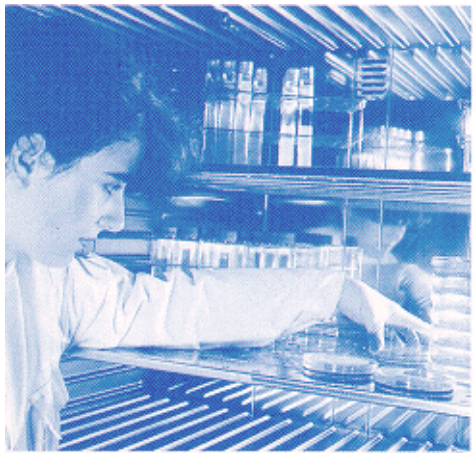
THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS



SECOND GENERAL REPORT 1996

European Agency for the Evaluation of Medicinal Products

Second General Report 1996

Adopted by the Management Board on 4 December 1996

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Contents

Annexes

Abbreviations used in this document

ADR	Adverse drug reaction
BEUC	Bureau Européen des Unions de Consommateurs
CPMP	Committee for Proprietary Medicinal Products
CVMP	Committee for Veterinary Medicinal Products
ECU	European Currency Unit
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries' Associations
EMEA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
ETOMEP	European Technical Office for Medicinal Products
EU	European Union
FEDESA	Fédération Européenne de la Santé Animale
GMP	Good Manufacturing Practice
ICH	International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
JRC	European Commission Joint Research Centre
MRL	Maximum Residue Limit
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
VICH	International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Veterinary Use

Foreword

from
Strachan Heppell
Chairman of the Management Board

I have pleasure in presenting the General Report for 1996 on the activities of the European Agency for the Evaluation of Medicinal Products.

Progress of the European registration system

The European system for the evaluation, authorisation and supervision of medicinal products has been in operation for two years. In that time it has established itself as an efficient and effective means of regulation and it has started to take its place as one of the world's leading regulatory systems for medicinal products.

Understandably, at the start there was considerable apprehension about how the system would work. This was particularly so with the centralised procedure which was seen as new and untested. But there was also concern about mutual recognition in the decentralised procedure, where there were fears that the procedure would be crippled by challenges to the original assessment.

These fears did not materialise. The centralised procedure, which is the responsibility of the Agency, has delivered a service which its customers have found satisfactory. Mutual recognition, which is the responsibility of national regulatory authorities, got off to a rather slower start but has established itself progressively since then.

Overall, the response to the system has been positive. I have seen this for myself during a programme of visits to Member States where I have discussed progress in detail with both national regulatory authorities and the pharmaceutical industry. The positive response has been equally evident in a variety of conferences and meetings involving those with a major interest in the system, including health care professions and consumer groups. In particular, this was the clear outcome of an audit of the system convened at Canary Wharf on 21 October 1996 by Dr Martin Bangemann, Member of the Commission responsible for the pharmaceutical industry.

Lessons learned: devolution and partnership

The Board has learned a number of lessons from the system's first two years. It has seen the importance of identifying and focusing on core responsibilities; recognised the value of good communication systems; and become convinced of

the need for performance goals and indicators and for transparency about that performance.

One lesson in particular has stood out - that devolution and partnership are critical to the success of the system.

The devolved nature of the system is made clear in this report. Its great value is that it makes such good use of experience and expertise across the whole of the EU, rather than trying to concentrate those skills in one place. In so doing, it reflects the spirit of subsidiarity. To operate such a system successfully requires all concerned to see themselves as partners with a shared responsibility to ensure that the enterprise is successful.

This partnership operates at four different levels, each of which makes an important contribution to the working of the system.

The first partnership is within the Agency between its four parts - the Management Board, the Committee for Proprietary Medicinal Products, the Committee for Veterinary Medicinal Products and the Secretariat. Within each part, we seek to build on the strengths of the different national and EU traditions and methods of working.

The second wider partnership is within the system as a whole between the Agency, the national regulatory authorities, the Commission and the pharmaceutical industry.

The third, wider still, is between the system's owners - the European Parliament, Council of Ministers, Member States, the Commission and the Agency.

Finally, there is the partnership between the regulators on the one hand and the customers on the other, the customers being the public, the health care professions and the pharmaceutical industry.

These partnerships are at the heart of the regulatory system. If any of them were weakened or fractured in any way, the effectiveness of the system would be threatened. The Board will therefore keep a careful watch on these partnerships and take them fully into account in shaping its policies.

Managing the business of the Board and the Agency

During 1996, the Board reviewed the way it managed its own affairs and its role in managing the business of the Agency.

The Board recognised that it must focus on its two main tasks:

- to seek to ensure that the Agency has the resources to carry out its responsibilities and uses those resources efficiently, effectively and economically
- to monitor the performance of the Agency and the parts of the system for which it is responsible to make sure that the performance is of high quality; and if it is not, to take steps to bring it up to standard

To carry out those tasks successfully, the Board concluded that it should:

- review its arrangements for managing its own affairs to make sure they work efficiently
- put in place effective monitoring so that the Board is well informed about the performance of the Agency and the system as a whole
- ensure that the Agency makes an appropriate contribution to the development of the regulatory framework for medicinal products in the EU and globally

These conclusions have now been implemented.

Challenges ahead

The Board recognises that the Agency and its partners face both short term and long term challenges.

The immediate challenge is to ensure that both the centralised and mutual recognition procedures are ready for 1 January 1998 when the national procedure will no longer be available for products to be marketed in more than one Member State.

In the longer term, the Board has to satisfy itself that the Agency has in place effective performance goals and indicators so that it can be confident that the regulatory process is working properly. Time limits must be met; costs should be no higher than necessary; performance should be of high quality; and the

expectations of customers and stakeholders must be met. The Board must also be sure that the outcome of that performance measurement is published. Transparency is an integral part of a good regulatory process.

The Board has set itself key objectives which focus on meeting these challenges successfully.

Looking ahead

In the first report for 1995 I said that I believed that the new system had got off to a good start. The second year's experience has reinforced that belief. And it has reinforced my admiration for the work carried out by the Executive Director and staff of the Agency and by the members of the two scientific committees, the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products. On behalf of the Board, I should like to thank them for their excellent contribution to the system's good start.

But there remains of course much to do and fresh challenges to meet. Our best way forward is to continue to work with our partners to tackle these challenges in the positive spirit of the first two years.

Introduction

by
Fernand Sauer
Executive Director

"1996: a second pioneering year - as well as one of consolidation"

This 1996 Activity Report is the first one covering a full year of operations. The delay in adoption of the Fee Regulation had meant that the EMEA was only operational for ten and a half months in 1995. The year 1996 has been of particular importance since it marks the shifting of the EMEA from its inauguration to its becoming a functional Agency. It was also a crucial year in the middle of the transition period - the EMEA is still in its growth process and will only become fully operational after 1998.

The good performance of the EMEA appears to have been recognised at the numerous conferences and meetings about the new European marketing authorisation system held during 1996. EMEA staff, members of the scientific committees and the many European experts from national competent authorities can be proud of their achievements during 1996, but we should all be aware that the EMEA must consolidate for the future. That much has been achieved in 1996 was indeed confirmed at the second audit of the European registration system chaired by Dr Martin Bangemann, and by the declarations made by representatives of consumers, pharmaceutical industry and other interest groups at that meeting.

The EMEA has kept within the strict 210-day limit of the centralised procedure, often being considerably faster. These figures - which even before formal performance indicators have been put in place are now being used as a benchmark of the Agency's activities - are published each month in tables made available by the EMEA. Within the centralised procedure in 1996, 30 opinions were adopted for human medicines by the CPMP, and 1 opinion for a veterinary medicinal product together with 9 recommendations for maximum residue limits were adopted by the CVMP, all by consensus. This has allowed a total of 30 Community marketing authorisations to be granted since the procedure began. Industry confidence in the centralised system is clear - two-thirds of the applications so far received have been voluntary applications which could have used national routes for authorisation.

The EMEA also performs additional functions to support European research-based industry, including the giving of scientific advice (30 procedures so far completed), issuing of WHO-compatible export certificates (about 1 600 certificates delivered in 6 months) and substantial technical contribution to European and international harmonisation (ICH and the new VICH initiative for veterinary medicines).

After a slow start in 1995, the mutual recognition ('decentralised') procedure appeared to function better during 1996, especially with the adoption of the 'Best Practice Guide' by national competent authorities. The EMEA was only called to arbitrate in exceptional instances, in fact in only 3 cases, but is fully prepared to continue to support the operation of the Mutual Recognition Facilitation Group as requested.

The Agency's infrastructure was expanded during 1996 and a great effort made to improving the quality of documents and the putting in place of an audit trail to permit a better follow-up to opinions and translations transmitted by the EMEA to the Commission. Adequate resources will be needed to consolidate the necessary scientific and administrative support and to meet the associated operating costs. Clearly without the proper resources the EMEA will not be able to meet all the expectations of industry or consumers alike, with detrimental consequences on the speed and quality of decisions.

As mentioned by the Chairman of the Management Board in his Foreword, the success of the European system and in particular the EMEA is also in a large part due to the considerable contributions of national competent authorities and, I should add, to the real enthusiasm of the individuals concerned. Their contributions were provided despite the fact that national authorities are not fully compensated for their work. In turn the EMEA has tried to assist not only the scientific committees and working groups, but also the national authorities where possible in the functioning of the Mutual Recognition Facilitation Group. The enthusiasm and commitment of EMEA staff, often quite junior, has also helped create a productive and positive working atmosphere.

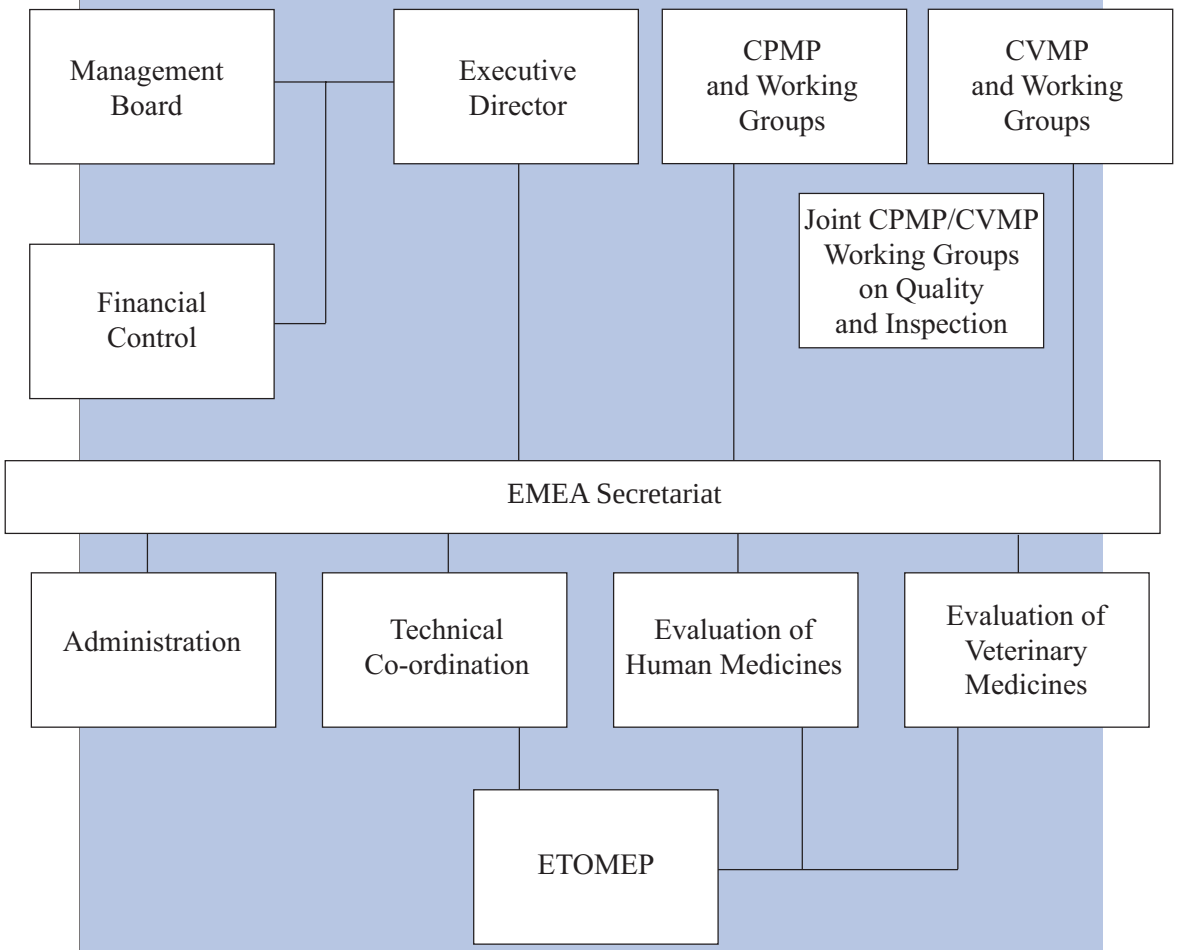
To help improve our understanding of how the national authorities and EMEA function, a survey into the costs associated with the centralised procedure was carried out. The relationship between national competent authorities and the EMEA was further consolidated with the conclusion of a partnership agreement at the end of the year. As Executive Director, I am particularly pleased that, after long discussion, the partnership agreement was adopted at the end of 1996. This agreement reflects in a detailed manner the contributions of national competent authorities and the EMEA Secretariat to the functioning of the Agency.

The publishing of EPARs became an established practice in 1996, with 28 EPARs now available. They have become one of the main attractions of the EMEA

homepage on the Internet, which also gives access to other key EMEA documents. With the higher profile of the EMEA has come also an increasing demand for information on our activities. Although the EMEA's open approach to information dissemination was confirmed in a survey of EU agencies carried out in 1996, the increasing number of demands and the different types of information requested mean that an internal review on how to improve the Agency's communication will be carried out.

This Second Activity Report sets out fully the operations of the Agency during 1996 and, read in conjunction with the 1995 Report, provides a comprehensive background to the first achievements of the European Agency for the Evaluation of Medicinal Products.

Organigram of the European Agency for the Evaluation of Medicinal Products



EMEA partners in the European marketing authorisation system

European Commission
(in particular DG III, VI, XII, JRC/ETOMEP)

National competent authorities in the human and veterinary sectors and about 2 000 European experts

European Pharmacopoeia and its Organisation of Medicines Control Laboratories network

1 EMEA in 1996 First full year of operation

The creation and setting-up of the EMEA was fully described in the First Activity Report covering the initial period in 1994 and 1995 (published by the Office for Official Publications of the EU, ISBN 92-827-7491-0). The Regulation and three Directives creating the centralised and decentralised procedures can be found in the EC Official Journal No L.214 of 24.8.93.

This Second Activity Report sets out the accomplishments of the first full year of operation of the EMEA and is presented by the Executive Director in accordance with Article 55(3) of Council Regulation (EEC) No 2309/93. This chapter sets out the activities of the Management Board, the Agency's relations with its partners both international and within the EU, and details the activities of the Administration Unit within the EMEA.

The operational and technical aspects of the Agency's work are set out in chapter 2 on human medicines, chapter 3 on veterinary medicines and finally chapter 4 looking at technical co-ordination activities. Information and relevant figures are given in annexes to the Report.

The year 1996 was an important one of preparation before the end of the transition period in December 1997, after which use of the mutual recognition procedure will become systematic for the majority of medicinal products for which the centralised procedure is not applicable. The Report, in accordance with Article 15c(1) of Council Directive 75/319/EEC, as amended, and Article 23c(1) of Council Directive 81/851/EEC, as amended, therefore also examines the functioning of the decentralised procedures for human and veterinary medicinal products.

1.1 Managing the business of the Agency

Meetings of the Board

The Management Board met four times in 1996 under the chairmanship of Mr Strachan Heppell (6 March, 2 July, 25 September and 4 December). An informal meeting of the Board was also held in Pavia on 30 April.

The composition of the Board changed a number of times during the year and membership as at the end of 1996 is shown in annex 1 to this Report.

The first mandate of the current Management Board finished at the end of 1996 and membership will either be renewed or new members nominated in 1997.

The Board looked at a number of issues during its meetings, focusing on a mix of operational and future policy issues.

A first Work Programme was considered by the Management Board in March 1996. Rolling work programmes were presented to the Board at its meetings in July

(EMEA/MB/023/96) and December 1996 (EMEA/MB/056/96), in particular to take into account the steadily changing workload and activities of the Agency.

These plans have allowed the Executive Director to set out the Agency's overall mission, responsibilities and priorities in the human and veterinary sector in consultation with the Management Board.

Budgetary decisions

The initial 1996 budget was adopted by the Management Board on 6 December 1995 amounting to ECU 23.55 million, including a Community subsidy of ECU 13.75 million. The European Parliament placed 20 percent of the subsidy in Reserve pending discussions with the Commission on budgetary discharge procedures and harmonisation of financial regulations of the EU decentralised agencies. This Reserve weighed heavily on the finances of the EMEA during the year and it was not until after negotiations with the European Parliament that it was finally released in the second half of 1996.

The Board consequently adopted a supplementary and amending budget on 26 September 1996 of ECU 22.55 million, which also took into account an expected shortfall of ECU 1 million in fee revenue. Budget summaries for 1994 to 1996 are presented in annex 5.

Looking to the future, the Board discussed a preliminary draft budget for 1997 in March 1996 of ECU 34.7 million, including a Community subsidy of ECU 17.5 million. Although this was reduced to ECU 12 million in initial EU budgetary negotiations, with the support of the European Parliament a subsidy of ECU 14 million was finally adopted by the EU budgetary authorities. The Board consequently adopted a total budget for 1997 on 4 December 1996 of ECU 28.2 million.

EMEA fees and cost of evaluation activities

The current level and structure of fees payable to the EMEA was adopted by the Council of Ministers on 10 February 1995 for a provisional period of three years (Council Regulation (EC) No 297/95, Official Journal No L.35/1, 15.2.95).

In its Decision on a Scale of Fees (EMEA/MB/037/95-final), the Management Board had previously decided that for 1995 and 1996 these fees should be divided half between the national competent authorities of the rapporteur and co-rapporteur, with the remaining half being retained to meet EMEA costs.

At the request of the Management Board an internal costing survey was carried out using questionnaires distributed by the EMEA Secretariat of both the costs of national competent authorities and the EMEA in relation to the centralised procedure. From the results of this survey, it appears that neither the costs of national competent authorities nor those of the EMEA are met by current fee levels. On this basis, the Management Board decided at its December 1996 meeting to extend its Decision on a Scale of Fees to 1997.

The results of this survey provided one of the starting points for a report prepared by the EMEA, at the request of the Commission, on its practical experience of the operation of the current fee system. This report is the EMEA contribution to the Commission's proposal for the reform of the fee system which should be transmitted to the Council of Ministers and European Parliament in early 1997. It should be noted that the new Council Regulation on fees payable to the EMEA by applicants will not impact on the Agency's revenue before 1998.

Partnership between EMEA and national competent authorities

The EMEA operates on the basis of partnership with the national competent authorities of the Member States in both the human and veterinary medicines sectors. The costing exercise revealed the considerable resource contributions made by national authorities to the functioning of the EMEA.

Basic estimated contributions, for which no compensation is made to national authorities, in 1996 to the scientific activities of the EMEA represented about 450 working days in the veterinary medicines sector, or more than 2 full-time equivalent people, per year per national authority. For human medicinal products this figure rises to 1 100 working days, or approximately 5 full-time equivalent people, per year per national authority.

These figures do not, in particular, take into account the resource contributions when a scientific committee member acts as rapporteur or co-rapporteur, for which national competent authorities are partially compensated. For human medicines, an average of 170 working days per evaluation team is required in addition to the basic contribution. Although final figures are not yet available for the veterinary sector a similar workload is expected, however in certain cases the workload of the co-rapporteur could be reduced.

The final adoption in December 1996 of a partnership agreement (EMEA/MB/030/95-Rev.1) was therefore a means of formalising what is a substantial partnership between the EMEA and the national competent authorities and finishing a process commenced by the Board in 1995.

In addition to the general statement of principles which had earlier been endorsed by the Board, the agreement also includes two annexes detailing the facilities and services offered by the Agency Secretariat and another containing the standard contract to be concluded between the EMEA and the national competent authority of the rapporteur, co-rapporteur or inspection service. This contract relates to the conditions under which evaluation activities are carried out for the EMEA.

Left: Canary Wharf (© Mr Mathews, Canary Wharf Ltd.)

European experts

An important part of the resources made available by the national competent authorities to the EMEA are the European experts, most of whom in fact work for the national authorities and are put at the disposal of the EMEA for evaluation work. The EMEA had about 2 000 European Experts on its list at the end of 1996, covering the full range of expertise needed to ensure the best possible quality of the Agency's scientific opinions. The scientific competence of each expert is guaranteed by the Member State which nominates them and their integrity is assured by a public declaration of interests. The list of European experts, together with their declaration of interests, is available for public inspection at the EMEA. This list is regularly reviewed and updated by the Management Board.

Only experts appearing on the EMEA list may be used by the CPMP and CVMP in the evaluation of medicinal products, public hearings, working groups and the activities of the

International Conferences for Harmonisation (ICH and VICH).

Performance indicators

Further to the Management Board mandate, the Executive Director continued to explore the possibility of putting in place performance indicators. Interested parties were contacted and various meetings were organised during 1996, notably with European representative organisations.

Tables of centralised opinions adopted by the CPMP and CVMP were systematically made available by the EMEA during 1996, giving key quantitative elements - including details of the Commission decision-taking phase - which was welcomed by all parties. The final tables for 1996 are given in annexes 6 and 7. Technical translation problems with the Luxembourg Translation Centre or on the part of applicants were often the cause of delays in the transmission of EMEA documents to the Commission during the 30 day post-opinion period.

From the consultation exercise a joint questionnaire was agreed for use in 1997.

Contribution to public health and other European policies

The Management Board Working Group on the contribution of the EMEA to public and animal health, chaired by Management Board Vice-Chairman Prof. Marabelli, met twice during the year on 5 March and 24 September, and reported back to the Board.

The Working Group in particular looked at four main issues: pharmacovigilance, innovation, small- and medium-sized enterprises, and orphan drugs.

Pharmacovigilance in the EU deals with three main categories of products, those authorised by the centralised procedure, those authorised through mutual recognition and products authorised under purely national procedures. Various issues were identified including the need for a better system for exchange of information between national competent authorities, European Commission and the EMEA.

The difficulties faced by small- and medium-sized enterprises (SMEs) in gaining information and access to the European registration procedures were looked at on the proposal of one of the European Parliament representatives.

Within the context of access to the centralised procedure for medicinal products which, “in the opinion of the Agency, constitute a significant innovation” (first indent, Part B of the Annex to Council Regulation (EEC) No 2309/93) the definition of innovation was repeatedly examined, involving consultation of the scientific committees.

Concerning the question of so-called ‘orphan drugs’, some of the contributions from the Group were transmitted to the Commission during preparation of its proposal for a Council Regulation on an EU orphan drugs policy. Pending adoption of this Regulation, the Executive Director again asked the Management Board in September 1996 to earmark, as it had done in 1995, ECU 750 000 of the Reserve released by the European Parliament to cover expenditure for the evaluation of orphan drugs for human use and their veterinary counterparts.

The Executive Director granted full waiver of fees for medicinal products for human use and maximum residue limit applications for veterinary substances, which were charged against the orphan drug fund carried over from 1995. The cost of meetings relating to the establishment of maximum residue limits for essential old veterinary substances was also charged to the funds carried over from 1995.

The demands for fee waivers increased in 1996 and, given the relatively limited amount of the orphan drug fund, partial waivers (e.g. 50 percent) were charged against the new orphan drug fund earmarked by the Board.

Financial and budgetary control

At the start of its activities the Agency had applied the Commission financial regulation to its financial operations. In consultation with the Commission and Court of Auditors, the Management Board adopted a first version of the EMEA Financial Regulation (EMEA/MB/016/96) at its March 1996 meeting. At the demand of the European Parliament, various changes were adopted to the Financial Regulation at the December meeting, mostly of a minor nature in order to harmonise the financial regulations of all new EU agencies.

At the same time the Board also adopted implementing rules for the Financial Regulation. Following the appointment of the Agency's own Financial Controller in July 1995, the Board also confirmed the nomination of an Assistant Financial Controller at its meeting of 2 July 1996.

A report from the Court of Auditors on the Agency's accounts in financial years 1994 and 1995, dated 3 October 1996, was considered by the Board at the December meeting.

Given the specificity of European financial regulations, a dedicated computer system was considered essential for efficient budgetary and financial management. No existing software appeared able to deal with the budgetary requirements of these rules. In an attempt to develop such a system the EMEA had, in conjunction with other decentralised EU agencies, earlier launched a public tender with disappointing results. It was therefore decided to proceed with a new system under development by the European Commission. However, the new project still requires substantial adjustments and the system will not be in place until the latter half of 1997, during which time spreadsheet analysis will continue to be used.

1.2 Personnel and administration

Staff

The Secretariat of the Agency is primarily responsible for providing administrative and technical support to the Management Board, scientific committees and their working parties.

The Agency does not have any permanent officials, but only Temporary Agents and Auxiliary staff. Recruitment is carried out through open selection and follows the rules and practices of the EU institutions. Once selected by an independent selection board, candidates are placed on a reserve list from which they may be selected for a post in line with the operational needs of the Agency. Successful candidates are offered five year contracts as Temporary Agents in the following grades: A (university graduates), B (assistants) and C and D (secretarial and clerical functions). Whilst there is no quota system for nationals of each Member State, the Agency seeks to respect the multi-cultural nature of the European Union. Staff come from throughout the EU and all nationalities, with the exception of Luxembourg, are represented. The delays in recruitment, and additional delays resulting from the recruitment procedures which comply with the EU staff regulations, meant that a large number of external interim staff were in place at the EMEA during 1996 in secretarial posts, amounting to about 20 percent of total staff.

The ratio of men to women is carefully monitored. At the end of 1996 of the total EMEA staff, excluding interim staff, there were 64 women and 39 men. At A-grade level the balance was 56 percent woman and 44 percent men and at B-grade women represented 47 percent and men 53 percent of staff. Women made up 78 percent of C- and D-grade staff and men 22 percent.

Starting from a small number of staff, the Agency recruited cautiously in 1996 in line with its budgetary possibilities to a total of 100 at the end of 1996. This included in particular the completion of recruitment to key posts, including the Head of Unit for Technical Co-ordination and Heads of Sector in the Human and Veterinary Medicines Units. The scientific and technical complement of staff has also been reinforced during the year.

Following an offer made by the Executive Director in 1995 to all national competent authorities, 3 national experts from France, Italy and Finland joined the EMEA on secondment during the year, reinforcing the links between the EMEA and the national competent authorities.

Eight new recruitment competitions were launched in 1996 to recruit staff for two Head of Sector positions and a number of technical positions (Official Journal No C.253A, 31.8.96 and Official Journal No C.326A, 31.10.96).

	01.01.95	31.12.95	01.07.96	31.12.96
A - temporary - auxiliary	 2 5	 15 14	 39 4	 45 1
B	6	8	15	17
C and D	1	13	23	37
Total EMEA staff	14	50	81	100
National experts on secondment	-	-	1	3
External interim staff	2	17	11	10

The EMEA was the first new EU decentralised agency to have created a Staff Committee right from the beginning of its operations. During 1996 the Staff Committee continued its work in both general and social matters. Given the increase in staff numbers since the Committee was elected, it was decided to organise new elections to ensure that all personnel were properly represented.

EMEA premises and security

At the beginning of 1996, the EMEA occupied two and a half floors of No 7 Westferry Circus, Canary Wharf, amounting to about 5 500 m^2. Further to the Management Board decision to exercise the option for the remaining space on the third floor, the Agency's support services supervised the fitting-out and installation of the extra 1 000 m^2 space, occupied since May 1996 by the Human Medicines Evaluation Unit. The fitting-out also allowed an additional meeting room to be created on the third floor for 50 people, complete with video-conferencing facilities.

Work was also started to create secure archiving space in order to provide flexibility to meet the increasing business of the Agency.

Security of the premises is a high priority for the EMEA. In 1996, the overall security situation at Canary Wharf had to be reviewed and tightened. Close circuit television cameras were installed at all entrances and exits to the EMEA premises, as well as improved coverage of the archive area. Given the necessity to protect confidentiality and the special risks of terrorism, there has been close co-ordination with Canary Wharf to improve security concerning visitors to the building. A

personalised electronic pass system for staff and delegates has been introduced and a computerised system for other visitors which allows the EMEA to know who is in the building at any time. In addition X-ray scanning equipment has been leased to allow incoming post to be examined.

1.3 International activities

The tasks set out in Article 51(f) of Council Regulation (EEC) No 2309/93 include the giving of technical and scientific support to improve co-operation between the Community, its Member States, international organisations and third countries.

The EMEA represents an appropriate technical forum to assist the EU in the preparation of negotiations and international co-operation initiatives. In particular this is done at the request of the European Commission with the support of national competent authorities through the provision of expertise in the EMEA scientific committees and working groups.

Complementing the Commission's policy role, the EMEA has continued to provide technical contributions to the progress of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and in particular to the work of the ICH Expert Working Groups during 1996. The EMEA, in conjunction with EFPIA, hosted the meeting of the ICH Steering Committee in November 1996.

This meeting, bringing together some 250 representatives of EU, Japanese, US and observer countries' regulators and industry, was a key step towards the expected completion of international technical harmonisation for human medicines.

The EMEA also hosted the October 1996 Committee meeting and seminar sessions of PER ('Scheme for the mutual recognition of evaluation reports on pharmaceutical products') of representatives of the regulatory authorities of EU and EFTA countries, Australia, Canada, New Zealand and South Africa.

In addition to EMEA participation in international activities, certain non-EU countries expressed interest in becoming associated to the structure and work of the Agency. Negotiations were started with Norway, Iceland and Liechtenstein who, within the context of the European Economic Area, should start participation early in 1997.

The achievements of the European registration system has encouraged many non-EU countries to visit the EMEA. During 1996 delegations from national authorities were received from Australia, China, Columbia, Cuba, Japan, Lithuania, Namibia, Russia, Singapore, South Africa and Thailand.

The EMEA was also invited by international organisations to present its work at various meetings at which representatives of a large number of competent authorities for both human and veterinary medicines were present. These included the International Technical Co-ordination of Veterinary Drug Registration conference in Prague in September, the International Conference of Drug Regulatory Authorities in Bahrain in November, and Codex Alimentarius in Costa Rica in November 1996. The EMEA also participated as part of the European Commission delegation at the three meetings of the European Pharmacopoeia under the aegis of the Council of Europe.

Outside the pharmaceutical field, the EMEA also hosted in October the 10th Plenary Session of the Council of the International Sugar Organisation, which represents 46 countries under the auspices of the United Nations.

1.4 Relations with interested parties

In accordance with Article 65 of Council Regulation (EEC) No 2309/93, appropriate contacts between the Agency and representatives of the industry, consumers and patients and the health professions continued in 1996.

At the initiative of Dr Martin Bangemann, Member of the Commission with responsibility for industrial policy, and the pharmaceutical sector in particular, a second hearing was held at the EMEA on 21 October 1996 to review the new European marketing authorisation system with representatives of various interest groups. In his conclusions, Dr Bangemann told the meeting that the centralised procedure appeared to be working well and concerning mutual recognition he urged companies to fully explore the procedure before it became systematic at the beginning of 1998.

The issue of single names for medicinal products was also reviewed by the EMEA and European Commission at a meeting convened at the Office for Harmonisation of the Internal Market at Alicante on 30 September 1996. The practical experience of the Agency was discussed and allowed some progress to be made.

Relations with EU institutions were also reinforced throughout the year, not only with the different services of the European Commission (in particular Directorates-General III - Industry affairs, XII - Science, research and technology, and the EC Joint Research Centre), but also with the European Parliament and its Committee on the Environment, Public Health and Consumer Protection. Together with Members of the Economic and Social Committee, Members of the European Parliament were able to visit the EMEA on 28 May 1996 to discuss its achievements and some of the difficulties faced by the EMEA. A joint workshop organised by the JRC, the Seville-based Institute for Prospective Technological Studies and the STOA group of the European Parliament took place on 29 November at the EMEA to examine pharmaceutical research in Europe based on a report from the London School of Economics.

The EMEA was particularly pleased to have hosted a formal session of the Economic and Social Committee's Section for Protection of the Environment, Public Health and Consumer Affairs on 2 December 1996.

The regular nature of contacts with interested parties at scientific committee level continued in 1996. Meetings with representatives of relevant interest groups were held every 3 or 4 months directly after the end of the CPMP and CVMP meeting. These included BEUC (Bureau Européen des Unions de Consommateurs), industry representative organisations (Association Européenne des Specialités Pharmaceutiques Grand Public, European Federation of Pharmaceutical Industries' Associations, European Generic Medicines Association, Fédération Européenne de la Santé Animale) and professional representative organisations (Federation of Veterinarians in Europe, Groupement des Pharmaciens de l'Union Européenne and the Standing Committee of European Doctors).

In addition a technical meeting was held with EuroBloc, which represents small and medium-sized enterprises. Special meetings were also held with some national trade associations, e.g. the UK ABPI, the VFA from Germany and the Irish Trade Board.

Meetings with special interest groups were also held in 1996 within the context of work of CPMP Working Groups, e.g. in the field of AIDS, vaccines and blood products, and non-profit professional organisations in the field of regulatory affairs, e.g. Belgian Regulatory Affairs Society, Drug Information Association, European Society for Regulatory Affairs, Pan-European Federation of Regulatory Affairs Societies and Regulatory Affairs Professional Society.

2 Medicinal products for human use

Preface by Prof. Jean-Michel Alexandre
Chairman, Committee for Proprietary Medicinal Products

Consolidation and confirmation provided the main themes for the CPMP in 1996.

Confirmation of the Committee's functioning. It has continued to divide the evaluation workload amongst itself in an equitable manner, it has adopted its scientific opinions by consensus and within the timeframe permitted.

Consolidation in several respects. In particular:

- *the CPMP worked in 1996 as a unified and experienced team*
- *the increase in the participation of European experts not only in the work of the CPMP, but also in the activities of the permanent Working Parties, ad hoc working groups and the CPMP Consultation Group on scientific advice to companies, has served to reinforce the quality of scientific opinions*
- *a number of standard operating procedures (SOPs) now permit a better and more transparent functioning of the Committee*
- *a procedure to allow accelerated evaluation of products which correspond to major public health needs has been introduced*
- *important technical recommendations have been developed on issues which are priorities for the CPMP by the permanent Working Groups which have assisted the Committee in its evaluation work; these Working Groups have also undertaken a fundamental revision of existing documents. The enormous volume of "acquis communautaire" built up over the past twenty years now finds itself reinforced and clarified; by the same token, international harmonisation (ICH) has also benefited from this same dynamic action*
- *the increased examination of pharmacovigilance problems has permitted the harmonisation of methodologies and evaluations*

The functioning of the Committee met the expectations of most observers.

The positive results achieved reflect the desire and commitment of Committee members to ensure that the scientific opinions adopted are of the best possible quality. Contributions from the national authorities have been essential in meeting this objective and the handling of the volume of work within the permitted timeframe has been possible only with the efficient and constant support of the staff of the EMEA Secretariat, which made enormous progress in 1996.

There is much work yet to do - to be achieved together.

In 1996, the CPMP continued to meet under the chairmanship of Prof. J.-M. Alexandre. Meetings, which lasted up to a week, were held monthly. In order to better cope with the increased workload, many parallel breakout sessions were also organised. The involvement of CPMP Members as well as the contributions from national competent authorities, in the provision of supplementary expertise, was considerable in 1996, amounting on average to five full-time equivalent persons during the year.

2.1 Unit for the Evaluation of Medicinal Products for Human Use

There was a steady increase during 1996 in the volume of work undertaken by the Unit for the Evaluation of Medicinal Products for Human Use. Particular emphasis was placed on the management of the pre-authorisation phase, the provision of regulatory and scientific advice, procedures for adoption of Opinions for centralised applications and the post-authorisation phase. The role and duties of the EMEA project manager were agreed by the CPMP together with a Standard Operating Procedure concerning the conversion of the rapporteurs' assessment reports into a European Public Assessment Report (EPAR).

In addition to the monthly CPMP press releases, a first 'EMEA Human Medicines Newsletter' was circulated in October 1996.

The increased volume and complexity of the work led to the recruitment of additional technical and administrative staff as well as a restructuring of the Unit into three sectors in August 1996:

- Sector for biotechnology products (Part A), headed by John Purves
- Sector for other products (Part B), headed by Josep Torrent-Farnell
- Sector for regulatory affairs and pharmacovigilance, headed by Noël Wathion

At the end of 1996 the complement of the Unit was 45 people including three Heads of Sector, two senior administrators and 20 other scientific collaborators (most of them junior collaborators), supported by 4 technical assistants and 15 secretaries.

2.2 Operation of the centralised procedure

Despite the steady increase in number of applications during 1996, the pharmaceutical industry has recognised that the EMEA was able to respect the time limits laid down in Council Regulation (EEC) No 2309/93. All CPMP opinions were issued by consensus in 1996 and therefore required no further scientific discussion during the Standing Committee phase. Consequently no substantial delays were encountered in the Commission decision-taking process.

This confirms that all CPMP opinions were consistent and of a high scientific quality. Furthermore, in a limited number of cases applications benefited from an accelerated evaluation when indicated for serious diseases.

The EPAR, which is made public once a Decision has been notified by the European Commission, has proven to be a very important tool in providing both health professionals and consumers with the necessary information on centrally-authorised

medicines which are available on the market. The number of requests for paper copies as well as the number of times that the website on the Internet has been visited was very high. The EPAR is a useful means of ensuring transparency and subjecting the EMEA's activities to effective public auditing.

The pharmaceutical industry frequently raises regulatory and procedural questions in relation to the use of the centralised procedure. In order to deal with these issues in 1996 the EMEA secretariat, organised 25 pre-submission meetings with companies intending to submit applications. Typical issues addressed at these meetings include eligibility for access to the centralised procedure (including eligibility for Part B status), requirements in relation to inspection in non-EU countries, and problems arising from the requirement for a single trademark.

Applications submitted for the centralised procedure

Figures on the number of applications submitted in 1996 as well as the number of Opinions given during 1996 are listed below and compared with the figures for 1995 figures which include 18 converted 'ex-concertation' applications submitted prior to January 1995.

Six applications were voluntarily withdrawn by applicants; 4 concerned converted 'ex-concertation' applications and 2 new applications. The full list of all Community marketing authorisations Decisions approved by the European Commission since October 1995 for human medicines are set out in annex 6.

Centralised procedure	1st half 1995	2nd half 1995	1st half 1996	2nd half 1996
Applications received				
List A	10	7	3	9
List B	11	8	12	11
Opinions given				
List A	2	4	6	8
List B	0	3	11	4
Opinions pending				
List A	8	11	7	9
List B	10	10	11	18
Type I variations				
List A	0	0	2	12
List B	0	0	2	11
Type II variations				
List A	0	1	1	2
List B	0	0	3	10
Extensions and abridged applications				
List A	0	0	0	3
List B	0	0	2	0

Rapporteurships

The choice of rapporteur and co-rapporteur for centralised applications continued in 1996 to be determined by taking into consideration two criteria: the applicants' preferences and the CPMP members' availability and expertise. In order to keep that balance, applicants were reminded to suggest three to four alternative CPMP members coming from three to four different members States. It should also be noted that the scientific committees are required under Council Regulation (EEC) No 2309/93 to ensure that all members undertake the role of rapporteur or co-rapporteur.

All delegations were able to act as rapporteur or co-rapporteur in the centralised procedure in 1996. The cumulative figures for 1995 and 1996 are: in 17 cases, CPMP members from

the United Kingdom were appointed rapporteur or co-rapporteur. Members from France and Sweden were appointed rapporteur or co-rapporteur in 10 cases. In 9 cases, CPMP members from Germany and Finland were designated rapporteur or co-rapporteur, with the members from Denmark and Ireland designated in 8 instances. CPMP members from the Netherlands were appointed rapporteur or co-rapporteur in 6 cases, whereas members from Austria and Italy were appointed in 5 cases. Members from Belgium and Spain were designated in 4 instances. Finally, members from Luxembourg and Portugal acted in 2 instances each, whereas a member from Greece was appointed in 1 case.

2.3 Other CPMP core activities

Scientific advice

Following the Scientific Advice already given in 1995 the CPMP decided to determine the principles and the details of the procedure by adopting an EMEA Standard Operating Procedure (SOP). In order to adequately respond to the complexity of the advice sought and the increasing workload, CPMP Consultation Groups were set up to discuss with the applicants the issues raised during the development phase of their products. In other situations CPMP Members or Working Parties were involved.

A total of 43 requests have so far been received, with final advice given in 24 instances. Discussion is on-going in 5 cases and the remaining 14 requests were not considered appropriate by the CPMP.

The requests focused mainly on the clinical development of new medicinal products and also on interpretation of biotechnology guidelines and safety findings. Based on the experience gained within the last two years, the Committee recently decided to further explore the way to optimise the provision of scientific advice by taking into account the advances in the biomedical knowledge together with the European regulatory requirements.

Pharmacovigilance

Although Pharmacovigilance issues related to centrally-approved medicinal products remained rather limited in early 1996, the increased number of marketing authorisations was accompanied by a steady increase in reports of suspected serious unexpected adverse drug reactions (ADRs) coming from third countries. Some 650 suspected serious unexpected ADR-reports from outside the European Union were received in 1996.

As far as nationally-authorised medicinal products are concerned, on the basis of existing CPMP opinions, the Commission notified decisions pursuant to Article 14 of Council Directive 75/319/EEC for naftidrofuryl (Official Journal No C.216/8, 26.7.96) and for sparfloxacin (Official Journal No C.188/5, 28.6.96). One referral in accordance with Article 12 of Council Directive 75/319/EEC, as amended, was

Above: A view of one of the EMEA Conference rooms (© Gensler and Associates; Mr Merrick, Hedrich Blessing)

made in 1996 for which no opinion has yet been adopted.

Furthermore, the referral procedure previously initiated for so-called slimming pills was completed and resulted in the adoption of 13 Opinions, involving 79 marketing authorisation holders and 136 national marketing authorisations for the following anorectic substances: amfepramone, clobenzorex, dexfenfluramine, fenbutrazate, fenproporex, fenfluramine, mazindol, mefenorex, norpseudoephedrine, phendimetrazine, phenmetrazine, phentermine, propylhexedrine. This referral illustrated the difficulties in administering and facilitating the adoption of decisions in relation to an entire class involving numerous national marketing authorisations.

In addition, the discussion on so-called third generation combined oral contraceptives containing gestodene or desogestrel, begun in October 1995, resulted in a revised Position Statement in April 1996, confirming the first Position Statement of the CPMP.

Finally, the Rapid Alert/Infofax system was used on 33 occasions either to exchange information or alert Members of the Pharmacovigilance Working Party. All these questions were fully discussed in the Pharmacovigilance Working Party.

CPMP organisational matters

In consultation with the CPMP, the Secretariat prepares draft position papers on specific issues to be handled either at a particular organisational CPMP meeting or during a plenary CPMP meeting. To facilitate the processing of applications submitted to the EMEA, standard operational procedures have been developed to improve these procedures in the light of experience.

The list of documents prepared by the EMEA Secretariat and subsequently adopted by the CPMP in 1996 is outlined below.

- Procedure for the appointment by the CPMP of Rapporteur/Co-Rapporteur responsible for evaluation in the Centralised Procedure (CPMP/034/96)
- Scientific advice to be given by the CPMP for innovative medicinal products (EMEA/SOP/002/95)
- Management of Type I Variations in the Centralised Procedure (CPMP/260/96)
- Centralised Procedure: Contribution to the Notice to Applicants (EMEA/NTA/002/95) and dossier requirements in the Centralised Procedure (EMEA/NTA/001/96)
- Arbitration under the Decentralised Procedure for marketing authorisations (EMEA/SOP/001/96)
- Accelerated evaluation of products indicated for serious diseases (CPMP/495/96)
- From Assessment Report to European Public Assessment Report (EPAR) (EMEA/SOP/005/96)
- Position paper on how to proceed with specific obligations and follow-up measures for the management of central marketing authorisations (CPMP/725/96)

2.4 Mutual recognition and other Community referrals

Council Directive 75/319/EEC, as amended, sets out the mechanism for the mutual recognition of nationally authorised medicinal products for human use. In order to provide a forum for the discussion and a platform for resolution of general and product related issues, the Mutual Recognition Facilitation Group, established on an informal basis in late 1995, continued to meet during 1996 at the EMEA on a monthly basis. In addition, in order to cope with the increased workload and to try to solve the outstanding public health issues during the clarification phase (the phase between day 60 and day 90 of the procedure), some 25 break-out sessions were held at the EMEA. The EMEA secretariat provided increasing assistance to this group; all parties concerned accepted that the procedure should be more transparent as described in the Best Practice guide.

Mutual recognition procedure in 1996	Total submitted since 1995	Under validation	Under evaluation	Ended positively	Withdrawn	Arbitration
New applications	171	54	17	94	4	2
Type I variations	83	7	8	67	1	0
Type II variations	170	19	53	91	6	1

There was an increased use of the mutual recognition procedure in 1996. Figures, on the number of new applications, as well as Type I and Type II Variations are set out below. It is expected that at a later stage names of the products authorised through the mutual recognition procedure will be made public by the national authorities.

Referrals to CPMP for an opinion may be initiated in accordance with Article 10 (arbitration in the mutual recognition procedure) or Article 11 (harmonisation) of Council Directive 75/319/EEC, as amended. In 1996, three Article 10 arbitrations came to the CPMP: two for new applications (one positively finalised and converted into a Commission Decision relating to Amaryl, one other finalised in December 1996) and one for a type II variation (also finalised in December 1996). One Article 11 referral was made at the initiative of the marketing authorisation holder and is still ongoing.

Fifteen of the so-called multi-State applications submitted before January 1995 remained and all were completed by the end of 1996. A total of 6 positive non-binding opinions were adopted and 3 applications were withdrawn in 1996 by the companies concerned.

2.5 CPMP Working Parties and ad hoc Groups

During 1996, the CPMP continued to be assisted by Working Parties which provide advice on specific issues relating to the quality, safety and efficacy of medicinal products. Their work programmes were updated and agreed by the CPMP twice in 1996. The CPMP and its Working Parties are supported by a pool of over 1 500 European experts from the national competent authorities (their declarations of interest are available to the public). Some of these experts also participated in the ICH activities.

There are four permanent CPMP Working Parties and one joint CPMP/CVMP Quality Working Party. One of the tasks of the CPMP and its Working Parties, in collaboration with the EMEA, consists of the preparation of guidelines, in accordance with the agreed work programme. In the preparation of guidelines for adoption by the CPMP, a procedure is followed which allows for transparency before final agreement taking into consideration the workload and involvement of interested parties at the appropriate stages. A procedure for an almost automatic updating system of pre-existing guidelines as influenced by new text has yet to be installed.

CPMP guidelines

In 1996 the CPMP adopted 17 final guidelines for implementation and released 20 draft guidelines for consultation with interested parties. These guidelines are indicated in the tables presented for each CPMP Working Party, with the exception of quality guidelines which are indicated in Chapter 4 concerning the Technical Co-ordination Unit. The Guidelines are either initiated within the International Conference on Harmonisation (ICH) process or are of purely European origin.

The total number of finalised ICH Guidelines is now 24, with an additional 9 subject to regulatory scrutiny. In comparison with the two other ICH regions, the CPMP adopts ICH guidelines very quickly and makes them available on the Internet.

Other and distinct CPMP Guidelines are developed to update existing guidance, to address issues not previously covered by guidance (e.g. therapeutic classes). Such guidelines play a vital role in supporting mutual recognition.

Biotechnology Working Party (BWP)

The Biotechnology Working Party, chaired by Prof. G. Vicari met on 9 occasions in 1996. It is responsible for giving specialist technical assistance to the CPMP on Part II of the dossier of certain applications submitted under the centralised procedure and on manufacture and control of medicinal products derived from blood and plasma, and of immunological products.

"Biotechnology" guidelines adopted or released for consultation by the CPMP in 1996 are outlined below.

The BWP in 1996 also initiated revision of existing guidance concerning vaccines (requirements for influenza and combination vaccines), medicinal products derived from blood and plasma (clotting factor concentrates, albumin and immunoglobulin control authority batch release) and issues about the potential risk of spongiform encephalopathy transmission via medicinal products (CPMP/384/96).

CPMP/BWP/268/95	Virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses	Adopted in February 96
CPMP/BWP/388/95	Guidelines to assess efficacy and safety of normal intravenous immunoglobulin products for marketing authorisations	Adopted in February 96
CPMP/BWP/198/95	Efficacy and safety of human plasma derived factor VIII.c and IX.c products in clinical trials in haemophiliacs before and after authorisation	Adopted in February 96
CPMP/BWP/269/95	Plasma derived medicinal products	Adopted in March 96 (revision)
CPMP/BWP/243/96	Allergen products	Adopted in March 96
CPMP/BWP/214/96	Harmonisation of requirements for influenza vaccines	Released for consultation in July 96 (revision)
CPMP/BWP/877/96	Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products	Released for consultation in November 96 (revision)

Efficacy Working Party (EWP)

The Efficacy Working Party, chaired by Prof. A. Hildebrandt, met 3 times in 1996, each session lasting 3 days. It is responsible for methodological guidelines on both general clinical aspects and on specific therapeutic areas. Upon request, the group is also involved in giving scientific and methodological input to the scientific advice given by the CPMP.

The following "efficacy" guidelines were adopted or released for consultation by the CPMP in 1996:

CPMP/ICH/135/95 (E6)	Good clinical practice: consolidated guideline	Adopted in July 96
CPMP/EWP/555/95	Haematopoietic growth factors	Adopted in March 96
CPMP/EWP/240/95	Fixed combination medicinal products	Adopted in April 96
CPMP/EWP/234/95	Anti-anginal medicinal products in stable angina pectoris	Adopted in November 96
CPMP/EWP/205/95	Evaluation of anti-cancer medicinal products in man	Adopted in December 96
CPMP/EWP/558/95	Anti-bacterial medicinal products	Released for consultation by CPMP in June 96 (revision)
CPMP/EWP/520/96	Pharmacodynamic section of the SPC for anti-bacterial medicinal products	Released for consultation by CPMP in June 96 (revision)
CPMP/EWP/462/95	Clinical investigation of medicinal products in children	Released for consultation by CPMP in September 96 (revision)
CPMP/ICH/291/95 (E8)	General considerations for clinical trials	Released for consultation by CPMP in November 96
CPMP/EWP/552/95	Involutional osteoporosis in women	Released for consultation by CPMP in November 96 (new)

The EWP initiated or is revising existing guidance concerning the treatment of obesity, hypertension, Parkinson's disease and arthritis. It is also examining prolonged and modified release forms and interactions.

Safety Working Party (SWP)

The Safety Working Party, chaired by Prof. P. Sjöberg, provides a forum for pre-clinical safety issues. It meets quarterly for one-day sessions to prepare guidelines for general methodological safety issues as well as for specific areas of safety assessment and animal welfare. When appropriate, it liaises with other CPMP Working Parties. The Working Party, upon request, also gives advice on safety aspects raised by the CPMP.

The Working Party continued to work in the following areas: pre-clinical testing for (DNA-) vaccines and for gene therapy, as well as discussions about appropriate testing of substances with long-term marketing experience and on replacement of animal studies by in vitro models.

The following "safety" guidelines were adopted or released for consultation by the CPMP in 1996:

CPMP/ICH/299/95 (SIB)	Carcinogenicity: testing of carcinogenicity of pharmaceuticals	Released for consultation in May 96
CPMP/ICH/383/95 (SIC-R-)	Addendum on the limit dose related to: dose selection for carcinogenicity studies of pharmaceuticals	Released for consultation in November 96
CPMP/ICH/302/95 (S6)	Safety studies for biotechnology products	Released for consultation in November 96
CPMP/SWP/997/96	Preclinical evaluation of anti-cancer medicinal products	Released for consultation in December 96

Pharmacovigilance Working Party (PhVWP)

The CPMP's Pharmacovigilance Working Party, chaired by Dr S. Wood, met 6 times in 1996 at two-monthly intervals. Topics discussed in 1996 fell into three broad categories: preparation of CPMP Guidelines on Pharmacovigilance, evaluation of product-related issues at the CPMP's request, and other inquiries at the request of national authorities.

The Working Party also made proposals to the European Commission on the recasting of human medicinal product legislation's provisions relating to pharmacovigilance.

The following "pharmacovigilance" guidelines were adopted or released for consultation in 1996:

CPMP/PhVWP/005/96	Rapid alert system in pharmacovigilance (RAS)	Adopted in June 96
CPMP/ICH/288/95 (E2C)	Clinical safety data management: periodic safety update reports for marketed drugs	Adopted in December 96
CPMP/ICH/287/95	Clinical data safety management: data elements for transmission of individual case safety reports	Released for consultation in May 96

Ad hoc CPMP Groups

In addition to the above mentioned permanent CPMP Working Parties, ad hoc Groups were formed to deal with specific scientific issues. Meetings of these ad hoc Groups convened in 1996 included:

- ad hoc group on Oncology to up-date the existing CPMP guideline on anti-cancer medicinal products in man
- ad hoc group on BSE to review the CPMP guideline on BSE
- ad hoc Influenza Vaccines expert group to discuss potency issues and choice of strains
- ad hoc group on harmonisation of specific Summary of Product Characteristics
- ad hoc group on anti-psychotic medicinal products
- ad hoc group on osteoporosis treatment and prevention of osteoporosis in women.

3 Medicinal products for veterinary use

Preface by Prof. Dr Reinhard Kroker
Chairman, Committee for Veterinary Medicinal Products

When one reviews the activities of the past year of the EMEA and the CVMP in particular, it becomes clear that there are a number of significant challenges that lie ahead.

Much of the Committee's work is taken up with the establishment of maximum residue limits (MRLs) and, whilst progress on setting MRLs for old substances has been good, there are 200 of them remaining. Even if the deadline to complete this work is extended beyond 1997, the task remaining is a daunting one. Whilst it is encouraging that so many more applications to set MRLs for new substances are being submitted, this work will undoubtedly stretch the resources of the experts assigned to the assessment process, they being the same persons reviewing the old ones as well.

The number of applications in 1996 for authorisation of veterinary medicines through the centralised system has been fewer than at first foreseen; 9 applications versus the 15 originally forecast by industry. Whilst the industry is in favour of the centralised procedure, it remains cautious, mainly due to the comparative small volume of the market and scarcity of innovative products in this sector of the pharmaceutical industry. However, the exclusion from the scope of List B of the annex to Council Regulation (EEC) No 2309/93 of new medicinal products solely intended for non-food species, is now identified as a significant barrier to the future success of the centralised procedure and must be addressed. Nevertheless, the CVMP, ably supported by the staff in the EMEA Secretariat, will continue to work hard in a spirit of consensus to ensure the success of the new European registration systems for veterinary medicinal products.

The Committee met 8 times in 1996 under the continued chairmanship of Professor Reinhard Kroker. One informal meeting of the CVMP took place in Dublin in September 1996. However, since the Committee did not meet on a monthly basis in 1996, it has on occasion proved difficult to complete the business within the two day time frame of the meetings and to comply with the procedural timetables for MRL and centralised applications; therefore the CVMP will meet each month in 1997, with the exception of August.

3.1 Unit for Evaluation of Medicinal Products for Veterinary Use

In anticipation of the increased number of applications for both the authorisation of veterinary medicines through the centralised procedure, and the establishment of maximum residue limits (MRLs) for new substances, the staffing of the Unit has increased in 1996 from the rather scarce resources which were available in 1995.

A Head of Unit was been appointed to this previously vacant post and is responsible for two sectors which have been created to manage the core business. A sector to co-ordinate the establishment of MRLs and to supervise veterinary pharmacovigilance now exists, to which a head has been appointed and one scientific administrator and one national expert on secondment to the Agency.

The other sector is responsible for the provision of full logistical and technical support to the CVMP as well as the project management of centralised applications for authorisation of new veterinary medicines. This sector has 3 scientific administrators appointed to it and a selection procedure to appoint a Head of Sector was initiated in 1996.

The total recruitment over the last twelve month period of 3 additional scientific staff, one national expert on secondment, one senior administrator and one additional secretary has been undertaken in line with the forecast of the growth in business anticipated for the Unit, and is consistent with the expected work load in the short to medium term.

The Unit incorporated into its business plan a number of key objectives to establish a mechanism of performance objectives for Unit staff. These were set according to sector responsibilities as well as general ones relating to the Unit's administrative tasks. Overall, good progress has been made in achieving these objectives and details of these indicators are given in the report.

3.2 Operations of the Committee for Veterinary Medicinal Products

Authorisations under the centralised procedure

The first Community marketing authorisation for a veterinary medicinal product was granted by the European Commission on 29 February 1996 for Nobi-Vac Porcoli by Intervet, following the positive CVMP opinion adopted in July 1995.

The CVMP reached a positive opinion by consensus for the first application submitted under the new centralised procedure in September 1996 and transmitted to the European Commission.

A total of 9 new applications were submitted in 1996. Some potential applicants have expressed disappointment at not being able to make a submission for a product containing a new entity for small animals, as such medicinal products are currently ineligible as they do not meet the criteria in list B of the Annex to Council Regulation (EEC) No 2309/93.

Of the 10 applications currently under consideration by the CVMP, 5 are eligible under list A and 5 under list B.

Scientific Advice

The CVMP received 6 requests for scientific advice from companies, almost all relating to challenges faced in research and development programmes for immunological veterinary medicinal products. On average, it took 5 months for the Committee to deliver its scientific opinions because advice from other experts was sought. A standard operating procedure has now been adopted by the Committee which lays down a time limit for giving such opinions within 3 months.

Guidelines - update on international harmonisation

Many guidelines have already been adopted by the CVMP and are published in Volume VII of the Rules Governing Medicinal Products in the European Community (see annex 8). During the last twelve months, the Committee has adopted a further three guidelines which include Environmental Risk Assessment for immunological veterinary medicinal products (EMEA/CVMP/74/95, adopted July 1996), In-Use Stability Testing (EMEA/CVMP/127/95, adopted March 96) and the Approach Towards Harmonisation of Withdrawn Periods (EMEA/CVMP/036/95, adopted April 1996).

Guidelines released for consultation in 1996 include:

EMEA/CVMP/080/96	Additional quality requirements for products intended for incorporation into animal feeding-stuffs (medicated pre-mixes)	Consultation deadline 30 June 1996
EMEA/CVMP/094/96	Quality of prolonged and controlled release dosage forms for veterinary use	Consultation deadline 30 June 1996
EMEA/CVMP/055/96	Environmental risk assessment of veterinary medicinal products	Consultation deadline 1 October 1996
EMEA/CVMP/144/96	Annex to the Note for Guidance on the Manufacture of the finished dosage form concerning the Start of shelf-life of the finished dosage form	Consultation deadline 1 February 1997
CPMP/QWP/115/95	CPMP Note for Guidance on Inclusion of antioxidants and antimicrobial preservatives in medicinal products	Consultation deadline 1 February 1997
EMEA/CVMP/128/95	Investigation of chiral active substances	Consultation deadline 1 February 1997
EMEA/CVMP/183/96	Pharmacovigilance of veterinary medicinal products	Consultation deadline 1 April 1997
EMEA/CVMP/116/96	Harmonisation of requirements for equine influenza vaccines	Consultation deadline 1 May 1997
EMEA/CVMP/183/96. Rev1	New pharmacovigilance guidelines	Consultation deadline 1 April 1997

CVMP guidelines have increasing significance as progress is made towards international harmonisation within the context of the VICH initiative. The first meeting of the steering group of VICH took place under the auspices of the OIE in Paris in April 1996 and 5 priority topics were agreed for consideration in 1996. These include review and adoption of ICH human guidelines on quality, genotoxicity and reproductive safety, as well as new guidelines on anthelmintic efficacy, good clinical practice and ecotoxicity. The CVMP and its working parties have made good progress in agreeing the European regulatory position on these topics before the scheduled meetings of the expert working groups early in 1997.

3.3 Establishment of maximum residue limits (MRLs)

MRLs for new substances

Contrary to earlier predictions there were 20 applications in 1996 for the establishment of MRLs for new substances, which is an encouraging indicator of new product development in the animal health industry. Some of these applications were in fact for existing substances which had not been defended earlier by the deadline for submission laid down by Council Regulation (EEC) No 2377/90. In addition a total of 10 applications for the modification or extension of existing MRLs were received by the EMEA in 1996.

Some difficulties with these applications for existing substances have been experienced because the submission files were often incomplete and the quality of data very poor and, as a result, a few could not be validated. However, the majority of submission for new substances progressed well and 80% completed validation in 23 days, in advance of the formal 30 day limit. The average time required by the CVMP to complete the evaluation for these substances, resulting in a recommendation for MRLs or agreement on a consolidated list of questions, stands at 95 days, well in advance of the legislative time frame of 120 days laid down in Council Regulation (EEC) No 2377/90.

In those cases where a consolidated list of questions was sent to the applicant, the average time required for CVMP to conclude its opinion equals 47 days, reflecting the Committee's determination to progress these applications in a timely manner consistent with maintaining the scientific norms expected. In 1996 the CVMP adopted opinions in respect of 3 full applications and 6 extensions or modifications of existing MRLs. Details of all MRL opinions adopted by the new CVMP are given in annex 7.

MRLs for old substances

The CVMP and its Safety of Residues Working Party continued to work extremely hard to finalise the establishment of MRLs for old substances as the deadline for completion of this task comes closer. This work had been taken over by the EMEA at the request of the European Commission in 1995 for which no fees were payable or compensation given for the work of the national competent authorities. The Secretariat has, with close co-operation of the Working Party, sought to increase the efficiency of the review process through a number of initiatives, including

- increasing the duration of the 8 meetings per year to 3 days each from 2 days
- reallocating substances from rapporteurs already burdened with too many applications to others
- increasing administrative support during meetings, enabling revisions and amendments to be made to summary and status reports at the time of meetings, thus avoiding further delay.

This has allowed the achievement of a major objective to cut down the review of discussion time for an application from three meetings to one or two. Whilst increasing the number of meetings was considered, this was felt inappropriate because of insufficient time for preparation of documents by members and full assessment and review.

The Commission, recognising that completion of the required work by the 1997 deadline would be impossible, had agreed to take the necessary steps to extend the deadline. The Secretariat and Working Party has completed an extensive and detailed work plan with the objective of completing the task by the revised deadline; any extension of

less than three years will make this particularly difficult.

Dr Kevin Woodward, Chairman of the Safety of Residues Working Party resigned from the CVMP in August and the Committee expressed its gratitude for the significant contribution made by Dr Woodward to the MRL work over several years. He is succeeded by Mr Gabriel Beechinor.

In total, the Working Party made considerable progress and recommended MRLs on which the CVMP agreed opinions for 52 substances. A total of 3 substances were recommended for addition to Annex I (formal MRL fixed), 34 to Annex II (MRL not required), 13 to Annex III (provisional MRL) and 2 were placed in Annex IV (prohibited substances).

For 45 substances assessed by the Working Party, the evaluation could not be completed due to the inadequacy of data provided, and status reports with lists of questions were agreed and sent to the applicants. Progress has been a little slower than anticipated for 3 main reasons. Firstly, substances with poor quality data files with scarce data have tended to be left till last, and these now account for a far greater majority of those applications remaining than was the case when the EMEA took over responsibility in early 1995. Secondly, the Standing Veterinary Committee requested greater detail and summary reports for Annex II candidates and, thirdly, the increased number of applications to CVMP for new substances are still reviewed by the same experts who are members of the Safety of Residues Working Party, which means greater pressure on limited resources.

3.4 Mutual recognition of veterinary medicinal products

As predicted in the First Activity Report, the number of new decentralised procedures increased in 1996. A total of 15 new procedures were finalised and 7 more are in progress. Variations to products previously authorised under the ex-concertation procedure were also processed; 14 Type I variations and 1 Type II variation were granted. It is envisaged that the number of procedures will increase further in 1997.

No requests were received for arbitration by the CVMP during 1996, either for new decentralised procedures or for variations to existing products, although a certain amount of difficulty was experienced in two procedures for which arbitration might have been a solution.

Mindful of the need to progress these procedures in a short period of time and that difficulties can arise in the final stages of recognition, the CVMP, in October 1996, endorsed the setting up of a Mutual Recognition Facilitation Group by the Member States. The Group will meet on an ad hoc basis at the EMEA and administrative support, as and when needed, will be provided by the EMEA Veterinary Unit.

3.5 CVMP Working Parties

The four Working Parties, including the joint CPMP/CVMP Quality Working Party, have met regularly throughout the year.

Safety of Residues Working Party

The Working Party met 8 times and achieved significant progress in the establishment of MRLs for old substances which has been reported elsewhere in this report. In addition, the Working Party is in the process of completing a guideline on the harmonisation of withdrawal periods in milk as well as drafting opinions on the applicability of ICH guidelines on genotoxicity and reproductive safety as the basis for the CVMP position on these topics for consideration at VICH. The CVMP has also requested scientific input to redraft its policy on establishing MRLs for minor species to detail what tissues are to be routinely considered as target tissues in establishing MRLs.

CVMP Pharmacovigilance Working Party

New pharmacovigilance guidelines were drafted by the Working Party and released for a six month consultation period by the CVMP. In addition, two ad hoc groups were created, one to support the development of the EudraWatch system for veterinary pharmacovigilance, whereby the reporting of serious adverse drug reactions and periodic safety updates will be reported throughout the Community via a dedicated telematic network; and the second to draw up a list of veterinary dictionary-defined terms for pharmacovigilance reporting (VEDDRA).

Immunological Veterinary Medical Products Working Party

The IVMP Working Party met 3 times in 1996 under the chairmanship of Professor P-P. Pastoret and has been responsible for the provision of scientific advice in response to all 6 requests for such advice received by the CVMP.

The Working Party Guideline on environmental risk assessment for IVMPs was adopted by the CVMP in July 1996 and a guideline on specific requirements for substitution of a strain of an equine influenza vaccine was released for consultation in November 1996. Preliminary discussions have begun on drafting guidelines for the following topics in 1996:

- Diminution of animal experimentation and control of veterinary vaccines
- Guidelines on potency tests for veterinary biologicals
- Use of adjuvants in veterinary vaccines
- Variation assessment reports for IVMPs

Joint CPMP/CVMP Quality Working Party

The Working Party's agenda is now structured to allow emphasis on veterinary quality matters, when required, in the presence of veterinary experts.

As well as the Quality Guidelines adopted by CVMP and those released for consultation, the Working Party began the process of drafting guidelines on a Note for Guidance on Chemistry of New Active Ingredients, and Excipients in the registration dossier of a veterinary medicinal product.

4 Technical co-ordination activities

4.1 Setting-up the Technical Co-ordination Unit

With the appointment of a Head of Unit for Technical Co-ordination, the EMEA management structure was completed as planned. The Unit had previously started under the guidance of the Head of the Human Medicines Unit.

To further improve the organisational structure of the EMEA, the distribution of functions over the four Units was reviewed. This lead to a split of the pharmacovigilance activities from the Technical Co-ordination Unit to the Human and Veterinary Medicines Evaluation Units for their respective areas of interest. The Sector for Information technology & conferences was recognised as two separate activities and both were assigned to the Technical Co-ordination Unit.

The structure at the end of 1996 was therefore:

- Sector for Inspections
- Sector for Documentation & archives
- Sector for Conference
- Sector for Information technology

At the end of 1996 the Unit had 19 staff members: 4 in Inspections, 5 in Documentation and archiving, 5 in Conferences and 5 in IT. To comply with the growing needs of the Agency, as well as to take on the specific tasks of the Technical Co-ordination Unit, two recruitment competitions were organised to identify new staff for positions in each of the four sectors.

The potential scope of activities for the Technical Co-ordination Unit is wider than resources allow. Goals were formulated during 1996 for each sector to help keep the main needs of the EMEA in focus. Several projects initiated by the Unit involved participation of other Units or groups external to the EMEA. The most important ones are listed here:

- the development of document templates by the ad hoc Working Group on Quality Review of Documents to facilitate the creation and management of EMEA opinions in 11 languages
- the initiation of a Quality Management System, to build in a systematic way on past experience by determining best practices and consolidating routine activities. This frees up resources for new and more challenging tasks, while setting explicit standards that allow for each individual, as well as for the EMEA as a whole, to perform better
- an internal regulatory affairs forum to facilitate the discussion of matters of legal, regulatory and procedural nature. A large variety of topics was discussed while the group also was assigned to promote a systematic approach to the development of SOPs
- a user-group consolidated the user requirements for the Application Tracking System (ATS) which were then implemented by a team from ETOMEP at JRC, Ispra. The daily management of both groups was taken on by EMEA with the result that the first production version of ATS was installed towards the end of 1996.

4.2 Co-ordination of inspections and quality of human & veterinary medicines

Good Manufacturing Practice inspections

For most applications one inspection is requested, but more than one per application is no exception. All inspections were focused on manufacturers of new human medicinal products. During the year 19 inspections were requested and 18 were included in positive CPMP opinions.

The time period from the request of the inspection until completion is, on average, 6 months with almost half of the inspections lasting 4 month or less.

Of the 25 inspections carried out, 17 confirmed that the manufacturer was in general compliance with Community Good Manufacturing Practice (GMP) and 5 were unsatisfactory, requiring 3 re-inspections. Inspectors from the national inspection services of Belgium, Denmark, Germany, Spain, France, Italy, Ireland, The Netherlands, Portugal, Sweden, Finland and the UK were involved. Seventeen inspections were carried out in the United States, 5 in Switzerland, 1 inspection in Canada and 2 in the EU.

The sector has been responsible for holding two ad hoc meetings at the EMEA of the heads of the Member State inspection services, along with observers from the European Pharmacopoeia and the Nordic Council countries. These meetings have enabled the Agency and inspectors to discuss the arrangements for inspections under the centralised system, problems encountered, reporting arrangements and other related issues. These meetings have complemented the activities of the European Commission's Control of Medicinal Products and Inspections 'Working Party' which meets in Brussels.

Certification of medicinal products

At the request of the European pharmaceutical industry, the EMEA was given a mandate from the European Commission in April 1996 to produce certificates for centrally-authorised medicinal products. Further to an exchange of letters with the World Health Organisation the EMEA in June 1996 introduced a system for issuing export certificates for centrally-authorised medicinal products.

Since their introduction, the demand for certificates has steadily increased and about 1 628 were issued in 1996 for more than 107 countries.

Joint CPMP/CVMP Quality Working Party

The sector provides secretarial support for the joint CPMP/CVMP Quality Working Party which met under the Chairmanship of Dr J-L Robert on three occasions during 1996. Two of these meetings involved additional veterinary experts and an extended agenda to include specific veterinary items.

'Quality' guidelines released for consultation or adopted in 1996 include:

CPMP/QWP/486/95	Manufacture of the finished dosage form	Re-issued in April 96
CPMP/ICH/279/95	Photostability testing of new active substences and medicinal products (Q1B)	Adopted in December 96
CPMP/ICH/280/95	Stability testing requirements for new dosage forms (Q1C)	Adopted in December 96
CPMP/ICH/281/95	Validation of analytical procedures: methodology (Q2B)	Adopted in December 96
CPMP/ICH/282/95	Impurities in new medicinal products (Q3B)	Adopted in December 96
CPMP/QWP/072/96	Start of shelf-life	Released for consultation in June 96
CPMP/QWP/159/96	Maximum shelf-life for sterile products for human use after first opening or following reconstitution	Released for consultation in June 96
CPMP/QWP/115/96	The use of antioxidants and preservatives in medicinal products	Released for consultation in July 96
CPMP/QWP/157/96	Reduced stability testing - bracketing and matrixing	Released for consultation in September 96
CPMP/ICH/283/95	Impurities: residual solvents (Q3C)	Released for consultation in November 96
CPMP/QWP/155/96	Development Pharmaceutics	Released for consultation in November 96 (revision)

The Working Party was also involved in preparing Scientific Advice on Quality topics for the CPMP/CVMP and has worked on guidance on other topics including chemistry of the active ingredient, declaration of storage conditions, dry powder inhalers, prolonged release forms and process validation.

4.3 Documentation and archiving

During the year the focus of interest for this sector gradually moved from initial activities like mail services, library and archiving, to document management and publishing, reflecting current strong business needs of the EMEA.

Document management and templates

Preparatory activities have resulted in proposals for a structured management of the document life cycle with special attention to document format, document identification, versioning and confidentiality. In addition several initiatives have been taken to prepare for the implementation of a workflow based document management system at the EMEA.

The quality of CPMP opinions in all 11 official Community languages received much attention. This led to the initiation of the ad hoc group on Quality Review of Documents with participants from Commission, national competent authorities, EU Translation Centre and EMEA. This group started work on the development of templates in all languages for all CPMP and CVMP opinions and other notification documents.

Initial experience with the template for a 'positive CPMP Opinion' showed that it was of substantial help and already saved much time in 1996. It is expected that, once relevant templates are widely available, not only document handling will take substantially less time, but that also the document quality will further increase.

EMEA website, library and mailroom

The EMEA Internet website, maintained and managed in London by the ETOMEP team from JRC, enjoyed great popularity and was visited from almost all points of the globe during 1996.

The website, which can be found at *http://www.eudra.org/emea.html*, was widely used for dissemination purposes in 1996 contained over 200 documents covering general EMEA information, scientific committee press releases, SOPs, guidelines, EPARs and newsletters.

Library services also increased with the addition of new books and journals. Information on the list of European experts was provided 31 times while 18 visitors used the opportunity to directly access the database on site.

Mail services during the year strongly increased with a two- to three-fold increase over the previous year, with over 26 500 items received and more than 7 500 items mailed out. A rather sophisticated system was set up with the express mail service provider allowing ongoing trace of mail sent out up to confirmation of receipt by addressee.

4.4 Conference and linguistic support

A total of 163 meetings was hosted of which 125 were statutory and 38 were external meetings with interested parties, providing for a total of 270 meeting days.

In total, 427 days of interpretation were provided during these meetings, usually allowing for at least 6 passive and 2 active languages.

Some 1 600 requests for reimbursement for delegates participating in EMEA meetings were handled. To further improve the service to delegates, new procedures were introduced in order to complete payments related to any meeting within 4 weeks after the meeting. Also, reimbursement of outstanding commitments was accelerated. In addition, and to simplify reimbursements, a system of cash settlements was put in place so that delegates would receive daily and local travel allowances directly at the meeting, thus further minimising banking charges.

Reprographics activities

The number of copies has reached an average of over half a million pages per month, distributed as:

- Human Medicines Unit 52.6 %
- Veterinary Medicines Unit 16.2 %
- Directorate & Administration 12.1 %
- Conferences 7.3 %
- Documentation & archiving 4.8 %
- Inspections 4.4 %.

Translations

The number of pages sent to the Luxembourg Translation Centre has reached a level of about 11 000 pages divided over a number of 225 documents.

In the second half of the year the work flow between EMEA, the Luxembourg EU Translation Centre and the various groups of translators was investigated showing ample opportunity to reduce the turn-around time of translation material. Also, the technicalities of communication were critically reviewed and standardised. It is expected that these improvements, together with increased staffing of the Translation Centre, will within the next year provide for a more adequate provision of translation facilities.

4.5 Information technology

Information technology is rapidly becoming the cornerstone supporting the virtual organisation that EMEA, Commission and the national competent authorities form. Strong demands for inter-connectivity are emerging and robust and reliable systems need to be put in place that are able to adequately scale for the large fluctuations in activity as well as for further anticipated growth. The internal organisation and architecture was reviewed in 1996 and it has become clear that EMEA's operation requires an industry standard information system preferably similar to those of EMEA business partners (Commission, Member State competent authorities, Translation Centre, pharmaceutical industry, etc).

In relation to the above a strategy of consolidation has been followed to optimise exploitation of investments. Increasing standardisation of workstations, concentrations of servers and network have led to a more manageable set up. Also the management of network and servers has been actively optimised. Daily production work has increasingly been brought in house thus optimising use of internal resources. Help desk operations were upgraded and although much support as well as training was given the call rate remains at a relatively high level of about 80 per week, reflecting ongoing influx of new personnel and related installations.

Several applications necessary to support the EMEA business processes have been identified and started, e.g. ATS, financial package, activity tracking. Optimised development of business supporting applications is expected to have a high priority during the next 2 years. For example systems to improve management of meetings, workflow, documents and much other information necessary to support the Agency's activities are urgently required. Development of a detailed plan describing the migration to a new IT architecture and the necessary development of those applications was begun in 1996.

5 European Technical Office for Medicinal Products (ETOMEP)

In accordance with the Agreement between the European Commission's Joint Research Centre and the EMEA, the ETOMEP Unit has continued to develop and maintain network-oriented systems and services within the scope of the EudraNet project. In 1996 this project was driven mainly through a contract awarded under the European Commission, 'Interchange of Documents between Administrations' (IDA) Programme.

ETOMEP has consolidated the telecommunications network between EMEA, European Commission and all EU Member State national competent authorities, in particular by the realisation of the EudraNet 'backbone' between London and Ispra and the connectivity of end users to EudraNet via special telecommunication lines (ISDN). At the end of 1996 connection between national competent authorities, European Commission and EMEA was almost complete, with the necessary telecommunication links still awaited with only a small number of national authorities.

ETOMEP also developed in 1996 a number of electronic applications, including:

- the first production version of the EMEA Application Tracking System (ATS) for the centralised procedure
- the first pilot version of the tracking system for the decentralised procedure, 'EudraTrack-MR'
- the first pilot version of the database on rules governing medicinal products in the EU, 'EudraLex'

In addition ETOMEP has continued to provide a number of essential support services to EMEA comprising

- Network publishing: The design, development and maintenance of the EMEA website has required the provision of technical competence in Internet Web technology, graphic design and editorial expertise. More than 1 300 000 successful requests for information ('hits') were recorded in 1996, with a total data transfer of over 9 300 Mbytes. Furthermore, ETOMEP has strengthened EudraNet connectivity to the Internet with two lines (JANET and PIPEX)
- E-mail services: The development and maintenance of electronic messaging (X400 and SMTP protocols) has involved the installation of a direct line between EMEA and the European Commission. During 1996 the number of e-mail messages exchanged by EMEA with the outside world averaged approximately 2 000 per month (140 Mbytes).

Annexes

Annex 1
Membership of the management board

Chairman
Strachan HEPPELL

European Parliament
Gianmartino BENZI
Dietrich HENSCHLER
Alternates
Roselinde HURLEY
Jean-Pierre REYNIER

European Commission
Stefano MICOSSI
Fernando MANSITO CABALLERO

Belgique/België
Eliane MESMAEKER ([1])
Jean-Antoine DE MUYLDER ([1])

Danmark
Ib VALSBORG
Mogens BJØRNBAK-HANSEN

Deutschland
Karl FEIDEN ([2])
Hermann PABEL

ΕΛΛΑΔΑ/**Greece**
Stavros KAZAZIS
Nikolaos KOKOLIS

España
Pilar GONZALEZ GANCEDO ([3])
Cleto SANCHEZ VELLISCO ([3])

France
Didier TABUTEAU
Jacques BOISSEAU

Ireland
Seamus HEALEY
Tom MOONEY

Italia
Luigi FRATI
Romano MARABELLI
(Vice-Chairman)

Grand-Duché du Luxembourg
Mariette BACKES-LIES

Nederland
André BROEKMANS
Christian van der MEIJS

Österreich
Alexander JENTZSCH
Ernst LUSZCZAK

Portugal
José ARANDA DA SILVA
Graça TEIXEIRA QUEIROS ([4])

Suomi/Finland
Mauno LINDROOS
Hannes WAHLROOS

Sverige
Birgitta BRATTHALL
Anders BROSTRÖM

United Kingdom
Keith JONES
Alistair CRUICKSHANK ([5])

(1) Jean-Paul DEROUBAIX and Michel CHOJNOWSKI replaced the former Belgian members as of the 2 July 1996 meeting
(2) Gerhard KOTHMANN replaced the former member as of the 26 September 1996 meeting
(3) Ana Maria NAVEIRA replaced one former Spanish member as of the 2 July 1996 meeting and Valentin ALMANSA the other as of the 26 September 1996 meeting
(4) Maria MIRANDA replaced Graça Teixeira Quieros as of the 26 September 1996 meeting
(5) Michael RUTTER replaced Alistair Cruickshank as of the 2 July 1996 meeting

Annex 2
Membership of the Committee for Proprietary Medicinal Products

Chairman
Prof. Jean-Michel ALEXANDRE

Belgique/België
Pharm. Noël WATHION ([1])
Dr Luk BLONDEEL

Danmark
Mr Henning HOVGAARD
(Vice-Chairman)
Dr Gorm JENSEN

Deutschland
Prof. Alfred HILDEBRANDT
Prof. Reinhard KURTH

ΕΛΛΑΔΑ/**Greece**
Prof. Marios MARSELOS
Mrs Julia YOTAKI

España
Ms Carmen COLLADO ALVAREZ
Prof. Fernando de ANDRES-TRELLES

France
Dr Patrick LECOURTOIS
Prof. Jean-Hughes TROUVIN

Ireland
Dr Mary TEELING
Dr David LYONS

Italia
Prof. Giuseppe VICARI
Prof. Vittorio SILANO

Grand-Duché du Luxembourg
Dr Jean-Louis ROBERT
Pharm. Jacqueline GENOUX-HAMES

Nederland
Dr Hans van BRONSWIJK
Mr Willem van der GIESEN

Österreich
Dr Heribert PITTNER
Dr Walter FUCHS

Portugal
Prof. José GUIMARAES MORAIS
Dr Henrique LUZ-RODRIGUES

Suomi/Finland
Dr Christer STROMBERG
Dr Eeva ALHAVA

Sverige
Prof. Kjell STRANDBERG
Dr Per SJOBERG

United Kingdom
Dr David JEFFERYS
Dr Susan WOOD

(1) Pharm. Geert DE GREEF replaced Noël Wathion as of the September 1996 CPMP meeting

Annex 3
Membership of the Committee for Veterinary Medicinal Products

Chairman
Prof. Dr Reinhard KROKER

Belgique/België
Prof. Paul-Pierre PASTORET
Mrs Françoise FALIZE

Danmark
Ms Birgitte KRISTENSEN
Dr Claus WILLADSEN

Deutschland
Dr Sabine EGLIT
Prof. Manfred MOOS

ΕΛΛΑΔΑ/**Greece**
Prof. Vassilios ELEZOGLOU
Mr Dimistrios MIGOS

España
Dr Luis Fernando CORBALAN
Dr Odon SOBRINO

France
Dr Jacques BOISSEAU
Dr Dominique MOUROT

Ireland
Mr Cyril O'SULLIVAN
(Vice-Chairman)
Mr Gabriel BEECHINOR

Italia
Dr Agostino MACRI
Ms Gabriella CONTI

Grand-Duché du Luxembourg
Mr Marc WIRTOR
Dr Albert HUBERTY

Nederland
Dr Herman LENSING
Dr Peter HEKMAN

Österreich
Mgr Eugen OBERMAYR
Dr Johannes DICHTL

Portugal
Ms Margaride PRATAS
Dr José BELO

Suomi/Finland
Dr Liisa KAARTINEN
Docent Satu PYÖRÄLÄ

Sverige
Dr Annika WENNBERG
Prof. Jan LUTHMAN

United Kingdom
Dr Michael RUTTER
Dr Kevin WOODWARD [1]

(1) Dr Woodward was replaced by Dr Jill ASHLEY-SMITH as of the September 1996 CVMP meeting

Annex 4
Organigram of the EMEA Secretariat

Directorate

Executive Director	Fernand Sauer
Financial control	Birgit Snoeren

Administration Unit

Head of Unit	Marino Riva
Personnel and support services	Frances Nuttall
Accounting	Gerard O'Malley

Evaluation of Human Medicines Unit

Head of Unit	Rolf Bass
Regulatory affairs and pharmacovigilance	Noël Wathion
Centralised procedures, List A	John Purves
Centralised procedures, List B	Josep Torrent Farnell

Evaluation of Veterinary Medicines Unit

Head of Unit	Peter Jones
Veterinary procedures and CVMP	....
Safety of residues (MRLs)	Kornelia Grein

Technical Co-ordination Unit

Head of Unit	Karel de Neef
Inspections	Stephen Fairchild
Documentation and archiving	Beatrice Fayl
Conferences	....
Information technology	....

Annex 5
EMEA budgets 1994 to 1996

The summarised comparative budget statements* for 1994 to 1996 are as follows:

	1994	1995	1996
Revenues			
European Community subsidy	6 800 000	10 150 000	13 750 000
Evaluation fees		4 000 000	8 600 000
Miscellaneous revenue	13 085	262 000	200 000
Total revenue	**6 813 085**	**14 412 000**	**22 550 000**
Expenditure			
1 Staff costs			
staff salaries and allowances	544 264	2 902 000	7 494 000
other staff costs	69 149	1 164 000	1 565 000
Total staff costs	613 413	4 066 000	9 060 000
2 Building equipment & other internal costs			
Fitting out, lease & other building related costs	4 811 000	2 420 000	2 205 000
IT, data processing	1 197 918	930 000	1 900 000
Other current administrative expenditure	110 754	1 396 000	1 150 000
Total internal costs	6 119 672	4 746 000	5 255 000
3 Operational and expertise related costs			
Committee meetings	80 000	1 540 000	2 210 000
Fees of rapporteurs and experts		3 550 000	5 250 000
Total operational and expertise costs	80 000	5 090 000	7 460 000
4 Luxembourg Translation Centre		500 000	735 000
5 Publishing and information		10 000	40 000
Total expenditure	**6 813 085**	**14 412 000**	**22 550 000**

(*) Including supplementary and amending budgets as adopted by the Management Board

Annex 6
CPMP opinions in 1996 on medicinal products for human use

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received on b) Decision c) Notification d) OJ No.
a) Gonal-F b) Follitropin-alpha c) Part A	a) Serono Laboratories b) IT/CH	a) G03G b) Treatment of infertility	a) Powder for injection b) 75 IU, 150 IU c) 16 Presentations	a) 01.01.95 b) 17.05.95 c) 107 days d) 30 days	a) 08.06.96 b) 20.10.95 c) 26.10.95 d) OJ No C.22 of 26.01.96
a) Betaferon b) Interferon beta -1b c) Part A	a) Schering AG b) DE	a) L03AA b) Immuno-stimulation, multiple sclerosis	a) Powder for injection b) 0.25 mg/ml c) 1 Presentation	a) 01.01.95 b) 12.07.95 c) 138 days d) 55 days	a) 11.08.95 b) 30.11.95 c) 06.12.95 d) OJ No C.22 of 26.01.96
a) Taxotere b) Docetaxel c) Part B	a) Rhone-Poulenc Rorer b) FR	a) L01X b) Treatment of breast cancer	a) Concentrate for infusion b) 80mg/2ml, 20mg/0.5ml c) 2 Presentations	a) 01.01.95 b) 12.07.95 c) 100 days d) 93 days	a) 11.08.95 b) 27.11.95 c) 29.11.95 d) OJ No C.22 of 26.01.96
a) NovoSeven b) Factor VIIa c) Part A	a) Novo-Nordisk b) DK	a) B02BD05 b) Coagulation factor	a) Powder for injection b) 60 KIU, 120 KIU, 240 KIU c) 3 Presentations	a) 01.01.95 b) 12.09.95 c) 210 days d) 80 days	a) 27.11.95 b) 23.02.96 c) 27.02.96 d) OJ No C.93 of 29.03.96
a) CellCept b) Mycophenolate mofetil c) Part B	a) Hoffmann-La Roche b) CH	a) L04AX b) Prevention of Kidney Transplant Rejection	a) Capsules, Tablets b) 250mg, 500mg c) 2 Presentations	a) 01.01.95 b) 17.10.95 c) 243 days d) 47 days	a) 20.10.95 b) 14.02.96 c) 15.02.96 d) OJ No C.54 of 23.02.96
a) Fareston b) Toremifene c) Part B	a) Orion b) FIN	a) LO2BA02 b) Treatment of Breast Tumors	a) Tablets b) 60mg c) 2 Presentations	a) 01.01.95 b) 17.10.95 c) 240 days d) 50 days	a) 20.10.95 b) 14.02.96 c) 16.02.96 d) OJ No C.54 of 23.02.96
a) Humalog b) Insulin lispro c) Part A	a) Lilly Industries b) US	a) A10AB04 b) Treatment of diabetes mellitus	a) Solution for injection b) 40 IU/ml vials, 100 IU/m vials + Cartridges c) 3 Presentations	a) 01.01.95 b) 22.11.95 c) 245 days d) 81 days	a) 15.01.96 b) 30.04.96 c) 01.05.96 d) OJ No C.156 of 31.05.96
a) Puregon b) Follitropin-beta c) Part A	a) Organon b) NL	a) GO3G b) Treatment of infertility	a) Powder for injection b) 50 IU, 100 IU, 75 IU, 150 IU c) 16 Presentations	a) 01.01.95 b) 20.12.95 c) 203 days d) 151 days	a) 08.02.96 b) 03.05.96 c) 07.05.96 d) OJ No C.156 of 31.05.96
a) Zerit b) Stavudine c) Part B	a) Bristol Myers Squibb b) UK	a) JO5AX04 b) Treatment of HIV infection	a) Powder for oral solution, capsules b) 1mg/ml,15mg/ml, 20mg/ml, 30mg/ml, 40mg/ml c) 9 Presentations	a) 14.08.95 b) 16.01.96 c) 150 days d) nil	a) 18.03.96 b) 08.05.96 c) 09.05.96 d) OJ No C.156 of 31.05.96

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received b) Decision c) Notification d) OJ No.
a) Rilutek b) Riluzole c) Part B	a) Rhone-Poulenc Rorer b) FR	a) NO7X b) Treatment of Amyotrophic lateral sclerosis	a) Tablets b) 50mg c) 1 Presentation	a) 19.07.95 b) 13.02.96 c) 161 days d) 41 days	a) 27.03.96 b) 10.06.96 c) 11.06.96 d) OJ No C.188 of 28.06.96
a) Caelyx b) Doxorubicin-HCl c) Part B	a) Sequus Pharmaceutical Inc . b) UK	a) LO1DB b) Treatment of AIDS-related Kaposi's Sarcoma	a) Concentrate for Infusion b) 20mg in 10ml/vial c) 1 Presentation	a) 01.01.95 b) 13.02.96 c) 222 days d) 150 days	a) 12.04.96 b) 21.06.96 c) 25.06.96 d) OJ No C.216 of 26.07.96
a) Bondronat b) Ibandronic Acid c) Part B	a) Boehringer Mannheim b) DE	a) MO5BA b) Treatment of tumour induced hypercalcaemia	a) Concentrate for Infusion b) 1mg in 1ml/ampulle c) 1 Presentation	a) 01.06.95 b) 13.02.96 c) 203 days d) 52 days	a) 11.04.96 b) 25.06.96 c) 27.06.96 d) OJ No C.216 of 26.07.96
a) Bonviva b) Ibandronic Acid c) Part B	a) Galenus Mannheim b) DE	a) MO5BA b) Treatment of tumour induced hypercalcaemia	a) Concentrate for Infusion b) 1mg in 1ml/ampulle c) 1 Presentation	a) 01.06.95 b) 13.02.96 c) 203 days d) 52 days	a) 11.04.96 b) 25.06.96 c) 27.06.96 d) OJ No C.216 of 26.07.96
a) Tritanrix-HB b) Comb. vaccine c) Part A	a) SmithKline Beecham b) BE	a) J07CA b) Vaccine against Hepatitis B, Diphteria Tetanus, Pertussis	a) Suspension for injection b) - c) 2 Presentations	a) 01.01.95 b) 12.03.96 c) 180 days d) 240 days	a) 30.04.96 b) 19.07.96 c) 19.07.96 d) OJ No C.252 of 30.08.96
a) Epivir b) Lamivudine c) Part B	a) Glaxo Wellcome b) UK	a) JO5AB10 b) Treatment of HIV infection	a) Tablets, Oral Solution b) 150mg, 10mg/ml c) 2 Presentations	a) 25.07.96 b) 16.04.96 c) 150 days d) 105 days	a) 10.06.96 b) 08.08.96 c) 09.08.96 d) OJ No C.252 of 30.08.96
a) CEA-Scan b) Arcitumomab c) Part A	a) Immunomedics b) US	a) VO9IA01 b) Diagnosis of colonic and rectal carcinoma	a) Powder for injection b) 1.25mg/vial c) 1 Presentation	a) 01.01.95 b) 21.05.96 c) 110 days d) 386 days	a) 11.07.96 b) 04.10.96 c) 07.10.96 d) OJ No C.316 of 25.10.96
a) Tecnemab K 1 b) Anti-melanoma antibody c) Part A	a) Sorin b) IT	a) VO9IA02 b) Diagnosis of cutaneous melanoma lesions	a) Lyophilisate for injection b) 3x6ml vials c) 1 Presentation	a) 01.01.95 b) 21.05.96 c) 187 days d) 320 days	a) 03.07.96 b) 05.09.96 c) 23.09.96 d) OJ No C.316 of 25.10.96
a) Rapilysin b) Reteplase c) Part A	a) Boehringer Mannheim b) DE	a) BO1AD b) Treatment of acute myocardial infarction	a) Freeze-dried powder b) 10 IU c) 2 Presentations	a) 01.08.95 b) 23.05.96 c) 204 days d) 83 days	a) 02.07.96 b) 29.08.96 c) 30.08.96 d) OJ No C.284 of 27.09.96

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received b) Decision c) Notification d) OJ No.
a) Ecokinase b) Reteplase c) Part A	a) Galenus Mannheim b) DE	a) BO1AD b) Treatment of acute myocardial infarction	a) Freeze-dried powder b) 10 IU c) 2 Presentations	a) 01.08.95 b) 23.05.96 c) 204 days d) 83 days	a) 02.07.96 b) 29.08.96 c) 30.08.96 d) OJ No C.284 of 27.09.96
a) Twinrix Adult b) Comb. vaccine c) Part A	a) SmithKline Beecham b) BE	a) JO7BC b) Vaccine against Hepatitis A and B	a) Suspension for injection b) 1.0ml dose/day c) 6 Presentations	a) 16.08.95 b) 22.05.96 c) 197 days d) 83 days	a) 12.07.96 b) 20.09.96 c) 23.09.96 d) OJ No C.316 of 25.10.96
a) Norvir b) Ritonavir c) Part B	a) Abbott b) US	a) JO5AX b) Treatment of HIV infection	a) Capsule, Oral Solution b) 200mg, 80mg/ml c) 3 Presentations	a) 13.03.96 b) 21.05.96 c) 69 days d) nil	a) 17.06.96 b) 26.08.96 c) 27.08.96 d) OJ No C.284 of 27.09.96
a) Indimacis 125 b) Igovomab c) Part A	a) CIS Bio International b) FR	a) VO9IB03 b) Diagnosis of Ovarian Adeno-carcinoma	a) Solution for injection b) 1mg in 1ml ampule c) 1 Presentation	a) 01.01.95 b) 19.06.96 c) 154 days d) 363 days	a) 13.08.96 b) 04.01.96 c) 10.10.96 d) OJ No C.360 of 29.11.96
a) Invirase b) Saquinavir c) Part B	a) Hoffmann - La Roche b) CH	a) JO5AX b) Treatment of HIV infection	a) Capsule b) 200mg c) 1 Presentation	a) 02.10.95 b) 19.06.96 c) 180 days d) 80 days	a) 13.08.96 b) 04.10.96 c) 04.10.96 d) OJ No C.316 of 25.10.96
a) Zyprexa b) Olanzapine c) Part B	a) Eli Lilly b) US	a) NO5AX b) Treatment of Schizophrenia	a) Tablet b) 2.5mg, 5.0mg, 7.5mg, 10mg c) 22 Presentations	a) 09.10.95 b) 19.06.96 c) 198 days d) 56 days	a) 30.07.96 b) 27.09.96 c) 27.09.96 d) OJ No C.316 of 25.10.96
a) Olanzek b) Olanzapine c) Part B	a) Eli Lilly Netherlands B.V. b) US	a) NO5AX b) Treatment of Schizophrenia	a) Tablet b) 2.5mg, 5.0mg, 7.5mg, 10mg c) 22 Presentations	a) 09.10.95 b) 19.06.96 c) 198 days d) 56 days	a) 30.07.96 b) 07.10.96 c) 08.10.96 d) OJ No C.316 of 25.10.96
a) Crixivan b) Indinavir c) Part B	a) Merck Sharp & Dohme b) US	a) J05AX07 b) Treatment of HIV infection	a) Capsules b) 200mg,400mg c) 5 Presentations	a) 13.03.96 b) 19.06.96 c) 85 days d) 12 days	a) 13.08.96 b) 04.10.96 c) 07.10.96 d) OJ No C.316 of 25.10.96
a) Hycamtin b) Topotecan c) Part B	a) SmithKline Beecham b) US	a) LO1X X17 b) Treatment of ovarian metastatic carcinoma	a) Powder for infusion b) 4mg c) 2 Presentations	a) 16.01.96 b) 19.07.96 c) 154 days d) 28 days	a) 20.08.96 b) 12.11.96 c) 13.11.96 d) OJ No C.360 of 29.11.96
a) Evotopin b) Topotecan c) Part B	a) Beecham Group b) US	a) LO1X X17 b) Treatment of ovarian metastatic carcinoma	a) Powder for infusion b) 4mg c) 2 Presentations	a) 16.01.96 b) 19.07.96 c) 154 days d) 28 days	a) 20.08.96 b) 09.12.96 c) 10.12.96 d) OJ No C.16 of 16.01.97
a) LeukoScan b) Sulesomab c) Part A	a) Immuno-medics b) USA	a) VO4CX b) Diagnostic agent	a) Powder for injection b) 0.31 mg c) 1 Presentation	a) 12.09.95 b) 16.10.96 c) 210 days d) 183 days	a) 05.12.96 b) 14.02.97 c) 17.02.97 d) OJ No C.63 of 28.02.97

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received b) Decision c) Notification d) OJ No.
a) .... b) .... c) Part A	a) .... b) DE	a) BO3XA b) Antianaemic	a) Powder for injection b) 500, 1000, 2000, 5000, 10 000, 50 000, 100 000 IU c) 42 Presentations	a) 01.11.95 b) 16.10.96 c) 209 days d) 140 days	a) 08.01.97 b) .... c) .... d) ....
a) Insuman b) insulin human c) Part A	a) Hoechst AG b) DE	a) A10A b) Treatment of Diabetes Mellitus	a) Solution for Injection, Suspension for Injection, Solution for Infusion b) 40 IU/ml, 100 IU/ml c) 27 Presentations	a) 06.12.95 b) 16.10.96 c) 158 days d) 182 days	a) 28.11.96 b) 21.02.97 c) .... d) ....
a) Twinrix paediatric b) Comb. vaccine c) Part A	a) SmithKline Beecham b) BE	a) .... b) Immunisation against Hepatitis A/B in children	a) Suspension for injection b) c) 5 Presentations	a) 21.05.96 b) 16.10.96 c) 132 days d) 35 days	a) 29.11.96 b) 10.02.97 c) 11.02.97 d) OJ No C.63 of 28.02.97
a) .... b) .... c) Part B	a) .... b) USA	a) JO5AB06 b) Treatment of CMV renititis in patient with AIDS	a) Tablet b) 4.5-6.4mg c) 1 Presentation	a) 20.01.96 b) 20.11.96 c) 183 days d) 119 days	a) 07.01.97 b) .... c) .... d) ....
a) .... b) .... c) Part A	a) .... b) USA	a) LO3A A... b) Immunostimulating agent	a) Powder for injection b) 30mg/vial c) 1 Presentation	a) 01.06.95 b) 20.11.96 c) 216 days d) 307 days	a) 07.01.97 b) .... c) .... d) ....
a) .... b) .... c) Part A	a) .... b) DE	a) B01AX b) Anti-coagulation therapy for heparin-associated thrombocytopenia	a) Powder for injection or infusion b) 50mg c) 1 Presentation	a) 15.0195 b) 20.11.96 c) 200 days d) 112 days	a) 09.01.97 b) .... c) .... d) ....
a) .... b) .... c) Part A	a) .... b) USA	a) .... b) Treatment of Diabetes Mellitus	a) Solution for injection b) 100 IU/ml Cartriges c) 2 Presentations	a) 10.09.96 b) 20.11.96 c) 70 days d)	a) 10.01.97 b) .... c) .... d) ....
a) .... b) .... c) Part B	a) .... b) USA	a) J05 b) Treatment of CMV renititis in patient with AIDS	a) Concentrate for infusion b) 375mg c) 1 Presentation	a) 16.01.96 b) 18.12.96 c) 209 days d) 112 days	a) 22.01.97 b) .... c) .... d) ....
a) .... b) .... c) Part A	a) .... b) USA	a) A10AB04 b) Treatment of Diabetes Mellitus	a) Solution for injection b) 40 IU/ml vials 100 IU/ml vials + Cartridges c) 3 Presentations	a) 28.10.96 b) 18.12.96 c) 48 days d)	a) 22.01.97 b) .... c) .... d) ....

Annex 7
CVMP opinions in 1996 on medicinal products for veterinary use

Centralised applications

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) Target species b) Indication*	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received b) Decision c) Notification d) OJ No.
a) Nobi-vac-Porcoli b) Inactivated vaccine c) List A	a) Intervet International b) NL	a) Piglets b) Neonatal colibacillosis	a) Solution for injection b) Multidose c) 2	a) 01.01.95 b) 27.07.95 c) 107 days d) 94 days	a) 24.08.95 b) 29.02.96 c) 04.03.96 d) OJ No C.96 of 29.03.96
a) Pentofel b) Vaccine c) List A	a) Fort Dodge Laboratories b) IRL	a) Cats b) Rhinotrachacheitis	a) Solution for injection b) Monodose c) 3	a) 16.06.95 b) 18.09.96 c) 208 days d) 235 days	a) 17.10.96 b) 05.02.97 c) 06.02.97 d) OJ No C.63 of 28.02.97

Establishment of maximum residue limits

Substance a) INN	**Therapeutic aera** a) Target species	**EMEA/CVMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Sent to Commission b) Date of the Regulation c) OJ No.
a) Difloxacin	a) Chicken, Turkeys	a) 16.05.95 b) 15.12.95 c) 134 days d) 49 days	a) 13.02.96 b) 08.07.96 c) OJ No L.170 of 09.07.96
a) Ketoprofen (extension)	a) Porcine	a) 15.05.95 b) 22.03.96 c) 85 days d) 217 days	a) 25.04.96 b) 06.09.96 c) OJ No L.226 of 07.09.96
a) Diclazuril	a) Ovine	a) 12.12.95 b) 24.04.96 c) 102 days d) nil	a) 24.05.96 b) 21.10.96 c) OJ No L.269 of 22.10.96
a) Eprinomectin	a) Bovine	a) 22.02.96 b) 25.06.96 c) 108 days d) nil	a) 26.07.96 b) 08.01.97 c) OJ No L.5 of 09.01.97

Annex 8
Rules governing medicinal products in the European Community

The Office for Official Publications of the European Communities produces in a series of eight volumes the legal texts and notices on human and veterinary medicinal products:

Volume I	The rules governing medicinal products for human use in the European Union *catalogue n° CO-86-94-319-EN-C, also available in ES, DA, DE, GR, FR, IT, NL, PT*
Volume II	Notice to applicants for marketing authorisations for medicinal products for human use in the European Union *catalogue n° CO-55-89-239-EN-C, also available in ES, DE, FR, IT*
Volume III	Guidelines on the quality, safety and efficacy of medicinal products for human use *catalogue n° CO-55-89-843-EN-C, also available in ES, DE, FR, IT* Addenda volumes published in July 1990 *(n° CB-59-90-936-EN-C, also in ES, DE, FR)*, May 1992 *(n° CO-75-92-558-EN-C, also in ES, DE, FR, IT)* and January 1995 (III/5415/95, not yet published)
Volume IV	Good manufacturing practices for medicinal products *catalogue n° CO-71-91-760-EN-C, also available in ES, DA, DE, GR, FR, NL, PT*
Volume V/A	The rules governing veterinary medicinal products in the European Community *catalogue n° CO-77-92-384-EN-C, also available in ES, DE, FR, IT*
Volume V/B	Notice to applicants for marketing authorisations for veterinary medicinal products in the European Union *catalogue n° CO-78-93-443-EN-C, also available in ES, DE, FR, IT*
Volume VI	Establishment in the EC of maximum residue limits for residues of veterinary products in foodstuffs of animal origin *catalogue n° CO-71-91-768-EN-C, also available in ES, DE, FR, IT*
Volume VII	Guidelines for the testing of veterinary medicinal products *catalogue n° CO-86-94-383-EN-C*

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