The European Agency for the Evaluation of Medicinal Products
*Evaluation of Medicines for Human Use*

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# CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) POINTS TO CONSIDER ON BIOSTATISTICAL/METHODOLOGICAL ISSUES ARISING FROM RECENT CPMP DISCUSSIONS ON LICENSING APPLICATIONS: CHOICE OF DELTA

## 1. INTRODUCTION

Following discussions surrounding a number of recent applications, a further topic has been added to the list of statistical/methodological refered to the Efficacy Working Party by CPMP. This is the choice of the margin of equivalence or non-inferiority ('delta' or Δ) in comparative clinical trials with these purposes. This issue is refered to in ICH Topics E9 (Statistical Principles for Clinical Trials) and in the Step 2 draft of ICH E10 and also in the recent CPMP position paper on Superiority, Non-inferiority and Equivalence. However, the discussion in these documents is limited.

## 2. PROBLEM STATEMENT: CHOICE OF DELTA

When a trial is designed to compare a new product with an active comparator, the objective is frequently to demonstrate:

- the non-inferiority of the new product or
- the equivalence of the two products.

In order to demonstrate equivalence, the conventional and prefered approach is to pre-specify a margin of equivalence in the protocol and then to show during analysis that a 95% confidence interval for the true difference between the two agents lies entirely within this interval. The same approach is used for non-inferiority trials, attempting to demonstrate that the 95% confidence interval lies entirely on the positive side of the non-inferiority margin.

Hence the choice of the margin of equivalence or non-inferiority is critical to the conclusions. Under some circumstance such as mortality studies, there is an understandable reluctance to lose any part of the treatment effect attributed to standard agents. However, if rigidly enforced, this would make it impossible to license new agents with equivalent efficacy. Under other circumstances it may be more acceptable to use a delta of one half or one third of the established superiority of the comparator to placebo, especially if the new agent has safety or compliance advantages. In some cases, such as antibiotics, the chosen equivalence margin may vary according to the expected response rate to the standard treatment.

There are a number of related problems. The effect of the active comparator relative to placebo in any trial (or even in a meta-analysis) is itself subject to uncertainty, reflected in a confidence interval, and this uncertainty is carried over to delta. There may be differing estimates of the effect of the comparator from different trials. Furthermore, the acceptable degree of inferiority may depend upon as yet unknown safety advantages.

This is a difficult topic because there is no body of conventional wisdom to draw on. It may not be possible to reach definitive conclusions.

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## 3. RECOMMENDATION

It is proposed that a paper be written for CPMP giving an EU understanding of the factors influencing the choice of delta and, if possible, proposing appropriate methods of making a choice and giving the circumstances when this choice would be appropriate. This might be adopted as a positon paper or a Points to Consider.

## 4. TIMETABLE

A draft should be available for circulation to EWP by end 1999 and the final version submitted to CPMP in March 2000 following further discussion as necessary with relevant experts.