COMMISSION OF THE EUROPEAN COMMUNITIES

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REPORT FROM THE COMMISSION

ON THE ACTIVITIES

OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

(Article 15 § 1 of Directive 75/319/EEC as amended)

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REPORT FROM THE COMMISSION TO THE COUNCIL ON THE ACTIVITIES OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

I. INTRODUCTION

1. Subject of the report

The present report of the Commission to the Council covers the operation of the various procedures within the framework of the Committee for Proprietary Medicinal Products (CPMP), of coordination of national authorizations to place medicines for human use on the market, established by Community law[1].

The Commission shall, in accordance with the first paragraph of Article 15 of Council Directive 75/319/EEC, as amended by Directive 83/570/EEC, "report to the Council every two years on the operation of the procedure laid down in this chapter and its effects on the development of intra-Community trade". As the first applications made in accordance with this procedure, called "multi-State", were only presented in 1986, it seemed reasonable to allow sufficient time to elapse so as to fully describe the operation of the new procedure.

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[1] In order to facilitate the reading of this report, texts of the Community pharmaceutical legislation cited are summarized in chronological order in annex I, with their publication references.

2. Content of the report

It is important to consider this "multi-State" procedure in relation to both, the preceding procedure which was completed in 1986 and the most recent procedure specifically designed for high technology medicines.

Indeed, in conformity with the time-periods set out in the Community Directives, the last applications made in accordance with the old procedure established by Directive 75/319/EEC, were examined at the start of 1986. It is useful therefore to prepare a comprehensive review of the 41 applications examined under that procedure between 1978 and 1986. This previous procedure has been the subject of 4 successive reports[2] and of a more general report[3] which accompanied the 5 proposals from the Commission to the Council regarding high technology medicines, particularly those produced by biotechnology.

Amongst these proposals adopted in the interim by the Council, Directive 87/22/EEC introduced in July 1987, a new Community concertation procedure applicable prior to all national decisions concerning high technology medicines, especially those produced by biotechnology, which will be briefly mentioned here, taking account of its very recent introduction.

With the passing of the years, the general role of coordination of the Committee for Proprietary Medicinal Products, beyond the specific procedures mentioned above, has progressively expanded. These other activities of the Committee should also be considered, especially pharmacovigilance and the continuous updating of requirements and practices in the grant of marketing authorizations in the Member States of the Community.

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[2] Reports from the Commission to the Council on the operation of the Committee for Proprietary Medicinal Products:
- COM(79)59 of 22.2.1979;
- COM(80)149 of 31.3.1980;
- COM(81)363 of 13.7.1981;
- COM(82)787 of 3.12.1982.

[3] COM(84)437 of 3.12.1984

3. Intra and extra Community trade

The number of applications discussed by the Committee for Proprietary Medicinal Products are still very few in comparison to the hundreds of national applications made separately each year in each Member State. Therefore, there is no scope for assessing the effect of the various Community procedures on the development of intra-Community trade. Nonetheless, some key statistical information relating to the pharmaceutical industry in the European Community has been presented in Annex II of this report. The European pharmaceutical industry still seems successful. It represents one quarter of the World market (approximately 25 billions ECU), and more than half of World pharmaceutical exports, thus yieldung a positive trade balance for the Community of approximately 3.5 billions ECU. It employs around 40,000 people in the Community, of which the level of qualification is generally high. Unfortunately, in the last twelve years, one can see a slow decline in our market share compared with the United States and Japan, as well as a reduction in the number of European new chemical entities at the research and development stage (40% versus 65% for the last 10 years). One of the reasons for this could be the relatively small size, with some notable exceptions, of European companies compared to large international firms. The size and scope of a single large market will probably encourage the optimization of research and production activities of European firms, in order to maintain their competitiveness.

II. THE COMMUNITY REGULATIONS AND RECENT DEVELOPMENTS IN THE PHARMACEUTICAL SECTOR

1. Community pharmaceutical legislation

For more than 20 years, the European Community has contributed to the improvement of the protection of public health by extending to all Member States, old and new, regulations for the placing on the market of medicines for human and veterinary use, guaranteeing quality, safety and efficacy to the highest international level (Annex I). Regarding access to and maintenance on the market of medicines, the Community experience is considerable and prevents now the repetition of long and expensive tests and trials in Europe.

Five important consequences have resulted for the circulation of medicines within the Community:

a) The criteria for quality, safety and efficacy of medicines have been progressively harmonized, as well as certain aspects of the procedures for marketing authorization (time-periods, motivation, publication) or for manufacturing (quality control, inspections).

b) Analytical, pharmaco-toxicological and clinical testing of medicines performed in conformity with Community rules need not be repeated within the Community.

c) Batch controls, carried out in the country of origin, are recognized in the other Member States.

d) The general requirements for labelling or for the package insert have been harmonized.

e) A list of colouring matters permitted for use in medicines has been adopted.

For the future, the up-dating of the technical requirements for the testing of medicines has been delegated by the Council to the Commission, in accordance with the so-called Regulatory Committee Procedure, which involves the participation of government experts. This legislation allows the Community to exercise its international competences in the pharmaceutical sector. Thus regular contacts take place with the USA, Japan and international organizations such as the Council of Europe and the World Health Organization.

2. The national authorities and the Committee for Proprietary Medicinal Products

Within the current framework of Community regulations, the 12 Member States remain fully responsible for deciding whether to grant or refuse a marketing authorization, in conformity with Community law. In spite of the agreed harmonization of regulations, divergences of evaluation have been found in the decisions taken by national competent authorities regarding marketing authorizations for medicines. To reduce these divergences a committee consisting of representatives of Member States and the Commission was formed in 1977: the Committee for Proprietary Medicinal Products (CPMP).

This committee may be invited by the Member States or the Commission to give an opinion, of an advisory nature, on particular medicines, especially for monitoring side-effects of medicines (pharmaco-vigilance). The Committee can also be called upon by pharmaceutical firms in accordance with the various Community procedures, designed to facilitate the adoption of a common position among Member States regarding marketing authorizations, and their operation will be described later.

The Members of the Committee are expressly charged in the Member States and the services of the Commission with matters relating to the authorization of medicines; they elect amongst themselves a president and a vice-president for a 3 year term, renewable once; the Commission nominates the other vice-president and acts as secretariat to the Committee. The presidency of the Committee has moved successively from Mr L. Robert (Luxembourg) to Dr C.A. Teijgeler (Netherlands).

Following election, the vice-presidents have been Pr D. Poggiolini (Italy), Pr B. Schnieders (Germany), then Dr G. Jones (UK). The list of members of the Committee is given in Annex III.

3. The pharmaceutical proposals of the White Paper

The role of the Community is to ensure a favourable regulatory environment for this industry which is already over-regulated, whilst also supporting the protection of public health and its improvement by increased development of pharmaceutical research in Europe.

This has led the Commission to propose 13 specific initiatives in the pharmaceutical sector, in its White Paper on the completion of an internal market.

Six measures are already adopted and in force:

- 4 directives of December 1986 in favour of high tech/biotech medicines;

- a new recommendation of February 1987 on the testing of drugs;

- a communication of December 1986 from the Commission on the compatibility with Article 30 of the EEC Treaty of price control measures.

Three initiatives have been submitted to the Council at the beginning and end of 1987:

- a proposal for a directive on to the transparency of national measures relating to the control of prices of medicinal products for human use and their inclusion within the scope of the national health insurance systems[4];

- a proposal regarding the adhesion of the European Community to the Convention on the elaboration of an European Pharmacopoeia and a report on the implementation of the mandate for negotiation given by Council on 26 May 1987[5];

- 4 proposals to extend the Directives to cover medicines not already included[6].

Four further initiatives are the subject of preparatory work and will be submitted to Council in due course:

- amendment of the Directives relating to veterinary medicines,

- selection of a definitive system for free circulation (mutual recognition or a single authorization, applicable throughout the Community),

- harmonization of the conditions of delivery of medicinal products to patients (over-the-counter and prescription medicaments),

- improvement of the information for doctors and patients with a view to more rational use of medicines.

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[4] COM(86)765 of 23.12.1986 and OJ C 17 of 23.1.1987

[5] SEC(86)2010 of 15.12.1986 and SEC(87)2001 of 21.12.1987

[6] COM(87)697 of 4.1.1988, OJ C 36 of 8.2.1988

III. REVIEW OF THE FORMER PROCEDURE OF DIRECTIVE 75/319/EEC (1978-86)

1. The former procedure

It is useful to recall that the procedure established by Articles 9 to 11 of Directive 75/319/EEC allowed a company to request a marketing authorization in five or more Member States, after having obtained a first authorization in accordance with Community Directives. During the time-period of 120 days for the examination of the application, the Member States concerned could raise reasoned objections, giving rise to an opinion of the CPMP, which had to be given within 60 days and followed within 30 days by a statement from the Member States concerned on their position.

2. The operation of the former procedure

This procedure was hardly used by the pharmaceutical industry, which led the Commission to propose substantial improvements resulting in the multi-State procedure. The essential details of the 41 applications made between 1978 and 1985 are given in Annex IV of this report. This sample is too small to allow a satisfactory statistical extrapolation. These 41 dossiers covered a total of 253 (individual) marketing applications made to 5 Member States or more. After a slow start, the number of applications increased from 1980 to 1983, and declined thereafter. Amongst those countries which had given the initial authorization, the UK is most evident with 16 of the 41 dossiers, followed by France (7) and Denmark (7), Germany (5), Belgium (5) and lastly Ireland (1). Of those countries receiving applications, the Benelux is the most frequent recipient: Luxembourg (37), Netherlands (35) and Belgium (33), then Italy (28), Denmark (28), Germany (25), Ireland (24), UK (18), France (15), and Greece (12). Due to the date of their accession to the Community, Spain and Portugal were not concerned by this procedure and Greece was involved only since 1981.

3. The companies concerned

This procedure therefore has involved the competent authorities of all Member States. It is interesting to note for these 41 dossiers the country of origin of the firms concerned, on the basis of available information:

9 companies from USA (11 dossiers), 7 French (7 dossiers), 4 Danish (11 dossiers), 3 German (3 dossiers), 3 Swedish (3 dossiers), 1 Belgian (3 dossiers), 1 UK (1 dossier), 1 Dutch (1 dossier) and 1 Swiss (1 dossier).

Furthermore, a majority of applications came from medium-sized pharmaceutical entreprises, as against only 9 applications from multinationals which are normally listed in the top 35 pharmaceutical companies in the World. Only a small number of applications concerned new chemical entities.

4. The outcome from the former procedure

So as to facilitate analysis of the position, a working group has graded the 41 opinions given by the CPMP according to a scale consisting of 7 levels, going from an unanimously favourable opinion (grade 1) to an unanimously unfavourable opinion (grade 7). It emerges from this that 28 opinions were favourable of which 20 were unanimous, whilst 13 were unfavourable of which 5 were unanimous. In other words, only one half of the initial authorizations given by one Member State were in principle acceptable to all other Member States, on the basis of the same harmonized legislation. The 253 applications coming from these 41 dossiers resulted in 175 marketing authorizations and 63 definite refusals. 15 cases remain suspended generally because the company has not supplied the Member State with the additional information requested, following the opinion of the Committee. Half of the definitive decisions have been taken in the year following the opinion of the Committee, with the exception of Italy where there exists an administrative practice which ties the marketing authorization to the fixing of price and is the subject of an infraction procedure under Article 169 of the EEC Treaty. It is, however, worrying to note that the other half of definitive decisions have taken more than 1 year and as much as 4 years in extreme cases, after the opinion of the Committee.

IV. THE "MULTI-STATE"PROCEDURE, INTRODUCED IN 1986 BY DIRECTIVE 83/570/EEC

1. The new rules of the "multi-State" procedure

In adopting, on the proposal from the Commission, Directive 83/570/EEC, the Council reformed many important aspects of the previous procedure which had been established by Directive 75/319/EEC. In the first place, Member States must in future take into due consideration the initial authorization, save in exceptional cases when they refer reasoned objections to the opinion of the Committee. Secondly, to make the procedure more attractive, the minimum threshold of Member States concerned has been reduced from 5 to 2, and firms have at their disposal direct access to the Committee by virtue of the introduction of the right to a hearing - which does not exist in many national procedures. Thirdly, in order to be in a position to reach a decision with full knowledge of the facts, the Member States concerned have at their disposal a detailed description of the content of the initial authorization in the form of a "summary of product characteristics" as well as a critical evaluation report prepared by the original country, at least in the case of new medicines. It is important however to point out that the procedure remains optional for the companies and that the opinions of the Committee are not legally binding on the Member States.

2. The operation of the multi-State procedure

Resulting from these improvements, the multi-State procedure has proven more attractive to pharmaceutical firms as, since 1986, 36 dossiers have been submitted until February 1988.

From the point of view of countries concerned, the tendencies of the previous procedure linger in the multi-State procedure. Spain just joined the procedure in 1986, while Portugal has, by virtue of the Treaty of Accession, a transitional period of 5 years to implement the pharmaceutical Directives. The list of countries considered most reliable by the companies as the starting point for the procedure confirms the previous experience. The UK still leads the countries who have granted the initial authorization, with 14 dossiers out of 36, followed by France (9), Germany (5), Ireland (3), Belgium (2) and Denmark (2), Italy (1).

Regarding countries receiving applications, the order is as follows: Belgium (23), Luxembourg (22), Greece (21), Italy (21) and Germany (21), Netherlands (19), Spain (18), Denmark (16), UK (13), Ireland (12) and France (12). These 36 multi-State dossiers cover 198 individual national applications, with an average of a little more than 5 States per application, and this is despite the lowering of the obligatory threshold to at least 2 Member States as indicated above. Taking account of the usual time-periods of the procedure and the additional time requested by the companies in order to better prepare their responses or hearings, the Committee has rendered 20 opinions to date, of which 17 were favourable. Companies have, in 7 cases, had recourse, at their request, to a hearing with the Committee.

3. Preliminary analysis of results

It is unfortunate that, to date, every dossier has systematically been the subject of reasoned objections, in spite of the obligation on Member States to take due consideration of the initial authorization, save in exceptional cases. In this system, similar legally to the model for mutual recognition of marketing authorizations, the safeguard clause, in this case the opinion of the Committee, is in fact systematically used by Member States; and this despite the fact that the initial authorizations were given by a limited number of national authorities whose scientific competence is internationally renowned. The political willingness, declared by certain Member States, to adopt the principle of mutual recognition, has not yet translated itself into the actual administrative practice of the competent authorities in granting authorizations in these same Member States. If the multi-State procedure is to serve as a testing ground leading to a system of mutual recognition of authorizations, the experience thus far is not very convincing. While within the CPMP, the introduction of the multi-State procedure was accompanied by a remarkable development of co-operation between the national delegates and their experts, the national committees responsible for the scientific evaluation of medicines have not always given the necessary priority to reinforce this European co-operation which they have followed rather than supported.

4. The crisis of national authorization procedures

Apart from a certain lack of information, progressively filled in by a multiplicity of symposia on the European procedures, and the natural fear of these national committees to see their own influence diminish, the relative inertia of national authorities can be attributed to the serious crisis which they have encountered over the last number of years in most of the national authority systems. In fact, since the beginning of the 80's, the number of applications has more than doubled in all industrialized countries, combined with increasing scientific complexity of the dossiers, whilst the human and material resources have generally evolved more slowly, indeed even stagnated. In the area of high technology, only some countries have available competent experts, and even these are limited in number. This results in a progressive lengthening of the delays in authorization, to the detriment especially of patients and European pharmaceutical research. To avoid these delays and the long national waiting lists, companies have turned more and more to the multi-State procedure, which risks being overloaded in its turn as it is in effect dependant upon the smooth operation of the national systems.

5. Development of the Committee

The CPMP, which has not been equipped with its own resources, has available only a tiny secretariat, provided by the services of the Commission. The principle of mutual recognition which under-writes the multi-State procedure introduced by Directive 83/570/EEC, should mean that only a limited number of exceptional cases would require an opinion of the Committee, the Member States taking into due consideration, in the great majority of cases, the initial authorization. The ability of the Committee to formulate opinions for the Member States and the Commission would be totally saturated if the number of cases submitted were to go beyond several dozen dossiers per year. The Committee is neither equipped nor legally mandated to become a systematic appeal authority against national decisions: it would be necessary then to radically change the system.

On the initiative of the president and vice-presidents of the Committee and its secratariat, initial considerations are in hand to improve the practical operation of the Committee, and to suggest

ultimately alternative operational rules. Thus, the various steps of the multi-State procedure have been clarified and the Member State of origin is usually designated as rapporteur, particularly to facilitate the liaison with the company, the other concerned countries and the secretariat (see Annex V).

6. A standard format for marketing authorization applications in Europe

Immediately after the adoption of Directive 83/570/EEC, the Commission began examining, with the help of an ad hoc group of the CPMP led by Prof. Poggiolini (Italy), the possibility of preparing a common standard format, acceptable to all the Member States, for the presentation of applications and a simplification of language requirements. The result was a guide entitled "Notice to applicants for marketing authorization 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", published for the first time in 1986 (see Annex I, N.B.).

The competent authorities have since then accepted the extension of the use of this single format to all national and Community applications, on the basis of a draft revised notice, lengthily discussed with the representative authority of the European pharmaceutical industry[7] and distributed by them under the title of "Notice to applicants for marketing authorizations for proprietary medicinal products in the Member States of the European Community", which will be published in due course. This standardization,hailed as major progress by the pharmaceutical industry, reduces considerably the administrative burden of companies and assigns major importance to the summary of the dossier; this avoids particularly the systematic manipulation of a full dossier, the volume of which can sometimes be several cubic metres. The standard EEC format has been largely accepted by the other countries of Western Europe and could in the future serve as the basis for international harmonization (see Annex VI).

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[7] EFPIA = European Federation of Pharmaceutical Industries' Associations

V. THE PROCEDURE RESERVED FOR MEDICINES OF HIGH TECHNOLOGY ACCORDING TO DIRECTIVE 87/22/EEC, IN OPERATION SINCE JULY 1987

1. The new procedure of Directive 87/22/EEC

For high technology/biotechnology medicines, Directive 87/22/EEC obliges the competent authorities to consult each other within the Committee for Proprietary Medicinal Products before deciding to authorize, refuse or withdraw a high technology medicinal product. With effect from 1 July 1987, this consultation procedure will apply systematically for biotechnology, which is considered to be a priority by the Community and in the case of other high technology medicinal products, at the request of the firm concerned. In the annex to the Directive, these medicinal products are defined by two lists. List A comprises medicinal products derived from new biotechnological processes (recombinant DNA, hybridomes/monoclonal antibodies and cell cultures). List B comprises several other categories of high technology medicinal products which, in the opinion of the competent authorities, must constitute a significant innovation. The principal steps of this procedure are illustrated in Annex VII.

2. The protection of innovation

High technology medicinal products which have followed the new procedure will benefit from a certain form of market exclusivity for a period of ten years running from the date of the first authorization to market the product within the Community. This ten year period may in certain cases extend the protection offered by patent. The protection conferred by patent law, and in particular the Munich Convention on the European Patent, is often insufficient because the maximum period of 20 years protection is frequently reduced by the time taken to complete testing and obtain authorization. In addition, the current protection offered by patent law for biotechnology inventions is generally not considered to be completely satisfactory.

The solution adopted by the Community in Directive 87/21/EEC mainly requires the copier:

- either to obtain the consent of the innovatory firm to refer to the original tests,
- or to wait ten years from the date of the first authorization to market the "high technology medicinal product" within the Community before being able to present an application in simplified form covering primarily the quality of the product and, if necessary, its bioavailability. This mechanism of protection is elaborated in detail in Annex VIII.

3. Operation of the procedure of Directive 87/22/EEC

Anticipating the adoption of Directive 87/22/EEC, and thanks to the good co-operation on the part of competent authorities, the Committee has had experience of an application introduced by France regarding a monoclonal antibody designed to prevent the rejection of renal grafts and had given a favourable opinion in June 1986 on the matter.

Since the entry into force of Directive 87/22/EEC, in July 1987, the Committee has so far only received 3 new applications for which its referral was obligatory (list A), with Denmark and France as rapporteur countries; the consideration of these applications is currently under way.

It would be premature at this point to draw conclusions from this new procedure which, while fundamentally national, nontheless represents a significant step in the direction of a single evaluation which is applicable throughout the Community. The crisis of national authorization systems, mentioned above, is also likely to affect countries acting as rapporteur in conformity with Directive 87/22/EEC. But this co-ordinated procedure presents for the Member States a first interesting opportunity to pool the expertises available and to attempt to compensate for the deficiencies of individual authorities working in isolation.

VI. OTHER ACTIVITIES OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

1. Emergency measures and pharmacovigilance

In accordance with the Directives, the competent authorities of the Member States are obliged to exchange all appropriate information in order to guarantee the quality, safety and efficacy of medicinal products. In addition they must immediately inform the Committee for Proprietary Medicinal Products of any refusal or withdrawal of a marketing authorization and of any prohibition on supply. In association with the Member States, the Commission has instituted a system of exchange of information about the dangers resulting from the use of medicinal products. A constantly updated list of contact persons makes possible the rapid exchange of urgent information by telex or telefax.

Every two months, if necessary every month, the Committee for Proprietary Medicinal Products considers questions linked to the adverse effects of medicines. The Committee also takes into account questions raised in the European Parliament and contributions coming from the European consumer organizations. This pharmacovigilance work has considerably intensified over the past few years, and currently covers some ten to fifteen products at each meeting.

Medicines thus examined become the subject of an information sheet, which indicates their status in the 12 Member States. These sheets are updated and collated in a confidential file sent every 2 months to the competent authorities. The exchange of this information could be facilitated by the installation, during the next 2 years, of a computerized system.

At the request of a Member State, the Committee can prepare an opinion on unwanted side-effects. In this context, and as an example, an important opinion was given in July 1986 on the use of aspirin in children and the so-called Reye's Syndrome; in May 1987, after a hearing with the company, an unfavourable opinion regarding the continued marketing of Suprofen, an analgesic, was given.

The president of the Committee and the representative of the Commission have requested a modification of the internal rules of the Committee, in order to allow greater public dissemination of the conclusions of the Committee when a medicine is in question.

2. Working Parties established by the Committee

In association with the Committee for Proprietary Medicinal Products, preparatory work is undertaken in order to codify and harmonize the detailed national practices in the implementation of the existing Community Directives and to prepare the technical updating of the Directives. The Pharmaceutical Committee, which consists of the Directors-General for pharmacy in the national ministries of health, and which meets about twice a year, is also consulted on these measures. This work has already been conveyed by two Recommendations on the testing of medicines (83/571/EEC and 87/176/EEC) and by the publication of the notice to applicants mentioned above. The work is continuing, with the participation of about one hundred government experts and in close consultation with the European pharmaceutical industry, in the following working parties:

a) The **Quality of Medicines** Working Party, chaired by Dr. Cartwright (United Kingdom), has prepared or is considering guidelines on stability, chemistry of the active ingredient, development pharmaceutics and process validation, analytical validation and some improvements to the Directives; a sub-group led by Dr. Hefendehl (Germany) is involved with the quality of herbal remedies; another sub-group led by Dr. Kristensen (Denmark) is involved with radiopharmaceuticals.

b) The **Biotechnology/Pharmacy** Working Party, chaired by Dr. Schild (United Kingdom) has prepared 3 guidelines on the quality of medicines derived from recombinant DNA technology, monoclonal antibodies as well as on the safety testing of medicines from biotechnology; it advises the Committee, in its consideration of these medicines, as well as the Commission, on the extension of the Directives for biotechnology products, especially vaccines.

c) The **Safety of Medicines** Working Party, chaired by Prof. Bass (Germany) studies particularly local toxicity testing and preclinical safety trials of medicines produced by biotechnology, in conjunction with the above group.

d) The **Efficacy of Medicines** Working Party, chaired by Prof. Alexandre (France), has finalized the "general rules and scientific principles for the conduct of clinical trials" which were adopted by the Committee in July 1987. Work is in hand on guidelines for clinical trials in the elderly and children, on anti-depressants, anti-arrhythmics and cardiac insufficiency; a sub-group is looking at anti-cancer medicines, with the participation of E.O.R.T.C. (European Organization for Research and Treatment of Cancer).

e) The ad hoc group on the **Evaluation Report**, chaired by Prof. Poggiolini, has prepared the "Notice to Applicants" relating to a standard European format for marketing applications, in conjunction with the chairmen of the other working parties; Annex II of the Notice, which concerns expert reports, is in the course of revision.

f) Lastly the activities of the drafting group for the preparation of an **"EEC guide to Good Manufacturing Practices (G.M.P.)"**, chaired by Dr. B. Hartley (United Kingdom), whilst not directly linked to the Committee, usefully completes the work of technical harmonization.

3. International spin-off of the Committees activities

On the World scene, the Community has shown its commitment to support international co-operation, in particular to guarantee the quality of medicines exported to third countries and to supply necessary information to developing. This stance has been defended at the World Health Assembly, as well as at the 4th meeting of I.C.D.R.A. (International Conference of Drug Regulatory Agencies) held under the aegis of the World Health Organization, at which the president, vice-presidents and several members of the Committee actively participated.

The Committee and the chairmen of the Working Parties equally provide technical support to the Commission in bilateral discussions. For example, after the success in July 1984 of an initial technical visit to Tokyo by pharmaceutical experts of the Committee, a second visit is in preparation for 1988.

At the European level, contacts were increased with the Council of Europe, which in the pharmaceutical sector has many technical activities complementary to those of the Community, in the form of the European Pharmacopoeia, the Committee of experts on pharmaceutical questions (Partial Agreement), and the Committee of experts on the blood transfusion. Close connections have also been established with the Nordic Council of Medicine and the system of the Convention of Pharmaceutical Inspections (PIC) related to the European Free Trade Association.

4. Other activities of interest to the Committee

The achievement of a single market by 1992 implies not only the free circulation of medicines, but also a much greater harmonization of the essential information accompanying these medicines, such as the main indications and their dosage regimen, contra-indications and precautions for use. A study initiated in 1985 for the Committee by Prof. Poggiolini, and which will be completed in 1988, shows that the great majority of preparations marketed in all the European markets are based on only a few hundreds of common active principles. The Committee could act as the forum to compare the summaries of product characteristics of a limited number of the medicinal products, appropriately selected so as to advise the Commission on the best means, in the future, of reducing the obvious differences in the information accompanying these hundreds of medicines of European significance.

In order to improve information for European patients, and in compliance with the conclusions of the Council of Ministers of Health of 15 May 1987, the Commission organized, at the end of 1987, the first meeting with representatives of the European Consumers Organizations and the pharmaceutical industry, i.e. EFPIA and AESGP[8].

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[8] Association Européenne des Spécialités Grand Public
(The Proprietary Association of Europe)

For many years, considerable attention has been paid to rare diseases which do not benefit from adequate treatment because the number of affected patients is low. The cost of pharmaceutical research for such so-called "orphan" drugs is generally dissuasive on industry.
Neither the European Community, nor its Member States, currently have any special legislation for orphan drugs, comparable to the "US Orphan Drug Act" of 1983. However, certain aspects of the Community pharmaceutical regulations can already favour the access to the European market of orphan drugs and can assure them some protection.
An exemption is already expressly foreseen for orphan drugs by the following terms, from point 5 of the last chapter of Directive 75/318/EEC:

"5. When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on therapeutic efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence,"

In such a case, the marketing authorization may be granted on conditions such as administration under medical supervision, possibly in a hospital and with information to the doctor on the incompleteness of the available data.

Some orphan drugs could also benefit from the advantages of the procedure, introduced by Directive 87/22/EEC, which is especially open to "medicinal products containing a new substance or an entirely new indication which, in the opinion of the competent authority concerned, is of significant therapeutic interest" as well as those "medicinal products administered by means of new delivery systems which, in the opinion of the competent authority concerned, constitute a significant innovation".

VII. CONCLUSION

In accordance with Article 15 of Directive 75/319/EEC as amended, and also with the legislative programme set out in the White Paper on the Internal Market, in the light of experience, the Commission must, before 1 November 1989, submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of medicinal products within the Community. The Commission hopes that the presentation of this report, which describes the experience acquired within the Committee for Proprietary Medicinal Products to date, will serve as a basis for reflexion by the Member States and interested parties as to the form which any definitive system for the free movement of medicinal products might take (mutual recognition, a centralized Community system or an intermediate approach).

The Commission therefore invites those concerned to submit comments on this question and also their comments and suggestions on the other matters described in this report. Any contributions should be addressed, before 1 September 1988, to:

Service III/B-6
"Pharmaceuticals, Veterinary Medicines"
Directorate-General for Internal Market and Industrial Affairs
Commission of the European Communities
200, rue de la Loi
B-1049 Brussels

Before the end of 1988, the services of the Commission will prepare a memorandum which will summarize the comments received and set out provisional conclusions which will serve as a basis for consultation during the elaboration of detailed formal proposals in 1989.

ANNEXES

ANNEX I

RULES GOVERNING PHARMACEUTICALS IN THE EUROPEAN COMMUNITY

- COUNCIL DIRECTIVE 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° 22 of 9.2.65).
- COUNCIL DIRECTIVE 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (O.J. n° L 147 of 9.6.75).
- 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.
- COUNCIL DIRECTIVE 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products (O.J. n° L 11 du 14.1.78).
- COUNCIL DIRECTIVE 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products (O.J. n° L 317 of 6.11.81).
- COUNCIL DIRECTIVE 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (O.J. n° L 317 of 6.11.81).
- COMMISSION COMMUNICATION on parallel imports of proprietary medicinal products for which marketing authorizations have already been granted (O.J. n° C 115 of 6.5.82).
- COUNCIL DIRECTIVE 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 332 of 28.11.83).
- COUNCIL RECOMMENDATION 83/571/EEC of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products (O.J. n° L 332 of 28.11.83).

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- COMMISSION COMMUNICATION on the compatibility with Article 30 of the EEC Treaty of measures taken by Member States relating to price controls and reimbursement of medicinal products (O.J. n° C 310 of 4.12.86).
- COUNCIL DIRECTIVE 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations or administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (O.J. n° L 15 of 17.1.87).
- COUNCIL DIRECTIVE 87/19/EEC of 22 December 1986 amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (O.J. n° L 15 of 17.1.87).
- COUNCIL DIRECTIVE 87/20/EEC of 22 December 1986 amending Directive 81/852/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (O.J. n° L 15 of 17.1.87).
- COUNCIL DIRECTIVE 87/21/EEC of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (O.J. n° L 15 of 17.1.87).
- COUNCIL DIRECTIVE 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology (O.J. n° L 15 of 17.1.87).
- COUNCIL RECOMMENDATION 87/176/EEC of 9 February 1987 concerning tests relating to the placing on the market of proprietary medicinal products (O.J. n° L 73 of 16.3.87).

N.B. The texts adopted before 1984 are contained in a publication entitled "The rules governing medicaments in the European Community", on sale at the Office for Official Publications of the European Communities, L-2985 Luxembourg, catalogue number CB-41-84-515.
The guide entitled "Notice to applicants for marketing authorizations for proprietary medicinal products in the Member States of the European Community on the use of the multi-state procedure created by Council Directive 83/570/EEC" is also on sale at the Office for Official Publications of the European Communities, L-2985 Luxembourg, catalogue number CB-47-86-163.

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ANNEX II

MAIN DATA ON THE PHARMACEUTICAL SECTOR

1) INTERNATIONAL TRADE OF PHARMACEUTICALS IN 1986 (NIMEXE 30)

   11) Imports in thousands of ECU

   12) Imports in market share (%)

   13) Exports in thousands of ECU

   14) Export in market share (%)

2) EVOLUTION OF EXTRA AND INTRA-EEC TRADE OF MEDICAMENTS, INCLUDING VETERINARY MEDICINES, (1981-1986) (NIMEXE 30.03)

   21) Imports (Millions of ECU)

   22) Exports (Millions of ECU)

3) PENETRATION OF EEC MARKET BY COMPANIES OF VARIOUS ORIGIN IN 1984

   31) Sale in millions of US $ (retail pharmacies at manufacturers'prices)

   32) % of EEC market held

   33) % of local market held

   34) Home sales on % of EEC sales

4) PHARMACEUTICAL PRICES AND CONSUMPTION IN THE EEC

   41) Indices of price levels

   42) Consumption per capita : in US $ (1984), as % of GDP (1984) and as % of health care costs (1983)

5) PHARMACEUTICAL RESEARCH AND DEVELOPMENT

   The top 100 companies in 1987
   (EEC companies underlined).

1. INTERNATIONAL TRADE OF PHARMACEUTICALS

/¯ NIMEXE 30, SOURCE: EUROSTAT _/

1 1. IMPORTS BY PARTNER AND REPORTER

1986 UNITS = VALUE (000 ECU)

NIMEXE SR=4 PHARMACEUTICAL PRODUCTS
30
BASE YEAR 1986

REPORTER

TO PARTNER	BELG.-LUXBG.	DENMARK	FR GERMANY	GREECE	SPAIN	FRANCE	IRELAND	ITALY	NETHERLANDS	PORTUGAL	UTD. KINGDOM
WORLD	610681	244053	1390309	112896	181339	452731	181925	816912	713428	115465	796578
INTRA-EC	471543	146944	757325	83653	106686	319276	171030	489657	583166	81601	569868
USA	40850	9165	123951	4865	41628	29203	4197	77540	23429	1907	68673
JAPAN	1917	1293	11665	605	1242	1204	42	4779	658	233	967
EXTRA-EC	138867	99905	632985	29234	74656	133445	10891	325843	130260	33862	226916
ACP COUNTR.	290	0	21	2	73	134	0	532	76	9	248

SOURCE EUROSTAT - COMEXT

1 2. IMPORTS BY PARTNER AND REPORTER

1986 UNITS = VAL MARKET SHARE

NIMEXE SR=4 PHARMACEUTICAL PRODUCTS
30
BASE YEAR 1986

REPORTER

TO PARTNER	BELG.-LUXBG.	DENMARK	FR GERMANY	GREECE	SPAIN	FRANCE	IRELAND	ITALY	NETHERLANDS	PORTUGAL	UTD. KINGDOM
WORLD	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
INTRA-EC	77.22	59.53	54.47	74.10	58.83	70.52	94.01	59.94	81.74	70.67	71.51
USA	6.00	3.71	8.92	4.31	22.96	6.45	2.30	9.49	3.28	1.65	8.62
JAPAN	0.31	0.52	0.84	0.54	0.68	0.27	0.02	0.59	0.09	0.20	0.12
EXTRA-EC	22.74	40.47	45.53	25.90	41.17	29.48	5.99	39.89	18.26	29.33	28.49
ACP COUNTR.	0.05	0.00	0.00	0.00	0.04	0.03	0.00	0.07	0.01	0.01	0.03

SOURCE EUROSTAT - COMEXT

1 3. EXPORTS BY PARTNER AND REPORTER

1986 UNITS = VALUE (000 ECU)

NIMEXE SR=4 PHARMACEUTICAL PRODUCTS
30
BASE YEAR 1986

REPORTER

FROM PARTNER	BELG.-LUXBG.	DENMARK	FR GERMANY	GREECE	SPAIN	FRANCE	IRELAND	ITALY	NETHERLANDS	PORTUGAL	UTD. KINGDOM
WORLD	812480	520194	2450828	37147	185420	1730968	176306	549123	648379	21752	1836273
INTRA EC	475904	186290	927530	14805	103353	649162	124718	220500	325809	7061	674498
USA	4315	50928	58921	4	1813	17823	12730	64641	23666	387	157523
JAPAN	27874	47756	285799	0	603	41590	5934	1554	15747	6	66920
EXTRA-EC	341542	333855	1523294	22337	82067	1001738	51587	320563	315480	14696	1161776
ACP COUNTR.	40235	10990	44604	2304	4920	308687	5435	26815	14637	5121	114067

SOURCE EUROSTAT - COMEXT

1 4. EXPORTS BY PARTNER AND REPORTER

1986 UNITS = VAL MARKET SHARE

NIMEXE SR=4 PHARMACEUTICAL PRODUCTS
30
BASE YEAR 1986

REPORTER

FROM PARTNER	BELG.-LUXBG.	DENMARK	FR GERMANY	GREECE	SPAIN	FRANCE	IRELAND	ITALY	NETHERLANDS	PORTUGAL	UTD. KINGDOM
WORLD	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
INTRA EC	58.58	35.81	37.85	39.86	55.74	37.50	70.74	41.61	50.25	32.46	36.73
USA	0.53	9.79	2.40	0.01	0.98	1.03	7.22	11.77	3.65	1.78	8.58
JAPAN	3.41	9.18	11.66	0.00	0.33	2.40	3.37	0.28	2.43	0.03	3.64
EXTRA-EC	41.78	64.18	62.15	60.13	44.26	62.49	29.26	58.38	48.63	67.55	63.27
ACP COUNTR.	4.92	2.11	2.64	6.20	2.65	17.83	3.08	4.88	2.26	23.54	6.21

SOURCE EUROSTAT - COMEXT

2) EVOLUTION OF EXTRA AND INTRA-EEC TRADE OF MEDICAMENTS (INCL. VETERIN.MEDICAM.)

(NIMEXE 30.03, SOURCE EUROSTAT)

2 1. IMPORTS (Mio ECU) Code NIMEXE 30.03 (EUROSTAT)

Year/To	EEC	DE	FR	IT	NL	B/L	UK	IRL	DK	GR	ES	PO
1981	2247	598	162	226	298	340	334	107	101	78		
intra EEC	1585	361	124	160	245	257	228	105	58	43		
1982	2581	674	173	269	349	368	431	117	124	72		
intra EEC	1813	408	132	179	274	278	302	114	77	46		
1983	2985	778	196	325	387	424	520	134	137	80		
intra EEC	2085	465	152	213	303	322	367	126	80	53		
1984	3625	882	252	428	588	456	619	151	159	86		
intra EEC	2592	525	191	267	503	347	453	142	99	62		
1985	4044	1033	310	524	612	495	638	164	179	86		
intra EEC	2900	631	235	327	516	383	474	156	110	64		
1986	4551	1085	363	602	630	544	695	161	209	93	72	97
intra EEC	3077	657	266	357	528	426	520	153	129	68	43	70

2 2. EXPORTS (Mio ECU) NIMEXE 30.03 (EUROSTAT)

Year/From	EEC	DE	FR	IT	NL	B/L	UK	IRL	DK	GR	ES	PO
1981	4567	1192	918	290	306	465	1091	57	218	24		
intra EEC	1576	356	283	76	160	268	317	38	72	1		
1982	5223	1345	1021	345	361	522	1227	85	280	33		
intra EEC	1180	495	333	87	175	299	399	58	98	3		
1983	5817	1470	1159	400	401	603	1300	105	338	35		
intra EEC	2108	472	380	105	203	331	420	72	116	5		
1984	6816	1683	1294	464	604	695	1492	135	339	46		
intra EEC	2484	566	451	148	227	366	503	89	125	7		
1985	7638	1876	1499	559	576	735	1731	146	464	47		
intra EEC	2895	671	54	211	247	396	563	100	145	9		
1986	9801	1998	1548	509	568	746	1596	159	494	36	135	14
intra EEC	3186	758	580	212	278	431	567	110	174	14	59	3

3. PENETRATION OF EEC MARKET BY COMPANIES OF VARIOUS ORIGIN IN 1984 (RETAIL PHARMACIES) - Economists Advisory Group

ORIGIN OF COMPANY →	BE	DK	DE	GR	ES	FR	IR	IT	NL	PO	UK	US	CH	SW	TOTAL
3 1. Sales in:															
US $ Mio BE	41	5	42			46		7	12		51	168	52	7	431
DK	8	120	32			14		3	5		27	5	20	14	248
DE	70	18	1938			176		32	69		171	683	379	58	3594
GR	3	4	31	30		9			3		24	50	37		191
ES	14	9	161		361	48		31	6		85	176	139		1030
FR	80	17	246			1775		11	56		156	726	243		3310
IR	1	3	5			3	1				22	30	8	2	75
IT	9	11	369			125		1061	28	16	221	511	279	27	2657
NL	8	10	46			25		3	40		76	116	47	16	387
PO	4	-	20			7		3		31	13	61	33		172
UK	20	33	165			60		6	14		513	614	133	28	1586
T O T A L	258	230	3055	30	361	2288	1	1157	233	47	1359	3140	1370	152	13681

ORIGIN OF COMPANY →	BE	DK	DE	GR	ES	FR	IR	IT	NL	PO	UK	US	CH	SW	TOTAL
3 2. % of EEC market held	1.8	1.7	22.4	< 1	2.6	16.8	< 1	8.5	1.7	< 1	10	23	10	1.1	100
3.3. % of local market held	10	48	63	16	35	54	1	40	17	18	32				
3 4. home sales as % of EEC sales	16	45	63	100	100	78	100	92	17	66	38				

4. PHARMACEUTICAL PRICES AND CONSUMPTION

	BE	DK	DE	GR	ES	FR	IR	IT	NL	PO	UK
4 1. PRICE INDEX											
EFPIA, 1985 (BE = 100)	100		170			109		103	160		142
BEUC, 1987 (EEC = 100)	80		153		61	69	142	72	140		123
EUROSTAT, 1985 EUR 12 = 100	94	134	160	63	69	77	127	83	140	63	76
4 2. CONSUMPTION PER CAPITA (Economists Advisory Group)											
in US $ (1984)	64	53	89	32	34	73	33	59	33	25	44
as % of GDP (1984)	0.81	0.50	0.89	0.95	0.81	0.81	0.67	0.91	0.38	1.08	0.59
as % of health care cost (1983)	8.6	7.0	11.0	20.2	12.1	8.8	8.8	12.4	4.1	18.9	9.6

5) PHARMACEUTICAL RESEARCH AND DEVELOPMENT :

The top 100 companies in 1987, Pharmaprojects, in SCRIP N° 1270 Jan 1st/ 6th 1988, (EEC companies underlined)

Position 1987('86)	Company	Compounds in R&D: No of R&D drugs	No of own drugs	No under licence
1 (2)	Merck & Co	110	85	25
2 (3)	Bristol-Myers	103	77	26
3 (4)	Ciba-Geigy	98	70	28
4 (1)	Hoechst	97	76	21
5 (8)	Lilly	88	73	15
6 (5)	SmithKline	88	64	24
7(11)	J&J	85	64	21
8(13)	Rhône-Poulenc	84	60	24
9 (9)	Roche	80	56	24
10 (6)	Warner-Lambert	79	65	14
	Subtotal: top 10	912(14.9%)	690(14.4%)	222(16.5%)
11(10)	Elan[1]	76	76	0
12 (7)	Wellcome	75	61	14
13(12)	Takeda	73	60	13
14(14)	Upjohn	65	48	17
15(18)	Sandoz	65	46	19
16(21)	Monsanto	62	40	22
17(15)	Am Home Prod	60	37	23
18(19)	Beecham	59	56	3
19(17)	Schering AG	58	47	11
20(22)	Pfizer	58	37	21
	Subtotal: top 20	1,563(25.5%)	1,198(25.0%)	365(27.1%)
21(23)	Fujisawa	57	45	12
22(16)	Boehringer Ing	57	43	14
23(20)	Roussel Uclaf	51	25	26
24(27)	Erbamont	49	42	7
25(30)	Am Cyanamid	47	34	13
26(31)	Bayer	46	40	6
27(34)	ICI	45	40	5
28(29)	Astra	45	26	19
29(24)	Sanofi	44	40	4
30(28)	Syntex	44	33	11
	Subtotal: top 30	2,048(33.4%)	1,566(32.7%)	482(35.7%)
31(26)	Schering-Plough	43	35	8
32(—)	Research Corp[1]	42	42	0
33(37)	Yamanouchi	42	23	19
34(33)	Sankyo	41	31	10
35(44)	Glaxo	40	30	10
36(32)	Squibb	40	28	12
37(38)	Genentech	38	34	4
38(25)	Merrell Dow	38	33	5
39(48)	Abbott	38	26	12
40(36)	Knoll	37	30	7
	Subtotal: top 40	2,447(39.9%)	1,878(39.2%)	569(42.2%)
41(35)	Sterling Drug	33	29	4
42(46)	Boehringer Mann	32	25	7
43(56)	Meiji Seika	32	21	11
44(45)	Kyowa Hakko	31	25	6
45(39)	Sumitomo	31	20	11
46(62)	Eisai	29	24	5
47(—)	Pharmacia	29	24	5
48(55)	Solvay	29	22	7
49(51)	Shionogi	29	14	15
50(67)	Mitsubishi Chem	27	20	7
	Subtotal: top 50	2,749(44.8%)	2,102(43.9%)	647(48.0%)

Position 1987('86)	Company	No of R&D drugs	No of own drugs	No under licence
51(50)	Daiichi Seiyaku	26	14	12
52(42)	Du Pont	26	14	12
53(41)	Green Cross	25	18	7
54(57)	Yoshitomi	25	17	8
55(54)	Akzo Pharma	25	16	9
56(66)	Recordati	25	12	13
57(40)	Alza	24	24	0
58(43)	Yissum	24	24	0
59(52)	Chiron	24	21	3
60(49)	Teijin	24	21	3
	Subtotal: top 60	2,997(48.8%)	2,283(47.7%)	714(52.9%)
61(72)	Otsuka	24	19	5
62(59)	Rorer	24	19	5
63(47)	Degussa	24	18	6
64(74)	A H Robins	24	15	9
65(73)	Dainippon	23	15	8
66(80)	Taisho	23	15	8
67(58)	Kaken Pharma	23	14	9
68(—)	BTG	22	22	0
69(64)	Chinoin	22	21	1
70(63)	Tanabe Seiyaku	22	18	4
	Subtotal: top 70	3,228(52.6%)	2,459(51.4%)	769(57.0%)
71(83)	Nova Pharma	22	17	5
72(—)	Boots	21	17	4
73(61)	Chugai	21	17	4
74(82)	E Merck	21	16	5
75(69)	Pan Medica	20	20	0
76(—)	Pharmatec (US)	20	20	0
77(68)	Beiersdorf	20	19	1
78(—)	Novo	20	18	2
79(70)	H G Pars	19	19	0
80(65)	Byk Gulden	19	17	2
	Subtotal: top 80	3,431(55.9%)	2,639(55.1%)	792(58.7%)
81(—)	S S Pharmaceutical	19	16	3
82(75)	California Biotech	18	17	1
83(60)	Richter	18	17	1
84(89)	The Liposome Co	18	16	2
85(—)	Ono	18	16	2
86(76)	Pierre Fabre	18	16	2
87(84)	Reckitt & Colman	18	16	2
88(88)	Yeda	18	16	2
89(—)	Ajinomoto	18	15	3
90(81)	Nippon Kayaku	18	11	7
	Subtotal: top 90	3,612(58.9%)	2,795(58.4%)	817(60.6%)
91(78)	Biogen	17	15	2
92(91)	Serono	17	7	10
93(—)	Eastman Kodak	17	1	16
94(—)	Pennwalt	16	16	0
95(87)	SRI International	16	15	1
96(—)	Procter & Gamble	16	13	3
97(97)	CDC Life Sciences	16	11	5
98(90)	KabiVitrum	16	11	5
99(—)	Sigma Tau	16	9	7
100(—)	Hercon	15	15	0
	Subtotal: top 100	3,774(61.5%)	2,908(60.7%)	866(64.2%)

ANNEX III

COMPOSITION OF THE

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

COMITE DES SPECIALITES PHARMACEUTIQUES

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

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Dr. C.A. TEIJGELER

Voorzitter College ter beoordeling van geneesmiddelen,
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Direction générale du Marché intérieur et des Affaires industrielles
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ANNEX IV

APPLICATIONS SUBMITTED UNDER THE 75/319/EEC DIRECTIVE PROCEDURE

(1978 - 1986)

REFERENCES FOR THE TABLES :

AUT	=	Date of marketing authorization.
REF	=	Date of refusal or withdrawal from the market.
OR	=	Country of "origin" which granted the initial authorization on which the procedure was based.
INF	=	Date of last information transmitted by the Member State as a follow-up to the opinion of the Committee.
*	=	Country not concerned in the procedure.
GRADING	=	Grading of the opinion of the Committee using the following criteria :

(0) no objection, no opinion by the CPMP	(no case)
(1) favourable opinion, except for formal reservations	(2 cases)
(2) favourable opinion, except for technical reservations	(18 cases)
(3) favourable opinion by a large majority	(3 cases)
(4) favourable opinion by a small majority	(5 cases)
(5) unfavourable opinion by a small majority	(6 cases)
(6) unfavourable opinion by a large majority	(2 cases)
(7) unanimously unfavourable opinion (not counting the originating Member State).	(5 cases)

MEDICAMENT	Opinion N°	PAYS / COUNTRIES										GRADING:
		B	DK	DE	F	GR	IRL	IT	LUX	NL	UK	
CEFACLOR (R) CEFACLOR	1 20.4.79	AUT 14.9.79	AUT 29.5.79	*	*	*	*	AUT 31.10.80	AUT 21.11.82	AUT 21.8.79	OR 21.8.78	2
CONOVA 30 (R) OESTR. COMBIN	2 20.4.79	AUT 29.7.80	AUT 22.11.79	*	*	*	AUT 8.3.79	AUT 30.9.81	AUT 16.6.80	AUT 17.6.80	OR 14.10.77	2
FLENAC (R) FENCLOFENAC	3 2.4.80	REF 12.5.80	REF 6.7.84	REF 23.5.80	REF 16.5.80	*	*	REF 22.10.81	AUT 17.1.83	REF 28.5.80	OR 16.5.78	7
SYNTARIS (R) FLUNISOLID	4 2.4.80	AUT 22.9.82	*	*	AUT 21.5.80	*	AUT 11.7.80	AUT 7.7.82	AUT 22.9.82	AUT 19.4.82	OR 29.3.78	1
LYCAMED (R) LYSINO-CALC.	5 10.2.81	OR 1.8.79	AUT 26.3.81	AUT 22.9.81	*	*	REF 22.4.83	INF 17.10.86	AUT 2.6.82	AUT 6.1.82	REF 30.12.81	2
DIOPINE (R) DIPINEFRIN	6 12.5.81	AUT 16.4.82	AUT 4.6.81	OR 19.7.78	*	*	*	AUT 31.12.83	*	AUT 3.12.81	AUT 27.10.83	2
ACETARD (R) A.S.A.	7 10.2.81	AUT 18.5.82	OR 2.7.80	AUT 7.9.81	*	*	AUT 2.2.84	*	AUT 29.9.82	AUT 26.1.82	AUT 10.5.83	3
OPREN (R) BENOXAPROFEN	8 10.2.81	REF 6.8.82	REF 7.4.81	*	*	*	*	REF 6.8.82	REF 6.8.82	REF 16.8.82	OR / REF 4.8.1982	4
FLOGAR (R) OXAMETACIN	9 10.3.81	OR 20.3.80	REF 12.7.82	*	*	*	REF 10.3.81	*	REF 7.6.82	REF 6.1.82	REF 10.5.82	7
PRESTIME (R) TIMOLOL COMBIN	10 10.3.81	AUT 11.5.82	AUT 4.10.84	AUT 3.11.81	AUT 14.4.81	*	*	*	AUT 25.1.82	AUT 24.5.82	OR 6.6.79	5
KALINORM (R) POTASSIUM Cl	11 12.5.81	AUT 6.7.82	OR 7.5.79	AUT 6.8.81	*	*	AUT 24.1.83	*	AUT 25.1.83	AUT 3.11.81	AUT 7.12.83	2
SUPROL (R) SUPROFEN	12 7.7.81	*	REF 15.12.86	[AUT 21.10.82]	[AUT 1.6.82]	*	REF 2.10.81	REF mars 87	[AUT 29.9.82]	[AUT 28.12.82]	OR/REF 16.10.86	3
DIDRONEL (R) ETIDRONAT	13 7.7.81	AUT 1.7.82	AUT 7.2.83	*	*	*	AUT 30.7.82	*	AUT 17.1.83	AUT 13.9.82	OR 14.11.80	3
NICORETTE (R) NICOTIN	14 7.10.81	AUT 2 mg 14.10.83	AUT 2 mg 9.3.84	AUT 27.12.82	AUT 2 mg 19.7.85	*	*	AUT 31.12.83	AUT 17.1.83	AUT 17.3.83	OR 20.8.79	6
IDURIDIN (R) IDOXURIDIN	15 7.10.81	AUT 24.2.83	OR 6.1.78	AUT 8.12.82 (5 %)	REF 29.7.82	*	*	AUT 31.12.83	AUT 29.9.82	AUT 25.3.83	*	4
PULMOCLASE (R) CARBOCISTEIN	16 9.12.81	OR 20.5.80	REF 3.12.85	*	AUT 7.8.86	*	AUT 8.2.83	*	AUT 29.9.82	*	REF 28.9.82	5
EQUIBAR (R) METHYLDOPA	17 7.4.82	AUT 3.83	*	AUT 3.5.83	OR 22.12.80	*	*	AUT 31.12.83	AUT 21.2.83	AUT 1.8.83	AUT 26.1.83	2
SELEXID (R) MECILLINAM	18 9.6.82	AUT 3.6.83	OR 30.5.79	AUT 11.9.84	AUT 5.3.84	*	*	AUT 31.12.83	AUT 21.2.83	*	*	2
CARBOSYLANE (R) CHARBON ACTIVE POLYSILANE	19 8.9.82	REF 4.3.83	REF 17.6.87	AUT 27.8.84	OR 16.2.81	AUT 4.4.84	AUT 19.3.86	REF 17.10.86	AUT 17.1.83	AUT 3.7.84	REF 31.1.86	6
RYTHMARONE (R) AMIODARON	20 9.9.82	AUT 7.87	*	AUT 2.5.84	OR 23.11.81	AUT 6.12.84	REF 3.3.87	AUT 31.12.83	AUT 17.1.83	AUT 4.3.83	*	2

MEDICAMENT	Opinion N°	PAYS / COUNTRIES										GRADING
		B	DK	DE	F	GR	IRL	IT	LUX	NL	UK	
VERRUMAL (R) FLUOROURACIL	21 18.12.82	REF 20.4.83	REF 15.6.84	OR 1.11.78	REF 15.7.86	REF 10.10.84	*	INF 17.10.86	*	*	REF 29.11.83	7
PERSTORP (R) CADEXOMERE I.	22 8.9.82	REF 9.6.83	AUT 24.9.82	AUT 8.9.83	AUT 14.2.85	INF 30.6.86	INF 21.11.85	AUT 30.7.87	AUT 25.4.83	AUT 18.10.83	OR 14.8.81	4
FORANE (R) ISOFLUORAN	23 18.11.82	OR 10.2.82	*	AUT 20.2.84	*	*	AUT 31.8.82	AUT 31.12.83	AUT 17.1.83	AUT 14.2.83	AUT 23.3.83	2
MIRAXID (R) PIVAMPICILLIN	24 18.11.82	REF 2.5.83	AUT 06.03.87	AUT 19.7.84	REF 5.3.84	REF 27.9.84	*	REF 17.10.86	AUT 17.1.83	REF 24.8.83	OR 30.6.81	5
ETHIBLOC (R) ZEIN, SODIUM DIATRIZOATE FP	25 28.1.83	AUT 14.12.87	AUT 15.6.84	OR 26.7.79	AUT 27.12.83	*	REF 11.82	REF 17.10.86	AUT 17.1.83	AUT 13.5.85	REF 21.8.85	5
NALGOFAN (R) GLAFENIN	26 28.1.83	AUT 25.5.83	*	REF 20.7.84	OR 26.3.82	*	*	REF 17.10.86	AUT 21.2.83	AUT 2.6.83	*	2
KERLONE (R) BETAXOLOL	27 28.1.83	AUT 11.5.83	AUT 31.12.82	AUT 7.9.83	OR 10.5.82	*	AUT 4.3.86	AUT 15.6.84	AUT 21.2.83	AUT 8.8.83	AUT 15.7.83	1
IBUMETIN (R) IBUPROFEN	28 8.3.83	AUT 9.84	OR 22.10.81	AUT 14.10.83	*	*	AUT 21.1.86	*	AUT 6.8.84	AUT 24.2.84	AUT 8.12.83	2
SABIDAL (R) THEOPHIL.	29 11.5.83	AUT 6.3.84	AUT 25.5.83	*	INF 20.1.87	AUT 10.84	AUT 2.2.86	AUT 30.7.87	AUT 1.8.83	AUT 22.8.84	OR 9.6.82	4
DUOLIP (R) CLOFIBR. ET.	30 11.5.83	REF 28.10.83	REF 3.12.85	OR 28.3.80	*	*	REF 8.2.83	*	AUT 20.6.83	REF 8.6.83	REF 18.10.83	7
BISMAG-LAC (R) MAGALDRAT	31 21.9.83	AUT 18.4.85	*	OR 25.2.81	*	*	AUT 24.9.84	*	AUT 1.8.83	AUT 9.7.85	AUT 25.10.83	3
INDOTARD (R) INDOMETACIN	32 11.5.83	AUT 2.7.84	OR 26.10.82	AUT 1.11.83	*	*	AUT 19.9.83	*	AUT 1.8.83	AUT 25.06.87	AUT 8.5.84	2
ANAUSIN (R) METOCLOPRAMID	33 9.11.83	REF 3.9.84	AUT 31.8.84	AUT 27.8.84	OR 27.12.82	REF 20.9.84	AUT 14.8.84	INF 17.10.86	AUT 21.11.83	AUT 19.7.85	AUT 14.3.85	5
EXIREL (R) PIRBUTEROL	34 11.1.84	AUT 10.84	AUT 1.2.84	*	*	*	*	AUT 30.7.87	AUT 13.2.84	INF 10.4.86	OR 21.5.82	4
AGREAL (R) VERALIPRID	35 11.1.84	*	REF 6.2.84	REF 6.5.85	OR 3.12.79	*	INF 28.3.84	*	*	REF 1.10.85	REF 6.2.84	5
BIDOCYL (R) SODIUM SALICYLAT	36 26.9.84	REF 19.2.86	REF 8.10.84	REF 2.9.85	*	REF 24.10.84	INF 17.2.86	REF 27.11.84	INF 18.3.85	REF 15.10.84	OR 31.1.83	7
OPTIMINE (R) AZATADINE MAL	37 14.11.84	*	AUT 31.12.85	REF 30.5.85	AUT 14.2.85	AUT 22.1.85	*	INF 17.10.86	*	*	OR 3.12.81	2
MST CONTINUS (R) MORPHINE SULPHATE	38 19.6.85	AUT 20.4.84	*	*	AUT 2.5.86	AUT 16.10.85	OR	INF 17.10.86	AUT 14.10.85	AUT 13.2.86	*	2
BISCASE (R) BROMOPAPAIN	39 13.11.85	OR 16.3.84	AUT 3.12.85	*	*	AUT 11.11.86	*	INF 17.10.86	AUT 25.2.86	*	*	2
NORMORIX (R) HYDROCHLOROTHIAZIDE	40 12.2.86	AUT 3.6.87	*	INF 21.4.86	*	*	AUT 1.8.86	*	AUT 21.4.86	*	OR 12.3.85	2
PIRIC (R) PIROXICAM	41 12.2.86	AUT	OR 25.5.79	INF 15.10.87	*	AUT 6.6.86	*	*	AUT 21.4.86	AUT 22.9.86	*	2

CPMP MULTI-STATE APPLICATION SEQUENCE

DIRECTIVE 83/570/EEC

1. A firm applying to use the multi-State procedure
   - consults the competent authority which granted the initial authorisation, agreeing any additions to be made,
   - submits a complete dossier to the other Member States concerned with the application, asking them to take into due consideration the initial authorisation (minimum of 2 other Member States),
   - notifies CPMP secretariat (Committee of Proprietary Medicinal Products).

2. CPMP secretariat sends a telex to all Member States, stating the name of the company and the product, the original country of authorisation and lists countries concerned. Concerned States are thereby invited to notify receipt of the dossier to the CPMP secretariat. All available assessment reports relating to the same product are immediately communicated by the competent authorities to the Member States concerned and to the Committee.

3. Concerned Member States confirm receipt of complete application (by telex or telefax, usually) to the secretariat. When all concerned countries have responded, the 120 day period of consideration commences. Only one telex per month will be sent, notifying the commencement of the 120 day period for all multi-State applications in that month.

   An opinion of the CPMP is not required, if no Member State puts forward any reasoned objection during the 120 day period.

4. In exceptional cases, if there are reasoned objections within the 120 days, the Member State concerned notifies directly to the applicant and the original authorising country. A copy is also sent to the CPMP secretariat for information.

5. After receiving all reasoned objections, the rapporteur enters into consultation with the applicant. The time needed by the applicant to respond is agreed. If an extension of the time is necessary, the rapporteur informs the secretariat of the Committee. The secretariat thereafter informs the Member States. A tentative date for the adoption of the opinion of the Committee is established.

6. In response to the reasoned objections, the applicant prepares a single reaction to each of the objections raised (questions + answers). The format of this response to be the same sequence as the dossier (i.e. Notice to Applicants format).

7. The company's response to be circulated to all members of the CPMP, by name, least 30 working days before the date of the meeting as agreed with (point 5) the company in the format of Notice to Applicants.

8. If the company wishes an oral presentation (hearing), this would be confirmed one month in advance.

9. The rapporteur keeps the CPMP informed of the progress of the application.

10. At the CPMP meeting, the rapporteur reports on the resolution of objections. The hearing (if any) takes place. The secretariat drafts the opinion after the discussion and/or hearing which the Committee adopts the second day.

11. Within 60 days of the issue of the Opinion, the Member States concerned notify the Commission of their decision taken regarding the application.

ANNEX VI

STANDARD FORMAT FOR APPLICATIONS IN THE EEC
(NATIONAL AND COMMUNITY PROCEDURES)

PART I: SUMMARY OF THE DOSSIER	I A - Administrative data
	I B - Summary of product characteristics
	I C - Expert Reports on chemical/ pharmaceutical, toxicological/ pharmacological and clinical documentation
PART II: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION	II A - Composition
	II B - Method of preparation
	II C - Control of starting materials
	II D - Control tests on intermediate products
	II E - Control tests on the finished product
	II F - Stability
	II Q - Other information
PART III: TOXICOLOGICAL AND PHARMACOLOGICAL DOCUMENTATION	III A - Single dose toxicity
	III B - Repeated dose toxicity
	III C - Reproduction studies
	III D - Mutagenic potential
	III E - Oncogenic/carcinogenic potential
	III F - Pharmacodynamics
	III G - Pharmacokinetics
	III H - Local tolerance
	III Q - Other information
PART IV: CLINICAL DOCUMENTATION	IV A - Human pharmacology
	IV B - Clinical documentation
	IV Q - Other information
PART V: SPECIAL PARTICULARS	V A - Dosage form
	V B - Samples
	V C - Manufacturers authorization(s)
	V D - Marketing authorization(s)

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"HIGH-TECH" CPMP CONCERTATION APPLICATION SEQUENCE

DIRECTIVE 87/22/EEC

1. A firm applying to use the concertation procedure
   - for Biotech : requests the first Member State to act as rapporteur;
   - for other Hightech : also requests the first Member State to accept the application as suitable for the procedure (the Member State may refer the matter to the CPMP for agreement).

2. The company makes a formal application to the first Member State who acts as rapporteur thereafter, and notifies the CPMP of the application.

3. The company makes a complete application to as many other Member States as possible and supplies (at least) a summary of the dossier to all other States, certifying that dossiers/summaries are identical. A full dossier plus a summary is supplied to the CPMP.

4. The commencement of the procedure is determined by the rapporteur State and communicated by the secretariat. Member States encountering difficulty regarding receipt of an application/summary notify the rapporteur State directly. The rapporteur establishes a time-table for review as in the Directives (for Bio/High Technology Applications which may be considered as exceptional, the period of review would usually be 120 plus 90 days).

5. The rapporteur State prepares a preliminary assessment report. All Member States are invited to add comment/questions to this.

6. The rapporteur State liaises with the company, particularly regarding questions raised.
   - straight forward questions may be answered directly;
   - complex issues may be discussed between the company and the rapporteur, working party or CPMP.

7. In the event that substantial additional information is required, the rapporteur State may 'stop the clock'. Recommencement of time-limits will be determined by the rapporteur State, who liaises closely with the company.

8. The rapporteur State keeps the CPMP informed of the progress of the application, and confirms the date for finalisation of the CPMP opinion.

30 days before the expiry of these time-limits, the CPMP gives its opinion

9. If the company wishes an oral presentation (hearing), this would be confirmed one previous month in advance.
The company's additional documentation to be circulated to all members of the CPMP, by name at least 30 working days before the meeting, in the format of Notice to Applicants.

10. At the CPMP meeting, the rapporteur State reports on the resolution of objections. The hearing (if any) takes place. The secretariat drafts the opinion after the discussion and/or hearing which the Committee adopts the second day.

11. Within 30 days of the issue of the opinion, the rapporteur State and other Member States concerned notify the Commission of their decision on the action to be taken following the opinion of the Committee.

12. The Member States not directly concerned inform the Committee of subsequent applications for marketing authorisation.

13. Member States inform the Committee in advance of any new regulatory action on pharmacovigilance matters, or in urgent cases, immediately thereafter.

ANNEX VIII

CONSEQUENCES OF THE ENTRY INTO FORCE OF DIRECTIVE 87/21/EEC

The objective of Directive 87/21/EEC is to achieve a greater degree of harmonisation in the rules of the Member States concerning the acceptability of abridged applications (which do not contain full pharmaco-toxicological and clinical data) for authorisation for products which are copies of established proprietary medicinal products. Although the fundamental aim of the Directive is to improve the protection of innovation, the Directive in no way modifies the legislative rules governing the authorisation of innovatory products, for which full data must always be provided. The directive is solely concerned with the conditions for the authorisation of copies.

It follows that the provisions of Directive 87/21/EEC apply to all applications submitted after 1 July 1987 for authorisation to market copies of established products to the competent authorities in Belgium, Denmark, Germany, France, Ireland, Italy, Luxembourg, the Netherlands and the United Kingdom. After 1 July 1987, any person submitting an application without full supporting data in those countries must show that the conditions set out in one of the subparagraphs (i), (ii) and (iii) in Article 4 point 8 (a) of Directive 65/65/EEC as amended are satisfied. Where the applicant seeks to rely on sub-paragraph (iii), he must show not only that his product is essentially similar to another product, but he must also demonstrate that the other product concerned has been authorised within the Community for at least six or ten years, as appropriate, and that it is being marketed in the Member State concerned. Since, in accordance with Article 12 of Directive 65/65/EEC, all decisions to grant marketing authorisation must be published, this should not present any undue difficulty.

So far as the actual length of the period of time for which the second applicant must wait before being able to rely upon sub-paragraph (iii) is concerned, the current situation is as follows :

a) Germany, France, Italy, Belgium, the Netherlands and the United Kingdom have informed the Commission that they intend to apply a period of ten years in respect to all medicinal products.

It should however be noted that this ten year period runs from the date of the first authorisation of the medicinal product in the Community, rather than the date of the authorisation in the Member State concerned.

b) In Denmark, Ireland and Luxembourg, the period of ten years protection will initially be reserved for medicinal products developed by means of one of the three biotechnological processes mentioned in List A of the Annex to Directive 87/22/EEC : recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes,including transformed mammalian cells; hybridoma and monoclonal antibody methods. In accordance with the principles outlined above, this ten year period will apply notwithstanding that the product concerned was first authorised in the Community prior to 1 July 1987. In addition, however, the ten year period of protection will, in the future, also apply to those other high technology medicinal products mentioned in list B of the Annex to Directive 87/22/EEC in respect of which the CPMP has given an opinion pursuant to the procedure provided for in that Directive. So far as other categories of medicinal products are concerned, a period of six years will apply, except in the case of Denmark where this period will not be applied beyond the date of expiry of a patent protecting the original product. Once again it should be noted that these six or ten year periods apply from the date of the first authorisation of the product in the Community rather than from the date of authorisation by the Member State concerned by the application.

c) In Greece, Spain and Portugal, special provisions apply and the rules described above will become applicable on 1 January 1992 at the latest.