EU Standard of Medicinal Product Registration: Clinical Evaluation of Risk/Benefit - The role of Comparator Studies

Problem statement

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

As regards the criteria for authorisation of a medicinal product it is set out in Regulation (EEC) 2309/93 Article 11(1) that a marketing authorisation shall be refused if it appears that the quality, the safety or the efficacy of the medicinal product have not been adequately or sufficiently demonstrated by the applicant. Article 26(1) of Council Directive 2001/83/EC is worded a little differently but the criteria are the same irrespective of the procedure for the marketing authorisation. Furthermore, it is set out in the legislation that marketing authorisation can be refused only on grounds set out in the legislation, cf. Article 68(1) of Regulation (EEC) 2309/93 and Article 126(1) of Council Directive 2001/83/EC respectively. Recital 3 of Regulation (EEC) 2309/93 provides: “Whereas in the interest of public health it is necessary that decisions on the authorization of such medicinal products should be based on the objective criteria of the quality, the safety and the efficacy of the medicinal product concerned to the exclusion of economic or other considerations; …” and recital 7 of Council Directive 2001/83/EC provides: “The concept of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorisation for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product”. These recitals explain the background of the criteria of quality, safety and efficacy and the risk/benefit assessment.

In the EU, the requirements and standards for clinical trials using medicinal products are set out in Regulations, Directives and Guidelines. The legislation provides for flexibility in the type and design of trials required for the demonstration of efficacy and safety. Annex I of Council Directive 2001/83/EC states that “in general clinical trials shall be done as “controlled clinical trials if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control group will vary from case to case and also will depend on ethical considerations and therapeutic area; 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”.

1 Article 26(1) of Council Directive 2001/83/EC: “The marketing authorisation shall be refused if, after the verifications of the particulars and documents listed in Articles 8 and 10 (1), it proves that: (a) the medicinal product is harmful in the normal conditions of use, or (b) that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or (c) that its qualitative and quantitative composition is not as declared.”
The EMEA/CHMP has previously expressed that it views placebo-controlled trials as essential to demonstrate the efficacy of some new medicinal products (EMEA/CPMP position statement on the use of placebo in clinical trials with regard to the revised declaration of Helsinki. EMEA/17424/01. London, 28 June 2001).

It is the objective of this communication to outline the study design relevant in different clinical scenarios and to further clarify the role of comparative studies against active comparators in facilitating the assessment of risk/benefit of any new medicinal product in the EU. Indeed, national competent authorities and EMEA/CHMP routinely perform risk/benefit assessments of new medicines, and active control trials may be an important source of information to take into account in assessing the risk/benefit of a new application.

Guidance on the design of trials in support of a marketing authorisation application is provided in the CHMP guidelines, either harmonised globally through the International Conference on Harmonization (ICH), or in the European Union. In this respect, guidance on the choice of control groups and on the various methodological problems is provided in the ICH Topic E 10 guideline (Choice of control group in clinical trials (CPMP/ICH/364/96)) and the various guidelines developed for particular therapeutic classes. CHMP scientific advice has also been made available to industry to aid in generating scientifically robust and reliable data for the assessment of comparative efficacy for individual products under development.

It should be pointed out that the notion of the assessment of risk/benefit of a new product being informed by an active comparator is considered part of the assessment of efficacy and safety and fundamentally different from the concepts of “placing the product in the therapeutic strategy” or “relative effectiveness” which implies two components: the added therapeutic value and cost effectiveness . These two components go beyond the standards of marketing authorisation (quality, safety, efficacy).

Design of clinical trials

There is no general rule applicable to all circumstances and the decision to require placebo and/or active control studies has been and will be taken on a case-by case basis although some fundamental principles apply.

It is useful to consider the following scenarios:

1) new medicine in the therapeutic area where no pharmacological treatment is available (scenario 1).
   Data will usually come from randomised and where possible double blind, placebo controlled trials. Sometimes no placebo is given and other designs are possible (see ICH/CPMP Topic E10 guideline)

2) new medicine in a therapeutic area where placebo is deemed unethical and active control exists (scenario 2).
   In this case, controlled trials will normally be against an active comparator, recognising the specific methodological aspects in assessing comparative data in the absence of a placebo group (see ICH/CPMP Topic E10 guideline).
   Other designs may also possible and should be justified (see ICH/CPMP Topic E10 guideline)

3) new medicine in a therapeutic area where placebo is deemed ethical and one or more established medicines are available (scenario 3).

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2 Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions. A stronger European-based pharmaceutical industry for the benefit of the patient – a call for action. 2003.
3 The ICH/CPMP guideline E10 use the terminology: „a pharmacological treatment that is shown to be lifesaving or to prevent irreversible mortality“.
Data on the effect size obtained through placebo controlled trials need to be put in perspective by considering the clinical context of the use of the product. This could be done through additional comparison with available established therapies and active-controlled trials/arms should be considered. The use of placebo will normally be necessary to determine the effect size and where necessary (see ICH/CPMP Topic E10 guideline) to ensure assay sensitivity in comparison with an active control. Three-armed trials provide means to assess clinical efficacy and should therefore be considered.

*The Risk/Benefit Assessment*

For recommendation of a marketing authorisation - in view of the clinical data - it is usually necessary to show:

- **In case no established pharmacological treatment is available (scenario 1),** that the R/B assessment of the new medicine is positive in the target population of the indication i.e. adequate therapeutic efficacy and acceptable safety profiles.

- **In case an established pharmacological treatment is available (scenario 2 and 3), two situations may be envisaged:**

  1) The new product does not compare unfavourably with an established active control in the target population of the indication, with (scenario 3) or without (scenario 2) a placebo controlled trial in the marketing authorisation application. Overall the benefits of the new medicine outweighs the risk and a marketing authorisation can be recommended. Should other clinical trial designs be used, these should be justified on a case-by-case basis and the same considerations should apply (namely that the new medicine does not compare unfavourably with existing medicinal products and/or is superior to placebo if an active comparator is not appropriate).

  2) The new product seems to compare unfavourably with an established medicinal product. It may for example be that the new product is shown to be more effective than placebo, but less effective than the active control. In such a case the overall R/B assessment taking into account all aspects of quality, efficacy and safety and the clinical context of use may still be positive, sometimes after introduction of relevant modifications to the product information. In this situation a recommendation of marketing authorisation will have to be discussed on a case-by-case basis.