



1 23 April 2015  
2 EMA/CHMP/281825/2015  
3 Committee for Human Medicinal Products (CHMP)

4 **Guideline on clinical development of fixed combination**  
5 **medicinal products**

6

Draft agreed by SAWP	6 November 2014
Adopted by CHMP for release for consultation	23 April 2015
Start of public consultation	13 May 2015
End of consultation (deadline for comments)	15 November 2015

7

8 This guideline replaces 'Guideline on clinical development of fixed combination medicinal products'  
9 (CHMP/EWP/240/95 Rev. 1).

10

Comments should be provided using this [template](#). The completed comments form should be sent to [FDCguideline@ema.europa.eu](mailto:FDCguideline@ema.europa.eu).

11

<b>Keywords</b>	Fixed combinations, guidance, clinical development
-----------------	--



12 **Guideline on clinical development of fixed combination**  
13 **medicinal products**

14 **Table of contents**

15 **Executive summary ..... 3**

16 **1. Introduction (background) ..... 3**

17 **2. Scope..... 3**

18 **3. Legal basis ..... 3**

19 **4. Clinical data requirement for fixed dose combinations ..... 5**

20 4.1. Treatment of insufficiently responding patients ('add-on indication') .....6

21 4.2. Switch in patients adequately controlled with two or more mono-components used in

22 combination ('substitution indication') .....7

23 4.3. Initial treatment.....7

24 4.4. Additional requirements for development of FDCs with new active substance(s) .....9

25 4.5. Generic medicinal products .....9

26 4.6. Demonstration of bioequivalence.....9

27 **Definitions ..... 10**

28 **References ..... 10**

29  
30

## 31 **Executive summary**

32 This guideline covers fixed combination (also referred to as fixed dose combinations, FDCs) medicinal  
33 products containing two or more active substances within a single pharmaceutical form. The active  
34 substances may be known active substances or substances that have not yet been authorised in the  
35 EU. This guideline addresses the clinical development requirements of fixed combination medicinal  
36 products, which shall reflect their intended therapeutic use and indication.

37 This revised guideline revisited scientific requirements for the development of an FDC independent of  
38 chosen legal basis for submission of an application for marketing authorisation.

## 39 **1. Introduction (background)**

40 Fixed combination medicinal products have been increasingly used due to the benefit of the combined  
41 effects of active substances given together. However, it is necessary to assess the potential  
42 advantages (e.g. product more rapidly effective, higher efficacy or equal efficacy and better safety) in  
43 the clinical situation against possible disadvantages (e.g. cumulative toxicity, difficult titration), for  
44 each fixed combination product and for each dose of the fixed combination product. Potential  
45 advantages of fixed combination products may also include the counteracting by one substance of an  
46 adverse reaction produced by another one, and simplification of therapy, leading to improved  
47 compliance.

48 Clinical development should correspond to each situation/intended claim. In addition, particular  
49 attention should be given to the doses of each active substance in the fixed combination product. Each  
50 dose combination should be scientifically justified and clinically relevant (e.g. in cases when each  
51 component of the fixed combination has several possible dosages, dosages that have shown benefit on  
52 hard clinical outcomes may be preferable for the fixed combination when compared with the dosages  
53 effective on surrogate endpoints only).

54 The proposed combination should always be based on valid therapeutic principles. When developing a  
55 fixed combination medicinal product, disease specific guidelines should be considered with regards to  
56 which principles are considered valid in the therapeutic area.

## 57 **2. Scope**

58 The combination of active substances within a single pharmaceutical form of administration is a 'fixed  
59 combination' medicinal product. This document provides guidance on the clinical strategy to be  
60 considered when developing a 'fixed combination' medicinal product.

61 The scientific principles set-out in this guideline are also applicable to a chemical substance that  
62 dissociates *in vivo* into two or more active substances.

63 The guideline does not address the requirements for combination packs, i.e. where active substances  
64 are included in separate pharmaceutical forms marketed in the same package.

65 This guideline should be read in conjunction with other relevant therapeutic EU guidelines.

## 66 **3. Legal basis**

67 The legal basis for applications concerning fixed combination medicinal products may vary depending  
68 on the particularities of the active substances in combination and the development undertaken.

69 The choice of legal basis lies with the applicant. In every case, the application must comply with the  
70 dossier requirements as set out in Directive 2001/83/EC and its Annex I (see also Notice to Applicants,  
71 Vol. 2A, Procedures for marketing authorisation, Chapter 1).

72 This guideline should be read in conjunction with the introduction and general principles (4) and part I  
73 and II of the Annex I to Directive 2001/83/EC as amended and other pertinent elements outlined in  
74 the EU and ICH guidelines, especially those on:

- 75 • Guideline on the investigation of bioequivalence - CPMP/EWP/QWP/1401/98 Rev. 1/ Corr;
- 76 • Guideline on the Investigation of Drug Interactions- CPMP/EWP/560/95/Rev. 1 Corr.;
- 77 • Guideline on clinical investigation of medicinal products in the treatment of hypertension  
78 (Rev.3) - EMA/238/1995/Rev.3;
- 79 • Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs  
80 belonging to different therapeutic classes in the field of cardiovascular treatment and  
81 prevention - CHMP/EWP/191583/05;
- 82 • Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4).

83

84

## 85 4. Clinical data requirement for fixed dose combinations

**Summary:** The basic requirements for any MAA for an FDC are:

1. Justification of the pharmacological and medical rationale for the combination.
2. Establishment of the evidence base for the:
  - a. relevant contribution of all active components to the desired therapeutic effect;
  - b. positive risk-benefit for the combination.
3. Verification that the evidence base presented is relevant to the product applied for.

86

87 Applicants are required to justify the rationale behind a particular combination of active substances  
88 proposed for the intended therapeutic indication. The rationale should also consider the posology,  
89 including the dosing frequency, of the components included in the FDC. The combined use of the active  
90 substances should improve the benefit/risk by either increasing or adding therapeutic efficacy, or by  
91 improving safety with the FDC in comparison to the use of the single active substance.

92 Data should be available to support use of all active components in the indication applied for. Fixed  
93 combinations that aim at treating patients with unrelated indications that do not have a therapeutic  
94 rationale are discouraged. A scientific advice from National Competent Authorities or the CHMP may be  
95 helpful in this respect. A non exhaustive list of examples of Fixed Dose Combinations in relation to  
96 pharmacodynamics effects and indications are given in the annex.

97 For any individual fixed combination it is necessary to assess the potential advantages in the clinical  
98 situation against possible disadvantages, in order to determine whether the product meets the  
99 requirements with respect to efficacy and safety. Disadvantages that should be addressed are the  
100 potential addition or strengthening of adverse effects, and that fixed dose combinations may not be  
101 ideally adjusted to the needs of individual patients. All components are required to have an established  
102 contribution to the desired therapeutic effect. In addition, the data should demonstrate a favourable  
103 benefit-risk balance for the combination across all dose and strength combinations of the FDC.

104 The **evidence base** for establishing the contribution to an overall effect and favourable benefit-risk  
105 balance of the fixed dose combination is expected to support that:

- 106 - the population in need of the FDC is clearly identified. Specific therapeutic guidelines on what  
107 may constitute an appropriate target population for combination therapy should be considered;
- 108 - the combination is pharmacologically plausible and based on valid therapeutic principles;
- 109 - each component contributes to efficacy and safety and/or enhances PK/PD of (main) active  
110 substance(s).

111 This evidence base can consist of dedicated clinical trials performed with the FDC and/or clinical trials  
112 with the combined use of the specific mono-components, literature data, or a combination of both  
113 clinical trial and literature data. The clinical requirements to establish the evidence for the therapeutic  
114 scenarios in which FDCs may be used are described below. These therapeutic scenarios are:

- 115 • add-on treatment of patients insufficiently responding to an existing therapy with one or more  
116 (mono-) components;
- 117 • substitution in patients adequately controlled with two or more mono-components used in  
118 combination;

- 119
- initial combination therapy for patients receiving previously neither of the substances.

120 If the FDC contains three or more active substances, all above requirements still apply. For each of  
121 these scenarios the appropriate studies are described in the following sections. Sections 4.1 through  
122 4.3 describe the studies required to fulfil the basic requirements 1 (rationale) and 2 (evidence base)  
123 for any MAA for a FDC, section 4.4 describes additional requirements for FDC's containing new active  
124 substances, and where sections 4.5 (generic FDC's) and 4.6 (other FDC's) describe the 3<sup>rd</sup> requirement  
125 (verify that the evidence base presented is relevant to the actual FDC).

#### 126 **4.1. Treatment of insufficiently responding patients ('add-on indication')**

127 In this scenario, the FDC is intended to be used in patients who are insufficiently responding to an  
128 existing therapy with one (or more) mono-component(s). Patients who respond insufficiently should be  
129 defined according to the response criteria that are valid in the respective therapeutic field an FDC is  
130 developed in. In general, these are patients who after a sufficiently long period of time and using an  
131 optimal dose of a given active substance do not respond satisfactorily to that treatment. A second or  
132 subsequent active substance may then be added to improve the intended treatment effect.

##### 133 **Pharmacokinetics**

134 The applicant should discuss the need for performing Drug-Drug Interaction (DDI) studies with the  
135 active component(s) in the FDC. Both, the absence and the presence of human DDI studies should be  
136 justified, considering the following aspects:

- 137 - knowledge from *in vitro* and/or mechanistic data of the PK interaction;
- 138 - potential impact on other concomitantly used drugs, especially if the FDC contains a PK booster;
- 139 - request for granting waiver for DDI study if the application is in the setting of long established and  
140 well documented use of the combination or when the PK effects of DDI are well known.

141 In addition, the potential impact of combined pharmacology in vulnerable subgroups (patients with  
142 renal impairment, elderly, etc.) should be addressed. Where possible this could be done using  
143 population PK analyses in the efficacy/safety studies.

##### 144 **Pharmacodynamics**

145 Pharmacodynamics data are valuable to understand the pharmacological interrelation between the  
146 active components in the FDC. However, separate PD data may not be required if superseded by  
147 available clinical efficacy/safety data. A factorial design study may be valuable to support the  
148 pharmacological additive effects or synergism of the proposed combinations, especially when different  
149 effective dose levels of the monocomponents exist. A full factorial design study may reduce the need  
150 for certain steps in the inadequate or non responder studies; e.g. a waiver for some potential dose  
151 steps of the FDC.

##### 152 **Clinical efficacy/safety studies**

153 A randomised controlled trial (RCT) to prove superiority in inadequate/non-responders to single (or  
154 multiple) active components of the FDC is required to demonstrate that the FDC has greater **efficacy**  
155 in comparison with the respective mono-components. Superiority – or 'add on efficacy' can only be  
156 claimed to (mono)components to which patients have been demonstrated to be non-responsive and  
157 where the FDC has been shown to be more effective than treatment continuation of that  
158 (mono)component. A way to do this is by performing a 3-arm study comparing AB versus A versus B,  
159 in patients inadequately/not responding to A and/or B. A 2-arm scenario could be appropriate if

160 available in vitro, preclinical and/or PD data show no contribution of the additional active substance to  
161 efficacy of the FDC, e.g. in the case of a PK enhancer (see section 4.3). When appropriate surrogates  
162 or intermediate outcomes exist, efficacy data may be replaced by PD data.

163 For study design considerations, such as inclusion and exclusion criteria, appropriate endpoints and  
164 expected study duration, the relevant therapeutic guidelines should be consulted. Data available from  
165 PK, PD and efficacy/safety studies should allow for evaluation of all dose strengths of the FDC.  
166 Available PK and/or PD data may allow interpolation or bracketing approaches of evaluating certain  
167 dose steps in the clinical studies.

#### 168 ***4.2. Switch in patients adequately controlled with two or more mono-*** 169 ***components used in combination ('substitution indication')***

170 In this scenario the FDC is intended to be used in patients who are already stabilised on an optimal  
171 dose of the mono-components, where the mono-components will be discontinued and the FDC started.  
172 It may be possible that those components belong to different therapeutic classes, e.g. an analgesic and  
173 anti-emetic agent in the treatment of migraine.

174 It is expected it to have been established previously that the particular combination of components in  
175 the FDC can be used in patients who are insufficiently responding to an existing therapy with one (or  
176 more) mono-component(s).

177 Evidence of documented clinical use of the combination should be provided either through clinical trials  
178 or through literature data, or a combination of both (see above). These data should support that the  
179 evidence base for combined use of the components is established, see the data requirements in section  
180 4.1 or 4.3 for fulfilment of the basic requirements 1 and 2 discussed in section 4. Evidence of combined  
181 use only will not suffice to establish the positive benefit/risk of the combination. Bioequivalence of the  
182 FDC versus mono-components taken simultaneously has to be demonstrated according to the criteria  
183 outlined in section 4.6.

#### 184 ***4.3. Initial treatment***

185 In this situation, the patient is to be treated with FDC immediately, instead of the stepwise addition of  
186 the components in the FDC depending on the individual patient response. The definition of the target  
187 population requires particular attention and should be justified considering the particular therapeutic  
188 area where the FDC is developed in. It should be justified that the benefits of starting two drugs at the  
189 same time outweighs its disadvantages (unnecessary treatment, safety issues).

##### 190 ***Pharmacokinetics***

191 The same requirements apply as in the 'add-on indication' scenario, see section 4.1.

##### 192 ***Pharmacodynamics***

193 The same requirements apply as in the 'add-on indication' scenario, see section 4.1

##### 194 ***Clinical efficacy/safety studies***

195 The clinical efficacy/safety studies to support an FDC application for initial treatment will depend on the  
196 rationale of the FDC.

197 If the rationale is an improved **efficacy** in terms of greater clinical response compared to an initial  
198 therapy with one of the monocomponent(s) by the second monocomponents(s), an RCT is required  
199 and should demonstrate:

200 1) superior efficacy on a clinical outcome at a given time point, AND

201 2) an acceptable safety profile.

202 An efficient way to evaluate this is by performing a 3-arm study comparing AB versus A versus B.

203 In this case faster achievement of a therapeutic goal may not be necessary, if adverse clinical  
204 outcomes (e.g. resistance) can be prevented with combined therapy in comparison to therapy with  
205 monocomponents(s).

206 A specific sub-scenario is where monocomponents(s) are usually up-titrated gradually, and the  
207 rationale is improved efficacy in terms of a more rapid response compared to a gradual up-titration of  
208 the monocomponents(s). In such case, an RCT should demonstrate:

209 1) faster achievement of therapeutic goals (using a 'time to' analysis) by demonstrating a  
210 larger therapeutic effect at an earlier time point, AND

211 2) similar control at another (later) time point when patients have been titrated to the maximal  
212 dose levels in both the FDC arm and in the traditional gradual up-titration mono component  
213 arm, AND

214 3) an acceptable safety profile.

215 This is the scenario as described in the Guideline on clinical investigation of medicinal products in the  
216 treatment of hypertension (EMA/238/1995/Rev. 3).

217 A separate scenario is where it is established that monotherapy will not be adequate or appropriate to  
218 reach the desired therapeutic effect. For example, in the field of HIV/AIDS and for some anti-  
219 microbials, monotherapy is not an acceptable comparator, due to rapidly evolving drug resistance. In  
220 such case, the new FDC will be tested against an established combination in the pivotal studies.

221 Another scenario may be where phase 3 trials would be unrealistic to perform against  
222 monocomponents, where compelling mechanistic data (e.g. using biomarkers) would suggest an  
223 inadequate response to monotherapy. In these cases clinical data may be replaced by mechanistic data  
224 (e.g. *in vitro* or PD data) to demonstrate improved efficacy of the FDC versus (stepwise) up-titration of  
225 monocomponents.

226 If the rationale is that the initial use of an FDC results in improved **safety**, an RCT should be  
227 performed to demonstrate similar control (efficacy) at a given time point when patients have been  
228 titrated to the optimal dose level of the active substance(s) in both, the FDC arm and the traditional  
229 gradual up-titration mono-component arm. In addition, the clinical trial should demonstrate improved  
230 safety of the FDC, utilising explicitly defined safety events as co-primary endpoint(s). These safety  
231 endpoints need to be clearly defined in the study protocol, and the study should be powered to show a  
232 safety benefit. Evaluation of safety should focus on events that may occur early after treatment  
233 initiation, and that are related to exaggerated pharmacology. Two sub scenarios are envisioned. The  
234 first sub scenario is where an active substance is added to counteract or ameliorate adverse events  
235 caused by the other active substance(s) in the FDC. In this case a comparator arm with the 'safety'  
236 active substance may be omitted, if available *in vitro*, preclinical and/or PD data show no contribution  
237 of this substance to efficacy of the FDC. The second scenario is where the FDC consists of sub  
238 therapeutic doses of the individual active substances, in which case a comparison should be made of  
239 the FDC against optimal dose of the monocomponents(s). A way to evaluate this is by performing a 3-  
240 arm study comparing low dose of A and low dose of B (as combined in the FDC) versus optimal dose A  
241 versus optimal dose B.

242 Finally, the rationale may be an enhanced **PK/PD** profile of the FDC. In this case it is expected that  
243 the study is designed to comply with the requirements as described under efficacy. However, it may be  
244 sufficient to study the FDC versus the main pharmacological active substance only. If appropriately  
245 justified - based on in vitro, preclinical and/or PK and PD data – a comparator arm with the PK or PD  
246 enhancing active substance is not required in the clinical studies.

#### 247 **4.4. Additional requirements for development of FDCs with new active** 248 **substance(s)**

249 Should any of the above described fixed dose combinations contain one or more new active  
250 substances, i.e. not previously authorised in a medicinal product, the following development  
251 requirements apply in addition to the above. In the **pharmacokinetics** section a full clinical  
252 development of the new active substance is expected to fully define ADME, DDI profile (including with  
253 other active(s) in the FDC) and PK in special populations as would be expected within the MAA dossier  
254 of any new active substance. Furthermore, a full development of the **pharmacodynamics** of the NAS  
255 is expected, with a special focus on the pharmacological synergism with other active substance(s) in  
256 the FDC. Also, the potential for potentiating safety concerns, e.g. QT prolongation should be evaluated.  
257 A full dossier, including an RCT demonstrating **efficacy/safety** of the new active substance according  
258 to disease specific guidelines should be compiled.

#### 259 **4.5. Generic medicinal products**

260 The development of a generic medicinal product is based on demonstrating bioequivalence to a  
261 reference FDC. Bioequivalence should be demonstrated for all active substances in the FDC according  
262 to the principles of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.  
263 1/Corr). Pharmacodynamics and clinical efficacy/safety studies are not needed, and will not rescue a  
264 failed bioequivalence study.

#### 265 **4.6. Demonstration of bioequivalence**

266 In addition to the evidence base presented in sections 4.1 through 4.3, bioequivalence of the FDC  
267 versus mono-components taken simultaneously is in general required to bridge existing clinical data  
268 obtained from the combined use of mono-components with those from the fixed dose combination  
269 formulation. This to satisfy the 3<sup>rd</sup> basic requirement for an MAA for an FDC (see section 4). Criteria  
270 are given in "Guideline on the Investigation of Bioequivalence" and the "Pharmacokinetic and clinical  
271 evaluation of modified-release dosage forms". In case of different dose interval or timing compared to  
272 individual mono-components, additional data may be required, e.g. as those described in Q&A  
273 Document on the clinical development of fixed combinations of drugs belonging to different therapeutic  
274 classes in the field of cardiovascular treatment and prevention (EWP/191583/2005).

275 The bioequivalence study may be waived if all clinical data supporting the combined use are obtained  
276 with the actual FDC formulation.

277

278

279 **Definitions**

280 FC/FDC Fixed Dose Combinations

281 RCT Randomised Controlled Trial

282 PK Pharmacokinetics

283 PD Pharmacodynamics

284 NfG Note for Guidance

285 NAS New Active Substance

286

287 **References**

288 • Directive 2001/83/EC;

289 • The Rules governing Medicinal Products in the European Community, Notice to Applicants,  
290 Volume 2A, Chapter 1 on 'Marketing authorisation'.

291

**Examples of Fixed Dose Combinations in relation to pharmacodynamics effects and indications:**

## Acceptable combinations

- FDC of two or more active components with the same pharmacodynamic effects, and the same indication as the monocomponents (e.g. an FDC containing two antihypertensive agents in hypertension).
- FDC of 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).
- A combination of two or more active components with different pharmacodynamic effects, and the same indication as one component, but with the other component(s) aimed at ameliorating/relieving adverse effects of the other active component(s) in the FDC (e.g. an FDC containing an NSAID and a gastro-protective agent for pain relief).
- A combination of two or more active components with different pharmacodynamic effects, and the FDC having the same indication as one of the components, but one or more component(s) aim at improving the pharmacokinetic profile of the other active component(s) (e.g. an FDC containing levodopa and carbidopa for Parkinson's disease).

## Unacceptable combination

- A combination of two or more active components that have different pharmacodynamics effects, but where these components treat generally unrelated conditions (e.g. a FDC containing an antidepressant and an oral anti contraceptive to treat women with depression who do not want to become pregnant).