

Official Journal

of the European Communities

ISSN 0378-6978

L 332

Volume 26

28 November 1983

English edition

Legislation

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II

(Acts whose publication is not obligatory)

COUNCIL

COUNCIL DIRECTIVE

of 26 October 1983

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

(83/570/EEC)

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 ⁽¹⁾,

Having regard to the opinion of the Economic and Social Committee ⁽²⁾,

Whereas the Directives on the approximation of the laws relating to proprietary medicinal products must be adapted to scientific progress and take account of the experience obtained since their adoption;

Whereas Article 15 (2) of Second 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 ⁽³⁾ provides that the Commission shall submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products, not later than four years after the entry into force of the abovementioned Directive;

Whereas it is necessary from the point of view of public health and the free movement of medicinal products for the competent authorities to have at their disposal all useful information on authorized proprietary products, based in particular on summaries, adopted in the other Member States, of the characteristics of products;

Whereas it is necessary to specify certain provisions relating to physicochemical, biological or microbiological tests on proprietary medicinal products and to introduce the principle of bio-availability and mutagenesis tests in order to safeguard public health;

⁽¹⁾ OJ No C 287, 9. 11. 1981, p. 127.

⁽²⁾ OJ No C 189, 30. 7. 1981, p. 39.

⁽³⁾ OJ No L 147, 9. 6. 1975, p. 13.

Whereas the approximation of laws brought about in this connection must enable a proprietary product, manufactured and marketed in one Member State on the basis of harmonized provisions, to be allowed into another Member State, taking into due consideration the initial authorization, save in exceptional cases submitted for an opinion to the Committee for Proprietary Medicinal Products set up by Directive 75/319/EEC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

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⁾ is hereby amended as follows:

1. The second paragraph of Article 4 is amended as follows:

- (a) in point 6, 'if less than three years' is deleted;
- (b) in point 8 (a) of the English version, 'a List of published references' is replaced by 'a bibliography';
- (c) point 9 is replaced by the following:

'9. A summary, in accordance with Article 4a, of the product characteristics, one or more specimens or mock-ups of the sales presentation of the proprietary product, together with a package leaflet where one is to be enclosed.'

2. The following Article 4a is inserted:

'Article 4a

The summary of the product characteristics referred to in point 9 of the second paragraph of Article 4 shall contain the following information:

- 1. Name of the proprietary product.
- 2. Qualitative and quantitative composition in terms of the active ingredients and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product; the international non-proprietary names recommended by the World Health Organization shall be used, where such names exist, or failing this, the usual common name or chemical description.
- 3. Pharmaceutical form.
- 4. Pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars.
- 5. Clinical particulars:
 - 5.1. therapeutic indications,
 - 5.2. contra-indications,
 - 5.3. undesirable effects (frequency and seriousness),
 - 5.4. special precautions for use,
 - 5.5. use during pregnancy and lactation,
 - 5.6. interaction with other medicaments and other forms of interaction,
 - 5.7. posology and method of administration for adults and, where necessary, for children,

⁽¹⁾ OJ No 22, 9. 2. 1965, p. 369/65.

- 5.8. overdose (symptoms, emergency procedures, antidotes)
- 5.9. special warnings,
- 5.10. effects on ability to drive and to use machines.

6. Pharmaceutical particulars:

- 6.1. incompatibilities (major),
- 6.2. shelf life, when necessary after reconstitution of the product or when the container is opened for the first time,
- 6.3. special precautions for storage,
- 6.4. nature and contents of container,
- 6.5. name or style and permanent address or registered place of business of the holder of the marketing authorization.'

3. The following Article 4b is inserted:

'Article 4b

When the marketing authorization referred to in Article 3 is issued, the person responsible for placing that product on the market shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by them. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.'

4. The following Article 9a is inserted:

'Article 9a

After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the control methods provided for in Article 4 (7), take account of technical and scientific progress and introduce any changes that may be required to enable the proprietary medicinal product to be checked by means of generally accepted scientific methods. These changes must be accepted by the competent authorities of the Member State concerned.'

5. Article 10 is amended as follows:

'Article 10

An authorization shall be valid for five years and be renewable for five-year periods on application by the holder at least three months before expiry.'

6. The second paragraph of Article 11 shall be amended as follows:

'An authorization shall also be suspended or revoked where the particulars supporting the application as provided for in Articles 4 and 4a are incorrect or have not been amended in accordance with Article 9a, or when the controls referred to in Article 8 of this Directive or in Article 27 of Second 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⁾ have not been carried out.

⁽¹⁾ OJ No L 147, 9. 6. 1975, p. 13.'

7. in the first paragraph of Article 13, points 1, 2 and 7 are amended as follows:

- '1. Name of the proprietary products, which may be a brand name or a common name accompanied by a trade mark or the name of the manufacturer, or a scientific name accompanied by a trade mark or the name of the manufacturer.

Where the special name of a medicinal product containing only one active ingredient is a brand name, this name must be followed in legible characters by the international non-proprietary name recommended by the World Health Organization, where such name exists, or, where no such name exists, by the usual common name.

2. A statement of the active ingredients expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a particular volume or weight, using the international non-proprietary names recommended by the World Health Organization, where such names exist, or, where no such names exist, the usual common names.'
- '7. Expiry date in plain language.'

Article 2

The Annex to Council Directive 75/318/EEC of 20 May 1975 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 ⁽¹⁾ is hereby amended as follows:

1. In part 1 (C) 1, the seventh paragraph is replaced by the following:

'The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.'

The following is added to the eighth paragraph:

'The competent authorities shall inform the authorities responsible for the pharmacopoeia in question.'

2. In part 1 (C) the following paragraph 3 is added:

'3. Physico-chemical characteristics liable to affect bio-availability

The following items of information concerning active ingredients, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active principles if the bio-availability of the medicinal product depends on them:

- crystalline form and solubility coefficients,
- particle size, where appropriate after pulverization,
- state of hydration,
- oil/water coefficient of partition ⁽¹⁾.

The first three indents are not applicable to substances used solely in solution.

⁽¹⁾ The competent authorities may also request the pK and pH values if they think this information is essential.'

3. In part 1 (E) the following is inserted as first paragraph:

'For the control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the

⁽¹⁾ OJ No L 147, 9. 6. 1975, p. 1.

same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all the units manufactured in a given period of time.'

4. The following fourth paragraph is added to part 1 (E) (1):

'Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active ingredient or ingredients; these studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary. The conditions of the test, the apparatus employed and the standards shall be described in precise detail as long as they are not given in the European Pharmacopoeia or the national pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.'

5. In part 1 (E) (2) the following new paragraphs are inserted between the second and third paragraphs:

'Unless there is appropriate justification, the maximum acceptable deviation in the active-ingredient content of the finished product shall not exceed $\pm 5\%$ at the time of manufacture.

On the basis of the stability tests, the manufacturer must propose and justify maximum acceptable deviations in the active-ingredient content of the finished product up to the end of the proposed shelf-life.'

6. In part 1 (E) (3), the third paragraph is replaced by the following:

'An upper limit test shall be obligatory in respect of preserving agents and any other excipient constituent liable to affect adversely physiological functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bio-availability of an active substance, unless bio-availability is guaranteed by other appropriate tests.'

7. In part 1 (E) (5), the first paragraph is replaced by the following:

'If general monographs on pharmaceutical forms appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeias of the Member States, finished products must meet the requirements contained therein. If not, the finished-product specifications should include the following tests as appropriate for the formulation.'

In addition, the ninth, 12th, 13th and 15th paragraphs are amended as follows:

Injectable preparations: '10 ml' is replaced by '15 ml'.

Ointments, creams, etc.: colour and consistency; particle size of the active ingredients; weight and acceptable margin of variation; nature of container; microbiological control tests, if necessary.'

Suspensions: colour, sedimentation rate; where settlement occurs, the ease with which suspensions can be restored.'

Suppositories and pessaries: colour; particle size of the active ingredients; weight and acceptable variations in unit weight; melting temperature or disintegration time, with the methods used to determine these.'

8. In chapter I of part 2, the following section Da is inserted between titles D and E:

'Da. MUTAGENIC POTENTIAL

The purpose of the study of mutagenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells and which have the effect of making successors permanently and hereditarily different from their predecessors. This study is obligatory for any new substance.

The number and types of results and the criteria for their evaluation shall depend on the state of scientific knowledge at the time when the application is lodged.'

9. In chapter I of part 2, section E is replaced by:

'E. CARCINOGENIC POTENTIAL

Tests to reveal carcinogenic effects shall normally be required:

1. in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;
2. in respect of substances which have given rise to suspicious changes during the long term toxicological tests;
3. in respect of substances which have given rise to suspicious results in the mutagenic-potential tests or in other short-term carcinogenicity tests.

Such tests may also be required in respect of substances to be included in proprietary medicinal products likely to be administered regularly over a prolonged period of a patient's life.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the details of the tests.'

10. In chapter I (G) of part 2, the following new paragraph is inserted between the fourth and fifth paragraphs:

'For medicinal products which must be subjected to a bio-availability assessment, the data must include changes in the results as a function of time and, more generally, indicate the bio-availability of the product or of its metabolites.'

11. Chapter II of part 3 is amended as follows:

— the title is replaced by:

'A. PHARMACOLOGICAL PARTICULARS (Clinical pharmacology and bio-availability)'

— the following paragraph is added:

- '5. The assessment of bio-availability must be undertaken in all cases where it is essential in the interests of patients, e.g. where the therapeutic safety index number is low or where the previous tests have revealed anomalies which may be related to variable absorption, or if this process is necessary for the proprietary products referred to in Article 4 (8) of Directive 65/65/EEC.'

Article 3

Chapter III of Directive 75/319/EEC is hereby replaced by the following:

CHAPTER III**Committee for Proprietary Medicinal Products***Article 8*

1. In order to facilitate the adoption of a common position by the Member States with regard to decisions on the issuing of marketing authorizations and to promote thereby the free movement of proprietary medicinal products, a Committee for Proprietary Medicinal Products, hereinafter referred to as "the Committee", is hereby set up. The Committee shall consist of representatives of the Member States and of the Commission.
2. The Committee's task shall be to examine, at the request of a Member State or the Commission and in accordance with Articles 9 to 14, questions concerning the application of Articles 5, 11 or 20 of Directive 65/65/EEC.
3. The Committee shall draw up its own rules of procedure.

Article 9

1. In order to make it easier to obtain a marketing authorization in at least two other Member States taking into due consideration an authorization issued in one Member State in accordance with Article 3 of Directive 65/65/EEC, the holder of the latter authorization may submit an application to the competent authorities of the Member States concerned together with the information and documents referred to in Articles 4, 4a and 4b of Directive 65/65/EEC. He shall testify to its identity with the dossier accepted by the first Member State, specifying any additions it may contain, and shall certify that all the dossiers filed as part of this procedure are identical.
2. The holder of the marketing authorization shall notify the Committee of this application, inform it of the Member States concerned and send it a copy of his authorization. He shall also inform the Member State which granted him the initial authorization and notify it of any additions to the original dossier; that State may require the applicant to provide it with all the particulars and documents necessary to enable it to check the identity of the dossiers filed with the dossier on which took its decision.
3. The holder of the marketing authorization shall notify the dates on which the dossiers were sent to the Member States concerned. As soon as the Committee has noted that all the Member States concerned are in possession of the dossier, it shall forthwith inform all the Member States and the applicant of the date on which the last Member State concerned received the dossier. The Member State(s) concerned shall either grant the authorization valid for their markets within a period of 120 days of the aforementioned date, taking into due consideration the authorization issued within the meaning of paragraph 1, or put forward a reasoned objection.

Article 10

1. Where a Member State considers that it is unable to grant a marketing authorization, it shall forward to the Committee and to the person responsible for placing

the proprietary medicinal product on the market its reasoned objection in accordance with Article 5 of Directive 65/65/EEC, within the time limits stipulated in Article 9 (3).

2. Upon the expiry of this period, the matter shall be referred to the Committee and the procedure referred to in Article 14 shall be applied.

3. On receipt of the reasoned objection referred to in paragraph 1, the person responsible for placing the product on the market shall immediately send the Committee a copy of the particulars and documents enumerated in Article 9 (1).

Article 11

If several applications submitted in accordance with Articles 4 and 4a of directive 65/65/EEC have been made for a marketing authorization for a particular proprietary medicinal product, and one or more Member States have granted an authorization while one or more of the other Member States have refused it, one of the Member States concerned or the Commission may refer the matter to the Committee for application of the procedure referred to in Article 14 of this Directive.

The same shall apply where one or more Member States have suspended or revoked a marketing authorization while one or more other Member States have not done so.

In both cases, the person responsible for placing the proprietary medicinal product on the market shall be informed of any decision of the Committee to apply the procedure laid down in Article 14.

Article 12

The competent authorities of Member States may, in specific cases where the interests of the Community are involved, refer the matter to the Committee before reaching a decision on a request for a marketing authorization or on the suspension or revocation of an authorization.

Article 13

1. The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and toxico-pharmacological tests on, and clinical trials of, any proprietary products containing a new active substance which are the subject of a request for a marketing authorization in the Member States concerned for the first time.

2. As soon as the notification referred to in Article 9 is received, the competent authorities shall immediately communicate to the Member States concerned any assessment report accompanied by a summary of the dossier relating to a particular proprietary product. This report shall also be communicated to the Committee where a matter is referred to the Committee pursuant to Article 10.

The assessment report shall also be forwarded to the other Member States concerned and to the Committee as soon as a matter is referred to the Committee under the procedure laid down in Article 11. Any assessment report so forwarded shall remain confidential.

The competent authorities shall bring the assessment report up to date as soon as it is in possession of information which is of importance for the evaluation of the balance between effectiveness and risk.

Article 14

1. When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 60 days of the date on which the matter was referred to it.

In the cases referred to in Article 10 the person responsible for placing the product on the market may, at his request, explain himself orally or in writing before the Committee issues its opinion. The Committee may extend the time limit referred to in the preceding paragraph to give the applicant time to explain himself orally or in writing.

In the case referred to in Article 11, the person responsible for placing the product on the market may be asked to explain himself orally or in writing.

2. The Committee's opinion shall concern the grounds for the objection provided for in Article 10 (1) and the grounds on which the marketing authorization has been refused, suspended or withdrawn in the cases described in Article 11.

The Committee shall immediately inform the Member State(s) concerned and the person responsible for placing the product on the market of its opinion or of those of its members in the case of divergent opinions.

3. The Member State(s) concerned shall decide what action to take on the Committee's opinion within 60 days of receipt of the information referred to in paragraph 2. They shall immediately inform the Committee of their decision.

Article 15

1. The Commission shall report to the Council every two years on the operation of the procedure laid down in this chapter and its effects on the development of intra-Community trade.

2. In the light of experience, the Commission shall, not later than four years after the entry into force of this Directive, submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products.

3. The Council shall decide on the Commission proposal no later than one year after its submission.

Article 4

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive within 24 months of its notification ⁽¹⁾. They shall forthwith inform the Commission thereof.

Requests for marketing authorizations lodged after expiry of the time limit referred to in the first paragraph must comply with the provisions of this Directive.

⁽¹⁾ This Directive was notified to the Member States on 31 October 1983.

Articles 1 and 2 of this Directive, where relevant, shall be progressively extended to existing proprietary medicinal products by the end of the period stipulated in Article 39 (2) of Directive 75/319/EEC.

Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 5

This Directive is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council
The President
G. MORAITIS

COUNCIL RECOMMENDATION**of 26 October 1983****concerning tests relating to the placing on the market of proprietary medicinal products****(83/571/EEC)**

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 235 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament ⁽¹⁾,

Having regard to the opinion of the Economic and Social Committee ⁽²⁾,

Whereas Council Directive 65/65/EEC of 26 January 1965 ⁽³⁾ led to the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products in the Member States; whereas Directives 75/318/EEC ⁽⁴⁾ and 75/319/EEC of 20 May 1975 ⁽⁵⁾ continued this approximation and developed the principles set out in Directive 65/65/EEC;

Whereas, in particular, Council Directive 75/318/EEC lays down a general framework for the testing of proprietary medicinal products, lists the various types of tests to be conducted and defines certain principles to be followed in the examination of applications for authorizations to place a proprietary medicinal product on the market;

Whereas experience has shown that the conduct and content of these tests should be defined more precisely so as to make possible an identical implementation of the Community Directives when such tests are carried out and when applications are examined by national authorities;

Whereas Notes for guidance are therefore necessary in order to prevent differences of interpretation in the implementation of the standards and protocols referred to in Directive 75/318/EEC; whereas this will help to promote the free movement of proprietary medicinal products;

Whereas tests designed to evaluate the quality, safety and efficacy of proprietary medicinal products must be constantly adapted to take account of the

latest scientific and technical knowledge without, however, giving rise either to a waste of resources or to the more than necessary use of laboratory animals;

Whereas it is therefore highly desirable that the Notes for guidance be periodically revised to take account of the state of the art and that new Notes for guidance be drawn up as and when required, in agreement with the national authorities;

Whereas such progress in harmonization, essential at Community level, will also promote international recognition of tests on medicinal products conducted in accordance with these Notes and will therefore tend to render unnecessary the repetition of tests on products intended for export to third countries;

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.

Done at Luxembourg, 26 October 1983.

For the Council

The President

G. MORAITIS

⁽¹⁾ OJ No C 287, 9. 11. 1981, p. 127

⁽²⁾ OJ No C 189, 30. 7. 1981, p. 39.

⁽³⁾ OJ No 22, 9. 2. 1965, p. 369/65.

⁽⁴⁾ OJ No L 147, 9. 6. 1975, p. 1.

⁽⁵⁾ OJ No L 147, 9. 6. 1975, p. 13.

ANNEX I

REPEATED DOSE TOXICITY

Note for guidance concerning the application of chapter I (B) (2) of part 2 of the Annex to Directive 75/318/EEC, with a view to the granting of a marketing authorization for a new drug

1. INTRODUCTION

The purpose of these studies is to obtain information on the toxicity of a product when repeated exposure to this medicinal product is anticipated, in order that an assessment may be made of the risk resulting from therapeutic administration of the product, taking into account the products of biotransformation.

The duration of these studies will be determined by the proposed use in man or by the intended duration of human exposure. The following periods of administration are suggested as a guidance to correlate the duration of the repeated dose toxicity studies with the proposed duration of human exposure to the drug:

<i>Proposed duration of human treatment</i>	<i>Suggested duration of repeated dose toxicity studies</i>
One or several doses within one day	two weeks
Repeated doses for up to seven days	four weeks
Repeated doses for up to 30 days	three months
Repeated doses beyond 30 days	six months

When human exposure is likely to be longer term, for example when frequent discontinuous administration results in a total period of exposure of one month or more in a period of one year, or when retention in the body of a single dose of the drug is prolonged, then the duration of the repeated dose toxicity studies will be six months.

When it is necessary to conduct toxicity studies of three or six months duration, a sub-acute toxicity study of two or four weeks duration may be designed and carried out in such a manner that it acts as a range-finding study for the longer term investigation (see 2.5).

The reason is that administration of too high a dose would leave too few animals alive at the end of the study lasting three months or more; administration of too low a dose would prevent the development of toxic changes.

1.1. General specifications with regard to the repeated dose toxicity study

In the Annex to Directive 75/318/EEC, part 2 concerning toxicological and pharmacological tests states that these tests should show *inter alia* the toxicity thresholds:

'Repeated dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally it is desirable that two tests be performed: one short-term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose shall be to determine by experiment the non-toxic dose range of the product'.

As these thresholds can only be determined when they have been crossed the repeated dose toxicity study must be conceived in such a way as to demonstrate signs of toxicity. This implies that:

- 1.1.1. In the selection of species for long-term studies prior to marketing, it is desirable that, with regard to the metabolism and the pharmacokinetics of the drug, the species should be as closely similar to man as is possible within the usual spectrum of laboratory animals used for repeated dose studies. If there are significant differences in metabolism these should be taken into account in evaluating the results.
- 1.1.2. It is desirable that the pharmacological target organs and the pharmacological effects of the product in the species used should be the same as those involved in the therapeutic effect envisaged for man where this is known and is practical.
- 1.1.3. The dosage, the route and the frequency of administration should be planned so as to promote a loading of the animal organism with the product and its metabolites sufficient to demonstrate the target organ(s) in terms of harmful secondary effects. In designing the protocol, account will be taken of the pharmacokinetics of the drug.

By continuous administration of a drug in sufficiently high doses the following principal stages may be reached:

- (a) the load of the drug in the organism builds up until a steady state is reached;
- (b) adaptation of the organism to the load with regard to the pharmacological target organs or the biotransformation enzymes or the excretory mechanisms;
- (c) in some cases a second metabolic pathway may be activated due to an overloading of the primary detoxication pathway; as a result a new toxic metabolite may be formed;
- (d) a phase of manifestation of target organ toxicity manifested by failure of physiological functions and ultimately by pathological changes.

Administration of the product in the repeated dose toxicity studies should be sufficient with regard to dosage and duration to reach this final stage (d) so that the type of toxicity produced by an excessive dose and the multiple of the therapeutic dose producing toxicity may be assessed. Not all drugs can be practically administered in dosages that produce target organ toxicity. Under such circumstances, evidence should be produced that the highest possible dose has been given and that the drug has been systemically absorbed.

2. SPECIFICATIONS WITH REGARD TO THE DRUG AND ITS ADMINISTRATION

2.1. Drug quality

The active substance should present the same pattern of impurities as the product to be marketed, when possible. Should drug substance in 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. When the drug is given orally its physical characteristics such as particle size may be important; therefore the physical characteristics and stability of the material used in the repeated dose toxicity studies should be stated in each case. Whenever more than one batch of active substance is used in repeated dose toxicity studies this must be stated and each batch identified. The batch or batches used in the repeated dose toxicity studies should not be of a higher degree of purity than those intended for the final product. When the drug is given in the diet or the drinking water it should be established that it is stable in that medium.

When a new excipient is used for the first time, it should be tested in accordance with the same criteria as a new active substance.

2.2. Duration of administration

The duration of these studies should be related to the duration of the proposed therapeutic use in man (see 1).

2.3. Route of administration

Whenever this is technically feasible, the product should be administered by the route intended for use in man and it is desirable that the pharmacological effect is demonstrable by this route. When this cannot be shown, the use of other routes should be considered. (Administration by inhalation is discussed in the Appendix.) The quantity of drug absorbed from the proposed site of administration should be known from pharmacokinetic studies. When the product is administered in the food or the drinking water, the applicant must give assurance that a reasonable and known amount of the drug ingested is absorbed. Dosing by incorporation of the test substance in the diet or drinking water requires regular adjustment of the amount of drug in the diet or drinking water to compensate for growth and changing consumption.

In addition to systemic toxicity the possibility of local toxicity at the site of application should be given due attention, for example in the case of application to the skin, intravaginal application, intravenous, intramuscular, rectal, subcutaneous, intra-articular, intrathecal, conjunctival, intranasal and aural application, or when the drug is given by inhalation.

2.4. Frequency of administration

The steady state of the loading of the organism with some products is reached only when they are administered for seven days a week. Usually the administration of a drug to animals should be conducted on this basis. If this is not possible the reason should be given. When the rate of elimination is slow, less frequent administration may be acceptable. A rapid rate of elimination or gastric intolerance may make it necessary to administer the products more than once a day.

2.5. Dose levels

The treatment should include:

- (a) a high dose, selected for the purpose of causing target organ toxicity whenever possible or, failing this, other non-specific toxicity, or until limited by volume of dose;

For a toxicity study of three or six months duration this dose should be derived from a subacute toxicity test of two or four weeks duration, designed and carried out as a dose range-finding study;

- (b) a low dose, sufficient to produce a pharmacodynamic effect or the desired therapeutic effect, or to produce blood levels comparable to those expected to produce these effects in man;
- (c) an intermediate dose, such as the geometric mean between the high dose and the low one;
- (d) The study should include appropriate control group(s); in special cases a positive control group may be necessary.

However, the above considerations do not apply when the pharmacodynamic effect by itself will cause toxicity; hypoglycaemia by antidiabetic agents serves as an example.

The investigator should indicate the rationale on which the dose levels were selected.

2.6. Pro-drugs

When the product administered is a pro-drug, its conversion to an active drug should be demonstrated in the species under study.

3. SPECIFICATIONS PERTAINING TO THE EXPERIMENTAL ANIMAL

3.1. Animal species: choice and characterizations

As far as possible, the species should be chosen on the basis of their similarity to man with regard to the pharmacokinetics including the biotransformation of the product (see 1.1.1).

The pharmacodynamic effect of the drug should, if possible, be demonstrated in at least one of the species, so as to provide information about the margin between therapeutic and toxic effects.

The investigator should justify the choice of the species and strain. Use of SPF animals usually increases the value of the study.

3.2. Sexes

Normally, equal numbers of male and female animals should be used.

3.3. Size of treatment groups

When the size of the treatment groups is being considered, attention should be given to the following:

- (a) the size of the treatment groups should be such that all toxicologically important effects due to treatment will be revealed;
- (b) the size of the treatment groups should be large enough to permit the sacrifice of animals at intervals before the end of the study without interfering with the final statistical analysis;
- (c) the size of the treatment groups should be large enough to allow some animals to be retained at the completion of the period of dosing so that the reversibility of toxic changes at the end of the treatment may be evaluated;
- (d) background knowledge concerning the ranges of variables to be studied in the species and strains used is also relevant to consideration of group size.

However, the size of control and treatment groups will always be limited for practical and financial reasons and for humane considerations.

3.4. Number of species

The purpose of the repeated dose toxicity studies is to provide an animal model for the repeated administration of the product to man. The value of the model for extrapolation to man depends to a large extent on the qualitative similarity between the animal model and man; this is usually unknown. To reduce the risk of error in extrapolation, due to effects or lack of effects, which are peculiar to one species, at least two species should be used, one being a non-rodent. The choice of species should be justified (see 1.1.1).

4. ANIMAL HUSBANDRY

A high level of animal husbandry is required and the environmental conditions should be controlled and the diet should be of known constant composition throughout. Measures taken to obtain these conditions should be recorded in the report.

5. OBSERVATIONS

5.1. Pre-treatment and control values

Control data from the colony are necessary for small mammals for all morphological, biochemical and physiological variables. In the case of larger animals, pre-treatment values should be obtained from the animals used in the study.

5.2. Monitoring during the study

5.2.1. General monitoring

General monitoring should be carried out during the study and should include food intake, body weight, haematology, clinical chemistry, urinalysis, ophthalmology, ECG and general behaviour. The selection of techniques used and the choice of other tests should be appropriate to the current state of knowledge and to the animal species being used. In rodents, if ECG and ophthalmological or other specialized examinations are required, it is acceptable that these are conducted in a limited number of animals at each dose level.

5.2.2. Frequency of monitoring

The frequency of monitoring in addition to pre-treatment studies and final monitoring should be adapted to the manifestations of toxicity and also to the pharmacokinetics of the drug. The tests performed (including the collection of blood samples) during the monitoring should also be performed on the controls, and should not affect the experimental animals in a way which would influence the final interpretation of the toxicity test results.

5.2.3. Food intake

When products are administered in the food, particular attention should be given to the effect of the product on food consumption. Allowance should be made for consequent effects on drug intake.

5.3. Terminal monitoring

Terminal observations should be as complete as possible. Autopsy must be conducted on all animals. Histopathology should be performed on all organs and tissues of the high dose and the control groups listed in the table. In rodents the examination of the lower dosed groups may be restricted to those organs and tissues showing pathological changes at autopsy. In other species where small numbers of animals are used, histopathology on those tissues listed should be conducted in all animals at all doses.

If organs are not examined microscopically, wax blocks or slides should be prepared and conserved for five years from the date of marketing for examination if required. Peculiarities in the distribution of the drug may necessitate further histopathological studies.

6. IMMUNO-INTERFERENCE

The expansive growth of immunology and the recognition of its importance has made it necessary to pay attention to interference with the immunologic system by drugs even when this does not belong to their intended activity. Such an interference may cause undesired side effects (interference with infection; carcinoma). Therefore it is particularly important to examine the spleen, the thymus and some lymph nodes macroscopically and microscopically at the termination of the toxicity study. These should indicate any effect on the immune system and thus the need for further tests.

Since our present knowledge in this field is rapidly increasing, any test used to investigate the immunological effects of a drug should rely on the state of the scientific knowledge at that moment.

7. CONCLUSIONS

Conclusions should be drawn from these studies by the investigator.

*Appendix A***List of tissues to be studied histologically in a repeated dose toxicity study**

- Gross lesions
- Tissue masses or tumors (including regional lymph nodes)
- Blood smears (in case of anaemia, enlarged thymus, lymphadenopathy)
- Lymph nodes
- Mammary glands
- Salivary glands
- Sternebrae, femur or vertebrae (including bone marrow)
- Pituitary
- Thymus
- Trachea
- Lungs
- Heart
- Thyroid
- Oesophagus
- Stomach
- Small intestine (Swiss roll method)
- Colon
- Liver
- Gall-bladder
- Pancreas
- Spleen
- Kidneys
- Adrenals
- Bladder
- Prostate
- Testes
- Ovaries
- Uterus
- Brain (coronal sections at three levels)
- Eyes
- Spinal cord

*Appendix B***Conduct of toxicity studies by inhalation****1. INTRODUCTION**

Medicinal products intended for administration to humans by inhalation may either be aerosols containing the pharmacologically active substance in solid or liquid state or they may be vapors or gases. The latter mentioned products are used as inhalation anaesthetics while aerosols in general contain a drug material in the form of particles delivered in a propellant which in principle ought to be biologically inactive.

Toxicological studies conducted by inhalation are necessary where:

- (a) pharmacokinetics after administration by inhalation may differ qualitatively or quantitatively from the pattern after other routes of administration; or
- (b) drug and propellant may interact in the body; or
- (c) the inhaled product may have a local effect in the airways, either a short-term effect (effect on ciliary function or other signs of local irritation) or a long term effect (emphysema, bronchitis, malignancy).

Aerosols are used for the administration of drugs either (i) to obtain a local effect in the respiratory system, or (ii) for the purpose of obtaining systemic effects by using the lining of the airways for absorption of the active compound or (iii) for circumventing the alteration of drugs in the gastro-intestinal tract.

In some circumstances toxicological studies on the drug may have been performed using other routes of administration, therefore extensive toxicological investigation by other routes of administration may already have been performed when inhalational studies are planned. In other cases, for example, locally acting compounds, such as mucolytic agents, toxicological investigation by other routes of administration may be non-existent or of little relevance. Planning of the toxicology studies by inhalation should take into consideration any already existing toxicological or pharmacological knowledge of the substance.

2. PHYSICO-CHEMICAL PROPERTIES

The information of the active substance's physico-chemical properties should be provided in the same way as for any other toxicological study. Additional information should be provided on the characteristics of the aerosol, which should include the distribution of the particle or droplet size of the active substance and the physico-chemical specification of the substance or substances used as the propellant.

The propellant system used in these studies should be that proposed for the final product. If a novel propellant system is used, this should itself be investigated to the same standard as a new active substance.

3. DOSING SCHEDULES**3.1. Administration**

The method of administration depends on the nature of the substance and the intended use in man. In acute studies it may be reasonable to administer the substance directly into the airways via a nasotracheal tube or through a tracheotomy. In this way the quantity administered can be determined directly.

In the case of long-term exposure studies it will usually be necessary to use either 'head only' or 'nose only' exposure chambers or masks for inhalation. If whole body exposure is used,

deposition of the drug on the skin, in the pelt, in the upper airways and the amount swallowed should be taken into account in determining the dose of substance administered.

It should be demonstrated that the method of administration ensures that the substance reaches the desired site.

3.2. Dose levels

In these studies, normally three dose levels and one or more control groups as appropriate should be used in both single dose and repeated dose studies. Different levels of drug exposure can be achieved by alteration of concentration of substance inhaled or by alteration of the duration of exposure. In the selection of dose levels the same principles should apply, as far as is possible to those used for toxicity studies by other routes.

The reasons for selecting particular dose levels should be given.

3.3. Duration of study

The duration of the study should be related, at least to some extent, to the proposed human exposure.

4. PHARMACOKINETICS AND METABOLISM

The metabolic pattern of the drug administered by inhalation may differ from the pattern observed following other routes of administration. The investigator should determine whether there are any pharmacokinetic or metabolic differences of relevance for the interpretation of the toxicological studies conducted by the inhalation route.

When biotransformation occurs in the lung itself, the possibility of enzyme induction of this process should be taken into consideration.

5. ANIMALS

The experimental animals used in these studies should be free of pulmonary infection and have a low incidence of other pulmonary pathology.

The number of experimental animals to be used in each group should be adequate for statistical analysis and will be determined by the duration of the experiment and by the number of observations, measurements and interim sacrifices to be made during the exposure periods. At least one rodent and one non-rodent species should be used for all repeated exposure studies.

6. OBSERVATIONS

Interim monitoring and terminal studies should be conducted as indicated for other toxicity studies. Particular attention should be paid to any local effects. If the drug is to be administered repeatedly, special studies of ciliary function and on the microflora may be necessary.

Blood-level monitoring of drug and propellant or other methods of assessing absorption of drug and propellant should be performed at intervals during repeated dose studies.

Terminal examination

At the conclusion of the study all animals should be subjected to autopsy and examination of tissues should be conducted as with other toxicological studies.

In studies conducted by the inhalational route the lungs should be weighed in all animals and histopathological examination conducted on tissues taken from all exposed levels of the respiratory tract and from associated lymphoid tissue.

7. PRESENTATION OF RESULTS AND CONCLUSIONS

These should be drawn up in the same manner as in other toxicity studies and the investigator should draw appropriate conclusions from the study.

ANNEX II**REPRODUCTION STUDIES**

Note for guidance concerning the application of chapter I (C) and (D) of part 2 of the Annex to Directive 75/318/EEC, with a view to the granting of a marketing authorization for a new drug

GENERAL STATEMENT

The study of drug effects on reproduction should be conducted on all new drugs in such a manner as would reveal the presence of any effect on mating behaviour and of any effect which might result in fetal loss, fetal abnormality and damage to the offspring in later life, e.g.:

- (i) changes in fertility or in the production of abnormal young due to damage to the male and/or female gametes;
- (ii) interference with preimplantation and implantation stages in the development of the conceptus;
- (iii) toxic effects on the embryo;
- (iv) toxic effects on the fetus;
- (v) changes in maternal physiology producing secondary effects on embryo or fetus;
- (vi) effects on uterine or placental growth or development;
- (vii) interference with parturition;
- (viii) effects on postnatal development and suckling of the progeny, and on maternal lactation;
- (ix) late effects on the progeny.

SPECIFIC GUIDELINES

In the interpretation of the following notes for guidance it must be appreciated that they are not rigid requirements and may not be universally applicable. Interpretation should therefore be flexible and related to the proposed use of the drug; justification for choice of studies must be given.

1. SELECTION OF SPECIES

Embryotoxicity studies should normally be conducted on two mammalian species one of which should be other than a rodent. Fertility and perinatal studies should be conducted in at least one species. Where metabolism of a drug in a particular species is known to be similar to that in man, it is desirable to include this species. It is desirable that one of the species is the same as in the long term toxicity studies. Studies in a third species may be helpful if conflicting results are obtained in the initial two species. The species and strains used in the studies should be specified.

2. DOSAGE

Dosing should normally be conducted at three dose levels. The high dose usually should be such that evidence of some maternal toxicity is produced, for example decrease in body weight gain. The low dose should be sufficient to produce a pharmacodynamic effect similar to the desired therapeutic effect, or to produce blood levels comparable to those required to produce the effect (this does not apply if the pharmacodynamic effect by itself will cause toxicity). The intermediate dose should be the geometric mean of the high and low doses.

Dosing should be conducted by the proposed route or routes of clinical administration.

Dosing schedules for investigation of drug effects on reproduction should normally include:

- (a) embryotoxicity studies; dosing throughout the period of embryogenesis (organogenesis) in two species one of which should be other than a rodent;
- (b) a fertility study which should be conducted in at least one species; dosing should commence in male and female animals at a sufficient time before the proposed mating so that any effects of the drug on gametogenesis could be revealed. Dosed animals may be mated with dosed partners but in the event of positive findings of a reproductive defect then the study should be repeated using dosed animals mated with undosed partners. After mating, the dosed females should continue to be dosed throughout pregnancy.

Half the females should be killed during gestation, preferably some days before the expected date of parturition, and the fetuses removed by Caesarean Section and examined. The remainder of the females should be allowed to litter normally and rear their progeny.

- (c) Perinatal studies which should be conducted in at least one species; dosing should cover the period of gestation from the end of organogenesis parturition and should extend throughout the period of lactation up to weaning.

3. NUMBERS OF ANIMALS

An adequate number of animals should be used at each dose level to enable valid assessments to be made. With the exception of primates, the following minimum numbers per dose level are suggested:

- (a) embryotoxicity studies: 20 pregnant females in rodents, 12 pregnant females in non-rodents;
- (b) fertility studies: 24 females and 24 males;
- (c) perinatal studies: 12 pregnant females.

Where a third species is used it is suggested that adequate numbers of dosed animals should be used together with controls to allow a clear conclusion to be drawn from the study.

4. HOUSING AND DIET

Full details of the housing and caging conditions of the animals must be given. The full specification of the diet (including additives) must be provided.

5. PHARMACOKINETICS

In the conduct of reproduction studies, account should be taken of the pharmacokinetics of the drug in the pregnant animal. The level of exposure of the fetus to the drug should have been determined as far as this is technically possible.

6. EVALUATIONS

- (a) Examinations should be made of the fetuses from the animals dosed during the period of embryogenesis. Animals should be killed and the fetuses removed by Caesarean Section. In these animals the numbers of corpora lutea, implantation sites (visible and those determined by special techniques e.g. by the Salewsky method), resorptions, the weight and sex of their individual fetuses should be recorded. The individual fetuses should be examined for external abnormalities and adequate examination of the skeleton or viscera or both made on all fetuses. Where obvious abnormalities are found further appropriate examination should be conducted. Special attention should be paid to abnormally high numbers of resorptions as this might indicate the need for further studies for teratogenic effects in the early stages of pregnancy.

- (b) In the fertility study, females killed during the period of gestation should have their fetuses delivered by Caesarean Section and the following information should be recorded: number of corpora lutea, implantation sites, resorptions, weight and sex of individual fetuses. All individual fetuses should be examined for either skeletal and/or visceral abnormalities.

From animals dosed during the fertility study and allowed to litter normally and rear their progeny to the stage of weaning, a large enough number of progeny to allow for the subsequent investigations should be allowed to live and reach maturity. Late effects of the drug on the progeny in terms of auditory, visual and behavioural impairment should be assessed. Reproductive function should be determined in the progeny by allowing at least one male and one female from each litter of dosed animals to breed and produce one litter (brother/sister mating is not envisaged).

- (c) The females dosed through the pre- and post-natal period should be allowed to litter spontaneously and the progeny examined at weaning. All animals killed at the end of lactation should be subjected to a thorough autopsy examination. Under certain circumstances some of the progeny may be allowed to live and reach maturity so that their reproductive capacity could be assessed, and other late effects of the drug on the progeny in terms of behavioural, visual and auditory impairment determined.

7. CONCLUSIONS

The investigator is required to draw overall conclusions from the results of these studies indicating either:

- (a) there is no evidence of adverse effects of the drug on reproductive function; or
- (b) there is evidence of adverse effects on reproductive function(s) to be specified; or
- (c) the data are inadequate to draw conclusions.

If particular studies have been omitted the investigator should justify the omission.

Appendix

Duration of gametogenesis

In rodent studies, dosing of the male should be for a minimum of 60 days and the female for a minimum of 14 days prior to mating. Animals should be about 40 days of age at the commencement of dosing. In the present stage of knowledge these times would be regarded as acceptable.

ANNEX III**CARCINOGENIC POTENTIAL**

Note for guidance concerning the application of chapter I (E) of part 2 of the Annex to Directive 75/318/EEC, with a view to the granting of a marketing authorization for a new drug

The strongest evidence that a compound is a carcinogenic hazard for man is epidemiological although most known human carcinogens are found to be carcinogenic for experimental animals. There is no evidence that all substances which are carcinogenic for animals are also carcinogenic for man, but it is difficult to declare any compound as being non-carcinogenic for man when it has been shown to be carcinogenic in animal studies.

Extrapolation to man is a difficult, sometimes arbitrary, procedure, and the ideal would be to analyze the mechanisms involved in increasing the incidence of the experimental tumours and to determine whether such mechanisms involving specific biochemical pathways and the formation of the proximate carcinogen would be applicable to man. The criteria on which extrapolation is based may vary with the agent under consideration, its projected use, dosage and mode of administration on the one hand, and the species, sites, incidence of tumours and required test dosage, on the other.

The likelihood of carcinogenic risk in man is increased if there is a high yield of malignant tumours involving a specific tissue when the test animal is given the test substance by the route to be used in man and at a dosage equal to or lower than that which induces minimal toxicity. However, since there is no good evidence of a threshold level, an increase in yield of benign tumours, or malignant tumours at higher dosage, or reduction of latency should be interpreted as constituting a possible risk for man. In such circumstances, the agent is generally regarded as less potent and the risk may more easily be reconciled with benefits associated with the therapeutic use of the compound.

1. REQUIREMENTS FOR CARCINOGENICITY STUDIES

Carcinogenicity studies will usually be required in the following circumstances:

- (a) when the medicine is likely to be administered regularly over a substantial period of life (continuously during a minimum period of six months, or frequently in an intermittent manner so that the total exposure is similar); or
- (b) where a substance has a chemical structure that suggests a carcinogenic potential; or
- (c) where a substance causes concern due to:
 - (i) some specific aspects of its biological action (e.g. a therapeutic class of which several members have produced positive carcinogenic results);
 - (ii) its pattern of toxicity or long-term retention (of drug or metabolites) detected in previous studies;
 - (iii) the findings in mutagenicity tests and/or short-term carcinogenicity tests.

Carcinogenicity testing may not be regarded as necessary where the substance in question will be used only in patients with a life expectancy shorter than that in which a chemical might reveal any carcinogenic hazard in man. If circumstances alter and a drug of the latter variety were used in less serious conditions then carcinogenicity testing would become necessary. Insoluble substances which are not absorbed may not require formal carcinogenicity studies.

2. SPECIES AND STRAIN SELECTION

Where carcinogenicity studies are required, they should normally be conducted on two species. The metabolic handling of the drug should be known in the species used and should preferably show similarities to the metabolism in man. Cognizance should be taken of known species and strain responses with similar chemicals. Species and strains with a high incidence of spontaneous tumour formation should normally be avoided. Those undertaking the study should select species and strains known to be sensitive to one or more carcinogens. Positive controls will not be required routinely but the spontaneous tumour incidence of the strains used should be recorded.

3. DOSAGE

(a) *Route and frequency of dosing*

Where possible, dosing should be conducted by the proposed clinical route of administration. Where relevant, evidence of absorption should be provided. The frequency of dosing normally will be daily.

(b) *Dose levels*

Carcinogenicity testing should normally be conducted at three dose levels. The top dose should produce a minimum toxic effect, for example a 10 % weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be demonstrated by failure of physiological functions and ultimately by pathological changes. The lowest dose should be of the order of two to three times the maximum human therapeutic dose or the dose that produces a pharmacological effect in animals. The middle dose should be the geometric mean of the high and low dose.

Exceptions to these principles may occur, for example where the toxic dose of the drug is a high multiple of the therapeutic dose; in these circumstances it is acceptable if the top dose is set at approximately 100 times the human therapeutic dose, where technically feasible.

4. PRACTICAL FEATURES

Animals should be in good general health initially and this should be maintained throughout the study. High standards of animal husbandry are essential. Special precautions are necessary when inhalational or volatile carcinogens are being tested.

The pharmaceutical quality of the batch(es) used should be clearly characterized.

(a) *Age of animals at commencement of study*

Carcinogenicity studies should commence as soon as possible after weaning; i.e. as soon as the animals are accustomed to their diet and surroundings.

(b) *Duration of studies*

The currently recommended practice is to conduct studies for 24 months in the rat and 18 months in the mouse and hamster. Where the survival rate is high there may be advantages in extending studies for 30 months in the rat and 24 months in the mouse, or for the lifespan of the animals; i.e. to 20 % survival in the controls.

(c) *Number of animals per group*

For routine tests with mice, rats and hamsters it is suggested that for each sex there should be 50 animals per treated group, and two control groups of 50 for each sex dosed with the vehicle by the same route (in most cases the drug will be administered in the diet).

(d) *Composition of diet*

Commercial diets are variable and steps should be taken to provide as uniform a diet as possible throughout the duration of the carcinogenicity study. Full specification of the diet should be given.

5. **ADDITIONAL MONITORING**

Carcinogenicity studies should be designed to obtain the maximum amount of information from the animals used but any investigations undertaken to elicit additional toxicological data should not prejudice the prime purpose of evaluating a drug's carcinogenic potential. Information on absorption, distribution and metabolism of the drug and on whether the drug accumulated or was an enzyme inducer should have been determined during other toxicity studies.

6. **STATISTICAL DESIGN OF STUDY**

An appropriate experimental design should be selected and in particular:

- (i) the cages containing the animals in the treatment and control groups should be distributed within the animal house so as to eliminate bias due to the effects of any local environmental factor;
- (ii) animals should be allocated at random to the various experimental units (e.g. cages) and the method used to achieve this randomization should be clearly stated;
- (iii) if for practical reasons of handling such large numbers of animals it is decided to stagger the start of the study it is desirable that all groups should be represented at each start in equal numbers. If the study is conducted using a staggered start the times at which the various batches of animals enter the study must be stated.

7. **TERMINAL INVESTIGATIONS**

7.1. **Autopsy**

A full autopsy should be made on all animals dying during the study or killed because of their poor condition.

At the conclusion of the study all surviving animals should be sacrificed and a full autopsy conducted on each animal. Previously demonstrated toxic effects may indicate particular topics for investigation. Haematological and biochemical investigations may be helpful in the interpretation of any lesions found.

7.2. **Histopathology**

7.2.1. *Carcinogenicity screening*

- (i) Microscopical examination should be carried out on all listed tissues and organs from all high-dose animals and from all controls; and
- (ii) tissues from any animal in any group in which macroscopical lesions of any kind are found at autopsy.

If the results from (i) indicate that tumours occur in one or more organs or tissues, then:

- (iii) those tissues and organs should be examined in the mid- and low-dose groups even when macroscopically normal.

All listed tissues should be microscopically examined from all animals dying or killed during the course of the study.

7.2.2. *Toxicity screening*

Previously demonstrated toxic effects may indicate particular aspects for investigation.

Haematological and biochemical investigations may be helpful in the interpretation of any lesion found. Particular attention should be paid to the site of application if the drug is administered other than by the oral route.

8. PRINCIPLES OF REPORTING ON CARCINOGENICITY STUDIES

8.1. Definitions

A neoplasm (tumour) is regarded as a population of abnormal cells with uncontrolled and usually increased proliferative activity and other less well-defined morphological and functional features.

A malignant neoplasm is one which invades surrounding tissues or metastasises. In general terms, the tumour is considered to be benign or malignant on the basis of its histopathological appearances and the correlation by the pathologist of such changes with biological behaviour known from previous experience to occur in tumours displaying comparable characteristics.

Tumours should be described in conventional histopathological terms according to well-defined classifications (e.g. WHO).

8.2. Presentation of the data

In the first instance the findings should be summarized for each treatment group and each control group separately, keeping the sexes separate, in terms of:

1. number of animals examined and their individual gross and microscopic examination;
2. numbers (and percentages) of animals with tumours of each identified type in a specified tissue, distinguishing malignant from benign tumours, wherever possible;
3. a frequency distribution of the total number of tumours found in an animal with one or more tumours of the same or different types; and another of the total number of malignant tumours found in the animal. If the tumours cannot be enumerated some grading of multiplicity of tumours should be used instead;
4. time to each interim death;
5. time of appearance of any mass (starting from clinical palpation) and its progress, as well as its eventual histopathology.

9. ANALYSIS OF THE DATA

The form of the analysis and the tests of statistical significance used should be appropriate to the type of data and to the basic experimental design. The statistical procedures used should be clearly stated.

The responses should be assessed in the following ways:

- (i) the total incidence of tumour bearing animals;
- (ii) the total incidence of tumours;
- (iii) the incidence of tumours involving a specific tissue;
- (iv) the incidence of tumours judged to be malignant;
- (v) the latent period to tumour appearance (using actuarial approaches).

The analysis should be directed towards:

- (a) the assessment of the presence of any effect of the substance under study, as shown by the contrast between the response in the three treatment groups, as a set, and the response in the two control groups, as a set;
- (b) the assessment of whether any effect is dose-related, as shown by a trend in the responses in the low-, mid- and high-dose groups. This assessment is statistically independent of that in (a).

Professional statistical advice should be available in order to assess the influence of other factors, such as death of test animals because of other diseases, and premature killing of animals because of clinical detection of tumours. The particular tests of statistical significance which should be used in assessing the presence of an effect or a dose-relationship are intentionally not specified. The data in one experiment may require a different approach from the data in another.

The test substance should be regarded as having the potential to increase the risk of neoplastic change if any of the above responses is materially increased (or the latent period is materially decreased). The compound may be regarded as possessing more powerful activity for the animal if several of the above responses are affected and if there is evidence of a dose-response as well as the presence of the effect. A raised incidence of tumours in treated as compared with control animals is of significance whatever the mechanism postulated or defined for the development of such tumours, but any particular circumstances should be identified or remarked. Examples include known pathways which may be peculiar to one species (griseofulvin and porphyrin metabolism in the mouse), severe stimulation of endocrine glands (especially in the dog), or the development of physical features peculiar only to the test species (vesical calculi in the rat).

Different circumstances may result in:

- (i) an increased incidence or reduced latency of malignant tumours;
- (ii) an increased incidence of benign tumours;
- (iii) local induction of tumours at the site of injection.

10. USE OF SHORT-TERM CARCINOGENICITY STUDIES

Evaluation of new compounds in a mutagenicity screen is desirable. However, available techniques involving short-term testing of chemicals for mutagenicity/carcinogenicity are not capable of replacing formal carcinogenicity testing in animals as a means of evaluating a drug's carcinogenic potential. Short-term studies giving positive results will always indicate the need for formal carcinogenicity studies if the drug is to be developed further; those giving negative results do not preclude the need for formal studies when these are advisable for the reasons given in paragraph 1.

11. CONCLUSIONS

Conclusions from these studies should be drawn by the investigator.

*Appendix***List of tissues to be studied histologically in a carcinogenicity study**

- Gross lesions
 - Tissue masses or tumors (including regional lymph nodes)
 - Blood smears (in case of anaemia, enlarged thymus, lymphadenopathy)
 - Lymph nodes
 - Mammary glands
 - Salivary glands
 - Sternebrae, femur or vertebrae (including bone marrow)
 - Pituitary
 - Thymus
 - Trachea
 - Lungs
 - Heart
 - Thyroid
 - Oesophagus
 - Stomach
 - Small intestine (Swiss roll method)
 - Colon
 - Liver
 - Gall-bladder
 - Pancreas
 - Spleen
 - Kidneys
 - Adrenals
 - Bladder
 - Prostate
 - Testes
 - Ovaries
 - Uterus
 - Brain (coronal sections at three levels)
 - Eyes
 - Spinal cord
-

ANNEX IV**PHARMACOKINETICS AND METABOLIC STUDIES IN THE SAFETY EVALUATION OF NEW DRUGS IN ANIMALS**

Note for guidance concerning the application of chapter I (F) and (G) of part 2 of the Annex to Directive 75/318/EEC, with a view to the granting of a marketing authorization for a new drug

1. INTRODUCTION

These notes are concerned with the time course of the absorption, distribution and excretion of new drugs and with their metabolism in relation to their safety. For many steps in the evaluation of a drug such data are essential, for example:

- (a) to assess the levels of the drug and of its metabolites and their kinetics in blood, body fluids and organs;
- (b) to obtain information on the relationship between target organ toxicity and the blood, body fluids and organ concentrations of the drug;
- (c) to assess the possibility of enzyme induction and of cumulation of the drug with repeated administration;
- (d) to choose where possible the animal species to be used in toxicological studies on the basis of their similarity to man in handling the drug, and to determine the relevance of these toxicity studies to man.

2. DRUG SPECIFICATION

Specification of the physical and chemical properties of the drug substance must be given and the stability of the preparation should be provided.

When a labelled drug is used the position of the label in the molecule and the specific activity of the material must be stated. Consideration should be given when selecting the position of the label to its likely metabolic fate.

3. METHODS

Data on the levels of drug and metabolites in blood, body fluids, organs and in the excreta can be obtained by physical, chemical or biological methods. The investigator should justify the details of the methods used, their validity and reproducibility, including the specificity, precision and accuracy. (The study of the time course of its pharmacodynamic effects may provide useful additional information.)

When using labelled drugs attention must be given to the fact that the measured label in body fluids may not correspond to that of the unmodified drug, but may include labelled metabolites and conjugates. Attention should be given to the possibility of isotope exchange with endogenous compounds.

4. SPECIES

The animal species in these studies usually should be those normally used in the laboratory for pharmacological and toxicological investigations. The reasons for selection of any other species should be given.

A preliminary study of kinetics and metabolism of the drug in a few human subjects could provide useful information in choosing the animal species to be used in repeated dose toxicity studies.

5. DRUG ADMINISTRATION

Doses and routes of drug administration should be related, when possible, to the proposed clinical use of the drug. One of the routes selected should ensure the absorption of the drug if this is relevant to human usage.

6. PRESENTATION OF RESULTS

Information should be presented on the following items:

- (i) absorption (fractional absorption, kinetics);
- (ii) distribution in the principal organs and tissues and the time course in body fluids;
- (iii) blood, plasma or serum half-life;
- (iv) plasma protein binding;
- (v) characterization of the pattern of metabolites in excreta, and where practicable, identification of major metabolites;
- (vi) route and time course of excretion of drug and metabolites;
- (vii) if biliary excretion is a major route of elimination, then the possibility of entero-hepatic recycling should be investigated;
- (viii) a quantitative account of the fate of the administered dose should be attempted;
- (ix) possibilities of enzyme induction should be investigated. If enzyme induction is found its relevance in the context of the proposed use of the drug should be examined.

7. CONCLUSIONS

Appropriate conclusions should be drawn from these studies in the context of the objectives indicated in paragraph 1.

ANNEX V**FIXED-COMBINATION PRODUCTS**

Note for guidance concerning the application of chapter II (C) (2) of part 3 of the Annex to Directive 75/318/EEC, with a view to the granting of a marketing authorization for a new drug

1. JUSTIFICATION

Applicants will be required to justify the particular combination of active ingredients proposed. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.

For any individual fixed combination it will be necessary to assess the potential advantages in the clinical situation against possible disadvantages, in order to determine whether the product meets the requirements of the standards and protocols with respect to efficacy and safety.

Potential advantages of fixed combinations include:

1. an improvement in the therapeutic:toxic ratio, e.g. as a result of the potentiation of the therapeutic effect;
2. simplification of therapy, resulting in improved patient compliance.

Disadvantages of fixed combinations include:

1. the fact that even a combination which meets the need of the average patient is unlikely to be ideally formulated for the needs of the individual;
2. accumulation of adverse reactions.

Combinations, in principle, may not be considered rational if the half-life and/or the duration of action of the components differ significantly, but this may not necessarily apply where it can be shown that the combination is clinically valid despite differences in this respect, e.g. if one component is intended to enhance absorption of the other or where the components are intended to exert their effects successively.

The inclusion of an ingredient to counteract an adverse effect of one of the other components may be considered justified, but only if the adverse reaction is a commonly occurring one.

The inclusion of a component intended to produce unpleasant side-effects as a means of preventing abuse is undesirable.

Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.

2. INDICATIONS

The indications claimed for a fixed-combination product should be such that the presence of each component is justified for each indication. The product should be formulated so that the dose and proportion of each component present is appropriate to all the recommended uses.

Clearly, an 'indication' must be a well-recognized disease state, dysfunctional state, syndrome or pathological entity. The individual components of a fixed combination may be intended to relieve simultaneously different symptoms of such a disease state, but it will not be proper to regard each individual symptom as an indication for the fixed combination, since it may also occur in other diseases and for treating this symptom alone the other constituents may be irrelevant.

3. SAFETY AND EFFICACY

It is permissible to distinguish between the extent of the studies required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use provided these are thoroughly and reliably documented, and those studies required in the case of those combinations which are essentially new (either because the drugs involved are not usually combined, because the quantitative composition is unusual, or because one of the components is entirely new).

Safety studies in animals with fixed combinations should, as a general rule, have been performed with the active ingredients in the proportions present in the product. Such studies will not be required where all the components have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well-documented.

Both the efficacy and the safety of a fixed-combination product should have been investigated in man. For well-recognized combinations well-founded bibliographical data will be acceptable in some cases. It will be necessary to test a new combination clinically against one or more of the components in order to define the role played by each in the total.

4. INTERACTIONS

The possibility of interactions between the components should always be considered. Where a pharmaceutical, pharmacokinetic or pharmacodynamic interaction appears possible, the applicant should submit data either to establish that such interaction does not occur, or that it is clearly recognized and defined.

5. ADVERSE EFFECTS

Where there are grounds to expect that a fixed-combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual components given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination, e.g. increased efficacy, outweigh such disadvantages.

6. DOSAGE

The combination product must be safe and effective throughout the whole of the recommended dosage range.

7. COMBINATION PACKS

The principles applicable to fixed-combination products will also be applied in the assessment of preparations consisting of different medicinal products in combination packs where the products are intended for simultaneous or sequential administration.

8. CHEMICAL COMBINATIONS AND COMPLEXES

Substances of this type which dissociate prior to absorption into two or more active components may be regarded for the application of the above provisions as fixed combinations of these substances rather than as chemical entities.

COUNCIL DIRECTIVE**of 26 October 1983****amending Directive 65/269/EEC concerning the standardization of certain rules relating to authorizations for the carriage of goods by road between Member States and the First Council Directive of 23 July 1962 on the establishment of common rules for certain types of carriage of goods by road between Member States****(83/572/EEC)****THE COUNCIL OF THE EUROPEAN COMMUNITIES,**

Having regard to the Treaty establishing the European Economic Community and in particular Article 75 thereof,

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

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

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

Whereas the introduction of a multilateral authorization for intra-Community removals carriage by road should ensure more efficient organization of such removals and hence increase the productivity of undertakings specialized in removals;

Whereas Directive 65/269/EEC ⁽⁴⁾, as last amended by Directive 73/169/EEC ⁽⁵⁾, should therefore be amended to include such an authorization;

Whereas the rules on intra-Community removals carriage should be combined in a single Directive; whereas the First Council Directive of 23 July 1962 ⁽⁶⁾, as last amended by Directive 82/50/EEC ⁽⁷⁾, should therefore be amended,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 65/269/EEC is hereby amended as follows:

1. In the first paragraph of Article 2 'or other' is deleted.

2. The following paragraphs are added to Article 2:

'The authorization granted for removals carriage carried out by undertakings having special staff and equipment for the purpose shall be valid for carriage between Member States and in transit through the territory of the Member States.

Such carriage shall not be subject to a quota system.

This provision does not alter the conditions to which each Member State subjects the admission of its own nationals.'

3. The model authorization annexed to this Directive is added to the Annex.

Article 2

Point 4 of Annex II to the First Council Directive of 23 July 1962 is hereby deleted.

Article 3

Member States shall take the measures necessary to comply with this Directive not later than 1 January 1984. They shall forthwith inform the Commission thereof.

Article 4

This Directive is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council
The President
G. MORAITIS

⁽¹⁾ OJ No C 307, 24. 11. 1982, p. 4.
⁽²⁾ OJ No C 277, 17. 10. 1983, p. 161.
⁽³⁾ OJ No C 90, 5. 4. 1983, p. 1.
⁽⁴⁾ OJ No 88, 24. 5. 1965, p. 1469/65.
⁽⁵⁾ OJ No L 181, 4. 7. 1973, p. 20.
⁽⁶⁾ OJ No 70, 6. 8. 1962, p. 2005/62.
⁽⁷⁾ OJ No L 27, 4. 2. 1982, p. 22.

ANNEX

**MODEL AUTHORIZATION
FOR INTERNATIONAL REMOVALS**

(White form — front)
(15 × 21 cm)

(To be worded in the seven official languages of the Community)

Issuing State

(International distinguishing sign)	(Competent agency)
-------------------------------------	--------------------

Period authorization

Authorization No

for international removals

This authorization entitles

.....

.....

(Name or trade name and full address of carrier)

to carry out international removals on routes between Member States of the European Community, by means of a single vehicle or a coupled combination of vehicles, and to run such vehicles unladen throughout the Community.

This authorization is valid from

to

Issued at Date

(Signature and stamp of agency issuing
authorization — State in which vehicle
is registered)

(White form — back)

General conditions

This authorization must be carried on the vehicle and be produced at the request of any authorized inspecting officer.

It authorizes only international removals. It is not valid for national transport.

It is not transferable.

The carrier is required to comply, in the territory of each Member State, with the laws, regulations and administrative provisions of that State, and in particular with those concerning transport and traffic.

COUNCIL DECISION
of 26 October 1983
concerning counter-measures in the field of international merchant shipping
(83/573/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 84 (2) thereof,

Whereas the results of the maritime information system set up under the provisions of Decisions 78/774/EEC ⁽¹⁾, 79/4/EEC ⁽²⁾, 80/1181/EEC ⁽³⁾, 81/189/EEC ⁽⁴⁾ and 82/870/EEC ⁽⁵⁾, together with the experience of certain Member States, show that it would be advisable to define an appropriate Community procedure concerning counter-measures in the field of international merchant shipping in relation to third countries to be taken by the Member States concerned,

HAS ADOPTED THIS DECISION:

Article 1

A Member State which has adopted or intends to adopt counter-measures in the field of international merchant shipping in relation to third countries shall consult the other Member States and the Commission in accordance with the consultation procedure established by Decision 77/587/EEC ⁽⁶⁾.

Article 2

1. The Member States shall endeavour, within the framework of the consultation referred to in Article 1, to concert any counter-measures they may take.

2. The Council may, acting unanimously, decide on the joint application by Member States of appro-

priate counter-measures forming part of their national legislation.

Article 3

When engaging in the consultation referred to in Article 1, Member States should, if appropriate, specify as far as possible the following:

- (a) the developments which have caused counter-measures to be taken;
- (b) the shipping area to which the counter-measure is to apply;
- (c) the nature of the shipping service affected (for example liner traffic);
- (d) the nature of the counter-measures taken or to be taken;
- (e) the duration of the counter-measure;
- (f) the proportionality of the counter-measure to the damage suffered.

Article 4

The Member States shall remain free to apply national counter-measures unilaterally.

Article 5

The Decision is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council

The President

G. MORAITIS

⁽¹⁾ OJ No L 258, 21. 9. 1978, p. 35.

⁽²⁾ OJ No L 5, 9. 1. 1979, p. 31.

⁽³⁾ OJ No L 350, 23. 12. 1980, p. 44.

⁽⁴⁾ OJ No L 88, 2. 4. 1981, p. 32.

⁽⁵⁾ OJ No L 368, 28. 12. 1982, p. 42.

⁽⁶⁾ OJ No L 239, 17. 9. 1977, p. 23.

COUNCIL DIRECTIVE

of 26 October 1983

amending for the third time Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products

(83/574/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

HAS ADOPTED THIS DIRECTIVE:

Article 1

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

Directive 76/768/EEC is hereby amended as follows:

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

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

1. Annex VII, in the form of the Annex hereto, is added. It lists the ultra-violet filters which may be included in cosmetic products under the conditions laid down therein.

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

2. The following items shall be added to Article 4:

Whereas Article 11 of Directive 76/768/EEC ⁽⁴⁾, as last amended by Directive 83/496/EEC ⁽⁵⁾, provides that the Commission shall, on the basis of the results of the latest scientific and technical research, submit to the Council appropriate proposals establishing lists of permitted substances;

‘(g) UV filters other than those listed in Part 1 of Annex VII;

(h) UV filters listed in Part 1 of Annex VII, beyond the limits and outside the conditions laid down therein.’

Whereas, on the basis of the latest scientific and technical research, a list of substances authorized as ultra-violet filters can be established;

3. The following paragraphs shall be added to Article 5:

‘Until 31 December 1988, Member States shall permit the marketing of cosmetic products containing the UV filters listed in Part 2 of Annex VII, within the limits and under the conditions laid down therein.

Whereas the amendments necessary to adapt Annex VII to technical progress must also be adopted in accordance with the procedure of the Committee established by Directive 76/768/EEC;

On 1 January 1989, these UV filters shall be:

- definitively permitted (Part 1 of Annex VII),
- definitively prohibited (Annex II),
- retained in part 2 of Annex VII for a specified period, or
- deleted from all Annexes.’

Whereas the indication of the expiry date for cosmetic products whose period of stability is less than three years, provided for in Article 6 (1) (c) of Directive 76/768/EEC, is not justified in the case of cosmetic products which may still be used after that period; whereas indication of the date of minimum durability is therefore more appropriate,

4. Paragraph 1 (c) of Article 6 shall be replaced by:

‘(c) the date of minimum durability. The date of minimum durability of a cosmetic product shall be the date until which this product, stored under appropriate conditions, con-

⁽¹⁾ OJ No C 32, 9. 2. 1982, p. 2.

⁽²⁾ OJ No C 307, 14. 11. 1983, p. 105.

⁽³⁾ OJ No C 310, 30. 11. 1981, p. 5.

⁽⁴⁾ OJ No L 262, 27. 9. 1976, p. 169.

⁽⁵⁾ OJ No L 275, 8. 10. 1983, p. 20.

tinues to fulfil its initial function and in particular remains in conformity with Article 2.

It shall be indicated by the words 'Best used before the end of ...' followed by:

- either the date itself
- or an indication of where it appears in the labelling.

If necessary, this information shall be supplemented by an indication of the conditions which must be satisfied to guarantee the stated durability.

The date shall be clearly expressed and comprise the month and the year, in that order. Indication of the date of durability shall not be mandatory for cosmetic products the minimum durability of which exceeds 30 months;

5. (a) In Article 6 (1) (d), 'Annexes III, IV and VI' is replaced by 'Annexes III, IV, VI and VII';
- (b) In the first subparagraph of Article 8 (2), 'Annexes II to VI' is replaced by 'Annexes II to VII';
- (c) In the second subparagraph of Article 8 (2), 'Annexes III to VI' is replaced by 'Annexes III to VII'.

Article 2

1. Member States shall take all measures necessary to ensure that, with effect from 1 January 1987,

neither manufacturers nor importers established in the Community place on the market products which do not meet the requirements of this Directive.

2. Member States shall adopt all measures necessary to ensure that the products referred to in paragraph 1 are not sold or disposed of to the final consumer after 31 December 1988.

Article 3

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 31 December 1984 at the latest. They shall forthwith inform the Commission thereof.
2. Member States shall ensure that they communicate to the Commission the text of such provisions of national law as they adopt in the field governed by this Directive.

Article 4

This Directive is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council
The President
G. MORAITIS

ANNEX

ANNEX VII

List of UV filters which cosmetic products may contain

For the purposes of this Directive, UV filters are substances which, contained in cosmetic sun-screen products, are specifically intended to filter certain UV rays in order to protect the skin from certain harmful effects of these rays.

These UV filters may be added to other cosmetic products within the limits and under the conditions laid down in this Annex.

Other UV filters used in cosmetic products solely for the purpose of protecting the product against UV rays are not included in this list.

PART 1

List of permitted UV filters which cosmetic products may contain

Reference No	Substances	Maximum authorized concentration	Other limitations and requirements	Conditions of use and warnings which must be printed on the label
a	b	c	d	e
1	4-Aminobenzoic acid	5 %		
2	<i>N,N,N</i> -Trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulphate	6 %		
3	Homosalate (INN)	10 %		
4	Oxybenzone (INN)	10 %		Contains oxybenzone ⁽¹⁾
5	3-Imidazol-4-ylacrylic acid and its ethyl ester	2 % (expressed as acid)		
6	2-phenylbenzimidazole-5-sulphonic acid and its potassium, sodium and triethanolamine salts	8 % (expressed as acid)		

⁽¹⁾ Not required if concentration is 0,5 % or less and when it is used only for product protection purposes.

PART 2

List of UV filters which cosmetic products may provisionally contain

Reference No	Substances	Maximum authorized concentration	Other limitations and requirements	Conditions of use and warnings which must be printed on the label
a	b	c	d	e
1	Ethyl-4- <i>bis</i> (hydroxypropyl) aminobenzoate, mixed isomers	5 %		
2	Ethoxylated 4-aminobenzoic acid	10 %		
3	Padimate (INN)	5 %		Contains padimate (!)
4	Glycerol 1-(4-aminobenzoate)	5 %	Free from benzocaine (INN)	
5	2-Ethylhexyl 4-dimethylaminobenzoate	8 %		
6	2-Ethylhexyl salicylate	5 %		
7	3,3,5-Trimethylcyclohexyl-2-acetamidobenzoate	2 %		
8	Potassium cinnamate	2 %		
9	4-Methoxycinnamic acid salts (potassium, sodium and diethanolamine salts)	8 % (expressed as acid)		
10	Propyl 4-methoxycinnamate	3 %		
11	Salicylic acid salts (potassium, sodium and triethanolamine salts)	2 % (expressed as acid)	The pH of the finished product shall be such that the acid is not liberated	Not to be used for children under three years of age
12	Amyl 4-methoxycinnamate, mixed isomers	10 %		
13	2-Ethylhexyl 4-methoxycinnamate	10 %		
14	Cinoxate (INN)	5 %		
15	3,4-Dihydroxy-5-(3, 4, 5-trihydroxybenzoyloxy) benzoic acid, trioleate	4 %		
16	Mexenone (INN)	4 %		Contains mexenone (!)

(!) Not required if concentration is 0,5 % or less and when it is used only for product protection purposes.

Reference No	Substances	Maximum authorized concentration	Other limitations and requirements	Conditions of use and warnings which must be printed on the label
a	b	c	d	e
17	Sulisobenzone (INN) and sulisobenzone sodium (INN)	5 % (expressed as acid)		
18	2-Ethylhexyl 2-(4-phenylbenzoyl)-benzoate	10 %		
19	5-Methyl-2-phenylbenzoxazole	4 %		
20	Sodium 3,4-dimethoxyphenylglyoxylate	5 %		
21	1,3-bis (4-methoxyphenyl) propane-1,3-dione	6 %		
22	5-(3,3-Dimethyl-8,9,10-trinorborn-2-ylidene) pent-3-en-2-one	3 %		
23	alpha'-(2-Oxoborn-3-ylidene)-p-xylene-2-sulphonic acid	6 %		
24	alpha-(2-Oxoborn-3-ylidene) toluene-4-sulphonic acid and its salts	6 % (expressed as acid)		
25	3-(4-Methylbenzylidene) bornan-2-one	6 %		
26	3-Benzylidenebornan-2-one	6 %		
27	alpha-Cyano-4-methoxycinnamic acid and its hexyl ester	5 %		
28	1-p-Cumenyl-3-phenylpropane-1,3-dione	5 %		
29	4-Isopropylbenzyl salicylate	4 %		
30	Cyclohexyl 4-methoxycinnamate	1 %		
31	1-(4-tert-Butylphenyl)-3-(4-methoxyphenyl) propane-1,3-dione	5 %		

COUNCIL DIRECTIVE**of 26 October 1983****amending Directive 71/316/EEC on the approximation of the laws of the Member States relating to common provisions for both measuring instruments and methods of metrological control****(83/575/EEC)**

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 ⁽¹⁾,

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

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

Whereas the purpose of Directive 71/316/EEC ⁽⁴⁾ is to ensure the free movement of measuring instruments within the Community by harmonizing the divergent national laws relating to metrological control and by establishing for this purpose adequate EEC pattern approval and initial verification procedures and EEC methods of metrological control;

Whereas the experience gleaned in recent years in the measuring instrument sector makes it necessary to amend certain Articles of the said Directive;

Whereas the methods of control applied at present make it possible for EEC initial verification to be carried out differently from the unit checking of instruments;

Whereas it was not possible for Directive 71/316/EEC, when it was adopted, to take these developments into account; whereas, since then, certain Member States have incorporated provisions into their national laws which take account of these developments;

Whereas it is advisable, in consequence, to amend and supplement the text of the European provisions currently in force in order to be able to harmonize the national laws adopted for that purpose,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 71/316/EEC is hereby amended as follows:

1. Article 1 is replaced by the following:

'Article 1

1. (a) This Directive applies to goods referred to as instruments, which include measuring instruments, components of measuring instruments, additional devices and measurement equipment.
- (b) This Directive also applies to units of measurement, the harmonization of methods of measurement and metrological control and, where appropriate, the means required for application of such methods.
- (c) It also applies to the prescription, methods of measurement, metrological control and marking of quantities of prepackaged products.

2. No Member State may, on the basis of this Directive and the separate directives relating to it, prevent, prohibit, or restrict the placing on the market and/or entry into service of an instrument or of a product described in paragraph 1 if that instrument or product bears EEC marks and/or signs in accordance with the conditions laid down by this Directive and by the separate directives relating to the instrument or product in question.

3. Member States shall attach the same value to EEC pattern approval and initial verification as to the corresponding national measures.

4. The separate directives concerning the subjects referred to in paragraph 1 shall specify:

— in particular, the measurement procedures and characteristics of, and the technical requirements for, their design and function-

⁽¹⁾ OJ No C 42, 15. 2. 1979, p. 9.

⁽²⁾ OJ No C 127, 21. 5. 1979, p. 80.

⁽³⁾ OJ No C 247, 1. 10. 1979, p. 22.

⁽⁴⁾ OJ No L 202, 6. 9. 1971, p. 1.

ing, as regards the products referred to in paragraph 1 (a),

- the requirements concerning paragraph 1 (b) and (c).

They may fix the date on which the existing national provisions are to be replaced by Community provisions.'

2. Article 2 is replaced by the following:

'Article 2

1. EEC pattern approval of instruments constitutes their admission to EEC initial verification and, where the latter is not required, the authorization to place them on the market and/or to put them into service. If the separate directive(s) applicable to a category of instruments exempt(s) that category from EEC pattern approval, the instruments in that category shall be admitted directly to EEC initial verification.

2. If their inspection equipment so permits, Member States shall grant EEC pattern approval for every instrument which satisfies the requirements laid down in this Directive and the separate directives relating to the instrument in question.

3. An application for EEC pattern approval may be made only by the manufacturer or his representative established within the Community. For one and the same instrument, application may be made in one Member State only.

4. A Member State which has granted EEC pattern approval shall take the necessary steps to ensure that it is kept informed of any modification or addition to the approved pattern. It shall inform the other Member States of such alterations.

Modifications or additions to an approved pattern must receive additional pattern approval from the Member State which granted EEC pattern approval, where such changes influence or might influence measurement results or the prescribed conditions for use of the instrument.

However, in the case of a modified pattern, a new EEC pattern approval shall be granted instead of an addition to the original EEC pattern approval certificate, if the pattern is modified after the provisions of this Directive or of the relevant special directive have been amended or adapted in such a way that the modified pattern could be approved only pursuant to the new provisions.

5. Member States shall grant EEC pattern approval in accordance with the provisions of this Directive and of the relevant separate directives.'

3. Article 4 is replaced by the following:

'Article 4

When an instrument has successfully completed the EEC pattern approval examination laid down in this Directive and in the separate directives relating to it, the Member State which carried out that examination shall draw up an EEC pattern approval certificate and forward it to the applicant. In the cases provided for in Article 11 or in a separate directive, the applicant must, and in all other cases he may, affix or cause to be affixed on each instrument conforming to the approved pattern the EEC approval sign shown in this certificate.'

4. Article 5 is replaced by the following:

'Article 5

1. EEC pattern approval shall be valid for 10 years. It may be extended for successive periods of 10 years; the number of instruments which may be manufactured in accordance with the approved pattern shall not be limited.

EEC pattern approvals granted on the basis of the provisions of this Directive and of a separate directive may not be extended after the date of the entry into force of any amendment to, or adaptation of, these Community provisions, in cases where such EEC pattern approvals could not have been granted on the basis of these new provisions.

When EEC pattern approval is not extended, this approval shall nevertheless continue to apply to EEC instruments already in service.

2. Where use is made of new techniques not provided for in a separate directive, EEC pattern approval with limited effect may be granted, after prior consultation of the other Member States.

It may include the following restrictions:

- limit on the number of instruments which may be covered by the approval,
- obligation to notify the competent authorities of the places of installation,

- restrictions on use,
- special restrictions concerning the technique used.

However, it may not be granted unless:

- the separate directive for that category of instruments has come into force,
- no derogation has been made from the maximum permissible errors laid down in the separate directives.

The period of validity of such approval shall not exceed two years. It may be extended by up to three years at most.

3. The Member State which has granted the limited EEC pattern approval referred to in paragraph 2 shall apply for adjustment to technical progress of the Annexes to this Directive, where appropriate, and of the separate directives, in accordance with the procedure set out in Article 18, as soon as it considers that a new technique has proved to be satisfactory.'

5. Items 3.3 and 6.3 of Annex I are replaced by the following:

'3.3. The sign mentioned in Article 6 of this Directive is the same as the EEC approval sign, except that the stylized letter E is reversed symmetrically about a vertical axis and bears no other indication unless the separate directives stipulate otherwise.

An example of this sign is shown in item 6.3.'

'6.3. Sign of exemption from EEC pattern approval (see item 3.3)

Example: 

6. (a) In Article 7 (1) (b), 'Article 5 (2) and (3)' is replaced by 'Article 5 (2)'.

(b) The following point (c) is added to Article 7 (1):

'(c) if it ascertains that approval was granted in an improper manner.'

7. (a) Article 8 (1) is replaced by the following:

'1. (a) EEC initial verification constitutes the examination of a new or reconditioned instrument and the confirmation of its conformity to the approved pattern and/or to the

requirements of this Directive and the separate directives relating to the instrument in question; it is certified by the EEC initial verification mark.

- (b) EEC initial verification of instruments may be carried out by a method other than unit checking in the cases specified in the separate directives and in accordance with the procedures adopted.'

(b) In Article 8 (3), 'Article 1 (1)' is replaced by 'Article 1 (2)'.

8. Article 9 is replaced by the following:

'Article 9

1. When an instrument is submitted for EEC initial verification, the Member State carrying out the examination shall determine:

- (a) whether the instrument belongs to a category exempt from EEC pattern approval and, if so, whether it satisfies the technical construction and functioning requirements laid down by the separate directives relating to that instrument;
- (b) whether the instrument has received EEC pattern approval and, if so, whether it conforms to the approved pattern, and to the separate directives relating to that instrument, in force on the date of issue of this EEC pattern approval.

2. The examination carried out in EEC initial verification relates in particular, in accordance with the separate directives, to:

- the metrological characteristics,
- the maximum permissible errors,
- the construction, in so far as this guarantees that the measurement characteristics are not likely to deteriorate to any great extent under normal conditions of use,
- the presence of prescribed inscriptions and stamp plates or provisions for EEC verification marking.'

9. Article 10 is replaced by the following:

'Article 10

When an instrument has successfully undergone EEC initial verification, in accordance with the requirements of this Directive and of the separ-

ate directives, the EEC partial or final verification marks described in Annex II to this Directive shall be affixed to that instrument under the responsibility of the Member State in accordance with the rules laid down in that Annex.'

10. Article 13 is replaced by the following:

'Article 13

Each Member State shall notify the other Member States and the Commission of the services, agencies and institutes which are duly authorized to carry out the examinations specified in this Directive and in the separate directives, to issue the EEC pattern approval certificates and to affix the EEC initial verification marks.'

11. Article 15 is replaced by the following:

'Article 15

The separate directives shall specify the control requirements for instruments in service which bear EEC signs or marks and in particular the maximum errors permitted in service. If national provisions on instruments which do not bear EEC signs or marks lay down less stringent requirements, the latter may serve as criteria for the controls.'

12. Chapter VI is repealed and Chapter VII becomes Chapter VI and reads as follows:

'CHAPTER VI

Adjustment of directives to technical progress

Article 16

The amendments necessary for adjusting to technical progress the Annexes to this Directive and the Annexes to the separate directives referred to in Article 1 shall be adopted in accordance with the procedure laid down in Article 18. However, this procedure shall not apply to the chapter relating to imperial units of measurement of the Annex to the Directive on units of measurement and the Annexes, concerning quantity ranges for pre-packed quantities of products, to the directives on pre-packed products.

Article 17

1. A Committee for adjustment to technical progress of the Directives referred to in

Article 16 (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 18

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. Opinions shall be adopted by a qualified majority 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.'

13. The title 'Chapter VIII' is replaced by 'Chapter VII' and Articles 20, 21 and 22 become Articles 19, 20 and 21, respectively.

14. In Article 19, 'prohibiting sale or use' is replaced by 'prohibiting the placing on the market or entry into service'.

Article 2

Member States shall put into force the laws, regulations and administrative provisions needed in order to comply with this Directive by 1 January 1985. They shall forthwith inform the Commission thereof.

Article 3

This Directive is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council
The President
G. MORAITIS
