COMMISSION OF THE EUROPEAN COMMUNITIES

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REPORT ON THE APPROXIMATION OF THE LAWS
RELATING TO PROPRIETARY MEDICINAL PRODUCTS

Proposal for a

COUNCIL DIRECTIVE

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

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Proposal for a

COUNCIL RECOMMENDATION

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

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(submitted by the Commission to the Council)

REPORT ON THE APPROXIMATION OF THE LAWS RELATING TO PROPRIETARY MEDICINAL PRODUCTS

1. The purpose of this report is to present the Commission's proposals and guidelines in the field of proprietary medicinal products in an overall framework. The two main lines of action of the Community work are to facilitate access to the market in order to create a large open market and to improve its operation in order to create a transparent and orderly market.

I. A large open market

1. The results achieved

2. Four Council Directives and one Council Decision, with the aim of abolishing barriers to the free movement of medicinal products, have been adopted. In abolishing these barriers, public health safeguards have been developed on two levels: that of the conception of the product and that of its manufacture.

3. The first safeguard for the proper conception of a medicinal product consists in the tests to be carried out and the principles to be followed during these trials.

   The second safeguard is the adoption of a system of prior authorization, this being subject to three fundamental conditions: the quality, harmlessness and therapeutic effect of the medicinal product.

4. The safeguards relating to good manufacture are based firstly on a manufacturing authorization issued in the light of conditions concerning premises, plant and staff, then on the compulsory presence of a qualified person in charge of manufacture and control tests and, lastly, on inspections carried out in manufacturing establishments.

5. Now that these safeguards have been developed, it has been possible to do away with systematic checks upon imports from one Member State to another; irrespective of the place of production in the Community, medicinal products are manufactured and tested in accordance with the same rules and under the supervision of persons with equivalent qualifications.

(1)

Nevertheless, marketing authorizations have remained a national matter. In order to obviate divergent decisions as far as possible, cooperation between competent authorites has taken place within a Committee for Proprietary Medicinal Products (hereinafter referred to as the CPMP).

6. Lastly, a Pharmaceutical Committee has been set up in order to provide the Commission with appropriate advice in the field of proprietary medicinal products.

2. The inadequacies noted

7. Generally speaking, the implementation of the Directives is satisfactory. All the Member States have introduced the system of prior authorization into their laws and only certain particular points of certain national laws have to be rectified. The Commission is dealing with this, as provided for in Article 169 of the Treaty of Rome, in relation to Belgium, Luxembourg and Italy.

8. The requirements of a unified market have not always been fully taken into account in the Directives already adopted. Provisions which are satisfactory in a national market may be unsuitable or inadequate in a common market.

   Since persons as well as goods circulate more and more on Community territory, it is important for public health that the same names should cover the same products, except where there are legitimate grounds to the contrary.

   Similarly, it is not enough for a competent authority to be aware of the marketing authorizations granted by the other Member States. It should also know what has been authorized and under what conditions.

   Finally, provisions which hamper trade between Member States must be kept to the minimum necessary for the protection of public health while provisions designed to guarantee the homogeneousness of the experimental work in the various Member States must be promoted and the alignment of decisions by the national authorities improved.

9. There is a third category of inadequacy which results from the very provisions which have been adopted or at least from the little use which has been made of them, i.e. the CPMP procedure for the marketing of proprietary medicinal products. By the beginning of September 1980, i.e. over a period of nearly

four years, only eight applications had been filed under this procedure. There has been, however, a tendency for the number of applications to increase during recent months which no doubt means that the circles concerned have been better informed.

Nevertheless, the pharmaceutical industry has reservations with regard to this procedure. Fundamentally, it considers that the existing procedure is not at all appropriate to the aim pursued and should be replaced by a system of mutual recognition. During an interim period, the present system could be modified in respect of two main points: the conditions for initiating the procedure are too restrictive; the applicant does not have any opportunity to be heard during the procedure.

The Consumers' Consultative Committee, or rather one of its working parties, also considers the present procedure to be unsuitable; in its opinion, the CPMP does not have sufficient powers to be able to work effectively. It is completely opposed to the recognition of authorizations and hopes for the gradual transformation of the CPMP into a European registration bureau.

3. The improvements and additions proposed

10. In view of the problems mentioned above and after extensive consultations with all the parties concerned, the Commission has adopted the following positions:

- the provisions of Directives 65/65/EEC and 75/318/EEC must be brought up to date and supplemented in order to keep pace with the progress of science and to take better account of the requirements of a single market;

- Chapter III of Directive 75/319/EEC setting up the Committee for Proprietary Medicinal Products as provided for by Article 15(2) of the aforementioned Directive should be amended; under present market conditions and in the absence of strong reasons based on public health, the setting up of a European body for the issue and revocation of marketing authorizations does not appear to be advisable nor does the extension of the present system, which is widely criticized and therefore has to be abandoned; recognition of authorizations seems to be the simplest and most effective solution: a medicine manufactured and marketed in one Member State on the basis of harmonized provisions must, in principle, be allowed on the market of any other Member State, disputed cases being submitted to the Committee for Proprietary Medicinal Products for an opinion;

- the principles to be followed when implementing the provisions of Directive 75/318/EEC relating to the standards and protocols applicable to the testing of proprietary medicinal products should be determined in order to promote the alignment of national decisions; a Council Recommendation appears to be the most appropriate means of keeping up with developments in science and technology and of taking into account the importance of protecting the patient and of pharmaceutical research.

II. A transparent and orderly market

11. Owing to the approximation of national laws and conceptions, the marketing of medicinal products no longer constitutes the barrier it did in the past. Other barriers consequently take on greater significance with regard to the proper functioning of the market. It is therefore of crucial importance that the Community use the powers of supervision conferred on it by the Treaty and take the necessary harmonization measures.

1. Prices

12. The problems of medicine prices and reimbursement by the social security organizations are major barriers to free movement. The fixing of prices that are too low or the debarring of a medicine from reimbursement constitute just as effective a barrier as the refusal of a marketing authorization.

With regard to supervision, the thinking of the Commission and the case law of the Court of Justice, having regard to the implementation of Articles 30 - 36 of the Treaty, are clear. The Treaty basically leaves completely intact the power of Member States to take appropriate measures with regard to price formation; at the same time, however, Article 30 is violated when a price system does not permit either a producer or a Community importer to sell his product on the market of that Member State at a remunerative price. Measures have already been taken and others are in preparation.

But it is equally necessary to overcome the present dichotomy whereby medicines and social security, consumer protection and growth in consumption are brought into conflict by outline measures and guidelines intended to improve competition by way of prices. Greater competition could only facilitate the reform of the social security systems.

It should be remembered in this context that the proposal for a Directive sent to the Council on 2 June 1980 aims at establishing a harmonized system for the registration of parallel importers of proprietary medicinal products. In particular, it proposes the prohibition of artificial distinctions between products in the various Member States brought about either by therapeutically unwarranted adjustments in composition or by changes in the name of the product without legitimate reasons.

The Commission will continue its efforts to establish a transparent and orderly market in which price could play the regulation role proper to it.

2. Advertising

13. Advertising is an important means of penetrating markets as well as being an instrument for the information of doctors and consumers. In a first approach the Commission attempted to harmonize the differences between the relevant national laws. It has proved impossible to find a common solution for the regulation of advertising: the preventive system (prior authorization), the repressive system (a porteriori penalty cases of infringement) and the system of self-regulation (voluntary code of conduct) seem to operate to the satisfaction of those acquainted with them.

In a second approach the Commission attempted to bring into line the principles determining the content of advertising. But it quickly emerged that these common principles constituting, as it were, base-level provisions could not have any consequences from the point of view of the movement of products or competition, since each Member State would have remained free to add to these provisions.

The advantage of these lengthy discussions in the first instance was to stimulate some hard thinking on the part of the various circles involved (authorities, industry, professional groupings etc.) and subsequently to show that a proposal for a Directive could not, in view of this situation, constitute real progress.

In addition, it should be remembered that there already is a proposal for a Directive on misleading and unfair advertising, which lays down the general basis for consumer protection.

In these circumstances, the Commission does not think it advisable to make a specific proposal on proprietary medicinal products.

3. The future

14. The economic, technical and financial problems, important as they are, must not be allowed to monopolize our attention. Research is the driving force of the pharmaceuticals industry and, according to a recent report, "biology and genetics are certain to play an increasingly important role in the manufacture of certain substances having a therapeutic action".

With regard to research, the Commission sent to the Council on 22 January 1980 a proposal for a five-year programme of indirect-action research in the field of biomolecular engineering. On 4 August 1980, it sent to the Council a proposal recommending to the Member States the registration of work on deoxyribonucleic acid (DNA) recombination.

It is time to think about the legal and regulatory consequences of the transposition of this research to the industrial stage, in particular its use in therapy.

15. Finally we should foster an awareness outside the Community of the guarantee conferred by this gradual and flexible process of harmonization. It constitutes a kind of European quality label which will henceforth be attached to all our products, and we should ensure that this has its effects at the level of international trade.

PROPOSAL FOR A COUNCIL DIRECTIVE

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

Summary

The purpose of this proposal is twofold:

- to bring up to date the Directives adopted in 1965 and 1975 in the field of proprietary medicinal products;

- to amend the procedure of the Committee for Proprietary Medicinal Products and introduce the principle of the recognition of marketing authorizations.

Explanatory memorandum

I. General considerations

1. This proposal by the Commission has a twofold aim:

   - firstly, to amend the procedure of the Committee for Proprietary Medicinal Products (CPMP) with a view to attaining the free movement of these products;

   - secondly, to amend and supplement the Directives already adopted on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products with a view to bringing them up to date.

2. As provided for in Article 15(2) of Directive 75/319/EEC, "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".

   Experience has shown that the barriers to free movement connected with the system of national marketing authorizations have not been substantially overcome by the Committee for Proprietary Medicinal Products (CPMP) procedure set up under Chapter III of the above-mentioned Directive.

3. The four years during which the CPMP procedure has operated adequately demonstrate the industry's reservations towards it.

   The procedure itself, as laid down in Directive 75/319/EEC, is certainly under fire. It should therefore be improved, especially with regard to two main points, according to the industry itself: the conditions for initiating the procedure must be made less restrictive and the applicants must have the opportunity to be heard during the procedure.

4. However, in addition to the procedure, it seems that the system itself is under fire.

   The pharmaceutical industry considers that the present procedures cannot be deemed in any way appropriate to the aim pursued. Mutual recognition, already adopted in many fields, is the only system it can accept.

   On the other hand, the consumers consider that recognition, like the present procedures, cannot lead to a common European policy for proprietary medicinal products. Only a system of Community authorizations issued by a European agency is compatible with this aim.

   The authorities of the Member States, which were consulted on various occasions within the Pharmaceutical Committee, were unable to reach a common position - although the majority were in favour - on the recognition of marketing authorizations in the fairly near future.

5. Bearing in mind these differing attitudes and the work of the Committee for Proprietary Medicinal Products, the Commission considers that merely improving the present procedure would not fundamentally alter the problems and would be contrary to the letter and the spirit of Article 15(2) of Directive 75/319/EEC.

   The Community authorization solution is, of course, very tempting as far as principles are concerned, but appears to be extreme in the present situation. The setting up of a European body with very highly qualified scientific experts, a large administrative staff and perhaps research laboratories needed by those experts would be prohibitive from the point of view of cost, all the more so since this European body would have to operate concurrently with the national bodies for an indefinite period.

   Even without considering the political, legal and material problems which would be involved in a solution of this kind, the financial burden of such a venture seems to be enormous compared with that of the present situation and the results which may be expected of it.

6. The Commission therefore proposes that recognition of marketing authorizations issued by the national authorities on the basis of harmonized provisions be introduced. A proprietary product manufactured and marketed in one State in accordance with the harmonized regulations must, with certain exceptions, be allowed on the markets of the other Member States.

In disputed cases, the CPMP shall be called upon to give an opinion.

Such, in brief, is the economic aspect of the proposal for the gradual achievement of the free movement of proprietary medicinal products.

The provisions intended to update and supplement the Directives already adopted will be dealt with one Article at a time in the commentary.

II. Commentary on the Articles

Article 1

7. The purpose of this Article is to amend Council Directive 65/65/EEC.

The chief amendment concerns the introduction of the data sheet (paragraphs 2 and 3) which is a sort of photograph of the authorized proprietary medicinal product. In other words, this is a document which provides a synthesis of the product's qualities and defects such as they have been recognized by the competent authorities.

This sheet should enable the competent authorities to keep track, in a summarized form, of what has been authorized.

It should enable manufacturers to know exactly what information they can impart in their communications to the general public and the professional circles concerned.

Owing to their changing nature, the economic particulars referred to in paragraph 3.8 have not been made compulsory. Nevertheless, it would appear useful to concentrate, as far as possible in the same place, all particulars concerning proprietary medicinal products whether medical, administrative or economic.

8. The other amendments do not call for any particular comment except that concerning Article 13.1. Regular mention of the international non-proprietary name recommended by the World Health Organization after the special name seems to be absolutely necessary to ensure at least some transparency in the medicines' market. For doctors and pharmacists it is the essential means of recognizing the real identity of products which appear under so many special names. This is, therefore, a fundamental provision from the point of view of health and competition.

Article 2

9. The purpose of this Article is to amend Directive 75/318/EEC.

The essential aim of the amendments relating to Part 1 of the Annex to the Directive (physico-chemical, biological or microbiological tests) is to clarify and define certain points.

10. On the other hand, the principle of the bioavailability and mutagenesis studies has been introduced as a result of progress in scientific knowledge. The bioavailability study provides information on the rate at which and in what proportions a medicine's active principle or fraction thereof reaches the site where its action should occur when the medicine is administered in a particular pharmaceutical form.

Mutagenesis concerns the changes in the genetic material of individuals or cells which are spontaneous or caused by chemical products or radiations and which result in the following generations differing abruptly from those which preceded them in a permanent and hereditary way. All present scientific knowledge in this field is based on the hypothesis that many chemical products possess much mutagenic properties and it is therefore necessary to identify and limit the diffusion of these products in the human environment. Any new therapeutic substance which contains new excipients and new active principles and to which extensive exposure is forecast must be tested for mutagenicity.

The tests involved and those for bioavailability will be conducted according to the principles expounded in Commission Recommendations.

Article 3

11. This Article amends Chapter III of Directive 75/319/EEC relating to the Committee for Proprietary Medicinal Products.

The previous system, which made the CPMP, to which reference was made from the very beginning, the hub of marketing authorization, is replaced by that of the recognition of the initial authorization which mainly concerns the manufacturer and the Member States to which he submits his application. The CPMP is simply informed and it steps in to give an opinion only in exceptional cases where recognition might be disputed.

12. The previous Article 8, which defined the role of the CPMP, is amended in respect of two points; the aim of the mutual recognition of authorizations is introduced and the CPMP's role is explained: it examines any question concerning the quality, safety and efficacy of a specific medicinal product or of a group of medicinal products.

13. The principle of recognition and the procedures for the application for recognition are laid down in Article 9. In order to make this application, the proprietary product in question needs only to have obtained a marketing authorization in another Member State. Under the previous system, not only was this initial authorization necessary to set the CPMP in motion but, in addition, a request had to be made for the product to be marketed in at least five other Member States.

14. The cases of referral to the Committee are laid down in the new Articles 10, 11 and 12.

- where an authority does not recognize the authorization (Article 10);
- where national decisions clash (Article 11);
- where, before taking a decision, an authority wishes to have the opinion of the CPMP concerning a problem of Community interest (Article 12).

15. Recognition is normally obtained within a fixed period of 120 days. This period is relatively long, bearing in mind the considerable work on the re-examination of old products at the expense of the authorities pursuant to Article 39(2) of Directive 75/319/EEC and bearing in mind the fresh tasks entrusted to the national authorities pursuant to the new Article 13 and the possibilities of shortening this period provided for in Article 15(2).

16. Thus, as soon as the Directive (Article 4) enters into force, the period of 120 days will be reduced to 60 in the case of the proprietary medicinal products referred to in Article 13(1). These are proprietary products containing a new active substance, i.e. one which is the subject of an application for marketing authorization for the first time in the Member State concerned. This new procedure is thus intended for new products rather than for old ones already sold on the various markets.

Compliance with this shorter period is facilitated by the existence of assessment reports on the results of tests drawn up by at least one Member State; these reports constitute, so to speak, the statement of the reasons justifying the grant of the authorization. At first sight, it may seem paradoxical to reserve this rapid procedure for new products which, by definition, are less well known than the old products. Nevertheless, the latter are the subject of national re-assessments (cf. Article 39(2) of Directive 75/319/EEC) which take into consideration experimental data and published particulars (cf. Article 4, item 8, 2nd subparagraph) that are often difficult to assess.

On the other hand, new products have been the subject of thorough experimentation in accordance with common principles which comply with the state of the art in science and which are expounded in explanatory notes concerning the tests concerned with the marketing of proprietary medicinal products. This experimental work has been carefully assessed by the competent authorities of at least one Member State which have provided all the justifications for their decision. Better knowledge of the medicine in question will be obtained not so much from a fresh administrative examination of the same data as from monitoring the product after it has been marketed.

Furthermore, the assessment report shall be supplemented, where necessary, by particulars stemming from drug-monitoring systems, for example (Article 13(3)), i.e. by information on the adverse reactions to medicinal products obtained after they have been marketed.

17. Article 14 contains the rules of procedure which apply when a matter is referred to the CPMP. Compared with the previous rules, there is a change of form, in so far as the rules which were previously dispersed over several Articles are gathered together here, and of substance. The person responsible for placing a product on the market may explain himself verbally or in writing before the CPMP, a prodedure which was strongly requested by the industry.

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

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

Having regard to the proposal from the Commission;

Having regard to the Opinion of the European Parliament;

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

Whereas the 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 entry into force;

Whereas Council Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (1) provides in Article 15(2) 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 above-mentioned Directive;

Whereas it is necessary from the point of view of public health and the free movement of products that the competent authorities, manufacturers and consumers may have readily at their disposal all useful information on authorized proprietary products, in particular by means of data sheets and appropriate labelling;

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

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(1) OJ L 147, 9.6.1975

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 on the market of any other Member State by virtue of the recognition of the initial authorization, save in exceptional cases subject to the opinion of the Committee for Proprietary Medicinal Products,

HAS ADOPTED THIS DIRECTIVE:

ARTICLE 1

Council Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (1) shall be amended as follows:

(1) Article 4 shall be amended thus:

(a) Point 6: the words "if less than three years" shall be deleted.

(b) Point 8(a) of the English version: the words "published references" shall be replaced by "published data".

(2) The following Article 4a shall be inserted after Article 4:

"The application referred to in Article 4 shall also be accompanied by a data sheet which shall contain the following information:

1. Name of the proprietary product;
2. International non-proprietary name recommended by the World Health Organization, where such name exists, of each active principle; or failing this, the generic name or chemical description;
3. Pharmaceutical form;
4. Pharmacological properties and, insofar 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 gravity)
   - 5.4 special precautions for use
   - 5.5 use during pregnancy and lactation
   - 5.6 interaction with other medicaments and other interactions
   - 5.7 posology and method of administration
   - 5.8 overdose (symptoms, emergency procedures, antidotes)
   - 5.9 special warnings.

(1) OJ 22, 9.2.1965

6. Pharmaceutical particulars:

6.1 qualitative and quantitative composition in active principles

6.2 constituents of the excipient which must be known in order to permit correct administration of the medicinal product

6.3 major incompatibilities

6.4 shelf life

6.5 special precautions for storage

6.6 contents of container

6.7 name or style and permanent address or registered place of business of manufacturer".

(3) The following Article 4b shall be inserted after Article 4a:

"The competent authorities of the Member States shall take all necessary measures to ensure that the contents of the data sheet are in conformity with those accepted when the authorization is issued or subsequently. In addition, the data sheet referred to in Article 4a shall be supplemented by the following information:

7. Administrative particulars:

7.1 marketing authorization number

7.2 conditions of sale to the public

7.3 date on which data sheet was drawn up and date of its last revision.

Moreover, the data sheet may be supplemented by the following information:

8. Economic particulars:

8.1 selling price to the public of the various sizes of packs

8.2 cost of daily treatment

8.3 situation in respect of health insurance."

(4) Article 5, paragraph 2, shall be amended thus:

"Authorization shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Articles 4 and 4a."

(5) The following Article 9a shall be inserted after Article 9:

"After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the control method provided for in Article 4, point 7, take account of technical and scientific progress and introduce any changes that may be required to enable the proprietary medicinal product to be more reliably checked."

(6) Article 10 shall be amended thus:

"An authorization shall be valid for five years and shall be renewed for five-year periods on application by the holder at least three months preceding expiry."

(7) Article 11, paragraph 2, shall be amended thus:

"An authorization shall also be suspended or revoked where the particulars supporting the application as provided for in Articles 4 and 4a are found to be 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 the 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 have not been carried out."

(8) Article 13, points 1, 2 and 7, shall be amended thus:

"1. Name of the proprietary product which may be a brand name, or a common name together with a trade mark or name of the manufacturer, or a scientific name together with a trade mark or name of the manufacturer.

Where the special name of a medicinal product containing only one active principle is a brand name, this name must in all cases be followed by the international non-proprietary name, in legible characters, recommended by the World Health Organization where such name exists."

"2. A statement of the active principles expressed qualitatively and quantitatively per dosage unit or as a percentage, according to the pharmaceutical form, using the international non-proprietary names where such names exist."

"7. Expiry date in plain language."

ARTICLE 2

The Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products[1] shall be amended as follows:

(1) In Part 1, C1, the seventh paragraph shall be replaced by the following text:

" The routine tests to be carried out on each batch of starting materials must be stated in the application for marketing authorization, with proof that each batch of starting materials meets the quality requirements of the monograph of the pharmacopoeia concerned."

The eighth paragraph shall be supplemented thus:

"They shall inform the responsible authorities which pharmacopoeia is referred to."

(2) In Part 1, C, the following paragraph 3 shall be inserted:

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

The following items of information concerning active principles, whether or not listed in the pharmacopoeias, shall be provided if they relate to the bioavailability of the medicinal product:

- crystalline form and solubility coefficients,
- particle size, where necessary after pulverization,
- state of hydration,
- oil/water partition coefficient,

the requirements of the first three indents not being applicable to substances used solely in solution."

(3) In Part 1, E, the following second paragraph shall be inserted:

"A batch of a proprietary medicinal product is all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of mechanical operations or a single sterilization operation."

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[1] OJ L 147 of 9.6.1975

(4) The first paragraph of Part 1, E, shall be supplemented by the following 4th subparagraph:

"Furthermore, solid pharmaceutical forms having to be administered by oral route shall, where necessary, be subjected to in vitro studies on the liberation and dissolution rate of the active principle or principles. Until standards are published by the European Pharmacopoeia, the conditions of the experiment and the apparatus employed shall be precisely described."

(5) In Part 1, E 2, the second subparagraph shall be supplemented thus:

"Except in the case of appropriate justification, the maximum acceptable deviations may not exceed 5%."

(6) In Part 1, E 3, the third subparagraph shall be replaced by the following text:

"An upper limit test shall be obligatory in respect of preserving agents and any other excipient constituent liable to affect physiological functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bioavailability of an active substance."

(7) In Part 1, E 5, the first subparagraph shall be replaced by the following text:

"If general monographs on pharmaceutical forms appear in the European Pharmacopoeia or in the national pharmacopoeias of the Member States, finished products must meet the requirements contained therein. If not, they shall be the subject of the determinations below."

In addition, the subparagraphs referred to above shall be amended as follows:

"Injectable preparations: "10 ml" shall be replaced by "15 ml"."

"Ointments, creams, etc.: colour and consistency; particle size of the active principles; 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 the suspension can be resumed."

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

(8) In Part 2, Chapter I, the following title D' shall be inserted between titles "D" and "E":

"D' 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."

(9) In Part 2, Chapter I, the title "E. CARCINOGENICITY" shall be replaced by: "E. CARCINOGENIC POTENTIAL".

In addition, the first subparagraph shall be amended as follows:

"Experiments intended to reveal carcinogenic effects shall normally be required:". (The rest remains unchanged).

Furthermore, a point 3 shall be inserted:

"3. in respect of substances having given positive results in the mutagenic potential tests or in other short term carcinogenicity tests".

(10) In Part 2, Chapter I, G, the following new subparagraph shall be inserted between the fourth and fifth subparagraphs:

"For medicaments which must be subjected to a bioavailability assessment, the data must include changes in the results as a function of time and, more generally, indicate the bioavailability of the product or of its metabolites.

(11) In Part 3, Chapter II, the title "A. Pharmacological Particulars (Clinical pharmacology)" shall be replaced by "A. Pharmacological Particulars (Clinical pharmacology and bioavailability)".

This same Chapter II, A, shall be supplemented by a paragraph 5, worded as follows:

"5. The assessment of bioavailability must be undertaken in all cases where it is essential in the interests of patients, e.g. where the therapeutic safety margin is narrow or where the previous tests have revealed anomalies which may be related to variable absorption."

ARTICLE 3

Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products shall be amended as follows:

The provisions of Chapter III shall be replaced by the following provisions:

"Article 8

1. In order to facilitate the adoption of a common position by the Member States regarding marketing authorizations and to permit their mutual recognition, 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 responsibility of the Committee shall be to examine, at the request of one of its members, any question concerning the quality, safety and efficacy of proprietary medicinal products and, in particular, in accordance with Articles 9 to 14, questions concerning the application of Articles 5 and 11 of Directive 65/65/EEC.

3. The Committee shall draw up its own Rules of Procedure.

Article 9

1. A holder of a marketing authorization issued in a Member State in accordance with the provisions of the Directives relating to proprietary medicinal products may request recognition of such authorization when he files an application for authorization in one or more Member States, in accordance with Article 4 of Directive 65/65/EEC.

2. He shall inform the Committee of this application, mentioning the Member States with which he has filed it, and also forward to the Committee a copy of the marketing authorization or authorizations already issued.

3. The Committee shall forward this information to the Member States.

4. The Member State(s) concerned shall grant recognition by issuing an authorization valid on their market within 120 days after the notification referred to above or within 60 days thereafter in the case of a proprietary medicinal product of the kind referred to in Article 13(1), without prejudice to the provisions set out below.

Article 10

1. Where a Member State considers that it is unable to recognize 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 on the basis of Article 5 of Directive 65/65/EEC, within the time limits stipulated in Article 9(4).

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 mentioned in paragraph 1, the person responsible for placing the proprietary medicinal product on the market shall immediately submit to the Committee one copy of the particulars and documents enumerated in Article 4(2) of Directive 65/65/EEC.

Article 11

If several applications submitted in accordance with Article 4 of Directive 65/65/EEC have been made 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, a member of the Committee may request the Committee to apply the procedure mentioned in Article 14.

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

Article 12

The competent authorities of Member States may, in specific cases where the interests of the Community are involved, request the Committee to apply the procedure provided for in Article 14, before they reach a decision on an application for a marketing authorization, its suspension or revocation and, in particular, when they intend to reject an application which concerns a new proprietary product such as that which is referred to in Article 13(1) and which has already been authorized in another Member State.

Article 13

1. In order to facilitate any discussions by the Committee, the competent authorities shall draw up a report to assess the results of the analytical and toxico-pharmacological tests and clinical trials of any proprietary product containing a new active substance which is the subject of an application for a marketing authorization in the Member State concerned for the first time or of any other proprietary product they may choose.

2. As soon as the notification referred to in Article 9(3) is received, the competent authorities shall forthwith forward to the other Member States and to the Committee any assessment report relating to the same proprietary product or to a proprietary product containing the same active substance. This shall also apply as soon as reference is made to the Committee pursuant to Articles 11 and 12.

3. If necessary, the assessment report shall be updated, namely by information stemming from the drug-monitoring systems.

Article 14

1. When reference is made to the procedure described in this Article, the Committee shall consider the matter and express 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 verbally or in writing before the Committee expresses its opinion. He may also obtain the suspension of the abovementioned time limit.

2. The Committee's opinion shall concern the compliance of the proprietary medicinal product in question with the conditions laid down in Article 5 or Article 11 of Directive 65/65/EEC.

   The Committee shall forthwith 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 differences of opinion.

3. The Member State(s) concerned shall decide on the action to be taken following the Committee's opinion within 30 days of receiving the information referred to in paragraph 2. They shall forthwith inform the Committee of their decision(s).

Article 15

1. The Commission shall report to the Council biennially 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, on the basis of Article 100 of the Treaty, propose by 1 January 1988 at the latest the reduction of the periods referred to in Article 10 and, where necessary, any additional measure aimed at facilitating the mutual recognition of marketing authorizations.

3. The Council shall decide on the Commission's proposal by 1 January 1989 at the latest."

ARTICLE 4

Member States shall bring into force the laws, regulations and administrative provisions needed in order to comply with this Directive by 1 January 1983 at the latest and shall forthwith inform the Commission thereof.

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 Brussels, ...

For the Council
The President

PROPOSAL FOR A COUNCIL RECOMMENDATION

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

PROPOSAL FOR A COUNCIL RECOMMENDATION

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SUMMARY

The Commission proposes that Member States should ensure that tests relating to the placing on the market of proprietary medicinal products are conducted and presented in accordance with the principles and methods set out in the notes for guidance pursuant to Directive 75/318/EEC on standards and protocols in respect of the testing of proprietary medicinal products.

These notes deal with the following aspects of safety and efficacy of drugs:

- single dose toxicity,
- repeated dose toxicity,
- reproduction studies,
- carcinogenicity,
- pharmacokinetics and metabolism in animals, safety studies,
- fixed combination products.

EXPLANATORY MEMORANDUM

1. For four years the Member States have been authorizing the placing on the market of proprietary medicinal products by applying at first three, and now four, Council Directives *.

   Directive 75/318/EEC relates in particular to tests designed to verify the safety, efficacy and quality of the drug before it is placed on the market. The Annex to this Directive describes in very general terms the various categories of tests to be carried out in the analytical, pharmaco-toxicological and clinical fields and gives some indication of how documents and results are to be presented.

2. Experience has shown that differences of opinion not infrequently arise between national authorities as regards the indications, contra-indications, etc. for a given drug and even as to the desirability of granting or refusing authorization to place it on the market.

   The Commission has found on the basis of this experience that the degree of harmonization achieved by the existing Directives would not be sufficient to create the conditions necessary for the free movement of proprietary medicinal products unless it were matched by greater co-operation between the competent national bodies.

3. The Committee for Proprietary Medicinal Products **, which was set up in order to facilitate the adoption of a common approach by the Member States on the question of marketing authorizations and is composed of representatives of the national authorities and the Commission, undertook to review the present national and international requirements and to seek joint solutions that take account of current scientific and technical knowledge. The Commission has from the outset supported this scheme, which is likely to bring about a significant alignment of the points of view of the national authorities. To this end the Committee has set up,

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* - Directive 65/65/EEC of 26 January 1965
- Directive 75/318/EEC of 20 May 1975
- Directive 75/319/EEC of 20 May 1975
- Directive 78/25/EEC of 12 December 1977

** Directive 75/319/EEC, Chapter III

under Article 13 of its rules of procedure, two groups of scientific experts designated by the Member States to draw up, in accordance with certain priorities, notes for guidance relating to the free movement of proprietary medicinal products within the Community.

4. The drafting and consultation procedure for these notes for guidance is designed to ensure that they will be valid and accepted both by the competent authorities and by the manufacturers concerned. The drafts of the two groups of scientific experts on "safety" and "efficacy" have been prepared in conjunction with specialists in the field concerned.

   The drafts approved by the Committee for Proprietary Medicinal Products were sent for consultation to the national authorities and to associations representing the pharmaceutical industry.

   The drafts were then re-examined by the experts in the light of the comments received and a final draft has been prepared which the Committee has unanimously approved.

5. In substance, these notes are based largely on current requirements or on requirements which are in the process of being drawn up at both national and international level. In the wider context of the toxicity of new chemical substances, similar texts will be recommended by the Commission in the sixth amendment to the 1967 Directive on dangerous substances.

6. The main advantage of these notes for applicants for marketing authorizations is to inform them in advance of the requirements of national authorities so that they avoid additional delays in the completion of their dossiers. For trade within the Community and, in the long run, with non-member countries as well, these notes will spare applicants the need to repeat similar tests. Up to now experimental models have been defined differently in different countries.

These additional delays and duplications exist at the moment and have a detrimental effect on the cost of new medicines. From an ethical point of view, it is desirable in particular to avoid the repetition of clinical tests on man and the pointless proliferation of animal experiments.

7. This first set of notes for guidance is concerned more particularly with all aspects of the safety of medicines, other than mutagenicity. The Commission intends to propose the introduction of that discipline into the categories of tests listed in Directive 75/318/EEC. The notes for guidance concerned with safety will be reviewed from time to time to ensure that they are continually adapted to scientific and technical progress.

8. This set also contains a note on the efficacy of proprietary medicinal products containing a fixed combination of active principles.

More specific notes dealing with clinical tests on medicinal products belonging to certain therapeutic categories are being elaborated.

9. These scientific texts, which are guidelines rather than binding requirements, must be interpreted in a flexible manner and shall be revised periodically. The Recommendation is therefore the most appropriate instrument.

As these guidelines are of major importance for patient protection and for pharmaceutical research, the Commission proposes to the Council to adopt such a Recommendation, after consultation of the European Parliament and the Economic and Social Committee.

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Parliament,

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

1. Whereas Council Directive 65/65/EEC of 26 January 1965*) 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 and 75/319/EEC of 20 May 1975**) continued this approximation and developed the principles set out in the original Directive;

2. 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 authorization to place a proprietary medicinal product on the market;

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

4. Whereas Notes for Guidance are therefore necessary in order to prevent differences of interpretation in the implementation of the standards and procedures listed in Directive 75/318/EEC and will help to promote the free movement of proprietary medicinal products;

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* OJ EC N° 22, 9.2.1965
** OJ EC N° L 147, 9.6.1975

5. 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 use of laboratory animals more than necessary;

6. 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;

7. 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 non-Member States;

8. 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;

3. apply these Notes for Guidance progressively and not later than three years after notification of this recommendation.

3)

ANNEX I: SINGLE DOSE TOXICITY

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

1. INTRODUCTION

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

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

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

2. PRODUCT SPECIFICATION

2.1 Drug Substance

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

2.2 Finished Product

When large animals are used in the acute toxicity study, it may be possible to conduct a study with the pharmaceutical formulation intended to be marketed, and this is desirable.

2.3 Excipients

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

2.4 Products containing a Combination of Active Substances

In the case of combination of active substances it is necessary to make a study of each active substance separately and of the combination of active substances in the same proportions as in the proposed final product in order that any change or potential toxic effects are revealed.

2.5 Degradation Products

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

3. ANIMALS

3.1 Single dose toxicity tests must be conducted on at least two mammalian species of known strain using equal numbers of both sexes. Rodents such as the mouse, rat and hamster are suitable for the qualitative study of toxic signs and the quantitative determination of the lethal dose. In the case of other mammals toxic signs should be observed and recorded in detail for each animal used.

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

4. ADMINISTRATION

4.1 Route of Administration

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

4.2 Conditions of Administration

Details of administration of the product should be provided and include particulars of the vehicle or adjuvants used, method of preparing the suspension in the case of insoluble products, concentration of the solution used and the volume administered. The route and the method of administration should be clearly given. If the intravenous route is used the rate of infusion (ml/min.) and the pH and temperature of the solution administered should be provided.

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

4.3 Dose levels

In rodents the number of dose levels used should be such as to enable the spectrum of acute toxicity to be revealed and to enable the LD_{50} value with its 95 % fiducial limits to be determined for each route and both sexes, if possible.

In other mammals the number of dose levels should be such that the spectrum of toxicity should be revealed and an estimate of the lethality obtained.

5. OBSERVATIONS

Animals should be observed at regular intervals and all signs of toxicity and the time of their first occurrence and their severity and duration recorded. The time and mode of any death should be documented. When large experimental animals are used any signs of toxicity should be presented separately for each animal.

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

6. AUTOPSY

All animals surviving to the end of the study and all animals dying during the period of observation should be subjected to autopsy. If in the latter cases autolysis is advanced this should be reported.

7. PRESENTATION OF DATA

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

The toxic effects should be described in each species and for each route of administration at all dose levels.

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

ANNEX II: REPEATED DOSE TOXICITY

Note for Guidance concerning the application of the Annex of Directive 75/318/EEC, 2nd part, Chapter I, B 2, 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.

Proposed duration of human treatment	Suggested duration of repeated dose toxicity studies
One or several doses within one day	2 weeks
Repeated doses for upto 7 days	4 weeks
Repeated doses for upto 30 days	3 months
Repeated doses beyond 30 days	6 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 1 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 subacute toxicity study of 2 or 4 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

The introduction of the "Norms and Protocols EC 75/318 Part II, Toxicological and Pharmacological Experiments" states that these experiments should indicate inter alia the toxicity thresholds: "Repeated dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by a 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 2 or 4 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 characterisations

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 Pretreatment 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 pretreatment 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, urinanalysis, ophthalmology, ECG and general behavior. 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 specialised 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
- gallbladder
- 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 gastrointestinal 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-existant 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 on 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 naso-tracheal 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 inhalational 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 III: REPRODUCTION STUDIES

Note for Guidance concerning the application of the Annex of Directive 75/318/CEE, 2nd part, Chapter I, C and D, 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, eg,

(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 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 should be conducted in at least one species. Dosing should cover the period of gestation from the end of organogenesis to 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 IV: CARCINOGENICITY

Note for Guidance concerning the application of the Annex of Directive 75/318/EEC, 2nd part, Chapter I, E, 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 analyse 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 6 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 (eg 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. Cognisance 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 3 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 2-3 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 characterised.

(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 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 randomisation 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. W.H.O.).

8.2 Presentation of the data

In the first instance the findings should be summarised 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. For animals with one or more tumours of the same or different type, a frequency distribution of the total number of tumours found in the animal; 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 3 treatment groups, as a set, and the response in the 2 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, middle 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 above.

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
- gallbladder
- pancreas
- spleen
- kidneys
- adrenals
- bladder
- prostate
- testes
- ovaries
- uterus
- brain (coronal sections at three levels)
- eyes
- spinal cord

ANNEX V: PHARMACOKINETICS AND METABOLIC STUDIES IN THE SAFETY EVALUATION OF NEW DRUGS IN ANIMALS

Note for Guidance concerning the application of the Annex of Directive 75/318/EEC, 2nd part, Chapter I, F and G, 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 enterohepatic 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 VI: FIXED COMBINATION PRODUCTS

Note for Guidance concerning the application of the Annex of Directive 75/318/EEC, 3rd part, Chapter II, C 2, 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 rational and based on valid therapeutic principles.

For any individual 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 Norms 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 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 occuring 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 each component is needed 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

A distinction must be made between those fixed combinations which correspond closely to combinations which are already in widespread use provided these are thoroughly and reliable documented, and 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 previous provisions as fixed combinations of these substances rather than as chemical entities.

9. LABELLING

The presentation and labelling of a fixed combination product should be such that it is clear to the prescriber or purchaser that the product contains more than one active ingredient and the pharmacological nature of the active ingredients should be clearly stated in appropriate terms.