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# Information and Notices

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*(Preparatory Acts)*

# COMMISSION

**Proposal for a Council Directive on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology**

*COM(84) 437 final*

*(Submitted by the Commission to the Council on 3 October 1984)*

(84/C 293/01)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the Economic and Social Committee,

Whereas 'high-technology' medicinal products requiring lengthy periods of costly research will continue to be developed in Europe only if they benefit from a favourable regulatory environment, particularly identical conditions governing their placing on the market throughout the Community;

Whereas Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], as last amended by Directive 83/570/EEC [2], makes provision for certain procedures for coordinating national decisions relating to the placing on the market of proprietary medicinal products for human use; whereas pharmaceutical firms may, according to these provisions, request a Member State to take due account of an authorization already issued by another Member State;

Whereas Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products [3] makes provision for a procedure for coordinating national decisions relating to veterinary medicines;

Whereas, however, these procedures are not sufficient to open up to high-technology medicinal products the large Community-wide single market which they require;

Whereas, in this technically advanced sector, the scientific expertise available to each of the national authorities is not always sufficient to resolve problems posed by high-technology medicinal products;

Whereas it is consequently important to provide for a Community mechanism for concertation, prior to any national decision relating to a high-technology medicinal product, with a view to arriving at uniform decisions throughout the Community;

(1) OJ No L 147, 9. 6. 1975, p. 13.
(2) OJ No L 332, 28. 11. 1983, p. 1.
(3) OJ No L 317, 6. 11. 1981, p. 1.

Whereas it is desirable to extend this Community concertation to immunological products and substitutes for blood constituents developed by means of new biotechnological processes, and to new products based on radioisotopes, the development of which in Europe can only take place if a sufficiently large and homogeneous market exists;

Whereas the necessity for the adoption of new technical rules applying to high-technology medicinal products or for the amendment of existing rules must be examined during a preliminary concertation between the Member States and the Commission within the competent Committees so as not to endanger the advance of pharmaceutical research whilst at the same time ensuring optimal protection of public health within the Community,

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

1. The Member States shall intensify coordination in respect of national measures relating to the placing on the market of medicinal products within the meaning of Article 1 of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1] in order to create a regulatory environment favourable to the development of pharmaceutical research in Europe, particularly in the field of biotechnology.

2. Before taking a decision on the authorization, suspension or withdrawal from the market of a 'high-technology' medicinal product, the authorities of the Member States shall, in accordance with the provisions of Articles 2 to 5, refer the matter for an opinion to the Committees mentioned in Article 12 of Directive 75/319/EEC and Article 22 of Directive 81/851/EEC.

3. The provisions of paragraph 2 shall apply to the medicinal products listed in the Annex.

*Article 2*

1. As soon as they receive an application for marketing authorization relating to a medicinal product developed by means of the new biotechnological processes mentioned in part A of the Annex, the competent authorities shall be required to bring the matter before either the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products, as appropriate, for an opinion. This requirement shall also apply for the other high-technology medicinal products listed in part B of the Annex, provided that the person responsible for placing the product on the market has expressly requested the competent authority concerned to refer the matter and has sent a copy of the request to the Committee concerned.

2. Where the Committee has, in accordance with the provisions of this Directive, issued an opinion favourable to the placing on the market of a high-technology medicinal product, the competent authorities shall bring the matter before the Committee for a new opinion before deciding on the suspension or withdrawal of the marketing authorization for the medicinal product in question.

3. Questions relating to medicinal products for human use, including the medicinal products referred to in the second paragraph of Article 34 of Directive 75/319/EEC, shall be brought before the Committee for Proprietary Medicinal Products set up by that Directive.

Questions relating to veterinary medicinal products, including those referred to in the second and third indents of Article 2 (2) of Directive 81/851/EEC shall be brought before the Committee for Veterinary Medicinal Products set up by that Directive.

*Article 3*

1. The representative of the Member State which initiated the procedure referred to in Article 2 shall act as rapporteur throughout the procedure. In this capacity, he shall ensure that there is close liaison between the Committee in question and the competent authorities concerned and shall provide all information relevant to the evaluation of the medicinal product. The information thus disclosed shall be strictly confidential.

2. When placing the matter before the Committee, the Member State concerned must forward to it at least:

— a summary of the product characteristics, as described in Article 4a of Directive 65/65/EEC, or an equivalent document provided by the applicant if a medicinal product referred to in the second paragraph of Directive 75/319/EEC or a veterinary medicinal product is involved,

[1] OJ No 22, 9. 6. 1965, p. 369/65.

— a summary of the documents contained in the file on the marketing authorization for the medicinal product in question.

3. Where they exist, evaluation reports and drug-monitoring reports relating to the same medicinal product shall be forwarded to the Committee by the authorities of the Member States which drew them up.

4. The person responsible for placing the medicinal product in question on the market shall immediately be informed of the referral to the Committee. He may, at his own request, provide the Committee with oral or written explanations and forward to it any documents that he judges to be relevant.

5. In order to speed up the examination of scientific and technical questions, the Committee, in agreement with the Commission, may assign certain preparatory tasks to an *ad hoc* group of experts or to highly qualified outside consultants. The members of the Committee, the experts and the outside consultants shall be obliged, even after their duties have ceased, not to disclose information which, by its nature, is covered by the obligation of professional secrecy.

*Article 4*

1. When the questions referred to it relate to an application for marketing authorization, the Committee shall issue its opinion 30 days before the expiry of the time limits provided for in Article 7 of Directive 65/65/EEC and Article 4 (c) of Directive 75/319/EEC, or in Articles 8 and 9 (3) of Directive 81/851/EEC, as appropriate. To this end, the Member State which referred the matter shall inform the Committee without delay of any extension and of the beginning and end of any suspension of the time limits concerned.

2. When a proposal to suspend or withdraw a marketing authorization is referred to it, the Committee shall fix an appropriate time limit for issuing its reasoned opinion, having regard to the requirements for the protection of public health. However, in cases of urgency, the Member States may suspend the marketing authorization in question without waiting for the opinion of the Committee provided that they forthwith inform the Committee thereof, indicating the reasons for the suspension and justifying the urgency of this measure.

3. The opinion of the Committee, which shall be adopted by an absolute majority of the members present, shall concern the conditions under which the marketing authorization should be granted or the reasons for which that authorization may be refused, suspended or withdrawn.

4. The Committee shall forthwith inform the Member State concerned and the person responsible for placing the product on the market of its opinion and, if necessary, of any dissenting opinions expressed.

5. The Member State concerned shall reach a decision on the action it intends to take following the Committee's opinion not later than 30 days after receipt of the information provided for in paragraph 4. It shall forthwith inform the Committee of its decision.

*Article 5*

Subject to the application of other Community provisions, the Member States shall communicate to the Commission and delay the adoption of draft technical regulations relating to the production, marketing or use of the medicinal products referred to in Article 1 of this Directive, in accordance with the provisions of Articles 8 and 9 of Council Directive 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations [1].

*Article 6*

Member States shall take the measures necessary to comply with this Directive no later than 1 July 1985. They shall forthwith inform the Commission thereof.

*Article 7*

This Directive is addressed to the Member States.

[1] OJ No L 109, 24. 4. 1983, p. 8.

*ANNEX*

## LIST OF 'HIGH-TECHNOLOGY' MEDICINAL PRODUCTS

A. **Medicinal products developed by means of new biotechnological processes**

which make use of genetic recombination, hybridoma technology, aneuploid cell strains and enzyme bioreactors.

*For example:*

- new vaccines, particularly synthetic vaccines,
- new antibiotics,
- interferons,
- immunotoxins,
- hormones, particularly peptide hormones (human insulin; growth hormone),
- monoclonal antibodies and DNA hybridization probes used *in vivo*,
- enzymes such as urokinase,
- blood proteins or substitutes thereof: alpha I, antitrypsin, human seralbumin, factor VIII, etc.

B. **Other high-technology medicinal products**

- Medicinal products administered by means of new delivery systems which constitute a major innovation: transcutaneous systems, encapsulation in liposomes or polymers, drug targeting systems, etc.
- Medicinal products containing a new substance claimed to be of major therapeutic interest.
- New medicinal products based on radioisotopes.
- Medicinal products the manufacture of which is based upon an advanced technique such as two-dimensional electrophoresis under gravity or microgravity.

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# Proposal for a Council Directive amending Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products

*COM(84) 437 final*

*(Submitted by the Commission to the Council on 3 October 1984)*

(84/C 293/02)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof;

Having regard to the proposal from the Commission;

Having regard to the opinion of the European Parliament;

Having regard to the opinion of the Economic and Social Committee;

Whereas the testing of proprietary medicinal products must regularly be adapted to scientific and technical progress in order to ensure optimum protection of public health in the Community;

Whereas, in order to achieve such optimum protection of health, the resources allocated to pharmaceutical research must not be squandered on obsolete or repetitive tests resulting from divergences between the Member States in assessing the state of the art in science and technology;

Whereas, for ethical reasons, it is necessary to replace existing methods as soon as scientific and technical advances so allow by methods involving as few laboratory animals as possible;

Whereas it is therefore necessary to introduce a rapid procedure for adapting to technical progress the requirements regarding the testing of medicinal products listed in the Annex to Council Directive 75/318/EEC (1), as amended by Directive 83/570/EEC (2), whilst ensuring close cooperation between the Commission and the Member States within a 'Committee for the Adaptation to Technical progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector';

Whereas the requirements relating to the testing of medicinal products must also be capable of rapid revision by the same procedure, having regard to the evolution of test methods and of good laboratory practices recognized by the Community or in international trade in medicinal products,

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

Directive 75/318/EEC is hereby amended as follows:

1. The following Articles 2a, 2b and 2c are inserted:

'*Article 2a*

Any changes which are necessary in order to adapt the Annex to take account of technical progress shall be adopted in accordance with the procedure laid down in Article 2c.

*Article 2b*

1. A Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector, hereinafter called "the Committee", is hereby set up; it shall consist of representatives of the Member States with a representative of the Commission as chairman.

2. The Committee shall adopt its own rules of procedure.

*Article 2c*

1. Where the procedure laid down in this Article is to be followed, matters shall be referred to the Committee by the chairman, either on his own initiative or at the request of the representative of a Member State.

2. The representative of the Commission shall submit to the Committee a draft of the measures to be adopted. The Committee shall deliver its opinion on the draft within a time limit set by the chairman, having regard to the urgency of the matter. It shall act by a qualified majority, the votes of the Member States being weighted as provided in Article 148 (2) of the Treaty. The chairman shall not vote.

3. (a) The Commission shall adopt the measures envisaged where they are in accordance with the opinion of the Committee.

(b) Where the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is adopted, the Commission shall without delay propose to the Council the measures to be adopted. The Council shall act by a qualified majority.

(c) If, within three months of the proposal being submitted to it, the Council has not acted, the proposed measures shall be adopted by the Commission.'

2. Part 2 of the Annex, 'Toxicological and Pharmacological Tests' is hereby amended as follows:

(a) The following paragraph is inserted after the introductory paragraph:

'The Member States shall ensure that the safety tests are executed in conformity with the principles of good laboratory practice recognized by Community law in the field of tests on dangerous substances, or in the absence thereof, with those recommended

(1) OJ No L 147, 9. 6. 1975, p. 1.
(2) OJ No L 332, 28. 11. 1983, p. 1.

by the Organization for Economic Cooperation and Development.'

(b) In Chapter I (B) 'Toxicity', the text of paragraph 1 is replaced by the following:

'1. Single dose toxicity

An acute test infers a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substance or substances contained in the proprietary medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The acute toxicity test must be carried out on two or more mammalian species of known strain unless a single species can be justified. At least two different routes of administration shall normally be used, one being identical with or similar to that proposed for use in human beings and the other ensuring systemic absorption of the substance.

This study will cover the signs observed, including local reactions. The period during which the test animals are observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually for a period of 14 days but not less than seven days, but without exposing the animals to prolonged suffering. Animals dying during the observation period should be subject to autopsy as also should all animals surviving to the end of the observation period. Histopathological examination should be considered on any organ showing macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals used in the study. The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be obtained, but a high level of precision is not required.

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.

In the case of active substances in combination, the study must be carried out in such a way as to check whether or not there is enhancement of toxicity or if novel toxic effects occur.'

*Article 2*

Member States shall take the measures necessary in order to comply with this Directive no later than 1 January 1986. They shall forthwith inform the Commission thereof.

*Article 3*

This Directive is addressed to the Member States.

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**Proposal for a Council Directive amending Directive 81/852/EEC 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 veterinary medicinal products**

*COM(84) 437 final*

*(Submitted by the Commission to the Council on 3 October 1984)*

(84/C 293/03)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof;

Having regard to the proposal from the Commission;

Having regard to the opinion of the European Parliament;

Having regard to the opinion of the Economic and Social Committee;

Whereas the testing of veterinary medicinal products must regularly be adapted to scientific and technical progress in order to safeguard the health of consumers of livestock products and to ensure optimum protection of animal health in the Community;

Whereas, in order to achieve this optimum protection of public health, the resources allocated to pharmaceutical research must not be squandered on obsolete or repetitive tests resulting from divergences between the Member States in assessing the state of the art in science and technology;

Whereas, for ethical reasons, it is necessary to replace the existing methods as soon as scientific and technical advances so allow by methods involving as few laboratory animals as possible;

Whereas it is therefore necessary to introduce a rapid procedure for adapting to technical progress the requirements regarding the testing of the medicinal products listed in the Annex to Council Directive 81/852/EEC (1), whilst ensuring close cooperation between the Member States and the Commission within a 'Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Veterinary Medicinal Products Sector',

Whereas the requirements relating to the testing of medicinal products must also be capable of rapid revision by the same procedure, having regard to the evolution of test methods and of good laboratory practices recognized by the Community or in international trade in medicinal products,

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

Directive 81/852/EEC is hereby amended as follows:

1. The following Articles 2a, 2b and 2c are inserted:

*'Article 2a*

Any changes which are necessary in order to adapt the Annex to take account of technical progress shall be adopted in accordance with the procedure laid down in Article 2c below.

*Article 2b*

1. A Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Veterinary Medicinal Products Sector, hereinafter called "the Committee", is hereby set up; it shall consist of representatives of the Member States with a representative of the Commission as chairman.

2. The Committee shall adopt its own rules of procedure.

*Article 2c*

1. Where the procedure laid down in this Article is to be followed, matters shall be referred to the Committee by the chairman, either on his own initiative or at the request of the representative of a Member State.

2. The representative of the Commission shall submit to the Committee a draft of the measures to be adopted. The Committee shall deliver its opinion on the draft within a time limit set by the chairman having regard to the urgency of the matter. It shall act by a qualified majority, the votes of the Member States being weighted as provided in Article 148 (2) of the Treaty. The chairman shall not vote.

3. (a) The Commission shall adopt the measures envisaged where they are in accordance with the opinion of the Committee.

(b) Where the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is adopted, the Commission shall without delay propose to the Council the measures to be adopted. The Council shall act by a qualified majority.

(c) If, within three months of the proposal being submitted to it, the Council has not acted, the proposed measures shall be adopted by the Commission.'

2. Part 2 of the Annex, 'Toxicological and Pharmacological Tests' is hereby amended as follows:

(a) The following paragraph is inserted after the two introductory paragraphs:

'The Member States shall ensure that the laboratory tests are executed in conformity

(1) OJ No L 317, 6. 11. 1981, p. 16.

with the principles of good laboratory practice recognized by Community law in the field of tests on dangerous substances or, in the absence thereof, with those recommended by the Organization for Economic Cooperation and Development.'

(b) In Chapter I (B) (1) the fourth subparagraph is replaced by the following:

'This study will cover the signs observed, including local reactions. The period during which the test animals are observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually for a period of 14 days but not less than seven days, but without exposing the animals to prolonged suffering. Animals dying during the observation period should be subject to autopsy as also should all animals surviving to the end of the observation period. Histopathological examination should be considered on any organ showing macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals used in the study. The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be obtained, but a high level of precision is not required.'

*Article 2*

Member States shall take the measures necessary to comply with this Directive no later than 1 January 1986. They shall forthwith inform the Commission thereof.

*Article 3*

This Directive is addressed to the Member States.

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## Proposal for a Council recommendation concerning tests relating to the placing on the market of proprietary medicinal products

*COM(84) 437 final*

*(Submitted by the Commission to the Council on 3 October 1984)*

(84/C 293/04)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the Economic and Social Committee,

Whereas in Council recommendation 83/571/EEC of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products [1], the Council adopted a first series of notes for guidance intended to prevent differences of interpretation in the implementation of the standards and protocols for the testing of 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 [2], as amended by Directive 83/570/EEC [3];

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 facilitat-

(1) OJ No L 332, 28. 11. 1983, p. 11.

(2) OJ No L 147, 9. 6. 1975, p. 1.

(3) OJ No L 332, 28. 11. 1983, p. 1.

ing 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. 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 notes for guidance, all applications for marketing authorization.

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*ANNEX I*

## SINGLE DOSE TOXICITY

Note for guidance concerning the application of the Annex to Directive 75/318/EEC, part 2, chapter I, paragraph B, point 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 adjuvants 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 toxic 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.

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*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 (Directive 75/318/EEC, as amended by Directive 83/570/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 numer (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, as amended by Directive 83/570/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) Although DNA is universal to both prokaryotes and eukaryotes, the organization of the genetic material is very different in these two types of organisms. The procedure should take this into account.

(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 mutation in eukaryotic system*

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 expen-

sive 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.

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*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, dos-

age 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,

— cardiversion,

— 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).

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*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 the First Directive (65/65/EEC) and 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 IIB if the following principles are borne in mind:

(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.

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*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 progestagens 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 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 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 instruction 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 include 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 diarrhoea.

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, 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.

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*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 or $m^2$ 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.

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*ANNEX VII*

## CLINICAL TESTING REQUIREMENTS FOR DRUGS FOR LONG-TERM USE

### INTRODUCTION

The general requirements for clinical trials are given in 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 long-term 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 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 endpoints 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 (3 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 (2 to 8 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 (points (b) and (c), an analgesic drug which has no material anti-inflamma-

tory 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.

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*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 on hospitalized patients only, it is essential in the later phases also to study the effectiveness and safety of the test drug when used on out-patients, 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 7 below).

## 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, cooordination, 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 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.

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*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 Directive 75/318/EEC, whilst referring both in the pharmacological (part 2, chapter 1, section G) and clinical pharmacoligical (part 3, chapter II, paragraphs 2A, 1c) 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 usefull 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 versus capsules). Clearly the concentration at the site of action will rarely be directly measurable and indirect parameters will often have to be employed (see paragraph 'Parameters').

## 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 drug 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 formulation 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 i.v. 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 (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.

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*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.

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*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 sub-groups 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 months 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 clearance as a measure of blood flow in the muscles, Doppler blood pressure measurements, oscillometry, calorimetry, muscular p $O_2$), 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 (6 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 even 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 sub-groups (see (a) above) will be required.

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*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 with 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 csf 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 (csf, 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 dialyzable 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: different 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 needs 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 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.

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## Proposal for a Council Directive amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

*COM(84) 437 final*

*(Submitted by the Commission to the Council on 3 October 1984)*

(84/C 293/05)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the Economic and Social Committee,

Whereas point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC (1), as last amended by Directive 83/570/EEC (2) provides that various types of proof of the safety and efficacy of a proprietary medicinal product may be put forward in an application for marketing authorization depending upon the objective situation of the medicinal product in question;

Whereas experience has shown that it is advisable to stipulate more precisely the cases in which the results of pharmacological and toxicological tests or clinical trials do not have to be provided with a view to obtaining authorization for a medicinal product which is essentially similar to an authorized product, while ensuring that innovative firms are not placed at a disadvantage;

Whereas additional details were provided in respect of the application of the abovementioned provision 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 (3), as amended by Directive 83/570/EEC;

Whereas, however, considerations of public policy are against the repetition of tests on animals or trials in man without pressing reasons;

Whereas it is also advisable to make the packaging of certain medicinal products, particularly sought after by drug addicts, more commonplace by suppressing the obligation to mark the outer packaging

(1) OJ No 22, 9. 2. 1965, p. 369/65.
(2) OJ No L 332, 28. 11. 1983, p. 1.
(3) OJ No L 147, 9. 6. 1975, p. 1.

and the container of medicines classified as narcotics with a special sign,

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

Directive 65/65/EEC is hereby amended as follows:

1. Point 8 of the second paragraph of Article 4 is hereby replaced by the following text:

'8. Results of:

— physico-chemical, biological or microbiological tests,

— pharmacological and toxicological tests,

— clinical trials.

However, and without prejudice to the law relating to the protection of industrial and commercial property:

(a) the applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:

(i) either that the proprietary product is essentially similar to a product authorized in the country concerned by the application and that the person responsible for the marketing of the original proprietary product has consented to the pharmacological, toxicological or clinical references contained in the file on the original proprietary medicinal product being used for the purpose of examining the application in question;

(ii) or, by reference to the published scientific literature, that the constituent or constituents of the proprietary product have a well-established medicinal use with recognized efficacy and an acceptable level of safety;

(iii) or that the proprietary product is essentially similar to a product which has been authorized for more than 10 years in the country concerned by the application;

however, where the proprietary product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials must be provided.

(b) in the case of a new proprietary product containing known constituents not hitherto used in combination for therapeutic purposes, the results of pharmacological and toxicological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.'

2. Article 16 is repealed.

*Article 2*

Member States shall take the measures necessary to comply with this Directive no later than 1 January 1986. They shall forthwith inform the Commission thereof.

*Article 3*

This Directive is addressed to the Member States.