



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE NON-CLINICAL DEVELOPMENT OF FIXED COMBINATIONS OF
MEDICINAL PRODUCTS**

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Disclaimer

This document aims at providing guidance on the development of a non-clinical program for fixed combinations. It is however, without prejudice to the legal basis for submission of a Marketing authorisation application for such product, which should be discussed with the relevant Competent authority on a case-by-case basis.

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MEDICINAL PRODUCTS**

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EXECUTIVE SUMMARY

When developing a fixed combination the non-clinical program will vary depending on the characteristics of the single components, on the existing non-clinical and clinical experience of their individual and concomitant use as well as the intended clinical use. When there is no experience from use of the combination, even if the individual components are known, bridging studies addressing expected and potential unexpected pharmacodynamic, pharmacokinetic and toxicological interactions are in principle needed. For any non-clinical combination study, the dose selection should be based on considerations of interspecies differences in pharmacokinetics as well as pharmacodynamics in order to, as close as possible, encompass the clinical situation, both in terms of systemic exposure of animals to the individual components as well as in relation to pharmacodynamic effects while avoiding high-dose non-clinical effects that may be irrelevant to human safety assessment.

1. INTRODUCTION

The rationale for a combination therapy and a fixed combination is often that pharmacological or pharmacokinetic interactions lead to improved efficacy or safety profiles, compared with the single components. Single components may also be combined for dosing convenience, to improve patient compliance.

The main aim with the non-clinical studies to support the clinical development of a fixed combination is to characterise potential additive, potentiation or antagonistic effects of the compounds when used together with respect to the pharmacology, pharmacokinetics or toxicology of the combination under development. Additionally, these studies may identify toxicity unique to the combination and previously not seen for either compound administered alone.

2. SCOPE

This document provides guidance on the non-clinical strategies to be considered when developing a fixed combination based on the different data available in order to support the safe human use as well as avoid unnecessary repetition of animal studies. The Guideline applies to fixed combinations consisting of chemically defined substances, biological substances or of herbal substances/herbal preparations. The guideline may also be considered in situations of development of a combination therapy not involving a fixed combination formulation.

The guideline does not apply to vaccines.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended), and relevant CHMP and ICH guidelines.

4. MAIN GUIDELINE TEXT

4.1 General Consideration

The extent as well as design of non-clinical studies needed to support development of a fixed combination will depend on the available data for the compounds to be combined, as well as the intended clinical use. Several scenarios are possible:

1. A fixed combination of compounds already approved as free combination therapy.
2. A fixed combination of approved compounds not approved as combination therapy.
3. A fixed combination containing one or more New Active Substances
 - 3.1. New Active Substance in combination with one or more approved /well known compound.
 - 3.2. Combination of two or more New Active Substances

4.2 Planning studies for a fixed combination

4.2.1 Fixed combination of compounds already approved as free combination therapy

When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). If the combination contains compounds from the same classes, as other compounds in well established combinations, for which there is considerable clinical experience and there are no pharmacokinetic interactions identified, further non-clinical studies may not be needed. A justification should in such case be provided. However in some situations certain non-clinical testing may still be warranted e.g. when the non-clinical data package does not fulfil the recommendations outlined on the draft Note for Guidance on the Non-Clinical Documentation of Medicinal Products for Mixed Marketing Applications (CPMP/SWP/799/95).

4.2.2 Fixed combination of approved compounds NOT approved as free combination therapy

For combination of approved compounds not approved as combination therapy, even though the safety and efficacy of the individual substances have been considered adequately documented for approval, some aspects regarding expected as well as potential unexpected interactions may still need to be addressed (CPMP/EWP/240/95). If pharmacodynamic interactions are the rationale for the combination, such effects should be documented. Relevant non-clinical studies may be part of the proof of principle. Pharmacodynamic data with the combination may also be justified to allow assessment of unexpected/undesirable interactions.

Non-clinical (*in vitro* or *in vivo*) or clinical pharmacokinetic interaction studies with the combination should be considered, when appropriate. Provided that the pharmacokinetics of the single components are adequately characterised in animals, including the profile for enzyme induction and inhibition and drug-drug interactions, additional non-clinical documentation on pharmacokinetic interactions is generally not needed (CPMP/EWP/240/95).

If a pharmacokinetic interaction constitutes the rationale for the combination, such interaction should be documented and appropriate non-clinical data may be needed.

For the safety evaluation of the fixed combination, safety pharmacology and toxicity studies should be considered. The need for (combination) studies will depend on the type of the anticipated interactions between the components and on the range of concentrations and exposures covered in the available studies with the single components. If the systemic exposure expected from the use of the fixed combination is not covered adequately by the existing data, additional studies may be warranted. Additional testing may also be justified if the compounds to be combined target the same organ system(s), or belong to a class of compounds associated with a specific type of toxicity. The toxicological profile of the combination may be studied in non-clinical bridging studies, to support the safe human use and identify potential interactions. In these bridging studies, specific endpoints addressing safety concerns based on the characteristics (pharmacology, toxicology) of the individual components may be included in addition to the conventional toxicological evaluation. If sufficient systemic exposure can be obtained, identified relevant safety pharmacology endpoints to be studied may also be included into the (bridging) toxicity studies. In addition, special and/or mechanistic studies may be warranted, e.g. studies addressing immunotoxicity or dependence, depending on the properties of the individual components in the combination.

4.2.3 Fixed combination containing one or more New Active Substances

For New Active Substances developed to be used in a fixed combination or for combined therapy, different possibilities can be envisaged. One approach may be to undertake a complete non-clinical development program with the New Active Substance(s), together with additional bridging studies with the combination, taking the considerations outlined in this document into account. Another approach may be to perform a more extensive non-clinical development program with the combination, together with a limited set of studies with the New Active Substance alone. In each situation, reference to relevant guidance documents should be made.

4.3 Dose Selection

It is desirable that the non-clinical studies are designed in such a way that the exposure range encompasses the anticipated human clinical situation while avoiding high-dose non-clinical effects that may be irrelevant to human safety assessment. Doses in nonclinical studies should be selected to cover for and allow the safe administration of different drug-drug ratios in clinical trials even if only one is ultimately selected for filing and marketing. Deviations from the clinical dose ratios may be necessary if there are marked interspecies differences in the pharmacokinetic or pharmacodynamic profiles of the compounds. In such a case, adjustment of the dose ratios may be needed to allow appropriate exposure and to avoid irrelevant pharmacodynamic effects in animals masking effects that are relevant for the human safety assessment.

4.4 Species Selection

For general toxicity studies usually one species only may be sufficient. The selection of the species used should be scientifically justified based on pharmacodynamic responsiveness to both components, pharmacokinetics, metabolism, target organs and sensitivity to the toxicological aspects.

4.5 Safety Pharmacology Studies

The need for safety pharmacology studies with the combination will depend on the type of anticipated interactions between the components. The range of concentrations and exposures covered in the available studies with the single components should be taken into consideration. Separate safety pharmacology studies to address specific endpoints (e.g. to study effects on organ systems of concern) may be needed before the initiation of clinical trials with the combination.

4.6 General toxicity studies

For a fixed combination containing approved compounds indicated for long-term use where experience of concomitant use is lacking, a 3-month repeat dose toxicity study in one appropriate species, supported by toxicokinetic data is generally recommended. The need for studies of longer duration or in an additional species will depend on the effects observed with the combination compared with those induced by the individual components, and on the anticipated pharmacodynamic and/or pharmacokinetic interactions. In cases with complex pharmacodynamic and/or safety profiles, (e.g. targeting of multiple receptors or signalling cascades) or if there is limited clinical experience with any of the components, further studies may be warranted (e.g. mechanistic studies addressing specific endpoints). On the other hand, a study of shorter duration may also be justified when the intended clinical use is of short duration. Depending on the pharmacological and toxicological profiles of the individual components, collection of data on specific endpoints in addition to the standard parameters monitored in such studies may be recommended. Study designs should be flexible enough to allow as much as possible the comparison with individual components. When the available information with the individual components is insufficient, inclusion in the bridging studies of comparator group(s) treated with the individual components may be needed.

4.7 Genotoxicity

For fixed combination of non-genotoxic substances, genotoxicity studies with the combination are not needed. If there are concerns regarding genotoxicity for one substance in the combination, further evaluation of e.g. the possibility of a potentiation of the identified effect may be needed. The rationale for addressing such a situation should be assessed on a case-by-case basis taking into consideration the available knowledge of the components and the possible potentiation of genotoxicity might have on the benefit-risk ratio of the combination in the intended indication.

4.8 Carcinogenicity

The carcinogenic potential of a combination should be addressed on the basis of existing information for the individual components. If the fixed combination contains compounds assessed as non-carcinogenic, carcinogenicity studies with the combination would not be needed. If there is any concern related to one compound in the combination, the risk that this concern increases due to

interactions with the additional components, should be carefully addressed. If possible and meaningful, it is advisable to include relevant endpoints e.g. for cell proliferation in the bridging repeated dose toxicity study(ies), to obtain further data to address any concern identified

As for general toxicity testing, comparator groups treated with the individual components may also be included if existing data are not considered to be sufficient.

If the combination contains one New Active Substance, the ideal situation would be that additional animal groups treated with the combination are included into the carcinogenicity study(ies) with the New Active Substance. Deviations from this approach may be acceptable and should be considered on a case-by-case basis. A similar approach as outlined above would apply.

4.9 Reproductive Toxicity Studies

When the single components have been adequately tested, and the reproductive/developmental toxicity profiles of these compounds are sufficiently characterised, additional studies with the combination may not be warranted. However, the decision will depend on the nature and properties of the individual components and of their potential interactions.

4.10 Timing on nonclinical studies

When deciding on the timing of studies with a combination in relation to clinical trials the principles of ICH M3 Guideline (CPMP/ICH/286/95: Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) will apply. Any deviations from ICH M3 guideline principles should be appropriately justified.

5. REFERENCES

- Note for Guidance of Fixed Combination Medicinal Products (CPMP/EWP/240/95).
- Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95).