COMMISSION OF THE EUROPEAN COMMUNITIES

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

1. INTRODUCTION

1. Objective of the report

The Commission has recently presented its proposals for the future system for the free movement of medicinal products (both for human and veterinary use) within the Community[1], including a substantial explanatory memorandum which provides the background to the introduction of the proposals. The objectives of the future system can best be met by a nuanced approach involving two authorization procedures; one decentralised and the other centralized. These procedures have been elaborated from the experience gained with the current Community procedures, namely the 'multi-state' and 'concertation' procedures. This report is an opportunity to present the experience and results of the current procedures in respect of medicinal products for human use, against which the proposals for the future system may be considered.

This document also reports, in accordance with the first paragraph of Article 15 of Council Directive 75/319/EEC[2], on the operation of the procedure laid down in chapter III of that Directive (i.e. multi-state procedure) and its effects on the development of intra-Community trade, thus updating earlier reports[3].

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(1) COM(90)283 of 14.11.1990

(2) In order to facilitate reading of this report, texts of the Community pharmaceutical legislation cited are summarized in chronological order in Annex 1.

(3) 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;
COM(84) 437 of 3.12.1984, (explanatory memorandum);
COM(88) 143 of 22.3.1988.

The first Community procedure for the co-ordination of national actions on applications for marketing authorizations, which had been established by Directive 75/319/EEC, was extensively documented in the 1988 report to the Council cited above. This earlier procedure ceased to function once the new 'multi-state' procedure came into operation towards the end of 1986. However, given certain similarities between it and the multi-state, it is illustrative to compare the experience gained with each procedure.

Directive 87/22/EEC introduced on 1st July 1987 a further Community procedure, namely the 'concertation' procedure. This Community procedure differs fundamentally from the multi-state procedure in that, it is applicable prior to any national decisions concerning high technology medicines, particularly those produced by biotechnology. Although only in place for a few years, some illustration of its operation can already be given.

2. Content of the report

The present report of the Commission to the Council relates to the global activities of the Committee for Proprietary Medicinal Products and its working parties, and includes the operation of the two Community procedures (multi-state and concertation) for the co-ordination of national authorizations to place medicines for human use on the market, in accordance with Community legislation, as well as developments in the area of pharmacovigilance and international harmonisation.

In performing its role as set out in Directive 75/319/EEC, the Committee for Proprietary Medicinal Products (CPMP) gives an opinion as to whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC. Its activities are therefore not restricted to new applications for marketing authorizations, but also include appropriate scientific and administrative requirements for the making of applications for marketing authorizations. Much of this work is accomplished by the CPMP through its working parties and expert groups, which provide an invaluable support to the Committee and to the Commission.

The work of the CPMP does not end with the decision to grant or refuse a marketing authorization. The Committee maintains a watchful eye on the medicinal products on the market and is constantly active in monitoring the safety and efficacy of medicines on the market, and any change to the side effect profile of a medicinal product. This latter activity, known as pharmacovigilance, has progressively expanded and a number of innovative procedures have been adopted.

On the basis of its expertise, the CPMP has also supported the Commission in international discussions on technical requirements for the authorization of medicinal products, the exchange of scientific knowledge and efforts towards international harmonisation of testing requirements for pharmaceutical products.

In order to reflect the wide scope of activity of the Committee, all of these aspects are considered.

II. ACTIVITIES OF THE CPMP

1. Membership of the Committee

1.1 The Committee for Proprietary Medicinal Products, in accordance with its Rules of Procedure (III/492/77), consists of one representative for each Member State and one representative of the Commission. One alternate is appointed for each of the representatives. A list of the current membership of the CPMP is given in Annex 2.

1.2 The Committee elects its chairman from among its members by absolute majority and secret ballot. The term of office of the chairman shall be three years, renewable once only. Until September 1988, Dr. Teijgeler, had served two successive terms. Professor D. Poggiolini was then elected and currently serves as chairman.

1.3 Two deputy chairmen are appointed, one elected by the Committee and the other appointed by the Commission. In May 1989, Professor J.M. Alexandre was elected deputy chairman, while Mr. Fernand Sauer continues to serve as deputy chairman representing the Commission.

2. Communication and information

2.1 The work of the CPMP is of pivotal importance in the application of the Community pharmaceutical directives. Equally the views of the CPMP on a range of issues are of considerable interest and relevance to the pharmaceutical industry. Given the volume of information produced, the services of the Commission have brought together the relevant texts and published them in a series entitled 'Rules governing Medicinal Products in the European Community'(4). This series was first published in January 1989, and in keeping with the Committee's policy of openness, will be updated and expanded progressively.

* Volume I of the series contains the binding texts adopted by the Community relating to medicinal products for human use. Catalogue number CB-55-89-706-EN-C.

* Volume II is the Notice to Applicants, which replaced the version published in 1986. Catalogue number CB-55-89-293-EN-C.

* Volume III contains technical guidelines dealing with quality including biotechnology testing, pharmaco-toxicological and clinical studies. Catalogue number CB-55-89-843-EN-C.

* Volume IV is the guideline on Good Manufacturing Practice. Catalogue number CB-55-89-722-EN-C.

There is also a Volume V to the series which deals exclusively with veterinary medicinal products.

(4) "Rules governing medicinal products in the European Community", available from the Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

3. Standard application dossier

3.1 At a very early stage, the CPMP identified the need to ensure a common base of information as a prerequisite for harmonised decisions on applications for marketing authorization, which also allowed simplification and transparency of the application process. Thus in 1986, a document known as the "Notice to Applicants" was produced. Since then this text has been extensively revised and expanded. This revised text was published in January 1989 and contains detailed information on the compilation of the application dossier, as well as the preparation of expert reports, the importance and value of which is highlighted.

3.2 The preparation of the Notice to Applicants was done by an ad hoc group of national experts specialised in regulatory affairs. During the course of preparing the document, a number of important points which required consideration became evident. Therefore, the group was formalised on 24.5.89 and became known as the Operations working party of the CPMP. Dr. Teijgeler (former chairman of the CPMP from 1983 - 1988) was appointed chairman of this working party.

This working party is concerned with the procedural and administrative requirements of applications for marketing authorizations, as well as other regulatory issues. Thus the group is preparing a harmonised administrative section (Part IA) of the application dossier for use in any Member State, as well as harmonised positions on general administrative aspects.

This working party will be active in preparing the third "Notice to Applicants" in parallel with the considerations of the Commission's proposals by Council and Parliament, which are planned for 1991; however the current text of Notice to Applicants will remain in force until 1992.

4. Harmonisation of scientific requirements

4.1 Council Directive 75/318/EEC, as amended, sets out the laws relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products. Since its establishment, the CPMP has attached a high priority to the preparation of guidelines on the quality, safety and efficacy of medicinal products.

4.2 These guidelines serve a two-fold objective. Firstly, they are intended to provide a basis for a practical harmonisation of the manner in which the Member States interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. Secondly, they are intended to facilitate the preparation of applications for marketing authorization which are recognised as valid by all 12 Member States.

4.3 The Rules governing Medicinal Products in the European Community, volume III (see 2.1 above) contains guidelines published up to January 1989. A list of guidelines adopted and prepared since then is given in Annex 3 and will be published as an addendum to Volume III of the series 'Rules governing Medicinal Products in the European Community'.

5. Working parties

5.1 At an early stage in its operation, the CPMP identified the need for specialist support in a range of scientific areas. Therefore a number of working parties were set up (Efficacy and Safety in 1977, Quality in 1985, Pharmacovigilance and Operations in 1989). These working parties which are intrinsically part of the CPMP, support the Committee in its role of giving scientific opinions on applications received through the Community procedures.

5.2 In parallel in 1985, the Commission set up a working party on biotechnology, with the joint tasks of helping the Commission in the preparation and technical requirements for the 'biotechnology' Directive (see Annex 1), and a second function which is of growing relevance, the preparation of discussions for CPMP opinions on applications for products derived from biotechnology.

5.3 With the growing numbers and indeed complexity of applications, the working party structures have adapted by operating in a flexible, responsive and selective manner. This involves the working parties working jointly on identified problems; individual experts being convened in ad hoc expert meetings; or invited specialists joining a working party for a specific discussion. A recent example was the special expert meeting on AIDS products held on 6.6.90.

5.4 The facility of convening disparate experts, from diverse disciplines has become an integral part of the operation of the CPMP and its working parties, given the necessity to merge and blend expertise so as to obtain an overall assessment of benefit/risk. The success of this flexible structure, which will be further developed, means that the CPMP will be well placed to deal with the wide array of applications and act as a bridge from today's activities into the future system.

5.5 This flexibility of the working party structure also permits a large number of European experts to feed into the system. Currently there are several hundreds of experts available for a CPMP opinion, and the lists of available experts nationally are continuously updated. The principle areas of scientific activity divide as follows:

* Efficacy: Guided by its chairman, Prof. J.M. Alexandre, the Efficacy working party has considered both general issues and topics of specific therapeutic concern. A most important guideline which was finalized in July '90 was "Good Clinical Practice (III/3976/89)". Over the period 1988 to October '90, the working party met 8 times, with 4 drafting group meetings. Special experts were co-opted for guidelines on Anti-cancer medicinal products (from EORTC), Radiopharmaceuticals and Bioavailability.

* Operations: As described above (paragraph 3.2 of this Chapter), this working party is chaired by Dr. C. Teijgeler.

* Pharmacovigilance: With Prof. Royer as chairman, this recently established working party is preparing harmonised approaches for the monitoring and collection of information on adverse drug reactions (ADR's). In addition to 11 meetings, the working party has liaised with the World Health Organisation on the international monitoring scheme.

* Quality: With the stewardship of its chairman, Mr. A.C. Cartwright, the quality working party has been confronted with and has successfully resolved an important number of difficult problems. The working party has collaborated with the Efficacy, Safety and Biotechnology working parties in turn on a range of guidelines and identified problems. In the last two years there have been 11 full meetings of the working party, two drafting groups i.e. Radiopharmaceuticals (Dr. K. Kristensen) and Herbal Remedies (Prof. Hefendehl); and 5 ad hoc groups.

* Safety: Under the chairmanship of Prof. R. Bass, the safety working party has considered a diverse range of topics. In parallel with its work on guidelines, the group has also considered the toxicology of a selection of substances. The working party met on 7 occasions, consulted outside experts on immmunotoxicity and reproduction toxicity and convened 3 drafting groups for selected topics.

5.6 Moreover, with effect from 1st July 1987, the Council has delegated to the Commission the power to amend the Annex to Directive 75/318/EEC which contains the legal requirements for the conduct of analytical and pharmaco-toxicological tests and clinical trials. With the adoption of the 'Extension' Directives setting out additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens; radiopharmaceuticals; medicinal products derived from human blood or human plasma, it is necessary to modify the technical Annex to Directive 75/318/EEC relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products.

The CPMP and its working parties have assisted the Commission in preparing appropriate revisions, in order to take account of scientific progress. 9 ad hoc drafting groups on immunological products, vaccines in general and influenza vaccine in particular, comprising experts from diverse disciplines, have considered the appropriate revisions, which will be considered by the Committee on the Adaptation to technical progress of the Directives in 1991.

III. MULTI-STATE PROCEDURE

1. Principles of the multi-state procedure

1.1 The legal rules governing the multi-state procedure are set out in Chapter III of Directive 75/319/EEC, as amended by Directive 83/570/EEC. A full explanation of the multi-state procedure is given in the Notice to Applicants.

1.2 The primary purpose of the multi-state procedure is to make it easier for a person who has already obtained a marketing authorization in one Member State to get further marketing authorizations for the product concerned in two or more of the other Member States. The reduction of the number of Member States concerned from five to two was one of the changes introduced in the new procedure (effective 1.10.86).

1.3 The basis upon which the multi-state procedure was established was that a medicinal product, manufactured and marketed in one Member State on the basis of harmonized provisions, should be allowed into another Member State, taking into due consideration the initial authorization, save in exceptional cases which would be submitted to the Committee for Proprietary Medicinal Products. On this account, only exceptional cases would be referred to the CPMP for opinion.

1.4 On the basis of the same documentation, and taking the marketing authorization granted by the first Member State in due consideration, the authorities of the Member States to which an application is addressed have 120 days to grant authorization to market the product in their country or to formulate reasoned objections.

1.5 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 opinion.

1.6 This opinion, which is not legally binding, is addressed to the Member States and to the applicant. Within a period of 60 days from the date of the opinion, the Member States must decide on what action to take pursuant to the CPMP opinion and must inform the CPMP of their decision.

2. Operation of the multi-state procedure

2.1 In order to examine the operation of the multi-state procedure, it is useful to identify the key steps that punctuate the procedure (figures for each step are up to the end of October 1990).

1st step: the applicant company notifies its intention to start a multi-state procedure.....142 applications (of which 3 applications were withdrawn as the applicant did not comply with the requirements of Article 9 of Directive 83/570/EEC, while 2 further applications were withdrawn due to detection of serious side-effects).

2nd step: the concerned Member States confirm the receipt of a valid application and the period of 120 days in Article 9 of Directive 75/319/EEC is initiated by a telex from the Commission to the Member States...122 applications

3rd step: a Member State takes due consideration of the first authorization and authorises the medicinal product ....no application ! i.e. 0% of applications

OR

raises reasoned objections within the 120 day period laid down by the Directive.....122 applications i.e. 100% of applications

4th step: the CPMP gives an opinion on applications referred to it ..... 92 applications

5th step: all concerned Member States notify the action they have taken on the basis of the opinion..... completed procedures i.e. for which all concerned Member States have notified their decision, 45 applications.

2.2 Up to the end of 1990, the multi-state procedure has proven to be much more popular than the previous procedure at 142 applications in four years vs. 41 applications in eight years.

The following chart illustrates the number of multi-state procedures which have started each year (i.e. based on the start of the 120 day period), broken down by quarter:

1986			1987				1988				1989				1990		
Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3
1	1	1	8	6	7	6	5	6	8	11	7	10	13	9	7	7	6

2.3 These 142 procedures correspond to a total of 738 national applications. Thus the average multi-state procedure concerns a little more than five (5.20) recipient countries. This is interesting as one of the improvements requested and indeed implemented with the introduction of the new multi-state procedure (Directive 83/570/EEC) was to reduce the threshold for entry to the procedure from a minimum of 5 countries to 2 countries. It might be suggested therefore that the benefit in reducing numbers was psychological rather than actual!

Of these 142 applications 52% were for more than 5 Member States, whilst only 18% were for 2 Member States. The breakdown is as follows:

Coverage (numbers) of countries by applications

No. of countries concerned:	2	3	4	5	6	7	8	9	10
No. of applications :	25	26	16	12	15	11	16	12	9

2.4 The task of originally authorizing Member State in the multi-state procedure has fallen most heavily on two Member States i.e. United Kingdom and France. The preference for these original Member States was also evidenced in the previous procedure.

Whilst all Member States are concerned in the multi-state procedure, Germany is by far the most frequent recipient. This may be due to the delays which currently exist with applications in Germany.

Former CPMP procedure (Directive 75/319/EEC) 1978-1986

	BE	DK	DE	GR	ES	FR	IR	IT	LX	NL	UK	Total
Country of origin	5	7	5	-	-	7	1	-	-	-	16	41
Recipient country	33	26	25	12	-	15	24	28	37	35	18	253

Multi-state procedure (Directive 83/570/EEC) 1986-October '90

	BE	DK	DE	GR	ES	FR	IR	IT	LX	NL	UK	Total
Country of origin	7	13	11	-	-	34	14	9	-	11	43	142
Recipient country	78	54	102	66	70	49	49	79	74	68	49	738

2.5 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, 83/570/EEC, until 1 January 1991.

However the Portuguese authorities have indicated that they will accept national applications presented in accordance with the standard Community format (i.e. Notice to Applicants).

3. Outcome of the procedure

3.1 The actual experience of the multi-state procedure is not consistent with the spirit of the directive which introduced it, since every single multi-state application has been referred for a CPMP opinion, even though the safeguard clause was only intended to be used in exceptional cases.

3.2 The degree to which Member States take into due consideration the first authorization can be seen from the frequency with which objections are raised. On a sliding scale, the concerned Member States may be rated. With such a grading, Luxembourg emerges as the Member State most consistently 'taking into due consideration' the first authorisation i.e. in all cases the first authorisation has been accepted (unless the Committee opinion has subsequently been negative). At the other extreme, Italy has systematically raised reasoned objections in 93% of applications, whilst the Netherlands have raised objections in 92% of applications which they have received.

	BE	DK	DE	GR	ES	FR	IR	IT	LX	NL	UK
Frequency of systematic objections raised, as a (%)	88	83	85	48	67	74	55	93	0	92	86

3.3 On the initiative of the Chairman, the CPMP adopted a programme for improving the efficiency of its procedures in March 1989. As part of this programme, a number of innovations were introduced.

a) In February '88, applicants were requested make available their single written response to objections raised 30 working days before the application would be considered by the CPMP.

b) The CPMP introduced in April '88 an informal meeting of rapporteurs of concerned Member States which considers the objections raised and the responses received, before the formal meeting of the CPMP.

c) Since May '89, for all positive opinions, the CPMP attaches a summary of product characteristics (prepared in accordance with Article 4a of Directive 65/65/EEC).

d) In November '89 the role of the "rapporteur" (III/3479/89) in the multi-state procedure was clarified.

Arising from these improvements, and the regular exchanges between the Member States, the resolution of objections has been facilitated.

However, the fundamental problem still remains, which is that objections are systematically made to every multi-state application and each application has to be discussed centrally in Brussels. Clearly the system was neither designed not resourced to cope with such a workload.

3.4 The CPMP has given 92 opinions for multi-state applications up and including October '90. Of these 83 have been positive (on a simple majority basis). However this figure can only be taken as a guide as many of these opinions in fact contain a dissension from one or more Member States.

Of the 92 opinions,

* 61 have been unanimously positive (28 of 41 in former procedure),
* 14 positive and 4 negative opinions have had a single dissenting Member State,
* 3 positive and 3 negative opinions have had two dissenting Member States,
* 3 positive opinions have had three dissenting Member States,
* 2 positive opinions have had four dissenting Member States.

3.5 In cases where a Member State dissents from the opinion of the CPMP, the reasons for their position are given in the opinion, as well as an indication of what corrective action may be taken by the applicant. However, as the multi-state procedure does not provide for an appeal mechanism, once the opinion is given, any further information supplied or any further appeal takes place nationally and in accordance with solely national provisions. Nevertheless, the CPMP follow closely the outcome of final decisions until all concerned Member States have properly notified the Committee.

3.6 The devolution of the resolution of outstanding problems back to national procedures has caused significant problems:

Article 14.3 of Directive 75/319/EEC as amended, requires notifation by the Member States to the Committee of decisions on action arising from opinions of the CPMP. Unfortunately, delays considerably longer than the given 60 days have been evidenced. Some of the delay is of course caused by the failure of the applicant to supply the missing data in an efficient manner. An illustration of the extent of delays can be seen from the following:

No. of months since opinion	No. of procedures	Total no. of countries concerned	No. of countries who have not finalised a decision
46	1	7	1
39	1	8	1
38	1	10	1
35	2	10	3
31	2	16	2
27	2	15	2
21	3	21	5
18	1	10	4
16	3	13	5
14	1	6	1
12	3	17	4
10	2	14	4
9	5	26	10
7	2	12	4
6	1	5	3

Additionally, the resulting decisions, each taken in isolation of the other, inevitably lead to different results and different authorizations in the Member States.

It is for this reason that the CPMP has focussed attention on the need to elaborate a guideline on the content of the summary of product characteristics, such that harmonised information may be made available throughout the Community. Work on this guideline is progressing and a draft is anticipated early in 1991.

4. Hearings

4.1 As part of the improvements introduced by the multi-state procedure, the opportunity for applicants to make written and oral explanations was established (Article 14 of Directive 83/570/EEC). Thus a company may present for an oral hearing in cases where one or more Member States have raised reasoned objections in the multi-state procedure, or in cases where one or more Member States have granted a marketing authorization while one or more Member States have refused it and the question has been referred to the CPMP.

4.2 Of course, the concertation procedure also has a facility for hearings with applicant companies. In fact, informal discussions with expert working parties also occur for concertation applications.

4.3 Companies may also be invited to present for an oral hearing in pharmacovigilance' cases (see Chapter IV).

4.4 Although there are no formal rules of procedure for the conduct of hearings, the CPMP recommends the following guidance:

- The applicant should liaise with the Member State/rapporteur regarding the need for a hearing. The hearing should focus on those issues which have not been resolved in previous written submissions.

- Without wishing to specify a formal time limit, the CPMP considers that hearings lasting more than half an hour will not usually be necessary, as a hearing is held to allow clarification of outstanding issues by questioning from the members of the CPMP.

- Any documents to be used in conjunction with a hearing should be distributed to the members of the CPMP 30 working days before the meeting. New studies/data cannot be fully taken into account during such a short hearing, and therefore such data should be made available to the Member States at least 30 working days before the meeting. Very large volumes of new data may require a deferral of discussion in order to allow adequate time for consideration.

- It would normally be appropriate for between one and four persons to appear on behalf of the company concerned.

4.5 The facility for hearings has been in place since 1986. Since then the usage has been as follows:

Multi-state procedure : 31
Concertation procedure : 10
Pharmacovigilance : 3

4.6 It is important to appreciate that a hearing takes place in an environment that is multi-lingual and that simultaneous technical interpretation during the hearing is necessary. Equally, given the very heavy workload of the Committee, and the consequent necessity for short hearings, it is not possible to resolve detailed and extensive technical points, and difficiencies in the dossier cannot be overcome through oral presentations. Therefore the value of the oral presentation should not be over-estimated.

5. Evaluation of the multi-state procedure

5.1 On the basis of the experience now gained, it is possible to draw some conclusions on the operation of the multi-state procedure:

- The procedure is popular and attractive to industry, as evidenced by the number of applications received.

- The eventual outcome of a procedure is generally positive, which is consistent with the underlying philosophy, bearing in mind that one Member State has already authorized the product.

- The procedure achieves results, although not by the principle foreseen in the Directive, but rather through the systematic use of the provision set up for dealing with objections, and not by virtue of its normal principle for functioning i.e. mutual recognition.

- The principle of mutual recognition as it underlines the multi-state procedure, has never worked. Many reasons have been put forward to explain this including national sovereignty and the need to apply a safeguard clause, administrative requirements in individual Member States and the absence of a clear national legal basis for the devolution of responsibility to the first authorizing Member State.

- The multi-state procedure, although currently operating effectively, cannot continue to do so if each and every case is referred to the CPMP because due consideration is not taken of the first authorisation. Given the volume increase in the use of the procedure, the CPMP itself has identified necessary goals in its "Proposals for the improvement of the current functioning of the CPMP" (III/3476/89):

  - A changed attitude to the multi-state procedure in order to obtain a consistent improvement in mutual recognition;
  - Improvement of the technical role of the CPMP, especially intended to render efficient the concertation procedure
  - Introduction of a binding European decision

5.2 The Commission has taken account of the views of the Committee for Proprietary Medicinal Products in the preparation of its proposals for the future system of registration of medicinal products (mentioned above), particularly in relation to the necessity for the highest scientific standard needed for the assessment of applications for marketing authorisations and also the need for a binding European decision.

IV. CONCERTATION PROCEDURE

1. Principles of the concertation procedure

1.1 The legal rules governing the special Community procedure are set out in Council Directive 87/22/EEC. The objective of the special procedure is to enable questions relating to the quality, safety and efficacy of medicinal products developed by means of new biotechnology processes and other high technology medicinal products to be resolved at Community level within the CPMP before any national decision is reached concerning a marketing authorization.

1.2 The concertation procedure is obligatory for all medicinal products developed by means of the following biotechnological processes (List A of the Annex of Directive 87/22/EEC):

- recombinant DNA technology
- controlled expression of genes coding for biologically active proteins in prokaryots and eukaryots, including transformed mammalian cells
- hybridoma and monoclonal antibody methods

1.3 In addition, applicants for marketing authorization for the following groups of products may request that the application be considered under this procedure (List B of the Annex of Directive 87/22/EEC):

- medicinal product developed by other biotechnological processes which constitute a significant innovation;
- medicinal product administered by means of new delivery systems which constitute a significant innovation;
- medicinal products containing a new substance or an entirely new indication which is of significant therapeutic interest;

- new medicinal products based on radio-isotopes which are of significant therapeutic interest;
- medicinal products the manufacture of which employs processes which demonstrate a significant technical advance such as 2-dimentional electro-phoresis under micro-gravity.

1.4 The timetable for the concertation procedure is based on the requirement of Article 7 of Directive 65/65/EEC. Since the applications relate to complex processes which are deemed to be exceptional, the rapporteur, in establishing the period for review, systematically extends the time period of 120 days to include the additional 90 days provided for in exceptional cases by the directive.

For variations however, the rapporteur is at liberty to reduce the period of review to less than 120 days, to as short a time as is practical, given the nature of the variation.

1.5 Given the very complex nature of the applications received in the concertation procedure, an expert working party, called the Biotechnology/Pharmacy working party, was established in 1986 to assist in the scientific evaluation of applications.

This working party (see Chapter I, paragraph 5), whose chairman is Dr. G. Schild, has given technical advice to the CPMP in the many concertation applications which the CPMP has considered.

2. Operation of the concertation procedure

Since this directive came into effect on 1st July '87, there have been applications in respect of 30 medicinal products. Of these 24 are for List A medicinal products, while 6 are for List B medicinal products.

Of the 30 applications, the number of Member States concerned is 337. In fact 25 applications concern all Member States except one.

3. Choice of rappporteur

3.1 Unlike the multi-state procedure, no Member State makes a decision regarding marketing authorization prior to the commencement of a concertation procedure. Therefore the applicant may invite the Member State of its choice to act as rapporteur.

3.2 The task of rapporteur is better distributed between the Member States than in the multi-state procedure, as can be seen from the following (the 1/2 refers to an application where the UK and Fr acted as joint rapporteurs).

	BE	DK	DE	GR	ES	FR	IR	IT	LX	NL	PO	UK	Total
Country of origin	1	5	4	-	-	4 1/2	1	2	-	4	-	8 1/2	30
Recipient country	29	29	29	25	28	29	28	28	27	29	27	29	337

3.3 The nationality of the applicants (by reference to their group headquarters) points up the degree of innovation of the pharmaceutical industry. 15 of the applications were from pharmaceutical companies of the Community (De = 6; Dk = 4; UK = 3; It = 1; Nl = 1), while 13 applicants were from the United States, and one each from Sweden and Switzerland.

4. Variations

A medicinal product which has been considered under the concertation procedure, also avails of co-ordinated review of variations or extensions to the medicinal product. In July '89, the CPMP clarified the position with regard to variations and extensions. Variations always concern all Member States which have authorised the medicinal product.

Given that the medicinal products considered under this procedure are innovatory by their nature, it is not surprising that a high number of variations and extensions are applied for each year. On the current database of medicinal products, the number of variations has been 16. Of these 16 variations, 9 opinions have been given, all of which have been positive.

5. Outcome of the procedure

5.1 Up to October '90, the CPMP has given 11 opinions under the concertation procedure. One opinion was given prior to the formal implementation of the Directive, to allow a 'test-run' of the procedure.

5.2 Of the 11 opinions given, all have been positive. Whilst this may sound impressive, in fact, the practice is for applicants to withdraw an application when it becomes evident that a negative opinion would be given. This practice of withdrawing the application is entirely consistent with a company's responsibility to patients, i.e. if a medicinal product does not meet the necessary standards of quality, safety and efficacy is should not be marketed. A total of two applications have been withdrawn to date.

5.3 For the 11 opinions given for first applications, these represent 121 national applications, for which 79 authorisations have been granted and 42 are awaiting national decision. If the 9 opinions on variations are added to this, the total number of national applications would rise to 217, of which 121 have received authorisations and 96 are awaiting national decision.

A problem similar to that encountered with the multi-state procedure is also evident with the concertation procedure. This is the delay between the giving of an opinion by the Committee and the notification of a national decision on that opinion. By far the worst case is the application, for which two Member States are outstanding for four years on a decision on the CPMP opinion. An illustration of the extent of delays can be seen from the following:

No. of months since opinion	No. of procedures	Total no. of countries concerned	No. of countries who have not notified a decision
27	1	12	1
26	1	12	1
24	1	1	1
16	2	19	4
12	1	11	5
10	1	12	6
7	1	12	3

6. Products authorised as a result of the concertation procedure

In accordance with Article 4.8.a) of Directive 65/65/EEC, an abridged application for a medicinal product essentially similar to a medicinal product of List A or List B, can be made after a period of ten years from the date of first authorisation in the Community. The following products have been considered under the concertation procedure and have received their first authorisation in the Community:

1. ORTHOCLONE (OKT3); authorization holder is Ciiag; first authorized in France on 03.06.1986:

2. NORDITROPIN (recombinant Human growth hormone); authorization holder is Nordisk Gentofte; first authorized in Denmark on 28.04.1988:

3. INSULIN (recombinant insulin); authorization holder is Novo Industri A/S; first authorized in Italy on 06.07.1988:

4. EPREX (erythropoeitin); authorization holder is Ciiag; first authorized in France on 04.08.1988:

5. MONOCLATE P (Mab purified factor VIII); authorization holder is Armour Pharmaceutical Company; first authorized in Italy on 03.10.1989:

6. PROLEUKIN (recombinant interleukin); authorization holder is Eurocetus; first authorization in Spain on 23.06.1989:

7. MYOSCINT (antimyosin Fab - DTPA); authorization holder is Centocor Europe; first authorization in Italy on 13.06.1989:

8. ENGERIX - B (recombinant hepatitis B vaccine); authorization holder is Smith Kline French Labo; first authorization in Belgium on 10.12.1986:

9. RECORMON (erythropoeitin); authorization holder is Boehringer/ Mannheim; first authorized in Denmark on 01.03.1990:

10. GENOTROPIN (recombinant human growth hormone); authorization holder is Kabi Biopharma; first authorization for 16 I.U. in Denmark on 19.02.1990:

11. RETROVIR (zidoduvine); authorization holder is The Wellcome Foundation; first authorisation for asymptomatic patients in Denmark on 20.06.1990.

V. PHARMACOVIGILANCE

1. Continued safety monitoring

1.1 During the period of marketing a medicinal product, it may be necessary, in order to safeguard public health, to take urgent measures such as the modification of the terms of marketing authorization, or its even suspension. The general activity of monitoring the side-effects of a medicinal product, including any active investigation of such incidence, may be included within the meaning of pharmacovigilance.

1.2 Ever since its establishment, the CPMP has exchanged important information (in accordance with Directive 75/319/EEC Articles 30 & 33) on matters of pharmacovigilance. Internal procedures had been described in 1979 (III/1816/79) and 1982 (III/1917/82) including a list of contact people for a system of rapid alert.

1.3 Given the importance of this activity and the need for a most effective exchange of information, particularly when public health is at risk, the CPMP has recently developed further the procedures in this area.

2. Drug monitoring/pharmacovigilance:

2.1 In the Member States, different systems of pharmacovigilance apply and consequently, information on medicinal products is collected in different ways. However, regardless of the method of collection used, be it spontaneous ADR reports, results of new studies, etc., the CPMP considered it essential that such information, properly validated, be communicated as soon as possible to the competent authorities of the other Member States. Therefore a system of communication falling into two parts, i.e. rapid alert and regular notification, was established.

2.2 In the Rapid Alert mechanism, the competent authority of the Member State of origin, i.e. the source of the information, is responsible for sending out the information to all other Member States and the Commission directly, with a copy to the CPMP secretariat.

On the basis of experience with alert reports, an INFO FAX was adopted which allows:

* the INN name (as the main identification); brand names, and company names although not necessarily the same in all Member States, are also be stated.

* the fax includes sufficient details of the incident/report to allow all recipients to appreciate the significance of the report.

* following a rapid alert communication, the competent authority of the Member State of origin prepares a background note for the next CPMP meeting.

2.3 With Regular Communication, the exchange of pharmacovigilance data takes place in the CPMP. Such exchange is a fundamental responsibility of the Committee. However, given its workload, the time of the Committee can be maximized by a preliminary screening of routine data.

Equally important is the communication of data on defective batches of medicinal products, which may, in some cases, be of interest to the pharmacovigilance activity. The working party of the Pharmaceutical Inspectors have established a system for notification and rapid action in these circumstances.

3. Screening of information

3.1 The growing importance of pharmacovigilance problems discussed by the CPMP, identified the need for a specialized group of experts dedicated to pharmacovigilance, with a view to screening the large volume of information and providing technical preparation for the CPMP meeting, leading to the setting up of a pharmacovigilance working party as mentioned in Chapter I, paragraph 5.

This group was set up in February 1989, and a first report on pharmacovigilance in the Member States was issued in September 1989 (report on pharmacovigilance III/3577/89).

3.2 The CPMP continues its responsibility for pharmacovigilance with on-going procedures:

* A DRUG INFORMATION monitor which identifies selected products and updates the information on marketing authorization status and related changes;

* Pharmacovigilance HEARINGS with companies, eventually leading to pharmacovigilance opinions;

* The standardization of the SUMMARY OF PRODUCT CHARACTERISTICS for some products of Community interest for which adverse effects have been identified which require changes to the product particulars.

4. Outcome of pharmacovigilance activity

4.1 In total, the CPMP has given 8 opinions on medicinal products arising from pharmacovigilance reports, covering the following substances:

Aspirin
Lofepramine
Suprofen
Isotretinoin
Isoxicam
Flunarizine
Flecanide/Encainide
Glafenine/Floctafenine

4.2 A total of 8 rapid alerts have been exchanged in the last two years, using the INFO FAX mechanism.

4.3 The Committee has considered the following products in its programme of monitoring from 1988 to 1990:

Adrianomycine, Arteparon, Ativan, Budesonide, Carbosylan, Cronassial, Diprivan, Exifone, Fenfluramine, Fenoterol, Flecanide, Flunarizine, Fluoxetine, Glafenine/floctafenine, Lidocaine, Propacetamol, PPSB, Prazosin, Phenothiazine, Ibuprofen, Isotretinoin, Isoxicam, Methaqualone, Metipranolol, Mianserin, Nitrendipine, Nitrofurazone/ Nitrofurantoin, Noscapine, Retinol, Segontin, Simvastatine, Sodium Aurothiomalate, Sulphamethoxazole, Sulphites, Terconazole, Thalidomide, Ticlopidine, Trimethoprim, Tryptophan, Warfarin.

VI. INTERNATIONAL TRADE AND OTHER ACTIVITIES

1. International Harmonisation

1.1 With the adoption and implementation of Community standards and texts in the pharmaceutical field, the acceptance of these standards and formats internationally has grown. The Notice to Applicants format for the preparation of the dossier is also accepted in the Nordic countries and by EFTA. The guideline on Good Manufacturing Practice has been accepted by the World Health Organisation. The guideline on stability testing is the first of its kind and caters for multiple climatic zones. Equally when embarking on more detailed activity, the CPMP first looks to internationally recognised methods and in general would adopt these if appropriate. For example, the WHO drug monitoring system.

1.2 During 1989 therefore, both the Nordic Council and EFTA were invited to liaise with the technical working parties of the CPMP. In turn, Community experts are invited to technical meetings of the Nordic Council and EFTA. Such exchange of technical expertise allows for the approximation of standards and the removal of technical barriers to trade.

1.3 The convention relating to the elaboration of a European Pharmacopoeia was signed in 1964 within the framework of the Council of Europe. The European Community gave legislative force to the standards of the European Pharmacopoeia in Directive 75/318/EEC and in November 1989, a protocol for the accession of the EEC to the European Pharmacopoeia was opened for signature by participating States. The Protocol will enter into force after its ratification by all 19 states which are Parties to the Convention.

1.4 In keeping with the general approximation of scientific standards, the Commission has established liaison with the United States Food and Drug Administration (FDA). Biannual meetings take place where exchanges of information facilitate understanding. The expertise of the CPMP has been fundamental in the preparation and successful outcome of these meetings.

1.5 Following various missions by European experts and the Commission and in particular the successful mission to Japan in September 1988, regular liaison with representatives of the Japanese Ministry of Health and Welfare (Koseicho) is maintained. The appointment of a pharmaceutical expert to the Japanese delegation to the European Community in Brussels has greatly assisted the exchange of information.

2. International Conference on Harmonisation

2.1 Arising from the excellent relations which have developed, the Commission in association with the FDA and Koseicho authorities, have agreed to jointly sponsor, with the international pharmaceutical industry (IFPMA; EFPIA; US-PMA; JPMA), an international conference on the harmonisation of technical requirements for registration of pharmaceuticals for human use, to be held in Brussels in November 1991.

2.2 This conference has as objectives:

- to provide a unique forum for dialogue between the main regulatory authorities and the pharmaceutical companies worldwide;

- to identify the degree of pharmaceutical harmonisation already achieved bilaterally and the outstanding differences;

- to agree on an action programme to complete international harmonisation (1991 - 1996) with a view to prevent unnecessary repetition of human and animal testing and to reduce pharmaceutical research and development costs.

3. Intra-Community Trade

3.1 From the previous reports (cited above) and from the many economic analyses (e.g. The Cost of Non-Europe in the Pharmaceutical Industry, Volume 15; catalogue number CB -PP -88 -P14 -EN -C, available from the Office for Official Publications of the European Communities), approximately 67% of sales of medicinal products in the Community come from the Member States. This level has been relatively constant for the last decade.

3.2 Figures for the geographic distribution of exports (for bulk and finished pharmaceuticals) are given in Annex 4, as well as the trade balance for pharmaceuticals for each of the Member States.

3.3 Even though the numbers of multi-state and concertation procedures are growing, they only represent less than 10% of the total number of applications made in the Community each year. Therefore the impact of the procedures on intra-Community trade has not been possible to quantify, but may be assumed not to be substantial. However, what has been significant has been the progress of harmonisation which already has produced savings and reduced costs, e.g. a single format for applications, non-repetition of testing, the same requirements throughout the Community. It may equally be said that the procedures have facilitated intra-Community trade and encouraged an appreciation of the resulting commercial opportunities, leading to an attitude of Community availability of medicinal products.

LIST OF ANNEXES.

Annex 1

LIST OF MAJOR COMMUNITY TEXTS APPLYING TO MEDICINAL PRODUCTS

- 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 DECISION 75/320/EEC of 20 May 1975 setting up a Pharmaceutical Committee (O.J. n° L 147 of 9.6.75)

- 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 of 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 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations (O.J. n° L 109 of 26.4.83)

- 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)

- 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 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (O.J. n° L 358 of 18.12.86)

- 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, pharmaco-toxicological 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, pharmaco-toxicological 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)

- COUNCIL DIRECTIVE 88/182/EEC of 22 March 1988 amending Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations (O.J. n° L 81 of 26.3.88)

- COUNCIL DIRECTIVE 88/320/EEC of 9 June 1988 on the inspection and verification of Good Laboratory Practice (GLP) (O.J. n° L 145 of 11.6.88)

- COUNCIL DIRECTIVE 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems (O.J. n° L 40 of 11.2.89)

- COUNCIL DIRECTIVE 89/341/EEC of 3 May 1989 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

- COUNCIL DIRECTIVE 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

- COUNCIL DIRECTIVE 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals

- COUNCIL DIRECTIVE 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulations or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma

- COUNCIL DIRECTIVE 90/18/EEC of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (GLP)

- COUNCIL REGULATION (EEC)2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin

- COUNCIL DIRECTIVE .../.../EEC of 13 December 1990 amending Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products

- COUNCIL DIRECTIVE .../.../EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products

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Annex 2

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STATUS OF CPMP GUIDELINES

1. GUIDELINES ADOPTED BY THE CPMP UP TO DECEMBER 1988:
PUBLISHED IN VOLUME III OF THE SERIES "RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY" (CATALOGUE NUMBER: CB-55-89-843-EN-C)

2. GUIDELINES ADOPTED FROM DECEMBER 1988 TO JULY 1990:
PUBLISHED (ADDENDUM VOLUME III, CATALOGUE NUMBER: CB-59-90-936-EN-C)

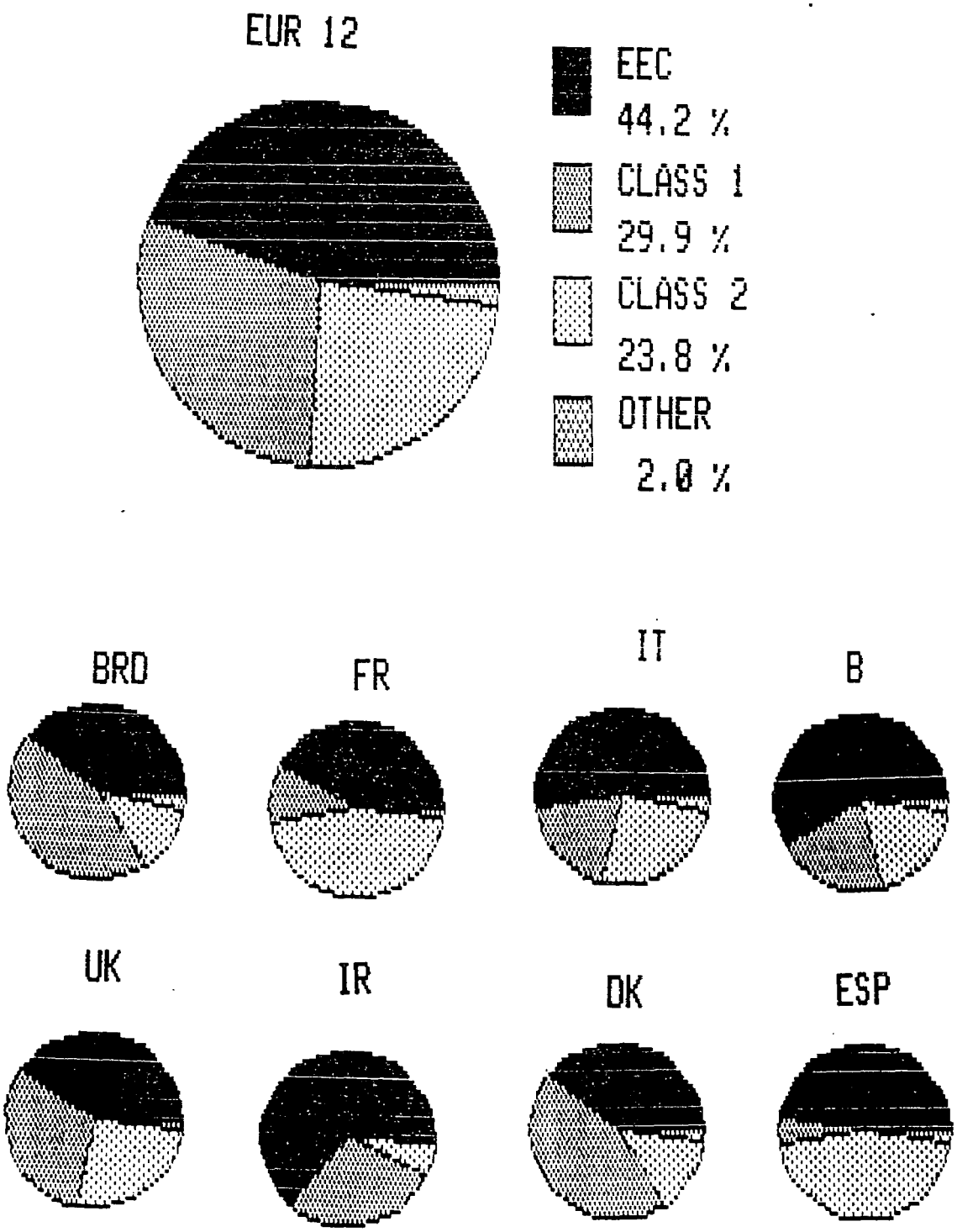
3. GUIDELINES ADOPTED BY THE CPMP

TITLE	NUMBER	LANGUAGE	DATE OF ADOPTION
Local tolerance testing of medicinal	III/3979/89	EN-FR-DE	December 1990
Radiopharmaceuticals	III/3936/89	EN-FR	December 1990

4. GUIDELINES RELEASED BY THE CPMP FOR CONSULTATION

TITLE	NUMBER LANGUAGE	DATE OF RELEASE	DEADLINE FOR COMMENTS	FINALIZATION
Radiopharmaceuticals based on monoclonal antibodies of human origin	III/3487/89 Draft n° 5 EN	Feb. 1990	01.09.1990	Ad Hoc Group March 1991 CPMP May 1991
Validation of virus removal and inactivation procedures	III/8115/89 Draft n° 6 EN-FR	March 1990	01.10.1990	Biotech Jan. 91 CPMP Feb. 91
Recommendations for the development of non clinical testing strategies	III/58/89 Draft n° 7 EN	July 90	15.01.1991	CPMP May 1991
Categorisation of medicinal products for use in pregnancy	III/3862/89 Draft n° 5 EN	July 90	15.01.1990	CPMP May 1991
Investigation of bioavailability and bioequivalence	III/54/89 Draft n° 8 EN	July 90	15.01.1990	CPMP March 1991
Specifications and control tests on the finished product	III/3324/89 Draft n° 7 EN-FR	Dec. 90	01.06.1991	Disc. in W.P. July 1991
Ethylene oxide	III/9261/90 Draft n° 1 EN	Dec. 90	31.03.1991	Disc. in W.P. April 1991
Clinical investigation of hypnotic medicinal products	III/3855/89 Draft n° 3 EN	Dec. 90	01.06.1991	Disc. in W.P. July 1991

GEOGRAPHICAL DISTRIBUTION OF EXPORTS FINISHED PHARMACEUTICALS



GEOGRAPHICAL DISTRIBUTION OF EXPORTS 1988.

EXPORTS 1988 (mecus)

BULK PHARMACEUTICALS.
(Vitamins,Hormones,Vegetable Alkaloids,Antibiotics)

	TOTAL	INTRA	EXTRA	CLASS 1	EFTA	USA	JAPAN	CLASS2	EAST.EUR
FR GERMANY	739	38%	62%	35%	8%	17%	3%	20%	3%
FRANCE	325	46%	54%	34%	21%	4%	5%	18%	1%
ITALY	513	33%	67%	44%	15%	15%	10%	16%	2%
BELG.-LUXBG	89	85%	15%	8%	4%	1%	1%	6%	0%
UTD. KINGDO	376	42%	58%	39%	6%	13%	13%	17%	1%
IRELAND	118	71%	29%	25%	9%	3%	11%	3%	1%
DENMARK	118	48%	52%	37%	11%	11%	0%	11%	.4%
GREECE	8	31%	69%	23%	8%	7%	7%	41%	2%
SPAIN	182	23%	77%	32%	13%	6%	9%	32%	4%
PORTUGAL	145	57%	43%	22%	3%	12%	3%	18%	3%
NETHERLANDS	66	95%	5%	3%	0%	1%	0%	2%	1%
EUR 12	2,680	44%	56%	34%	11%	12%	6%	17%	2%

EXPORTS 1988 (mecus)

FINISHED PHARMACEUTICALS
(CN 30)

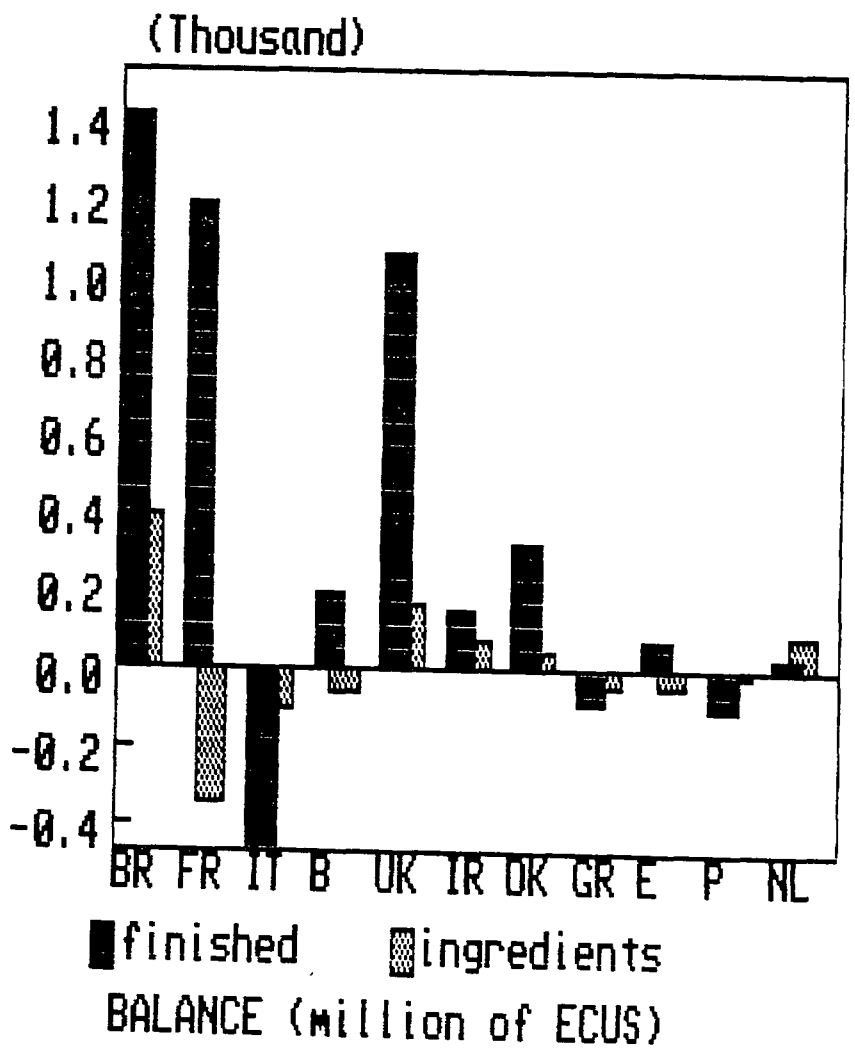
	TOTAL	INTRA	EXTRA	CLASS 1	EFTA	USA	JAPAN	CLASS2	EAST.EUR
FR GERMANY	3,040	39%	61%	45%	20%	3%	16%	13%	2%
FRANCE	1,865	42%	58%	12%	6%	2%	2%	45%	1%
ITALY	585	52%	48%	19%	6%	8%	1%	26%	2%
BELG.-LUXBG	914	58%	42%	21%	13%	1%	2%	19%	2%
UTD. KINGDO	2,156	41%	59%	31%	9%	9%	4%	27%	1%
IRELAND	354	64%	36%	30%	4%	16%	4%	7%	0%
DENMARK	596	39%	61%	45%	25%	8%	9%	14%	2%
GREECE	46	58%	42%	5%	0%	0%	0%	35%	0%
SPAIN	362	47%	53%	6%	4%	0%	0%	45%	0%
PORTUGAL	31	30%	70%	14%	9%	4%	0%	56%	0%
NETHERLANDS	777	51%	49%	31%	18%	2%	3%	16%	1%
EUR 12	10,725	44%	56%	30%	13%	5%	7%	24%	1%

Source:Eurostat.

TRADE IN PHARMACEUTICALS 1988.

	FINISHED PHARMACEUTICALS (mecus)			BULK PHARMACEUTICALS (mecus)		
	IMPORTS	EXPORTS	BALANCE	IMPORTS	EXPORTS	BALANCE
GERMANY	1,623	3,040	1,416	482	863	381
FRANCE	684	1,865	1,181	667	325	-341
ITALY	1,058	585	-473	613	514	-98
BELG.-LUXBG	734	920	186	141	90	-51
UTD. KINGDO	1,094	2,156	1,061	220	376	157
IRELAND	213	354	141	55	118	64
DENMARK	280	596	316	86	129	43
GREECE	128	47	-81	45	0	-45
SPAIN	295	362	67	233	189	-44
PORTUGAL	126	31	-96	49	37	-12
NETHERLANDS	763	786	23	130	219	89
EUR 12	6,998	10,741	3,743	2 [illegible]	2,862	142

Source:Eurostat.



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