NOTICE TO APPLICANTS

For marketing authorizations for proprietary medicinal products in the Member States of the European Community on the use ot the new multi-state procedure created by Council Directive 83/570/EEC

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NOTICE TO APPLICANTS

FOR MARKETING AUTHORIZATIONS FOR PROPRIETARY MEDICINAL PRODUCTS IN THE MEMBER STATES OF THE EUROPEAN COMMUNITY ON THE USE OF THE NEW MULTI-STATE PROCEDURE CREATED BY COUNCIL DIRECTIVE 83/570/EEC

Document

This notice which has no legal force has been prepared by the Committee for Proprietary Medicinal Products in consultation with the competent authorities of the Member States, in order to provide general guidance on the use of the new multi-State procedure for applying for marketing authorisation. In cases of doubt, reference should be made to the relevant Community directives.

S U M M A R Y

I. FOREWORD

Since 1977, persons responsible for marketing proprietary medicinal products have been able to use an alternative procedure in order to obtain authorization to market their products within the Member States of the European Communities. Instead of submitting separate applications directly to the competent authorities of each Member State in which the product is to be marketed, they have been able to submit a common application to five or more Member States using the Committee for Proprietary Medicinal Products (hereinafter CPMP) attached to the Commission of the European Communities, after first having obtained a marketing authorization in one Member State.

Following the entry into force of Council Directive 83/570/EEC in November 1985, major changes are made to the Community procedures, the minimum number of Member States to which a common application may be made is reduced from five to two, and the Member States to which the application is addressed must take the the authorization granted by the original Member State into due consideration.
This notice describes the administrative steps to be followed when applying for marketing authorization (hereinafter MA) through the new Community procedure and provides general guidance on the manner in which applications should be presented. This notice cancels and replaces the earlier notices published in the Official Journal of the European Communities (OJ No. C 302/6 of 15.12.77 and OJ No. C 162/3 of 2.7.80).

The rules governing proprietary medicinal products for human use have, to a large extent, been harmonized within the Member States of the European Community. These rules, which apply equally to applications for MA submitted through purely national procedures and to applications submitted through Community procedures, are contained in the following legal texts:

- Council Directive 65/65/EEC of 26.1.1965 relating to proprietary medicinal products (OJ No. 22, 9.2.1965)

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- Council Directive 75/318/EEC of 20.5.1975 relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ L 147 of 9.6.1975)

- Council Directive 75/319/EEC of 20.5.1975 relating to proprietary medicinal products (OJ L 147 of 9.6.1975)

- Council Directive 83/570/EEC of 26.10.1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC relating to proprietary medicinal products (OJ L 332 of 28.11.1983)

- Council Recommendation 83/571/EEC of 26.10.1983 concerning tests relating to the placing on the market of proprietary medicinal products (OJ L 332 of 28.11.1983)

- Council Directive 78/25/EEC of 12.12.1977 relating to the colouring matters which may be added to medicinal products (OJ L 11 of 14.1.1978)

These texts may be obtained from national official publication offices or from the "Office des publications officielles des Communautés européennes", L-2985 Luxembourg, tel. 49 00 81, Postal cheque account: 19 190-81 - Bank current account: B.I.L. 8-109/6003/200; Citibank Brussels: 570-1121200-35; Sogenal Luxembourg: 04-3-2600-490226 (*).

A brochure entitled "The Rules governing Medicaments in the European Community" contains the full texts of all the relevant Community law before 1.1.85, and is available from the same addresses (ISBN 92-825-4531-8; EC catalogue No. CB-41-84-515-EN-C).

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(*) In September 1984, the Commission of the European Communities put forward a series of proposals to amend some of the above mentioned texts (see OJ No. C 293 of 5.11.84). At the time of going to press, modifications to these proposals were submitted on 4 March 1986 (COM(86)117).

II. PURPOSE AND SCOPE OF THE NEW MULTI-STATE (CPMP) PROCEDURE

The legal rules governing the new Community procedure, which is subsequently referred to as the "multi-state" procedure, are set out in Chapter III of Directive 75/319/EEC, as amended by Directive 83/570/EEC. Applications must, if necessary, be updated to comply with the rules in force at the time of submission.

The primary purpose of the multi-state procedure is to make it easier for a person who has already obtained a MA in one of the Member States to get further MAs for the product concerned in two or more of the other Member States. On the basis of the same complete documentation, and taking the MA granted by the first Member State into due consideration, the authorities of the Member States to which the application is addressed have 120 days to put forward their reasoned objections to the CPMP. If no objections are lodged within this time limit, each Member State concerned has granted MA and the applicant will be informed accordingly. Where one or more objections are advanced, the matter is referred to the CPMP which considers the grounds for the objections and any written or oral explanations provided by the applicant before issuing its own reasoned opinion, normally within a period of 60 days. This opinion is addressed to the Member States concerned. Within a further 60 days they must decide on what action to take pursuant to the Committee's opinion and must inform the CPMP of their decision.

Certain categories of proprietary medicinal products may not benefit from this procedure, because they are not yet covered by the Community directives: vaccines, toxins, sera, products based on human blood or blood constituents, radioactive isotopes, homeopathic medicines (Article 34 of Directive 75/319/EEC).

In addition, the multi-state application must relate to a proprietary medicinal product which has been authorized by one Member State in accordance with the criteria laid down by the Community directives. Thus products marketed by virtue of previous national provisions are not covered by the new procedures unless their quality, safety and efficacy have been reviewed in accordance with Article 39 of Directive 75/319/EEC.

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III. NEW DRUG APPLICATIONS AND ABRIDGED APPLICATIONS

The multi-state procedure may be used not only for new drug applications but also for abridged applications submitted pursuant to point 8 of Article 4 of Directive 65/65/EEC. However, the submission of abridged applications through the multi-state procedure may give rise to particular difficulties and the attention of applicants is specifically drawn to four points.

i) The fact that in one Member State a given substance is sufficiently well-known for an abridged application to be acceptable does not necessarily imply that the same is true of all the other Member States. In certain Member States there may be no experience of the medicinal use of the product and complete documentation may therefore be required.

ii) The experts reports submitted in connection with an abridged application must clearly state the grounds for using published references under the conditions set out in Directive 75/318/EEC (see Art. 2(c) of Directive 75/319/EEC).

iii) The provisions of Council Directive 75/318/EEC on the analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products apply in like manner to references to published data submitted pursuant to Article 4 point 8 of Directive 65/65/EEC (Art. 1 of Directive 75/318/EEC).

iv) Where necessary, bioavailability studies must be undertaken (Annex to Directive 75/318/EEC as amended, Part 3, Chapter II A, paragraph 5).

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IV. SUBMISSION OF THE MULTI-STATE APPLICATION

The person responsible for placing the product on the market submits an application directly to the competent authorities of each of the two or more Member States concerned, referring to the procedure laid down in Chapter III of Directive 75/319/EEC, as amended by Directive 83/570/EEC.

Each application should be accompanied by the documents referred to in Articles 4, 4(a) and 4(b) of Directive 65/65/EEC.

The applicant should also testify that each dossier is identical to that accepted by the first Member State, or when necessary, he should specify any additions or modifications that have been made.
In addition, he should indicate whether an application to market the proprietary medicinal product has been made to or granted by any other Member State under purely national procedures.

The applicant notifies the Secretariat of the CPMP of the multi-state application, informs it of the Member States concerned and of the dates on which the dossiers were sent to those Member States and sends it a copy of his authorization, including the summary of the product characteristics approved by the first Member State (Article 4(b) of Directive 65/65/EEC).

In addition the applicant should inform the competent authority of the Member State which granted the initial authorization of the application and of any additions made to the original dossier.
This authority may require the applicant to provide such information and documents as are necessary to enable it to check the identity of the dossier filed under the multi-state procedure with the dossier on which it took its own decision.

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As soon as all the Member States concerned have confirmed receipt of the application, the Secretariat notifies all the Member States and the applicant of the start of the 120 day period referred to in Article 9(3) of Directive 75/319/EEC as amended.

No specific fee is payable in respect of the work of the CPMP, but national registration fees remain payable in accordance with the rules of the Member State concerned.

In accordance with Article 13 of Directive 75/319/EEC as amended, immediately a multi-state application is lodged the competent authority of the Member State which granted the initial application is required to communicate a copy of any assessment report relating to the particular product to the Member States concerned by the application.
Persons preparing a multi-state application are therefore strongly advised to contact this authority at an early stage to make the administrative arrangements necessary to ensure that any necessary translations of the assessment report into a language or languages acceptable to the countries concerned by the application are available at the same time as they formally submit the application. The applicant will be expected to pay any translations of the assessment report which are necessary to consider his application. In order to reduce these costs to a minimum, all the competent authorities except the French authorities have indicated that they are prepared to accept official assessment reports in English if they are not available in their own national language.

The names, addresses, telex and telephone numbers of the competent authorities of the Member States are:

Belgium:
Ministère de la Santé publique
Inspection générale de la Pharmacie
Cité Administrative, Quartier Vésale
1010 Bruxelles
Tel.: (2) 210.49.00 and 210.49.01
Telex: 25.768 MVGSPF B

Denmark:
Sundhedsstyrelsen, Farmaceutiske Laboratorium
Frederikssundsvej 378
DK-2700 Brønshøj
Tel.: (2) 94.37.73
Telex: 35333 IPHARM DK

Germany:
Institut für Arzneimittel des
Bundesgesundheitsamtes
Seestr. 10
D-1000 Berlin 65
Tel.: (30) 450.22.03
Telex: 183310 BGESA D

France:
Ministère des Affaires sociales et de la
Solidarité nationale
Direction de la Pharmacie et du Médicament
1, place de Fontenoy
F-75700 Paris
Tel.: 567.55.44
Telex: 250011 SANTSEC F

Greece:
E.O.F. (National Drug Organisation)
Voulis Str. 4
Athens 10562
Tel.: 323.09.11
Telex: 223514

Ireland:
National Drugs Advisory Board
63-64 Adelaide Road
Dublin 2
Tel.: 76.49.71 - 7
Telex: 90542

Italy:
Ministero della Sanità
Servizio Farmaceutico
Viale della Civiltà Romana, 7
I-00144 ROMA, EUR
Tel. (6) 592.58.63 and 592.58.24
Telex: 610453 MINSAN I

Luxembourg:
Direction de la Santé
Division de la Pharmacie et des Médicaments
10, rue C.M. Spoo
L-2546 Luxembourg
Tel.: (352) 4.08.01
Telex: 2546 SANTE LU

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Netherlands:	College ter beoordeling van geneesmiddelen P.O.Box 5811 NL-2280 HV Rijswijk Tel.: (70) 94.95.05 Telex: 32691 VMRWK NL
United Kingdom:	Department of Health and Social Security Medicines Division Market Towers 1 Nine Elms Lane London SW8 5NQ Tel.: (1) 720.21.88 Telex: 883669 DHSSHQ G
Spain:	Ministerio de Sanidad y Consumo Direccion General de Farmacia y Productos Sanitarios Paseo del Prado, 18-20 E-28014 Madrid Tel.: 467.34.28 Telex: 22.608 MSASS
Portugal: (*)	Ministerio da Saude Direcção Geral dos Assuntos Farmacêuticos Av. Estados Unidos da America, 37 Tel.: 80.41.31 Telex: 15655 MAS P

The address of the Secretariat of the CPMP is:

D.G. III A 3 "Pharmaceuticals, veterinary medicines"
Commission of the European Communities
Rue de la Loi 200
B-1049 Brussels

Tel.: 235.51.80 / 235.69.35

Telex: 21.877 COMEU B

(*) For applications concerning Portugal, see page 11.

V. PRESENTATION OF THE MULTI-STATE APPLICATION

1. Order of presentation and content of the dossier

Detailed guidance on the presentation of the different parts of a multi-state application is given in the Annex I. Although it has no legal force, this guidance has been prepared in consultation with the competent authorities of all the Member States, in order to facilitate the examination of the application.

2. Expert reports

In accordance with Directive 75/319/EEC, Article 2, the pharmaceutical, pharmaco-toxicological and clinical parts of the complete dossier should each include an expert report. It is important to emphasize that well prepared expert reports greatly facilitate the task of the competent authorities in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of the experts reports, and the guidance contained in Annex II should be followed.

Where relevant Community guidelines on the conduct of tests and trials on a proprietary medicinal product exist, these should be taken into consideration when the report is prepared and any deviation from them should be discussed and justified. A list of the guidelines currently available is included in Section IX of this Note.

3. Summaries of the dossier

Where in addition to copies of the complete dossier a Member State concerned by an application requires the submission of additional copies of summaries of the dossier, these should consist of the summary of product characteristics proposed by the applicant (Article 4(a) of Directive 65/65/EEC as amended) bound together with the experts reports on the three parts of the dossier: pharmaceutical, pharmaco-toxicological and clinical (1).

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(1) For applications concerning the United Kingdom, however, the analytical report should be bound separately from the other two parts.

4. Number of copies and accepted languages

Information on the number of copies of the application to be submitted to the authorities of each Member State and on the languages in which applications should be drafted is set out in the table on the following page. Further copies of the application may be required by the authorities in certain exceptional cases.

5. Specimens and Samples

In accordance with Article 4, second paragraph, point 9, of Directive 65/65/EEC as amended, a specimen or mock up of the sales presentation of the proprietary product, together with a package leaflet where one is to be enclosed, must be included in each complete dossier submitted.

Moreover, for the purposes of implementing Article 4 of Directive 75/319/EEC, samples of the active principles and of the finished product must be supplied as a matter of course to the competent authorities in Belgium, Greece, Ireland, Italy, Luxembourg, Spain and the Netherlands. For Belgium and Spain, samples will also be required of other starting materials in respect of which the applicant has introduced a monograph. In other cases, samples should be provided at the request of the competent authorities.

6. Applications concerning Portugal

In accordance with the terms of the Act of Accession, Portugal is not required to implement Council Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 78/25/EEC and 83/570/EEC until 1 January 1991.

Unless the Portuguese authorities indicate otherwise, applications to market a medicinal product in Portugal should therefore be submitted in accordance with national procedures and the multi-State procedure should not be used.

However the Portuguese authorities have indicated that they will accept applications presented in accordance with the standard Community format described in this Notice to Applicants. Two complete dossiers are required together with two summaries and six additional copies of Part III (Toxicological and Pharmacological) and Part IV (Clinical). The basic data in Parts III and IV may be presented in English or French provided they are accompanied by a very detailed and precise synthesis in Portuguese containing, in particular, references to the pages containing the data in question.

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TABLE: NUMBER OF COPIES AND ACCEPTABLE LANGUAGES

I. NUMBER OF COPIES	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	UK	CPMP
- Full dossiers	1(1)	1	4	3(2)	2(2)	2	3	3	1	2	6	1
- Part II Pharmaceutical	+ 2			+ 3	+ 3				+ 1		+ 14	
- Summary of the dossier	20	1	8	12	50	5	3	10	1	4	6	13

II. LANGUAGES	BE	DK	DE	ESP	FR	GR	IRL	IT	LUX	NL	UK	CPMP
In principle: Other languages accepted for:	FR or NL	DK	DE	ESP	FR	GR	EN	IT	FR	NL	EN	EN or FR (4)
Part II Pharmaceutical	DE or EN	EN	EN			EN			DE or EN	EN or FR or DE		
Part III Pharmacol. toxicological and Part IV Clinical	DE or EN	EN	EN	(3) EN or FR	(3) EN	EN		EN or FR	DE or EN	EN or FR or DE		
Summaries of the dossier, Expert Reports	DE or EN	EN	EN			EN		EN or FR	DE or EN	EN or FR or DE		EN or FR

(1) In Belgium two additional copies are required of Part III(g) Pharmacokinetics and Part IV(a) Human Pharmacology.

(2) In Spain and France, one additional copy of Part III Toxicology is required.

(3) In Spain and France, these basic raw data are accepted in the other language mentioned if accompanied by a very detailed and precise synthesis in the national language containing, in particular, references to the pages containing the data in question.

(4) The CPMP also accepts the full dossier in German when the language is accepted by all the Member States concerned by the procedure.

VI. CASES WHERE A CPMP OPINION IS REQUIRED

As noted above, an opinion of the CPMP is not required for every multi-state application. If no Member State has put forward reasoned objections during the 120 day period allowed for national examination of the application, marketing authorisation has been granted by each of the Member States concerned.

If, however, one or more of the Member States concerned does lodge reasoned objections to the application within the 120 days, the objections are formally notified to the applicant by the authority concerned and the matter is referred to the CPMP for its opinion. In this case the applicant is required to send to the Secretariat of the Committee a complete copy of the application together with 13 copies of the summaries as soon as possible after the receipt of reasoned objections from a Member State. Although the complete dossier may be submitted in English or French, it will greatly facilitate the work of the Committee if copies of these summaries are made available in both English and French. At the same time copies of any existing assessment reports will be circulated to all the Member States.

The Committee is required to give its opinion within 60 days of the date on which the matter was referred to it, that is the date of the expiry of the 120 day period for national examination of the application. As soon as possible after the receipt of reasoned objections from a Member State, the Secretariat of the Committee will notify the applicant of the date on which the Committee proposes to consider the application and of the deadline for the submission of any written representations the applicant may wish to make in accordance with Article 14 of Directive 75/319/EEC, as amended. An applicant may also request an oral hearing before the Committee. If the applicant considers that the date proposed for the examination of his application by the Committee does not provide sufficient time for the preparation of these submissions he may request that examination of the application be postponed to a subsequent meeting. At the present time the Committee usually meets once every two to three months.

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The reasoned opinion of the CPMP is exclusively concerned with the grounds for the objections put forward by the Member States concerned. The opinion of the Committee, or in the case of divergent opinions, the opinions of its Members are immediately notified to the applicant and to the Member States.

The opinions of the CPMP do not replace national decisions. However, within 60 days of the receipt of the opinion, the Member States concerned must decide what action to take on the Committee's opinion and inform the Committee of that decision. The Member States keep the Committee informed of the action they are taking pursuant to an opinion until such time as a definitive decision is adopted.

In accordance with Article 214 of the EEC Treaty and Article 19 of its rules of procedure, the deliberations of the CPMP and all documents submitted are confidential.

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VII. CONSIDERATION OF DIVERGENT NATIONAL DECISIONS

When a proprietary medicinal product has been authorized for use in one or more Member States, and has been refused authorization or suspended or withdrawn from the market in one or more of the Member States, Article 11 of Directive 75/319/EEC as amended empowers a Member State or the Commission to refer the matter to the CPMP for its opinion. The opinion of the Committee, which must be given within 60 days, will concern the grounds on which the marketing authorization for the proprietary product has been suspended, refused or withdrawn, and the Committee may invite the person responsible for marketing the product to explain himself in writing or in person before the Committee.

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VIII. WRITTEN REPRESENTATIONS AND ORAL HEARINGS

The purpose of written representations and oral hearings is:

- in the case of multi-state applications for MA submitted pursuant to Article 9 of Directive 75/319/EEC, as amended, to enable the applicant to make observations on the reasoned objections put forward by one or more of the Member States concerned by the application.

- in the case of matters referred to the Committee pursuant to Article 11 of Directive 75/319/EEC, as amended, to enable, where the Committee considers it appropriate, the person responsible for marketing the product to make observations on the grounds for the refusal, withdrawal or suspension of the MA given by one or more Member States.

Applicants using the multi-state procedure should bear in mind that oral or written representations are made to the CPMP as a whole, which comprises representatives from all the Member States of the Community, and not just to the countries concerned by the application. Although the authorities which are not directly concerned by the application will not necessarily have seen the complete dossier, they will have seen the summaries of the dossier, the reasoned objections of the Member States which are directly concerned by the application and any available assessment reports.

In order to enable the CPMP to concentrate on the important issues raised concerning the acceptability of a proprietary product on grounds of quality, safety and efficacy, applicants using the multi-state procedure are advised to try to resolve any minor objections, particularly those concerning the analytical part of the dossier, directly with the competent authorities concerned, if possible before the date on which the Committee will consider the application.

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Written representations should be sent directly to all the Members of the CPMP, with a copy to the Committee's secretariat, whose addresses have been given above, and should reach the members at least ten days before the meeting. So far as the languages in which representations should be drafted are concerned, the guidelines relating to the submission of summaries of the three parts of the dossier should be followed (see the table on p. 13). It should therefore be noted that it will usually be necessary to provide any representations in English and French. Any written representation should set out the name of the proprietary product concerned, its composition in terms of active principles and the name and address of the person responsible for marketing the product.

Although the CPMP does not, at present, wish to lay down formal rules of procedure governing the conduct of oral hearings, the following general notes are offered for guidance. These notes are necessarily subject to revision in the light of experience and persons contemplating requesting an oral hearing are advised to seek the advice of the Secretariat at an early stage.

i) It is important that persons preparing for and attending hearings bear in mind that the oral proceedings of the Committee are multi-lingual and that simultaneous technical interpretation during the hearing will be necessary. For this reason arguments of a very technical or scientific nature are better expressed in writing.

ii) Any new written documents to be used in conjunction with a hearing should be distributed to the Members of the CPMP before the meeting. In addition the Secretariat will require an additional 10 copies of any document to which more than passing reference is to be made for the interpreters.

iii) Certain visual aids may be made available upon request, and persons preparing for a hearing should discuss their requirements with the Secretariat. Where appropriate, printed copies of the material used should be made available to the Secretariat in advance.

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iv) Without wishing to specify a formal time limit, the CPMP considers that hearings lasting more than one hour, including both the presentation by the company and questions from the Committee, will not usually be necessary. Depending on the issues raised in the reasoned objections of the Member States, it would normally be appropriate for between one and four persons to appear on behalf of the company concerned.

v) Persons attending hearings should notify the Secretariat in good time of the language in which they propose to express themselves so that arrangements for interpretation can be made.

vi) Persons attending hearings may present their arguments in whatever manner they think fit, but they are advised not to spend time on arguments which are not relevant to the reasoned objections of the Member States to an application for MA or to the grounds advanced by Member States for refusal, suspension or withdrawal of a MA.

vii) After the representatives of the company concerned have presented their case, the chairman will allow members of the CPMP to put questions. Thereafter, the representatives will be asked to withdraw while the Committee discusses its opinion, which will be sent in writing to the company.

IX. LIST OF COMMUNITY GUIDELINES ON THE CONDUCT OF TESTS AND TRIALS OF TESTS AND TRIALS OF PROPRIETARY MEDICINAL PRODUCTS (AS AT 1.7.85)

A) PHARMACO-TOXICOLOGICAL TESTS

1. Repeated dose toxicity (1)
2. Reproduction studies (1)
3. Carcinogenic potential (1)
4. Pharmacokinetics and Metabolic Studies in the Safety Evaluation of New Drugs in Animals (1)
5. Single dose toxicity (2)
6. Testing of Medicinal Products for their Mutagenic Potential (2)

B) EFFICACY STUDIES

1. Fixed Combination Products (1)
2. Cardiac Glycosides (2)
3. Clinical Investigation of Oral Contraceptives (2)
4. User Information on Oral Contraceptives (2)
5. Data Sheets for Antimicrobial Drugs (2)
6. Clinical Testing Requirements for Drugs for Long Term Use (2)
7. Non-Steroidal Anti-Inflammatory Compounds for the Treatment of Chronic Disorders (2)
8. Anti-Epileptic / Anticonvulsant Drugs (2)
9. Investigation of Bioavailability (2)
10. Clinical Investigation of Drugs for the Treatment of Chronic Peripheral Arterial Diseases (2)
11. Pharmacokinetic Studies in Man (2)
12. Anti-Anginal Drugs (3)
13. Corticosteroids intended for Use on the Skin (3)

Notes

(1) Adopted by the Council and included in Council Recommendation 83/571/EEC of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products (O.J. L 332/11 of 28.11.83).

(2) Accepted by the Committee for Proprietary Medicinal Products and included in the Commission Proposal of 25 September 1984 for a Council Recommendation concerning tests relating to the placing on the market of proprietary medicinal products (COM(84)437 final, O.J. C 293 of 5.11.84).

(3) Accepted by the Committee for Proprietary Medicinal Products and included in the modifications to the Commission Proposals of 25 September 1984 submitted to the Council on 4 March 1986 (COM(86)117).

ANNEX I

PRESENTATION OF APPLICATIONS FOR MARKETING AUTHORIZATION

Part I: General information

Part I A: Administrative data

1. Name of the proprietary medicinal product

2. Pharmaceutical form (including route of administration), strength and presentation

3. Name or business name and address of the applicant

4a. Name and address of the company responsible for the marketing of the product

4b. Name(s) and address(es) of the manufacturer(s) involved in the manufacturing process (including a description of the steps they perform)

5. Name and address of importer (where applicable)

6. Name and address of distributor (where applicable)

7. Number of volumes supplied in support of the application. In case of a multi-State application differences from the file on the basis of which the marketing authorization in the Member State of origin was granted should be indicated

8. Date and signature of the applicant.

Part I B : Summary of product characteristics

1. Name of the proprietary medicinal product

2. Qualitative and quantitative composition in terms of the active ingredients and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product; the international non-proprietary names recommended by the World Health Organization shall be used, where such names exist, or failing this, the usual common name or chemical description

3. Pharmaceutical form (including route of administration)

4. Pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars.

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5. Clinical particulars:

   5.1. therapeutic indications

   5.2. contra indications

   5.3. undesirable effects (frequence and seriousness)

   5.4. special precautions for use

   5.5. use during pregnancy and lactation

   5.6. interaction with other medicaments and other forms of interaction

   5.7. posology and method of administration for adults and, where necessary, for children (and/or the elderly)

   5.8. overdose (symptoms, emergency procedure, antidotes)

   5.9. special warnings

   5.10. effects on ability to drive and use machines.

6. Pharmaceutical particulars:

   6.1. incompatibilities (major)

   6.2. shelf life, when necessary after reconstitution of the product or when the container is opened for the first time

   6.3. special precautions for storage

   6.4. nature and contents of container

   6.5. name, or style and permanent address or registered place of business of the holder of the marketing authorization.

   For multi-State applications: where the information given above differs from the text approved by the Member State from which the application originates, the divergences should be marked (e.g. with an asterix).

Part I C: Expert reports on:

1. Chemical and pharmaceutical documentation

2. Toxicological and pharmacological documentation

3. Clinical documentation.

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Part II: Chemical and pharmaceutical documentation

Part II A: Composition

1. Composition of the proprietary medicinal product

Names of constituents	Quantity	Reference to standards
Active constituents		
Other constituents		

2. Container (brief description)

3. Clinical trial formula(e)

4. Development pharmaceutics
   Explanation with regard to the choice of the composition, constituents and container, supported, if necessary, by data on development pharmaceutics. The overage, with justification thereof, should be stated.

Part II B: Method of preparation

1. Manufacturing formula (including details of batch size)

2. Manufacturing process (including in-process control and the pharmaceutical assembly process

3. Validation of the process (experimental data showing that the manufacturing process, using starting materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality).

Part II C: Control of starting materials

1.1. Active constituents (specifications and routine tests)

1.1.1. Active constituents described in a pharmacopoeia

1.1.2. Active constituents not described in a pharmacopoeia

- Appearance
- Identity tests
- Physical tests
- Chemical tests
- Other tests
- Assay(s)

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1.2. Active constituents (scientific data)

1.2.1. Nomenclature

- International non-proprietary name (INN)
- Chemical name
- Other name(s)
- Laboratory code

1.2.2. Description

- Physical form
- Structural formula
- Molecular formula
- Molecular weight

1.2.3. Manufacture

- Name(s) and address(es) of the manufacturing source(s)
- Synthetic route
- Description of process
- Solvents and reagents
- Catalysts
- Final purification

1.2.4. Quality control during synthesis

- Starting materials
- Intermediates tested

1.2.5. Development chemistry

- Evidence of chemical structure (synthetic route, key intermediates, elemental analysis, mass spectrum, NMR, IR, UV, other)
- Potential isomerism
- Physico-chemical characterisation (solubility, physical characteristics, polymorphism, pKa and pH values, other)
- Analytical development

1.2.6. Impurities

- Potential impurities originating from the route of synthesis
- Potential impurities originating from degradation as evidenced by exposing the material to stress conditions (heat, light, acids, bases etc.)
- Analytical methods and their limits of detection
- Impurities found

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1.2.7. Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size, and use of batches)
- Results of tests
- Reference Standard (results of tests)

2.1. Other constituents (specifications and routine tests)

2.1.1. Constituents described in a pharmacopoeia

2.1.2. Constituents not described in a pharmacopoeia

- Appearance
- Identity tests
- Physical tests
- Other tests
- Assay(s)

2.2. Other constituents: data, when necessary, e.g. excipients used for the first time in medicinal products (see II C.1.2.)

3. Packaging material

- Type of material
- Construction
- Quality specifications (routine tests)
- Development/validation studies.

Part II D: Control tests on intermediate products (if necessary)

A distinction should be made between in-process controls (part II B) and control tests on intermediate products.

Part II E: Control tests on the finished product

1. General characteristics, other quality control tests required by the nature of the product;
   - description and general characteristics (dimension, shape, colour, odour and distinguishing features)

2. Identification and quantitative determination of the active principle or principles, other quality control tests, with a description of the methods employed (including, if necessary, and depending on the nature of the product, biological and microbiological methods)

   - Identification tests
   - Quantitative determination of active ingredients
   - Pharmaceutical/technical tests e.g. dissolution rate

./.

- Identification of colouring matter
- Determination of antimicrobial or chemical preservatives

3. Validation of the methods employed
4. Batch analysis

Part II F: Stability

1. Proposed shelf life (depending on the type of container and storage precautions)
   When necessary the shelf life after reconstitution of the product or when the container is opened for the first time.

2. Information concerning stability, including physical stability, of the finished product:
   - Number of batches tested
   - Storage conditions
   - Methods employed
   - Description of containers
   - Analytical methods (if different to those in Part II E) and specifications
   - Results of tests and interpretation

3. Stability tests on active constituent(s)
   - Number of batches tested
   - Storage conditions
   - Methods employed
   - Description of containers
   - Analytical methods
   - Results of tests and interpretation

4. Validation of the methods employed

Part II Q: Other information

This part is intended for information not covered by any of the previous parts e.g. the analytical tests used in studies concerning metabolism and bioavailability.

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Part III: Toxicological and pharmacological documentation

If use is made of a list of published references pursuant to point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC (OJ No 22 of 9 February 1965), the expert must show that this is justified.

The following information must be provided in respect of each test:

1. Animals used (species, strain, sex, age, weight etc.)
2. Product used (number of the batch, quality etc.)
3. Experimental conditions including diet and husbandry
4. Results.

Part III A: Acute toxicity

Part III B: Toxicity with repeated administration

B.1. Subacute toxicity trials

B.2. Chronic toxicity trials

Part III C: Foetal toxicity and fertility studies

C.1. Tests for teratogenicity (dosing during period of organogenesis)

C.2. Pre- and postnatal dosing of the mother to demonstrate effects on late pregnancy, parturition and lactation, behavioural and developmental effects on the offspring

C.3. Fertility studies

Part III D: Mutagenic potential

Part III E: Carcinogenic potential

Part III F: Pharmacodynamics

F.1. Actions relevant to the proposed therapeutic uses

F.2. Other actions investigated

F.3. Interactions

Part III G: Pharmacokinetics

G.1. Absorption

G.2. Distribution in normal and pregnant animals

G.3. Metabolism

G.4. Excretion of the parent compound and its metabolites

Part III Q: Other information

This part is intended for possible information not covered by any of the previous parts.

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Part IV: Clinical documentation

If use is made of a list of published references pursuant to point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC (OJ No 22 of 9 February 1965), the expert must show that this is justified.

Part IV A: Human pharmacology

(where appropriate in healthy volunteers, patients and special risk groups)

A.1. Pharmacodynamics

1.1. Pharmacological actions

1.2. Pharmacodynamic mechanisms underlying the therapeutic effects

A.2. Pharmacokinetics

2.1. Absorption, including bioavailability

2.2. Distribution and protein binding

2.3. Metabolism

2.4. Excretion

2.5. Kinetic interactions

Part IV B: Clinical documentation

B.1. Individual trials and summaries thereof (efficacy and tolerance) (including unfinished studies)

1.1. Detail research design (protocol)

1.2. Final or intermediate report including statistical and medical evaluation and, where necessary, individual patient data. Submission of the raw data is necessary only on request.

1.3. Summary of each trial

1.4. Detailed clinical and laboratory monitoring results which should be capable of easy relation to individual patients.

B.2. Postmarketing experience

2.1. Adverse reaction monitoring and reports

2.2. Number of patients exposed

B.3. Published and unpublished experience (other than B.1.)

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B.4. Conclusions

4.1. Therapeutic effect

4.2. Adverse reactions

4.3. Interactions

4.4. Drug dependence

4.5. Car driving

4.6. Pregnancy, breast feeding, elderly people, children, special pathological conditions (e.g. impairment of liver and kidney functions)

4.7. Dosage (dosage interval, duration of therapy)

4.8. Overdosage and intoxication

Part IV Q: Other information

This part is intended for information not covered by any of the previous parts.

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Part V: Special particulars

Part V A: Dosage form

1. Packaging
2. Label
3. Package insert

Part V B: Samples

(where applicable; see page 11 of the Notice to Applicants)
List and description of samples accompanying the application.

Part V C: Manufacturers authorization(s)

Part V D: Marketing authorization(s)

1. Marketing authorization from Member State of origin and summary of product characteristics approved by it
2. Copies of marketing authorizations granted by other Member States
3. Third countries in which a marketing authorization is granted.

ANNEX II

PREPARATION OF THE EXPERTS REPORTS OF APPLICANT

I. INTRODUCTION

In accordance with Directive 75/319/EEC, article 2, the pharmaceutical, pharmaco-toxicological and clinical parts of the complete dossier should each include an expert report. It is emphasized that well prepared expert reports greatly facilitate the task of the competent authorities in evaluating the dossier and contribute to the speedy processing of applications. For these reasons particular care should be taken in the preparation of the expert reports.

In these notes for guidance the structure of the expert reports is described and some indications are given with regard to their content.

The experts selected by the applicant to draw up the report should be able to present a full and accurate summary of each part of the dossier in accordance with this explanatory note. It is not, however, necessary for them to have been personally involved in the performance of the tests they describe.

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II. GENERAL CONSIDERATIONS

1. In order to produce an expert report it is essential to consult "The Rules Governing Medicaments in The European Community" (see page 4 for bibliographical data).
The structure proposed in this Annex follows the order of presentation for applications for authorizations to market proprietary medicinal products described in Annex I.

2. The expert report should consist of a concise and comprehensive synopsis, briefly but exhaustively describing the quality of the products and the investigations on animals and human beings. It should include a critical comment of the expert. It must be worded so as to enable the reader to obtain a good understanding of the properties, the quality, the proposed control methods, the safety, the efficacy, the advantages and the disadvantages of the product.

3. The facts and data mentioned in the report should refer to the relevant place or page in the documentation.

4. All important data should be summarized. The presentation in tabular or graphic form is often advantageous. Some examples of tables are annexed, where appropriate other tables may be used.

5. Each application shall contain three expert reports, covering the three parts of the file:

   a. Chemical and pharmaceutical documentation (normally less than 25 pages)

   b. Toxicological and pharmacological documentation (normally less than 25 pages)

   c. Clinical documentation.

6. An expert report should bear the signature of the expert(s) and the place and date of its issue.
Attached to the report there should be brief information on the expert(s): their name(s), educational background training and occupation.
The professional relationship of the expert to the applicant should be declared.

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III EXPERT REPORT ON THE CHEMICAL AND PHARMACEUTICAL DOCUMENTATION

The expert report should consist of the following sections:

1. Composition
2. Method of preparation
3. Control of starting materials
   a. Active constituents
   b. Other constituents
   c. Packaging material
4. Control tests on intermediate products
5. Control tests on the finished product
6. Stability
7. Miscellaneous
8. Conclusion
9. Reference list
10. Information on the expert(s)

Examples of suitable forms which may be used, if desired, by the expert as a format for the relevant expert work are attached (Pages 47 - 61). Use of the forms facilitates a clear and well-ordered presentation of the data. Individual sections of the forms can be adapted as required by expanding or contracting them. Page references on the forms should be made to the appropriate page and column of the full dossier. The comments column should be left blank by the applicant.

1. Composition (part II A)

The complete qualitative and quantitative composition of the finished product must be given with a brief description of the container(s) in which it will be put on the market.
If the composition used in clinical trials differs from the finally chosen composition the differences should be indicated and their significance discussed.

Development pharmaceutics

The essential elements of the development work undertaken to produce the final formulation is to be summarized, together with any relevant analytical data on raw materials and the finished products. This summary should explain the choice of constituents and container(s).

2. Method of preparation (part II B)

The method of preparation of the finished product, the in-pro-

cess controls and the particular manufacturing precautions should be summarized and evaluated.

An opinion should be given on the process validation studies. The expert should indicate how the process validation data guarantees the production of a medicinal product of consistent quality.

3. Control of starting materials (part II C)

a. Active constituents

b. Other constituents

c. Packaging material

An opinion on the analytical testing of starting materials which are described in a recognised pharmacopoeia is required only if additional tests have been carried out. If the method of synthesis of a starting material gives reason to expect impurities in it which are not taken into account in the monograph published in the pharmacopoeia, the analytical results should show that no impurities have been introduced in manufacture, storage etc. which are not covered by these additional tests.

If the starting materials (including container materials) are tested in accordance with test specifications developed on the pattern of a pharmacopoeia monograph, the expert should indicate how certain the identity of the material is. For the purity test it must be evident from the opinion that no impurities resulting, for example, from manufacturing methods or storage are present which are not covered by the purity test. The expert should summarize the data on validation of the analytical methods to show their sensitivity, precision, linearity etc. The specificity of the assay methods for starting materials must be described.

For new active principles the expert should summarize the studies showing their chemical and physical properties (including comment on the significance of these properties in relation to the bioavailability and pharmacokinetic properties of the preparation.

4. Control tests on intermediate products (part II D)

5. Control tests on the finished product (part II E)

Control methods for intermediate products and the finished product are to be assessed in each case even if they are, or are derived from, pharmacopoeia methods.

The expert should summarize the data on validation of analyti-

cal methods. He should comment on how the tests proposed guarantee that the finished product made on a production scale does not differ in respect of assay, physical and organoleptic properties, composition or pharmaceutical properties from the scale of manufacture described in the application for marketing authorisation.

6. Stability (part II F)

For new compounds the possible degradation and degradation products should be discussed.

It should be indicated whether degradation can develop during storage or manufacture of the finished product, how testing was carried out, with what certainty the degradation products were covered by the tests, what detection limits are to expected from the proposed methods. The shelf-life should be stated together with proposals for any storage warnings.

7. Miscellaneous

Under this heading other relevant information is described, which is not covered by the previous headings.

8. Conclusion

The conclusion should show in particular whether the proprietary medicinal product is of the appropriate quality and whether the proposed control methods correspond to the state of the art and are an appropriate means of assessing quality.

9. Reference list

References should be complete and formulated in accordance with internationally accepted standards, and include all literature cited.

The references must be numbered and each reference should be easily located in the application file in question.

10. Information on the expert(s)

IV EXPERT REPORT ON THE TOXICOLOGICAL AND PHARMACOLOGICAL DOCUMENTATION

The expert report should consist of the following sections:

1. Introduction
2. Toxicity
2a. Acute toxicity
2b. Toxicity with repeated administration
2c. Foetal toxicity and fertility studies
2d. Mutagenic potential
2e. Carcinogenic potential
3. Pharmacodynamics
4. Pharmacokinetics
5. Miscellaneous
6. Conclusion
7. Reference list
8. Information on the expert(s)

1. Introduction

2. Toxicity (part III A - (III E)

For all toxicological tests the reasons for the selection of species, dose, application, duration of treatment/experiment and the number of animals used should be justified, having regard to pharmacokinetic/metabolic data, and to pharmacodynamic effects relating to the toxicological studies, and to the relationship between the animal species used and between animal and man.

Toxicological studies relating to the same problem should be documented together and state the value of their extrapolation to man. If other experimental models than whole animals are used their validity should be established.
Consequences regarding special populations at risk, and need for further studies should be stated and judged.

2.A. Acute toxicity (part III A)

The acute toxicity tests should be summarized (tabulated) for each species and route of administration. (An example of a tabular presentation is given in the annex.) Toxic symptoms should be described as well as any other relevant information e.g. cause of death. Any species or sex differences should be stated.

An evaluation should be given of:

- local damage at the site of administration and organ damage
- time course of behavioural modification and death
- interactions with other ingredients of the proprietary medicinal product (fixed combinations).

Dose-response relationships should be evaluated. Precise information on the lethal dose-response relationships is not required if the maximum non-lethal dose and/or the minimum lethal dose can be judged.

2.B. Toxicity with repeated administration (part III B)

Data should be summarized for each species, specifying the duration of the test and the route of administration. For each investigation the dosage is to be stated as well as the number of animals per dose level, the sex of the animals and now frequently the drugs have been given. (An example of a tabular presentation is given in the annex.) The dosages chosen should be discussed and justified, giving special regard to the relationship between duration of study and dose (pharmacokinetics).

The parameters studied, including laboratory tests and pathological investigations, should be stated, and the results that are relevant to the assessment should be summarized.

The evaluation of toxic effects should consider the time of appearance, dose dependency, their reversibility (irreversibility), and their possible causes.

2.C. Foetal toxicity and fertility studies (part III C)

Investigations into teratogenic and other embryotoxic effects, peri- and postnatal toxicity, and fertility should be summarized for each species and route of administration. For each study the dosage, the number of animals per dose and the period of administration in relation to gestation should be specified. The parameters studied as well as the methods used

to examine foetuses should also be described. Maternal and paternal reactions should be reported, as well as the drug's effect on the course of pregnancy, the foetus and the young. The risk involved when using the drug in connection with pregnancy in man should be discussed.

2.D Mutagenic potential (part III D)

All mutagenicity studies should be summarized. The mutagenic potential must be discussed taking into account the chemical structure of the compound, the mode of action, relationship to known mutagens, the pharmacokinetics in man.

2.E Carcinogenic potential (part III E)

Data from carcinogenicity studies must be summarized, stating animal species, dosages, route of administration, length of test, number and sex of animals. The results must be statistically analysed. If tumours are observed, their type, frequency and time of occurence must be summarized, and their possible cause should be discussed.

The estimation of the carcinogenic potential of the drug must take into account the chemical structure, relationship to known carcinogens, mode of actions (if possible), mutagenicity studies and carcinogenicity studies in animals.

If epidemiological data, or data from clinical trials are available, these should be included in the discussion.

The estimated carcinogenic risk for man should be discussed.

3. Pharmacodynamics (part III F)

Studies of the primary pharmacological effects and mode of actions forming the basis for the drug recommended use should be summarised, with particular reference to quantitative aspects. The relation between dose and effect should be described.

Studies of secondary pharmacological effects of the drug must also be reported.

The data should be discussed with regard to:

- desired effects:
  species used (strain, sex), rearing methods, anesthesia of experimental animals, etc.;
- mode of action (if possible):
  systemic actions, actions on cells and subcellular structures and biochemically detected actions;

- safety:

  indications of undesirable actions, e.g. interactions, tolerance and possible acute poisoning.

4. Pharmacokinetics (part III G)

   Studies of absorption, distribution, metabolism and excretion should be summarized, with reference to any species differences for the relevant routes of administration and dosage forms. A comparison to human kinetics should be made. The relevance for the toxicological studies should be discussed. Possible kinetic interactions should also be discussed. The choice of pharmacokinetic models and calculations for pharmacokinetic constants should be explained. When statistical calculations are included the methods used and reasons for their use should be stated. Bioavailability data should be summarized and discussed.

5. Miscellaneous

   This section is intended for summaries of studies not covered by any of the previous headings e.g. tissue-irritant effects, sensitization, risk of addiction or dependency, specific toxic effects or comparison of different dosage forms.

6. Conclusion

   The expert should state what conclusions can be drawn from the results of the tests. The pharmacological and toxicological observations should be discussed in the light of relevant scientific literature, paying particular attention to the drug's characteristics in comparison with those of any related already known drugs. The pharmacological and toxicological data presented in this section should be evaluated where possible in relation to the proposed clinical use of the compound. Both efficacy and risk aspects derived from the preclinical documentation should be considered.

   Points to be included in the discussion:

   - choice of doses or effective concentrations;
   - plausibility in the selection of species, e.g. by kinetics and metabolism;
   - assessment of a possible cumulation, tachyphylaxis, tolerance development or withdrawal symptoms;
   - assessment of pharmacological data for treatment of acute poisoning, e.g. antidotes or other specific measures;

- formal compilation of results, especially a critical examination of the statistical methods used;
- shortcomings existing at the beginning of testing, in the performance of the tests or in the conclusions;
- risk criteria, i.e. indication of narrow therapeutic range;
- results of animal experiments related to clinical trials;
- animal husbandry and standards of good laboratory practice

7. Reference list

References should be complete and formulated in accordance with internationally accepted standards, and include all literature cited.

The references must be numbered and each reference should be easily located in the application file in question.

8. Information on the expert(s)

V EXPERT REPORT ON THE CLINICAL DOCUMENTATION

The expert report should consist of the following sections:

1. Introduction
2. Human pharmacology
3. Clinical documentation
4. Miscellaneous
5. Conclusion
6. Reference list
7. Information on the expert(s)

1. Introduction

2. Human pharmacology (part IV A)

2.1. Pharmacodynamics

The effect and mode, if possible, of action of the product, relevant to the indications for which it is intended, must be described. The duration of action and the relationships between the dose, plasma concentration, effect and time should be elucidated. Effects on other organ systems should also be included, as well as tolerability in general.

The documentation should cover i.a.:

- definition of healthy volunteers and patients
- number of subjects
- age groups
- methods of registration and evaluation
- mode of action(s)
- desired effect(s)
- effect(s) of different organ systems
- possible side effects
- dose-response relationship
- time-effect relationship
- dose-plasma concentration relationship
- optimal dose and dose regimens
- statistical methods

2.2. Pharmacokinetics

A summary of the pharmacokinetics profile of the drug, as well as adequate curves and tables must be presented.
The documentation should cover i.a.:

- aims of the investigation
- methods
- number of subjects
- age-groups
- healthy volunteers or patients
- design of trials
- dosage, modes of administration
- intersubject variability

The report should comprise inter alia : rate and extent of absorption, distribution, protein binding, metabolism, including any results on possible genetic polymorphism, occurence of active and inactive metabolites, if possible, and elimination characteristics (e.g. total body clearance and elimination halflife) and excretion pathways including the metabolites. When relevant, information should be included concerning old age, children and patients with impaired renal and/or hepatic function, and other risk groups. For drugs intended for chronic use information on steady state kinetics should be given. Kinetic interactions should be elucidated if suspected. Differences between human and animal pharmacokinetic features should be emphasized.

2.3. Interactions

It should be stated whether interactions exist between the drug in question and relevant other drugs likely to be coadministered.

3. Clinical documentation (part IV B)

3.1. Therapeutic effect

The main purpose of the clinical documentation is to demonstrate the therapeutic effect of the proprietary medicinal product, where appropriate, in comparison with existing therapy. The expert report should reflect this. The data and the qualified evaluation should give a clear picture of the therapeutic characteristics, efficacy and tolerance.
A tabular presentation of all clinical trials should be given. This should contain the main characteristics of the

trials, such as the title of the study and the country in which it was carried out, the type, the number of patients, the dose regimen and route of administration, the duration of treatment, the diagnosis and the reference drug, if any (An example is given in the annex.).

The most important trials should be summarized individually (An example for a tabular presentation is given in the annex.).

Therefore special emphasize should be given in the presentation of those trials (phase II) which give unequivocal evidence of the efficacy and provide justification of the proposed therapeutic dosage regimens. Any relationship between efficacy and dosage and/or duration of treatment and/or particular patient populations should be described. If the treatment with the product could be improved through plasma concentration monitoring, documentation for e.g. an optimal therapeutic plasma range should be included.

If different formulations and/or different routes of administration have been used the tables should show the number of patients subjected to each formulation and route of administration.

The results should be summarized (therapeutic results, observed side effects, observed interactions ect.).

For each indication the evidence for efficacy at the dosage proposed should be given. The objective and subjective criteria for efficacy should be specified (e.g. reduction of blood pressure, reduced need for escape analgesia).

The number of trials showing a positive result and those showing a negative result should be given together with a suitable explanation.

The number of drop-outs should be mentioned together with the reason for drop-out.

The expected and unexpected effects of therapeutic doses as well as overdoses (if information is available) and the contra indications are to be described and compared with other drugs with analogous effects.

For drugs to be administered long-term attention should be paid to long-term efficacy. Regarding fixed ratio combination products it is essential to include commented documentation showing the therapeutic value in comparison with the single ingredients, when taken separately in therapeutic doses. The doses of the individual components should be justified. A thorough evaluation of such a product's therapeutic advantages should be given.

Insofar as chemical incompatibilies (e.g. with other drugs and/or solutions) are considered clinically relevant, a discussion of such problems should be included in the reports.

3.2. Adverse reactions, tolerance and interactions

Documentation covering adverse reactions (including clinical and laboratory changes), should be exhaustive and their relevance and profile discussed. The number of patients studied, the dosage regimens (including duration of treatment) and methods of assessment should be stated.

If there is a different spectrum of adverse reactions for different diseases being treated this should be pointed out.

The frequency of adverse reactions should be described and should be compared with that of the reference drugs.

When the product is already on the market in some countries, the adverse reactions reported and the figures of consumption in these countries should be reported.

Interactions, overdosage reactions and intoxications, drug dependence potential, rebound phenomena after discontinuation of therapy, possible use during pregnancy and breast feeding and possible influence on e.g. car driving should all be considered.

4. Miscellaneous

This section is intended for information not covered by any of the previous headings.

5. Conclusion

In this chapter the following items should be discussed:

a. rationale of the product (especially in the case of fixed combinations, new dosage forms);

b. efficacy;

c. safety aspects (e.g. adverse reactions, contra indications, interactions, warnings and precautions);

d. proposed dosage (range, frequency, age, sex, duration of therapy, etc.);

e. the balance between the benefits and the risks of the product, taking the results of the pharmacological and toxicological tests into account.

6. Reference list

References should be complete and formulated in accordance with internationally accepted standards, and include all literature cited.

The references must be numbered and each reference should be easily located in the application file in question.

7. Information on the expert(s)

VI. SAMPLE PHARMACEUTICAL EXPERTS REPORTS FORMS:

PART II A COMPOSITION	
Description : Page(s) -	COMMENT
Complete composition : Page(s) -	
Active constituents Other constituents	
Container(s) & Closure(s) (brief description) Page(s)	
Clinical trial formula(e) : Page(s) -	

PART II A	DOSAGE FORM
Development Pharmaceutics : Page(S) -	COMMENT

PART II B METHOD OF PREPARATION	
Method of Preparation of Dosage Form. Page(s)	COMMENT
Batch size: Manufacturing formula:	
Manufacturing process	

PART II B	DOSAGE FORM
Process validation : Page(s) -	COMMENT

PART II C	CONTROL OF STARTING MATERIALS
II C 1.a.: Active constituents (routine tests)	COMMENT
(a) Active constituents described in a pharmacopoeia (b) Active constituents not described in a pharmacopoeia	
SPECIFICATION AND TEST METHODS	
Appearance : Page(s) -	
Identity test(s) : Page(s)	
Physical test(s) : Page(s) -	
Chemical test(s) : Page(s) -	
Other test(s) : Page(s) -	
Assay(s) : Page(s) -	

PART II C	CONTROL OF STARTING MATERIALS
II C 1.b.: ACTIVE CONSTITUENTS (DATA)	
ACTIVE CONSTITUENT	
1. NOMENCLATURE : Page(s) -	COMMENT
Laboratory Code / National approved name(s)	
I.N.N.	
Chemical name	
Other name(s)	
2. DESCRIPTION : Page(s) -	
Physical form	
Structural formula	
Molecular formula / Molecular weight	

PART II C	CONTROL OF STARTING MATERIALS	
II C 1.b.: ACTIVE CONSTITUENTS (DATA)		
3. MANUFACTURE		COMMENT
Synthetic route(s) : Page(s) -		
Description of process : Page(s)		
Solvents and reagents		
Catalysts		
Final purification		
4. Quality control during synthesis : Page(s) -		
Starting materials	Specifications	
Intermediates tested	Tests Applied	

PART II C	CONTROL OF STARTING MATERIALS	
II C 1.b.: ACTIVE CONSTITUENTS (DATA)		
5. DEVELOPMENT CHEMISTRY		COMMENT
Evidence of chemical structure : Page(s) -		
Synthetic route		
Key inter-mediates		
Elemental analysis		
MS		
NMR		
IR		
UV		
Other methods		
Potential isomerism : Page(s) -		
Asymmetric carbons		
Optical rotation		
Cis-trans Isomerism		
Threo-erythro isomerism		
Other isomers		
Physico-chemical characterisation : Page(s) -		
Solubility		
Physical characteristics		
Polymorphism		
pKa and pH values		
Other characteristics		
Analytical development : Page(s) -		

PART II C	CONTROL OF STARTING MATERIALS
II C 1.b.: ACTIVE CONSTITUENTS (SCIENTIFIC DATA)	
6. IMPURITIES	
Potential impurities : Page(s) -	Analytical methods of detection
Impurities found : Page(s) -	
COMMENT	

PART II C	CONTROL OF STARTING MATERIALS	
II C 1.b.: ACTIVE CONSTITUENTS (SCIENTIFIC DATA)		
7. BATCH ANALYSIS		COMMENT
Batches tested : Page(s) -		
Date(s) of manufacture: Place(s) of manufacture: Batch size(s) and No.(s) Use of batche(s)		
Results : Page(s) -		
Batch Nos		
Appearance: Identity test(s): Physical test(s): Chemical test(s): Other test(s): Assay(s):		
Reference Standard : Page(s) -		
Appearance: Identity test(s): Physical test(s): Chemical test(s): Other test(s): Assay(s):		

PART II C CONTROL OF STARTING MATERIALS	
II C 2.a.: OTHER CONSTITUENTS (ROUTINE TESTS)	COMMENT
(a) Other constituents described in a pharmacopoeia	
(b) Other constituents not described in a pharmacopoeia	

PART II D CONTROL TESTS ON INTERMEDIATE PRODUCTS	COMMENT
PART II E CONTROL TESTS ON THE FINISHED PRODUCT:	
Page(s) -	
Description and general characteristics	
Identification tests	
Quantitative determination of active ingredients : page(s) -	
Other QC tests	
Identification and quantitatives determination of other constituents	

PART II E DOSAGE FORM	
Control tests on finished product Analytical validation : Page(s) -	COMMENT

PART II F STABILITY

Information concerning stability of the finished product (Page(s) -

Number of batches tested:

Storage conditions:

Description of containers:

Results of Tests

Analytical methods (if different to those in Part II E):

Proposed shelf-life and storage precautions

COMMENT:

PART II F STABILITY	
Stability tests on active constituent	
Batches examined : Page(s) -	
Conditions of storage	Results
Analytical methods	
COMMENT:	

VII. SAMPLE EXPERT REPORT TABLES:

- PHARMACOTOXICOLOGICAL
- CLINICAL

Part III A: Acute toxicity

Species + Strain	No of animals + sex/group	Route of administr.	Formu-lation and dosage	Time of deaths + period of observation	Approximate lethal dose + method of calculation	Symptoms	Volume + Page

Part III B: Toxicity with repeated administaration

(Title of the study + reference)

Species + Strain	No of animals + sex/group	Duration	Route of administr.	Formulation	Doses + frequency

Results

Dose	Biochemistry + Haematology	Behaviour/Gross pathology/Histology

SUMMARY OF REPORTS OF CLINICAL TRIALS COMPANY: NAME OF DRUG:

INVESTIGATION	VOLUME, PAGE	DESIGN	NUMBER OF PATIENTS	DOSE REGIMEN AND ROUTE OF ADMINISTRATION	DURATION OF THERAPY	DIAGNOSIS	REFERENCE DRUG	CRITERIA	ADVERSE REACTIONS

Clinical expert report
(table)

SUMMARY OF REPORT OF CLINICAL TRIAL

NAME OF COMPANY	
NAME OF DRUG	
TITLE OF STUDY	
INVESTIGATORS	
LOCATION OF TRIAL	
PERIOD OF TRIAL	
PUBLICATION	
PURPOSE OF TRIAL	
CLINICAL PHASE	
DESIGN	
NUMBER OF PATIENTS	
DIAGNOSIS	
DRUG FORM, ROUTE OF ADMINISTRATION, DOSE REGIMEN	
DURATION OF THERAPY	
REFERENCE DRUG, DOSE REGIMEN	
APPL. VOL. AND PAGE	
SUMMARY	

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Notice to applicants - For marketing authorizations for proprietary medicinal products in the Member States of the European Community on the use of the new multi-state procedure created by Council Directive 83/570/CEE

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