CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR LONG-TERM USE

Guideline Title	**Clinical Investigation of Medicinal Products for Long-Term Use**
Legislative basis	**Directive 75/318/EEC as amended**
Date of first adoption	**February 1987**
Date of entry into force	**August 1987**
Status	**Last revised February 1987**
Previous titles/other references	***Clinical testing requirements for drugs for long-term use***
Additional Notes	**This note for guidance concerns the application of Part 4, section C of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. It provides advice on the planning and design of clinical trials likely to be demanded for long-term use.**

CONTENTS

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR LONG-TERM USE

INTRODUCTION

The general requirements for clinical trials are given in the Annex to Directive 75/318/EEC as amended. This note for guidance advises on those clinical trials likely to be demanded for long-term use. The planning and design of pre-marketing long-term studies should take into account specific problems raised by each type of substance and disease; the following are general guidelines and do not exclude specific recommendations for particular therapeutic classes.

1. DEFINITION OF LONG-TERM USE

a) The CPMP has already defined long-term use in its carcinogenicity guidelines as 'where the medicine is likely to be administered regularly over a substantial period of life, i.e., continuously during a minimum period of six months or frequently in an intermittent manner so that the total exposure is similar'.

b) Medicinal product therapy may therefore be classified as:

i) occasional, e.g., the infrequent use of an analgesic for occasional toothache or headache, the prescription of an antibiotic unlikely to be repeated, or an anaesthetic gas. This is not long-term use;

ii) intermittent use, e.g. an antibiotic regularly prescribed for chronic bronchitis, or regular use of an analgesic for dysmenorrhoea;

iii) prolonged use

iv) life-long use

} e.g., treatment of epilepsy, hypertension, rheumatoid arthritis, or heart failure.

Categories (iii) and (iv) are considered as long-term use and will be applied to any medicinal product when current medical practice is likely to bring the medicinal product into one of these categories, irrespective of any particular recommendation of the company concerned. Whether ii. constitutes long-term use in the sense of the present note for guidance will depend upon the circumstances of the case, especially the nature of the disorder, but also the risks thought to be involved and the novelty of the compound. The examples given are illustrative and not meant to be an exclusive list.

2. INVESTIGATION OF EFFICACY IN LONG-TERM STUDIES

a) The need for evidence of long-term efficacy generally assumes that efficacy in short-term use has been established for each proposed use by properly controlled studies with the formulation and dosage proposed. Evidence should also be provided that efficacy is maintained in long-term or repeated interrupted use.

b) Where relevant objective criteria of efficacy are available these should be used rather than subjective criteria.

c) Patients entering trials should be well defined with respect to diagnosis and presence of risk factors and should be as representative as possible of the population which will be later treated by the substance. Particularly, the extreme age-groups (elderly, children) should be appropriately included.

As with efficacy generally, evidence for each proposed use should be presented from well-controlled studies, each with an adequate number of comparable patients for scientific validity, with appropriate and well-defined end-points as criteria of efficacy.

The sample size must be sufficient to demonstrate adequate significant differences. In case of non-significant differences from control substances, it is necessary to demonstrate through calculation of power or confidence intervals that the sensitivity of the trial would have been sufficient to show relevant differences.

Randomised controlled trials should normally be carried out, placebo being employed in appropriate cases.

Other types of study, if carefully designed and executed, can contribute supplementary evidence of efficacy.

The duration of the studies may vary depending on the purpose of the trials and the nature of the substance. It should be sufficient to take into account any spontaneous variations in the course of the disease, possible effects of the substance on the course of the disorder and changes in compliance which are likely to occur.

If seasonal variations are believed to influence the course of the disease or response to therapy, this must be taken into account in arranging the trials and interpreting the results.

Evaluation of results should always include at least one analysis of all the patients allocated to treatment and control groups, including all withdrawals for whatever reason. The reasons why patients have failed to complete the study period should wherever possible be recorded. Description, fully documented, of all critical events, even those occurring after withdrawal from therapy, is required.

d) Where efficacy has been established in short-term studies at dose levels higher than proposed in the long-term studies, evidence for efficacy needs to be based on adequate numbers studied at the actual dose or within the dose range proposed.

3. INVESTIGATION OF SAFETY IN LONG-TERM STUDIES

a) As with medicinal products for short-term use, it is important that evidence should be provided that an adequate number of patients have been monitored to rule out the occurrence of frequent serious adverse reactions and to define the frequency of less serious complications. Claims as to a relatively low frequency of adverse reactions will have to be supported by comparative studies.

The total clinical experience must generally include data on a large and representative group of patients (e.g. 100) exposed to the substance for at least 12 months, irrespective of the indications. In certain cases the applicant may be able to justify investigating a larger number of patients (200 to 300) for a shorter period of

time (six months). This may be relevant particularly when dealing with medicinal products for intermittent use. When the medicinal product's sole indication is a rare disease a smaller number of patients may be accepted.

These patients should be fully monitored for clinical, biochemical and haematological adverse reactions. Moreover, for certain medicinal products it would be useful to know the effect of the immune system. The exact requirements will necessarily vary with the nature of the substance and the disorder and the known adverse effects of related compounds. Naturally, this fully monitored group will, as a rule, only comprise part of the total clinical experience relating to long-term use. Data on individual patients who have received the medicinal product for longer periods should be presented if available.

b) The following specific points also need attention in any medicinal product proposed for long-term use:

i) No pre-marketing study is likely to provide a complete picture of long-term adverse reactions, and manufacturers are urged to undertake post-marketing monitoring;

ii) Evidence is needed on accumulation of the substance at the proposed dosage schedule, and that this schedule is safe and appropriate. Such evidence needs to be supplemented by clinical evidence of safety;

iii) With long-term use there is obviously an increased likelihood of concurrent use of other substances, and particular attention should be paid to the problem of substance interactions;

iv) Where there may be adverse reactions with a seasonal occurrence, e.g. photosensitivity, evidence of safety needs to be demonstrated accordingly. Where adverse reactions may occur in particular categories of patients (e.g. elderly, children) who are likely to receive the substance, then evidence for safety for such patients needs to be established;

v) Where adverse effects occur in a particular category of patients, and where it is proposed that the substance is safe for use in categories excluding such patients, then the evidence for safety needs to be based on adequate numbers studied in the subset for whom the use of the substance is proposed;

vi) Investigations should, where appropriate, be performed to determine whether withdrawal symptoms or a rebound effect occur when the medicinal product is stopped. Such effects should where possible be distinguished from mere recrudescence of the original symptoms;

vii) Where adverse effects have occurred at a higher dose than that proposed, evidence for safety must be based on adequate numbers studied at the proposed dose range.

4. FIXED COMBINATIONS

(See note for guidance on Fixed-Combination Medicinal Products.)

In principle the present note for guidance applies to new fixed combinations as well as to entirely new compounds. However, requirements in the individual case will depend upon the nature of the compounds and the originality of the fixed combination and its proposed use.