II

(Acts whose publication is not obligatory)

COUNCIL

COUNCIL RECOMMENDATION

of 9 February 1987

concerning tests relating to the placing on the market of proprietary medicinal products

(87/176/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas, in Council recommendation 83/571/EEC (4) concerning tests relating to the placing on the market of proprietary medicinal products, the Council adopted a first series of notes for guidance intended to prevent differences of interpretation in the conduct and evaluation of the tests on proprietary medicinal products provided for by Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (5), as amended by Directive 83/570/EEC (6);

Whereas the adoption of new notes for guidance, supplementing those annexed to recommendation 83/571/EEC, will help to promote the free movement of proprietary medicinal products by facilitating the taking into consideration by Member States of marketing authorizations already granted by other Member States;

Whereas the Pharmaceutical Committee and the Committee for Proprietary Medicinal Products have been consulted on the measures contained in this recommendation,

HEREBY RECOMMENDS THE MEMBER STATES TO:

1. seek to ensure that, in the conduct of tests and in the presentation of results, applicants for authorization to place proprietary medicinal products on the market comply with the principles and adhere to the methodology set out in the notes for guidance annexed hereto;

2. examine and evaluate, in accordance with the said notes for guidance, all applications for marketing authorization.

Done at Brussels, 9 February 1987.

For the Council

The President

P. DE KEERSMAEKER

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(1) OJ No C 293, 5. 11. 1984, p. 8.
(2) OJ No C 36, 17. 2. 1986, p. 152.
(3) OJ No C 160, 1. 7. 1985, p. 18.
(4) OJ No L 332, 28. 11. 1983, p. 11.
(5) OJ No L 147, 9. 6. 1975, p. 1.
(6) OJ No L 332, 28. 11. 1983, p. 1.

ANNEX I

SINGLE-DOSE TOXICITY

Note for Guidance concerning the application of the Annex to Directive 75/318/EEC, Part 2, Chapter I (B)(1), with a view to the granting of a marketing authorization for a new drug.

1. INTRODUCTION

These guidelines deal with the qualitative and quantitative study of toxic phenomena and their occurrence related to time after a single administration of the substance, or combination of substances.

These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the relevant animal species.

The single-dose toxicity tests should be conducted in such a way that signs of acute-toxicity are revealed and the mode of death determined. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be made, but a high level of precision is not required.

Toxicologists should use their best judgements in designing the studies so that the maximal amount of relevant information is obtained from the smallest number of animals.

2. PRODUCT SPECIFICATION

(a) **Drug substance**

The active substance should have the same pattern of impurities as the product to be marketed, when possible. Should the final dosage form be shown to have impurities significantly different either in quantity or quality from those in the test batch then further steps should be taken to ascertain their possible toxicity. Consideration should be given to the physical characteristics of the drug substances in relation to the route of administration, e. g. the particle size of a compound given orally.

(b) **Finished product**

When large animals are used in the acute toxicity study, it may be possible to conduct a study with the pharmaceutical formulation intended to be marketed. This is particularly desirable when the pharmaceutical formulation is likely to lead to major changes in the bioavailability of the active ingredient(s).

(c) **Excipients**

Where a new excipient is used for the first time it should be evaluated as a new active substance.

(d) **Products containing a combination of active substances**

In the case of combination of active substances it is necessary to make a study of each active substance separately and of the combination of active substances in the same proportions as in the proposed final product in order to check whether or not there is enhancement of toxicity or if novel toxic effects occur. Deviations from this protocol should depend on documented pharmacokinetic or pharmacodynamic differences between the animal species studied and man.

(e) **Degradation products**

Where degradation products occur under conditions of storage, consideration should be given to their possible toxicity and this might be best evaluated initially by an acute-toxicity study.

3. ANIMALS

(a) Single-dose toxicity tests must be conducted on at least two mammalian species of known strain using equal numbers of both sexes. Rodents such as the mouse, rat and hamster are suitable for the qualitative study of toxic signs and the quantitative determination of the approximate lethal dose. If no difference in response is observed between the animals of the two sexes

of the first rodent species, then only animals of one sex need be used in the other acute toxicity studies. Toxic signs should also be observed and recorded in detail for each animal used in the case of other mammals.

(b) Whatever species or strain of animals are selected it is essential that the following information should be provided: age, sex, weight, origin and the time in the laboratory before test, whether or not the animals are classified as being free of specific pathogens, whether or not the animals have been vaccinated or submitted to any other procedure. Details of housing and environmental conditions should be given. Access to and the nature of the diet and the availability of water should be stated. All the above factors are known to affect the acute toxicity of substances.

4. ADMINISTRATION

(a) **Route of administration**

In the case of rodents in general, two routes should be used and when possible should include those routes proposed for man and at least one should ensure full access of unchanged drug into the circulation. If the proposed route of administration to man is intravenous, then use of this route alone in animal testing is acceptable.

(b) **Conditions of administration**

Details of administration of the product should be provided and include particulars of the vehicle or adjuvans used, method of preparing the suspension in the case of insoluble products, concentration of the solution used and the volume administered. The route and the method of administration should be clearly given. The formulation to be administered should be as bland and as close as possible to physiological pH and osmolality.

Special attention should be paid if the formulation is alkaline, acid or potentially corrosive. Exceeding the tolerable volume should be avoided. If the intravenous route is used the rate of infusion (ml/min) and the pH and temperature of the solution administered should be provided.

If it is necessary to use more than one injection site for parenteral administration, this should be stated.

(c) **Dose levels**

In all species used the number of dose levels should be such that the spectrum of toxicity is revealed. In rodents a quantitative estimate of the approximate lethality and the dose-effect relationship should be obtained.

5. OBSERVATIONS

Animals should be observed at regular intervals and all signs of toxicity and the time of their first occurrence and their severity, duration and progression recorded. The time and mode of any death should be documented, any signs of toxicity should be presented separately for each animal.

Observation should usually be for 14 days, but should continue so long as signs of toxicity are apparent, e.g. progressive loss of weight or inhibition of growth.

6. AUTOPSY

All animals surviving to the end of the study and all animals dying during the period of observation should be subjected to autopsy. Any organ showing macroscopic changes (other then agonal changes) should be subjected to histopathological examination unless these changes are well documented and adequate explanation for them can be given on the basis of previous experience in the strain of animal used.

7. PRESENTATION OF DATA

The results from which any calculations have been made should be given in detail; the methods of calculation used should be stated.

The toxid effects including assessment of morbidity should be described in each species and for each route of administration at all dose levels.

The investigator should draw all relevant conclusions from the data obtained in these studies.

Any significant deviations from these guidelines should be justified.

ANNEX II

TESTING OF MEDICINAL PRODUCTS FOR THEIR MUTAGENIC POTENTIAL

1. INTRODUCTION

'Mutagenesis' refers to those changes in the genetic material in individuals or cells brought about spontaneously or by chemical or physical means whereby their successors differ in a permanent and heritable way from their predecessors. Current scientific knowledge overwhelmingly supports the concept that many chemicals possess mutagenic properties which present a potential genetic hazard to future generations as well as a potential cancer risk to the present one. Therefore there is a necessity to identify chemicals with such properties and to limit human exposure. Positive evidence of mutagenicity must be taken into consideration when evaluating the risk of carcinogenicity (see Directive 75/318/EEC). The primary object of these guidelines, however, is to determine the possible existence of a mutagenic hazard.

Damage to the genetic apparatus may be at the level of individual genes (point mutations) or the interference may be of a grosser type in which the structure of the chromosomes (chromosome mutations) or their number (genome mutations) is altered. If the structural alteration is small and results in the deletion of one or a few genes the net effect can be difficult to distinguish from a point mutation. A wide variety of procedures has been devised to test the ability of a chemical to induce these various kinds of mutations in organisms ranging from those with the simplest arrangement of the deoxyribonucleic acid molecule (DNA) in bacteria (prokaryotes) to those in which the DNA is arranged in a most complex association with proteins and enzyme systems (chromatin) to form the chromosomal system found in eukaryotes ranging from simple organisms such as fungi to insects and finally mammals.

2. OBJECTIVES OF A MUTAGENICITY TESTING PROCEDURE

Directive 75/318/EEC, states that any new substance for use in medicinal products prior to being marketed has to be investigated for mutagenic properties. The objective of these notes is to provide some guidance on how to conduct such investigations. In designing a mutagenicity testing procedure the following points are of primary importance:

(a) the procedure should be able to identify chemicals with mutagenic properties, with maximum accuracy and at reasonable cost. Therefore, from the wide variety of available tests a deliberate choice has to be made;

(b) the procedure should be capable of detecting the main classes of relevant genetic damage, notably gene mutation, chromosome mutation and, when possible, genome mutation;

(c) the procedure should take into account the fact that, although DNA is universal to both prokaryotes and eukaryotes, the organization of the genetic material is very different in these two types of organisms;

(d) the capacities to metabolize xenobiotic compounds differ widely between organisms and between test systems. In *in vitro* procedures mammalian metabolism is simulated by the addition of one or more extrinsic metabolic activation systems. However, these may fail to mimic the *in vivo* situation at critical points. Therefore it is necessary to include one *in vivo* test. In all tests the characteristics of the metabolism of the substance should be taken into account.

3. PROPOSED MUTAGENICITY TESTS FOR MEDICINAL PRODUCTS

It is generally acknowledged that the above requirements and considerations are not met by any single test but only by a well-selected combination of procedures. However the combination of tests applied should in each case depend on the specific characteristics of the substance to be tested.

Based on current knowledge, a system using four categories of tests is proposed as an appropriate approach to meet the conditions set out in paragraph 2 (a) to (d). This is not to imply, however, that other tests are inappropriate, or that evidence from other tests would not be acceptable as alternatives to part of the package. Deviations from these procedures could be indicated, for instance, by particular characteristics of the compound under study, or a particular feature of its metabolism. For example it may be considered inappropriate to evaluate a potent antibacterial agent in a

bacterial test. Conversely, when toxicity studies have revealed an effect on the reproductive system, the use of germ cells under 3 (d) may be indicated. In any event, the responsibility will be on the applicant to justify the reasons for the selection of individual tests used, as well as explaining the overall strategy used in the system of tests chosen. Normally one test from each of the following four categories should be selected.

(a) **Test for gene mutations in bacteria**

These are the most widely used tests for assessing the mutagenic properties of chemicals. Tests are carried out using several well-established bacterial strains designed to detect various types of genetic change, including frame shift and base change mutations. Tests are carried out with and without extrinsic metabolic activation.

(b) **Test for chromosomal aberrations in mammalian cells *in vitro***

For this procedure human lymphocytes can be used as well as several mammalian cell lines. The damage is scored by microscopic examination of chromosomes at mitotic metaphase. Tests are carried out with and without extrinsic metabolic activation.

(c) **Test for gene mutations in eukaryotic systems**

The relevance of this test is that a positive result found in bacteria can be additionally studied in a system which has the complex eukaryotic chromosomal structure. This structural complexity also allows the possibility of detection of mutations arising through mechanisms that cannot occur in the simple bacterial genome. Suitable tests include those using mammalian cells designed to detect the induction of mutations at specific loci such as the ones coding for the enzymes hypoxanthine-guanine-phosphoribosyl-transferase or thymidine kinase. Other eukaryotes, such as fungi and insects, may be considered. As appropriate, extrinsic metabolic activation may be incorporated into this test.

(d) ***In vivo* test for genetic damage**

The main role of the *in vivo* test in the four categories of tests is to ascertain if a mutagenic compound has been missed by the *in vitro* tests because of inappropriate metabolic activation systems having been used. The best validated tests are those which have end points of chromosomal damage e.g. bone marrow metaphase and micronucleus tests and the dominant lethal test. As an *in vivo* test for somatic gene mutations the mouse spot test is becoming more widely used.

All tests used should be well validated and conducted in line with established procedures set out in the current international literature.

There is one notable omission in the recommended test package as described above in that it does not include a test primarily designed for the detection of genome mutation (non-disjunction, aneuploidy). Specific methods presently under development are not sufficiently validated to incorporate them.

These Notes for Guidance were prepared in the light of current knowledge. It is to be expected that in the future, new and modified test procedures may be evolved, and will be applied in practice. In order to accommodate such future developments, these Notes for Guidance need to be periodically updated.

4. INTERPRETATION OF THE RESULTS

The objective of the mutagenicity testing procedures is to establish with reasonable certainty whether a substance possesses mutagenic properties or not. Following from this is a second quite separate issue which is the significance of the obtained results in terms of genetic hazard to man. If all results indicate convincingly that a substance has no effect in any of the tests then it would seem reasonable to conclude that the possibility of mutagenic hazard is of an acceptable low order (although it may be considered insufficient evidence of absence of carcinogenic potential). If all results both *in vitro* and *in vivo* indicate that the compound has mutagenic properties this would argue strongly for the existence of a risk for humans. An often occurring situation is that the results are non-uniform. This is to be expected since the tests are designed to have different end points and/or different characteristics for metabolic activation. In such cases the significance of positive and negative results is to be judged not by their number but by their nature. For instance, in the above package a positive result in an *in vivo* test deserves more weight than a positive bacterial test. This difference does not apply to negative results, implying that one negative *in vivo* test does not necessarily invalidate a series of positive results obtained *in vitro*. A better understanding of the genotoxic potential of the substance may be gained by carrying out supplementary investigations. The manufacturer should decide whether supplementary tests should be carried out and which ones

should be selected. This selection should be based on the results already obtained as well as on other properties of the compound and its intended use. Consultation with the regulatory authorities may be appropriate.

5. RISK/BENEFIT CONSIDERATIONS

When a compound has been shown to possess mutagenic properties this indicates the potential of the substance to present a genetic hazard to man (and at the same time to constitute a possible risk for tumour induction).

Mammalian tests, such as the heritable translocation test or the specific locus test may occasionally be useful for such assessment of the genetic risk in humans. These tests are expensive and require large numbers of animals; their application is justified only in well-founded cases.

The overall risk/benefit assessment of a mutagen should take into consideration not only the results of mutagenicity testing, but also the pharmacokinetics, metabolism, and the whole toxicity profile. In addition, the intended use of the medicinal product, its degree of exposure, the age and reproductive status of the patient, as well as the aspect of the potential risk of alternatively available substances have to be taken into consideration.

ANNEX III

CARDIAC GLYCOSIDES

1. GENERAL

The following Notes are designed with a view to clinical evaluation of cardiac glycosides and may also apply to other drugs which share the same pharmacological actions on the heart, i. e. positive inotropic and negative chronotropic and dromotropic effects.

These Notes for Guidance should be read in the light of the Norms and Protocols (Directive 75/318/EEC) and are intended solely to assist applicants in the interpretation of the latter with respect to the specific problems presented by cardiac glycosides and analogous drugs.

Management of cardiac disease in clinical practice using these drugs (and hence the evaluation of such drugs for use in this situation) is fraught with difficulties, resulting for example from:

— the low therapeutic/toxic dose ratio of these compounds,

— problems with respect to their pharmacokinetics, such as a tendency to accumulation,

— bioavailability problems,

— the multitude of extrinsic and intrinsic factors which influence their therapeutic efficacy,

— the fact that studies of such drugs inevitably involve critically ill patients with unstable disease patterns of varying aetiology.

2. PROBLEMS ARISING FROM THE LOW THERAPEUTIC/TOXIC DOSE RATIO

(a) **General remarks**

Not infrequently a modest overdose causes extracardiac symptoms of toxicity without evidence of cardiac toxicity. In addition undertreatment may be difficult to define. Assay methods of plasma concentrations have provided some insight, though the relationships between pharmacokinetics, pharmacodynamics and therapeutic and toxic effects are not as yet fully understood.

(b) **Recommendations**

Notwithstanding the problems concerning plasma concentration assays, as mentioned above, such assays should be performed since they can provide valuable information as to whether unexpected side effects are related to toxic concentrations of the drug or its metabolites at the receptor site or other target organs, and whether failure of treatment is linked to unexpectedly, low values. It will be useful to provide, if possible, quantitative information on the therapeutic/toxic plasma concentration ratio and its correlation with dose.

3. TENDENCY TO ACCUMULATION

(a) **General remarks**

Cardiac glycosides are commonly characterized by a relatively slow tissue uptake, extensive tissue binding and a prolonged half-life with a long duration of action. Such pharmacokinetic and pharmacodynamic factors must therefore be well-defined.

(b) **Recommendations**

Clear evidence should be obtained as to the limits of dosage if excessive accumulation is to be avoided; clinical, and if possible pharmacokinetic, data should be available justifying dosage regimens during chronic treatment both with (if judged necessary) and without loading dose(s) in patients in whom the use of such drugs is indicated, together with data concerning the time which is expected to elapse between starting therapy and the first signs of a clinical effect. Even initial clinical studies of the effect of the drug should thus continue longer than the time necessary to obtain steady-state plasma levels; the duration of the basic investigation hence depends on the pharmacokinetics of the individual glycoside. In addition, as with other drugs for long-term use, the efficacy, adverse effects and particularly possible clinical evidence of accumulation should be studied for a longer period, and during such studies further evidence

to exclude the risk of accumulation should be sought. Clinical factors such as are listed under paragraph 4, which may profoundly alter the pharmacokinetic behaviour of the drug, should be taken into account in analyzing data.

4. PROBLEMS RELATING TO BIOAVAILABILITY

(a) General remarks

Relatively slight differences in pharmaceutical formulation can result in marked variations in plasma concentrations between individuals due to differences in the rate and extent of absorption of cardiac glycosides after oral absorption. In view of their narrow therapeutic index such variations in plasma concentrations can be hazardous. It has been shown clearly that this factor is of paramount importance for most cardiac glycosides; every possible degree of bioavailability varying from approximately 3 % for oral ouabain to about 90 % in the case of digitoxin may be encountered in clinical practice. Individual and intersubject variations in plasma concentration increase as bioavailability decreases..

The oral absorption depends on the pharmacochemical properties of the glycoside and its pharmaceutical formulation.

(b) Recommendations

If the drug is available both in an intravenous form and as an oral form the percentage bioavailability of the oral tablet, capsule or solution should ideally be assessed by comparing the pharmacokinetic data after oral administration with that obtained after intravenous administration. A full description of radiochemical or other biochemical methods used in such studies to assay plasma or urine concentrations of the drug and/or its metabolites should be given, and the accuracy, sensivity and specificity of the method stated. In calculating the area under the curve (AUC) the relatively long distribution phase of cardiac glycosides should be taken into account and the area calculated by extrapolation of the elimination phase to infinity.

Bioavailability below the order of magnitude of 50 % is unlikely to be acceptable for any cardiac glycoside. Individual variations should be defined and should be as small as possible.

For every new glycoside the *in vitro* dissolution rate should be determined. Any subsequent alterations in the pharmaceutical formulation or processing create the need to submit new and adequate *in vitro* dissolution rate studies. In some such instances, depending on the *in vitro* findings and the extent of the modification, *in vivo* comparison of the rate and extent of the absorption of the new formulation with the old one should be furnished, using either single-dose or multiple-dose plasma concentration studies.

It is advisable to submit studies of steady-state plasma concentrations during chronic oral administration (multiple-dose studies).

If it has been demonstrated that a known and substantial proportion of the drug is excreted unmetabolized in the urine, urinary assays may be acceptable for comparative bioavailability studies.

5. CLINICAL INVESTIGATIONS AND FACTORS AFFECTING EFFICACY AND SAFETY

(a) General remarks

The clinical efficacy of a glycoside has to be demonstrated in patient groups of sufficient size, with clinical syndromes forming the principal indication for using cardiac glycosides, e. g. left ventricular failure and rapid atrial fibrillation. The clinical efficacy and safety depend on many individual patient factors and data obtained in healthy volunteers may not apply in the presence of one or more of these factors. Whereas the influence of factors like youth and old age, and disturbed renal and hepatic function may usually be reasonably well assessed by pharmacokinetic studies, such will not be the case with factors influencing the pharmacodynamics such as hypokalaemia and thyroid dysfunction.

(b) Recommendations

It is necessary to provide a full assessment of the clinically relevant effects of the glycoside on patients with atrial fibrillation along with estimates of the plasma concentrations.

Although it is more difficult, it is highly desirable and may even be essential to have quantitative data on cardiac function (e. g. cardiac index) in at least some patients with heart failure and regular sinus rhythm in whom cardiac glycosides are used to produce a positive inotropic

effect or to prevent the occurrence of tachyarrhythmias. Plasma concentration data, if obtainable, should be recorded. For new drugs it is to know whether there is a correlation between plasma levels and the appearance of undesired effects.

Adverse reactions occuring during these studies should be carefully monitored; though most adverse reactions to cardiac glycosides are symptoms of overdosage, both the extracardiac and the possible cardiac adverse reactions (arrhythmias) should be clearly described. The number of patients so studied need not necessarily be large, but the investigations should be carefully designed, executed and recorded. Clinical studies should preferably be done in patients without the complicating factors mentioned above (5 (a)) but data obtained in patients with complications will not be excluded *per se.*

6. DIFFICULTIES IN DEVELOPING ADEQUATE DOSAGE RECOMMENDATIONS

Recommendations on dose (including loading doses) should be based on sound pharmacokinetic evidence. Claims for dosage regimens which are at variance with normal usage should be based on well-documented observations in appropriate clinical syndromes such as rapid atrial fibrillation, abnormal renal, hepatic, or thyroid function, or during cardiac surgery and cardioversion. If specific claims are made concerning safety or efficacy in certain clinical conditions, appropriate pharmacokinetic and pharmacodynamic studies must have been carried out.

7. RECOMMENDATIONS WITH RESPECT TO DATA SHEETS AND DIRECTIONS FOLDERS

(a) **Dosage recommendations**

Recommendations for dosage in children, elderly patients and other groups requiring special dosage regimens should always be given. Since a multitude of intrinsic and extrinsic, pharmacokinetic and pharmacodynamic factors may affect the therapeutic efficacy of cardiac glycosides, and most of these occur in serious clinical situations, dosage recommendations (changes in dose or dose interval or other therapeutic measures), whether or not based on clinical data, should be given for the following conditions:

— diminished renal function,

— hepatic failure,

— hypo- and hyperthyroidism,

— youth and old age.

Proper warnings should be given concerning the use of the cardiac glycoside in the following conditions:

— hypokalaemia,

— hypercalcaemia,

— hypomagnesaemia,

— cardioversion,

— cardiac surgery.

(b) **Interactions**

If there are indications that interactions may occur and that they may be clinically relevant they should be studied in detail and mentioned in the directions folder.

(c) **Precautions**

All available information concerning therapeutic measures in accidental overdosage or deliberate (self-) poisoning should be provided.

8. FIXED COMBINATIONS

In view of the narrow therapeutic index of the cardiac glycosides and the need for careful individual titration of dosage, fixed combinations of cardiac glycosides with other drugs are extremely unlikely to meet the standards set by the Norms and Protocols (see the Notes for Guidance on Fixed Combination Products).

ANNEX IV

CLINICAL INVESTIGATION OF ORAL CONTRACEPTIVES

1. GENERAL

These Notes for Guidance should be read in the light of the Norms and Protocols (Directive 75/318/EEC) as well as Directive 65/65/EEC) [1]; they are intended solely to assist applicants in the interpretation of these documents with respect to the specific clinical problems involved in establishing the safety and efficacy of oral contraceptives.

The present notes have been compiled primarily with those contraceptives in mind which have hormonal activity and are administered orally to women. It is evident that for other contraceptive products subject to medicines legislation the investigational approach required to assess efficacy and safety will be analogous but not necessarily identical.

A contraceptive preparation consisting of two or more components should also be investigated so as to elucidate the points listed in the Notes for Guidance on Fixed Combination Products, i.e. the properties of the individual components and their contribution to the total effect should be known.

Where a new contraceptive can be considered as a modification of one already recognized as being efficaceous and safe (particularly where there is merely a minor change in dosage, or where one oestrogen is replaced by another accepted oestrogen) it may be possible to simplify the investigations provided the theoretical basis for the new formulation appears to be sound.

2. CLINICAL-PHARMACOLOGICAL STUDIES

Clinical-pharmacological studies performed with an oral contraceptive (and in the case of a fixed combination also with its components) are most likely to meet the standards set by the norms and protocols section, Part 3, Chapter IIA, paragraphs 1 to 4 if they are designed to provide data on:

(a) the pharmacological action or actions in man by virtue of which a contraceptive effect is attained;

(b) other pharmacological effects on the reproductive system and process, including those on hypothalamic and pituitary activity, ovarian endocrine secretion, ovulation, endometrial histology and biochemical activity, cervical mucus and vaginal cytology and secretion. Effects on tubal function, which cannot currently be studied in human subjects, can be investigated in animals;

(c) the degree of progestogenic, oestrogenic, androgenic, corticosteroid and other hormonal or anti-hormonal activity of the product and its components in man. It is appreciated that the quantitative study of some of these effects (particularly androgenicity and anti-androgenicity) in the clinical-pharmacological phase may be difficult, but conclusions on these points may also be drawn from animal studies and from side effects occurring during efficacy investigations;

(d) the nature and hormonal activity of the principal metabolites;

(e) suspected drug interactions likely to impair the efficacy of the product;

(f) those adverse effects likely to be detectable with products of this type even in a limited population, including those involving liver function, adrenal activity, lipid and carbohydrate metabolism, the thyroid and haemostatic mechanisms.

3. CLINICAL INVESTIGATIONS OF EFFICACY AND SAFETY

Clinical studies with an oral contraceptive are most likely to meet the standards set by the Norms and Protocols, Part 3, Chapter II (B) if the following principles are borne in mind:

[1] OJ No 22, 9. 2. 1965, p. 369/65.

(a) **Trial population**

The population studied should be reasonably comparable to that in the country or countries in which it is proposed to introduce the product. It should be realized that dietary habits, endemic diseases, body weight, illiteracy, etc., can substantially affect the results obtained with a given contraceptive method.

(b) **Scope of trials**

The clinical investigation should be sufficiently large to render possible a reliable calculation of efficacy (in terms of the Pearl Index and the Life Table method) and of the incidence of adverse reactions. In practice it generally proves desirable for an entirely new contraceptive product (e.g. one incorporating a new progestagen) to study some 20 000 cycles of treatment. Where a modification of an existing product is investigated, valid conclusions may sometimes be drawn from more limited material.

Since both the effect of the product and the degree of precision with which it is used may alter during long-term use, a substantial part of the total population studied should have used the contraceptive for a period of not less than 12 months, e.g. about a quarter of the total data available should relate to prolonged use.

Although any large-scale study of an oral contraceptive will as a rule have to be conducted on a multi-centre basis, only data from those centres which have gained substantial experience with the product should be included in the total analysis.

(c) **Studies on admission**

History-taking and clinical examination at the time of admission to the trial should provide a detailed record of any risk factors, relative contra-indications or other elements which may subsequently be relevant to the assessment of efficacy and supposed adverse effects, e.g.:

— age,

— obesity,

— smoking habits,

— alcoholism,

— cardiovascular disease,

— psychic disorders or symptoms,

— migraine,

— endocrine and metabolic disorders,

— epilepsy,

— anaemia,

— disorders of the haemostatic system,

— renal disorders,

— hepatic disorders,

— tumours.

The prior obstetric, gynaecological and contraceptive history should be known and recent and current drug intake recorded. The findings on certain of the above points will clearly lead to the exclusion of some subjects from the trial.

(d) **Recording of data**

It is recommended that in a contraceptive study individual patient data be recorded on a well-recognized form, such as that advocated by the World Health Organization. Trial subjects should be seen by investigators at intervals of not more than three months.

In all subjects taking part in such studies there should be a periodic gynaecological examination including cervical smear, as well as examination of the breast, weight and blood pressure, a test for glycosuria, and a close record of the menstrual history and any suspected adverse reactions. Intercurrent illness as well as adverse events noted by the patient should be recorded and any change in libido registered.

In a subgroup detailed laboratory examinations should be performed to detect any change in the normal endometrium, hepatic function, lipid metabolism, haematological parameters, protein spectrum, serum electrolytes urine composition, adrenal activity, carbohydrate metabolism, and any parameter an effect on which might be anticipated in view of the pharmacological and toxicological findings. Where clear abnormalities are detected, the patient should be

examined clinically and the findings recorded, irrespective of whether the subject continues to take part in the trial or not.

Any patients admitted to the study despite the presence of certain risk factors or functional disorders at the time of admission, should undergo regular re-examination in these respects during the trial.

In cases of contraceptive failure, data on the pregnancy and the condition of the neonate or embryo should be recorded and the possibility of patient failure assessed.

Where a subject withdraws from the study the reasons for withdrawal should be recorded and where possible the subject should be followed up to determine the time of resumption of menstruation and fertility and any possible effect on subsequent pregnancy.

Follow-up. Any subject who has shown significant variation in metabolic functions should be followed up to determine if and when these return to normal after termination of the trial.

(e) **Analysis of data**

(i) *General*

Data relating to efficacy, cycle control, adverse reactions and laboratory findings should be presented for the investigational programme as a whole and for the individual studies and also analyzed to try and find correlations with factors likely to be capable of affecting the findings.

(ii) *Efficacy*

If pregnancies have occurred during the study, a detailed analysis of each individual case should be presented.

(iii) *Cycle control*

Data on cycle control should be recorded and presented in such a manner that the incidence and severity of menstrual irregularity, spotting, breakthrough bleeding and amenorrhoea are clear, and so that any variation therein between individuals or over a period of time can be discerned. It is useful to indicate to what extent such events have been regarded as acceptable by the trial subjects and the investigators.

(iv) *Laboratory findings*

Abnormal laboratory findings should be analyzed, *inter alia*, with respect to any possible correlations with clinical findings in the subjects concerned.

(f) **Absolute and relative efficacy and safety**

An oral contraceptive is likely to be regarded as effective if the degree of contraceptive efficacy attained when the product is employed under field conditions by a normal population is not less than that currently attained with other contraceptive methods which have obtained wide acceptance. Some lesser degree of efficacy may be acceptable if it is outweighed by advantages in terms of safety and tolerance, and provided the chances of contraceptive failure can be quantified and are clearly explained in the texts made available to the user.

An oral contraceptive is likely to be regarded as not harmful if its adverse effects are not more severe or prolonged than those of oral contraceptives in current use, and provided that it does not result in persistent derangement of the menstrual bleeding pattern during long-term use or persistent changes after withdrawal.

(g) **Post-marketing studies**

Whilst Directives 65/65/EEC and 75/318/EEC impose no requirement that post-marketing studies be conducted, applicants proposing to market oral contraceptives of a new type are urged to consider the possibility of continuing long-term clinical investigations and monitoring subsequent to introduction of the products concerned; this will greatly facilitate the assessment of reports on supposed adverse reactions.

ANNEX V

USER INFORMATION ON ORAL CONTRACEPTIVES

1. GENERAL

The following text is intended to indicate the information on oral contraceptives which should be provided for users of these products, for example in the packaging leaflet (Article 6 of Directive 75/319/EEC).

It should be noted that:

(a) The present text is directed exclusively to the woman using the product, and is therefore selective and written in non-technical language. If a packaging leaflet is also supposed to provide information to the physician or pharmacist it will have to be considerably more extensive; in that case it will be advisable to separate this technical information from that directed to the user;

(b) The text is drawn up in the light of current knowledge and relates to oral contraceptives containing progestogens and oestrogens, employed to inhibit ovulation. For contraceptives of other types some adaptation of this text may be required;

(c) The text represents only a general standard; in some situations it may be considered more appropriate to provide more detailed or extensive information, or to omit points which in the national situation are irrelevant;

(d) The text should be presented in a manner which can be readily understood by the average user;

(e) The order in which the information is given need not necessarily follow that of the present notes for guidance.

2. NATURE OF THE PRODUCT

The nature of the product and the purpose(s) for which it is intended should be indicated. This means that where a product is destined both for use as an oral contraceptive and in gynaecological treatment this should be made clear.

3. CONSULTING YOUR DOCTOR

This section should include statements of the following type:

(a) You should consult a doctor before starting to take this preparation; only (s)he can determine whether it is suitable for you. You should also consult your doctor before changing from one oral contraceptive to another.

(b) There are some conditions in which it is generally inadvisable to take oral contraceptives. It is particularly important to tell your doctor if you have ever suffered from any of these illnesses:

— clots in the legs or lungs,

— strokes, heart attacks or angina pectoris,

— known or suspected cancer or tumours,

— unusual vagina bleeding, the cause of which has not been found,

— jaundice.

For the same reason you should also tell your doctor if there is any reason to think you may already be pregnant.

(c) In some conditions the doctor may wish to take special precautions or may advise you to use another type of contraception. Be sure that (s)he knows if you have been found to be suffering at any time from:

— any disorder of the breast, or discharge from the breast,

— diabetes,

— high blood pressure,

— high blood fat levels,

— migraine,

— heart disease,

— kidney disease,

— epilepsy,

— deafness,

— mental depressions,

— fibroids of the uterus,

— gall bladder disease.

For the same reason you should tell the doctor about your smoking habits, (particulary since heavy smoking can increase the chance of certain side effects), and about any medicines which you often need to take, including pain relievers.'

4. HOW TO USE THIS PRODUCT

This section should include:

(a) Clear instructions as to:

— the day when the first tablet is taken,

— the time of day when the tablet is to be taken (if relevant),

— the duration of ingestion in each cycle,

— the order in which the tablets are to be used (if these are arranged in a fixed order in the package),

— the day when the second and subsequent cycles of treatment should start;

(b) Clear advice as to how the user should act:

— if a tablet (or more than one tablet) has been forgotten,

— if no withdrawal bleeding occurs;

(c) Warnings as to conditions under which the reliability of the preparation may be impaired should be indicated. These will vary with the nature and dosage of the product but may indlude the first cycle of treatment (particularly if a preparation with a higher dose has previously been used), the simultaneous use of certain other drugs, and the occurrence of vomiting and severe diaarhoea.

5. GENERAL INFORMATION AND ADVICE

(a) The degree of reliability of the preparation should be indicated in general terms.

(b) The user should be advised to inform any other doctor or surgeon whom she consults for any reason that she is taking oral contraceptives, since this may be important in diagnosis or treatment.

(c) The user should be recommended to consult once more the doctor who has prescribed the product at regular intervals, as agreed with him or her, and in addition:

— if any severe symptoms occur whilst using it,

— if she has any reason to think that she has become pregnant,

— before restarting treatment after interruption,

— before restarting treatment after pregnancy or during lactation.

(d) The user should be informed as to the likely course of events if she stops taking the product (e.g. the time of onset of the next period and the resumption of fertility) and advised to see the doctor again if anything unusual happens at this time.

(e) A woman who wishes to become pregnant should be advised not to do so for three months after stopping the product, so that reproductive function can return completely to its previous pattern.

6. ADVERSE REACTIONS

(a) Commonly occuring adverse reactions should be listed, with some indication as to whether or not they are more common at the start of treatment. Effects listed here should include gastrointestinal symptoms, mild headache, mammary discomfort or swelling, some increase in weight, chloasma and mild depression. The effects on the menstrual cycle should be described in terms appropriate to the product concerned.

(b) Less common but severe adverse reactions should be mentioned, particularly thrombosis and cholestasis, and a list provided of those warning signs which justify consulting the doctor at once, such as:

— mammary discharge and nodule formation,

— severe changes in the monthly bleeding pattern,

— marked vaginal secretion,

— vertigo, faintness,

— jaundice,

— sudden impairment of vision,

— sudden pain in the chest or abdomen,

— pain or swelling in the legs,

— severe headache or migraine,

— any other unexpected symptom.

ANNEX VI

DATA SHEETS FOR ANTIMICROBIAL DRUGS

1. GENERAL REMARKS

Because of the wide range of antimicrobial products available and the complexity of the information on each of them, which is required if the most suitable product for a given case is to be selected and optimally employed, it is advantageous to standardize to some extent the presentation of technical information on products of this type.

The present document is not intended to replace or modify any existing or future national or international guideline for the presentation of 'data sheets', 'fiches techniques' or 'package inserts', but merely suggests the topics to which particular attention should be paid when such documents for antimicrobial drugs are drawn up and how the information can best be worded.

These notes for guidance are for all antimicrobial drugs irrespective of the mode of administration or the pharmaceutical form.

In the presentation of information on an antimicrobial drug, comparisons with other antimicrobial agents, which should be mentioned by generic name, are defensible only when they constitute an essential element in understanding the proper use of the product.

In view of the possibility of changes in resistance of micro-organisms, data sheets for antimicrobial agents should be dated, and should be revised whenever necessary.

2. GENERAL FORMAT

The text should contain the following sections, arranged and headed in accordance with Article 4 a of Directive 65/65/EEC:

— composition,

— microbiology,

— pharmacokinetics,

— indications,

— contra-indications,

— use during pregnancy,

— use during lactation,

— warnings,

— precautions,

— interactions,

— dosage and other instructions for use,

— adverse reactions,

— human toxicology and treatment of overdosage,

— storage and stability,

— packaging form.

Not all the sections of this document will apply strictly to every type or presentation of antimicrobial agent. For some externally or orally applied drugs which are poorly absorbed it will for example be sufficient to mention this fact, instead of including detailed pharmacokinetics, though if the absorption of this kind of drug is considerably increased in such circumstances as damage to the skin or intestine this should be stated.

The following sections are particularly relevant for antimicrobial agents:

(a) **Microbiology**

The classification, nature and mode of action of the drug should be indicated. The groups of micro-organisms sensitive to the drug should be indicated. These data should be based on tests using multiple recently isolated epidemiologically unrelated strains of each species for which an effect is claimed. Special attention should be devoted to micro-organisms which are particularly sensitive or insensitive, especially when this is unexpected having regard to the nature of the drug. The text should indicate to what extent resistance can develop and how rapidly and under what conditions this occurs. The occurrence of cross-resistance to other antimicrobial agents should be mentioned. Break points should be indicated if possible.

If MIC (Minimum Inhibitory Concentration) data are included, such information should, in order to be meaningful, meet the following standards:

— the sensitive micro-organisms should be listed in groups in a table in order of increasing MIC values,

— specifications should be given briefly with respect to the microbiological methods employed for the determination of the MIC values, for example the size of the inoculum, the origin of the organisms and the number of strains tested, the medium and the date of study,

— if the difference between MIC and MBC (Minimum Bacteriocidal Concentration) values is very narrow or very large this should be stated. When, during therapeutics use, concentrations are attained which are bacteriocidal *in vitro* this can be mentioned provided it is clinically relevant; the micro-organisms concerned and the site at which the concentrations are attained should be specified.

If a significant degree of synergism or antagonism with other antimicrobial drugs has been found this should be specified.

(b) **Pharmacokinetics**

It is advisable to group the information on human pharmacokinetics in subsections concerning absorption, distribution, biotransformation and excretion.

(i) *Bioavailability and absorption*

The bioavailability of the active drug should be indicated.

Factors which influence to an important extent the degree and rate of absorption should be listed.

(ii) *Distribution and plasma levels*

For antimicrobial drugs clinically relevant information in regard to distribution should be given.

The following points are of particular importance:

— the average maximum and trough serum or plasma concentrations after administration in the appropriate way should be given, specifying the dose administered, the dosage regimen and the time intervals at which a maximum concentration is attained. When the individual variation in drug concentration is large this should be specified,

— half-life in plasma,

— penetration into other body fluids in so far as relevant to the indications and/or toxicity,

— where the drug penetrates intracellularly this should be stated,

— when the distribution is predominantly extracellular it is sufficient to indicate the free drug concentration in plasma,

— in so far as it is relevant to the therapeutic use, the organs or tissues into which the drug penetrates poorly (e.g. eye, prostate, CNS) should be listed,

— where animal studies indicate that the drug accumulates in particular organs or tissues and this is clinically or toxicologically relevant, this should be stated.

(iii) *Bio-transformation*

The pattern of bio transformation should be indicated; for antimicrobial drugs it is particularly important to include available data on any metabolites which have relevant antimicrobial or toxic effects.

(iv) *Excretion*

The excretion patterns of the drug and its important metabolites should be indicated. Excretion into the urine, bile and faeces should be given as a percentage of the total dose administered and, where this is clinically relevant, the concentrations likely to be attained should be listed. In so far as relevant to the indications the excretion into sputum should be given.

(c) **Indications**

It should be made clear that the drug is only indicated for diseases caused by micro-organisms which are sensitive to it. Even within this field it is desirable to restrict the indications of a new antimicrobial drug in order to preserve its usefulness for as long a period as possible.

It is acceptable to give a summary of the organs and tissues, microbial disorders of which can be treated effectively. It is not desirable to mention specific diseases, except where the clinical usefulness of a drug can only be defined in terms of a particular disease, or where it is necessary to point out that the drug is unsuitable for treating a particular condition. When prophylactic indications are listed it will be proper to mention the diseases concerned in general or specific terms, provided the value of the drug for this purpose has been adequately demonstrated.

General fields of indication (e.g. surgical infections, paediatric infections) are inadmissible.

When in certain situations it is better to use another form of administration of the drug this should be stated.

(d) **Use during lactation**

It should be stated if the drug is excreted in the milk and if there is any risk of sensitization of the infant.

(e) **Warnings**

Other antimicrobial drugs to which cross-hypersensitivity and/or cross-resistance may occur should be listed.

If relevant, the possibility of superinfection with insensitive micro-organisms should be mentioned.

(f) **Dosage and other instructions for use**

The usual doses in the various clinical situations in which the drug is useful, which may differ substantially, should be listed.

It should be specifically stated whether adaptation of dosage is necessary in renal failure or the presence of other concomitant disease, and whether the drug can be used in the very young and the very old.

If the drug can be used in children, neonates and premature infants, then a dosage schedule for children under the age of three must be provided in which the dose is expressed per kilogram of m^2 per day. For older children and adults a total dose may be indicated.

If relevant, a special dose regimen for aged persons should be indicated, particularly where the physiological decline in renal function renders this necessary.

Maximum safe total doses for the entire course of therapy should be listed wherever they are known.

Compatibility with infusions should be specified where the drug is likely to be used in this way.

ANNEX VII

CLINICAL TESTING REQUIREMENTS FOR DRUGS FOR LONG-TERM USE

INTRODUCTION

The general requirements for clinical trials are given in the Annex to Directive 75/318/EEC, Part. 3. These Notes for Guidance advise on those clinical trials likely to be demanded for long-term use. The planning and design of pre-marketing longterm studies should take into account specific problems raised by each type of drug and disease; the following are general guidelines and do not exlude 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) Drug 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 drug when current medical practice is likely to bring the drug 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 Notes 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 drug. 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 drugs, 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.

Randomized 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 drug. It should be sufficient to take into account any spontaneous variations in the course of the disease, possible effects of the drug 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 drugs 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 drug 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 drugs for intermittent use. When the drug'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 drugs it would be useful to know the effect on the immune system. The exact requirements will necessarily vary with the nature of the drug 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 drug for longer periods should be presented if available.

(b) The following specific points also need attention in any drug 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 adequate post-marketing monitoring;

(ii) Evidence is needed on accumulation of the drug 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 drugs, and particular attention should be paid to the problem of drug 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 drug, then evidence for safety for such patients needs to be established;

(v) Where adverse effects occur in a particular category of patient, and where it is proposed that the drug 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 drug is proposed;

(vi) Investigations should, where appropriate, be performed to determine whether withdrawal symptoms or a rebound effect occur when the drug 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 EEC Notes for Guidance on Fixed Combination Products.)

In principle the present Notes for Guidance apply 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.

ANNEX VIII

NON-STEROIDAL ANTI-INFLAMMATORY COMPOUNDS FOR THE TREATMENT OF CHRONIC DISORDERS

INTRODUCTION

These Notes for Guidance should be read in the light of the general requirements set by the Norms and Protocols (Directive 75/318/EEC).

1. DEFINITION

This document relates to applications for registration of non-steroidal anti-inflammatory products intended primarily for symptomatic long-term treatment of such disorders as rheumatoid arthritis and osteoarthrosis and other disorders of joints, muscles and tendons. Such terms as 'anti-rheumatic' and 'anti-phlogistic' are commonly used in various languages to characterize these drugs.

These notes are not primarily intended to apply to drugs used to produce remission.

2. STAGES OF CLINICAL INVESTIGATION

(a) **Initial short-term studies in patients (three to 14 days)**

The initial clinical studies undertaken in patients will serve to define the anti-inflammatory effect of the preparation and some adverse reactions occuring in short-term use, as well as to estimate the approximate dosage range. At least, some of these studies should be conducted against placebo.

(b) **Medium term studies in patients (two to eight weeks)**

In subsequent controlled studies it is advisable to compare the anti-inflammatory properties of the product at various dose levels with those of at least one other well-studied drug of similar type given in fully-effective doses.

(c) **Long-term clinical investigations (see also Notes for Guidance on Drugs for Long-Term Use)**

The fact that these products are intended to be used over very long periods at least for some indications means that it is of the greatest importance both from the point of view of efficacy and safety to study their effects during prolonged use.

(i) *Efficacy*

The pattern of long-term efficacy for drugs of this type can generally be adequately defined in controlled studies of up to six months in each of the major indications claimed.

Where drugs of this type are indicated primarily in rheumatoid arthritis, such a long-term study should relate to that condition. The known seasonal variations in rheumatoid arthritis should be taken into account in arranging these trials and interpreting the results.

Where osteoarthrosis or ankylosing spondylitis are claimed as indications, long-term investigations should also have been performed in these conditions, but the extent and duration of this work will depend upon the totality of clinical evidence available on the drug, e.g. the availability of similar studies in rheumatoid arthritis.

In long-term clinical investigations, particular attention must be devoted to all other factors which might influence the results, e.g. other forms of treatment. Because of the prolonged nature of this phase, most patients will be on some concomitant therapy which should be noted. In particular and irrespective of the type of trial (see (b) and (c)), an analgesic drug which has no material anti-inflammatory effect, may be used as supplementary therapy if the need arises. Such treatment should be reported separately.

(ii) *Safety*

With respect to numbers of patients and duration of treatment see Notes for Guidance on Drugs for Long-Term Use.

The exact requirements are bound to vary to some extent from one country to another, because of climate variations; in more temperate climates these drugs are generally given throughout the year, whereas in warmer climates treatment tends to be suspended during the summer. Nevertheless, trials should be designed to take into account possible seasonal variations of adverse effects.

The dosage and pattern of use should be that which is likely to be employed in practice. The trial patients should include substantial numbers of the elderly.

3. ANALGESIC AND ANTIPYRETIC ACTIVITY

Where specific analgesic or antipyretic activity is claimed or implied, this must have been investigated directly in controlled studies which include short-term double-blind comparison against placebo and comparisons with other compounds.

4. CLINICAL PARAMETERS

The clinical parameters in all studies must be such that they give a clear picture of the extent to which the disorder, the symptoms and physical function are influenced. Existing sets of criteria for the diagnosis and grading of rheumatoid arthritis may be regarded as a basis.

5. EXTRAPOLATION OF RESULTS

Since the various disorders of the joints, tendons, bursae, etc., which are usually treated with anti-inflammatory and analgesic drugs differ pathologically, it is important to study the therapeutic effects of a drug in various types of well-defined and carefully diagnosed clinical conditions. Extrapolation of the results to another disorder is only permissible where the two are pathologically and clinically closely allied. When juvenile rheumatoid arthritis is claimed to be an indication for the drug, this must be justified by studies conducted in children suffering from this disease.

6. SIDE EFFECTS

A careful study of adverse effects (their nature, frequency and severity) is necessary. Any claim that the frequency of certain adverse effects is lower than with other products of this type must be supported by adequate evidence obtained with administration in fully effective doses. In the assessment of this material, particular attention will be devoted to the question of gastro-intestinal tolerance, effects on blood and haemopoiesis, effects on platelet aggregation, to those adverse reactions which might be anticipated in the light of the animal pharmacology and toxicology, and to the extent to which the major adverse reactions are dose related.

Data on the reasons for drop-outs in clinical studies should be available since they may throw light on the severity of adverse effects.

Where the pharmacological and/or toxicological data suggest that a drug may stimulate or suppress the immune response or interfere significantly with the immune system, work should be undertaken using therapeutic doses, to determine whether these effects are of clinical importance.

7. INTERACTIONS

Interactions with other drugs prescribed concurrently, as is often the case in the elderly, should be looked for during clinical trials and a careful record kept of all concurrent medication.

Specific studies of possible interactions with particular drugs likely to be used concurrently should be undertaken where there is reason to think that they are present.

ANNEX IX

ANTI-EPILEPTIC/ANTICONVULSANT DRUGS

1. GENERAL

The following notes are concerned primarily with the clinical evaluation of medicines intended for long-term use in epileptic disorders. Properly designed long-term clinical studies are essential, and should be submitted together with short-term studies of special aspects of efficacy, tolerance and safety. Experience to date shows that manufacturers and physicians would be well-advised, irrespective of any legal obligation, to continue to study drugs of this type after they have been registered and marketed, in order to detect unusual effects, long-term adverse reactions or alterations in the therapeutic effect over a long period (see also Notes for Guidance on Drugs for Long-Term Use).

2. INVESTIGATORS

Except for the very earliest phase of tolerance studies it is generally desirable that clinical assessment of anti-epileptic drugs is performed by clinicians experienced in the medical evaluation and management of epilepsy.

3. SELECTION OF PATIENTS

Particularly in the early stages of therapeutic studies it is advisable to select individuals suffering from one or more types of seizures which are well defined and of known frequency. Patients selected for the main therapeutic studies should preferably have a stable form of epilepsy, and if they have received drugs already, their therapeutic response to previous therapy must be known. Some studies should also include investigations of the therapeutic outcome in patients with various degrees of severity of epilepsy.

It is recognized that in the interest of the patient new anti-epileptic drugs often have to be evaluated while combined with other, established drug treatments and during the earlier phases of evaluation this approach will generally be essential. Patients who are incompletely controlled on existing drugs constitute an important subgroup for study with a view to defining the spectrum of activity of the new drug. In such cases, it is essential that the previous drugs have been prescribed for a sufficiently long period to attain a steady state. The blood levels of these previous treatments must be known and stable and they should continue to be studied after the new compound is administered. Once the efficacy of the new compound in combination with others has been determined, it is equally important to assess the efficacy of the drug when given alone. While initial therapeutic studies usually will be performed among hospitalized patients only, it is essential in the later phases also to study the effectiveness and safety of the test drug when used in outpatients, including those engaged in normal daily activity.

4. PHARMACOKINETICS AND BIOAVAILABILITY

Among existing anti-epileptic drugs several examples are present of kinetic problems which are of significance for therapeutic control (non-linear kinetics, alterations in protein-binding, active metabolites, etc.). Thorough kinetic exploration is therefore particularly needed for such drugs, and should include information on the degree of individual variation in clinically relevant kinetic parameters. For this reason data on such parameters should be submitted for an adequate number of patients. These investigations are often closely related to those concerned with drug interactions (see below). Existing anti-epileptic drugs have certain characteristics (such as a narrow therapeutic margin and/or complex relationships between dose and serum level) which raise problems of bioavailability: if the new substance is chemically similar to existing drugs, particular attention to these problems will be necessary (see Notes for Guidance on Bioavailability).

5. CRITERIA OF EFFICACY

In early studies continuous observation is desirable. At this stage and subsequently, reduction in the frequency of seizures is the main clinical parameter of efficacy. In assessing ambulant and in particular *petit mal* cases use of telemetry may be advisable. Effects on the EEG and on behaviour should be recorded systematically at least in some studies, irrespective of whether or not they correlate with the anticonvulsant potential of the drug. In subsequent work, reduction in both frequency and severity of seizures should be measured and quantified under controlled conditions. It is important to assess social and working capacity at the same time. As a measure of benefit, decrease in adverse reactions should also be kept in mind. It is recommended that data be obtained on the effects of more than one dose level and that serum level monitoring be employed (see paragraph 7).

6. COMPARATIVE STUDIES

The use of placebo alone in patients with convulsions should be avoided, but the use of placebo comparisons should be possible (and is of value) when assessing the benefit of a new drug as an addition to a known but inadequate regimen. In assessing the effect on some other forms of epilepsy (e.g. *petit mal*) a new drug may also be tested againt placebo. Since a full placebo comparison will not often be feasible or ethically acceptable in convulsive epilepsy, it is important in the later phases of evaluation to carry out controlled (randomized) clinical trials in which the drug is compared with other drugs or other combinations of drugs usually employed for the seizures in question.

7. SERUM LEVELS

Dose/response evaluation (both effect and dose-related side effects) should not be considered complete until a clear impression has been gained of the drug's therapeutic and toxic range, including serum level studies. The latter are particularly important in determining whether or not serum concentration monitoring in the therapeutic situation is meaningful and advisable in practice.

If other monitoring parameters are proposed, for example salivary levels, their significance and reliability must be adequately studied.

8. ADVERSE REACTIONS

Events occurring during the course of treatment should be carefully recorded, with particular regard to neurological and psychological changes (e.g. those involving thought processes, gait, speech, coordination, nystagmus or lethargy), and any problems which may arise in long-term use, and clinical observations supplemented by appropriate laboratory tests.

9. INTERACTIONS

Anti-epileptic pharmacotherapy is not infrequently performed with a combination of two or more drugs and it is therefore of particular significance that studies to detect clinically important drug interactions be carried out. Such studies should include those anti-epileptic drug combinations which are likely to be used in practice and those which seem likely to give rise to interactions.

Many existing anti-epileptic drugs (e.g. phenytoin, barbiturates, carbamazepine) are also well known for their interference with the metabolism of other types of drug, involving enzyme induction or inhibition; it is therefore advisable to conduct studies to detect effects of this type, particularly if they involve drugs the dosage of which is critical (e.g. cardiac glycosides, anticoagulants, oral contraceptives) or interactions with alcohol.

10. DURATION OF TRIALS

The principles set out in the Notes for Guidance on Drugs for Long-Term Use will clearly be applicable to anti-epileptic/anticonvulsant drugs. Well-documented observations on patients treated for 12 months should be available in order to assess the safety and efficacy of these drugs in long-term use. Data relating to safety should be available on at least 100 of such patients.

11. SPECIAL CLAIMS

New anti-epileptics are sometimes claimed to have special properties, e.g. psychostimulating effects. Such claims must be substantiated in controlled clinical trials, specially designed for such purpose.

12. FIXED COMBINATIONS

Some epileptic patients are treated with two or more anticonvulsants. However, initial individual adjustment of the dose of each drug is particularly important in such cases because of individual variations in their dose/response curves, their varying kinetics and their sometimes narrow therapeutic margin. Unless there is a special rationale, fixed combinations of drugs used for convulsive disorders are generally undesirable and are unlikely to be acceptable until or unless extensive field experience over some years has indicated that a particular mixture is in fact of value and well tolerated in practice (see Notes for Guidance on Fixed Combination Products).

13. CHILDREN

In the light of the Annex to Directive 75/318/EEC, Part 3, Chapter III, final paragraph, an epileptic drug is unlikely to be acceptable for unrestricted use in children until sufficient experience has been gained in various groups and patient types (e.g. infantile spasms, akinetic seizures) to determine dosage, serum levels and effectiveness. If possible, long-term studies should be designed to detect any possible effects on learning, intelligence, growth and puberty. As pointed out in paragraph 1, such studies may need to be conducted subsequent to marketing.

ANNEX X

INVESTIGATION OF BIOAVAILABILITY

1. GENERAL REMARKS

Bioavailability studies evaluate the performances *in vivo* of dosage forms. They require generally a knowledge of the pharmacokinetics of the drug. Broadly, there are two types of bioavailability studies:

(a) studies done during the development of a new product;

(b) comparisons between existing and new formulations.

It will be noted that the Annex to Directive 75/318/EEC, whilst referring, both in the pharmacological (Part 2, Chapter I (G) and clinical pharmacoligical (Part 3, Chapter II (A) (1) (c) sections, to the need for pharmacokinetic studies, does not set requirements with respect to the study of bioavailability. This reflects the fact that when a medicinal product has been subjected to the various pharmacological, pharmacokinetic and therapeutic studies specified in the Directive, the reports on these studies will generally include precise data on the absorption and fate of the drug, from which it will be possible to draw clear conclusions as to the adequacy and reliability of its bioavailability from the form which is to be marketed. However, a number of specific situations do arise in which the question of bioavailability assumes especial importance, and may have to be studied more extensively and more explicitly. Some of these situations are indicated in the present Notes.

It should be noted that a number of topics commonly dealt with as aspects of bioavailability in fact relate to pharmacokinetics; for these matters reference should be made to the separate Notes for Guidance on Human Pharmacokinetic Studies.

2. DEFINITIONS

For the present purpose, bioavailability means the rate and extent of delivery to the site of action of an active drug ingredient or therapeutic moiety when a drug is administered in a particular pharmaceutical form. Bioavailability is a characteristic of this form and does not necessarily run parallel to particular pharmacological or therapeutic effects. Bioavailability is generally determined by the extent and rate of absorption of a drug from its pharmaceutical form, but there may be other important determinants such as first-pass metabolism. It may be useful to distinguish between the 'absolute' bioavailability of a given pharmaceutical form when compared with that (100 %) following intravenous administration, and the 'relative' bioavailability as compared with another form administered by any route other than intravenous (e.g. tablets v. capsules). Clearly the concentration at the site of action will rarely be directly measurable and indirect parameters will often have to be employed (see 3).

3. PARAMETERS

Questions of bioavailability most commonly arise with products administered by the oral route, and the present Notes are formulated with such products in mind. In these cases, the most convenient measure of bioavailability is as a rule the concentration/time curve in the blood of the active component and/or its active moiety or metabolites, since this will presumably reflect the concentration attained at the site of action. However, administration by other routes will obviously sometimes raise analogous problems, requiring a comparable (though different) approach. Studies of blood concentrations are sometimes not feasible, and in other instances they are not directly relevant to the effects of a drug; in such cases the measurement of concentrations elsewhere (e.g. in urine), of pharmacological effects or therapeutic efficacy, using sensitive and reproducible methods, may be acceptable and occasionally more realistic.

It is felt to be undesirable to lay down here detailed rules as to the method of studying bioavailability, but some general points may be made:

(a) The absorption of a medicine in different individuals may be influenced by genetic, environmental, dietary and nutritional factors, as well as by age and previous exposure to the same drug; in order to eliminate or at least minimize those factors not related to the formulations, it is necessary to conduct comparative studies in well-defined and controlled conditions. Such

studies are generally performed using a crossover design which requires fewer subjects than parallel studies. The approach using stable isotope-labelled and unlabelled drugs permits simultaneous administration by different routes and thus simplifies the protocol;

(b) Alongside bioavailability studies which will normally be conducted on an empty stomach there will sometimes be a reason to perform kinetic studies designed to determine the fate of a drug when the stomach is filled, as it will often be when the drug is employed in practice.

4. APPLICATIONS WITH FULL CLINICAL DOCUMENTATION

For medicines based on new chemical substances and new forms of administration of known substances it may be assumed that all the material specified in Directive 75/318/EEC will be submitted. As pointed out above, this may well provide all the information on the bioavailability from the final pharmaceutical form which is required in order to draw conclusions. More explicit and extensive investigations of bioavailability are likely, however, to be needed in some situations, examples of which are give below:

(a) where the results of any studies conducted in animals or man are highly variable, and the possibility exists that this variation may be due to a particularly marked effect of pharmaceutical processing on absorption;

(b) where it is particularly important to ensure exact dosage, e.g. because the drug has a steep dose/response curve or a narrow margin between therapeutic and toxic dosage, and/or where there is a hazard to the patient in the event of inefficacy;

(c) where the substance is closely related to one which is known to raise problems of bioavailability;

(d) where the physico-chemical or pharmacokinetic properties of a drug are such that any subsequent change in pharmaceutical formulation or processing is likely to alter bioavailability;

(e) where the pharmaceutical process employed is unusual, or such that constancy of bioavailability is difficult to foresee. This may, for example, be the case where tablets have a protective coating, where a slow-release form is involved, or where the active substance comprises only a very small part of the total formulation;

(f) where the product contains more than one active component, in so far as there are theoretical or experimental grounds for anticipating that one of these may increase or decrease the bioavailability of the other(s).

5. APPLICATIONS WITHOUT FULL DOCUMENTATION

Certain applications relate to new specialities which are very similar or even identical in their composition to existing specialities. Other applications relate to modifications in existing products. It is evident that in such cases it will not be necessary to repeat all the studies performed with the original speciality. The essential question to be answered is whether the older and the newer formulations are bioequivalent (see Appendix) and whether any differences in bioavailability between them are likely to induce significant change with regards to efficacy and/or safety.

The following principles are applicable:

(a) Where a substantial departure from the original formulation is involved, or where problems such as those listed under 'Applications with full clinical documentation' are known to exist with respect to the medicine, clinically and statistically adequate bioavailability studies, comprising direct comparison of the two formulations in man, will be required in order to draw conclusions. They may be usefully complemented by pharmacokinetic studies or therapeutic trials;

(b) In those other cases where only a very minor modification to an existing product is being made, there should be an appropriate *in vitro* comparison between the older and the newer formulation, e.g. with respect to their dissolution time profile or the release of the active component.

6. SITUATIONS IN WHICH BIOLOGICAL AVAILABILITY NEED NOT BE STUDIED

Studies of bioavailability are generally not required:

(a) when the drug is intended solely for intravenous use;

(b) when the drug is destined for local therapeutic use (though this does not necessarily exclude the need for studies of its passage into the general circulation);

(c) when the drug is an oral product not required to be absorbed (though this does not necessarily exclude the need for studies of its passage into the general circulation);

(d) when the drug differs only as regards the quantity of active substance from another having the same pharmaceutical form, the same proportion of active component and excipients, made by the same manufacturer, provided the bioavailability of the latter has been demonstrated and the two products meet the requirements of an appropriate *in vitro* test;

(e) when the drug has been reformulated but remains an identical drug (except as regards the colorant, sweetener or preservative) to the drug previously prepared by the same manufacturer, provided the bioavailability of the latter is known and the two versions meet the requirements of an appropriate *in vitro* test.

Appendix

FDA definition of bioequivalence

(*Federal Register*, Vol. 42, No 5, 7 January 1977)

'Bioequivalent drug products' means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absoprtion do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labelling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

ANNEX XI

CLINICAL INVESTIGATION OF DRUGS FOR THE TREATMENT OF CHRONIC PERIPHERAL ARTERIAL DISEASES

1. INTRODUCTION

Drugs influencing peripheral haemodynamics, whether acting on the vessel wall, the blood itself or in other ways, are commonly marketed for the relief of intermittent claudication, rest pain or symptoms related to vasospasm. The value of the drugs available for this purpose is disputed and the reliability or relevance of much clinical investigation performed with these products is questionable.

2. GENERAL PRINCIPLES

The clinical section of submissions relating to drugs of this type should meet the standards generally considered applicable to good investigational practice.

In particular:

(a) indications claimed should be based on studies demonstrating directly a clinically relevant and statistically significant effect on the patients' symptoms or the course of the disease, and not on pharmacodynamic findings or laboratory data alone;

(b) results relating to specific pathological entities, types of patient or forms of administration should not without justification be extrapolated to other situations;

(c) the reasons why patients have failed to complete the study period should wherever possible be recorded;

(d) attention should be devoted to the long-term efficacy and safety of these products and to any effect which may follow their withdrawal.

3. SPECIFIC RECOMMENDATIONS

In planning and analyzing clinical studies which are intended to form part of a submission, applicants are particularly urged to bear the following points in mind. They are listed primarily with respect to studies in intermittent claudication, but certain points are also applicable to studies of other peripheral ischaemic conditions.

(a) **Definition of patients**

In order to make valid comparisons and constitute homogenous subgroups for analysis, it is vital to characterize trial subjects at the time of admission with respect to a number of variables, particularly:

(i) the nature, site and extent of the peripheral vascular disorder, which should be determined as objectively as possible. Angiography, which is often performed in this type of patient, will be of great value in this respect;

(ii) the duration and severity of the clinical symptoms. In studies involving the lower limbs, only patients who display a pronounced reduction of the ability to walk are eligible for the trial;

(iii) relevant dietary habits and body weight;

(iv) intake of alcohol, smoking habits;

(v) use of other drugs;

(vi) the presence of any relevant concurrent disease (e.g. diabetes, hypertension);

(vii) the usual degree of physical activity.

Changes relating to (iii), (iv), (v), (vi) and (vii) during the study should be recorded.

(b) **Use of controls**

Because the course of symptoms due to peripheral ischaemia can fluctuate spontaneously and can be very strongly influenced by factors such as training and other behavioural measures, etc., treated patients must be compared with a contemporaneous control group. Since the merits of all existing drugs in this field are widely disputed, no valid reference compound can be proposed, i.e. the comparison should at the present time include a placebo.

(c) **Patient selection**

Alert, ambulatory outpatients with stable intermittent claudication, generally at a non-advanced stage of the chronic arterial disease, will be selected. In this document, stable should be defined as having no significant change in severity of symptoms during a previous three-month period.

A long observation period is necessary to characterize the fluctuation of the symptoms and for the patients to reach stability under general measures such as exercise, limitation of use of tobacco and alcohol, appropriate diet, and treatment of concomitant diseases; these measures should be kept as constant as possible during the whole trial.

Before the actual study begins, patients considered to be stable under the above conditions will enter a placebo run-in period intended to check their stability and to assess their base-line. During this pretreatment period, appropriate standardized exercise tests should be carried out at intervals (e.g. two weeks) until sufficiently reproducible results are obtained. Experience has shown that a period of four to six weeks will often be sufficient for this purpose.

Random allocation of patients to the treatment or placebo groups should be made after this run-in period.

(d) **Parameters**

The most essential parameters are those reflecting measurement of the clinical effect claimed.

Any effect claimed on intermittent claudication should be studied in standardized exercise tolerance tests, e.g. using a treadmill. Such tests should be performed under controlled temperature conditions and with a prolonged period of acclimatization. These studies may be supplemented by scoring the patients' own assessment of the improvement attained.

Whilst drugs developed in this field may affect the outcome of various types of purely objective study (e.g. involving venous occlusion, plethysmography, xenon clearence as a measure of blood flow in the muscles, Doppler blood pressure measurements, oscillometry, calorimetry, muscular pO_2), there appears as yet to be no such method available which is both entirely dependable and correlates to any useful extent with the effects desired clinically. Such methods may be of some value in screening new products, but if an applicant wishes to claim that such a technique actually demonstrates the clinical usefulness of a product its relevance must be proven.

(e) **Comparative studies**

(i) In order to allow for spontaneous fluctuations in the course of the disease and to detect the possible development of tolerance and some delayed adverse effects, the double-blind phase of treatment should last for prolonged periods (six to 12 months).

(ii) Enrolment of patients should take into account the seasonal influences on the evolution of such disorders and occurrence of adverse effects.

(iii) Any relevant event occurring after treatment withdrawal during or after the trial should be taken into account.

(f) **Analysis of results**

Any clinical effect obtained is unlikely to extend to all the types of patient treated and in order to obtain a clear impression a careful analysis of the results obtained in predefined subgroups (see (a)) will be required.

ANNEX XII

PHARMACOKINETIC STUDIES IN MAN

GENERAL

The present Notes are designed to provide guidance on, and assist applicants in the interpretation of, preclinical and clinical pharmacokinetic investigations of a new drug, irrespective of the nature, mode of action or route of administration.

These Notes for Guidance should be read in the light of the Norms and Protocols (Directive 75/318/EEC) and are intended solely to assist applicants in the interpretation of the latter with respect to the specific problems of pharmacokinetic studies, including drug metabolism, in healthy volunteers and patients.

These Notes only consider general rules; all the points mentioned do not necessarily apply to each substance; therefore each study should be planned and designed taking into account the properties and indications of the drug concerned.

The relation between dose, plasma concentrations and therapeutic or toxic effects, where this is feasible, should be studied. Pharmacokinetic studies are as a rule necessary in order to employ drugs under the best conditions of efficacy and safety. They are essential to establish therapeutic schedules, to evaluate their relevance or to proceed to dosage adjustments in particular patients. This particularly applies to drugs with a narrow therapeutic range and to those for which a close relation between plasma concentrations and therapeutic and/or toxic effects can be demonstrated or expected.

In some instances, pharmacokinetic studies may be impossible or limited, e.g. where their provision raises insuperable difficulties or would create risks for test subjects; in these cases, the use of drug is partly or completely based upon pharmacodynamic and clinical studies.

The present notes consist of two sections:

I. Pharmacokinetic factors to be studied

which deals with:

1. absorption,
2. distribution,
3. elimination,

as well as with interactions and adverse reactions,

and

II. Methodology and conditions of study

which deals with:

1. choice of administration (route, dosage, dosage intervals),
2. choice of subject (healthy volunteers, patients wich relevant disorders, patients with other interfering conditions),
3. choice of methodology (sampling and analysis, data processing and statistics).

I. PHARMACOKINETIC FACTORS TO BE STUDIED

1. **Absorption**

Both the *rate* and *extent* to which the active drug ingredient or therapeutic moiety are absorbed should be known.

Data on *bioavailability*, which is referred to in the EEC Notes for Guidance on Investigation of Bioavailability, should be provided.

(a) *Substances intended to produce systemic effects*

Whatever the route of administration (e.g. buccal, sublingual, parenteral, rectal, percutaneous, pulmonary), direct or indirect data on the extent of absorption should be submitted; whenever possible, comparison with an intravenous dose should be made. Preferably a precise pharmacokinetic analysis of the entire plasma profile, including absorption, distribution and elimination, should be given since these various steps may be interrelated to a great extent. This applies particularly to special dosage forms for which delayed release of the active substance or a prolonged duration of action is claimed. Failing this, at least data on drug concentration at peak (C_{max}), time to reach peak (t_{max}) and area under the concentration/time curve (AUC) should be provided.

If there is reason to suspect that certain physiological or pathological factors, such as the presence of food or certain food constituents (e.g. dairy products) in the stomach, or certain functional or anatomical disorders of the gastrointestinal tract might substantially alter absorption, separate pharmacokinetic studies in suitable volunteers or patients should be performed.

(b) *Substances not intended to produce systemic effects*

In the case of drugs with a high intrinsic activity (i.e. topical corticosteroids, some aerosols for respiratory disease), it is often desirable to study the passage into the circulation, since pronounced systemic effects can be produced. The same principle holds good for topical application of drugs in patients suffering from disorders of the skin or mucous membranes. Data on systemic effects should therefore be submitted or direct pharmacokinetic data otherwise.

2. **Distribution**

Data on adequate mathematical analysis (descriptive and/or interpretative analysis or models) including data on model independent parameters should be provided.

The percentage and characteristics of binding to serum proteins should be studied using appropriate *ex vivo* or *in vitro* methods. Particularly in the case of drugs or their active metabolites of which a high percentage is bound to plasma proteins, factors which might alter protein binding and so alter therapeutic response should be studied. Binding to red blood cells and other blood components should also be known.

Some disease states may significantly alter the distribution pattern of a drug. If such changes (e.g. decreased volume of distribution in renal insufficiency, changes in penetration of antibiotics into cerebrospinal fluid in meningitis, changes in the concentrations of individual proteins to which a drug is bound, etc.) could lead to alterations in dosage schemes or indications, they should be studied in suitable patients.

In so far as relevant to the claims, distribution to accessible body fluids (cerebrospinal fluid, synovial fluid) should be investigated.

Actual drug concentrations in tissues can rarely be measured; nevertheless, such data should be submitted when they are particularly desirable or even necessary to solve some important problems related to efficacy or safety and when such measurements are feasible.

3. **Elimination**

The elimination rate for the parent compound (e.g. total body clearance, elimination half-life) should be studied in volunteers with normal elimination mechanisms, and whenever possible also in patients with functional disturbances of these elimination mechanisms. The nature of the main routes of elimination and their relative importance in regard to total elimination should be known.

(a) *Metabolism*

With few exceptions drugs are to a greater or lesser extent subject to metabolic breakdown within the human body. Pharmacokinetic studies should indicate whether the rate of biotransformation may be substantially modified in case of genetic enzymatic deficiency and whether within the dosage levels normally used, saturation of metabolism may occur, thereby inducing non-linear kinetics. The possibility of enzymatic induction should also be studied if metabolic clearance as a fraction of the systemic clearance is relatively high. If there is an indication that pharmacologically active metabolites (the qualitative activity of which may also occasionally differ from that of the parent drug) are formed, this should be ascertained and, if there is reason to suspect that they contribute to a significant extent to the therapeutic activity and/or adverse reactions in man, they should be examined in suitable animal models or if necessary in appropriate human clinical-pharmacological studies. The pharmacokinetic data on such metabolites, the rate of their formation and elimination and their distribution and clearance characteristics should be known.

(b) *Excretion*

The urinary excretion should be defined by parameters such as:

— total cumulated amounts of unchanged and metabolized drug found in the urine following a single dose,

— renal clearance of the drug.

The excretion half-life and the extent of variation between individuals should be determined. In drugs which show a high renal clearance or form pharmacologically active metabolites to a significant level with a predominantly renal clearance and are liable to be used in patients with renal insufficiency, the elimination and accumulation characteristics in patients with varying degrees of reduction of glomerular filtration rate should, when possible, be examined. Further quantitative data on the relation between the elimination rate constant and the glomerular filtration rate should be provided, or evidence be presented that such data can be derived from the measurement of the fraction of the absorbed dose excreted in unchanged form in the urine of patients or healthy volunteers with normal renal function.

If renal clearance constitutes a substantial proportion of systemic clearance (e.g. more than 30 %), the existence of tubular secretion and/or reabsorption and pH dependency of secretion should be investigated. In so far as relevant to the claims (i.e. prolonged duration of action caused by enterohepatic recirculation), other routes of excretion (bile, milk) should be investigated. It may be useful to know if the substance is dialysable and/or can be removed by haemoperfusion.

4. Interactions and adverse reactions

Pharmacokinetic interactions may occur during the absorption phase, as well as during the distribution and the elimination phase. If such interactions are suspected on the basis of animal data, expected on the basis of the physico-chemical or pharmacological properties of the drug or similar compounds (i.e. protein binding, enzyme induction), or observed during (pre)clinical studies, the pharmacokinetic changes due to such interactions should be measured and, whenever possible, the mechanisms elucidated (e.g. enzyme induction, competition for renal elimination sites, etc.).

Certain types of adverse reactions are due to unusual genetic pharmacokinetic variations; though it will rarely be possible to study such aberrant behaviour in a prospective manner every effort must be put into elucidating the pharmacokinetic mechanism(s) if there is any reason to suspect that the adverse reaction is caused by the altered pharmacokinetics of the drug.

II. METHODOLOGY AND CONDITIONS OF STUDY

1. Scheme of administration

Both single-dose and multiple-dose studies should be performed within the recommended dose range and dose intervals.

Multiple-dose studies should be, whenever possible, continued long enough to establish steady-state concentrations of the drug, and for such steady-state levels, their dose dependence and variability should be determined. Accumulation kinetics of the drug predicted from the kinetic constants obtained from single-dose studies should be verified experimentally: differ-

ent doses should be included in one study to determine dose dependence and to decide whether changes from linearity to non-linearity occur at dosage levels which are normally used. After discontinuation of a prolonged treatment, the possibility of a very slow terminal decrease in plasma concentrations, which can reflect the existence of a deep compartment, should be investigated. This might explain the discrepancy between the long action of the substance and the apparent short elimination half-life as measured after a single-dose administration.

Though these principles should normally be followed in detail, it is acknowledged that this is not always feasible.

2. **Subjects**

(a) *Initial studies*

Initial studies are generally performed in a restricted number of fasting, healthy, adult volunteers, in well-defined and controlled conditions. When the substance carries too serious a risk to healthy volunteers (e.g. cytostatics), they are conducted in patients suffering from diseases for which the drug is considered to be indicated.

(b) *Further studies in patients*

Further studies should be conducted in patients suffering from diseases for which the drug is claimed to be indicated. The relation between dose, plasma concentration and therapeutic effect, where this is feasible, should be studied. Particularly, it should be established that the pharmacokinetic behaviour of the drug in patients corresponds to that in healthy subjects. The full range of kinetic studies need only be repeated in patients if studies indicate that the pharmacokinetics in this group differ from those in healthy volunteers.

(c) *Influence of various patho-physiological states*

It is very useful to know the kinetics of drugs in a very large number of patho-physiological situations; however, it is clear that this knowledge requires multiple, long and expensive studies which cannot all be performed before licensing.

Therefore, the only studies which should be reasonably submitted before marketing are those which seem to be necessary in regard to the properties, indications, contra-indications, routes of elimination, scheme of administration of the drug and which are required to define the necessary dosage changes which cannot be calculated from the pharmacokinetic parameters available from volunteers under standardized conditions and in patients without functional disturbances of the systems of absorption, distribution or elimination.

In so far as the indications render this relevant, kinetics should be studied in patients of extremes of age (infants, children and the elderly). For drugs intended to be orally administered, it is important to study the effects of food on absorption. Other factors like body weight, time of the day, environmental factors, genetic differences, alcohol, smoking habits, concomitant medication, sex, may markedly interfere, and if there is particular reason to believe that these may markedly influence the results and the interpretation of later clinical studies, kinetic studies should be extended accordingly.

3. **Methodology**

The quality of pharmacokinetic analysis can be no better than the quality of the experimental data that serve as input for such analyses. The following principles should therefore be kept in mind:

(a) *Sampling*

The number of blood samples should be large enough and the timing appropriate to allow an adequate determination of the absorption and/or distribution and elimination phases. Plasma concentrations in the post-absorptive phase should, whenever possible, be determined over at least two or three half-lives to avoid confusion between distribution, and elimination half-lives. If there is any evidence for a very long terminal half-life, plasma concentrations should be followed for a much longer time. If urinary data are obtained, the urine should be collected until there is no further detectable excretion of parent drug or metabolites within the limits of the method used.

(b) *Stability*

The stability of the substance during sampling and storage requires careful attention.

(c) *Analytical procedures*

Specificity, precision (sensitivity and reproducibility) and accuracy (e.g. as regards recovery) of the methods should be mentioned. Both for reasons of safety and for technical reasons, cold analytical methods are often to be preferred to tracer radioactive techniques. If radioactive isotopes are used the tracer dose should always be combined with a quantity of non-labelled drug within the therapeutic dose range. However, in most cases it will be necessary to develop suitable cold analytical methods to separate and assay quantitatively the metabolites and/or the parent compound.

(d) *Interpretation of data*

The mathematical methods used (graphical representation, computer analysis, pharmacokinetic formulas) should be stated, including the confidence limits.

(e) *Presentation and evaluation of the results*

In summarizing data obtained from more than one subject, it is usually preferable to analyze individual data and at a later stage to average the pharmacokinetic constants so obtained.

Proper statistical analysis of the data obtained should be made and the inter- and intra-individual variations estimated, in at least some of the studies where the number of subjects is large enough.

ANNEX XIII

ANTI-ANGINAL DRUGS

1. GENERAL

The present Notes are designed to provide guidance on clinical investigations to determine the value of drugs in preventing attacks of angina pectoris, irrespective of the nature, mode of action, or route of administration of these drugs.

These Notes for Guidance should be read in the light of the Norms and Protocols (Directive 75/318/EEC) and are intended solely to assist applicants in the interpretation of the latter with respect to the specific problems presented by anti-anginal drugs.

The clinical profile of such a drug needs to be studied both in the acute (experimental) situation, i.e. with provocation of anginal attacks or ischaemic episodes, and under conditions of normal practice. In both situations, valid data are only likely to be obtained if sufficient account is taken of such factors as the pronounced placebo effect in angina pectoris, the substantial variation in the nature and severity of the symptoms, and the subjective character of 'chest pain'. At all phases of study, the possibility that sudden withdrawal of an effective drug may cause an aggravation of symptoms should be considered. In those instances where the mechanism of action appears to be novel, special effort should be made to investigate it. Full studies of kinetics are highly desirable.

A distinction has to be drawn between angina of effort and spontaneous angina (angina at rest). The mechanisms of the two may be different and they require separate investigation.

2. ANGINA OF EFFORT

Angina of effort is characterized by transient episodes of chest pain precipitated by exercise or by other situations resulting in an increased myocardial oxygen demand.

2.1. **Definition and selection of patients**

Patients deemed suitable for any phase of these studies should have coronary insufficiency with or without anginal pain, and reproducible ischaemic changes on exercise testing.

(a) For any phase of clinical trials (see 2.5: field studies), patients should be suffering from stable angina of effort: their condition should be approximately stable, e.g. over a period of at least one month [1] there should have been no clear deterioration or improvement. The severity of their condition should be accurately known. Since angina of effort is linked to fixed coronary artery occlusive disease, selective coronary arteriography, which is often performed in this type of patients, is of great value in this respect. Patients with resting ECG anomalies from whatever origin, which render interpretation of ST-T changes difficult, should be excluded from trials. Risk factors such as smoking, hypertension or hypercholesterolaemia, as well as the use of anti-anginal and other drugs, should be carefully recorded. Other aspects of life style which may be relevant, e.g. exercise habits, should be noted and changes recorded.

The following classes of patients should be excluded from the study:

(a) those who have had a myocardial infarction during the preceding months (at least three months);

(b) those with a clinical picture of impending infarction;

(c) those who suffer from angina at rest;

(d) those whose angina is due in whole or part to diseases other than coronary artery disease;

(e) those suffering from any condition which might invalidate the results of the study.

[1] Nomenclature and criteria for diagnosis of ischaemic heart disease. *Circulation*, 1979, 59, 607 – 9.

A single-blind placebo run-in period is necessary to:

(i) establish or verify the stability of the patients' condition;

(ii) assess the severity of the patients' condition, i.e. the degree of physical effort or the intensity of provocation test required to elicit a positive response and/or the number of anginal attacks per week: a certain minimum is necessary in order to include the patients in the trial;

(iii) obtain information about the patients' capability to keep a diary of angina attacks and nitrate use;

(iv) accustom patients to the experimental routine and minimize subsequent placebo reaction during the study;

(v) eliminate carry-over effects from previous treatment.

The run-in period should last several weeks (e.g. two to six weeks), the exact duration depending on the severity and frequency of the anginal attacks and the nature of previous treatment; the period must be clearly long enough to meet aims (i) to (v) above.

(b) For the acute experimental phase (see 2.4), e.g. quantified exercise tests, a run-in period of a few days may be adequate to familiarize patients with the exercise test to assess their physical performance but it must be shown that this period is long enough to ensure a sufficient wash-out of the previously administered anti-anginal drugs.

2.2. **Use of placebo**

Because of the marked placebo effect in the treatment of angina pectoris, certain studies with a new drug in this field must be performed against a placebo and will be referred to below. All subjects engaged in studies of anti-anginal drugs should have short-acting nitrate available for use should an anginal attack occur, such use being recorded.

2.3. **Comparative studies**

To distinguish placebo reactions from drug effects, the initial (acute) investigations should be planned as double-blind comparative trials, e.g. with a cross-over design. In these studies it is useful to compare the agent being studied with a placebo. Each of the initial clinical studies should involve comparison either with a placebo and/or with a drug of recognized value. In the study as a whole there should be some comparisons with anti-anginal drugs of recognized value: these comparisons are useful for the future clinical use of the product.

2.4. **Acute (experimental) phase**

Anginal pain or signs of an acute ischaemic state should be provoked under controlled conditions, i.e. reproducible quantified exercise tests are required, performed with close supervision and monitoring. The tests should be performed under well-defined conditions, e.g. as regards the time of day, the period which has elapsed following administration of the drug or placebo, and the timing with respect to meals. The manner of administration should be appropriate to the suggested use of drug.

The main objective variables are the maximum work-load and/or the total work-load reached at the time of:

(a) pain of characteristically anginal nature;

(b) ST-T changes;

(c) dyspnoea;

(d) maximal heart rate;

(e) disturbance of rhythm and conduction;

(f) inappropriate blood pressure changes;

(g) excessive fatigue.

The observations on (a) and (b) are directly concerned with the myocardial ischaemic state and should be considered separately from the observations on (c) to (g) which, whilst important, cannot be regarded themselves as specific criteria for an anti-anginal effect.

Heart rate and systolic blood pressure should be recorded. Techniques are now becoming available for detecting ischaemia and studying myocardial oxygen consumption and may prove of value (e.g. thallium scan, isotopic angiography).

The design of the experiments should include the study of dose/effect relationships, the duration of effects of a single dose and if possible the relationship between blood levels and effects. The demonstration of a haemodynamic effect does not automatically imply that the drug will be effective in the relief of anginal pain. If such a parallel is postulated, it should be adequately demonstrated during long-term use of the drug.

2.5. **Clinical studies**

(a) Short-term studies (e.g. lasting some weeks) should be well designed and controlled to provide data on the efficacy of the experimental drug as compared to another agent. At least some of these investigations should be performed double-blind against placebo. These initial studies should provide sufficient data on the dosage, duration of action and possible adverse reactions to define the pattern of further investigations.

(b) Medium-term studies (e.g. lasting up to six months) should be designed to study efficacy and safety of the drug under conditions as close as possible to those in which it would be used, as well as to detect any decrease or increase of effect of the drug in prolonged use. Some of these studies should be comparative. Criteria of efficacy may be the number of anginal attacks, the nitrate consumption and/or exercise tolerance. Data on nitrate consumption should be regarded with some reserve unless it has previously been constant over a long period, which is rarely the case. In some studies exercise tolerance should be systematically explored. The drop-out rate and the reasons for drop-out, i.e. side effects, myocardial infarction, death with the diagnosis whenever possible, should be recorded. The possibility that sudden withdrawal of the drug might cause an aggravation of symptoms should be considered.

Data should also be available to evaluate results obtained in earlier studies (e.g. with regard to adverse reactions), special claims which the manufacturer wishes to make (e.g. as regards the mechanism of action) and possible interactions with other drugs commonly taken by this category of patients.

(c) Long-term studies (see also Notes for Guidance on Drugs for Long-Term Use)

Certain clinical observations (e.g. on 100 patients) should have been made over a period of at least one year, to detect any changes over this period in the clinical effect and to define undesirable effects. Long-term studies need not be comparative. Reasons for drop-out should be documented.

It is clear that the planning of any study in which angina or ECG changes are provoked must take into account the need to avoid undue risks for the patient; see, for example, *American Heart Journal*, 1978, 95, No 1, 102-14.

3. SPONTANEOUS ANGINA (ANGINA AT REST)

Spontaneous angina (angina at rest) is characterized by chest discomfort and/or ischaemic episodes occuring at rest and often somewhat atypical, in the absence of any apparent eliciting factor. It is usually due to coronary arterial spasm (vasospastic angina). Many patients exhibit a mixed form of angina where spasm is associated with fixed coronary artery stenosis; these patients should be studied separately. Spasm may be elicited by agents which increase coronary artery tone such as ergonovine maleate and to a lesser extent alpha adrenergic receptor agonists or cold; however, such tests are hazardous and will not normally be demanded. Nevertheless, if the investigator himself considers them necessary for diagnosis and/or treatment, evidence from such procedures may be acceptable provided they are carried out in a coronary care unit, using standard methods to limit the risks. Some of the diagnostic methods used for angina of effort may be of value in this field, such as thallium scan or isotopic angiography.

The following specific points should be taken into account:

(a) circadian fluctuations;

(b) extreme spontaneous variability of the disorder;

(c) frequent recurrence of transient ECG changes typical of myocardial ischaemia in the absence of chest pain;

(d) difficulty of diagnosis and frequency of severe complications which require admission of the patient to coronary care unit;

(e) ethical considerations raised by the serious nature of the disease.

Although new methods of evaluation will probably become available in the future, the following general principles of testing provide a guide compatible with current practice.

3.1. **Patient selection**

Patients will be suffering from episodes of uncomplicated angina at rest associated with electrocardiographic changes of ischaemia and angiographic evidence in favour of vasospastic angina.

Patients most suitable for investigation with currently available techniques are those experiencing painful and/or painless ischaemic episodes recurring at least three times per day.

3.2. **Clinical studies**

All subjects should have short-acting nitrates available for use should an anginal attack occur, such use being recorded.

(a) *Very short-term studies* (some days) should be performed under close supervision in specialized units. The efficacy is assessed on one or several of the following criteria:

— occurrence of spontaneous or evoked ST-T changes detected by continous ECG monitoring,

— frequency of spontaneous or evoked anginal attacks,

— consumption of short-acting nitrates.

Double-blind crossover studies against placebo are highly desirable and feasible. Considerable concern has been expressed about the use of double-blind randomized controlled studies, mainly against placebo, in patients with vasospastic angina. Acute myocardial infarction and sudden death have been reported to occur in such patients. However, if intractable angina with ECG evidence of ischaemia occurs during those trials, the patient should be withdrawn from the trial and given the appropriate treatment.

(b) *Medium-term studies* (several weeks to several months)

New compounds should generally be tested against drugs of established value. The main objective criteria of evaluation are:

— frequency of chest pain,

— consumption of short-acting nitrates,

— number of episodes of transient ST segment shift detected through ambulatory ECG monitoring (e.g. monthly),

— failure of treatment leading to instability of angina or impending myocardial infarction,

— sudden deaths

and eventually, periodic responses to provocation tests.

Side-effects should be carefully monitored. Particular attention should be devoted to a possible rebound effect on withdrawal of the drug.

(c) *Long-term studies*

Patients suffering from vasospastic angina may be treated for months or years; therefore it is desirable, as in the case of angina of effort, to have long-term studies performed over a period of at least one year.

When a new substance is claimed to be effective in angina of effort and angina at rest, clinical observations (e.g. 100 patients: see 2.5 (c)) should be conducted with consistant and representative groups of each type of angina.

When angina at rest only is being studied, fewer than 100 patients can be accepted, considering the difficulty of such studies: nevertheless, the number of patients should be sufficient to follow clinical activity and define long-term adverse effects.

ANNEX XIV

CORTICOSTEROIDS INTENDED FOR USE ON THE SKIN

1. INTRODUCTION

The following guidelines on clinical testing hold good in principle for all topical corticosteroids which are intended to be used on the skin. The effects including local adverse reactions are, in principle, the same for all corticosteroids, due to common properties, i.e. anti-inflammatory and mitosis-reducing action and inhibition of collagen synthesis. Apparent differences between substances in fact reflect differences in strength, concentration and rates of absorption and elimination.

These Notes for Guidance should be read in the light of the Norms and Protocols (Directive 75/318/EEC) and are intended solely to assist applicants in the interpretation of the latter with respect to specific problems presented by topical forms of corticosteroids. The document deals with:

— general characteristics of topical corticosteroids (see 2),

— specific points which should be investigated in man for each new product containing a corticosteroid as active ingredient (see 3).

The document does not specifically apply to studies on fixed combinations; nevertheless for such products, the general principles drawn up in the Notes for Guidance on Fixed Combinations are fully applicable; in particular, the advantages of such combinations and the significant contributions of each of their active ingredients to the clinical activity should be demonstrated.

2. GENERAL CHARACTERISTICS OF TOPICAL CORTICOSTEROIDS

2.1. **Penetration and local activity**

To be locally effective, corticosteroids must penetrate the skin. The extent of absorption and therefore the clinical activity, as well as most of the adverse reactions, have been demonstrated to depend, both on the substance itself and, for a given corticosteroid, on several factors:

(a) *Concentration of the drug*

however, above a certain concentration in a given vehicle, a further increase in concentration does not result in a proportionately greater effect but does increase the occurrence of side effects;

(b) *Pharmaceutical formulation*

the penetration of the active substance depends on the physico-chemical properties of the base. The presence of other components or excipients can modify the penetration through the stratum corneum and/or the effect (e.g. salicylic acid, urea, propylene glycol, antibiotics and antiseptics, tar);

(c) *Site of application*

a thick stratum corneum is responsible for the weak penetration in areas such as soles and palms. Due to opposite conditions, a very rapid and important absorption may occur, for example, through mucosa, the scrotal skin, eyelids, and to a somewhat lesser extent, the skin of the forehead and the hair zone of the head;

(d) *Skin condition*

penetration is increased in damaged skin (e.g. abrasion or pathological situations like parakeratosis). Damaged stratum corneum, however, often recovers within a few days of treatment;

(e) *Conditions of application*

occlusion promotes the penetration: it may be unintentionally produced by napkins in babies or may result from application in intertriginous areas or flexures.

The influence of these different factors should be taken into account during the clinical trials.

2.2. **Levels of activity and indications**

The activity of a product is controlled by the extent of cutaneous penetration (see 2.1), the intrinsic activity of the compound and the rate of its elimination. Among the known corticosteroids, it is customary to distinguish, depending on the substance and the concentration, four levels of activity ranging from mild via moderately strong and strong to very strong. The data in Table I annexed are adapted from J. A. Miller and D. D. Munro (*Drugs*, 1980, 19, 119-34).

This is a rough guide, as no direct comparison has been made between all these preparations. The borderline between the classes, in particular between the intermediate classes 'moderately strong' and 'strong' is not easy to define. Some corticosteroids are available in different concentrations, which may qualify them for inclusion in a different category of clinical activity. In addition, the influence of the vehicle can result in a shift to an adjacent level of activity (see 2.1, subparagraph (b)). In view of these variables it would in principle be desirable to have available an objective comparison of all existing proprietary products of this type using a method the validity of which is universally acknowledged. However, in view of the large number of proprietary products and methodological uncertainties this is not yet feasible.

It is generally accepted that some indications of corticosensitive dermatosis are directly linked to the level of activity of the preparation as reported in Tables I and II annexed: this list is only for guidance and may be adapted to national practices.

2.3. **Adverse effects**

With the majority of corticosteroids, under normal conditions of use, it is not the possible systemic adverse effects due to percutaneous resorption which are the first concern, but the often irreversible local side effects on the skin, such as dermatrophia.

2.3.1. *Local adverse reactions*

The stronger the preparations, the greater the chance of development of adverse effects, such as:

(a) skin atrophy which becomes often irreversible producing clinical thinning of the skin, teleangiectasia, purpura, striae;

(b) rosacea-like and perioral dermatitis with or without skin atrophy;

(c) rebound which may lead to steroid 'dependence';

(d) impairment of healing;

(e) effects on the eye: increased risk of glaucoma, cataract, exacerbation of mycosis and of herpes simplex;

(f) miscellaneous: depigmentation, hypertrichosis, etc.

The chance of development of dermal toxicity also increases with duration of treatments and when application is performed under occlusion or on particular sites such as the face (see 2.1, subparagraph (c)).

Due to the ingredients of the base, or to a substance incorporated in the preparation, and rarely to the corticosteroid itself, contact allergy may also occur. Due to the suppression of immune defence, masking and/or worsening of infection may be observed in case of erroneous use of corticosteroid preparations in fungal, viral or bacterial cutaneous diseases.

2.3.2. *Systemic effects*

In adults, as a result of hypothalamo-pituitary-adrenal (HPA) axis suppression, a fall in plasma cortisol levels can generally be observed within the first days of treatment. Those systemic effects occur rarely. They occur more readily in children (e.g. acute adrenal insufficiency at the discontinuation of the drug, hypercorticism, arrest of growth, intracranial hypertension) because of the high surface/weight ratio and unintentional occlusion by napkins.

These systemic effects are due to the high penetration of a strong compound (or of its active metabolite(s)); this occurs because one or more of the factors promoting penetration (see 2.1) apply. The risk of systemic effects increases with applications over large areas, use of large amounts of material, and prolonged administration.

Local and systemic adverse effects can be generally avoided with well-studied and well-defined products, when the strength of the preparation and the nature of the pharmaceutical form are adequately chosen with regard to the type of dermatosis, the site of application, the period of treatment and the patient's age and when products are applied according to appropriate conditions of use as validated by clinical trials.

3. GUIDE FOR CLINICAL TESTING

In view of the characteristics listed under paragraph 2, it is necessary that a new product of this type be examined in such a way that the place of the corticosteroid in question (used in the concentration and base specified in the application) in the spectrum of corticosteroid products can be determined and conditions of use be defined.

3.1. **Pharmacodynamic studies**

The place of a new product in the spectrum of corticosteroid preparations and the optimal concentrations for clinical use can to a large extent be predicted on the basis of the results of a number of pharmacological tests (anti-inflammatory effect, mitosis inhibition) in animals or *in vitro*.

Corticosteroid induced vasoconstriction in man may provide a preliminary rough but useful guide to topical anti-inflammatory activity. Vasoconstriction tests derived from McKenzie and Stoughton (*Archives of Dermatology*, 1962, 86, 608-10), using the new drug incorporated in its base should therefore be compared with the effects of established corticosteroid preparations, not only with those of approximately equal activity, but also with stronger and weaker preparations.

Other methods can also be used or are currently under development. It is not considered desirable to specify particular methods of investigation as obligatory; regulatory agencies will be prepared to consider new methods provided the clinical relevance of these methods is demonstrated. The level of activity estimated in the light of these tests will always have to be confirmed by clinical investigation (see 3.2.1).

3.2. **Clinical investigation**

3.2.1. *Efficacy*

The level of activity, as estimated in the tests listed under 3.1, will have to be confirmed clinically.

(a) A product should be studied in randomized double-blind investigations; single-blind investigation should only be permitted if it is virtually impossible to perform double-blind tests. Parallel groups are probably superior in most instances, but there have been conflicting opinions expressed about whether parallel groups are preferable to intra subject half-side studies (left-right comparisons). If studies of the latter type are used, however, attention should be paid to possible interactions of the treatments due to systemic transfer from one side to the other, especially when the comparison is being made between products of different activities applied on large areas. A product should be studied in principle against its base but also against known products of different activity. Where the product can be regarded as a minor modification of an existing one, it will often be possible to rely on a comparison with this latter product used as a reference, at least through an adequate vasoconstriction test.

For new corticosteroids the optimal concentration for clinical use will have to be confirmed by comparative investigation of various concentrations. This is important because of the possibility of increase in the occurrence of adverse effects above a certain concentration (see 2.1, subparagraph (a)) without notable improvement of therapeutic efficacy. Reports should give a clear picture of the frequency of application, especially in the initial period of treatment. When frequencies differ from those usually recommended (i.e. once or at most twice daily), it is desirable that this should be justified by the applicant. Reports should also clearly state the sites of application, the areas which have been treated and the amounts of product used per week.

If the preparation is intended to be used under occlusion, the influence of this on the effect in clinical studies should be examined.

(b) Valid comparisons can only be made between treatments given for the same condition. A product should be tested in a series of conditions, each requiring different degrees of intensity of treatment.

Dermatoses advisable for clinical trials are listed in the left column of Table III. They are presented in two groups: one requiring preparations of very strong and strong activity and the other where moderately strong and mild products can be used, with psoriasis and atopic dermatitis, respectively, being the most suitable conditions for testing. From the efficacy observed in the different clinical forms of these dermatoses, the indications can be defined and the place of the new product in the spectrum of corticosteroid preparations definitively established (see classes of Table II). Provided they require treatment with products from the same class, extrapolation of the results is possible for skin conditions listed in the right column of Table III. Clinical trials may also be performed in skin conditions listed in the right column, but they do not allow extrapolation to other skin diseases. Indications other than those listed can also be suggested, provided that positive results have been obtained in specific clinical studies conducted with an adequate methodology.

As a general principle it is not satisfactory to assume that a substance active at a certain level of dose will be equally suitable at other levels for more-severe or less-severe disease. However, it is recognized that under conditions of normal practice, a failure of treatment with a given product might lead to the use of a stronger preparation for only a few days, followed by the use of a weaker product for maintenance treatments. This mode of use should be mentioned in data sheets.

(c) Short term studies over one or two weeks may not be the only relevant investigation for the clinical comparison of two topical steroids. In practice, these are sometimes applied over long periods of time and differences in clinical efficacy and safety may only become apparent after treatment for several weeks or months. For this reason, depending on the novelty of the product and the indications claimed, certain studies of efficacy as well as of safety in long term use (e.g. over a period of three months) will sometimes be necessary.

3.2.2. *Safety*

Since the importance of adverse effects may not inevitably run parallel with clinical activity, the possibility of their occurrence should be studied during clinical investigation.

Where a product is claimed to produce less frequent or severe adverse effects than a well-established drug of the same degree of activity, this should be justified by controlled studies.

(a) Local adverse effects

— *Atrophogenic activity*

The degree of atrophy induced by the product will have to be determined, after application of the product. The mode of use including the sites of application should be specified. The changes due to thinning of the epidermis and alteration of the dermis can be detected by different methods, such as measurement of the thickness of the skin (radiographical techniques, ultrasonography), histology, measurement of collagen fibrils, stereomicroscopy. They cannot be detected until a topical treatment has been given under normal conditions of use for four weeks. Nevertheless, in experimental conditions where application is performed with occlusion, the exposure can be shorter.

— In any study, tolerance will have to be determined (drying of skin, irritation, sensitization) both for the product as a whole and for the base. After conclusion of the trial, patch tests should be performed with the pharmaceutical formulation and the base.

(b) Systemic actions

Interesting and practicable is the direct assessment of the effect on the HPA axis. In this respect, plasma cortisol determinations give more information than studies of cortisol metabolites in urine. When performing plasma cortisol determinations account must be taken of the diurnal rhythm exhibited by plasma cortisol levels and of factors which influence these levels, such as stress, sex, seasonal influences, use of oral contraceptives etc. Since healing of damaged stratum corneum, which often occurs within eight days of treatment, produces a decrease in the systemic passage, it is necessary to make repeated determinations during the exposure period. It is also customary to determine plasma cortisol levels under normal and extreme conditions of application, the latter predisposing to maximum absorption. Therefore, it is desirable to determine plasma cortisol levels under such conditions as:

— at the fifth and at the 20th day of treatment without occlusion and at the fifth day with occlusion on the normal and diseased skin,

— several times, in a number of patients treated for long periods.

The ability of the HPA axis to respond to a stimulation can also be usefully assessed by determination of plasma cortisol after stimulation (i.e. adrenocorticotrophic hormone).

Comparative data with one or several reference products used under the same conditions would in principle be necessary to assess fully the extent of systemic absorption.

Because the passage into the circulation depends on various factors (see 2.3.2), the precise conditions (i.e. sites and percentage of body surface treated, weight of product used) and mode of use should be specified for each subject treated. In the case of products for which the manufacturer wishes to claim the treatment of chronic conditions in an area of high absorption, an investigation of absorption will have to be performed after application to this area. If the product is to be recommended for use in young children, systemic effects should also be recorded in this age group, but particular attention should be given to the ethical aspects of such an investigation.

TABLE I

LEVELS OF ACTIVITY OF KNOWN CORTICOSTEROIDS

(Adapted from J. A. Miller and D. D. Munro, Drugs, 1980, 19, 119-34)

Corticosteroid	very strong	strong	moderately strong	mild
Beclomethasone dipropionate	0,5 %	0,025 %	—	—
Betamethasone benzoate	—	0,025 %	—	—
Betamethasone dipropionate	—	0,05 %	—	—
Betamethasone valerate	—	0,1 %	—	—
Clobetasol propionate	0,05 %	—	—	—
Clobetasone butyrate	—	—	0,05 %	—
Desonide	—	0,05 %	—	—
Desoxymethasone	—	0,25 %	—	—
Dexamethasone	—	—	—	0,01 %
Diflorasone diacetate	—	0,05 %	—	—
Diflucortolone valerate	0,3 %	0,1 %	—	—
Fluclorolone acetonide	—	0,025 %	—	—
Fludroxycortide (flurandrenolone)	—	0,05 %	0,0125 to 0,025 %	—
Flumethasone pivalate	—	—	0,02 %	—
Fluocinolone acetonide	0,2 %	0,025 %	0,01 %	—
Fluocinonide	—	0,05 %	—	—
Fluocortin butylester	—	—	0,25 %	—
Fluocortolone	—	0,5 %	0,2 %	—
Fluoprednidene acetate	—	0,1 %	—	—
Halcinonide	—	0,1 %	—	—
Hydrocortisone	—	—	—	0,1 to 1 %
Hydrocortisone butyrate	—	0,1 %	—	—
Methylprednisolone	—	—	—	0,25 %
Triamcinolone acetonide	—	0,1 %	—	—

TABLE II

INDICATIONS FOR TOPICAL CORTICOSTEROIDS IN RELATIONSHIP TO THEIR LEVEL OF ACTIVITY

VERY STRONG ACTIVITY	Localized and resistant plaques of: psoriasis lichenification discoid lupus erythematosus lichen hypertrophic Hypertrophic scars
STRONG ACTIVITY	Psoriasis Lichenifications Lichen planus Lichen sclerosus and atrophicus Granuloma annulare Discoid lupus erythematosus Pustulosis palmaris and plantaris Mycosis fungoides
MODERATELY STRONG ACTIVITY	Atopic dermatitis Irritant and/or allergic contact dermatitis Nummular dermatitis Pompholyx ('dyshidrosis')
MILD ACTIVITY	Seborrhoeic dermatitis Stasis dermatitis Ano-genital pruritus

TABLE III

SKIN CONDITIONS ADVISABLE FOR CLINICAL INVESTIGATION OF TOPICAL CORTICOSTEROIDS

Advisable	Non-advisable
VERY STRONG AND STRONG CORTICOSTEROIDS	
— Psoriasis — Lichen planus — Lichen sclerosus and atrophicus (genital) — Pustolosis palmaris and plantaris — Localized lichenifications	— Granuloma annulare — Discoid lupus erythematosus — Mycosis fungoides
MODERATELY STRONG AND MILD CORTICOSTEROIDS	
— Atopic dermatitis — Seborrhoeic dermatitis — Nummular dermatitis	— Irritant and/or allergic contact dermatitis — Stasis dermatitis — Pompholyx ('dyshidrosis') — Ano-genital pruritus