

## FIXED-COMBINATION MEDICINAL PRODUCTS

<b>Guideline Title</b>	<b>Fixed -Combination Medicinal Products</b>
<b>Legislative basis</b>	<b>Directive 75/318/EEC as amended</b>
<b>Date of first adoption</b>	<b>October 1983</b>
	<b>This version adopted April 1996</b>
<b>Date of entry into force</b>	<b>October 1996</b>
<b>Status</b>	<b>Last revised April 1996</b>
<b>Previous titles/other references</b>	<b><i>Testing and Licensing Criteria for Fixed-Combination Medicinal Products/ III/5773/94, CPMP/EWP/240/95</i></b>
<b>Additional Notes</b>	<b>This note for guidance concerns the application of Part 4, section C 6, of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. It replaces the previous 1983 guideline: <i>Fixed Combination Products</i>. It should be read in conjunction with other guidelines in this volume (e.g <i>Clinical Investigation of Oral Contraceptives; Investigation of Chiral Active Substances; Biostatistical Methodology in Clinical Trials; Dose Response Information to Support Product Authorisation</i>).</b>

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# FIXED-COMBINATION MEDICINAL PRODUCTS

Note for guidance concerning the application of section C.6 Part 4 of the Annex to Directive 75/318/EEC as amended, with a view to the submission of an application for a marketing authorisation for a new medicinal product. This guideline should be read in conjunction with current EC guidelines (e.g. *Clinical Investigation of Oral Contraceptives; Investigation of Chiral Active Substances; Biostatistical Methodology in Clinical trials; Dose Response Information to support Product Authorisation*).

## 1 JUSTIFICATION

- 1.1 Applicants will be required to justify the particular combination of active substances proposed. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.
- 1.2 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 of the standards and protocols with respect to efficacy and safety.

Potential advantages of fixed combinations include one of the following:

- a) an improvement of the benefit/risk assessment due to:
  - i. addition or potentiation of therapeutic activities of their substances, which results in:
    - a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile;
    - or
    - a level of efficacy above the one achievable by a single substance with an acceptable safety profile.
  - ii. the counteracting by one substance of an adverse reaction produced by another one.
- b) a simplification of therapy which improves patient compliance. When it is the only claim, it would be restricted to particular situations (e.g. non-prescription products).

Disadvantages of fixed combinations include:

- i. the fact that even a combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient;
- ii. the addition of the different adverse reactions specific to each substance.

### 1.3 General rules

Combinations, in principle, may not be considered rational if the duration of action of the substances differ significantly. This may not necessarily apply where it can be shown that the combination is clinically valid despite differences in this respect, e.g. if one substance is intended to enhance absorption of the other or where the substances are intended to exert their effects successively.

Each substance of the fixed combination must have documented contribution within the combination.

The inclusion of a substance to counteract an adverse reaction of an other substance may be considered justified, but only if the adverse reaction is a serious or a commonly occurring one.

The inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse is undesirable.

Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.

## 2. INDICATIONS

The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect. The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use.

An indication must be a well-recognised disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity. The individual substances of a fixed combination may be intended to relieve simultaneously different symptoms of such a disease state. In this case, it should be a prerequisite that these symptoms regularly occur simultaneously in a clinically relevant intensity and for a relevant period of time. It will not be proper to regard each individual symptom as an indication for the fixed combination, since it may also occur in other diseases and for treating this symptom alone the other substances may be irrelevant.

Fixed combination medicinal products may be indicated in different situations:

- in first line therapy, for patients receiving previously neither of the substances;
- in second line therapy, when monotherapy has not demonstrated a satisfactory benefit/risk ratio.

The applicant should clearly state if the claimed indication is first line, second line therapy or other uses and the clinical development should be performed accordingly.

## 3. PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

The possibility of interactions between the substances should always be considered. The applicant should submit data either to establish that such interactions do not occur or that they are clearly recognised and defined.

### 3.1 Pharmacodynamic studies

Frequently, the addition or the potentiation of the pharmacodynamic effects of the various substances may constitute the rationale of the fixed combination.

In this case several dose combinations for each substance might have to be tested and the concentration-response information can help to select the fixed combination leading to a satisfactory response.

### 3.2 Pharmacokinetic studies

In general, the applicant must demonstrate that the various substances do not affect each others respective pharmacokinetic patterns.

In some cases, however, a pharmacokinetic interaction (i.e. combination with a metabolism inhibitor) constitutes the rationale of the fixed combination.

These interactions should be studied in healthy volunteers but also in patients if the disease modifies the pharmacokinetics of one substance and in high risk subgroups (elderly, patients with renal failure or hepatic impairment).

## 4. EFFICACY AND SAFETY

It is permissible to distinguish between the extent of the studies required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use provided these are thoroughly and reliably documented, and those studies required in the case of those combinations which are essentially new:

- a) When the fixed combination corresponds closely to combinations that are already in widespread use, a well founded bibliographical data analysis should be submitted. Provided that the respective data are thoroughly and reliably documented, this analysis may be helpful in reducing the amount of clinical trials to be performed and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination.
- b) When the fixed combination is essentially new (active substances not usually combined, unusual quantitative composition of usually combined substances or one substance entirely new), the data needed are similar to a new chemical entity in the situation where the fixed combination is to be proposed (first line or second line therapy). Existing experience with the substances should be taken into account.

### 4.1 Composition and dosage regimen

**The proposed dosage regimen must be justified.**

The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone.

The multilevel factorial design may be used but other confirmatory strategies exist to prove that the combination is superior to its substances. Descriptive tools such as response-surface methods may be useful (see *Dose Response information to Support Product Authorisation*).

In some cases, studies have to be specifically designed to determine the minimal effective dose and usual effective dose of the fixed combination. Multiple dose-effect studies may be required.

Where substances are intended to relieve simultaneously different symptoms or to prevent different diseases, selected doses of each substance are often those commonly used for the treatment of each symptom or the prevention of each disease.

## 4.2 Therapeutic trials

Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible.

Comparative clinical studies of the fixed combination versus reference treatment might be necessary.

## 4.3 Safety aspects

Safety studies in animal should, as a general rule, have been performed with the active substances of the fixed combination in the proportion present in the product. Such studies will not be required where all the substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented.

In the case of combinations for long-term use (note for guidance on *The Extent of Population Exposure to Assess Clinical Safety for Medicines intended for Long-term Treatment of Non-life-threatening Conditions*), safety data on 300-600 patients for six months or longer will be required. The absence of such data should be justified by the applicant.

Where there are grounds to expect that a fixed-combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual substances given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination e.g. increased efficacy, outweigh such disadvantages.

## 5. COMBINATION PACKS

The principles applicable to fixed-combination products will also be applied in the assessment of preparations consisting of different medicinal products in combination packs where the products are intended for simultaneous or sequential administration.

## 6. CHEMICAL COMBINATIONS AND COMPLEXES

This guideline is also applicable to a new chemical substance which dissociates in vivo into two well known active substances. A rationale should be given.