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4 Guideline on clinical development of fixed combination 5 medicinal products

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

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Guideline on clinical development of fixed combination medicinal products

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Executive summary

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. The active substances may be known active substances or substances that have not yet been authorised in the EU. This guideline addresses the clinical development requirements of fixed combination medicinal products, which shall reflect their intended therapeutic use and indication.

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

1. Introduction (background)

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

Clinical development should correspond to each situation/intended claim. In addition, particular attention should be given to the doses of each active substance in the fixed combination product. 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).

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

2. Scope

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 combination' medicinal product.

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.

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.

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

3. Legal basis

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

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

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 and ICH guidelines, especially those on:

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

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.

Applicants are required to justify the rationale behind a particular combination of active substances proposed for the intended therapeutic indication. 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 should improve the benefit/risk by either increasing or adding therapeutic efficacy, or by improving safety with the FDC in comparison to the use of the single active substance.

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

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

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

- 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;
- the combination is pharmacologically plausible and based on valid therapeutic principles;
- each component contributes to efficacy and safety and/or enhances PK/PD of (main) active substance(s).

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

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

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

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

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

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

Pharmacokinetics

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

- knowledge from *in vitro* and/or mechanistic data of the PK interaction;

- potential impact on other concomitantly used drugs, especially if the FDC contains a PK booster;

- 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.

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

Pharmacodynamics

Pharmacodynamics data are valuable to understand the pharmacological interrelation between the active components in the FDC. However, separate PD data may not be required if superseded by available clinical efficacy/safety data. A factorial design study may be valuable to support the pharmacological additive effects or synergism of the proposed combinations, especially when different effective dose levels of the monocomponents exist. 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.

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 the case of a PK enhancer (see section 4.3). When appropriate surrogates or intermediate outcomes exist, efficacy data may be replaced by PD data.

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

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

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

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).

Evidence of documented clinical use of the combination should be provided either through clinical trials or through literature data, or a combination of both (see above). 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. Evidence of combined use only will not suffice to establish the positive benefit/risk of the combination. Bioequivalence of the FDC versus mono-components taken simultaneously has to be demonstrated according to the criteria outlined in section 4.6.

4.3. Initial treatment

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

Pharmacokinetics

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

Pharmacodynamics

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

Clinical efficacy/safety studies

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

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, AND

2) an acceptable safety profile.

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

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

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

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

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

3) an acceptable safety profile.

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

A separate scenario is where it is established that monotherapy will not be adequate or appropriate to reach the desired therapeutic effect. For example, in the field of HIV/AIDS and for some anti-microbials, monotherapy is not an acceptable comparator, due to rapidly evolving drug resistance. In such case, the new FDC will be tested against an established combination in the pivotal studies. Another scenario may be where phase 3 trials would be unrealistic to perform against monocomponents, where compelling mechanistic data (e.g. using biomarkers) would suggest an inadequate response to monotherapy. In these cases clinical data may be replaced by mechanistic data (e.g. *in vitro* or PD data) to demonstrate improved efficacy of the FDC versus (stepwise) up-titration of monocomponents.

If the rationale is that the initial use of an FDC results in improved ***safety*****,** an RCT should be performed to demonstrate similar control (efficacy) at a given time point when patients have been titrated to the optimal dose level of the active substance(s) in both, the FDC arm and the traditional gradual up-titration mono-component arm. In addition, the clinical trial should demonstrate improved safety of the FDC, utilising explicitly defined safety events as co-primary endpoint(s). These safety endpoints need to be clearly defined in the study protocol, and the study should be powered to show a safety benefit. Evaluation of safety should focus on events that may occur early after treatment initiation, and that are related to exaggerated pharmacology. Two sub scenarios are envisioned. 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 FDC. In this case a comparator arm with the 'safety' active substance may be omitted, if available in vitro, preclinical and/or PD data show no contribution of this substance to efficacy of the FDC. The second scenario is where the FDC consists of sub therapeutic doses of the individual active substances, in which case a comparison should be made of the FDC against optimal dose of the monocomponents(s). 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.

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

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

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

4.5. Generic medicinal products

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

4.6. Demonstration of bioequivalence

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

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

Definitions

FC/FDC Fixed Dose Combinations

RCT Randomised Controlled Trial

PK Pharmacokinetics

PD Pharmacodynamics

NfG Note for Guidance

NAS New Active Substance

References

- Directive 2001/83/EC;
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 on 'Marketing authorisation'.

Annex

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 conceptive to treat women with depression who do not want to become pregnant).