

# **Guidelines for preclinical and clinical testing of new medicinal products**

Part 2 – Investigations in man



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## **Part 2 – Investigations in man**

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## Foreword

These guidelines, which are published as separate pre-clinical (Part 1) and clinical (Part 2) sections, have been prepared for the Scientific and Technical Council by its Research and Development and Medical Committees. They represent the consensus views of the Committees' experts on good practice in the pre-clinical and clinical testing of new medicinal products for human use. As the title indicates, these documents are intended to provide *guidance* only and do not attempt to establish requirements for testing. The problems encountered in drug research demand a flexible approach and, depending on the precise nature of a new medicinal compound, it is appropriate to undertake evaluation by different methods or to different standards.

On behalf of Council I thank all the Committee members and other co-opted experts who have participated in the lengthy task of preparing these guidelines. I commend both documents to all member companies in anticipation that they will make a positive and helpful contribution to their experimental programmes.

P T Main

*Chairman of the Scientific and Technical Council*

## General introduction

Early in 1973 the Scientific and Technical Council of the ABPI accepted a proposal from its Research and Development Committee that an effort be made to define good current practice for testing new medicinal products in human beings. This meant bringing up to date the ABPI *First Report of the Expert Committee on Drug Toxicity* which was published in 1964 and amended in 1968, and extending it to include a greater consideration of pharmaceutical and medical problems. Like that report, this also is mainly a guide to good current practice for the member companies of the ABPI. The detailed development programme for any new medicine depends on its nature and intended use. The definition of the programme and of the safety measures needed to protect all the individuals concerned in it is the responsibility of the scientists and physicians of the company concerned.

The administration of any medicine to human beings inevitably carries some risk of side-effects that cannot be foreseen because human beings differ from one another, and from the animals used for pharmacological and toxicological studies in their responses to drugs. That component of the risk associated with the drug substance itself is potentially greater in the early stages of the testing of new medicines in man and so there must always be a good reason for such experiments. Here it is assumed that each test compound or preparation has already been shown to possess properties which might reasonably lead to the development of an improved medicine for a significant human ailment.

The subjects who receive test substances must be safeguarded by adequate prior experimentation in animals and by close medical surveillance. Part 1 of this report, prepared under the aegis of the Research and Development Committee, deals with the type of pharmacological, toxicological and biochemical information that should be known about any medicament before it may reasonably be given to man. Part 2 was prepared by the Medical Committee and is concerned with the other essentially medical safeguards for the subjects involved in human pharmacological and clinical trials.

The guidelines relate to any substance or combination of substances intended to be used in man for the diagnosis, prevention, or treatment of disease, for the mitigation of symptoms of disease, or for the alteration of physiological function. Vaccines and serological preparations are excluded.

The bioavailability studies required in the development of new drugs have been considered by a Working Party set up by the Research and Development Committee and are reported in a separate document.

# Introduction

Guidance on the administration of a new substance to man will vary according to the type of subject used and the stage of development of the drug, so that some division of the possible types of studies is required with separate recommendations for each. First, however, some definitions are made and, additionally, to avoid repetition later, some recommendations are given which apply to all studies. Statutory requirements are not directly referred to herein as these vary from time to time and from country to country, but they must be observed throughout the evaluation programme.<sup>1</sup>

## 1 General considerations

### 1.1 Objectives of these guidelines

These guidelines indicate those medical and scientific factors which are currently considered to form good medical practice for evaluating medicinal products. Full legal aspects such as indemnity, and financial questions such as payments to investigators are not discussed. Emphasis in this report is placed on clinical safeguards for the human subject (both non-patient volunteers and patients) in all stages of the investigations. These guidelines provide standards for any research organisation, but particularly for pharmaceutical companies engaged in human studies of the kind envisaged.

### 1.2 Definitions

The descriptions 'healthy human volunteer' or 'normal volunteer' describe an individual who is apparently in normal health as decided by routine history, physical examination, plus biochemical, haematological and other relevant screening procedures. The subject must be capable of volunteering in the legal sense and without suggestion of coercion, after he has had the study and its possible effects explained to him. It is not, therefore, possible for children to be covered by these descriptions (see also 3.2). The term 'non-patient volunteer' as suggested in the Medico-Pharmaceutical Forum Report<sup>2</sup> encompasses in addition to the above, individuals with minor abnormalities or diseases not likely to benefit from the therapeutic potential of the substance under test. If such patients are used the clinician in charge of the study should be different from the doctor responsible for their continuing medical care.

The WHO description<sup>3</sup> of an 'adverse reaction' to a drug is accepted: '... one which is noxious and unintended, and which occurs at doses

used in man for prophylaxis, diagnosis or therapy'. Adverse reactions include both 'toxic effects' (which are unwanted actions of the substance on organs or tissues of the body sufficient to impair their function or to cause cell death) and 'side-effects' (which are unwanted effects caused by known or expected pharmacological actions of the substances at therapeutic doses).

An independent clinical investigator is a registered medical practitioner not employed by the pharmaceutical company but who has experience and expertise in drug evaluation.

A pharmaceutical physician (or medical adviser) is a registered medical practitioner employed by the pharmaceutical company and who has been suitably trained and is experienced in initiating, conducting and co-ordinating drug evaluation programmes.

Pharmacodynamic effects describe those quantitative actions which the substance has on major body systems, whereas the pharmacokinetic effects describe quantitatively the manner in which the body absorbs, distributes, metabolises and excretes the substance. Pharmacology incorporates both pharmacodynamics and pharmacokinetics.

### **1.3 Basic requirements**

Before the first administration of a substance to a human, it is necessary to complete adequate pharmacodynamic, pharmacokinetic, reproductive and toxicological studies to justify progression to human studies. One of the objectives of early human studies in the development of a substance is that comparative pharmacokinetic studies may establish the similarity of the metabolic fate of the new substance in man and experimental animals and will both guide and validate the long-term animal studies (see Part 1, 4.3). If interspecies differences are great, those experimental animals which metabolise the compound in a manner most closely to man should be used for long-term toxicity studies unless there are good reasons to the contrary.

The physico-chemical quality of the substance used in initial studies has been covered in Part 1, 1.2.

The formulation used should be the simplest presentation consistent with the objectives of the study.

All human studies should be the responsibility of a registered medical practitioner who must be informed by the pharmaceutical physician of appropriate results and conclusions drawn from the earlier studies.<sup>5</sup>



#### **1.4 Stages of drug evaluation**

In this document, the following simple division of trials is used:

- i Human volunteer studies carried out in non-patient volunteers.
- ii Pre-marketing studies performed in patients before the medicinal product is marketed.
- iii Post-marketing evaluation continued in patients by trials and other studies after marketing.

When a substance already marketed for one type of use is being considered for clinical trial for another clinical indication, or by a different route of administration, or in a new dose regimen, consideration should be given to the need for further laboratory, animal and human volunteer studies.

#### **1.5 Design of trials**

A clinical trial is a deliberate and scientific study in a well categorised group of patients who have been selected, according to a prearranged protocol, to receive defined doses of a medicinal product for a specified time by a chosen route. The protocol should detail appropriate measurements of efficacy and safety (see 1.6).

The design of a trial inevitably causes some artificiality of therapy and involves some compromise between scientific and clinical needs. However, initial clinical trials should be so designed as to ensure that the maximum useful information can accrue from studies in minimal numbers of subjects thus reducing the spread of risk. If practical, results should be tested statistically and this requires an adequate number of patients and criteria of sufficient precision.<sup>4</sup> The general principles which govern the design of trials are those which are scientifically acceptable. An exacting list of principles has been published<sup>5</sup> but it may not be practical or desirable to demand that all of them be fulfilled on every occasion.

#### **1.6 Documentation of trials**

Each trial should have a written protocol, which should specify the following:

The clinical investigator

The place where the work is to be conducted

The rationale, aims and design of the study

The selection, exclusions and numbers of subjects

A statement on the information to be given to the subjects

The form of consent to be obtained

The criteria for diagnosis of the disease (where appropriate)  
The nature, formulation, dosage and routes, frequencies and durations of administration of the drugs  
The variables to be measured and the frequency of their measurement  
The criteria for withdrawal of subjects from the study  
The methods of identifying adverse reactions  
The proposed method of statistical analysis.

Each subject should be identified anonymously in a way that maintains confidentiality. For example, the list of patients' names and numbers should be kept separately from the individual's clinical data which contains a number but no name. A useful summary of such data has recently been produced by the EEC<sup>4</sup> and is reproduced in Appendix B. Trials in which detailed and numerous observations are made on each subject require a separate pro forma for each individual. In other trials where larger numbers of patients are studied with fewer individual observations it may be sufficient and more convenient to record the data in the form of a register.

Adequate documentation serves several important and useful purposes. For example, unusual reactions or associations can be quickly checked against other information and can help in identifying a causal effect. When recorded in a suitable form, data can be utilised in other countries. In addition, if the trial is published further scientific data will be available to answer questions that might arise.

### **1.7 Location of studies and available facilities**

Good medical practice must dictate the extent of the resuscitation and other equipment, drugs and medical skills that are available. These must be commensurate with the likely pharmacological activity of the substance and allow for unforeseen hazards, in particular they should include facilities for ventilatory and cardiovascular resuscitation. Initial studies in patients, except when it is considered that the potential hazard is minimal (for example the evaluation of compounds applied topically), should be conducted in patients in hospital throughout the course of the experimental procedure.

All studies of new substances involving patients must have the approval of independent clinicians who have responsibility for the continued medical care of the patients. For the initial studies in patients the clinical investigators should be chosen from those who have experience in testing new substances, and those who have wide experience in the disease area in which the new substance has potential therapeutic value.

## **1.8 Ethical considerations**

It is recommended that the principles adopted should accord with the Declaration of Helsinki<sup>6</sup> (Appendix c). In particular, the principle that clinical research '... cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject' is emphasised. A child cannot be included unless direct benefit to that individual is probable. Also, if it is not medically justifiable to withhold treatment from patients, a placebo should not be given, but the information must be obtained in other ways such as by comparison of the test substance with an acceptable therapy. The Royal College of Physicians<sup>7</sup> has considered the conduct of trials in institutions and has recommended discussion of proposed trials with colleagues and peers and, finally, the gaining of approval from Ethics Committees. Certain studies are conducted within pharmaceutical companies by members of their staff. Such institutions do not normally have such committees. It would be prudent, however, for studies to be approved by a registered medical practitioner not involved with the investigation.

## **1.9 Subjects for trials**

With volunteer studies the decision as to which types of subjects should be recruited must rest with the named doctor undertaking the work. Subjects from the company or hospital staff or from students may be obtained by personal contact or preferably by circulated notes or by displaying a notice in an appropriate place, e.g. staff or student notice boards. In the case of studies on hospital patients, the recruitment is entirely the responsibility of the independent clinical investigator, with the guidance of the pharmaceutical physician of the pharmaceutical company providing the new substance.

Two broad groups of subjects have been recognised.<sup>1,7</sup> The first group consists of both patient and non-patient volunteers for whom the procedure is not of direct therapeutic benefit; the second comprises patients who may be anticipated to derive direct benefit. Most of the initial studies with a substance are performed on subjects in the first group. The nature of the trial, its objectives and likely adverse effects should be explained to each volunteer who should be asked to sign a simple form stating that he understands these facts and freely gives his consent to be a subject for the experiment.<sup>8</sup> In patients of the second group the validity of the results of certain types of investigation may be reduced by full disclosure to patients (e.g. suggesting side-effects can induce them) and a certain latitude in explanation may be exercised. The information given to the patient is at the discretion of the clinician in charge of the trial,<sup>6,7</sup>

but unless there are any real medical contraindications, it is wise to obtain consent after describing the study to the individual. For patients with physical or legal incapacity (e.g. minors) consent must be obtained from the legal guardian. In the case of company employees, medical students, or patients there must be no suggestion of any requirement or expectation on the part of the employer, tutor or doctor. The subject must agree of his own free will to participate in the study and must feel free to withdraw at any time.

For non-patient volunteers a modest reward, either monetary or in kind, may be offered related to the effort and discomfort involved; but the reward should not be allowed to reach a level which could be considered an inducement to volunteer.<sup>8</sup> Patients should be offered reimbursement for any expenses they may have incurred by participating in the trial, e.g. fares for extra attendances or loss of earnings.

## **2 Non-patient volunteer studies**

### **2.1 Objectives**

The aims of the initial investigation of a new substance in man are (a) to establish the pharmacokinetics and bioavailability for a range of doses; (b) to determine whether the pharmacological profile established in a number of animal species is similar in man; (c) to assess local and systemic tolerance and (d) by this information to guide and validate the long-term animal studies. With some substances (e.g. cytotoxic agents and anaesthetics) this stage is inappropriate and the first introduction into man requires study in patients (see 3).

Since the safety of the subject is of prime consideration (see 1.7) the studies should be designed to achieve the objectives with exposure of the new substance to the smallest number of subjects possible.

### **2.2 Types of subjects** (see also 1.9)

The non-patient volunteers should be selected for this stage of drug evaluation after (i) taking a personal medical history (especially of any adverse reactions to drugs), (ii) medical examination, (iii) blood, urine and other screening tests (see 2.3), (iv) written notification to the subject's general practitioner, and after (v) it has been ascertained from specially designed registers (usually held by the company industrial medical officer) that the individual is not experiencing undue industrial or other hazard by nature of his job or by frequently volunteering for similar studies.

The volunteers may be male or female; if both are admitted to the study there should, if possible, be equal numbers of each. Unless it is not absorbed, a substance should never be given to female volunteers of child-bearing potential until the results of adequate foetal toxicity tests are available in animals (Part 1). Even then a pregnancy screening test must be carried out on the volunteer as near as possible before the trial and menstruation should have begun not more than 10 days previously.

Additional constraints need to be applied for the administration of radio-labelled compounds. The minimum age for male subjects should be 35 years and women of child-bearing potential must be excluded. Many variables will influence both the radiation dose and the chemical dose. The results of the pharmacokinetic studies in animals (see Part 1, Section 9) will have identified any tissue or organ which might be expected to concentrate the substance. The radioisotope chosen will depend upon these data as well as the chemical nature of the substance and the objectives of the human studies. In order to reduce any radiation hazard to a minimum, the smallest radio-chemical dose which is thought to be able to yield the relevant information should be used. Special care must be taken to ensure that no volunteer is exposed to unacceptable doses of radiation either by volunteering for such studies too often or because the nature of his employment already exposes him to abnormal degrees of radiation. The total chemical dose and route of administration will be dependent upon the animal toxicity data or previous human data (see Part 2, 2.3). An outline of the procedure together with any other relevant data should be drawn up by the clinician and physicist and for the UK sent to the Isotope Advisory Panel, DHSS (HS2A4), Hannibal House, Elephant and Castle, London SE1 6TE. Guidelines are issued by the Isotope Advisory Panel and have been reproduced in Appendix D but it is emphasised that the overall use of the radioisotopes should accord with the Code of Practice for the Protection of Persons against Ionising Radiation arising from Medical and Dental Use (Appendix D). Full consideration must be given to any reply from the Isotope Advisory Panel.

In some instances, pharmacological activity of potential benefit in disease can be demonstrated in non-patient volunteers by the treatment of induced effects. It may be possible by such models to compare the effects of analogues early in the drug development programme, but only after adequate animal studies (see Part 1). However, the limitations of such studies must not be forgotten and the safety of the subjects must be the primary consideration (see 1.7).

More details are included in a separate ABPI document on bio-availability studies in drug development and in the report of the

Stuart-Harris Committee.<sup>8</sup> Both of these documents should be consulted before embarking on clinical trials.

### **2.3 Design of studies**

Experiments in animals or experience with other drugs having a similar chemical structure or similar pharmacological activity may have indicated organ systems requiring special vigilance. However, screening and monitoring by clinical, biochemical, haematological and any other pertinent methods (see footnote) must be comprehensive in order to detect any adverse reactions.

A named, medically-qualified investigator is responsible for the safety and well-being of the volunteer throughout and for the period following the experiment, ensuring his safe return home, and should be available for consultation in case of an unsuspected reaction at home. The volunteer should be supplied with a card containing the name and telephone numbers of the investigator or other suitable colleague, for use in any such emergency.

The initial dose of a novel compound should be a small fraction of the predicted single therapeutic dose,<sup>9</sup> which itself should be estimated by discussions between pharmacologists, toxicologists and clinicians. Definite recommendations are not possible to make but it is suggested that the first administration should not exceed one tenth of the predicted therapeutic dose.<sup>2</sup> With drugs likely to have marked pharmacological activity it is wiser to use doses much smaller than this. On the first occasion one subject only should be given one dose. Subsequent single doses should be given to different individuals and may be increased in steps to the predicted therapeutic dose, or above, if problems do not arise and sufficient animal toxicity tests have been carried out. Before even single doses are given to human volunteers, adequate pharmacological, reproductive and toxicity studies should have been completed in animals (see Part 1).

When satisfactory human data are available, repeated dosing may follow to provide further pharmacokinetic information. However, at this stage in the evaluation, the number of doses given to any non-patient volunteer must be the minimum that will yield the required information and animal toxicology of appropriate duration must have been carried out in two species at three doses (see Part 1).

*Footnote* The following are suggested: haemoglobin concentration, red and white cell indices, sedimentation rate, platelet and reticulocyte counts, plasma creatinine, urea and glucose, serum electrolytes and liver function tests, microscopy of urine and urinalysis for protein, glucose and blood. In addition, attention should be paid to the special senses and to any other tests relevant to the likely action of the substance.

The number of subjects should be the smallest adequate to achieve the objectives and thus allow proper execution of pre-marketing clinical trials in patients.

The initial route of administration is usually the intended final therapeutic route. Intravenous injection is additionally permissible if it is important to assess the effect of a known dose providing that cardiovascular and respiratory resuscitative facilities are available.

If change from the original simple formulation (1.3) is made, the need for further bioavailability studies should be considered.

### **3 Pre-marketing clinical trials**

#### **3.1 Objectives**

This will be the first time at which patients with disease appropriate to the action of the drug are involved and the immediate objectives are to ensure that pharmacokinetics and bioavailability in these patients are comparable to those already found in non-patient volunteers. The main objective of this stage is the demonstration of efficacy and the degree of safety in patients with defined disease and as a preliminary this requires adequate dose-response studies. A further requirement is comparison with standard drugs or other therapy to establish the advantages and disadvantages of the new medicinal product.

#### **3.2 Types of patients**

Adults should be studied unless the drug is intended only for use in children. They should have disease, confirmed and categorised by generally acceptable diagnostic criteria, responsive to the anticipated therapeutic actions of the drug. In the first instance subjects with incompetence of any target organs which are expected to respond to the pharmacological action of the compound, or of any other important organs (especially the liver and kidney), must be excluded unless this type of abnormality is an integral part of their disease process.

With a few exceptions (for example, the application of topical preparations) the initial studies with a new compound should be conducted on hospital patients, preferably inpatients. Outpatients are acceptable if the study is of short duration, the subjects are observed for an adequate period within the hospital and the clinical investigator is satisfied that no subsequent effects are likely to occur. If outpatients are used, each individual should be given a card with

names and telephone numbers of the investigators in case of adverse reactions. Later in this stage it becomes desirable and, indeed, often essential to proper evaluation, that some patients with compromised function of vital organs are included; these functions must be carefully monitored. Any variations that such functional abnormalities cause to pharmacokinetics and bioavailability must be considered in the design of studies.

If the substance is intended for use both in adults and children, the latter can be included in the later part of this stage, but it is only permissible to do so if direct benefit to that individual is likely. It is not acceptable to conduct unduly detailed pharmacodynamic or pharmacokinetic studies on minors who are unable to give informed consent in law (see 1.8; 1.9).

Later, outpatients can be widely used, if applicable, and studies in general practice can be started provided appropriate facilities exist for assessment of efficacy and adverse reactions.

Females should be included in the pre-marketing clinical trials unless the medicinal product is intended only for males. For studies in female patients who are not likely to benefit directly from the drug, the same conditions must be observed as those listed in Part 2, 2.2. The clinician in charge of the study has the responsibility for deciding whether to include or exclude any female of child-bearing potential depending upon his assessment of the probable benefits and possible adverse effects.

### **3.3 Design of studies**

The design of the initial studies in patients is based upon the predicted properties of the new compound, the results from the normal subjects and from any knowledge of established drugs with similar properties.

If the major pharmacological properties demonstrated in laboratory animals can be measured in patients too, this should be done first. The studies should correlate pharmacological activity with drug blood levels and aim to show a therapeutic dose range for single and multiple dosing.

Not more than three centres are usually recommended for the first part of this stage, but for uncommon diseases, or if data are available on safe use in considerable numbers of patients from other countries, then more centres can be involved initially. For certain agents (for example, anaesthetics or cytotoxic agents) where the substance has not previously been given to man, it is prudent to limit the trial to one centre at first. Expansion of trials to other centres can occur if safety appears satisfactory.



Expected drug effects together with monitoring of the functions of vital organs should be measured adequately, if possible by non-invasive techniques.

Animal toxicology required for these early studies in patients is the same as that recommended for the various stages of non-patient volunteer studies (2.3).

It is prudent to begin with a single dose smaller than the expected therapeutic dose taking into account any differences in the absorption, distribution and metabolism which might arise from abnormalities resulting from disease processes.

Once the predicted therapeutic dose has been given without untoward effects, multiple dosing may commence. The half-life of the compound in blood will act as a guide to the interval between individual doses. It must be remembered, however, that there is not always a close relationship between the half-life in the plasma and duration of its biological effects. Later, repeated doses are given to check accumulation or difference in metabolism with regular use.

The route of administration should be that which is to be used for the marketed product and ideally the formulation should be one which is expected to be the final market presentation. If the medicinal product is produced in several formulations which by the same route of administration have similar blood level characteristics, it is not necessary to test the clinical efficacy of each.

In later trials the range of doses should be those which are likely to be the final recommendations of the pharmaceutical company. In some trials fixed dosages are adequate, but in others the design may need to allow for dosage adjustment based on specified criteria. The duration of therapy should be long enough to induce a satisfactory response of the disease under study and be related to the probable use by patients. For example, if long-term therapy is likely it may be necessary to monitor safety and efficacy for prolonged periods to provide adequate data.

If the substance is normally to be given concurrently with one (or more) other medicinal products it is important to investigate possible interactions by suitable compatibility and stability experiments and animal *in vivo* studies before the question of interaction in man is investigated (see Part 1). Both design and interpretation of clinical trials should take into account drug combinations and possible interactions.

Later studies should be controlled with suitable randomisation of drugs, placebos and patients as necessary. They should be designed so that valid statistical conclusions can be made. It is important

always to interpret the clinical significance of any differences. Such interpretation is best done by the investigator and should appear in his summary and conclusions.<sup>4</sup>

Any abnormality either in the clinical signs or symptoms or in the laboratory screening tests will require further investigation in the patient. If it is thought that the abnormality may be drug-related then this should be taken into account in the design of other studies either underway or planned. The interpretation of the results of the study and of the appearance of any adverse reaction is easier if the patients are not receiving any other medication immediately before or during the dosing period with the substance under test.

When necessary on clinical grounds to continue previous medication the possibility of adverse reactions from the drugs separately or by interaction must be considered. If a major unexpected adverse reaction is attributable to the new substance, it is important to try to identify the likely mechanism. This will often be attainable only by recourse to appropriate laboratory experiments.

The decision on the numbers of patients or the rate of their intake into the trials during the pre-marketing evaluation must be the responsibility of the pharmaceutical physician in charge of the progression of the clinical trials on that medicinal product. He will be guided by factors such as the innate pharmacological properties of the compound and its toxicological potential, the rate of accumulation of data on the clinical pharmacokinetics of the substance and its safety and efficacy, particularly in comparison with standard therapy.

## **4 Post-marketing evaluation**

### **4.1 General considerations and objectives**

In spite of all the animal and human studies conducted before the product is marketed, unexplained side-effects may occur and can go unrecognised. This emphasises the need for reporting side-effects of new drugs.

Once the medicinal product has been marketed it is available for widespread use and such use is not always in accordance with the manufacturer's recommendations. The product is likely to be used in diseases less closely defined and in doses less well supervised than in the earlier trials.

Also, more patients are now likely to receive the substance so that unusual effects with a low frequency (say less than 1:1,000) may only occur after marketing.

These aspects often produce reports, sometimes anecdotal, of new effects either advantageous or, more often, disadvantageous.

The objectives of the post-marketing stage of drug evaluation in addition to continuing clinical trials are to carry out long-term surveillance of the drug in general use with regard to both its efficacy and safety (4.4).

#### **4.2 Clinical trials**

The clinical trials in the post-marketing part of the evaluation programme differ from those in the pre-marketing stage mainly by the smaller amount of data required from each patient and in the larger numbers of subjects studied. The post-marketing clinical trials, as the earlier ones, must have a scientific objective and be co-ordinated by the pharmaceutical physician or a member of his or her staff, who arranges for the written protocol and pro forma to be drawn up. Trials must be of adequate scientific standard and sufficiently well documented to allow compilation of a report which would be expected to be acceptable to a medical journal. Due consideration should be given to the principles inherent in the important criteria which have been published for certain trials.<sup>10</sup> In addition, in the UK there is a need to conform to the Code of Practice of the Association of the British Pharmaceutical Industry.

#### **4.3 Types of subjects and dosage for clinical trials**

In all formal trials in this stage, as in the previous stages, the subjects should be well documented and like those in the pre-marketing trials should be patients with well-defined appropriate disease. Whether the patients are studied in the wards, as outpatients, or in general practice will be determined by the nature and use of the medicinal product. They will be selected from appropriate clinical groups. The recommended posology determined from the pre-marketing studies will determine that used in the post-marketing evaluation.

#### **4.4 General long-term surveillance**

Adverse reactions to drugs which are notified represent a small proportion of those occurring, nevertheless a record of all the adverse reactions reported to the pharmaceutical company should be kept in an appointed register. Relevant details such as age, sex, race, disease(s), appropriate clinical findings and laboratory investigations, full description of the reaction, the relationship to any other drugs or possible contributory causes and the dose and batch number of the new medicinal product should be sought. Documenta-

tion of unusual effects should be such to include enough data of all of the above so that retrospective analysis of the files would allow consideration of any possible causes or contributory factors.

In addition, samples of the medicinal product from the same batch as that implicated in the reaction should be obtained whenever possible and subjected to suitable analytical tests. Clues which may suggest some abnormality in a specified batch would include a high incidence of reactions in one geographical area or related closely in time.

Should the incidence of a relatively severe reaction seem unexpectedly frequent, serious consideration must be given to the collection of prospective data by epidemiological methods. In addition, if a likely mechanism is suspected then discussions with pharmacologists, toxicologists, immunologists or pathologists, etc, should ensue to try to investigate the mechanism by suitable experimental studies *in vivo* or *in vitro*.

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## Appendix A

A trial may be 'uncontrolled' or 'controlled' the latter being subdivided into 'open' (non-blind), 'single-blind', or 'double-blind'; it may be a 'cross-over' (within-patient) comparison or 'between patient' comparison. These varieties have been discussed by the Medico-Pharmaceutical Forum<sup>2</sup> and in other literature.<sup>11</sup>

A controlled trial is one which includes a control group and a test group allowing the results to be compared, and such trials are the preferred type. The design of the trials will vary from case to case. Thus, often depending on ethical considerations, it may be more pertinent to compare the therapeutic effect of a new substance with that of an established medicinal product rather than with the effect of a placebo.<sup>4</sup>

The control group, therefore, may receive no treatment, placebo or active treatment (of established kind). Disguising the treatments in an attempt to reduce bias can introduce other variables such as bioavailability. The decision to employ or avoid the double-blind technique must be given careful consideration based upon the aim of the trial. For example, if the aim is to discover whether substance x is more effective and better tolerated than substance y then the double-blind technique may be ideal. If the aim is to find out whether presentations of the same drug in small black pills is preferred in the widest sense to the same product in large white pills a double-blind comparison is not possible.

## Appendix B

### Documentation of clinical trials\*

- 1 Identification of the patient (e.g. by reference to the number of his medical file);
- 2 criteria determining admission of the patient to the trials;
- 3 patient's age;
- 4 patient's sex;
- 5 diagnosis and indication for which the product was administered and the patient's history; relevant particulars of any previous illnesses shall be given;

- 6 dosage and method of administration of the products;
- 7 frequency of administration and any precautions taken at the time of administration;
- 8 duration of treatment and of the subsequent observation period;
- 9 details of medicinal products administered previously or concomitantly, i.e. at any time during the period covered by the investigation;
- 10 dietary regimen, if pertinent;
- 11 all results of the clinical trials (including unfavourable or negative results) with a full statement of clinical observations and results of clinical investigations (such as x-rays, electroencephalograms, electrocardiograms, laboratory analyses, physiological tests, etc), required to evaluate the application. The techniques used must be specified, and the significance of any variations in the results explained (for example, variance in method, variance between individuals or the effects of treatment);
- 12 all particulars of the observed side-effects, whether harmful or not, and any measures taken in consequence. Relation of cause and effect must be investigated with the same care normally accorded to identify therapeutic action;
- 13 an opinion concerning each individual case.

\*Reproduced from: Official Journal of the European Communities, 9 June 1975, No. L147/10-12.

## **Appendix C**

### **DECLARATION OF HELSINKI** Recommendations guiding medical doctors in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and as revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

#### **Introduction**

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest.'

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

## **I Basic principles**

**1** Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

**2** The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially



appointed independent committee for consideration, comment and guidance.

**3** Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

**4** Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

**5** Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

**6** The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

**7** Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

**8** In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

**9** In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

**10** When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case

the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

**11** In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

**12** The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

## **II Medical research combined with professional care (clinical research)**

**1** In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

**2** The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

**3** In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

**4** The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

**5** If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.<sup>1,2</sup>

**6** The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

## **III Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)**

**1** In the purely scientific application of medical research carried

out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2 The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3 The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4 In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

## **Appendix D**

### **Isotope Advisory Panel**

1 The Isotope Advisory Panel advises on the use of radioactive isotopes in clinical medicine and research in the UK.

2 Requests for advice in respect of clinical projects that are being carried out in that institution for the first time by those concerned, whether diagnostic or therapeutic or for the purposes of research in human subjects, should be submitted jointly by the responsible clinician and physicist, and information should be provided under the following heads:

- a Name of the institution at which the work will be undertaken.
- b Names and qualifications of the applicants and any other participating workers, including other clinicians associated with the work.
- c Purposes for which the material will be used.
- d Age range and clinical condition of patients, and whether pregnant women will be included; the number, age range and sex of any normal control subjects to be studied.
- e Isotope proposed, chemical form, method of administration, proposed dosage, whether repeat doses will be administered, and whether isotopes will be given simultaneously or sequentially to individual patients.

f Where new techniques or research investigations are proposed, an estimate of the radiation dose to the whole body and to critical organs should be enclosed. Such estimates should be included in any publication of results.

g Where it is proposed to administer rare or unusual substances, information or references relating to intermediary metabolism or alternatively excretion data from preliminary animal experiments should be supplied. Where new drugs are to be used, pharmacological details including the chemical formula, the position of labelling and the possibility of radioactive impurities should be indicated.

**3** Requests should be addressed to The Secretary, Isotope Advisory Panel, DHSS (HS2A4), Hannibal House, Elephant and Castle, London SE1 6TE. Urgent applications may be made by telephone to the same section, telephone 01-703 6380 ext 3482 or 3306.

**4** The possibility that a person may have had a radioisotope administered previously should always be investigated. When considering requests for the use of radioisotopes in humans, the Panel assumes that such persons have not previously been exposed to similar procedures.

**5** Applicants are required to give the following undertakings:

a That the materials will not be used in a manner other than that disclosed in the application, or elsewhere than at the specified centre without prior reference to the Advisory Panel.

b That steps will be taken to maintain all necessary protection and safety measures as indicated in the *Code of Practice for the Protection of Persons against Ionizing Radiations arising from Medical and Dental Use\** to avoid the special hazards to health arising out of the possession, handling, use and disposal of radioactive isotopes, and that all such protection and safety measures will be open to examination by representatives of the Panel.

c That arrangements will be made, in the case of radioactive isotope therapy, to register the patients in accordance with the cards and systems of the Statistical Department of the General Register Office. This applies at present only to the *treatment* of thyrotoxicosis and other non-malignant thyroid disorders with  $^{131}\text{I}$ . Hospitals in any part of the United Kingdom proposing to carry out such treatment are invited to participate in a scheme of registration of cases through the General Register Office.

\*Code of practice for the protection of persons against ionizing radiations arising from medical and dental use (1972). HMSO.

Further information and a supply of the necessary cards can be obtained from: The General Register Office, Segensworth Road, Titchfield, Fareham, Hants.

**6** Applicants are expected to be familiar with the contents of the Medical Research Council's pamphlet *Responsibility in Investigations on Human Subjects*, copies of which may be obtained from the MRC, 20 Park Crescent, London W1N 4AI, and it is assumed that the approval of local ethical committees will be obtained prior to the submission of applications for experimental procedures.

**7** Users are expected to submit progress reports if requested, and are asked to notify the Panel of any untoward or unexpected effects observed in the course of work with radioactive isotopes.

