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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
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**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**

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# 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

## I. INTRODUCTION

In the recent past, a number of scientific advices, both centralised and decentralised, have been requested on the clinical development of fixed combinations of drugs intended for the prevention and treatment of cardiovascular diseases. These combinations consist of drugs (two or more), combined in a unique formulation, in order to cover a wider spectrum of the cardiovascular prevention and treatment. The pharmacological strategies may involve use of antiplatelet, antihypertensive, lipid-lowering and glucose-lowering therapies.

## II. PROBLEM STATEMENT

These therapeutic strategies are likely to be common in the future. It is anticipated that applications of fixed drug combinations containing two or more drugs intended mainly for cardiovascular prevention are likely to appear in the near future. The heterogeneity of this therapeutic field makes it difficult to develop a standard Note for Guidance or Points to Consider document. Therefore a Question and Answer document, addressing the crucial points that should be discussed within scientific and regulatory frameworks, is considered necessary.

## III. QUESTIONS

### III.1 Question 1

**What would be the clinical data needed for a fixed combination aimed to cover a SUBSTITUTION INDICATION: Medicinal product Z (combination of Y and X at doses D1 and D2) is indicated as substitution therapy of patients adequately controlled with Y and X, given concurrently, at the same dose level as in the combination.**

Under this circumstance, only a mere replacement indication (i.e. those patients in need of both monocomponents and adequately controlled on the proposed doses) would be acceptable. This approach is, in principle, only expected when tackling with drugs with a wide therapeutic experience and an adequately established benefit/risk ratio. The fixed combination is then just expected, at least from a theoretical point of view, to improve therapeutic compliance over the drugs administered separately. However, any specific claim in this regard should be supported by experimental data.

These combinations should not be intended for the first line therapy, since the verification that the patient is adequately controlled with the same doses of both products given separately is a prerequisite. Pharmacokinetic and (occasionally) pharmacodynamic data would generally suffice for this type of applications. Depending on the dose interval and timing of each component of the combination, three different clinical scenarios can be anticipated:

***III.1.1 Scenario A. The components of the combination (Y and X) are administered at the same dose interval (generally QD or BID) and timing.***

Formal bioequivalence studies testing the rate and extent of absorption of each component of the combination as compared to each substance administered in monotherapy should be carried out. The recommendations issued in the *CPMP/EWP/QWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence* are fully applicable with regard to the following aspects: type and design of study depending on the type of formulation, need of food interaction assessment, dose proportionality and pharmacokinetic acceptance criteria. Depending on the knowledge and clinical

experience with the components of the combination the need for additional safety data should be considered.

**III.1.2 Scenario B. The components of the combination (Y and X) are administered at the same dosing interval (generally QD or BID) but different dose timing (e.g. Both, X and Y are administered QD, but X is administered at breakfast time in the morning and Y at night time) (e.g. antihypertensive plus statin).**

In addition to the above mentioned requirements and unless properly justified, the MAH should demonstrate that the change in the timing of administration of one of the components of the combination does not affect the pharmacodynamic effect of any of the constituents of the combination. Therefore, in addition to the demonstration of a similar pharmacokinetic profile, a non-inferiority pharmacodynamic study assessing the effect of the combination as compared with both components administered at their usual dose timing is expected. The delta for each pharmacodynamic endpoint should be prospectively defined and its clinical relevance justified. If relevant, the circadian rhythm of the pharmacodynamic effect should also be assessed and its clinical implication discussed. Depending on the knowledge and clinical experience with the components of the combination the need for additional safety data might be considered.

**III.1.3 Scenario C. The components of the combination (Y and X) are administered at a different dose interval (generally QD and BID) and consequently at a different dose timing as well.**

Generally, one of the components will be kept at its usual dosing recommendation while the other one (normally the one administered BID) will change. Therefore, this combination would mean an entirely new dose regimen for one of the components of the combination, involving a change in the dose interval, the dose per intake, and potentially the overall daily dose. As such, the data required for the clinical development of a new combination should address separately the pharmacokinetic similarity of the unchanged component as compared with the substance used in monotherapy and the therapeutic equivalence of the other component in clinical studies as compared with the normal dosing schedule as given in monotherapy. As stated above, the non-inferiority margin should be properly discussed and pre-defined in the study protocol. Last but not least, in case that the simplification of the dosing regimen implies the administration of higher dose per drug intake, the clinical safety of the combination should be also properly addressed in order to rule out that the increased dosing will not impair the safety profile of the therapeutic regimen.

## **III.2 Question 2**

**What would be the clinical data needed for a fixed combination aimed to cover a wider indication than the intersection of target populations for both drugs administered as monotherapy.**

In this case, the combination is aimed to cover a target population that surpasses the pure substitution indication. In that sense, the outermost case would be the claim of an entirely new indication (e.g. prevention of CV events in patients at high risk of CV events) contemplating a new and wider target population not covered by any of the components of the combination. This case should be considered as an entirely new clinical development. The dose selection for each component should be properly justified, preferably through a clinical study with a factorial design. The efficacy and safety profile of the combination in the target population should be fully documented. In this regard, the contribution of both components to the intended therapeutic effect should be clearly demonstrated. Depending on the nature of the claimed indication, outcome studies will be probably needed.