The European Agency for the Evaluation of Medicinal Products
Pre-authorisation evaluation of medicines for human use

London, 28 June 2001
EMEA/17424/01

EMEA/CPMP POSITION STATEMENT ON THE USE OF PLACEBO IN CLINICAL TRIALS WITH REGARD TO THE REVISED DECLARATION OF HELSINKI

The scientific committee of the European Agency for the Evaluation of Medicinal Products, the Committee for Proprietary Medicinal Products (CPMP), is responsible for providing scientific opinions to the European Commission for the granting of Marketing Authorisations for medicinal products within the European Union (EU).

In the EU, the requirements and standards for clinical trials using medicinal products are set out in Regulations, Directives and Guidelines. According to Council Directive 65/65/EEC of 26 January 1965 as amended, marketing authorisations may be granted provided that quality, safety and efficacy of medicinal products have been satisfactorily demonstrated by the applicant. Granting marketing authorisations to new medicinal products when their benefit to risk balance is at least the same as that of established therapies, if any, is a basic public health principle. These criteria form the basis of the CPMP's scientific opinions. The legislation provides for flexibility in the type and design of trials required for the demonstration of efficacy and safety. Council Directive 75/318/EEC as amended, states that "*in general clinical trials shall be done as 'controlled clinical trials' and if possible, randomised; any other design shall be justified. The control treatment of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo*".

Guidance on the design of trials in support of a marketing authorisation application is provided in the CPMP guidelines, either harmonised globally through the International Conference on Harmonization (ICH), or in the European Union (this is one task of the Efficacy Working Party of the CPMP). In this respect, guidance on the choice of control groups is provided by the ICH E10 guideline and the various guidelines developed for particular therapeutic classes.

Council Directive 75/318/EEC also specifies that "*all clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinski*".

A revised version of the Declaration of Helsinki was issued recently (October 2000) and it remains a vital expression of medical ethics whose aims deserve unanimous support. Section 29 in particular states[1] that "*The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not preclude the use of placebo, or no treatment in studies where no proven prophylactic, diagnostic or therapeutic method exists.*" A strict interpretation of the Declaration appears to rule out clinical trials that use a placebo control arm whenever authorised therapeutic methods already exist, preferring active controls.

Although the efficacy of some new medicinal products can be satisfactorily demonstrated without the use of a placebo, for others the judicious use of placebo remains essential to demonstrate their value. Where medicinal products do exist for a given indication, active controlled trials are encouraged provided that a methodologically acceptable demonstration of efficacy and safety can be obtained. However, trials that seek to prove that a new agent and an active control have similar efficacy are inherently less reliable than trials that seek to prove the superiority of the new agent to a comparator, whether inactive or active. Increasing the size of trials does not alleviate this problem. In some areas of medicine this lack of reliability means that it is only possible to obtain convincing scientific evidence of the efficacy of a new medicinal product by means of superiority trials. The use of an active control in such an area of medicine would mean that a new product would always have to demonstrate an improvement in efficacy over a currently authorised treatment. This may be too

[1] this was maintained with small modifications from the 1996 version

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restrictive as, for example, granting an authorisation to a new medicinal product with similar efficacy and improved safety, may also be in the best interest of patients.

There are a number of conditions that govern and restrict the use of placebo in order to avoid un-ethical use. First and foremost, the period during which a placebo is administered must not entail any additional risk of irreversible harm to the patient. Also, the patient included in the trial, or his/her legal representative, must receive and understand appropriate information on the trial, and give informed written consent. The patient's right to withdraw at any time, but still receive conventional treatment must be respected. It is acknowledged that un-ethical abuses of placebo in trials of medicinal products may occur in any country, and this potential for abuse should be eliminated. Similar ethical standards should be applied in trials performed in the European Union as well as in foreign countries. These aspects fall within the responsibilities of Ethics Committees reviewing protocols of clinical trials; they are also emphasized in ICH E6 guideline on Good Clinical Practice and in the recent Council Directive 2001/20/EC on Good Clinical Practice[2].

Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products. Reliable scientific evidence of efficacy and safety ensures that a reliable evaluation of the balance of benefits and risks for a particular medicinal product can be made, avoiding erroneous decisions of either withholding or mistakenly granting a marketing authorisation. Provided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP and the EMEA that continued availability of placebo-controlled trials is necessary to satisfy public health needs.

[2] In the 'Whereas' of the Directive: "*The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration"*. and in article 3, "*A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored."*