen in the guideline should be applicable to all types of products .
1	The proposed revision touches on the requirements for bioequivalence to demonstrate equivalence between the mono-constituents and the combination product; however, it does not currently provide guidance for those instances where the constituents of a combination would not function separately, therefore their efficacy as a mono constituent vs. in a combination would not be relevant. If possible, can further guidance be provided for such cases?	Accepted. Bioequivalence is a requirement to be demonstrated between (two or more) separate components and the fixed combination medicinal product. Whether the efficacy of the mono-components is proven separately or together should make no difference for this requirement. Section 4.3.C addresses the clinical requirements for combinations where one (or more) active substance has no individual efficacy in the targeted population.
2	EFPIA welcomes the release of the new draft Guideline on clinical development of fixed combination medicinal products EMA/CHMP/281825/2015. In summary, EFPIA highlights the below key criteria for a successful guideline and additional more specific enablers, which will be followed by more detailed line-by-line comments: The section on **scope** of the guideline needs to specify the type of products exempted: Fixed combination products of vitamins, oligoelements and minerals should be accepted as being effective and	Accepted. It is agreed that clinical development of fixed dose combinations composed of herbal products, vitamins, oligoelements and minerals is outside the scope of this guideline. Section 2 of the Guideline i.e Scope has been updated with the addition of the following text: “ The clinical development of herbal fixed dose combinations as well as those composed of vitamins, oligoelements and minerals, are outside of the scope of this guideline. For information on herbal combination products, refer to Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations” (EMEA/HMPC/166326/05).”

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	safe considering that such active ingredients have a well-established medicinal use with recognized efficacy and acceptable level of safety. This exemption shall be applicable to fixed combination products containing solely vitamins, oligoelements and/or minerals.	
2	The section on scope of the guideline needs to specify the type of products not covered but addressed by other existing EMA guidelines: Fixed combination of herbal substances / herbal preparations containing or not vitamins and/or minerals are covered by the existing “Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations” EMEA/HMPC/166326/05.	See above
2	It would be helpful to highlight the distinct features of a FDC containing new active substances only. In particular, Phase 3 studies should be designed to show efficacy relative to placebo and powered accordingly; i.e. the proposed 3-way design (A, B, A+B) would not suffice. In addition, differences in PK and intrinsic pharmacological characteristics between the components will be more critical, especially since patients will be simultaneously exposed to two new active substances. This does not apply to the two other scenarios for development of a FDC. It is highly recommended that the updated version on the FDC guideline describe the requirements for the different development stage of the monocomponents:	Partially accepted. Section 4.4 describes additional requirements for development of fixed combination medicinal products with new active substance(s). The sentence states: “Based on appropriate scientific justification, e.g. when the NAS is a PK enhancer, has no efficacy in the targeted indication (based on mechanistic and human PD data), or is added to improve safety of the main active substance, RCTs demonstrating efficacy of the NAS as monotherapy may be waived.” Clinical requirements for this scenario are described specifically in section 4.3 B (PK enhancer) and 4.3 C One (or more) active substance has no individual efficacy in the targeted indication. Combination therapy should always be justified, especially for combinations of new active substances. See e.g. section 1, and section 4 rationale: “For any fixed combination medicinal product, it is necessary to assess the potential clinical advantages of combination

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	• Two well-known and authorised active substances • One well-known and authorised and one entirely new un-authorised active substance • Two entirely new un-authorised active substance. This last group is part of the Summary scope, although not covered in the main text of the guideline.	therapy against the use of monotherapies, in order to determine whether the product meets the requirements with respect to efficacy and safety. It should be justified that the advantages of combination therapy outweigh its inherent potential disadvantages such as addition or strengthening of adverse effects, and the fact that fixed combination medicinal products may not always be easily adjusted to the need of individual patients."
2	Because of the range of new studies and/or bibliographic data that are used to support FDC applications, we feel that some mention of legal basis/dossier requirements is needed in the revised section 4 of the new draft guideline. For example, it would be helpful to know when the Article 8(3) mixed marketing application (Annex I, Part II, section 7 of Directive 2001/83/EC) may be relevant or where the applicant may be justified in taking a more minimal approach, and what that would comprise (*eg, case of substitution for existing mono-components where* ***clinical use in combination*** *is established by literature data*). Although we recognise why the new draft guideline does not address the requirements for combination packs, we feel that this needs to be addressed in a separate guideline. Combination packs are not prohibited in the EU. Section 5.5, Chapter 1, Volume 2A of NTA states that: "... in very exceptional circumstances, which must be considered on a case by case basis, the marketing of	Partially accepted. The current guideline is meant to focus on the scientific data required to support the safety and efficacy of fixed combination medicinal products, references to any specific legal basis have been intentionally removed in view of this. Any clarification regarding the choice of legal basis should be sought in the Notice to Applicants, Chapter 1. As per the concept paper, the current guideline does not address combination packs, as these fall outside its scope: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139482.pdf

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	distinct medicinal products in the same package may be indispensable for public health reasons...” It would be helpful if the EMA could develop a short guideline on what these “exceptional circumstances” might be.	
2	Fixed combinations of other administration forms than oral, e.g. parenteral, as all biopharmaceuticals are not covered. The guideline uses 'Fixed dose combination', but some combination products will be titratable rather than fixed dose. This should be reflected by deleting 'dose' throughout the text. Requirements for development including bioequivalence and confirmatory clinical trials of fixed combinations of other administration forms than oral, e.g. parenteral and including titrable injection medicinal products are missing. 'bioequivalence is in general required' - It would be helpful with elaboration on scenario for situations where bioequivalence may not be required to bridge to existing clinical data	Accepted. Terminology of “fixed combination medicinal product” has been agreed for use in the guideline, also in view of the definition included in Notice to Applicants, Volume 2A, Chapter 1 i.e. ‘The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called ‘fixed combination’.’. The scope of the guideline states the guideline is applicable to all products irrespective of administration route and dosage form. The demonstration of similar pharmacokinetics may be waived if all pivotal clinical data as described in sections 4.1 and 4.3 supporting the combined use are obtained with the actual fixed combination medicinal product formulation.
2	The guideline is focusing on FDCs with 2 components, industry would like to point out that for other type for FDC such as FDCs with 3 or more components additional guidance should be provided.	Accepted In principal, the requirements set out are also applicable to combination products with multiple components. The guideline is meant to be general and cannot go into defined therapeutic areas.

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	Design for FDCs with 3 components could be different, especially in disease areas where a triple combination is considered as a first line e.g. AIDS therapy combining a 2 nucleoside reverse transcriptase inhibitors (NRTIs) with 1 non-nucleoside reverse transcriptase (NNRTI) inhibitor (the latest EU clinical guideline supporting triple therapy for AIDS: EACS Treatment Guidelines, was updated in November 2014), while for other diseases a triple combination cannot be first line (e.g. triple therapy is not approved and not recommended by international guidelines for hypertension) (see also general comment below). We propose to list bifunctional molecules, such as bifunctional antibodies, that target two different receptors or molecular entities as out of the scope of the FDC guidance.	Section 2. Scope clarifies that '*The guideline does not apply to a single molecule active substance that affects multiple pharmacological targets (i.e. has affinity to multiple receptors involved in the desired therapeutic outcome)*'.
2	The guideline lists <u>general comments that are not disease specific</u> and this might be triggering some confusion. • The guidelines purpose is to provide general direction regarding FDCs to the reader who should then refer to disease-specific guidelines. It would be helpful to list the all available disease-specific guidelines that discuss the use of FDCs (e.g. hypertension, AIDS, COPD). These should be listed with the DMPK guidelines at the beginning (lines 74 to 82).	Not accepted. It is not in the scope of the current guideline to provide an exhaustive list of available specific therapeutic area guidance documents where use of fixed dose combination products could be relevant, especially as this could easily become obsolete and incomplete in the future. Hence, lines 72-74 are amended as follows: "This guideline should be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83/EC as amended, and other pertinent elements outlined in the EU, ICH and CHMP therapeutic guidelines, for example:…" The applicants are advised to keep up to date with newly developed and

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		revised guidelines in the relevant therapeutic areas.
2	Editorial comments • The acronym FDC is not used consistently. After the definition in line 32, FDC should be used throughout. • The spelling for 'mono-component/monocomponent' should be consistent throughout the document. In the comments/suggested changes, 'mono-component' has been used throughout.	Accepted. The terminology has been aligned throughout the guideline.
2	The guidance calls repeatedly for RCTs needed in order to approve the FDC. Could such guidance also be put into perspective of the guidance for CMA or in the broader context of adaptive pathways where these RCTs may only be provided in the context of specific obligations?	Not accepted. This proposal cannot be accommodated by the current guideline as it is out of the scope.
2	Please consider the creation of subsections in the introduction paragraph of section 4 to match with the basic requirements 1, 2 and 3 detailed in the grey box (Summary): subsection 1 "rational", subsection 2 "evidence base" and subsection 3 "Verification". In addition please move the therapeutic scenarios paragraph to the subsection 1. It is not detailed in the introduction paragraph of section 4 the HA expectation related to the basic requirement 3 "verification". If requirement 3 "verification" is related to	Accepted. Appropriate formatting has been used for the basic scientific requirements in section 4.

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	the demonstration of the bioequivalence (section 4.6), rewording may be helpful to improve the understanding.	
2	The paediatric regulation should apply and those concerned guidelines should be listed in the legal basis paragraph (Section 3).	Not accepted. The guideline is general in terms of fixed combination medicinal products and does not detail requirements for specific patient groups.
2	A dedicated section to common data requirements for the therapeutic scenarios detailed in the current sections 4.1, 4.2 and 4.3 is needed as a prerequisite of the specific requirements.	Accepted. Details were included in the mentioned sections.
3	Section 4.1 Clinical Efficacy /safety studies *"A randomised controlled trial (RCT) to prove superiority in inadequate/non-responders to single (or multiple) active components of the FDC is required to demonstrate that the FDC has greater* ***efficacy*** *in comparison with the respective mono-components. Superiority – or 'add on efficacy' can only be claimed to (mono)components to which patients have been demonstrated to be non-responsive and where the FDC has been shown to be more effective than treatment continuation of that (mono)component. A way to do this is by performing a 3-arm study comparing AB versus A versus B, in patients inadequately/not responding to A and/or B. A 2-arm scenario could be appropriate if available in vitro, preclinical and/or PD data show no contribution of the additional active substance to efficacy of the FDC, e.g. in*	Partially accepted. The first scientific requirement for a fixed combination medicinal product is to have a rationale for combined use of the active substances in the formulation. The guideline then continues to describe how the evidence base is generated to justify the positive B/R of the combination and contribution of the individual components. "*Part of the rationale for fixed combination medicinal products may be to optimise the use of the medicine in terms of (number of) doses administered and patient adherence, or to help prescribers optimise and/or implement treatment where use of multiple active substances is indicated. Such simplification of therapy is, however, insufficient by itself for a complete justification of a fixed combination medicinal product.*" This 'simplification of therapy' may be acceptable for approval of a fixed combination medicinal product provided the basic scientific requirements (section 4) are met. A greater efficacy from a fixed combination medicinal product over combined use of its components is neither required nor expected from a regulator's perspective per se.

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	the case of a PK enhancer (see section 4.3). When appropriate surrogates 161 or intermediate outcomes exist, efficacy data may be replaced by PD data." The requirement should not be that the FDC has greater efficacy than either A or B given as mono-components. This is not an equivalent comparison – it only shows how the FDC of A+B performs relative to either A or B. The comparison of interest when deciding to use a FDC is whether the FDC formulation is superior to the component drugs given as single drug formulations. The correct study is a 2-arm study to include a comparison to show how the FDC of A+B performs relative to A+B given as single drug formulations/ mono-components. The 3-arm study with comparison against either A or B alone takes no account of the possibility that A and B may interact (synergistically or detrimentally) when combined in a single dose form and that in a FDC they may actually have less or more efficacy compared to A + B given as single drug formulations/ mono-components. This is critically important from the efficacy perspective – it is necessary to know exactly what the 'true' comparison yields so that patients and prescribers alike understand the true state of play. Comparisons with A and B individually might also be undertaken but these are not the core point which should show how the FDC compares to A and B taken	

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	together as single drug formulations /mono-components. The consideration for DDI studies in the pharmacokinetic section is insufficient to take account of actual clinical effects. The document takes no account of WHO guidance on FDCs (TRS929, Annex 2, 2005).	
4	Reference to duration of trials as mentioned in therapeutic guidelines is made (e.g. line 163-164). It would be worthwhile to include whether long-term efficacy and safety studies would be required for FDCs, when such information (especially lack of long-term adaptation and lack of side effects unique to long-term treatment) would already be available for the mono-components.	Not accepted. Given that the duration of trials is specific for each therapeutic area, this general guideline will not make specific recommendations. Acceptability to replace long term safety and efficacy data with the combination with data available for the mono-components would require scientific assessment and would have to be looked at on a case-by-case basis.
4	The therapeutic strategy of a FDC where one component alleviates some adverse effect of the other component, but does not contribute to (or increase) efficacy of the other component, is missing at least in the initial parts of the guidance. It is mentioned in fact as a sub-strategy in line 234 and the 3rd bullet on p11. Thus this scenario should be added throughout the document (see some particular suggestions below).	Accepted. This scenario is now described throughout the guideline.
5	The EMA guideline does not address the situation where component B enhances/improves the efficacy of component A but where component B alone is not effective for the intended indication.	Accepted. This is now described in section 4.1 under 'Improved Safety'. "*If the rationale of the fixed combination medicinal product is to improve safety, an RCT should be performed to demonstrate improved safety /tolerability of the fixed combination medicinal product, versus the*

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	In this case it can be expected that component A will require a full development program whereas component B would not require study as a single drug beyond initial phase 1 safety studies. Likewise in this situation dose-response would only be determined for component B in combination with component A. In the same way it would not be valuable to have a phase 3 with drug B alone and the combination AB would be compared to component A in a superiority trial (e.g. a two-arm design comparing AB versus A may be sufficient to demonstrate that component B contributes to the activity of the combination). This can be addressed as part of the discussion on line 202: An efficient way to evaluate this is by performing a 3-arm study comparing AB versus A versus B… **or a 2-arm scenario could be appropriate versus A when one of the two components applied alone has no or minimal activity for the intended indication.**	*single active substance(s), utilising explicitly defined adverse event(s) as co-primary endpoint(s). Another co-primary endpoint is needed to establish that there is no loss of efficacy, compared to administration of the single active substance(s).* *Two sub-scenarios are envisaged.* ***The first sub-scenario is where an active substance is added to counteract or ameliorate adverse events caused by the other active substance(s) in the fixed combination medicinal product. In this case a comparator arm with the active substance added to enhance safety may be omitted****, if available in vitro, preclinical and/or PD data show that this substance does not have efficacy in the targeted indication by itself. The second sub-scenario is where the fixed combination medicinal product consists of doses that are below those at which the individual active substances are licensed or used. In this scenario a comparison should be made of the fixed combination medicinal product against an optimal dose of the individual active substances*." (emphasis added)
5	In both the 'Add-on indication' and 'Initial treatment' scenarios, this guideline indicates that a 3-arm study comparing AB versus A versus B will in general be suitable for establishing superior efficacy or improved safety. However, prior to any comparative efficacy/safety trial, the contribution of each mono-component should either be understood or alternatively be evaluated in a pharmacodynamic study including multiple dose levels to	Partially accepted. The value of choosing the proper dose of the active substances is described throughout. Moreover, both sections 4.1 ('Add-on indication') and 4.3 (Initial combination treatment) have been extensively rewritten. The value of factorial design studies for designing phase 3 is specifically mentioned in section 4.1 and applies equally to 4.3. "*A factorial design study may support the pharmacological additive effects or synergism of the proposed combinations, especially when different effective dose*

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	document the therapeutic rationale and therapeutic window of both components. This is a logical development option, comparable to the practice of conducting a phase 2 dose-range study prior to conducting an efficacy/safety study with one or two selected doses when developing a mono-drug. In addition, the case may be that a comparative efficacy/safety study contributes little to the therapeutic rationale for an FDC, since it does not allow assessing whether the effects of the FDC could be achieved with a different dose of one of the mono-components instead. Thus an efficacy/safety study alone may be insufficient for justifying the therapeutic rationale for the FDC. To address this, we propose the following insertions: on line 149 after '..dose levels of the monocomponents exist': *When sufficient dose levels are studied in patients, these data can provide the therapeutic rationale for the selected doses in the clinical efficacy/safety trial.* Under '4.3 Initial treatment', on line 202: '*Alternatively, in the case that an adequately designed pharmacodynamic study in patients provides a strong therapeutic rationale for the FDC at the selected doses, this can be evaluated by comparing AB versus A or placebo or standard of care.*' Lastly, establishing efficacy or safety benefits of the FDC in a pharmacodynamic study would align the guidance on this point with the FDA guidance 'Codevelopment of Two	*levels of the individual active substances exist. A factorial design study with pharmacodynamics endpoints that includes all dose permutations may reduce the need for certain dose steps in studies of patients with insufficient response, e.g. a waiver for some potential dose steps in studies of clinical efficacy and safety. When sufficient dose levels are studied in patients, these data can provide the therapeutic rationale for the selected doses in the clinical efficacy/safety study(ies)*." In general, in phase 3 studies the added value of combination therapy should be confirmed over administration of single active substances. A comparison against SOC may be acceptable in some situations if sufficiently justified. See section 4.1: "*In certain therapeutic areas there*

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	or More New Investigational Drugs for Use in Combination' from 2014, which states 'If findings from in vivo or in vitro models and/or phase 2 trials adequately demonstrate the contribution of each new investigational drug to the combination, phase 3 trials comparing the combination to SOC or placebo generally will be sufficient to establish effectiveness.'. We suggest adding similar wording into the present guideline.	*may be a need, or it may be considered more appropriate, to compare the combination of active substances against an established standard of care product. This product would, in that case, usually be of the same therapeutic class as A or B and with an established similar performance to allow the add-on effect of the second active substance to be quantified and should be justified based on appropriate specific clinical guidance. The contribution of each active substance to efficacy is expected to be demonstrated.*" A comparison against placebo is not usually considered appropriate.
5	The Draft Guideline does not discuss data exclusivity in respect of fixed combination products in case of one or two authorized products.	Not accepted. The proposed regulatory discussion on data exclusivity is outside of the scope of the scientific current guideline. Please refer to Notice to Applicants, Volume 2A, Chapter 1 instead.
6	EUCOPE welcomes the clarifications included in the 'Draft Guideline on clinical development of fixed combination medicinal products' and has no further comments on its content. The updated guidance does not address the development of combination products based on approved active ingredients which are, included in currently approved/marketed combination products regarded as the standard of treatment, but in a new combination and in a new combination pack. The guideline only seems to recognise new combination products that use approved active ingredients from currently approved/marketed mono-therapies only, new	Not accepted. As per the concept paper, the guideline under revision does not address the combination packs, as these are outside its scope : http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139482.pdf Reference to combination packs is made in the Notice to Applicant, Vol. 2A, Chapter 1, section 5.5. The additional requirements for fixed combination medicinal products with new active substances are described in section 4.4.

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	combination products that use new active ingredients (not previously authorised in a medicinal product) or generic combinations using the same combination as approved previously.	
6	The updated guidance only discusses improvements in safety or efficacy and does not mention improvements in patient acceptability, compliance, palatability or physical improvements in the product delivery as examples.	Accepted. Most of these improvements would be interpreted as 'simplification of therapy' and are described in the guideline in section 4 subheading 'rationale'. Improved palatability and /or physical improvements may require usability studies, and safety of any added components will have to be justified.
7	CORS welcome this update, since modern pharmacotherapy often involves simultaneous treatment of more than one target. We want to bring attention to the fact that the example of new drug combinations with marketed products aimed for other therapeutic indications than both components originally were approved for, are not described. Thus, we think it is relevant to stress that for new drug combinations where one or all of the constituents of the combination will actually be directed to a new therapeutic indication should have a clinical development path that focuses on exploring the efficacy/safety/PK of the combination and not the individual compounds characteristics of this, ie. it should be the 2-arm scenario and not the 3-arm where comparisons are made to the	Accepted. This situation is addressed in section 4.3, section c (One (or more) active substance has no individual efficacy in the targeted indication). Clinical requirements are described specifically in section 4.3 c (One (or more) active substance might have no individual efficacy in the targeted indication). Having no individual efficacy is however not the same as not being authorised in the indication. It would have to be demonstrated that there is no individual efficacy e.g. based on mechanistic and human PD data.

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	mono-treatment. Arguments calling for this is that none of the mono-treatments are authorised for the new indication hence there are no labels and no official (clinical) dosing directions established. In this context, such a direct comparison would have a very limited value. This does not mean that a proper dose range finding with each compound in combination is not needed. It should be done with the combined drug formulation and as a factorial design but without the mono treatment arms. Phase III should cover the same requirements as set for an NCE. The safety assessment requirements, however might be reduced based on the obtained characteristics for each of the compounds in the combination. Further we miss description of other administration forms than oral e.g. biopharmaceuticals for parenteral use. Also we miss a more extended description of the requirements For: a) two well-known active substances authorised for the same or other indications than the indication for the new FDC; b) one well-known and authorised and one entirely new un-authorised active substance; c) two	Combination therapy should always be justified, especially for combinations of new actives or known actives in a new indication. See e.g. section 1, and section 4 rational: "*For any fixed combination medicinal product, it is necessary to assess the potential clinical advantages of combination therapy against the use of monotherapies, in order to determine whether the product meets the requirements with respect to efficacy and safety. It should be justified that the advantages of combination therapy outweigh its inherent potential disadvantages such as addition or strengthening of adverse effects, and the fact that fixed combination medicinal products may not always be easily adjusted to the need of individual patients*." Section 2 Scope now states: "The guidance applies primarily to small molecules irrespective of route of administration and dosage form (immediate versus modified release), but the general principles also apply to biological products." Section 4.4 describes additional requirements for development of fixed combination medicinal products with new active substance. In the last sentence: "Based on appropriate scientific justification, e.g. when the

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	entirely new un-authorised active substances.	NAS is a PK enhancer, has no efficacy in the targeted indication (based on mechanistic and human PD data), or is added to improve safety of the main active substance, RCTs demonstrating efficacy of the NAS as monotherapy may be waived." Clinical requirements for this scenario are described specifically in section 4.3 b (PK enhancer) and 4.3 c (One (or more) active substance has no individual efficacy in the targeted indication). And also here combination therapy should always be justified, especially for combinations with new actives. See e.g. section 1, and section 4 rational: "*For any fixed combination medicinal product, it is necessary to assess the potential clinical advantages of combination therapy against the use of monotherapies, in order to determine whether the product meets the requirements with respect to efficacy and safety. It should be justified that the advantages of combination therapy outweigh its inherent potential disadvantages such as addition or strengthening of adverse effects, and the fact that fixed combination medicinal products may not always be easily adjusted to the need of individual patients*."
8	The SÚKL welcomes the Draft Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/281825/2015). However, we have additional comment regarding the section that sets requirements for applications in so called substitution indication. One of these requirements is demonstration of bioequivalence (BE) of the FDC versus mono-components taken simultaneously. Taking into account the fact that the revisited guideline on FDC is independent of chosen legal	Accepted. The potential risk of 'bioequivalence drift' is now addressed in section 4.5 generic medicinal products. "*Also, for generic fixed combination medicinal products it needs to be verified that the evidence base that may have been generated for the reference product with individual active substances (rather than with the fixed combination medicinal product, to which reference is being made) applies to the generic fixed combination medicinal product. In this case two pharmacokinetics bridges may need to be built, one between the reference fixed combination medicinal product and its active substances*

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	basis (as stated in the introductory part of the guideline) this generally accepted prerequisite (resulting from the meaning of substitution indication) is expected to be required across various legal bases. This approach is scientifically sound and endorsed, but the potential risk of “bioequivalence drift” for future generic applications referring to the FDC products with substitution indication should be eliminated. This arises from the fact that FDC indicated for a substitution indication only (authorized primarily on BE study against monocomponent formulations) may become reference products for subsequent generics. The subsequent generics referring to the FDC thus in fact become products based on two subsequent BE studies from the original monocomponent formulations, which generates unacceptable risk of bioequivalence drift. In case of authorization of a generic product with reference to already authorized medicinal product with substitution indication (authorization based on the bioequivalence study (BES) which is in line with the draft guideline on FDC), this theoretical worst-case scenario PK difference can be up to 95.31% between the generic FDC and generic mono-component product (for detailed calculations please see Annex I).	*and one between the generic and reference fixed combination medicinal product. A justification should be provided why ‘drifting’ of bioavailability is not considered relevant and hence why the original demonstration of efficacy and safety is relevant to the generic.*”

Stakeholder number	General comment (if any)	Outcome (if applicable)
	Therefore, abridged applications referring to FDC with substitution indication should demonstrate the same level of BE proof towards original monocomponent formulations, although such a requirement for BES with mono-components is against the essential principle of abridged applications, where bioequivalence with reference medicinal product (in this case FDC product, not mono-components) is required. Moreover, the bioequivalence study with reference medicinal product (ie. FDC with substitution indication) is not scientifically needed for generic products referring to FDC with substation indication, provided BE with monocomponents is shown. This would only create unnecessary clinical testing in healthy volunteers. Therefore we propose that this issue of the possible bioequivalence drift between monocomponent reference medicinal products and FDC generics inheriting substitution indication should be addressed in this guideline or in the Guideline on the Investigation of Bioequivalence. **Annex I** Let us suppose that target PK parameter lie within the most common range 0.8-1.25 and negligible uncertainty (given by 90% confidence interval) is associated with	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	point estimate of ratio based on ANOVA model as stated in bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, section 4.1.8 Evaluation and its part Statistical analysis). In the following paragraphs we consider following drugs and their mean bioavailabilities: - reference drug: two monocomponents o 1st monocomponent has mean bioavailability R1 o 2nd monocomponent has mean bioavailability R2 - first test drug: generics to individual monocomponents for reference drug o 1st monocomponent has mean bioavailability T1 o 2st monocomponent has mean bioavailability T2 - second test drug: fixed combination generic to reference drug o 1st monocomponent in fixed combination has mean bioavailability TF1 o 2st monocomponent in fixed combination has mean bioavailability TF2 - third test drug: “generic from generic”, i.e. fixed combination generic to second test drug o 1st monocomponent in fixed combination	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	has mean bioavailability TFF1 o 2nd monocomponent in fixed combination has mean bioavailability TFF2 At first, let us consider extreme cases of bioequivalence for first test drug and second test drug, both with respect to reference drug. If T1/R1 = T2/R2 = 1.25 then first test drug has 25% higher mean bioavailability than reference drug. If TF1/R1 = TF2/R2 = 0.8 then second test drug has 20% lower mean bioavailability than reference drug. Relative difference between first test drug and second test drug via reference drug is (T1/R1)/(TF1/R1) = T1/TF1 = 1.25/0.8, analogously (T2/R2)/(TF2/R2) = T2/TF2 = 1.25/0.8. This “ratio of ratios” equals to 1.5625 and tells us that first test drug can have theoretically up to 56.25% higher mean bioavailability than second test drug, which is similar to switching from one generic formulation to another one. At second, let us consider extreme case of bioequivalence between second test drug and third test drug where third test drug has 20% lower bioavailability than second test drug, i.e. TFF1/TF1 = TFF2/TF2 = 0.8. What is then relative difference in mean bioavailability between third test drug (“generic from generic”) and first test drug (“generics to monocomponents”)? The answer lies in relating mean bioavailability for third test drug to	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	mean bioavailability for reference drug because mean bioavailability for first test drug was previously also related to mean bioavailability for reference drug. Ratio of mean bioavailability of third test drug and reference drug is given as follows. We know that TFF1/TF1 = 0.8 (relative difference between mean bioavailability of third test drug and second test drug) and TF1/R1 = 0.8 (relative difference between mean bioavailability of second test drug and reference drug). Thus, TFF1 = 0.8*TF1 = 0.8*(0.8*R1) = 0.64*R1 (relative difference between mean bioavailability of third test drug and reference drug). Further, we know that T1/R1 = 1.25 (relative difference between mean bioavailability of first test drug and reference drug) which implies R1 = T1/1.25. Putting equations TFF1 = 0.64*R1 and R1 = T1/1.25 together with respect to mean bioavalability R1, we obtain TFF1 = 0.64*R1 = 0.64*(T1/1.25) = 0.512*T1, so T1 = TFF1/0.512 = 1.9531*TFF1. Analogic calculation leads to expression T2 = 1.9531*TFF2. Thus, first test drug can have theoretically up to 95.31% higher mean bioavailability than the third test drug.	
9	Mentioning other relevant guideline is very welcome. Issues of those guidelines should be stated if this guideline must be read differently for FDCs than stated in the guideline or if something needs to be highlighted	Not accepted. The current guideline sets out general principles of fixed combination medicinal products clinical development. Specific aspects of fixed combination medicinal products for individual therapeutic areas are set out by additional guidelines and should be followed.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	especially for FDCs.	
9	Please note that for Global development programs, efficacy of FDC is usually demonstrated against the same dose of the monotherapy component as that contained within the FDC. Clarification is requested that the term 'optimal' dose in regards to the monotherapy comparator arms refers to the same principles.	Accepted. The guideline clarifies that these are the patients who after being treated with an optimal dose and for a sufficiently long period of time do not respond satisfactorily (see section 4.1).
10	Galapagos welcomes the opportunity to comment on this revised draft guideline on clinical development of fixed combination medicinal products (EMA/CHMP/281825/2015). Galapagos has one general comment on the draft guideline text. It is acknowledged that any fixed dose combination (FDC) requires adequate pharmacological and medical rationale to justify the combination. In the situation whereby the patient is to be treated with FDC immediately (section 4.3, lines 184-246) and in the examples in the Annex of the draft guideline, various acceptable approaches and combinations are described. In these examples the rationale for the combination in terms of improved efficacy or safety is demonstrated through comparison of the FDC versus the effects	Accepted. The requirements for this scenario are described in section 4.3 and more specifically in section c titled "One (or more) active substance has no individual efficacy in the targeted indication." Though it would have to be demonstrated that the monocomponent does not have any efficacy in the indication i.e. based on mechanistic and human PD data. Of note, the guideline can not provide guidance on individual products or developments.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	achieved by the individual monocomponents. Few exceptions are listed in case it is established that monotherapy will not be adequate or appropriate to reach the desired effect. However, none of the described examples account for FDC products whereby the pharmacological modes of action of the respective components are inherently interdependent in such manner that none of the monocomponents triggers a clinical effect on its own. As such, including monocomponent arms in clinical studies would not be ethical. A concrete example is provided in CFTR protein modulator therapies developed for treatment of cystic fibrosis (CF). CF is caused by mutated CFTR gene which encodes an ATP-binding transporter class ion channel formed by the CFTR protein, embedded within the membrane of epithelial cells. Within the CF population, a specific mutation known as F508del is by far the most frequently occurring. To restore F508del defective CFTR function, stability defects in several domains of the CFTR protein need correction, and to date, a single molecule that can do that has not been found. As a result, the therapeutic strategy necessarily relies on a combination of different types of molecules with interdependent mode of action, i.e. so-called corrector and potentiator molecules. Corrector molecules bind to CFTR during synthesis, facilitate its folding and stability, and ensure it	Still, the principle of multicomponent fixed combination medicinal products is well established in e.g. the field of HIV/AIDS as acknowledged in the guideline. Scientific advice is recommended for any clinical development programmes of multicomponent (i.e. more than two) fixed combination medicinal products, especially in therapeutic areas without precedents.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	can become expressed at the cell surface. Nonetheless, the CFTR protein that is able to reach the cell membrane doesn't work well and therefore potentiator molecules are needed to enhance the gating function of CFTR when present at the cell surface. Separate administration of either a corrector or a potentiator molecule will not produce any clinical effect. As such, separate testing or up-tiration of monocomponents is not appropriate. Galapagos is of the opinion that this clinical reality is not sufficiently addressed in the draft guideline and guidance for an acceptable approach to justify such combination can greatly facilitate product development, especially as triple or even quadruple FDC products are coming to age.	
11	We propose that there is an important potential role for FDCs that is not sufficiently addressed in the current guidelines. Specifically, the role of FDCs in reducing undertreatment and improving long-term adherence among currently undertreated patients. This reflects the important potential role of FDCs in overcoming physician inertia and/or patient-related barriers to the prescription and continuation of recommended medicines long-term. We suggest therefore that a fourth category of clinical use is defined: "step-up therapy in patients who are currently not receiving recommended medicines" To provide some more background, substantial research	Partially accepted, This is outside the remit of the regulatory authorities as it pertains more to quality of care and clinical practice improvement strategies. Nevertheless, in Section 4 rationale, this potential use of fixed combination medicinal products is acknowledged; "*Part of the rationale for fixed combination medicinal products may be to optimise the use of the medicine in terms of (number of) doses administered and patient adherence,* ***or to help prescribers optimise and/or implement treatment where use of multiple active substances is indicated****. Such simplification of therapy is, however, insufficient by itself for a complete justification of a fixed combination medicinal product.*" (emphasis added)

Stakeholder number	General comment (if any)	Outcome (if applicable)
	indicates that many patients with major chronic conditions do not receive recommended medications long-term, despite having clear indications for such treatment. This can be due to multiple different and inter-related factors, which are at least partly remediable with better access to FDCs. First, and of increasingly recognised importance, are barriers to starting (or re-starting) recommended therapy – FDCs could provide a way to overcome physician inertia, or overcome patient-related resistance to being prescribed multiple different medications. Second, FDCs can help overcome barriers to long-term adherence by addressing many patient-related factors, such as improved regimen simplicity, reduced prescription charges, and preference to take fewer pills. In short, for reasons unrelated to pharmacological efficacy or safety of the component medicines, FDCs may provide a simpler, quicker, more affordable and more acceptable way for under-treated patients to be stepped up to recommended medications and to stay on such treatment long-term. Patient-related and physician-related factors predisposing to under-treatment and reduced long-term adherence are ubiquitous and inevitable – just because they are challenging to measure and define, does not we would suggest mean that they should be ignored. Recent research suggests that overcoming inertia to	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	begin (or restart) recommended treatment may often be more important than the well-recognised ability of FDCs to improve adherence compared to separate component medicines. For example, three recent trials compared FDC-based care to usual care among patients for whom there was a clear indication for statin, aspirin and blood pressure lowering medicines.1-3 However, as is the norm in all clinical situations, just because an indication exists, that does not guarantee that all patients were taking those medications: about one-third of the patients in these trials were not taking all indicated medicines at baseline. FDC-based care led to a much larger benefit in adherence among those who were initially under-treated, compared to patients who were not receiving all recommended treatments at baseline. There was an increase in treatment rates in both groups after randomisation, but this was much greater in the FDC group. However, for patients already taking all recommended medicines at baseline ("substitution" population) – there was only a very modest improvement in adherence with allocation to a FDC-based care. These trial results clearly indicated that an FDC was an important tool in 'stepping up' patients on to recommended treatment, and out-performed standard approaches using separate component medicines. We note that the current draft of the guidelines notes	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	that an acceptable FDC could have “two or more active components with different pharmacodynamic effects, and a different indication than the monocomponents, but where the combined use of the active substances is based on valid therapeutic principles (e.g. an FDC containing an analgesic and anti-emetic agent in the treatment of migraine, or an FDC with a cholesterol-lowering agent and an antihypertensive with the ultimate aim to prevent (re-) occurrence of cardiovascular events).” We note that this proposed ‘step-up therapy’ use of an FDC does not fall in to the three categories mentioned in the current draft EMA Guidance: 4.1 Treatment of insufficiently responding patients (‘add-on indication’) – is only relevant to conditions for which ‘response’ can be measured, such as blood pressure. For a patient who has had a myocardial infarction, one institutes therapy with a statin, aspirin, beta-blocker and ACE inhibitor routinely for most patients to prevent future cardiovascular events; one treats based on the clinical history, not on a measurement of response 4.2 - straight substitution – is not relevant, because, by definition, patients with problems with initiating and/or adhering to recommended treatments would not be on	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	the right drugs in order to have a straight substitution. The essence of the problem is that there are barriers to initiating and continuing such treatment; and previous trials have shown this patient group has relatively little to gain from FDCs, at least in comparison to step-up therapy 4.3 Initial Treatment – could be relevant, but more commonly the requirement is 'step-up substitution' ie. replacement of current partial therapy with an FDC containing more or all of the recommended medications. For example for a patient with a previous myocardial infarction who was just taking aspirin and a beta-blocker, swapping current treatment for an FDC containing aspirin, statin, beta-blocker and ACE-inhibitor therapy. **Proposed change** We therefore propose a fourth possible use of FDCs: 4.4 "step-up therapy". Use of an FDC among patients not currently taking all recommended medicines, as a means to overcome barriers to initiating and continuing adherence to recommended medicines. The indication would be "patients with a clinical requirement for all the component medicines of the FDC at the given doses."	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	Of importance, this does not require prior stabilisation on the same drugs at the same doses. We also note suggested use of the term 'recommended medicines' and 'clinical requirements' rather than indicated medicines. This is because current labelled indications for generic medicines can be decades out of date since there is no current system to update these indications when evidence emerges of new indications. For example, every clinical guideline recommends beta-blockers for patients following a myocardial infarction, but almost all labels for appropriate beta-blockers have not been updated since they were first registered for treatment of hypertension. We suggest the approval for FDCs under this new usage category would involve the following type of trials and outcome criteria: • Trials in which patients not currently taking all recommended medicines are randomised to FDC-based care or usual care with separate component medicines. An alternative control group would be usual care with a broader range of comparable medicines, and/or a broader range of dose options; such variations could be reflected in alternate labelling of the FDC.	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	• Free provision of medicines in both groups is likely to be recommended. However, we would note that this will underestimate benefits of FDCs in settings in which patients would save money from reduced prescription charges • Outcomes – superiority of adherence in the short-term (eg. 1 month) and non-inferiority for long-term adherence. We suggest that the outcome should be adherence – since the drugs are already recommended in the target population a measure of adherence is appropriate, rather than requiring other clinical measures. It is preferable to adopt quantitative objective measures of adherence, such as drug levels, and/or assess triangulation of effect with physiological measures eg. changes in LDL-cholesterol for FDCs containing a statin. One particular challenge with the evaluation of FDCs in this setting is that patients who are non-adherent to recommended therapy are the least likely to join intensive clinical trials with a heavy data collection burden. Therefore there should be a requirement for such trials to be streamlined, with as few barriers as possible to ensure easy patient participation and minimise loss to follow-up. **(additional information provided)**	
12	The European Generic and biosimilar medicines	Not accepted. The legal basis is the choice of the applicant depending

Stakeholder number	General comment (if any)	Outcome (if applicable)
	Association (EGA) welcomes the opportunity to comment on the "'Draft guideline on clinical development of fixed combination medicinal products ". In view of increased interest in developing fixed combination products from the perspective of patients and health care professionals, more clarity on scientific and regulatory requirements will be highly appreciated to create an environment encouraging the development of such products. The EGA would like to highlight the following general comments : The EGA would welcome to re-include the recommended legal basis. The separation between regulatory aspects (legal basis) and scientific requirements proposed in the Draft Guideline as well as preceding Concept Paper, without addressing the legal basis in an appropriate manner in the same time leads to unequal treatment of different applicants who develop Fixed Combination products. Art 10b applications should be allowed to be filed more often than once to allow products developed by different organizations with same development scope to be granted a marketing authorization. If a second or further company develops a fixed combination product with the same development scope (e.g. based solely on a bioequivalence study) no cross reference to the product which was first granted a marketing authorization is required, and therefore no use of data	the type of development undertaken. This is a scientific guideline and issues of legal basis, data protection etc are not within its scope. Please refer to Notice to Applicants, Volume 2A, Chapter 1.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	protected by Data Exclusivity takes place.	
12	There is currently significant uncertainty regarding supporting data requirements for applications for new fixed dose combination products. In this regard, the EGA would very much welcome a more detailed guidance on the demonstration of bioequivalence for combination FDCs in order to foster a common interpretation of the guidance. Proposals for further details to be clarified are outlined in the specific comments below.	Accepted. The guideline describes requirements for bioequivalence in the context of the need to bridge efficacy/safety data that are often established in studies using individual active substances that are used in combination. See sections 4.5 and 4.6 of the guideline.
12	The EGA would like to highlight that the requirements supporting substitution indication in the draft guideline are very stringent. In the detailed comments below we put forward a proposal for the reformulation of these requirements.	Noted, please see response to specific comments below.
12	Finally the EGA would like to highlight that there are many cross-references throughout the guideline that sometimes make the interpretation of the requirements difficult (e.g. cross-referencing in Chapter 4 / Sub-chapters of Chapter 4).	Accepted. Lay-out changes have been implemented.
13	We are supporting revision of the Guideline, however, we suggest a few changes. In the case of substitution scenario, wording of the FDC indication has to suggest that the substitution with FDC is possible where mono-components are taken in the same dose interval and time. In the case that FDC is intended to substitute mono-components that could be co-administered in different	Accepted. The guideline indicates that additional PD and/or clinical data may be needed to support therapeutic equivalence in the 'substitution' setting.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	dose interval and/or time of administration, in addition to bioequivalence, evidence of clinical efficacy and safety has to be provided to justify substitution indication.	

2.

3. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 32-33	2	Comment: To be aligned with the scope section Proposed change: "This guideline covers fixed combination (also referred to as fixed dose combinations, FDCs) medicinal products containing two or more active substances within a single pharmaceutical form ***and also to a chemical substance that dissociates in vivo into two or more active substances***"	Accepted. Section is extensively reworded. The proposed addition is reflected in Section 2. Scope. i.e. '*The scientific principles are also applicable to a substance designed to dissociate in vivo into two or more active substances that form its principal therapeutic moieties*'.
Lines 40-47	2	This sentence is complex and could benefit from some clarification. 1. It is not clear against what the potential advantages and disadvantages of FDCs should be measured: vs mono-components or vs free combination? 2. An FDC aiming to replace an already existing free combination (simplification of therapy) would need BE trials only, but not a comparison to the free combination. 3. Higher efficacy and equal/acceptable safety should also be seen as an advantage. 4. Cumulative toxicity could be further described/defined	Accepted. Section has been extensively reworded. The requirements for a fixed combination medicinal product are described throughout and address all four points raised in the comment.
Line 48	2	It is not clear to which context the term "each situation" refers. We would welcome a substantiation of those different situations. A cross-reference to the various sections 4.1-4.6 can possibly be made at this stage if this was the intended	Partially accepted. Sentence reworded: "*Clinical development should correspond to the intended claim (see sections 4.1 to 4.5).*"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		purpose.	
Lines 50-53	2	Comment: In therapeutic areas where the use of a specific surrogate endpoint is common and well accepted as a substitute for a clinical endpoint, it does not seem justified to recommend the use of hard clinical outcomes if the use of surrogate endpoints is acceptable for the study of monotherapy therapies. Proposed change (if any): "Each dose combination should be scientifically 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 when compared with the dosages effective on surrogate endpoints only)~~"	Accepted. Sentence reworded: "*Particular attention should be given to the doses of each active substance in the fixed combination medicinal product, with each dose combination being scientifically justified and clinically relevant.*"
Line 54	2	"The proposed combination should always be based on valid therapeutic principles." Please clarify meaning of the term, "valid therapeutic principles". Alternatively, include a cross-reference to the table in the Annex where the term is properly described.	Accepted. This aspect is considered evident, and is explained further in the 'rationale' in section 4.
Lines 58-60	2	"The combination of active substances within a single pharmaceutical form of administration is a 'fixed combination' medicinal product. This document provides guidance on the clinical strategy to be considered when developing a 'fixed	Accepted. This is now specified in section 2 Scope. "*The guidance applies primarily to small molecules irrespective of route of administration and dosage form (immediate*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		combination' medicinal product." Suggest clarifying that the guidance does not only apply to solid oral dosage forms and covers immediate release and modified release formulations We also propose to clarify that the active substances can be small or large molecules or a combination of both	*versus modified release), but the general principles also apply to biological products."*
Lines 61 - 62	1	Comment: *"The scientific principles set-out in this guideline are also applicable to a chemical substance that dissociates in vivo into two or more active substances."* This statement is unclear. Proposed change (if any): Please specify that active metabolites are not in the scope. Furthermore, an example may be helpful. Please also clarify whether this would apply to drugs that split into active and inactive enantiomers. Additionally, guidance as to the definition of active would be helpful. E.g. are there minimum levels at which an active would need to be present, for example in the case of a medicine that *in vivo* may dissociate into a major product and a minor product, where the minor product moiety, while classed as a medicine, would pre present in therapeutically	Partially accepted. The sentence has been adapted as follows: "*The scientific principles are also applicable to a substance designed to dissociate in vivo into two or more active substances that form its principal therapeutic moieties."* We have refrained from mentioning examples as they may sometimes be misinterpreted. This is beyond the scope of this guideline and should be assessed on a case-by-case basis. If in doubt, scientific advice is recommended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		negligible quantities, and the primary mode of action of the medicinal product would be executed through the primary major dissociation product)?	
Lines 61 - 62	9	Comment: “The scientific principles set-out in this guideline are also applicable to a chemical substance that dissociates in vivo into two or more active substances.” This statement is unclear. Proposed change (if any): Please specify that active metabolites are not in the scope. Furthermore, an example may be helpful.	See above
Lines 61-62	2	The following statement is unclear: “The scientific principles set-out in this guideline are also applicable to a chemical substance that dissociates in vivo into two or more active substances.” Please specify that active metabolites are not in scope. Furthermore an example may be helpful. We also suggest clarifying that the “active” substances as part of a FDC do not necessarily have to have pharmacological activity in the human body; i.e. one substance may contribute to the overall therapeutic effect by altering the PK characteristics of the other substance.	See above The aspect of PK enhancers is described specifically in section 4.3.B “A PK enhancer with one (or more) active substance(s) with established efficacy in the targeted indication”.
Lines 61-63	12	Comment: We regret that the removal of the combination packs in the	Not accepted. The current guideline under revision does not address the combination

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		scope of the guideline. We would have welcomed these to be kept in and have current existing advice extended with requirements. There is a lack of any EU guidance on co-packaging of products. There is significant divergence in opinion between the regulators and therefore there is a real need to create guidance. Proposed change (if any): Include the combination packs back into the scope and provide proper guidance on requirements.	packs, as per the rationale included in the concept paper: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139482.pdf
Lines 63 – 64	1	Comment: “The guideline does not address the requirements for combination packs, i.e. where active substances are included in separate pharmaceutical forms marketed in the same package.” Proposed amendment: “Nevertheless the general principles set out for fixed combinations are also applicable to combination packs.”	See above
Lines 63-64	2	“...The guideline does not address the requirements for combination packs, i.e. where active substances are included in separate pharmaceutical forms marketed in the same package...” Comment: We appreciate that the draft guideline does not address this	See above

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		scenario but recommend that a separate guideline be created to address this or further detail provided in Chapter 1, Volume 2A, Notice to Applicants, i.e. under what circumstances is this acceptable	
Line 63	6	Comment: Please confirm if combination packs would be included in a new separate guideline, now they have been removed from the fixed combination guideline? The updated guideline does not consider separate combination products contained within a combination pack. Proposed change: Consider discussion on separate combination products in a combination pack either in updated fixed combination guideline or in a new separate guideline.	See above
Lines 66-74	12	Comment: We regret the removal of the link between legal basis and FDCs. It leaves Industry with no idea whether previous feedback from the Commission on the need for clinical, and/or pre-clinical data for new FDCs under Art 10b or 8(3), remains valid. Proposed change (if any): Instead of removing the link between the legal basis, we would have welcomed a recommendation concerning the choice of legal basis.	Not accepted. The guideline does not make reference to any legal basis, since this is the choice of the applicant and depends on the type of development undertaken. The current guideline is meant to focus on the scientific data required to support the safety and efficacy of fixed combination medicinal products, references to any specific legal basis have been intentionally removed in view of this. Any clarification regarding the choice of legal basis should be sought in the Notice to Applicants, Volume 2A, Chapter 1.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 67-71	2	"... The legal basis for fixed combination medicinal products may vary depending on the peculiarities of the active substances in combination and the development undertaken..." Comment: The guidance provided here is not helpful (see general comment above) The statement, "...the application must comply with the dossier requirements as set out in Directive 2001/83/EC and its Annex I..." is self-evidently the case and could apply to any marketing authorisation application, i.e. the message conveyed here is: please comply with the law Proposed change (if any): More detailed guidance on the appropriate legal basis and dossier requirements in line with the general comment above.	See above
Lines 74-82	2	The list of pertinent guidelines should be extended to cover all disease-specific guidelines that discuss the use of FDCs. (see also general comment above)	Not accepted. This guideline discusses overarching principles for the development of fixed combination medicinal products. The development programme for any product

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			should be designed considering any specific therapy area guidance that is available on the EMA website. The views of those guidelines on combination therapy may be updated / reviewed and should be consulted when applicable.
Lines 77-81	4	Comment: inclusion of these two cardiovascular (CV) guidelines in this section may be interpreted as indicating that these guidelines would also apply to other non-CV indication areas. Proposed change (if any): disaggregate these 2 CV guidelines to a standalone section below the bullets and add them as examples of existing therapeutic area-specific guidelines that may be available and also address FDC-specific issues	Not accepted. This guideline discusses overarching principles for the development of fixed combination medicinal products. We have therefore removed the references to any specific therapeutic area guidance, but indicated instead that relevant therapeutic area guidance documents should be consulted.
Line 83	2	It is proposed to add the Guideline on "*Pharmacokinetic and clinical evaluation of modified-release dosage forms*" since it is mentioned in line 270.	Accepted.
Lines 83-84	13	Comment: We suggest the blanks to be populated with data on guidelines related to medicinal products for treatment of diabetes (including biological medicinal products) and Guideline EMA/CPMP/EWP/280/96 Corr1 which is already mentioned in line 270.	See above, no specific therapy area guidance documents are referred to in this guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (underlined): • <u>Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. CPMP/EWP/1080/00 Rev. 1</u> • <u>Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)</u>	
Line 85	1	Comment: Although simplification of therapy is not an aspect of the clinical development of a fixed combination it should be mentioned for the sake of completeness. Proposed Amendment: “Simplification of therapy”	Accepted. The following sentence is included in section 4 Rationale: “Such simplification of therapy is, however, insufficient by itself for a complete justification of a fixed combination medicinal product.”
Line 85	2	Section 4: The guidance text can be interpreted to focus on FDCs with all components effective in the indication although the appendix gives examples for e.g. combination with substances for PK improvement. Proposed change (if any): We propose to reword the section to also address acceptable examples, which are given in the appendix.	Accepted. The section has been extensively reworded. The Annex has been removed.
Line 85 (bullet 3) & 125 & 269	2	Does this refer to the third basic requirement that is the demonstration of bioequivalence? The current wording is	Accepted. The third requirement has been reworded: “*Demonstration that the evidence*

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		unclear and unhelpful to the reader. Please revise.	*presented - if based on combined administration of separate active substances - is relevant to the fixed combination medicinal product for which the application is made*."
Line 85	9	Comment: Although simplification of therapy is not an aspect of the clinical development of a fixed combination it should be mentioned for the sake of completeness. Proposed Amendment: "Simplification of therapy"	See two comments above.
85	12	Comment: The guideline mentions that the basic requirements for any MAA for an FDC are (1) justification <u>of product rationale</u> (2) <u>Establishment</u> of evidence base <u>(3) Verification</u> that evidence base serves the purpose of the product rationale is required. This last step appears to be redundant and therefore further clarification is needed on what would constitute an appropriate <u>*verification*</u> step, if such is indeed required (any new data/information?). Proposed change: Deletion of point 3 or clear statement of what is meant by *3. "Verification* that the evidence base presented is relevant to the product applied for".	Partially accepted. The third requirement has been further explained: "*Demonstration that the evidence presented - if based on combined administration of separate active substances - is relevant to the fixed combination medicinal product for which the application is made*." It is not agreed that the last step is redundant.

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Line 85	13	Comment: In Summary 2.b. “b. positive risk – benefit” should be replaced with; Proposed change (underlined): “b. positive benefit-risk	Accepted. The text is reworded.
Lines 88-91	2	Comment 1: Posology covers both dose and dose frequency, therefore dosing frequency not needed to be specified. Comment 2: It is not enough to say that the aim is to either improve efficacy **or** safety. Safety and efficacy should be always considered together (e.g. improve efficacy with acceptable safety, or improve safety having at least similar efficacy with the monotherapy…) Proposed change: “The rationale should also consider the posology, including the dosing frequency, of the components included in the FDC. The ~~combined~~ use of the ~~active substances~~ **FDC** should improve the benefit/risk by either increasing or adding therapeutic efficacy **with acceptable safety**, or by improving safety **with equal efficacy** with the FDC in comparison to the combined use of the ~~single active substance~~ specific *mono-components*”.”	Comment 1: Partially accepted, it was rather meant to stress these aspects of the posology (dose, frequency and schedule): “*The rationale should also account for the posology, including dosing frequency and dosing schedule of the active substances included in the fixed combination medicinal product.*” Comment 2: This is addressed by: “*The combined use of the active substances is expected to improve the benefit/risk by increasing efficacy and/or improving safety in comparison to the use of (any of) the single active substance(s).*”
Lines 89-91	2	Comment: To remain consistent with the rest of the document (i.e. lines 45-47 and section 4.2), one should refer the other potential advantages of fixed combination products which also	Not accepted. The intention was to avoid repetition of these statements. Specific requirements for fixed combination medicinal

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		include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy (improved compliance). Simplification of therapy is the principle underlying the “substitution indication” which is the subject of section 4.2.	products with a safety advantage rationale are described in section 4.3.
89-91	12	Comment: Simplification of therapy is mentioned in line 46 as an advantage of a fixed dose combination. Improved patient’s compliance is the main advantage for the substitution indication approach which is also explicitly addressed in the Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4). For the therapeutic scenario of substitution indication no improved benefit/risk neither by increasing or adding therapeutic efficacy, nor by improving safety with the FDC in comparison to the use of the single active substances is expected. Proposed change (if any): Potential advantages of FDC (L90-91) should be expanded to include improvement of patient's compliance.	Partially accepted. A reference is made to patient adherence as a potential advantage of a fixed combination medicinal product: “*Part of the rationale for fixed combination medicinal products may be to optimise the use of the medicine in terms of (number of) doses administered and patient adherence, or to help prescribers optimise and/or implement treatment where use of multiple active substances is indicated.*”
Line 92	2	“Data should be available to support use of all active components in the indication applied for”. This sentence appears as not consistent with the proposed acceptable combination (different pharmacodynamic effects, and a different indication than the monocomponents) described in the Annex.	Partially accepted. The sentence is reworded: “*The use of all active substances in the indication applied for should be justified. Fixed combinations that aim at treating patients with unrelated conditions that do not have a therapeutic rationale are discouraged. Scientific advice from National Competent*

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			Authorities or CHMP may be helpful in such situations." The Annex has been removed in the final version of the Guideline.
Line 97	2	The word "individual" associated with fixed combination is confusing; it should be clarified if it refers to each dose and strength of the combination.	Agreed, the word "individual" is removed.
Lines 102-103	2	The guidance should clarify the requirement to demonstrate benefit-risk balance for the combination across all dose and strength combinations. For the FDC products requiring dose titration, efficacy and or safety of only the final achieved dose might be available. Such data might not be available for the entire dose range.	Accepted.. Although this aspect is not specifically addressed by the guideline, but the approach could be justified based on the knowledge generated with the single active substances. The respective sentence and paragraph have been reworded accordingly.
Lines 101-102 Lines 109-110 Lines 115-119	4	Comment: the sentence "All components are required to have an established contribution to the desired therapeutic effect. ", when applied literally, would discourage (or even make non-approvable) a FDC where one component alleviates some adverse effect of the other component, but does not contribute to (or increase) efficacy of the other component. This scenario is also missing in the 3 bullets on line 115-119 and deserves a 4th bullet as it is a truly different scenario. Proposed change (if any): rephrase such that also a FDC with a component to alleviate side effects of another component is considered of potential value. Line 109 may be improved with "each component contributes to efficacy and / OR safety	Accepted. The scenario of a fixed combination medicinal product with a safety rationale is acknowledged in the guideline. Explicit recommendations are given in section 4.3.

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		and/or ..... “.	
104-114 (109-110)	12	Comment: Examples of acceptable data would be appreciated. In this respect co-prescription data from different sources, available literature data on the clinical use / studies of combination (which are not subject to data exclusivity), data from PAS studies etc. should also be considered besides data from prospective clinical trials, especially for substitution indication. Proposed change (if any): Examples of data which would be acceptable for substitution indication (and less demanding than for add-on or first-line therapy) would be appreciated.	Accepted. In sections 4.1 through 4.5, an explicit description of the data required to support the specific therapeutic scenarios is provided. Of note, the requirements for a substitution indication are not lower. It is, however, acceptable to provide evidence on combined clinical use from published literature or own studies. Evidence of combined use only (drug utilisation data of combined prescriptions) is not considered sufficient by on its own to establish a positive benefit/risk.
Lines 106-107	2	“- The population in need of the FDC is clearly identified. Specific therapeutic guidelines on what may constitute an appropriate target population for combination therapy should be considered;” If the target population for the FDC does not overlap with that of either of the individual components, additional clinical data may be required to support authorization and serve as basis for the indication wording in the prescribing information of the FDC.	Accepted. Identification of an appropriate target population is considered important. Specific requirements for the scenario described are provided in section 4.3 C.
Lines 109-110	2	Clarification needed if PD data also include safety parameters.	Accepted. This sentence has been reworded, indicating that it is ultimately the combination

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of benefits and risks that count. "Demonstrate that each active substance contributes to efficacy and/or benefit-risk balance. Active substances may have additive effects or synergistic effects. In the latter case individual substances may have no or only minimal efficacy on their own."
111-113	2	This sentence implies that the evidence base can consist solely of literature data. It is recommended that some further clarity is added regarding the use of literature data to support all required rationales for justification of a FDC. For example, in what types of situations would this be acceptable, etc. (see also comment in line 153)	Accepted. Solely literature data may be acceptable if these provide the necessary evidence on combined use as described in sections 4.1 to 4.3. To bridge the literature data to the proposed fixed combination medicinal product, BE data are expected.
Line 112	2	"literature data" It would be helpful to clarify if this includes treatment guidelines	Noted. Treatment guidelines may provide part of the rationale, but RCTs with the specific components are considered key.
Line 119	2	Comment: To complete the initial combination therapy scenario. Proposed change (if any): • "*Initial combination therapy for patients receiving previously neither of the substances* • *Initial combination therapy for patients presenting a cluster of symptoms and in need of different substances of a FDC, exerting a specific activity against 1 or more symptoms.*	Not accepted. Not in agreement with the second bullet point. While fixed combination medicinal products may be used to treat related symptoms of the same underlying disease, fixed combinations that aim at treating patients with unrelated conditions that do not have a therapeutic rationale are discouraged. Scientific advice from National Competent Authorities or CHMP may be helpful in such

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			situations.
Line 120	2	The guideline states that 'if the FDC contains three or more active substances, all above requirements still apply'. However, the therapeutic scenarios described in the following sections seem to refer to FDCs of 2 mono-components. The Design for FDCs of 3 mono-components or more can generally not be directly derived from design for FDCs with 2 components in hypertension for example (i.e. triple antihypertensive therapy is neither registered first line nor recommended in any of the current existing guidelines). It would be helpful to describe scenarios in the context of FDCs of 3 mono-components or more as the design of the trial is in principle more complex than for FDCs of 2 mono-components, and might trigger some questions. (see also general comment above)	Partially accepted. As indicated above, the principles for multi-component (>2) fixed combination medicinal products are generally the same. If in doubt Scientific Advice would be recommended.
Lines 127-128 Lines 131-132	2	The guideline does not take into account a situation where the FDC used as an add-on in patients does not contain the same components as those in the existing therapy to which there is an insufficient response. In the respiratory area, an FDC may be added on top of therapy to which patients do not respond sufficiently (provided there is no negative interaction).	Accepted. Although this will have to be justified and applies only in specific therapeutic areas.. See section 4.1; "*In certain therapeutic areas there may be a need, or it may be considered more appropriate, to compare the combination of active substances against an established standard of care product. This product would, in that case, usually be of the same therapeutic class as A or B and with an established similar performance to allow the add-on effect of the second active substance to be quantified and should be justified based on*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			appropriate specific clinical guidance. The contribution of each active substance to efficacy is expected to be demonstrated."
Lines 131-132	2	Comment: It is unclear what is meant by the last sentence in the paragraph "A second or subsequent active substance may then be added to improve the intended treatment effect." Proposed change: This sentence should be deleted and/or replaced by wording clarifying its context in this paragraph.	Accepted. The sentence has been deleted.
Line 138	2	"- potential impact on other concomitantly used drugs, especially if the FDC contains a PK booster;" Please rephrase the term, "PK booster", as metabolic or transport inhibitor/inducer.	Accepted. PK booster has been changed to PK enhancer throughout the guideline.
Lines 138, 161, 242	2	Please clarify if a PK booster which is an active substance, designed to enhance local absorption of the other active substance in a formulation, and itself has minimal systemic absorption (e.g in the nano range), would this PK booster be considered an excipient or a monocomponent of a FDC?	Not accepted. This comment refers to the definition of an active substance, which is outside of the scope of this guideline.
Lines 139-140	2	"request for granting waiver for DDI study if the application is in the setting of long established and well documented use of the combination or when the PK effects of DDI are well known." The last part of the sentence should be clarified.	Accepted. The paragraph has been rewritten: " A drug-drug interaction (DDI) study between the active substances in the fixed combination medicinal product should be conducted unless the presence or absence of a pharmacokinetic

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			interaction can be established through other evidence (knowledge from in vitro data, mechanistic understanding or other published clinical trials). A DDI study may be waived if the combined use is established to be without important consequences for clinical safety."
139-140	12	Comment: Request for granting waiver for DDI study is mentioned if the application is in the setting of long established and well documented use of the combination. Further clarification is needed what evidence for long established and well documented use of FDC is considered acceptable. The wording suggests that the DDI study could be waived for long established and well documented use of the combination but might not be sufficiently clear if such interpretation is correct. Proposed change: Please add a more explicit statement whether a waiver of the DDI study is acceptable in cases of long established and well documented use of the combination. Please clarify what constitutes long-established and well documented use.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 141-142	2	Comment: We propose to include paediatric population in the list of vulnerable subgroups. Proposed change (if any): In addition, the potential impact of combined pharmacology in vulnerable subgroups (patients with renal impairment, elderly, **paediatric population**, etc.) should be addressed.	Not accepted. The paediatric population is usually not the most likely target for fixed combination medicinal products, therefore they are not listed here as an example.
Lines 141-143	2	Clarification should be given on whether using established data from the mono-components can be used to support the potential impact of a combined effect in vulnerable subgroups (e.g. patients with renal impairment, patients with hepatic impairment, elderly, etc.). If so, the situations when data from the mono-components may be sufficient in lieu of conducting a study with the FDC should be described.	Accepted. It is acceptable to provide information on the potential impact of a combined drug effect in vulnerable subgroups using data obtained in studies of the individual substances when used in combination or by performing population PK analyses.
Lines 142-143	2	"~~Where possible~~ This could be done either using population PK analyses in the efficacy/safety studies or through literature data, or a combination of both."	Partially accepted. Literature data containing the evidence described here can be acceptable, as implied in the general statement on the evidence base. There is no need to describe that specifically here.
Lines 146-147	2	"However, separate PD data may not be required if superseded by available either clinical efficacy/safety data or through literature data, or a combination of both."	Partially accepted. The following statement has been added: "The potential impact of combined pharmacokinetics in vulnerable subgroups (patients with renal impairment, elderly, etc.) should be addressed. Where possible, this may

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			be done using population PK analyses in the efficacy/safety studies. A dedicated study or analysis of the combination in the vulnerable population may be waived if *in vitro* mechanistic and/or clinical data confirm lack of PK interaction."
Line 150	5	It is unclear what is meant with 'steps' in 'A full factorial design study may reduce the need for certain steps in the inadequate or non responder studies; e.g. a waiver for some potential dose steps of the FDC.' Please rephrase to clarify.	Accepted. This has been further clarified: "*…A factorial design study with pharmacodynamics endpoints that includes all dose permutations…*"
Lines 150, 153, 158	2	Comment: It is unclear what is meant by "…in the inadequate or non responder studies…" (lines 150 and 153) or "…patients… demonstrated to be non-responsive" (line 158). If it refers to insufficiently responding patients as in the title of section 4.1 then the same terminology should be used. It is suggested that a more clear explanation of such studies is provided or that the test is changed. Proposed change: "in studies ~~in the inadequate/non-responders~~ **insufficiently responding** patients", "patients have been demonstrated to be ~~non-responsive~~ **insufficiently responding**"	Accepted. Terminology has been adapted to "insufficiently responding patients". See e.g. section 4.1 Clinical efficacy/safety: "*Randomised controlled trials (RCT) to prove superiority in insufficient responders to the one (or more) active substances of the fixed combination medicinal product…*"
153-154	12	Comment: The requirement for a randomized controlled trial 'to prove superiority in inadequate/non-responders' may be relevant only for combinations with two active substances,	Accepted. This scenario is acknowledged and described specifically in section 4.2 [Switch in patients adequately controlled with two or

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		both of which act on the same pharmacodynamic parameter (e.g. blood pressure). A combination of e.g. statin and antihypertensive does not comply with the requirement in terms of both pharmacodynamic parameters – blood pressure and lipid levels (e.g. comparing lipid lowering effect of a combination statin + antihypertensive and statin by itself is not expected to demonstrate superiority). In addition, suitable clinical data might also be derived from literature references, own clinical experience etc. Proposed change (if any): Please add that this requirement is applicable in case of FDC of drugs with same PD endpoint.	more active substances used in combination ('substitution')] "*Specific considerations apply for fixed combination medicinal products where the active substances have different – but related - therapeutic indications and different pharmacological targets, e.g. a fixed combination medicinal product for treating patients at high cardiovascular risk containing a lipid-modifying agent and an antihypertensive agent. A relevant contribution of all active substances and existence of a positive benefit-risk for these fixed combination medicinal products should be documented as indicated above. In addition, as a minimum requirement, in the absence of clinical trial data studying the specific free active substances used in combination on clinical (here cardiovascular) outcome, the potential for PK and PD interactions should be established to understand if the effect of the individual active substances may be modified by their combination. Usually, PK data (a DDI study) will suffice. Fixed combination medicinal products combining active substances with unrelated therapeutic indications are strongly discouraged.*"

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Lines 153-155	2	Having to conduct a RCT seems contradictory to the sentence in section 4 (line 111-113) about obtaining evidence from literature data.	Partially accepted. Literature data is expected to comprise of published clinical trial data on the use of the specific combination, but other type of data may also be considered supportive.
Lines 153-158	2	Clinical efficacy/safety studies: For the add-on indication, the guideline states that a randomised controlled trial (3-arm study) is required to prove the superiority in inadequate/non-responders to single (or multiple) active components of the FDC in comparison to the respective mono-components. Comment: The following alternative is proposed: If the bioequivalence is demonstrated between the FDC (AB) and the co-administrated monocomponents (A+B) **and if** results from a phase III randomised clinical trial demonstrate the statistically significant efficacy of adding B to the non-responders of A (at the same doses as in the proposed FDC) + good safety profile of the combination, therefore the add-on indication could be claimed. If one of the 2-monocomponents is not a first line treatment (not given as single therapy but as add-on to another treatment), the 3-arm study is not applicable in that case and the study design should be adapted according to current medical practice and claimed indication.	Accepted. The data generated as described will result – in principle – in a restricted 'add on' indication in patients non-responsive to treatment A. This is situation is acknowledged in the guideline, section 4.1 "*If there is a strong clinical preference – appropriately justified by clinical guidelines/practice – for either A or B as initial therapy, a comparison of AB against A or B only may also suffice, but this will result in an indication restricted to insufficient responders to A or B, whichever is used as reference*."

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155	12	Comment: Is the term 'add-on efficacy' a synonym to 'superiority' and under which circumstances? Proposed change (if any): Please clarify.	Accepted.
Lines 158- 159	2	Comment: If A and B are defined as the monocomponents that the patients have failed to respond to individually, and AB is the FDC in an add-on indication, then the 3-arm study should compare AB versus A versus B in patients inadequately/not responding to A or B. Proposed change (if any): "A way to do this is by performing a 3-arm study comparing AB versus A versus B in patients inadequately/not responding to A and/or B"	Accepted. This has been further clarified in section 4.1: "*The usual approach is that patients insufficiently responding to A are randomised to receive B or placebo in addition to continued use of A, and vice-versa.*"
Lines 158-159	2	Comment: Please provide clarification of instances when placebo would be required. Proposed change: Adding in a reference as to when it is recommended to also include a placebo comparator for FDC studies.	See above.
Lines 159 - 161	1	Please consider also a 2-arm design if the sequence of treatment start is well established and described in treatment guidelines.	Accepted. See section 4.1 "*If there is a strong clinical preference – appropriately justified by clinical guidelines/practice – for either A or B as initial therapy, a comparison of AB against A*

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			or B only may also suffice, but this will result in an indication restricted to insufficient responders to A or B, whichever is used as reference."
Lines 159 - 161	2	Please consider also a 2arm design if the sequence of treatment start is well established and described in treatment guidelines Proposed change (if any)	See above.
Lines 159 - 161	9	Please consider also a 2-arm design if the sequence of treatment start is well established and described in treatment guidelines.	See above.
Line 160	2	Comment: This could also be shown by clinical data. Proposed change: "…available in vitro, preclinical, **clinical** and/or PD data show no contribution…"	Partially accepted. This situation is considered more likely to apply in the setting of a fixed combination medicinal product intended for initial combination treatment. See section 4.3 B and 4.3 C.
Lines 168-169	2	Title can be misinterpreted. Given the first paragraph, the use of the word 'substitution' and 'switch' is unclear. Two FDCs could be almost identical, but with one mono-component substituted for another mono-component of the same therapeutic class.	Not accepted. The first paragraph in section 4.2 clarifies what is meant. This does not refer to two FDCs with one common mono-component and the other not identical but from the same class (AB vs AC). The switch/substitution refers to A+B used as monotherapies vs FDC AB.
Lines 168-183	12	Comment: The requirements for a substitution indication (Chapter 4.2) are very demanding – the requirements for	Not accepted. It is not agreed that the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		antihypertensive combinations can be considered more demanding than according to the Guideline on clinical investigation of medicinal products in the treatment of hypertension. Substitution indication in case of antihypertensive combinations (EMA/CHMP/29947/2013/Rev. 4, Chapter 9.2.3) includes ''Moreover, this approach may also be acceptable for combinations of drugs for which a wide therapeutic experience is available (e.g. 5 years or more), provided there is a good plausibility and that the pharmacological rationale for the use of both drugs in combination is adequately justified. Provided that the respective data are thoroughly and reliably documented, a well-founded bibliographical data analysis may be helpful in reducing the amount of clinical trials to be performed. In this case comparative PK data are needed, demonstrating that the two components of the FDC do not affect each other's PK patterns. Showing bioequivalence of the components in free combination with the FDC is the pivotal aspect in this setting.'' It remains unclear whether the wording "in free combination" describes the same design as described in L182-183 with "mono-components taken simultaneously" a formal BE two period cross-over bioequivalence approach is regarded acceptable in case of established therapeutic experience. It should be noted that substitution indication is intended for patients who *are already* treated with mono-components. The decision to prescribe two active substances to these patients lies fully with the doctor before the patients can even be	requirements are different from e.g. the CHMP Guideline on clinical investigation of medicinal products in the treatment of hypertension. Also in the CHMP hypertension guideline it is mentioned that the number of specific trials with the combination may be reduced, [but] this should be done based on well-founded, thorough and reliable bibliographical data. This generally implies RCT data, where in the current fixed combination medicinal product guideline a stronger emphasis is put on evidence generated on efficacy and safety with the specific combination. It is acknowledged, however, that literature data (from published trials) may contain less detailed information on safety (or efficacy) outcomes as that is obtained from own clinical studies. If properly justified, e.g. based on known safe use, this could be acceptable. Scientific advice is recommended in the mentioned specific disease settings. As stated explicitly in the guideline: "*Evidence of combined use only will not suffice to establish the positive benefit/risk of the combination.*"

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		suitable for the treatment with a product claiming *substitution indication.* As substitution therapy *does not mean a change of the treatment* but *only a change in the pharmaceutical form* it is not reasonable to request for substitution therapy the same clinical development program as for add-on or first-line therapy (in respect of amount / quality of clinical data). Therefore, showing bioequivalence of the established combination of mono-components and the newly developed fixed dose combination would be sufficient to bridge the literature data available with the newly developed FDC given the same dose interval and timing, especially in case of FDCs containing drugs with different mechanism of action and without PK interactions. Proposed change: The requirements supporting substitution indication should be reformulated. The requested quality / amount of clinical data on the combination should be less demanding compared to data requested for the registration of add-on or first line therapy. In case of unchanged posology of the fixed dose combination compared to administration of mono-products and provided that clinical rationale for the combination is adequately established, the following clinical data should suffice for the registration of FDCs intended for substitution indication: - evidence of a wide spread use of the particular combination in the clinical practice, - justification/evidence for safe use of the combination,	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		- evaluation of PK interaction (without a request for PK studies on sub-populations), - bioequivalence study of FDC compared to co-administration of corresponding mono-components, - literature clinical data on combination, which should, however, be less demanding (quality and amount of the data) than for add-on or first line therapy, as the safety and efficacy of the product claiming substitution indication is essentially comparable to those of concomitantly administered active substances in separate tablets. This should be applicable especially in case of combinations of drugs belonging to different therapeutic classes and without known PK interactions for which, moreover, the bioequivalence study between FDC and mono-products administered concurrently should be sufficient for granting MA. In this respect more detailed explanation of data and evidence base is needed in case of previously established combined use of mono-components would be appreciated: 1. What evidence for long established and well documented use of FDC might be acceptable? (see comment L 139-140) 2. Whether prescription data would be an acceptable reference for the established use of a combined therapy (L 177-178)? 3. whether a waiver of the DDI study is acceptable in cases of long established and well documented use of the combination (see comment L 139-140) 4. We request confirmation whether / in which case a	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		two period, cross-over bioequivalence study comparing the simultaneous application of mono-products and the FDC is the adequate clinical approach to bridge the clinical data available from literature (in case of same dose interval and timing) . Examples of data which would be acceptable / sufficient to fulfill requirements for the registration of substitution indication would be appreciated. Potential advantages of FDC should be updated with improvement of patient's compliance.	
Lines 171, 172	13	Proposal to better define 'substitution indication'. Proposed change (underlined): …"optimal dose of the mono-components, <u>taken in the same dose interval and time</u>, where the mono-components will be discontinued and the FDC started. <u>If FDC is intended to substitute mono-components that could be co-administered in different dose interval and/or timing of administration, evidence of clinical efficacy and safety has to be provided to justify substitution indication with FDC (please see the criteria outlined in section 4.6).</u>"	Partially accepted. The paragraph has been reworded: "*In this scenario the fixed combination medicinal product is intended to be used in patients who are already stabilised on optimal doses of the combination of the same, but separately administered, active substances, taken at the same dose interval and time. Patients will discontinue taking the single active substance products and initiate therapy with the fixed combination medicinal product.*"
Line 174	2	"It is <u>it</u> to have been established..." Comment: Typographical error	Not accepted. No longer applicable as the sentence has been revised.

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		Proposed change (if any): Remove second “it”	
Lines 174 – 176	1	Comment: The second paragraph in section 4.2 “Switch In Patients Adequately Controlled With One Or More Monocomponents Use in Combination”, which discusses contraindications for patients who are not responding to existing therapy appears to be more relevant to section 4.1 “Treatment of Insufficiently Responding Patients…”. Proposed change (if any): Propose to move lines 174-176 to section 4.1.	Not accepted. No longer applicable as the section has been revised.
Lines 174-176	2	“It is expected it to have been established previously that the particular combination of components in the FDC can be used in patients who are insufficiently responding to an existing therapy with one (or more) mono-component(s).” On the same note, please amend, “patients who are insufficiently responding …”, to “patients who require concomitant treatment with both mono-components for adequate control”.	See above response to stakeholder 12 (Lines 168-183) comments. The section has been reworded: “*…it should be justified that each substance makes a relevant contribution to the desired therapeutic effect and that the benefit-risk for the combination is positive. The evidence base available and the indications of the monotherapies will determine the therapeutic indication targeted, e.g. when the evidence base documents treatment of patients with insufficient response to monotherapy, the indication should be proposed accordingly.*”
Lines 174 – 176	9	Comment: The second paragraph in section 4.2 “Switch In	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Patients Adequately Controlled With One Or More Monocomponents Use in Combination", which discusses contraindications for patients who are not responding to existing therapy appears to be more relevant to section 4.1 "Treatment of Insufficiently Responding Patients…". Proposed change (if any): Propose to move lines 174-176 to section 4.1.	
Lines 177-180	5	Please clarify whether a pharmacodynamics trial in the absence of an efficacy/safety study could be considered sufficient.	See above comments on sections 4.1 and 4.3 for the role of PD data in relation to efficacy/safety data. PD data e.g. may be used in clinical efficacy studies, where disease specific guidance acknowledges specific established biomarkers.
Line 178	13	Proposal to clarify text in brackets: "(see above)", since it is not clear to which part of the guideline it is referring to. We believe that it is referring to line 104).	Accepted. It is clarified that reference is made to sections 4.1 and 4.3.
Lines 178-180	2	Comment: Editorial change proposed for clarity. Proposed change: "These data should support that the evidence base for combined use of the components is established, (see the data requirements in section 4.1 or 4.3 for fulfilment of the basic requirements 1 and 2 discussed in section 4).	Partially accepted. Section has been extensively reworded.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 188	2	This sentence should be changed for broader application. Proposed change: “It should be justified that the benefits of starting two (or more) drugs at the same time…”	Accepted. The last sentences of this paragraph have been reworded: “*It should always be justified that the advantages of starting the therapy with two (or more) active substances at the same time outweigh its disadvantages (see above). However, depending on the therapeutic context, initial combination therapy may be considered acceptable or even advantageous.*”
Line 189	2	Comment: suggest to add in the list of disadvantages: Single component is not a standard of care Proposed change: it should be justified that the benefits of starting two drugs at the same time outweighs its disadvantages (unnecessary treatment, safety issues, single component(s) not standard of care).	See previous comment.
Lines 197 - 199	1	Comment: It is suggested to revise the sentence for a clearer understanding. Proposed change: “If the rationale is <u>that the use of the FDC results in</u> an improved *efficacy* in terms of greater clinical response compared to an initial therapy with <u>either</u> ~~one~~ of the monocomponent~~(s) by the second monocomponents(s)~~...”	Partially accepted. Section 4.3 has been extensively revised, the comment here refers to fixed combination medicinal products that aim for “*superior efficacy by combining:* *A. Two (or more) active substances that each have established efficacy in the targeted indication.* *If two (or more) active substances with established efficacy in the targeted indication are combined this should be done to improve*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			efficacy in terms of greater clinical response compared to an initial therapy with either single active substance. An RCT is generally required and should demonstrate: *1) Superior efficacy on a clinical outcome at a given time point, AND* *2) An acceptable safety profile.* *An efficient way to evaluate this is to perform a 3-arm RCT comparing AB versus A versus B. An adequately designed factorial design study in patients may provide further support for the combined use of active substances at the selected doses.* *Equally superior efficacy also applies to the situation (e.g. hypertension) where the primary goal of initial combination therapy is to achieve the desired treatment response more rapidly. In this case also a benefit in terms of obtaining a more rapid and at least comparable effect at a later time point compared to stepwise dose titration of the free combination should be demonstrated.*"
Line 197ff	2	Comment: In case of a development rationale 'improved efficacy' the guideline asks to show "superior efficacy on a clinical outcome at a given time point". However, we feel the guidance omits the possibility to use a non-inferiority design	Partially accepted. This is considered to fall under the second sub-scenario in Section 4.3. of fixed combination medicinal products aiming for ' Improved safety' :

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		to show an improved efficacy because in fact if the FDC contains a lower amount of the active substances compared to the single products at the time point of optimal dosing the FDC can be considered superior to the single components in terms of efficacy. Proposed change (if any): We propose to add the option for a non-inferiority design for the above mentioned situation.	"*If the rationale of the fixed combination medicinal product is to improve safety, an RCT should be performed to demonstrate improved safety /tolerability of the fixed combination medicinal product, versus the single active substance(s), utilising explicitly defined adverse event(s) as co-primary endpoint(s). Another co-primary endpoint is needed to establish that there is no loss of efficacy, compared to administration of the single active substance(s).* *Two sub-scenarios are envisaged. … The* ***second sub-scenario*** *is where the fixed combination medicinal product consists of doses that are below those at which the individual active substances are licensed or used. In this scenario a comparison should be made of the fixed combination medicinal product against an optimal dose of the individual active substances*."
Lines 197-198	2	It is suggested to revise the sentence for a clearer understanding. Proposed change: "If the rationale is that **the use of the FDC results in** an improved efficacy in terms of greater clinical response compared to an initial therapy with **either** ~~one~~ of the monocomponent(s) ~~by the second monocomponents(s)~~..."	See above comments, this section has been extensively reworded.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 197- 200	2	Comment: In some areas, it might be necessary and acceptable to demonstrate additive or synergetic effect of the combination versus each monotherapy by demonstrating superiority based on a surrogate biomarker, rather than a hard clinical outcome. Reference should be made to relevant therapeutic area guidelines, applicable to the indication of interest, where the use of surrogate endpoint may be well recognised and acceptable. Flexibility should also be allowed in cases where demonstration of superiority of the combination versus each monotherapy based on clinical outcomes might require very long and large studies, which might make the study operationally unviable. In such, early dialogue should be recommended. Proposed change (if any): “If the rationale is an improved efficacy in terms of greater clinical response compared to an initial therapy with one of the monocomponent(s) by the second monocomponents(s), an RCT is required and should demonstrate: 1) superior efficacy ~~**on a clinical outcome**~~ at a given time point, […]”	Partially accepted. Section is reworded, but ‘clinical outcome’ in the respective sentence is maintained. Surrogate markers (PD endpoints) may be used in accordance with disease specific guidance documents.
Line 200	5	‘superior efficacy on a clinical outcome at a given time point’ seems to exclude the possibility of evaluating efficacy based on time-course observations, e.g. using a mixed model for repeated measures. This is an established approach and more efficient than evaluation based on a single time point.	Not accepted. Considerations on the exact statistical approach are beyond the scope of the guideline. Ultimately, superior efficacy of the fixed combination medicinal product is determined by both statistical and clinical

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			significance.
Line 202	2	"An efficient way to evaluate this is by performing a 3-arm study comparing AB versus A versus B." Please comment on the need for placebo control in Phase 3 studies of a FDC containing new active substances only (see general comment). In those instances, the proposed 3-way design (A, B, A+B) would not suffice.	Accepted. In addition to the response to the general comments to development of a fixed combination medicinal product comprised of new active substances, please consider section 4.4: "*A programme of trials corresponding to what would be expected in a full dossier, including clinical trials demonstrating efficacy/safety of the new active substance as monotherapy according to disease specific guidelines would usually be expected. Based on appropriate scientific justification, e.g. when the NAS is a PK enhancer, has no efficacy in the targeted indication (based on mechanistic and human PD data), or is added to improve safety of the main active substance, RCTs demonstrating efficacy of the NAS as monotherapy may be waived.*" It is recommended to seek scientific advice when engaging in the development of a fixed combination medicinal product containing more than new active substances.
Line 202	2	Comment: in some cases the comparison to the individual components separately may make more sense Proposed change (if any): Suggest to change '3-arm study comparing AB versus A versus B' to '3-arm study comparing	Not accepted. It is considered that the current wording within the context of this guideline is sufficiently clear that a comparison of the fixed combination medicinal product should be made against both individual components.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		AB versus A and B' to avoid misunderstanding.	
Line 202	2	Comment: 'Efficient' does not seem like the appropriate word here. Proposed change: "~~An efficient~~ way to evaluate..." (which is consistent with rest of document).	Not accepted. Wording has been maintained.
Lines 202, 240-241	4	Comment: "comparing AB versus A versus B. " could be read that A needs to be compared against B which would be irrelevant. Proposed change (if any): "comparing AB versus A <u>and</u> versus B. "	Not accepted. The wording and context are considered to be sufficiently clear that a comparison of the fixed combination medicinal product should be made against both individual components.
Line 211	2	Comment: clarification suggested. Proposed change: "better or similar ~~control~~ **therapeutic effect** at **a** ~~another~~ (later) time point…"	Accepted.. The wording was too complex and has been rewritten for this scenario (section 4.3): "*Equally superior efficacy also applies to the situation (e.g. hypertension) where the primary goal of initial combination therapy is to achieve the desired treatment response more rapidly. In this case also a benefit in terms of obtaining a more rapid and at least comparable effect at a later time point compared to stepwise dose titration of the free combination*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			should be demonstrated."
Lines 209-213	4	Consider adding further specification whether "similar" is meant to indicate, or better be replaced, by non-inferiority (and also consider making cross-reference to statistical guideline(s) on non-inferiority if that is the case). In addition consider making explicit whether the faster efficacy and "similar" efficacy after completion of titration are to be evaluated as co-primary endpoints, or one (faster efficacy) could be primary and the other one key secondary.	See above, as this is a very specific scenario mostly in the area of hypertension and the specific CHMP guideline should be consulted.
Line 219	2	Comment: Section 4.3: "In such case, the new FDC will be tested against an established combination in the pivotal studies." It should be clarified that in such a case demonstration on non-inferior efficacy would be acceptable. This is not transparent from the current wording. Proposed change (if any): Please add that a non-inferior design would be acceptable in such a case.	Accepted. See section 4.3 last paragraph: "*…The goal would be to demonstrate superior efficacy, improved safety or comparable efficacy/safety (non-inferior) to established combination(s). In this context a new fixed combination medicinal product may contain a similar or different number of active substances as the comparator product.*"
Line 221	2	More examples could be helpful. E.g. mention of rare disease with patient number constraints	Not accepted. Due to the complexity of the guideline and the various scenarios described, it was decided to refrain from giving specific examples.
Lines 221-223	2	"Another scenario may be where phase 3 trials would be unrealistic to perform against monocomponents, where compelling mechanistic data (e.g. using biomarkers) would	Accepted. This is now addressed in section 4.3 C. The mechanistic data are needed to support a

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		suggest an inadequate response to monotherapy." In addition to mechanistic data, suggest considering historical data, i.e. efficacy and safety data from clinical trials that were not concurrently controlled with either of the mono-components.	synergistic effect, not demonstrate absence of effect. Historical study data could be used to support absence of efficacy of a monocomponent in the targeted population.
Lines 226-241	2	Assuming that by co-primary it is meant to show similar efficacy **and** improved safety, it is suggested to emphasize this in the Guideline.	Accepted. This section has been rewritten. "*Improved safety* *If the rationale of the fixed combination medicinal product is to improve safety, an RCT should be performed to demonstrate improved safety /tolerability of the fixed combination medicinal product, versus the single active substance(s), utilising explicitly defined adverse event(s) as co-primary endpoint(s). Another co-primary endpoint is needed to establish that there is no loss of efficacy, compared to administration of the single active substance(s).*"
Lines 226-241	2	In the situation described in this paragraph, other elements should also be taken into account: 1. Tolerability Improved tolerability is an important endpoint. However, the frequencies of certain safety events (i.e. specific adverse events) may be low which may have a significant impact on	Accepted. Tolerability has been added to the wording (see above). The 'sustainability' scenario is not fully understood. What is described seems to fit somewhat with the more rapid attainment of response (antihypertensives), as discussed a above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		sample size with the requirement of powering the study in this regard. Perhaps an approach where the totality of the tolerability data (overall AEs, SAEs, discontinuations, laboratory data, etc.) is summarized and discussed with respect to clinical relevance in a study with a clinically determined sample size would be more feasible. Proposed change in line 229: In addition, the clinical trial should demonstrate improved <u>tolerability</u> of the FDC….” 2. Sustainability One scenario with FDC as initial treatment is where the FDC does not provide greater clinical response but improves the sustainability of efficacy, over the mono-component(s). In the case where the most common clinical practice is to start with an initial therapy and then add on a second therapy when needed, is it required to demonstrate using a RCT that the FDC as initial treatment has better risk-benefit profile compared to “add-on”?	
Lines 226-241	2	It is unclear what happens when FDC contains mono-component(s) that may have a delayed/accumulated safety effect. Suggestion to rephrase more generally to reflect the mono-component(s)’s mechanism of action / pharmacology profile.	Accepted. Indeed, throughout the guideline the emphasis is on the efficacy / safety profile of the combined use of monocomponents. This also involves long-term safety of using multiple rather than single components.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 227	2	Comment: clarification suggested. Proposed change: similar **therapeutic effect** ~~control (efficacy)~~	Partially accepted. Sentence has been reworded: "*If the rationale of the fixed combination medicinal product is to improve safety, an RCT should be performed to demonstrate improved safety /tolerability of the fixed combination medicinal product, versus the single active substance(s),…*"
Lines 229 - 241	1	Comment: in some cases it may not be feasible to conduct a study which is large enough to show safety advantages of the FDC vs. individual components which are normally taken acutely and already have a favourable safety profile. Proposed change: The second scenario is where the FDC contains a lower dose of each individual mono-component than the optimal dose of each when given alone, and there is no additive toxicity when the two mono-components are administered together, then it can be inferred that the FDC has a safety advantage due to lower exposure to each medication, and it is adequate to demonstrate that the FDC is at least as efficacious as the optimal dose of each mono-component given alone. A way to evaluate this is by performing a 3-arm study comparing low dose of A and low dose of B (as combined in the FDC) versus optimal dose A versus optimal dose B.	Not accepted. Without clinical evidence the safety advantage cannot be simply assumed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 229 - 241	9	Comment: In some cases it may not be feasible to conduct a study which is large enough to show safety advantages of the FDC vs. individual components which are normally taken acutely and already have a favourable safety profile. Proposed change: The second scenario is where the FDC contains a lower dose of each individual mono-component than the optimal dose of each when given alone, and there is no additive toxicity when the two mono-components are administered together, then it can be inferred that the FDC has a safety advantage due to lower exposure to each medication, and it is adequate to demonstrate that the FDC is at least as efficacious as the optimal dose of each mono-component given alone. A way to evaluate this is by performing a 3-arm study comparing low dose of A and low dose of B (as combined in the FDC) versus optimal dose A versus optimal dose B.	See previous comment.
Line 230	2	Could other approaches (e.g. hierarchical testing) also be appropriate instead of limiting only to safety co-primary endpoints?	Not agreed. Specific statistical analysis strategies are beyond the scope of the guideline. It is in principle, however, important to demonstrate that a safety advantage does not come at a cost of a loss of efficacy.
Lines 232-233	2	“Evaluation of safety should focus on events that may occur early after treatment initiation, and that are related to exaggerated pharmacology.”	Partially accepted. This statement has been deleted from the final guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Please clarify that “early after treatment initiation” may also include a time point during the period of titration in the mono-component only arm.	
Line 242	2	“Finally, the rationale may be an enhanced PK/PD profile of the FDC.” What is meant with an “enhanced PK/PD profile”; e.g. less hysteresis (tolerance) with the FDC than either of the mono-components? Surely, this does not refer to a more rapid onset of therapeutic effect. If it does, then this requires clarification.	Partially accepted. See section 4.3 B, where this is explicitly described.
Line 246	2	Proposed change (if any): To add following paragraph: “If the rationale is to relieve different symptoms of the disease, it is expected to demonstrate that the evidence base for combined use of components is established through clinical trials, or through literature data or a combination of both. See the data requirements in section 4.1 “pharmacokinetics and pharmacodynamics” for fulfilment of the basic requirements 1&2 discussed in the section 4. Bioequivalence of the FDC versus mono-components taken simultaneously has to be considered according to the criteria outlined in section 4.6.”	Partially accepted. This section has been revised and is now described in sections 4.3 B and 4.3 C.
Lines 249-250	2	Comment: (editorial) need to define acronym. Proposed change: “…one or more new active substances	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(NAS)..."	
Line 257	2	"A full dossier, including an RCT demonstrating efficacy/safety of the new active substance according to disease specific guidelines should be compiled." Please clarify that a RCT demonstration efficacy and safety (Phase 2/3 study) would only be required in those instances where the target population can be expected to derive a direct therapeutic benefit from treatment with the mono-component that qualifies as a new active substance.	Accepted. This is addressed in the last sentences of section 4.4: "*programme of trials corresponding to what would be expected in a full dossier, including clinical trials demonstrating efficacy/safety of the new active substance as monotherapy according to disease specific guidelines would usually be expected. Based on appropriate scientific justification, e.g. when the NAS is a PK enhancer, has no efficacy in the targeted indication (based on mechanistic and human PD data), or is added to improve safety of the main active substance, RCTs demonstrating efficacy of the NAS as monotherapy may be waived.*"
Lines 257-258	2	Also, this sentence implies that a RCT for safety and efficacy is needed for any new NAS intended for use in a FDC. However, the NAS may be not be used for its efficacy, but because it is able to enhance the PK/PD of the main active substance(s). Please clarify in such circumstances whether a RCT would truly be necessary.	See, the comment above and sections 4.3 B and 4.3 C.
Lines 257-258	4	This sentence appears to waive a general requirement for 2 pivotal RCTs demonstrating efficacy of a NAS, is that intended?	Not accepted The evidence for NAS should follow general and disease-specific regulatory guidance. The sentences have been adjusted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 259-264	12	Comment: Recommend adding clarifications on requirements for demonstration of bioequivalence for combination products consisting of different release characteristics (example: immediate release for active ingredient 1 and modified release for active ingredient 2). In the case that the components of the combination product follow different release characteristics, the studies required to demonstrate bioequivalence should be consistent with the recommendations in the individual applicable guidelines. For instance, the component (active ingredient) formulated as modified release may require a multiple-dose study to satisfy requirements set forth in the "Pharmacokinetic and clinical evaluation of modified-release dosage forms" guidance, whereas the component formulated to release immediately would follow the "Guideline on the Investigation of Bioequivalence" which does not require multiple-dose study for immediate release formulations. Therefore, measurements of the immediate release component in a multiple dose study conducted to evaluate bioequivalence of the MR component should be considered unnecessary. Proposed change (if any): Add "In case the combination product consists of different release mechanisms (immediate release and modified release components), the bioequivalence guidelines for the respective individual mono-components can be followed to establish	Accepted. This is addressed in section 4.6: "*An efficient study design is to compare AB versus concurrent administration of A and B as individual active substance products, in which case bioequivalence can be evaluated for each active substance separately considering individual active substance product characteristics; e.g. highly variable drug, narrow therapeutic index, biopharmaceutics classification system (BCS) classification, appropriate sampling schedule, and release mechanism (requirements differ for immediate- and modified-release products)*."

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		bioequivalence between the individual active ingredients".	
Lines 259-264	12	Comment: If one component of the fixed dose combination product is BCS class I and the other is not, is it possible to claim a BCS-based biowaiver of in vivo BE study for one component and conduct an in vivo study only for the other? Proposed change (if any): Add "Fixed dose combination products are eligible for BCS-based biowaiver for one or more components of the combination product."	This is covered by the same sentence as in the previous comment.
Lines 259-264	12	Comment: If only one component in the FDC is a narrow therapeutic index drug, is it permissible to apply the tightened 90%CI (90-111.11%) BE criteria for that component only? Proposed change (if any): Add "In case the pharmacological properties of the individual components of the combination product differ (eg. one is a narrow therapeutic index drug, and the other is not), the applicable guidelines can be applied to the individual components of the fixed dose combination product."	This is covered by the same sentence as in the previous comments.
Lines 259-264	12	Comment: If only one component in the fixed dose combination product is a highly variable drug (HVD), is it permissible to have the widened 90%CI on Cmax (to a maximum 69.84-143.19 depending on ISCV) BE criteria for that component only. Can reference scaled average	This is covered by the same sentence as in the previous comments. The widening of the CI is, however, only acceptable as indicated in the Guideline on the investigation of bioequivalence - CPMP/EWP/QWP/1401/98

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		bioequivalence (RSABE) approach be applied to one component only? Proposed change (if any): Add “In case the pharmacokinetic properties of the individual components of the combination product differ (eg. one is a highly variable drug, and the other is not), the applicable guidelines can be applied to the individual components of the fixed dose combination product.”	Rev. 1/ Corr. For specific details on demonstrating BE see the appropriate guidelines, including PKWP drug-specific guidance.
Lines 259-264	12	Comment: There are cases that the pharmacokinetics of the active ingredients in a fixed dose combination product are vastly different, and thus could require different clinical study design. Please clarify whether separate bioequivalence studies can be performed on the individual active ingredients and used together as a demonstration of bioequivalence of the fixed dose combination product. Proposed change (if any): Add “The bioequivalence of the individual active ingredients within the fixed dose combination product may be demonstrated after measuring the analytes together in the same study, or in separate studies. “	This is covered by the same sentence as in the previous comments.
Lines 259-264	12	Comment: Please clarify for the case that the same method is used to measure more than one component of the fixed dose combination product, whether it is necessary to report all	Not accepted This is beyond the scope of this guideline. Relevant PK, BE and other appropriate guidance should be followed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		concentrations measured by the method for analytes with different pharmacokinetics (i.e. analyte 1 characterization of extent of absorption sufficient to 12 hours, but analyte 2 characterization of extent of absorption required to 72 hours). It is felt to be sufficient to use and report only those concentrations established by the protocol to be necessary to adequately capture the pharmacokinetics of the individual analytes. Proposed change (if any): Add “If the same analytical method is used to measure concentrations of more than one component of the combination product which have very different pharmacokinetics, the protocol should define the sampling schedule to be used to characterize the individual components. It is not necessary to use or report concentrations for an analyte measured beyond the time specified in the protocol to establish a reliable AUC. “	
Lines 259-264	12	The guideline states that generic fixed dose combinations must be tested against the reference fixed dose combination. Is there an option of demonstrating bioequivalence of the generic fixed dose combination against the co-administered mono products?	The development of a generic product is based on demonstrating bioequivalence with the reference fixed combination medicinal product. It however needs to be verified that the evidence base that has been generated for the reference product with the individual active substances, also applies to the generic. In this case, two pharmacokinetic bridges may need

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			to be built. See section 4.5 for further details.
Line 261	2	It is proposed to add reference to section 4.6.	Accepted.
Lines 263 - 264	1	Pharmacodynamics and clinical efficacy/safety studies are not needed for a generic FDC. However, if this FDC would be completely characterised with regard to safety and efficacy, no BE is needed for this FDC.	The example provided does not appear to be consistent with the requirements laid down in Article 10(1) Of Directive 2001/83/EC.
Lines 263 - 264	2	Pharmacodynamics and clinical efficacy/safety studies are not needed for a generic FDC. However, if this FDC would be completely characterized with regard to safety and efficacy, no BE is needed for this FDC. Proposed change (if any):	See previous comment.
Lines 263 - 264	9	Pharmacodynamics and clinical efficacy/safety studies are not needed for a generic FDC. However, if this FDC would be completely characterised with regard to safety and efficacy, no BE is needed for this FDC.	See previous comment.
Line 267	2	Comment: in some cases the comparison to the individual components separately may make more sense Proposed change (if any): suggest to revise as follows: ...taken simultaneously (or on separate occasions, which is more clinically relevant)	Not accepted. It is not really clear under what circumstances this can occur, therefore the wording was not changed in this respect.
Lines 275-276	2	Comment: The bioequivalence study may be waived if all clinical data supporting the combined use are obtained with the actual FDC formulation."	The comment is not fully understood, but also in this setting BE for all mono components in the fixed combination medicinal product should generally be obtained, unless all clinical data

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Similarly, the requirement for bioequivalence studies with the two mono-components administered simultaneously may not apply to FDCs that are being developed for initial treatment. In those instances, bioequivalence studies with either one of the mono-components, as required during pharmaceutical development of the FDC, may suffice. The guidance should also cover or refer to requirements of the biowaiver as well as in vitro dissolution requirements for fixed dose combinations.	supporting the combined use are obtained with the actual fixed combination medicinal product formulation.
Lines 275-276	12	Bioequivalence may be waived if all clinical data supporting the combined use are obtained with the FDC. Proposed change: It needs to be clarified whether this includes the need of DDI studies as well.	Not accepted. An understanding of the DDI potential of the components in the fixed combination medicinal product should be clarified as described in the PK paragraphs of section 4.1.
Lines 292 -293 – Annex to the guideline	2	Comment: Under 'unacceptable combination' (fifth bullet point) "and an oral anti conceptive [*sic*] to treat women..." Comment: typographical error Proposed change (if any): replace underlined with "contraceptive"	Not accepted. The Annex with examples has been removed in the final version of the guideline as the guideline does not mention examples throughout the text.
Line 293	1	Comment: A FDC containing an antidepressant and an oral anti	Not accepted. The Annex with examples has been removed in the final version of the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		conceptive to treat women with depression who do not want to become pregnant may be not completely out of scope if the antidepressant shows strong reprotoxic properties. Proposed change (if any): Please consider another example for an “unacceptable combination”.	guideline as the guideline does not mention examples throughout the text. final version of the guideline.
Line 293	2	A FDC containing an antidepressant and an oral anti conceptive to treat women with depression who do not want to become pregnant may be not completely out of scope if the antidepressant shows strong reprotoxic properties. Proposed change (if any): Please consider another example for an “unacceptable combination”	Not accepted. The Annex with examples has been removed in the final version of the guideline as the guideline does not mention examples throughout the text.
Line 293	13	Comment: In Annex, under ‘Acceptable combinations’ subheading, in order to be consistent, the proposal is to highlight *different but related indication*, since subheading ‘Unacceptable combination’ defines that *unrelated conditions* are unacceptable. Proposed change (underlined): “FDC of two or more active components with different pharmacodynamic effects, and a different <u>but related</u> indication than the mono-components, but where the combined use of the active substances is based on valid	Not accepted. The Annex with examples has been removed in the final version of the guideline as the guideline does not mention examples throughout the text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		therapeutic principles”…	