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Guideline on clinical development of fixed combination medicinal products

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Guideline on clinical development of fixed combination medicinal products

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Executive summary

This is the 2nd revision of the guideline on clinical development of fixed combination medicinal products containing two or more active substances within a single pharmaceutical form. The active substances may be authorised 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 independent of the chosen legal basis for the submission of the marketing authorisation application.

1. Introduction (background)

Combinations of medicinal products are administered in a number of scenarios to improve clinical outcomes for patients. Potential advantages for combinations of medicinal products compared to treatment with monotherapy could be that:

- The combination improves response in those with inadequate response to monotherapy, has a greater overall effect and/or is more rapidly effective;
- The combination improves safety due to one active substance counteracting the adverse drug reactions of another or by combining doses that are sub-therapeutic when used in monotherapy.

Fixed combination medicinal products offer the possibility to simplify administration where a combination of active substances is already recognised with an existing therapeutic claim. Alternatively, a fixed combination medicinal product may be developed de novo to address a new therapeutic claim.

Clinical development should correspond to the intended claim (see sections 4.1 to 4.5). 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. The proposed combination should always be based on valid therapeutic principles. Also, the combined safety (and efficacy) profile of all active substances in the fixed combination medicinal product should be considered.

2. Scope

This document provides guidance on the clinical development strategy for a fixed combination medicinal product. 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. 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. 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).

The guideline primarily discusses the development of fixed combination medicinal products with two active substances. However, it is expected that the same principles would generally apply to fixed combination medicinal products containing three 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. The clinical development of herbal fixed combinations as well as those composed of vitamins, oligo-elements and minerals are also outside of the scope of this guideline.

3. Legal basis and relevant guidelines

The legal basis for applications concerning fixed combination medicinal products may vary depending on the particularities of the active substances in the combination and on 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), part I and II of the Annex I to Directive 2001/83/EC as amended and other pertinent elements outlined in the EU and the International Council for Harmonisation (ICH) guidelines, especially those on:

- Guideline on the investigation of bioequivalence - CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.
- Guideline on Pharmacokinetic and clinical evaluation of modified-release dosage forms - EMA/CHMP/EWP/280/96.
- Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents - CHMP/EWP/239/95 final.
- Guideline on the Investigation of Drug Interactions- CPMP/EWP/560/95/Rev. 1 Corr.
- Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4).

This guideline discusses overarching principles for the development of fixed combination medicinal products. The development programme for any product should be designed considering any specific therapy area guidance that is available on the EMA website.

4. Clinical data requirements for a fixed combination medicinal product

Summary: The basic scientific requirements for any fixed combination medicinal product 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 substances to the desired therapeutic effect (efficacy and/or safety);
    b. positive benefit-risk for the combination in the targeted indication.

    Three therapeutic scenarios are foreseen: add-on treatment, substitution therapy and initial combination treatment requiring different types of evidence.
3. ***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.

Rationale

Applicants are required to justify the pharmacological and medical rationale for the particular combination of active substances within the fixed combination medicinal product and for the intended therapeutic indication. 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. 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. 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).

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 Authorities or CHMP may be helpful in such situations.

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.

Evidence base

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

- Identify the population in need of the fixed combination medicinal product. Specific therapeutic guidelines on what may constitute an appropriate and defined target population for combination therapy should be considered.
- 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.

This evidence base can consist of dedicated clinical trials performed with the fixed combination medicinal product and/or clinical trials performed with the combined use of the individual active substances, literature data, or a combination of both clinical trials and literature data.

The *therapeutic scenarios* in which fixed combination medicinal products may be used are as follows:

- Add-on treatment of patients insufficiently responding to an existing therapy with one or more active substances (see section 4.1).
- Substitution therapy in patients adequately controlled with two or more active substances used in combination (see section 4.2).
- Initial combination therapy for patients receiving previously neither of the substances (see section 4.3).

Relevance of the evidence base to the fixed combination medicinal product

An additional requirement is to demonstrate that the evidence base presented is relevant to the actual fixed combination medicinal product. This is required where the evidence base is not generated with the fixed combination medicinal product itself. In section 4.6, the general expectations for bridging data obtained with concurrent use of active substances to a single fixed combination medicinal product are described. This requires demonstration of similar PK behaviour, usually through demonstrating bioequivalence. In this way, data obtained with combined use of individual active substance products are bridged to the use of the fixed combination medicinal product.

In case the active substances in the fixed combination medicinal product do not lead to systemic exposure, the CHMP guidance on locally applied locally acting products containing known constituents should be followed.

Clinical data requirements

For each of the three therapeutic scenarios the appropriate clinical requirements are described in the sections 4.1, 4.2 and 4.3, respectively. 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. Section 4.4 describes additional requirements for fixed combination medicinal products containing new active substances. Section 4.5 describes the requirements for generic products of already approved fixed combination medicinal products.

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

In this scenario, the fixed combination medicinal product is intended for use in patients who are insufficiently responding to existing therapy with one (or more of the) active substance(s) in the fixed combination medicinal product. In general, this scenario covers patients who after being treated with an optimal dose and for a sufficiently long period of time do not respond satisfactorily.

Pharmacokinetics

Pharmacokinetics of the individual active substances should be well understood.

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 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.

The potential impact of combined pharmacokinetics in vulnerable subgroups (patients with renal impairment, elderly, etc.) should be addressed. Where possible, this may 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.

The presence or absence of human DDI studies of the fixed combination medicinal product with other medicinal products should be duly justified considering the potential impact on other concomitantly used drugs, especially if the fixed combination medicinal product contains a PK enhancer (metabolic or transport inhibitor/inducer).

Pharmacodynamics

Pharmacodynamic data are valuable to understand the pharmacological interrelation between the active substances in the fixed combination medicinal product. A factorial design study may support the pharmacological additive effects or synergism of the proposed combinations, especially when different effective dose 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).

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 are required to demonstrate that the fixed combination medicinal product has greater efficacy in comparison with the respective individual active substances. Superiority or 'add on efficacy' can only be claimed to active substances to which patients have been demonstrated to be responding insufficiently. 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. 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. If appropriate surrogates or intermediate outcomes exist, they may be used in lieu of clinical outcome variables. 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 appropriate specific clinical guidance. The contribution of each active substance to efficacy is expected to be demonstrated.

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 fixed combination medicinal products.

If there is a considerable documented concomitant long-term use (as appropriate for the therapeutic area)of all active substances in the fixed combination medicinal product these data could be used to replace long-term studies with the fixed combination medicinal product itself.

4.2. Switch in patients adequately controlled with two or more active substances used in combination ('substitution')

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.

As detailed earlier, 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.

Pharmacokinetics/Pharmacodynamics

Bridging studies comparing pharmacokinetic data between the fixed combination medicinal product and authorised active substances taken simultaneously is essential and bioequivalence according to the criteria outlined in section 4.6 should be demonstrated. If the fixed combination medicinal product is administered at a different dose interval or time than (one of) the active substances, additional PD and/or clinical data are needed to support therapeutic equivalence. In case the different dosing regimen results in higher doses per administration, special emphasis should be put on the evaluation of safety.

Clinical efficacy/safety

As detailed in sections 4.1 and 4.3, documentation of clinical use of relevant medicinal products in combination should be provided either through clinical studies or published literature, or a combination of both. These data should support the rationale for combined use of the active substances (see above). Evidence of combined use only will not suffice to establish the positive benefit/risk of the combination.

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.

4.3. Initial combination treatment

In this situation, the patient is to be immediately treated with a combination of medicinal products, instead of the stepwise addition of the active substances in the fixed combination medicinal product based on the individual patient response. The definition of the target population requires particular attention and should be in accordance with the specific therapeutic area in which the fixed combination medicinal product is being developed. 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.

Pharmacokinetics/Pharmacodynamics

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

Clinical efficacy/safety

The design of clinical efficacy/safety studies to support a fixed combination medicinal product application for initial treatment will depend on its rationale, specifically to achieve superior efficacy or improved safety compared to use of the single active substances. In situations when it has been established that monotherapy will not be adequate, appropriate or ethical to reach the desired therapeutic effect, initial use of combination therapy should be easily justified (e.g. HIV).

Superior efficacy

Superior efficacy can be achieved 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 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.

B. A PK enhancer with one (or more) active substance(s) with established efficacy in the targeted indication

If a PK enhancer is added to one (or more) active substance(s), it is expected that the study is designed to comply with the requirements as described above under A). In this case, however, and if appropriately justified based on in vitro, preclinical and/or PK and PD data, a comparator arm with the PK enhancing active substance alone is not required in the clinical studies.

C. One (or more) active substance has no individual efficacy in the targeted indication

If one (or more) of the active substances has no efficacy in the targeted indication by itself and compelling mechanistic data (e.g. using biomarkers) would suggest a synergistic effect, mechanistic data (e.g. in vitro data), preclinical and human PD data may be sufficient to support a claim of improved efficacy of the fixed combination medicinal product instead of (stepwise) up-titration or addition of those active substances in a clinical efficacy/safety study. Still, improved efficacy over (an) individual active substance(s) that have established efficacy in the targeted indication needs to be shown as usual. The design of the pivotal clinical studies should be according to specific clinical guidance, where placebo or standard of care – instead of these individual active substances - may be acceptable as comparators. A direct comparison against individual active substances with established efficacy in the targeted indication would still be expected.

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).

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.

Omission of one component not appropriate/ethical

For example, in the field of HIV/AIDS and for some antimicrobials, monotherapy is not an acceptable comparator, due to rapidly evolving drug resistance. In such cases, new fixed combination medicinal products will be tested against an established combination of active substances in the pivotal studies.

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.

4.4. Additional requirements for development of fixed combination medicinal products with new active substance(s)

Should any of the above described fixed combinations contain one or more new active substances (NAS), i.e. not previously authorised in a medicinal product, the following development requirements apply in addition to what has already been mentioned earlier. In the ***pharmacokinetics*** section clinical development of the new active substance is expected to fully define absorption, distribution, metabolism, and excretion(ADME), DDI profile (including with other active components in the fixed combination medicinal product) and PK in special populations as would be expected within the marketing authorisation application (MAA) dossier of any new active substance. Furthermore, a full development of the ***pharmacodynamic*** properties of the NAS is expected, with special focus on the pharmacological synergism with other active substance(s) in the fixed combination medicinal product. Also, the risk for potentiating safety concerns, e.g. QT prolongation should be evaluated. 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.

4.5. Generic medicinal products

The development of a generic medicinal product is based on demonstrating bioequivalence with the reference fixed combination medicinal product (see also first paragraph section 4.6).This should be demonstrated for all active substances in the fixed combination medicinal product according to the relevant guidelines that are mentioned in section 3.Pharmacodynamic and clinical efficacy/safety studies are not needed, and will not rescue a failed bioequivalence study. 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 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.

4.6. Bridging the evidence base to the fixed combination medicinal product

Clinical data establishing the contribution of each active substance and the positive benefit-risk are often obtained from the combined use of individual active substances. In this case demonstration of similar pharmacokinetics (usually through demonstrating bioequivalence) of the fixed combination medicinal product versus its individual active substances taken simultaneously is required. This is to satisfy the third basic requirement for an MAA for fixed combination medicinal products. 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).

In case of different dose interval or timing compared to individual active substances, additional data may be required, see section 4.1.

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.

In those cases where the active substances in the fixed combination medicinal product do not lead to systemic exposure, guidance on the clinical requirements on locally applied, locally acting products containing known constituents should be followed.

5. References

Directive 2001/83/EC;

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

Definitions

BCS	Biopharmaceutics Classification System
COPD	Chronic Obstructive Pulmonary Disease
DDI	Drug-drug interaction
EU	European Union
ICH	International Council for Harmonisation
RCT	Randomised Controlled Trial
PK	Pharmacokinetics
PD	Pharmacodynamics
NfG	Note for Guidance
NAS	New Active Substance
SoC	Standard of care
ADME	absorption, distribution, metabolism, and excretion
MAA	Marketing authorisation application