THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS

FIFTH GENERAL REPORT

1999

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Fifth General Report on the Activities of the European Agency for the Evaluation of Medicinal Products

1999

Adopted by the Management Board on 1 December 1999

EMEA mission statement

To contribute to the protection and promotion of public and animal health by:

- **Mobilising scientific resources from throughout the European Union to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health professionals**
- **Developing efficient and transparent procedures to allow timely access by users to innovative medicines through a single European marketing authorisation**
- **Controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals**

The 1999 Annual Report is presented to the Management Board by the Executive Director in accordance with Article 55(3) of Council Regulation (EEC) No 2309/93. It is forwarded to the European Parliament, Council, Commission and Member States. It is available on request in all official EU languages.

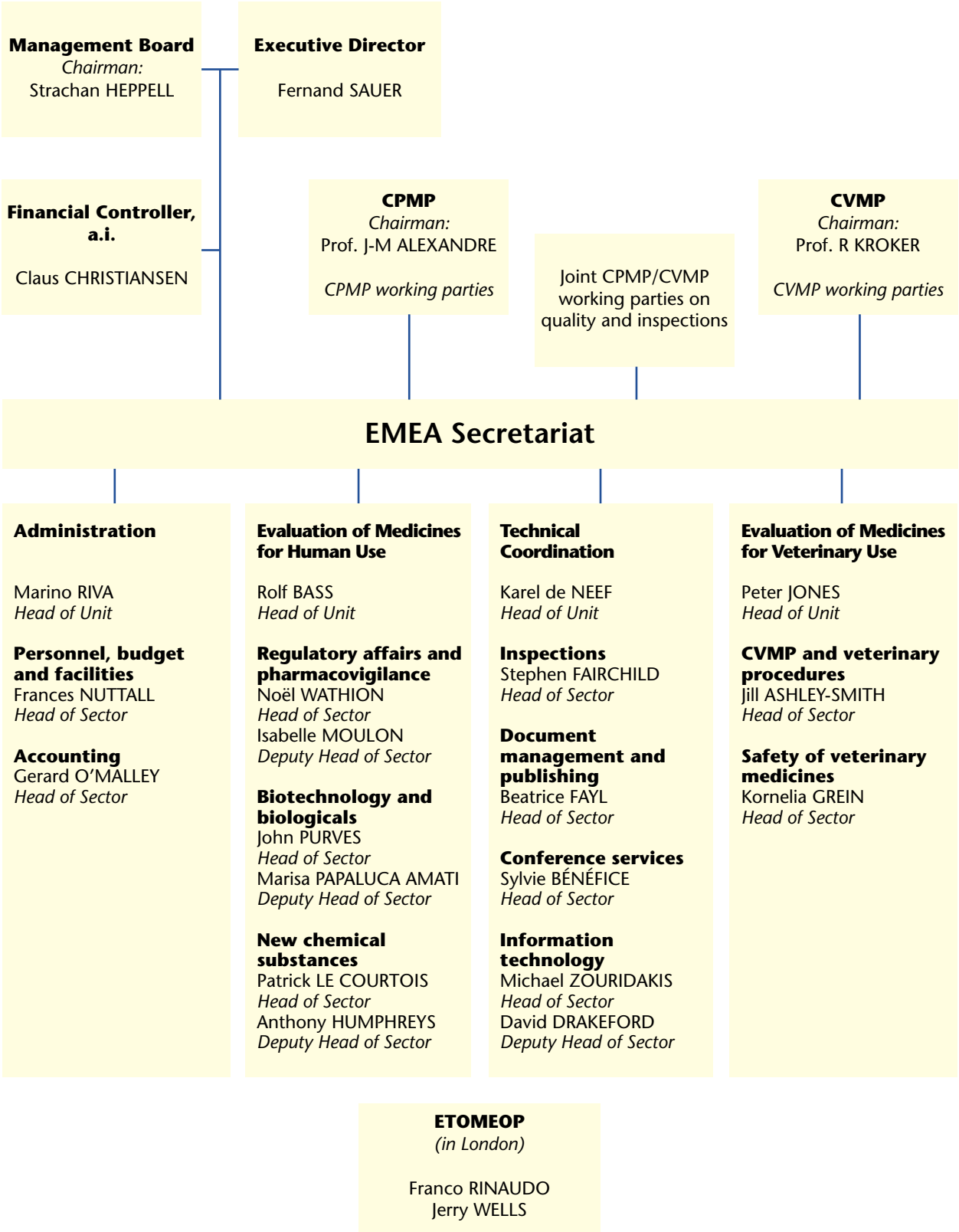
Previous annual reports and other reference documents are available from the EMEA web site at **http://www.eudra.org/emea.html** and further details are set out in annex 1.

This report covers activities of the EMEA in 1999. Chapter 1 sets out the activities of the Management Board and the Agency's administration. It also covers the Agency's partnership with national competent authorities and European institutions, and other general aspects of the EMEA, including transparency and international activities.

The operational and technical work of the EMEA in 1999 are reported in chapter 2 on human medicines, chapter 3 on veterinary medicines and chapter 4 on technical coordination. Administration and accounting matters are described in chapter 5.

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, also summarises the operation of the decentralised (mutual recognition) procedure during 1999.

Structure of the EMEA



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Foreword by the Chairman of the Management Board

Strachan Heppell

At the end of 1999, the EMEA completed its first five years as an operational body. I want to take this opportunity to reflect on the lessons learned so far and to look forward to the next five years. I should also like to reflect on my own experience as chairman, since my second term of office comes to end early in 2000 and, in accordance with our rules, I shall then stand down.

There seems to be general agreement that over the past five years the Agency has established itself as a reliable regulator, which has carried out its responsibilities effectively and become an important player on the global regulatory scene. This is a notable contrast to the position in 1994 when there was widespread concern that the Agency might not be able to live up to the demands and expectations that would be made of it.

The Agency's success is a tribute to the hard work and commitment of many. The staff of the Agency, led by the Executive Director – who I congratulate on his re-appointment by the Board for a further five years – played a vital role. So did the staff and heads of agency of our partners, the national regulatory authorities; the members of our two scientific committees, ably led by their chairmen; and the national experts. The agency has also been much helped by the positive approach and co-operation of the pharmaceutical companies and by the support of the European Institutions. For my own part, I should like to pay tribute to the wise advice and support I have received throughout from my colleagues on the Management Board.

Of the many factors that have contributed to the Agency's progress, three have been of particular value. The Board has from its early days placed great emphasis on accountability and transparency. It's policy has been that the Agency should explain what it is doing, why it is doing it and whether it has succeeded in meeting the performance targets it has set. The Board has consistently believed that if this is done, the Agency will perform well and secure the confidence of the public. Secondly, it is clear that the close partnership between the Agency and the national regulatory authorities has underpinned the new European system. Thirdly, the existence of alternative and complementary routes to market authorisation through the centralised and mutual recognition procedures has been widely welcomed and helped to improve the quality of performance under both procedures.

Looking forward, we can be confident that the regulatory system will continue to change and develop. But regulatory development, whilst desirable and necessary, needs to be managed with care. A reputation for good regulation is difficult to gain, but easy to lose. The tradition of regulatory change since the first European legislation in 1965 has been to build on experience. It would be wise to continue doing so. Incremental improvement, as I have pointed out in previous reports, has shown itself to be an effective way of achieving good regulation and maintaining public confidence.

Indeed, a policy of incremental improvement would provide a good basis for responding to three key challenges ahead – the enlargement of the European Union, the demand for more information about medicines and the current review of the regulatory system by the European Commission. The Agency is playing its part in responding to each of these challenges, as the Executive Director explains in his introduction.

A major issue already raised in the current review is whether the evaluation process for a new medicine should include economic or social criteria. If it were decided to do this, it would be important to distinguish between those regulatory tests applied to the granting of marketing authorisation and those applied for other purposes. My personal view is that the decision whether to grant a marketing authorisation should continue to be based on quality, safety and efficacy alone. This will ensure both that public confidence in the transparency of the present system is maintained and that the reimbursement of medicines is treated separately from the granting of marketing authorisations.

Introduction by the Executive Director

Fernand Sauer

This fifth annual report on the Agency's activities shows that the European marketing authorisation system and the EMEA have now reached a stable and mature level of operation. Users of human and veterinary medicines are getting access to new medicines faster than ever before, in the knowledge that they have been evaluated to the highest standards. As has been said many times before, the key to the success of the European system is the partnership between national competent authorities, EMEA and the EU institutions.

The costs of the European and national authorisation systems were the subject of much discussion in 1999. The reform of the fee structure introduced at the beginning of the year brought with it an obligation to produce detailed costing data for the activities of both the EMEA and national competent authorities. The EMEA put in place an activity tracking system for all staff that will generate better data for future reviews of fees.

Cooperation between all competent authorities saw a marked acceleration in 1999 at all levels, with some 230 meetings – many lasting 2 or more days – bringing together representatives of national authorities and EU institutions. The Agency also participated in all meetings of heads of national authorities for human and for veterinary medicines organised under both the German and Finnish presidencies of the European Union.

The European Union institutions underwent a number of important changes in 1999. Elections to the European Parliament and organisational changes in the European Commission brought new people and structures into the partnership. The re-establishment and creation of new relations with these partners was a particularly important task as we begin to think of the review of the European system in 2001.

Improvements in the transparency of the EMEA have been made, including the introduction of a Code of Conduct for all committee members, experts and EMEA staff, and the production of a regularly updated catalogue of EMEA public documents.

Much attention was focused on cooperation with central and eastern European countries. A collaborative agreement with the national authorities of these countries (CADREAC) came into force at the beginning of 1999. This was followed with the launch of the Pan-European Regulatory Forum on pharmaceuticals (PERF). Funded by the Commission and run by the EMEA, the PERF concentrates on the practical aspects of transposition of EU pharmaceutical requirements into the national legislation of the EU candidate countries.

The Agency celebrates the fifth anniversary of its inauguration on 26 January 2000. As we prepare for the review of the European system in 2001, it is interesting to look back over the past years and consider some of the important moments that helped shape the system. Looking over the key events set out in the following pages, the role of the EU institutions and Member States is clear. I would in addition like to give special recognition to the professionalism and commitment of EMEA staff who have worked so hard in the setting up and operation of the Agency and the centralised procedure.

EMEA Milestones

1993

July	Council Regulation (EEC) No 2309/93 creating the EMEA is adopted.
October	European Union Heads of State and Government choose London as seat for the Agency.
December	Management Board meets for the first time.

1994

April	Management Board elects Strachan Heppell as Chairman and appoints Fernand Sauer as Executive Director.
June	Management Board elects Romano Marabelli as Vice-Chairman and chooses Canary Wharf as location for EMEA headquarters.

1995

January	The new CPMP meets for the first time and elects Jean-Michel Alexandre and Henning Hovgaard as chairman and vice-chairman. The new CVMP meets for the first time and elects Reinhard Kroker and Cyril O'Sullivan as chairman and vice-chairman. Inauguration of the EMEA, followed by first information day organised with the European trade associations (EFPIA, FEDESA and AESGP).
May	First opinion (positive) for a medicinal product for human use (Gonal-F).
July	First opinion (positive) for a veterinary product for veterinary use (Nobi-vac-Porcoli).
September	EMEA web site (**http://www.eudra.org/emea.html**) launched.
October	First EU marketing authorisation granted and publication of first European Public Assessment Report (EPAR) on Internet. First audit meeting of the European authorisation system chaired by Dr Martin Bangemann.

1996

April	Veterinary medicines International Conference on Harmonisation (VICH) initiative launched.
June	EMEA introduces 'certificates of medicinal products' under WHO system.
October	Second audit meeting of the European authorisation system chaired by Dr Martin Bangemann.
November	International Conference on Harmonisation (ICH) Steering Committee held at EMEA.
December	Economic and Social Committee Section for Environment, Public Health and Consumer Affairs meets at EMEA.

1997

February	Second mandate of the Management Board begins. Strachan Heppell and Romano Marabelli re-elected chairman and vice-chairman.
	Ministers and officials of national authorities of Ibero-American countries visit EMEA.
April	'Quality Management System' initiative launched at the EMEA.
September	CPMP adopts crisis communication plan for centrally authorised medicines.
October	Joint WHO-EMEA meeting with competent authorities of the New Independent States.
	Workshop on transparency and access to documents of the EMEA.
November	Representatives of the competent authorities of central and eastern European countries meet at the EMEA for the first time.
	European Parliament Committee on the Environment, on Public Health and on Consumer Protection meets at the EMEA.

1998

January	Second mandate of the CVMP begins. Reinhard Kroker and Cyril O'Sullivan elected as chairman and vice-chairman.
	Second mandate of the CPMP begins. Jean-Michel Alexandre and Mary Teeling elected as chairman and vice-chairman.
May	Economic and Social Committee Single Market Observatory meets at EMEA.
June	European Commission Group on Ethics in Science and New Technologies meets at the EMEA.
July	Workshop on a Medicines Information Network for Europe (MINE).
November	CPMP adopts its 100th opinion on a medicinal product for human use.

1999

January	Recognition by central and eastern European countries of medicinal products evaluated by the EMEA.
March	Third audit meeting of the European authorisation system chaired by Dr Martin Bangemann.
April	VICH safety working party meets at the EMEA.
May	CPMP adopts 100th scientific advice opinion.
June	Management Board re-appoints Fernand Sauer as Executive Director.
	50th meeting of the CPMP.
July	Pan-European Regulatory Forum (PERF) initiative with competent authorities of central and eastern European Countries launched.
August	CVMP completes assessment for MRLs for most of the remaining 'old substances'.
December	50th meeting of the CVMP.
	Final ratification of decision allowing Iceland and Norway to join the EMEA.

Chapter 1

The EMEA in 1999

The Management Board and EMEA Directorate

Chairman of the Management Board	**Strachan HEPPELL**
Vice-chairman	**Romano MARABELLI**
Executive Director	**Fernand SAUER**
Financial controller, a.i.	**Claus CHRISTIANSEN**

A small team assists the Executive Director in the general management and functioning of the European Agency for the Evaluation of Medicinal Products, legal affairs, external relations and liaison with the European Union institutions and Member States. The Directorate also provides the secretariat of the Management Board.

Major changes were introduced at the beginning of 1999 in the levels and structure of fees paid to the EMEA by applicants and marketing authorisation holders. As part of this, the EU institutions requested costing data from both the EMEA and national competent authorities that will be used as part of the review of the European marketing authorisation system in 2001. The redefinition of EMEA core activities in relation to the source of revenue received for those activities is the guiding principle in this annual report.

A time management system – called ActiTrak – is used by all members of staff. It allows the Agency to collect data on the time involved for each of the different activities and their associated costs.

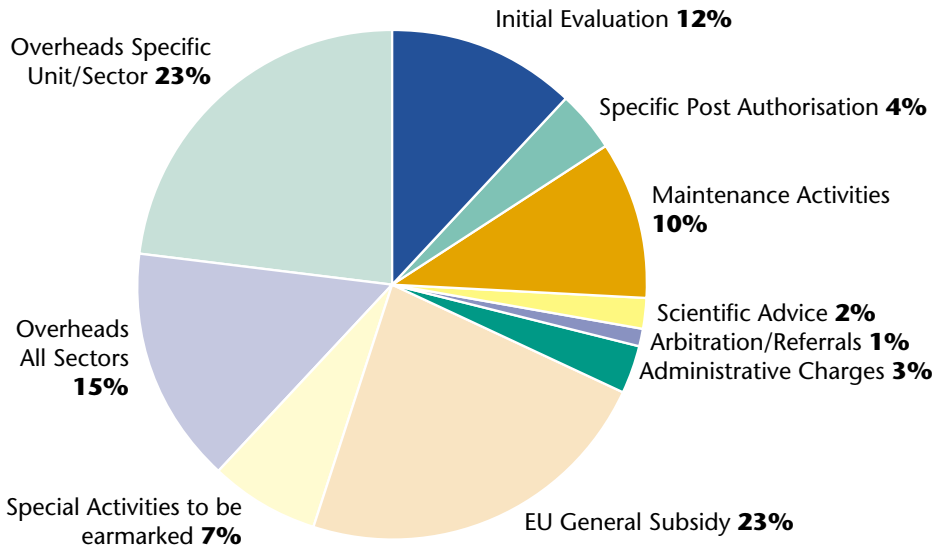
Definition and measurement of EMEA activities – ActiTrak

ActiTrak collects data in eight principal categories of activity based on the source of the revenue used to cover the activity and 2 additional categories for overheads:

1. Initial evaluation activities (initial fees and inspection fees)
2. Specific post-authorisation activities (type I and II variations, extensions, transfers)
3. Maintenance activities such as periodic safety updates, pharmacovigilance, sampling and testing (annual fee)
4. Scientific advice (specific fee)
5. Arbitrations and Community referrals (specific fee)
6. Administrative charges for WHO certificates, parallel distribution, subscriptions (specific administrative charges)
7. General harmonisation activities (EU general contribution)
8. Special activities at the request of the EU institutions (e.g. international harmonisation, Pan-European Regulatory Forum on Pharmaceuticals, orphan medicinal products, herbal medicines, establishment of maximum residue limits for old veterinary substances)
9. General overhead activities for the whole agency, including staff management, internal meetings
10. Specific overhead activities of non-operational sectors, including administration and financial control.

An overview for whole EMEA secretariat is given here. Data are also presented for the three operational Units in the relevant chapters.

All EMEA



1.1 The Management Board

The Management Board met four times in 1999:

- 10 February
- 2 June
- 29 September
- 1 December

The composition of the Board changed a number of times during the year, in particular with representatives of Iceland and Norway joining as observers. Details can be found in annex 1.

Budgetary and financial decisions

The Board adopted the 1999 budget of €41.35 million at its 2 December 1998 meeting. A supplementary and amending budget amounting to €42.65 million was adopted at the 29 September meeting, principally to take into account increased revenue from the operation of the Pan-European Regulatory Forum (PERF). The supplementary and amending budget was adopted in consultation with the EU Budgetary Authorities and in accordance with the budgetary code of conduct agreed in 1998 with all EU decentralised bodies.

Following the opinion of the European Court of Auditors, the Board granted discharge to the Executive Director for the execution of the 1998 budget at its 1 December meeting. Discharge was also given to the accounting officer.

The Board adopted the budget for 2000, amounting to €49.559 million, at the 1 December meeting. This includes forecasted fee revenue of €34.775 million and a contribution from the EU general budget of €13.2 million. The EU budgetary authority was also requested to create a special reserve for the EMEA to finance the Agency's activities in 2000 relating to orphan medicinal products once the Council Regulation on orphan medicinal products comes into force (OJ C 317, 4.11.1999, p. 34).

Following the entry into force of the new fee regulation (Council Regulation (EC) No 2743/98, OJ L 345, 19.12.1998, p. 3), the Management Board reconsidered the mechanism for payment of national competent authorities for the provision of evaluation, surveillance and inspection services. The scale of fees payable by the EMEA to national competent authorities was adopted at the February 1999 meeting (EMEA/MB/035/98). At its 1 December 1999 meeting, the Board decided to continue with this scale of fees for 2000.

The Board also approved a methodology for determining the costs of the EMEA secretariat and agreed to look at the costs of national competent authorities over the next two years. This costing exercise is being carried out at the request of the European Parliament and the European Court of Auditors ahead of the future review of the fee system in 2002.

Financial control

EU institutions continued their discussion during 1999 on the proposals from the European Commission to transfer financial control responsibility from all of the EU decentralised bodies to the Commission (COM (1997) 489 final, OJ C 335, 6.11.1997, p. 15). The function of financial control therefore continued to be exercised by the Agency's interim financial controller and an assistant. In accordance with the targets set for 1999, there was an improvement in the quality of financial transactions and the turn-around time.

	Revision of dossiers (annual average)	Turn-around time in financial control (annual averages)	
		within 2 days	within 5 days
1997	4.48 %	74 %	91 %
1998	2.64 %	80 %	96 %
1999	1.39 %	89 %	99 %

Review of the European marketing authorisation system

The Management Board began preparations to assist the future review of the European marketing authorisation system in 2001 by the European Union institutions. Heads of national competent authorities that are not members of the Management Board were invited to the Board's meeting of 2 June 1999 for a preliminary discussion on a range of issues. These included the scope of the regulatory system, governance of the EMEA and management of regulatory business, structure of the regulatory system, and regulatory performance indicators and benchmarking.

The Board also noted that the Commission had appointed a consultant to conduct an initial review of, "the operation of Community procedures for the authorisation of medicinal products". The final report should be submitted to the European Commission in November 2000. In parallel, the principal European trade associations also began preparations for their own contributions to the debate.

1.2 The EMEA and its institutional partners

European institutions

Partnership with the services of the European Commission:

- Directorate-General for Enterprise
- Directorate-General for Agriculture
- Directorate-General for Research
- Joint Research Centre
- Directorate-General for Health and Consumer Protection
- Directorate-General for External Relations
- Directorate-General for Enlargement
- Directorate-General for Personnel and Administration
- Directorate-General for Budget
- Directorate-General for Financial Control

The principal contact within the services of the European Commission continued to be the Pharmaceuticals and Cosmetics Unit of the Directorate-General for Enterprise (formerly the Directorate-General for Industry, DG III). The Agency and the Directorate-General for Health and Consumer Protection (formerly the Directorate-General for Consumer Policy and Consumer Health Protection, DG XXIV) continued to exchange information and representatives at meetings of the scientific committees on a regular basis.

There was also increased dialogue with the Directorate-General for Research and the Joint Research Centre in the context of the European Community fifth framework programme for research and development. A memorandum of understanding between the EMEA and the Joint Research Centre concerning cooperation between the two organisations was renewed in April 1999. In particular this concerns the activities of the European Technical Office for Medicinal Products (ETOMEP) that is based in the offices of the EMEA.

The election of a new European Parliament in June gave the Agency the opportunity to present its work to new Members and newly constituted committees. A first exchange of views with the Committee on the Environment, Public Health and Consumer Policy, chaired by Dr Caroline Jackson, was held on 18 October. Contacts were also established with the Committee on Budgets, the Committee on Budgetary Control and the Committee on Industry, External Trade, Research and Energy.

European Technical Office for Medicinal Products (ETOMEP)

ETOMEP is part of the European Commission Joint Research Centre's Institute for Health and Consumer Protection. Based at the EMEA in London, the group supports the IT network that connects all national competent authorities, the European Commission and EMEA (EudraNet). The national authorities of Iceland and Norway were connected to the EudraNet at the end of 1999.

A new mechanism for the secure exchange of documents through the Internet was put in place in 1999 – called EudraSafe. This is particularly important for the transmission of individual case safety reports within the pilot project on pharmacovigilance between EMEA, national authorities and the pharmaceutical industry (**http://icsr.eudra.org**).

The tracking system for the mutual recognition procedure was progressed (EudraTrack 5.0). A prototype version of MINE I (Medicine Information Network for Europe) was demonstrated to the EMEA and national authorities in December 1999.

The web sites for the EMEA and Directorate-General for Enterprise have been continuously upgraded and a new site was made available, the Pan-European Regulatory Forum on Pharmaceuticals (**http://perf.eudra.org**).

Year 2000 compatibility problems were addressed in all the systems concerning EudraNet services.

Joint Interpreting and Conference Service (JICS)

The Joint Interpreting and Conference Service of the European Commission is the largest in the world with some 500 staff interpreters and over 1,600 freelance interpreters. It serves the institutions of the European Union, as well as the decentralised agencies and bodies located in the EU member states.

As part of the cooperation between institutions and agencies, the decision was taken in 1999 to base a representative of the JICS at the EMEA. This person has the task, within Ireland and the UK, to coordinate conference and interpreting needs at multi-lingual meetings, assisting and advising on multi-lingualism, communication, conference organisation and briefings for interpreters as well as other language-related matters. Progress was made in the development of a glossary of specialised and technical EMEA terms to assist interpreters when working at an EMEA meeting.

The European Department for the Quality of Medicines (EDQM)

European Pharmacopoeia

The European Pharmacopoeia is part of the Council of Europe and comprises 27 Member States, the European Union and 16 other European and non-European observer countries. The EMEA participates in the work of the European Pharmacopoeia Commission as part of the EU delegation. The Pharmacopoeia secretariat and experts participate in a number of EMEA working groups and undertook several tasks at the request of the EMEA in 1999.

The European Pharmacopoeia also maintains an up-to-date list of standard terms used in product information for health professionals and patients. A revised version was issued in December 1999 and is available in 21 languages, including all 11 official EU languages. (see **http://www.pheur.org**).

European Network of Official Medicines Control Laboratories (OMCL)

Set up as a joint project between the EU and Council of Europe, the network allows the coordination of laboratory controls between EU and EFTA States. In June 1999, a contract between EMEA and the EDQM was signed to organise sampling and testing of centrally authorised medicinal products by the OMCL network.

Cooperation with national competent authorities

A network of some 2,300 European experts was available at the end of 1999 to assist the EMEA in the performance of its scientific tasks. This continues to be the central element of the contribution of national competent authorities to the EMEA. An electronic database containing the records of all European experts was tested and launched in 1999. The new system allows remote access by national competent authorities to all records and facilitates the updating of information. The full declarations of interests continue to be available for inspection upon request at the EMEA.

About one-third of the EMEA budget is paid to national competent authorities for the provision of external scientific services, from fee revenue paid by applicants and marketing authorisation holders.

The Management Board decided in February 1999 to continue the mechanism (the 'Scale of fees') by which half of most types of fees are redistributed to national competent authorities. A new distribution was decided for the new annual fee as follows:

- 30 % to cover EMEA staff costs
- 30 % is paid to the rapporteur and co-rapporteur for the medicinal product concerned for the production of annual safety reports and other supervisory tasks
- 30 % attributed to special activities and projects agreed by the Management Board, in consultation with the scientific committees (i.e. pharmacovigilance meetings, availability of veterinary medicines, crisis management and other post-marketing projects)
- up to 10 % for sampling and testing costs for centrally authorised medicines under an agreement with the Council of Europe's European Department for the Quality of Medicines and the network of Official Medicines Control Laboratories

The EMEA continued to give support to the working of the mutual recognition facilitation groups for human and veterinary medicines, details of which are given in chapters 2 and 3 of this report. National experts from the national authorities of Germany, Sweden and United Kingdom spent extended periods with the EMEA in 1999. Cooperation and coordination with Member States increased in 1999, in particular through meetings with the heads of national agencies for human and veterinary medicines.

Informal meetings between competent authorities in 1999:

• 29 January	Heads of agencies for human medicines *(Paris)*
• 25 February	Heads of agencies for veterinary medicines *(Langen)*
• 7-8 March	Heads of agencies for human medicines *(Berlin)*
• 1 June	Heads of agencies for veterinary medicines *(London)*
• 2 June	Heads of agencies invited to Management Board 'brainstorming' meeting *(EMEA)*
• 3-4 June	Heads of agencies for human medicines *(Berlin)*
• 3-4 June	Informal meeting of the Mutual Recognition Facilitation Group for human medicines *(Berlin)*
• 7-8 June	Informal meeting of the CPMP *(Berlin)*
• 28-29 June	Informal meeting of the CVMP *(Berlin)*
• 13-14 September	Informal meeting of the Management Board *(Helsinki)*
• 30 September - 1 October	Informal meeting of the CPMP *(Helsinki)*
• 5-6 October	Heads of agencies for human medicines *(Helsinki)*
• 22 October	Heads of agencies for veterinary medicines *(Helsinki)*
• 25-26 November	Heads of agencies for human medicines *(Kuusamo)*

Further information on the work of the heads of agencies for human and veterinary medicines can be found at the following Internet web sites: **http://heads.medagencies.org** and **http://www.hevra.org**

1.3 Transparency and relations with interested parties

Following the creation of the inter-institutional European Anti-Fraud Office (OLAF), the Executive Director took a decision on 1 June 1999 concerning cooperation with the Office (EDIR/006/1999).

Following public consultation, the Management Board finalised an EMEA Code of Conduct at its December meeting. The EMEA Code incorporates and develops existing practice and provides specific guidance concerning conflicts of interest, confidentiality and discretion, and gifts and invitations. The EMEA Code applies to members of the Management Board and scientific committees, European experts and EMEA members of staff. The Agency also responded positively to the request of the European Ombudsman to adopt a Code of Good Administrative Behaviour, which was integrated as part of the EMEA Code of Conduct at its 1 December 1999 meeting.

The Agency continued to work with various interested parties, in particular the European Consumers' Organisation (BEUC), on the readability of patient information and the information given to health professionals. The European public assessment report (EPAR), that the Agency issues for each of the medicines it evaluates, saw a number of changes in 1999 that should allow better multi-lingual availability through the EMEA web site.

The emergence of several new European patient groups was noted in 1999. The EMEA also reinforced dialogue with those European-level umbrella patient groups with which it already had contacts.

Further to discussions by the Management Board in 1998, a demonstration of a pilot project for the Medicines Information Network for Europe initiative (MINE I) was given at the EMEA on 2 December with representatives of the Board and national competent authorities. The pilot project includes information about centrally authorised and mutual recognition products, in particular summary of product characteristics and labelling.

The Agency has constantly sought to measure its performance and find ways of introducing improvements. For the first time, the ongoing joint EMEA-EFPIA performance exercise covered the period before submission and the withdrawal of applications for medicines for human use during the evaluation process. The results of the 1999 exercise, presented at an information day held on 22 October 1999, showed an increased confidence of applicants and marketing authorisation holders in the centralised procedure and the operation of the EMEA.

A similar exercise for veterinary medicines was announced at the EMEA-FEDESA information day on 16 April 1999. The questionnaires, developed with the Committee for Veterinary Medicinal Products, cover applications for centralised authorisations and extensions to authorisations. Initial results of the survey are expected in early 2000.

The improvements on the part of the EMEA secretariat are largely due to an increased impact of the quality management system initiative (QMS). A large number of standard operating procedures have now been developed and are made available in the form of interactive electronic guidance for use by staff.

A programme of internal audits was also begun in 1999 with the aim of ensuring that procedures are properly followed and of identifying areas for improvement for all activities of the Agency. The audits, some 14 in total, included the provision of scientific advice, pre-submission guidance, conduct of pharmacovigilance, crisis management, the quality of translations and archiving.

Interested parties

Interested parties play an important role in the activities of the EMEA, particularly in the consultation on draft guidelines of the CPMP and CVMP. Regular quarterly meetings are organised between interested parties and members of the scientific committees, allowing for exchanges of views and concerns, including:

- Bureau Européen des Unions de Consommateurs (BEUC)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Association of the European Self-Medication Industry (AESGP)
- Fédération de la Santé Animale (FEDESA)
- European Generic medicines' Association (EGA)
- Comité Permanent des Médecins Européens (CP)
- Committee of Agricultural Organisations in the EU/General Committee of Agricultural Cooperation in the EU (COPA-COGECA)
- Groupement des Pharmaciens de l'Union Européenne (GPUE)
- European Association of Genetic Support Groups (EAGS)
- Federation of Veterinarians in Europe (FVE)

Other interest groups for more specialised topics include:

- European Citizens' Association (ECAS)
- European AIDS Treatment Group (EATG)
- European Association of Veterinary Consultants (AVC)
- Drug Information Association (DIA)
- Health Action International (HAI)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- International Society of Drug Bulletins (ISDB)
- European Scientific Cooperative on Phytotherapy (ESCOP)
- European Federation of Associations of Health Product Manufacturers (EHPM)
- European Herb Growers Association (Europam)
- European Society of Ethnopharmacology (SEE)
- European Herbal Practitioners Association (EHPA)
- European Federation of Natural Medicine Users (EFNMU)

A number of technical workshops were also organised during 1999 on topics including pre-submission dialogue, validation of application dossiers, scientific advice and variation applications. For a wider audience, information days are regularly organised by the EMEA and trade associations. In 1999, information days were organised with AESGP on 28 January, with FEDESA on 16 April and with EFPIA on 22 October.

1.4 International aspects

The European Economic Area Joint Committee adopted a decision on 28 May 1999 to bring Iceland and Norway formally into the European marketing authorisation system. Further to the formal ratification by the Icelandic and Norwegian parliaments, the decision will come into force on 1 January 2000. Over 30 European experts nominated by the competent authorities of Iceland and Norway participated in the work of the EMEA as observers during 1999.

The relationship with national authorities of central and eastern European countries became closer in 1999. In particular since 1 January 1999, centrally authorised medicinal products benefit from a simplified recognition by the national authorities of central and eastern European countries through the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC).

The EMEA undertook a major commitment at the end of 1999 with the organisation of the Pan-European Regulatory Forum on pharmaceuticals (PERF). The Forum concentrates on a number of priority action areas: pharmacovigilance; EU requirements in the assessment of quality, safety and efficacy; responsibilities of competent authorities; good manufacturing practices; the use of information technology; establishment of maximum residue limits for veterinary medicines.

The Forum, which continues into the beginning of 2000, is conducted as a series of 31 meetings, bringing together experts from EU Member States, from participating CADREAC authorities and from the EMEA. PERF is financed by European Commission PHARE programme for a total of €800,000. A special Internet site was launched in November 1999 (**http://perf.eudra.org**) to accompany the Forum.

National experts from the Czech, Estonian and Japanese authorities spent extended periods with the Agency in 1999.

Good progress on both the human and veterinary medicines International Conferences on Harmonisation (ICH and VICH)) was made in 1999. Further details are available on the Internet at **http://www.ifpma.org/ich1.html** and **http://vich.eudra.org**. These initiatives involve the regulatory authorities and pharmaceutical industry representatives from the European Union, Japan and US, with the participation also of international organisations and various observers.

As part of EMEA cooperation with other international public health organisations, the Agency began the co-development in 1999 with the World Health Organisation (WHO) of an application tracking system called SIAMED. Based on an existing earlier version, the aim of the collaboration is to develop a new version for use by the EMEA. It is intended that the system will then be made available to other regulatory authorities in the European Economic Area, central and eastern Europe and other European countries to facilitate harmonisation in tracking systems within Europe.

The interest of non-EU authorities in the operation of the European authorisation system continues and a number of delegations visited the EMEA in 1999, including delegations from Argentina, Australia, Brazil, Bulgaria, China, Japan, Slovenia, South Africa, Switzerland and the Ukraine.

Chapter 2

Evaluation of medicines for human use

Overview of the CPMP and the Unit for Evaluation of Medicines for Human Use

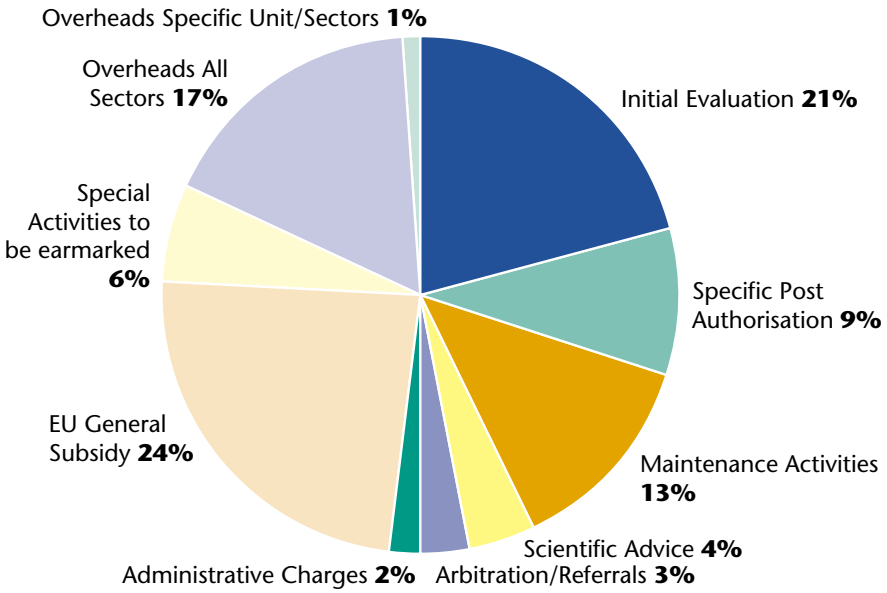
Chairman of the CPMP	**Jean-Michel ALEXANDRE**
Vice-chairman of the CPMP	**Mary TEELING**
Head of Unit	**Rolf BASS**
Head of Sector for regulatory affairs and pharmacovigilance	**Noël WATHION**
Deputy Head of Sector	**Isabelle MOULON**
Head of Sector for biotechnology and biologicals	**John PURVES**
Deputy Head of Sector	**Marisa PAPALUCA AMATI**
Head of Sector for new chemical substances	**Patrick LE COURTOIS**
Deputy Head of Sector	**Anthony HUMPHREYS**

The Unit for the Evaluation of Medicines for Human Use is responsible for:

- management and follow-up of marketing authorisation applications under the centralised procedure
- post-marketing maintenance of authorised medicinal products
- management of Community referrals and arbitrations arising from the mutual recognition procedure
- provision of support to European and international harmonisation activities of the CPMP and its working parties

Jean-Michel Alexandre

Unit for the Evaluation of Medicines for Human Use



2.1 Operation of the CPMP

Centralised procedures	1997	1998	1999	Total 1995-1999
Applications received				
Part A	20	12	18	224
Part B	40	33	29	
Withdrawals				
Part A	3	8	1	38
Part B	4	12	7	
Opinions adopted by product				
Part A	6	11	9	133*
Part B	19	30	17	
Opinions adopted by substance				
Part A	6	11	8	105*
Part B	13	19	15	
Type I variations				
Part A	57	50	68	569
Part B	52	108	207	
Type II variations				
Part A	19	26	48	239*
Part B	28	40	61	
Extension & abridged applications				
Part A	32	11	6	73
Part B	2	4	13	

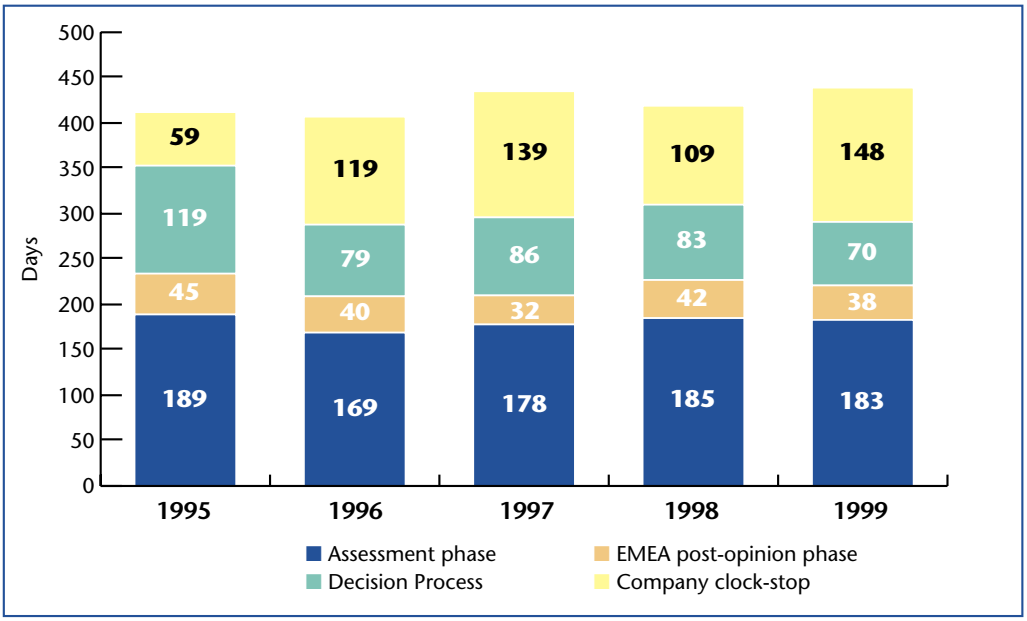
** These figures include negative opinions given for 7 products (representing 4 substances), and for 2 variations.*

Performance indicators

The joint EMEA/EFPIA project on performance indicators continued in 1999. The degree of satisfaction with the initial dossier as assessed by the Rapporteurs and of the quality of the assessment reports as seen by the applicants is broadly similar, with a high level of satisfaction. A major effort was directed towards a better understanding of negative outcomes.

A special review on withdrawals was carried out by the EMEA in 1999 and an in-depth review was presented at the EFPIA information day on 22 October 1999. Applicants' satisfaction – 76 % – with the overall handling of the procedures by the CPMP and the EMEA secretariat remains very high, even for withdrawals.

The EMEA was able to maintain its high performance in terms of compliance with the time frame required for the evaluation of medicinal products, as well as for the finalisation of the CPMP opinion in the 11 official EU languages. Particular effort has been made in the improvement of the scientific and linguistic quality of summary of product



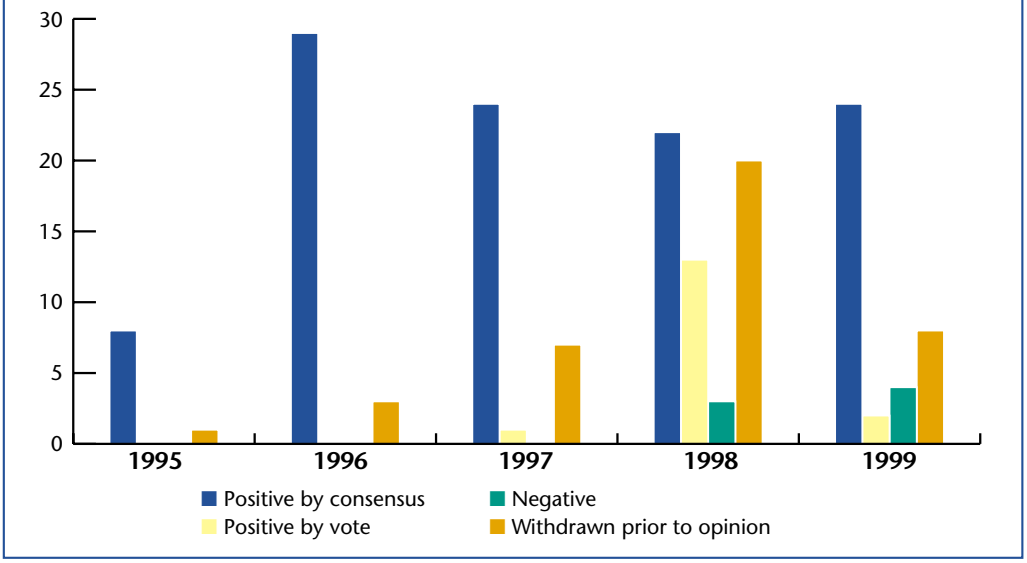
characteristics, package leaflets, product labelling and European public assessment reports (EPARs) through major contributions to the Product Information Quality (PIQ) and Quality Review of Documents (QRD) groups.

The management of centralised procedures has been further improved by developing and implementing QMS standards for the preparation of scientific advice and opinions, and by the development of tracking throughout the life-cycle of centrally authorised products.

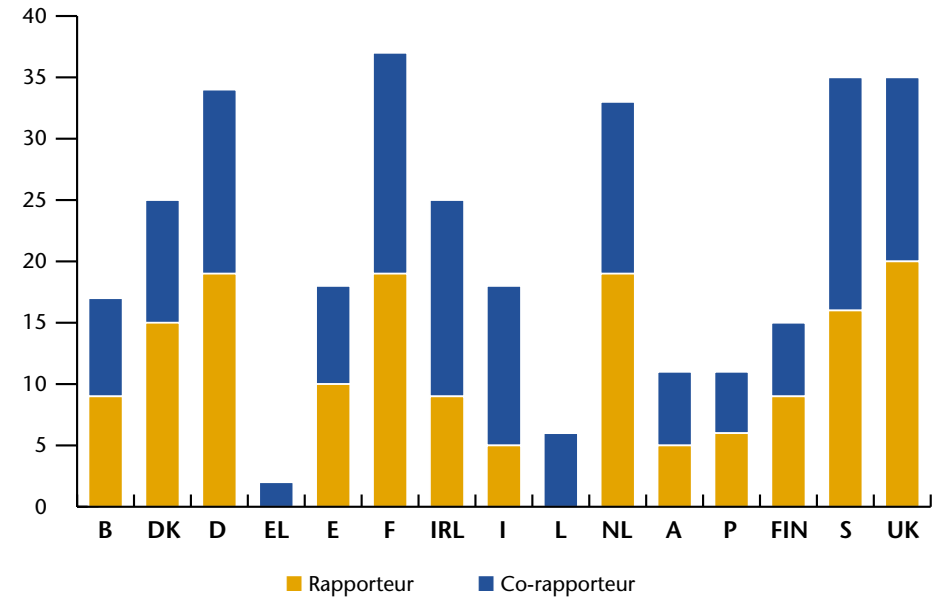
The various phases of the centralised procedure have been monitored in internal audits in a number of areas. Steps are being taken to improve the content of scientific documents (templates for the CPMP list of questions and a modular EPAR).

Centralised procedures

CPMP opinions on initial applications under the centralised procedure 1995-1999

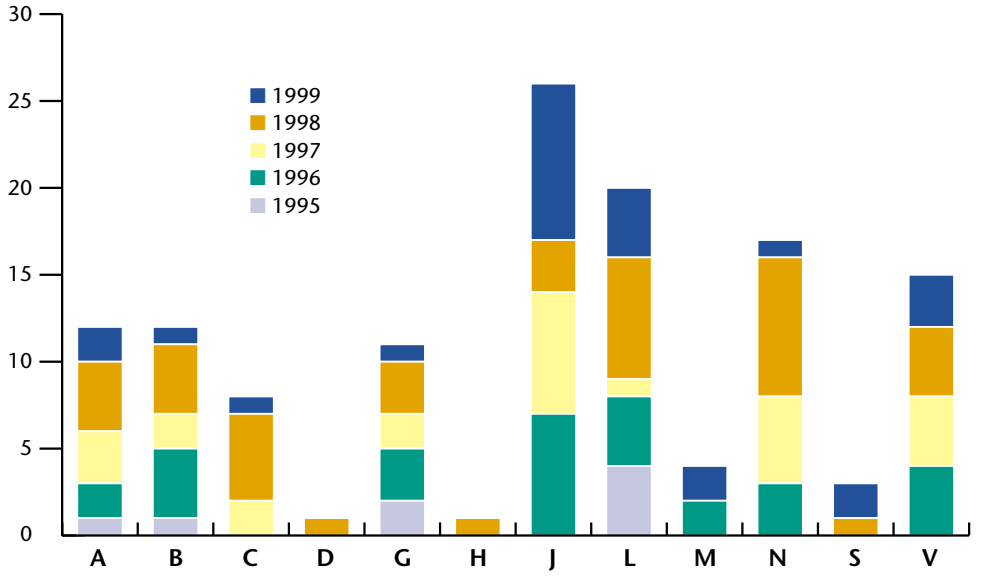


Distribution of rapporteurships by national delegations 1995-1999



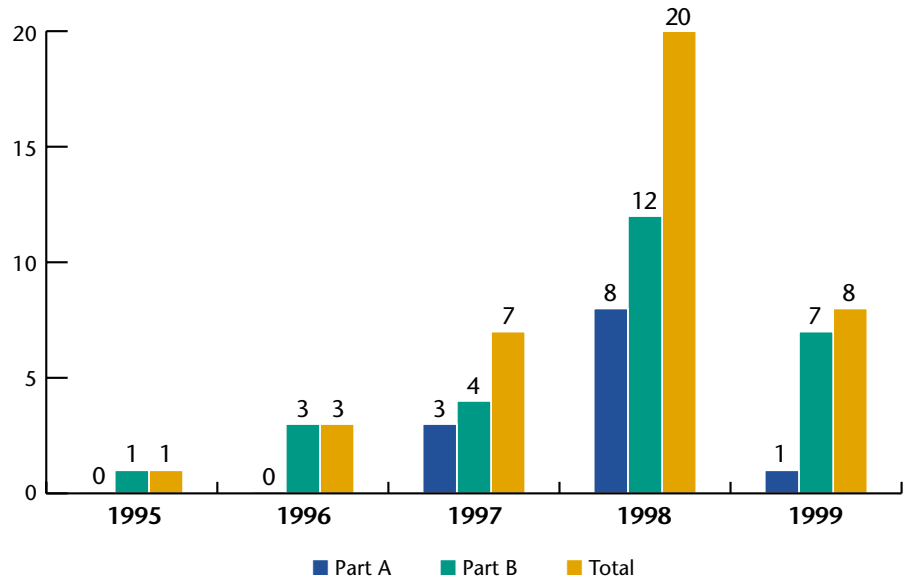
The highest number of opinions adopted within a therapeutic class in 1999 was in the anti-infective area. About half of all withdrawals fall into the three ATC categories of blood, neurology and oncology, which had major difficulties in their clinical development, as well as quality and preclinical development at the time of submission and review of centralised applications.

CPMP opinions by therapeutic class (Anatomical Therapeutic Chemical Classification Code) 1995-1999



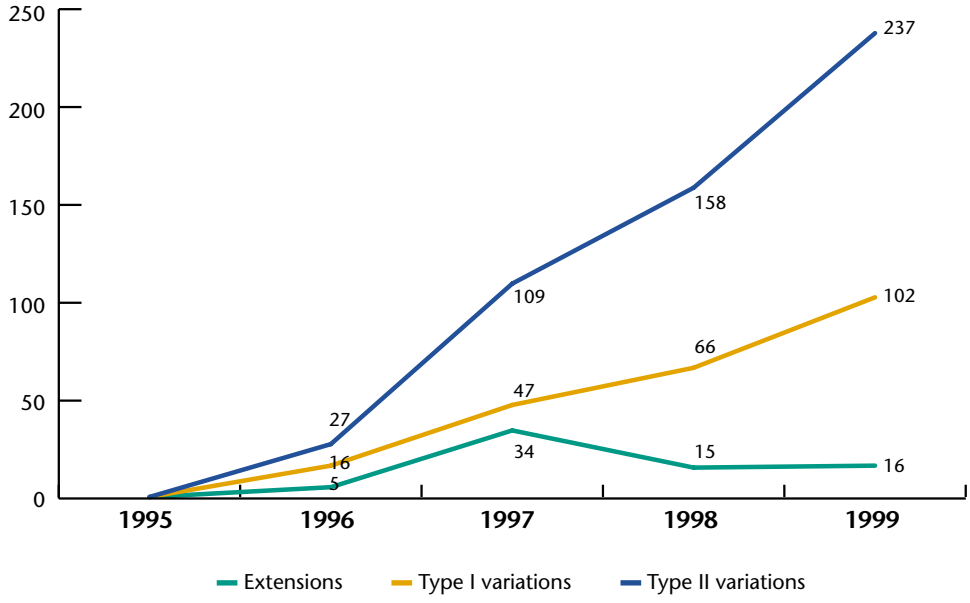
A: Metabolism
B: Blood
C: Cardiovascular
D: Dermatologicals
G: Genito-Urinary, Sex Hormones
H: Endocrinology
J: Antiinfective
L: Antineoplastic – Immuno-modulating
M: Musculo Skeletal
N: Nervous System
S: Sensory organs
V: Diagnostic agents

Withdrawal of applications 1995-1999

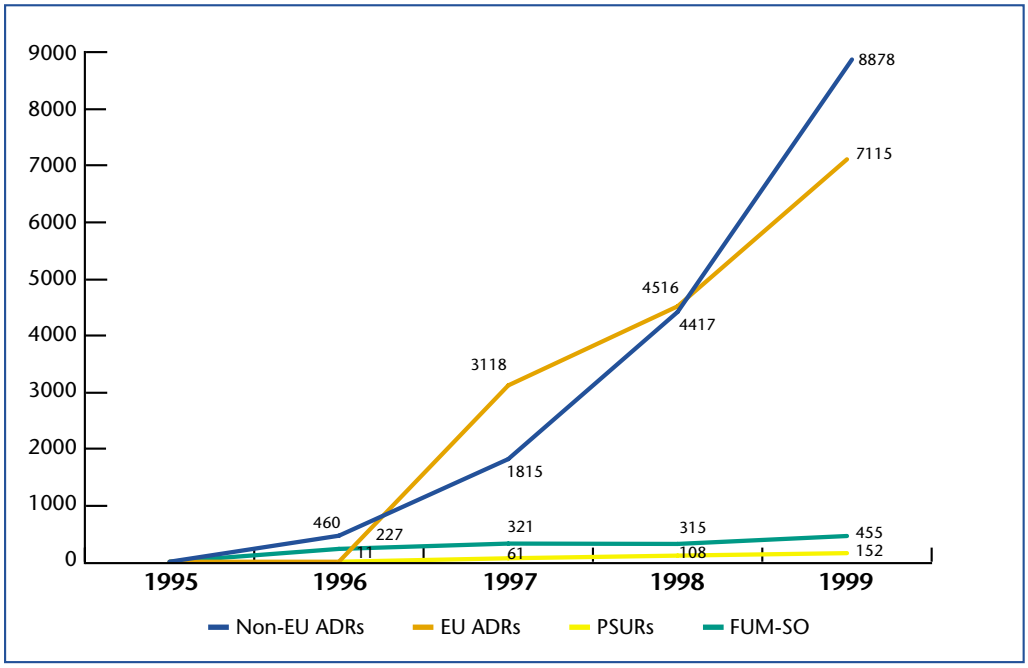


Post-authorisation activities

There was a significant increase in the number of variations and extensions finalised in 1999, in line with forecasts in the EMEA Work Programme. Rapporteurs played a major role with these post-authorisation procedures and maintenance activities.



The work load arising from the handling of adverse drug reactions (ADRs), periodic safety update reports (PSURs) and follow up measures and specific obligations (FUM-SOs) increased during 1999. Rapporteurs and co-rapporteurs were extensively involved in pharmacovigilance activities, particularly in suspension procedures (e.g. trovafloxacin/ alatrofloxacin) and other urgent safety restriction procedures.



Parallel distribution

Since the procedure for notifications of parallel distribution of centrally authorised products came into force on 20 November 1998, the EMEA has received 85 new 'parallel distribution notifications' and 19 'notifications of a change', for which 33 and 8 EMEA notices were granted respectively. The average checking time for finalised notifications was 18 working days after receipt of a valid notification. The average checking time of a "notification of a change" was 9 working days.

The main destinations for parallel distributed products were primarily Germany and the UK, whilst the main Member States of origin were Belgium, France, Italy and Spain.

2.2 Scientific advice

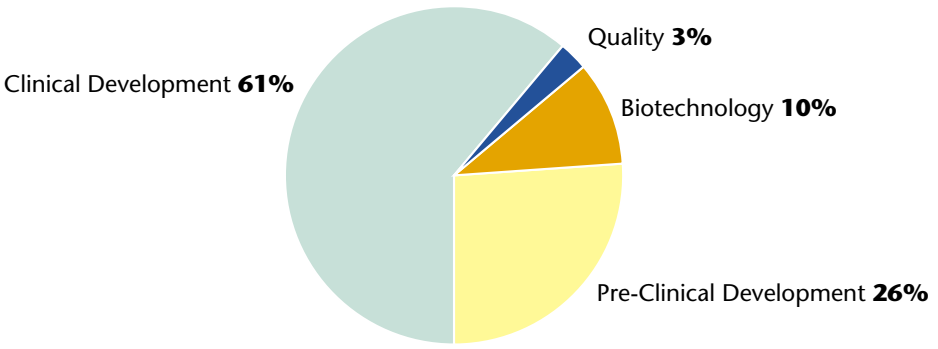
Scientific advice	1997	1998	1999	Total 1995-1999
Scientific advice given	20	35	60	138
Follow-up to scientific advice	3	8	4	17

The number of requests for scientific advice rose considerably in 1999. The average duration of the procedure was less than three months, despite the complex and novel questions to be dealt with.

The CPMP decided to set up a Scientific Advice Review Group, chaired by Mary Teeling, to strengthen and to widen CPMP input and to guarantee availability of proper expertise, and improve management of the additional workload. A standard operating procedure for the giving of scientific advice by the CPMP for innovative medicinal products (EMEA/SOP/2072/99) was adopted by the CPMP and endorsed by the Management Board.

A total of 13 applications for marketing authorisation were submitted to the EMEA between 1995 and 1999 for which EMEA scientific advice had been given. These have resulted in 5 positive opinions from the CPMP, with 5 applications remaining under evaluation at the end of 1999. Applications were withdrawn by the applicants in 3 instances.

Distribution of the 60 new requests for scientific advice in 1999



2.3 Working party activities

Highlights from working parties

The CPMP working parties and the Joint CPMP/CVMP Quality Working Party (QWP, see chapter 4) met regularly in 1999. Details of notes for guidance, points to consider documents and position papers prepared by the working parties for the CPMP are given in annex 9.

Biotechnology Working Party (BWP) – Chairman: Giuseppe Vicari and Vice-chairman: Jean-Hugues Trouvin
The working party met 9 times in 1999 to consider aspects of the manufacture and control of biotechnological and biological medicinal products. It was also involved in the provision of scientific advice addressing public health matters. A workshop on the application of assays for markers of transmissible spongiform encephalopathies (TSE) was held on 19-22 January 1999. Another workshop on the potential risk of transmitting new variant Creutzfeldt-Jakob Disease (nv-CJD) through plasma derived medicinal products was held in December 1999.

Blood and Plasma Working Group (BPWG) – Chairman: Manfred Haase
The group met 5 times to deal with efficacy and safety-related aspects of blood products, including the release of 8 guidelines for consultation.

Efficacy Working Party (EWP) – Chairman: Alfred Hildebrandt and Vice-chairman: Barbara van Zwieten-Boot
The working party met 5 times to look at clinical trial methodology and special disease-related therapeutic fields. Co-operation with the other working parties was strengthened, particularly concerning guidance on modified release oral and transdermal dosage forms, on pharmacokinetics, and on clinical investigation of new vaccines, gene therapy and cell-cultured influenza vaccines.

Joint EWP/QWP Group on Pharmacokinetics – Chairman: José Guimarães Morais
The group continued its task of updating the existing note for guidance on bioavailability and bioequivalence. The group also worked on the issue of population pharmacokinetics.

Pharmacovigilance Working Party (PhVWP) – Chairman: Patrick Waller and Vice-chairman: Anne Castot
This working party met 8 times to consider safety-related issues at the request of both the CPMP and national competent authorities, resulting in the harmonisation of summary of product characteristics and package leaflets. In July 1999, the working party began regular videoconferences with the US Food and Drug Administration (FDA) to discuss issues of mutual interest.

A pilot project began in November 1999 for the electronic transmission of individual case safety reports with a restricted number of participants from national authorities and marketing authorisation holders.

Safety Working Party (SWP) – Chairman: Per Sjöberg
The working party met 3 times to discuss pre-clinical and safety issues. In cooperation with the BWP, the SWP was involved in the preparation of the note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products.

An ad hoc expert meeting on immunohypersensitivity testing was held in November 1999.

Ad hoc expert group on excipients – Chairman: Willem van der Giesen
The group met three times in 1999. The main task was to improve the quality and relevance of information to be given to the patient concerning excipients present in medicinal products, where these may have a recognised action or effect.

Ad hoc working group on Lipodystrophy – Chairman: Bo Odlind
This ad hoc group met in March 1999 in order to discuss the research strategy on particularly the long-term medical consequences of the treatment of HIV infection with protease inhibitors and the associated body composition and metabolic changes. Consultation took place with experts from US FDA, representatives of patients groups, academia and industry.

Ad hoc working group on antiretroviral medicinal products – Chairman: Bo Odlind
Following CPMP concerns over the increased clinical problems associated with the emergence of HIV resistance, the ad hoc group convened to discuss and began in November 1999 to make an inventory of the current knowledge in this rapidly moving field

Thiomersal multidisciplinary group – Chairman: Mary Teeling
A multidisciplinary group was set up to evaluate medicinal products containing thiomersal with a view to limiting exposure to mercury and organomercurial compounds. It met 2 times in 1999 and consulted with the European Pharmacopoeia, World Health Organisation, FDA and relevant trade associations. CPMP recommendations on thiomersal were published in July 1999 and a position paper on warning statements relating to sensitisation was released in October 1999.

Multidisciplinary group on the note for guidance on summary of product characteristics – Chairman: Mary Teeling
This group coordinated contributions from the CPMP working parties and other EMEA groups on a note for guidance on summaries of product characteristics. A note for guidance was adopted by the CPMP in October 1999.

2.4 Cooperation with competent authorities

Referrals and arbitrations

Public health concerns in relation to nationally authorised products may be referred to the EMEA for arbitration.

Type of referral	Date of CPMP final opinion	International non-proprietary name (INN)
Pharmacovigilance referrals		
Article 12, Council Directive 75/319/EEC	20/05/1999	Vigabatrin
	Procedure ongoing	Sibutramin
Article 15, Council Directive 75/319/EEC	31/08/1999	Dexfenfluramine; Fenfluramine
	31/08/1999	Phentermine; Amphepramone
	31/08/1999	Clobenzorex; Fenbutrazate; Fenproporex; Mazindol; Mefenorex; Norpseudoephedrine; Phenmetrazine; Phendimetrazine; Propylhexedrine
Article 15, Council Directive 75/319/EEC	23/06/1999	Sertindole
Arbitration referrals		
Article 10, Council Directive 75/319/EEC	25/03/1999	Tirofiban
	16/06/1999	Interferon alpha 2a

There are 4 ongoing arbitrations within the framework of the mutual recognition procedure. Information in relation to these procedures once finalised will be published on the EMEA web site.

Relations with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

Technical collaboration with EMCDDA increased in 1999. The Agency participated to 3 meetings, supporting the development of guidelines on risk assessment of new synthetic drugs and the assessment on 4-Methylthio-amphetamine, which as a consequence had been placed under control (1971 United Nations Convention) following a Council Decision of 13 September 1999.

International Conference on Harmonisation (ICH)

In support of the CPMP the Unit is in charge of the technical co-ordination in the ICH process. Support was provided to the CPMP Vice-chairman, Mary Teeling, in her function as Steering Committee member, to EU topic leaders, to the CPMP and the working parties for the various phases of ICH.

In 1999, 4 guidelines were released for consultation, including a number of elements of the 'common technical dossier'. Discussion also began on globalising the use of ICH beyond the three originator regions of EU, Japan and US.

Central and eastern Europe

The simplified procedure for the recognition of centrally authorised medicinal products by the national authorities of central and eastern European countries came into force at the beginning of 1999. A total of 293 procedures were submitted, relating to 50 centrally authorised medicinal products, resulting in 52 positive decisions, 9 positive decisions with modifications and 232 ongoing procedures.

In addition, observers from central and eastern European authorities attended a number of CPMP working parties in 1999. Within the context of the Pan-European Regulatory Forum, the Unit is actively involved in a number of topics including the implementation of Community legislation, pharmacovigilance and the assessment of dossiers for marketing authorisation for quality, safety and efficacy.

EMEA Working Party on Herbal Medicinal Products

Further to a decision of the EMEA Management Board, the former ad hoc working group is now a permanent EMEA working party. The working party met 3 times in 1999 under the chairmanship of Konstantin Keller, with observers from central and eastern European countries.

The working party finalised a number of proposals for guidance on the quality, safety and efficacy of herbal medicinal products, taking into account the Commission Directive 1999/83/EC of 8 September 1999 (OJ L 243, 15.09.1999, p. 9) amending the Annex to Council Directive 75/318/EEC in relation to 'well established medicinal use'. A hearing with interested parties was held in October 1999.

2.5 Activities of the mutual recognition facilitation group

The mutual recognition or decentralised procedure is one of the two procedures of the European marketing authorisation system. It continues to be employed as a means of cooperation between Member States.

Dr Birka Lehmann (Germany) chaired the Mutual Recognition Facilitation Group in the first half of 1999. From July to December 1999 Dr Veijo Saano (Finland) was chairman. The Group met 11 times in the course of the year.

The pronounced increase in mutual recognition procedures in 1999 required strong support from the EMEA to facilitate the smooth running of the Mutual Recognition Facilitation Group, subgroup meetings and break-out sessions (secretarial assistance, meeting rooms, videoconferencing).

The use of the procedure in 1999 was:

Mutual recognition procedure	Total submitted in 1999*	Under evaluation in 1999	Ended positively in 1999	Arbitrations in 1999
New applications	275	48	210	2
Type I variations	695	90	625	0
Type II variations	254	109	292	2
** The number includes multiple procedures*				

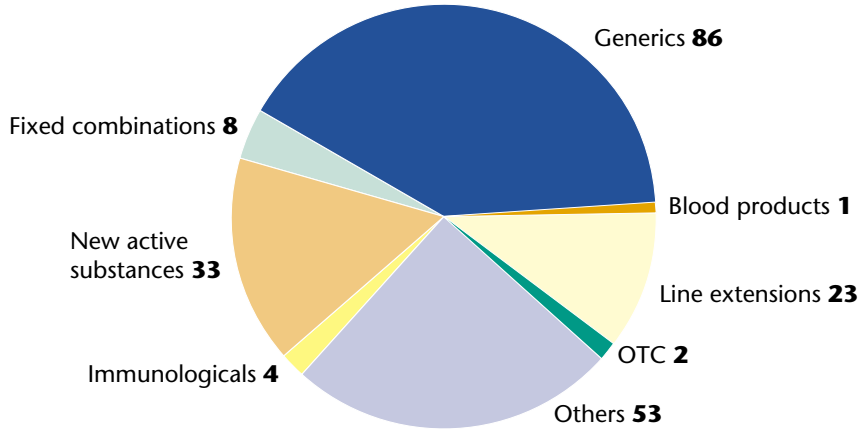
The total number of both submitted and completed applications increased. The number of arbitrations remained at a low level.

A total of 48 breakout sessions were organised by reference Member States (referring to 41 new applications, 4 variations, 3 others). In relation to the number of new applications, the number is smaller than in 1998. Breakout sessions for variation procedures became more frequent.

The frequency of withdrawals of applications – 34 % – (at least one withdrawal per procedure) from individual Member States in the mutual recognition procedure continues to be an issue of concern. An in-depth analysis of withdrawals began in September with the aim to identify the underlying causes of withdrawals and to suggest solutions to prevent a similar development in the future.

Nearly all Member States have now acted as reference Member State. The distribution between Member States continues to be uneven, with a number of Member States continuing to play a dominant role.

Total number of finalised procedures by type in 1999



Transparency and visibility of the mutual recognition procedure has improved considerably. A product index of procedures was made available in April 1999 with electronic links to the web sites of national competent authorities giving access to published summaries of product characteristics. Regular joint meetings of the Group with interested parties, as well as participation of members at seminars related to regulation of pharmaceuticals, have been informative for the pharmaceutical industry and offered opportunities for discussion.

Collaboration with the European Commission Directorate-General for Enterprise continues to be important and the Commission's participation in the Group's meetings is particularly valuable.

A number of guidance papers were published in 1999 to assist applicants and marketing authorisation holders in the use of the mutual recognition procedure. These include position papers on duplicate and multiple applications, on links between marketing authorisation holders, on line extensions and on repeat use of the mutual recognition procedure. Recommendations on informed consent applications and a best practice guide for the handling of variation applications in the mutual recognition procedure were also published.

A pilot project was launched in July 1999 with the aim of promoting the harmonisation of summary of product characteristics of medicinal products. Production of updated assessment reports was agreed and will start for all procedures commencing January 2000. These reports give a comprehensive overview of the documentation of products and decisions taken during the mutual recognition procedure in order to help communication between EU national authorities and authorities outside the EU, as well as to facilitate the repeat use of the procedure.

In preparation for their participation in the mutual recognition procedure, observers from Iceland and Norway attended meetings of the Mutual Recognition Facilitation Group in 1999. The Group agreed to invite observers representing the national authorities of central and eastern European countries as of January 2000.

Chapter 3

Medicinal products for veterinary use

Overview of the CVMP and the Unit for the Evaluation of Medicinal Products for Veterinary Use

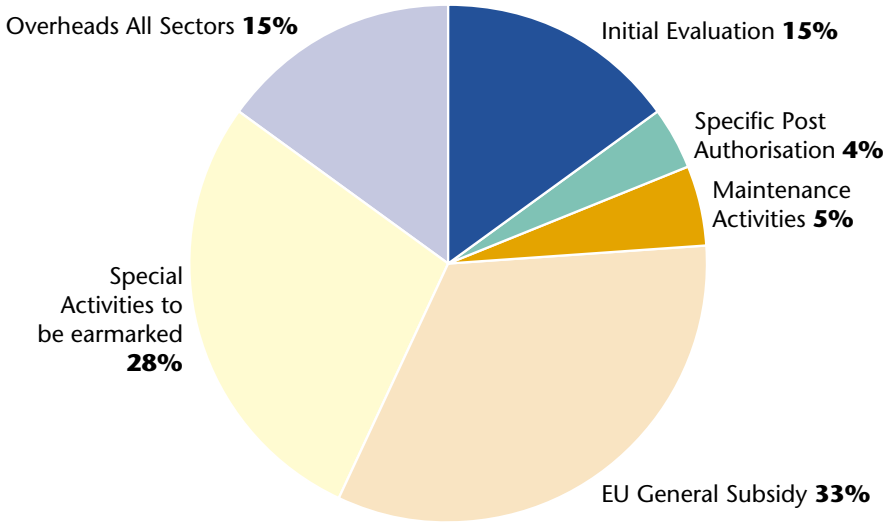
Chairman of the CVMP	**Reinhard KROKER**
Vice-chairman of the CVMP	**Gabriel BEECHINOR**
Head of Unit	**Peter JONES**
Head of Sector for CVMP and veterinary procedures	**Jill ASHLEY-SMITH**
Head of Sector for safety of veterinary medicines	**Kornelia GREIN**

The Unit for the Evaluation of Medicines for Veterinary Use is responsible for:

- management and follow-up of marketing authorisation applications under the centralised procedure
- management of applications for the establishment of maximum limits for residues of veterinary medicinal products that may be permitted in foodstuffs of animal origin
- post-marketing maintenance of authorised medicinal products
- management of Community referrals and arbitrations arising from the mutual recognition procedure
- provision of support to European and international harmonisation activities of the CVMP and its working parties

Reinhard Kroker

Unit for the Evaluation of Medicines for Veterinary Use



The targets set by the Unit in the Work Programme 1999-2000 were met in several key areas, in particular 100 % compliance with regulatory deadlines and completion of assessment for maximum residue limits for all old veterinary substances ahead of the 1 January 2000 deadline. Significant progress was also made in the re-drafting of volume VI of the Rules governing medicinal products in the European Union (see Annex 1 for details of this series). A significant portion of the work carried out by the Sector for the safety of veterinary medicines related to activities to establish of maximum residue limits for old substances, for which no fees are payable.

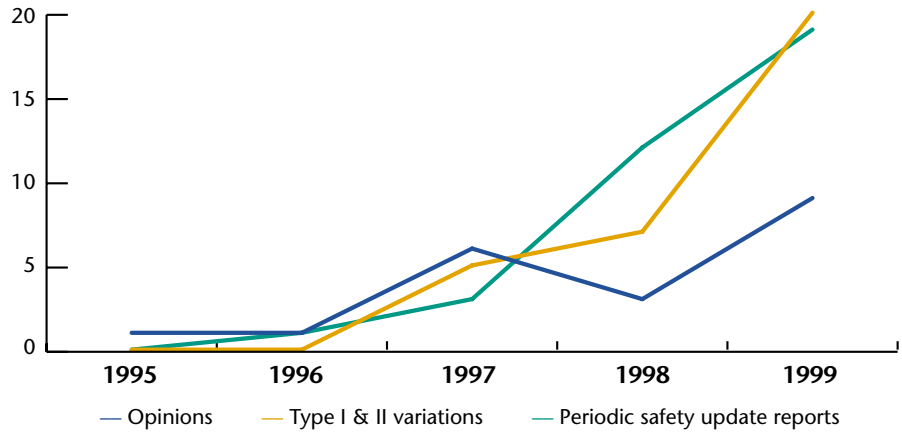
3.1 Operation of the CVMP

Centralised procedures	1997	1998	1999	Total 1995-1999
Applications received	2	14	4	32
Withdrawals	0	1	0	3
Opinions adopted by product	6	3	9	20
Type I variations	5	7	16	28
Type II variations	0	0	3	3
Extension & abridged applications	2	7	6	15

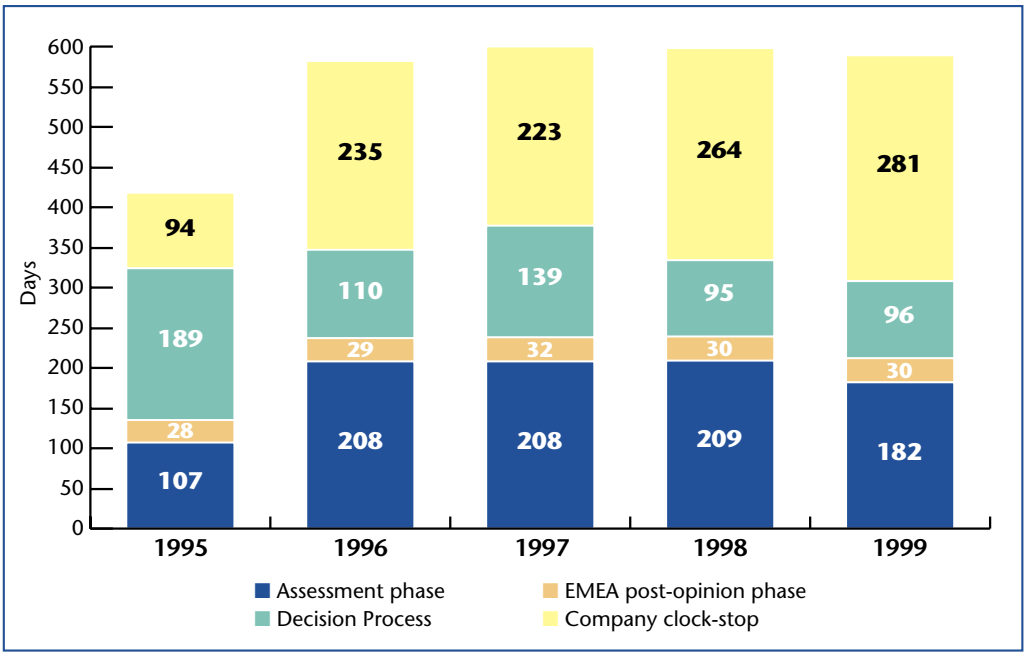
Centralised procedures

Applications under part B of the annex to Council Regulation (EEC) No 2309/93 (where the applicant has a choice of procedure) account for about two-thirds of total applications. The total number of authorisations and the consequent significant increase in variations and extensions has required additional effort in post-authorisation work, including supervision of periodic safety updates.

Opinions, Variations and Maintenance Activities of Marketing Authorisations 1995-1999



Performance measures of the centralised procedure

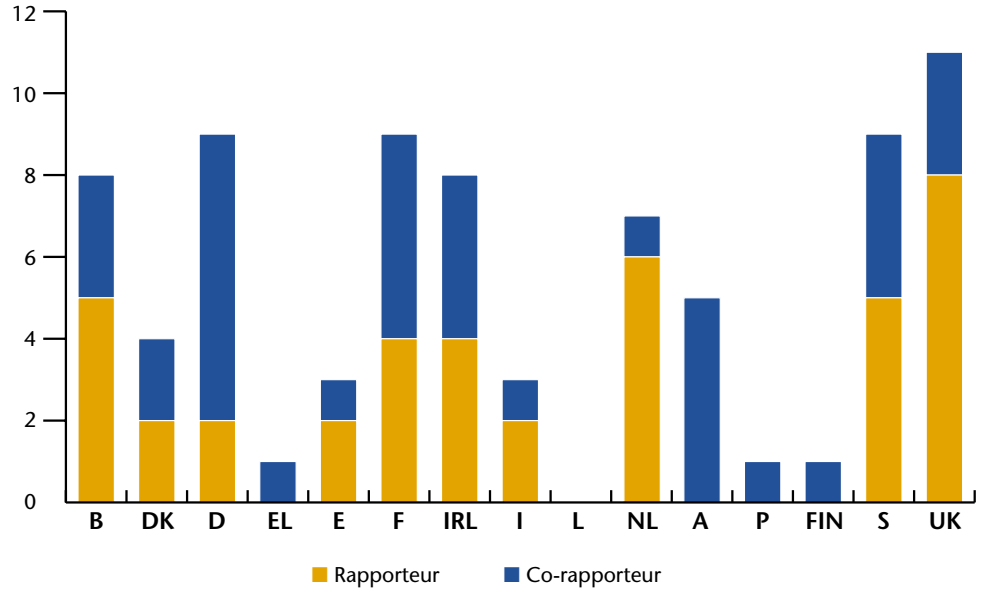


In accordance with the Unit's target in the 1999 Work Programme, all opinions have been finalised and transmitted to the Commission within the required timeframes.

Rapporteurships

A better distribution of rapporteur and co-rapporteurship appointments for centralised procedures is evolving. However it remains evident that some delegations have a heavier workload.

Distribution of rapporteurships by national delegations 1995-1999



International harmonisation

The CVMP developed a broad range of new guidelines in 1999 intended to provide assistance to applicants engaged in the research and development process of new products, where it was quite apparent that previously such advice did not exist. Details of these are presented in the reports of the key activities of the CVMP Working Parties below.

The contribution of the EMEA to the advances made in international harmonisation was noted at the first public conference of the Veterinary International Conference on Harmonisation (VICH) initiative held in Brussels in November 1999. A reduction in the amount of testing by the avoidance of duplication in experimental studies in animals have all been advanced significantly by the progress made in the VICH process in 1999. In total 12 guidelines have been finalised covering a broad range of topics.

The first joint meeting organised by the EMEA with the European Commission's Technical Assistance Information Exchange Office (TAIEX) took place in 1999. The purpose of this meeting is to support the countries of central and eastern Europe in their preparations for harmonising with EU requirements for authorisation of veterinary medicines. This first meeting focused on the main elements of the centralised procedure and the role of CVMP and its working parties; further meetings of this sort are planned for 2000.

Within the Pan-European Regulatory Forum on pharmaceuticals (PERF) initiative in 1999, the Unit for the Evaluation of Medicinal Products for Veterinary Use addressed issues of consumer safety in the establishment of maximum residue limits and was jointly represented with the Unit for the Evaluation of Medicinal Products for Human Use in the activities concerning the responsibilities and mandate of competent authorities, implementation of Community legislation and the quality of medicinal products.

Safety and availability of medicines

Establishment of maximum residue limits (MRLs)

Maximum residue limits	1997	1998	1999	Total 1995-1999
Establishment of MRLs for old substances	60	114	157	573
Applications for new maximum residue limits	6	4	3	38
Withdrawal of applications for new maximum residue limits	0	0	0	3
Applications for modifications and extensions of new maximum residue limits	13	10	12	49
Withdrawal of applications for modifications and extensions	1	1	0	3
Opinions on new maximum residue limits	10	27	32	79

When the EMEA opened in January 1995, more than six hundred 'old' substances remained for which maximum residue limits (MRLs) had to be established. This challenge has been met and the goal of completing the assessments as set out in the EMEA Work Programme for 1999 was achieved so that CVMP opinions can be transposed into decisions before the 1 January 2000 deadline.

Applications to set new MRLs continue at a steady pace, with numbers similar to those forecast for 1999. This provides a signal for the number of new substances evolving from research and development for food animals, which by all accounts, is disappointingly low. However, the numbers of extensions of existing MRLs to minor species is encouraging.

Availability of medicines

Availablity of medicines

- Spring 1998: Establishment of ad-hoc group
- May 1998: Adoption of CVMP position paper for presentation to Management Board
- June 1998: Brainstorming session on this issue at Management Board together with Commission
- March 1999: CVMP Position paper on availability identifying essential substances likely to be lost
- August 1999: Establishment of ad-hoc group on risk assessment in respect to establishment of MRLs
- October 1999:
  - Update on position paper and of list of essential substances
  - First meeting of EMEA Task Force on availability with participation of Commission and Interested Parties

The Agency is very aware of the implications of not completing the MRL assessment for old substances; that being the loss of some essential medicinal products for the practising veterinarian and the consequential effects on animal health and welfare.

The EMEA fully supported the initiatives being undertaken within the availability of medicines programme and a timetable of events in which it has actively participated with CVMP is outlined.

Antimicrobial resistance

There was much discussion on the subject of antibiotic resistance in 1999. It was therefore timely that the Agency adopted and published its own report on antibiotic resistance in the European Union associated with the therapeutic use of veterinary medicines in July 1999.

Antimicrobial resistance
Report and Qualitative Risk Assessment

- Probability of Adverse Health Effects in Humans due to the presence of Fluoroquinolone Resistant Salmonella typhmurium derived from animals is low, but with a high degree of Uncertainty and Variation in the different Member States
- Regular monitoring Required of Usage of all Antibiotic Agents in Animals in all EU Member States
- National Programme Needed for Monitoring Antibiotic resistance in Animals
- Authorisation of Antibiotics to be conditional on Pre-Marketing Surveillance
- Post Marketing Sensitivity is a Necessity
- Strategic Steps to Ensure Efficacy is Maintained
- Adoption of Prudent Use Policy throughout the Community

The report concludes that the use of antibiotics sooner or later always leads to resistance, whether their use is in human or veterinary medicine, growth promotion in animals, agriculture or horticulture and its major recommendations are summarised.

3.2 CVMP working parties

Highlights from working parties

Efficacy Working Party (EWP) – Chairperson: Liisa Kaartinen
Work continued on revising the guideline on bioequivalence and two new drafts of ectoparasiticide guidelines, one for dogs and cats and the other for cattle and sheep. In addition good progress is being made to draft new guidance notes on testing of non-steroidal anti-inflammatory drugs and biostatistical methodology in clinical trials.

Preparations began for a policy paper on efficacy requirements in relation to minor indications and minor species that will make a significant contribution to the availability of medicines initiative, and also on a glossary of terms for therapeutic claims.

Safety of Residues Working Party (SRWP) – Chairperson: Michèle Dagorn
In spite of the enormous workload that the Safety of Residues Working Party faced during 1999 concerning the establishment of MRLs for old substances, the Group also contributed to the preparation of the notes for guidance on determination of withdrawal periods in milk and the assessment of the effect of antimicrobial substances on dairy starter cultures. The working party also participated actively during the year to the CVMP input to VICH safety guidelines.

Pharmacovigilance Working Party (PhVWP) – Chairperson: Gabriella Conti
With the authorisation of more products through the centralised procedure, the CVMP is committed to consolidating the guidance available on pharmacovigilance both on the reporting requirements and the conduct of post-marketing surveillance studies for veterinary medicines.

The VEDDRA list of clinical terms/terminology for animal suspected adverse reactions to veterinary medicines, originally created in 1998, was advanced in 1999 and is available on the EMEA web site.

Immunologicals Working Party – Chairperson: Paul-Pierre Pastoret
The working group addressed a number of topics relating to veterinary vaccines. Two notes for guidance on the requirements for combined veterinary vaccines and on the duration of protection achieved by veterinary vaccines were released for consultation during 1999. The group also worked on guidance on field trials for veterinary vaccines and discussed strain replacement in swine influenza vaccines. The working party also responded to 3 referrals from the CVMP during the year.

Joint CPMP/CVMP Quality Working Party – Chairperson: Jean-Louis Robert
A number of specific veterinary guidelines were adopted or released by the Joint CPMP/CVMP Quality Working Party and details are given in annex 9.

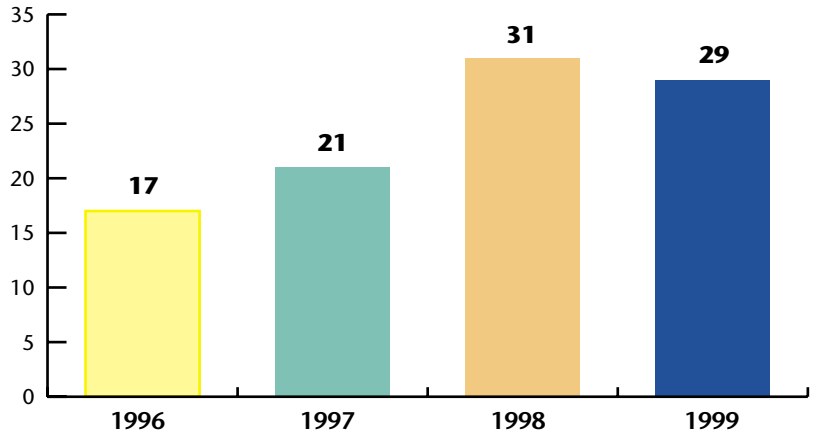
3.3 Activities of the veterinary mutual recognition facilitation group

The Veterinary Mutual Recognition Facilitation Group met each month except August at the EMEA under the chairmanship of Germany followed by Finland. The EMEA continued to provide full secretarial and administrative support to the Group, crucial for its effective operation.

The participation of the European Commission at meetings of the Group was also useful, particularly with regard to discussion of organisational matters. The Group exchanges all its documentation in electronic form using EudraMail. The web site of the Head of European Veterinary Regulatory Agencies (**http://www.hevra.org**) was opened in April 1999, giving access to documents of the Group.

The number of mutual recognition procedures for marketing authorisations is given in the table below. Figures cover the procedures that were begun in 1999 and include both new applications as well as repeat procedures. So far, eight Member States have acted as reference Member State. The number of variations increased steadily in 1999.

Number of procedures for marketing authorisations



Major activities in 1999 included the facilitation of applications, the study of reasons for withdrawal of applications in mutual recognition procedures, the initiation of a joint survey with FEDESA on the mutual recognition procedure and the development of a Veterinary Mutual Recognition Product Index, as well as work on orphan medicinal products and product availability. The automatic validation of the application has been set in place. The Group met regularly with interested parties during 1999.

Chapter 4

Technical Coordination

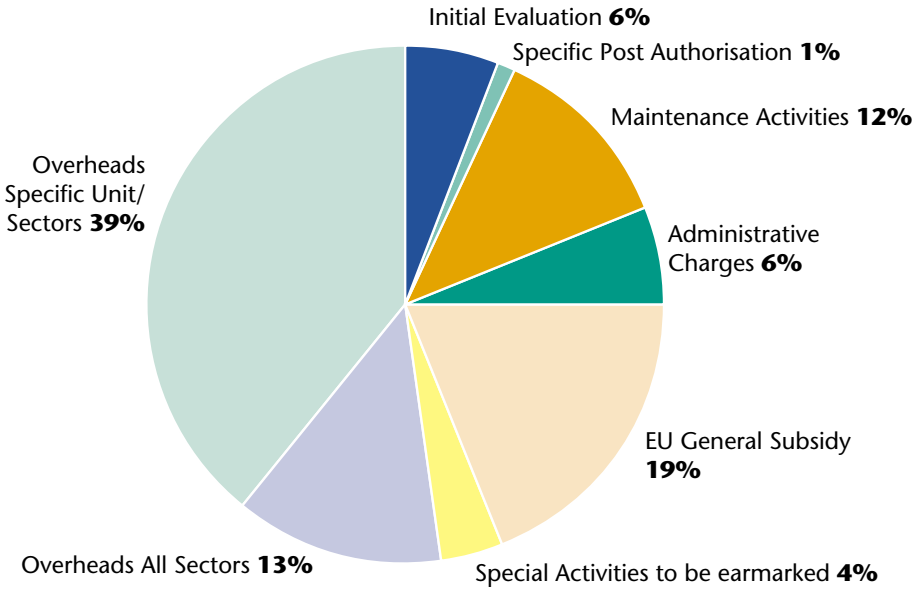
Overview of the Technical Coordination Unit

Head of Unit	**Karel de NEEF**
Head of Sector for inspections	**Stephen FAIRCHILD**
Head of Sector for document management and publishing	**Beatrice FAYL**
Head of Sector for conference services	**Sylvie BÉNÉFICE**
Head of Sector for information technology	**Michael ZOURIDAKIS**
Deputy Head of Sector	**David DRAKEFORD**

The Technical Coordination Unit is responsible for providing logistical support to both human and veterinary medicines evaluation activities as well as a number of general services to the EMEA, including document management, conference services and information technology support.

In addition, the Unit coordinated all meetings required for the Pan-European Regulatory Forum on Pharmaceuticals (PERF) and the preparation of an electronic submission data standard within the International Conference on Harmonisation process.

Technical Coordination Unit



4.1 Coordination of inspections and quality of human and veterinary medicines

Year 2000 compliance

Marketing authorisation holders for centrally authorised products were asked to confirm that they have investigated the impact of the year change 1999 to 2000 on their products and also to provide undertakings that the quality and availability of their products would not be affected. All confirmed that they have investigated the potential impact of date changes and provided assurances that the quality and availability of their products will be maintained. Only a small number were not able to provide specific assurance due to factors outside their control (e.g. external suppliers).

Coordination of inspections for centralised procedures

The number of good manufacturing practice (GMP) inspections requested has remained stable over the last few years, with 21 GMP inspections actually performed in 1999. This is lower than for 1998 when the backlog of requests from 1997 had to be dealt with.

Of the inspections carried out in 1999, 9 were performed in the USA, 6 in the European Union, 3 in Switzerland and one each in Japan, Puerto Rico and Switzerland. The inspection teams were drawn from Belgium, Finland, France, Germany, Ireland, Italy, Netherlands and the UK.

The preparations for the introduction of good clinical practice (GCP) inspections for centralised products continued through the work of the ad-hoc group of GCP inspectors and a major input from the CPMP. GCP is now part of the pre-submission and validation process for applications. For the first time, 2 good laboratory practice (GLP) inspections were carried out in 1999.

The GMP ad hoc inspectors group met 5 times and the GCP ad hoc inspectors group met 3 times in 1999. Details of the procedures and documents worked on during 1999 in these groups is given in annex 9.

Sampling and testing of centrally authorised products

A contract was signed between the EMEA and the European Department for the Quality of Medicines to coordinate a sampling and testing programme to monitor centrally authorised products in the year following the third anniversary of the granting of the Community marketing authorisation.

During 1999, 6 minor quality defects were reported to the EMEA, relating to sterile production, stability, particulate contamination and packaging. These incidents were investigated by the relevant national competent authorities and reported back to the EMEA, leading to the recall of certain batches of products. In none of these cases was public health at risk.

Mutual recognition agreements

Significant progress was made with the implementation of mutual recognition agreements (MRAs) with Canada and the USA. Both agreements have now entered the confidence-building phase required prior to full implementation. A comprehensive programme for the evaluation of equivalence of GMP systems is being coordinated by the EMEA and carried out by the inspectorates of the EU Member States. MRAs with Australia and with New Zealand became operational during 1999.

Certification of medicinal products

The demand for certificates has increased from 9,300 in 1998 to 9,562 during 1999 despite changes in scope which allow several pack types to be covered by one set of certificates. The certificate production process was reviewed during the year to review the service provided and ensure that the target of 5 days per request was met.

Joint CPMP/CVMP Quality Working Party

The Joint CPMP/CVMP Quality Working Party met 3 times in 1999 under the chairmanship of Jean-Louis Robert. The work completed by the working party is summarised in annex 9.

4.2 Document management and publishing

Product information

The Working Group on Quality Review of Documents, which includes experts on terminology from the national competent authorities, met six times in 1999 and worked on a wide range of methodological issues and the updating of public information published on the EMEA web site. The change in working practices to systematic and formal use of electronic communication via EudraNet worked well. A total of 48 products have now been through the formal Quality Review of Documents process.

The work of the Quality Review of Documents group is supported by an internal network of EMEA staff from all Units that looks at the quality of all product information prior to submission to the working group.

Together with the Human and Veterinary Units, the workflow for Product Information management between the EMEA and its partners was mapped out. The aim of this work is to put in place procedures and a system to handle this information throughout the lifecycle of a product, including updates and variations.

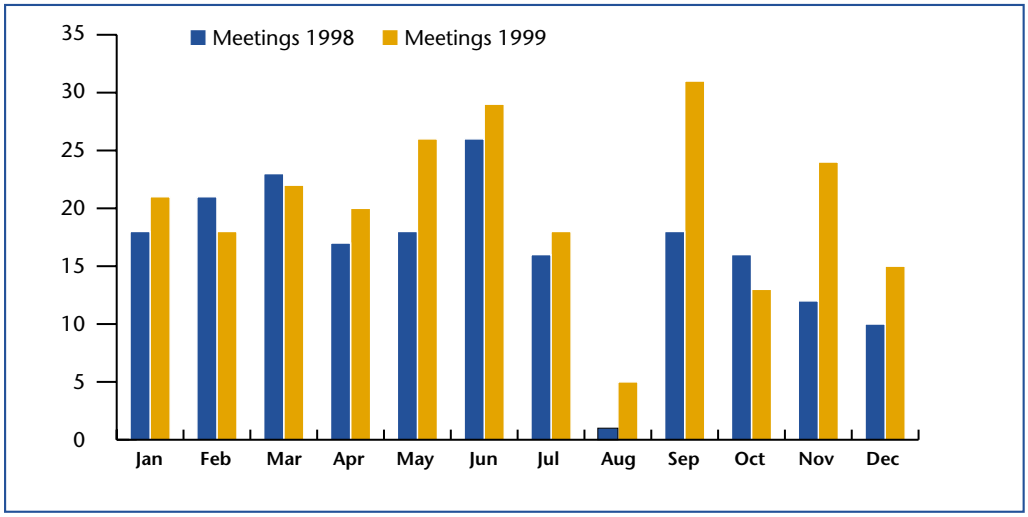
In response to increasing demand and in line with the Agency's policy on transparency of publications, the European public assessment report (EPAR) was presented in a new modular, multilingual format. The publication of some modules in the official EU languages will reach a wider audience both in Europe and world-wide.

Archives, mailroom and library

During the year, the Agency's archives were restructured and a substantial volume of documents moved to a secure off-site location. The Mailroom continued to provide consistent support while the volume of mail despatched from the Agency increased by 24 % compared with 1998. The library began the provision of electronic access to professional literature.

4.3 Conference services

In 1999 the number of meetings held at the EMEA as compared to 1998 increased by 33.7 %, to 262 meetings. The number of meeting days and interpretation days also increased, by 35.8 % and 3.8 % respectively. A total of 2,538 delegate visits (an increase of 19.2 %) were reimbursed in 1999. The implementation of the PERF project over the second half of 1999 resulted in the organisation of 22 additional meetings within Europe including technical support.



Videoconferencing

Videoconferencing was increasingly utilised for routine consultations with the European Commission, Member States and for meetings with industry and other partners of the EMEA such as the US Food and Drug Administration. It has enabled the EMEA to increase the range of meetings that may be held in support of the evaluation process.

Reprographics

The workload of the Reprographics service continued to reflect both the cyclical activity pattern of the EMEA and increasing levels of activity. Overall, the number of photocopies produced by Reprographics increased by 42.7 % to 11,981,000 in 1999.

4.4 Information technology

The Sector focused on compliance with year 2000 requirements, system security and efficiency.

An electronic database of European experts was implemented to allow remote access and updating by national competent authorities. A joint project was initiated with the World Health Organisation for the further development of their application tracking system, SIAMED, following termination of a development with the Joint Research Centre of the European Commission.

Several new features were developed in SI2 (the EU specific budgetary accounting system) including a new fees handling system and ActiTrak – the EMEA time recording system – was extended to include a costing module.

To assess the Agency's year 2000 compliance, five steps were undertaken:

- identifying all the items that might be at risk
- qualitative assessment of the risk associated with any given automated system, physical facility or device, the focus being on the potential for causing harm or disrupting critical functions
- testing and analysis
- assessment as to the level of compliance of individual items and hence of the extent of remedial action necessary
- corrective action including abandonment or replacement if necessary

Chapter 5

Administration

Overview of the Administration Unit

The Administration Unit is responsible for carrying out administrative and financial functions to ensure that the Secretariat and staff are able to perform their statutory tasks under satisfactory conditions.

Head of Unit	**Marino RIVA**
Head of Sector for personnel, budget and facilities	**Frances NUTTALL**
Head of Sector for accounting	**Gerard O'MALLEY**

The responsibilities and workload of the Administration Unit span all sectors. Within the Agency wide increase in activities and workload, the Unit structure has remained stable in 1999 with the consequent productivity achievements.

The Agency does not have permanent officials, but is staffed by temporary agents recruited through open competitions. Recruitment to the Agency follows the rules and practices of the EU institutions and successful candidates are offered five-year renewable contracts. There is no quota system for the nationals of each Member State, the Agency however seeks to respect the balance of nationalities of the European Union. EMEA staff comes from throughout the EU and all nationalities with the exception of Luxembourg are represented.

EMEA staff	31.12.1997	31.12.1998	31.12.1999
A	72	73	90
B	21	22	19
C and D	50	59	72
Total EMEA staff	143	154	181
National experts on secondment	2	3	3
External interim staff	9	9	9

The staff whose recruitment in 1998 was postponed for financial reasons were recruited in 1999, with a total of 41 additional staff recruited.

Staff received basic training on management techniques and language courses in 1999. In addition to the established programmes, and following recommendations from the QMS initiative, personal development courses have been held, a second media handling course was held as well as additional training for staff using the new financial accounting system. As part of the QMS initiative a total of 15 days' training was given for the 23 staff members who had volunteered as internal auditors. The European Commission Directorate-General for Budgets, the European Parliament and the European Commission UK representation office in London made presentations to staff on the European Union.

Nationalities	B	DK	D	EL	E	F	IRL
A	7	3	13	3	4	14	7
B	1	2	2	2	1	1	0
C	5	3	6	3	3	8	1
D	0	0	0	0	1	0	0
Total Temporary and Auxiliary agents	13	8	21	8	9	23	8
National experts	0	0	0	0	0	0	0
Interims	0	0	1	0	1	1	0
TOTAL	13	8	22	8	10	24	8
Nationalities	I	NL	A	P	FIN	S	UK
A	7	3	1	4	2	6	16
B	3	1	0	0	0	0	6
C	7	2	0	2	5	3	18
D	0	0	0	1	0	0	4
Total Temporary and Auxiliary agents	17	6	1	7	7	9	44
National experts	0	0	0	0	0	1	1
Interims	0	2	0	0	0	0	4
TOTAL	17	8	1	7	7	10	49

A flexitime system for the management of personnel and their hours worked was introduced in May 1999 in order to ensure that business needs are catered for during core hours. The system facilitates the management of peaks and troughs in workload leading to increased personal responsibility and productivity. The system showed in 1999 that a number of staff across the Agency consistently works long hours. The additional staff recruited in 1999 will allow work to be better allocated so that their hours can be reduced. The ActiTrak system is used to record time worked.

A system of permanence was also introduced in 1999 to ensure adequate cover during weekends and holiday periods in the case of pharmacovigilance or crisis events. A 24-hour alert system is also in place to handle such events on normal business days.

In agreement with the Management Board, the EMEA took an additional floor at 7 Westferry Circus amounting to approximately 1,460 m^2 in 1999, giving the Agency a total space of a little under 8,000 m^2 on four floors. The fitting-out work on this floor began in 1999 and when completed it will be occupied by the Unit for the Evaluation of Medicines for Human Use.

Progress was made in 1999 towards the integration of the computerised system for budget and financial management – SI 2 – introduced in 1998. In particular work was done to implement the revenue accounting module of the system, taking into account the provisions of the new fee regulation, to record income received. The system also facilitated internal budget monitoring for management purposes.

Annexes

Annexes

1. EMEA contact points and reference documents

2. EMEA budgets 1997 to 1999

3. Members of the Management Board

4. Members of the Committee for Proprietary Medicinal Products

5. Members of the Committee for Veterinary Medicinal Products

6. National competent authority partners

7. CPMP opinions in 1999 on medicinal products for human use

8. CVMP opinions in 1999 on medicinal products for veterinary use

9. EMEA guidelines in 1999

Annex 1: EMEA contact points and reference documents

EMEA contact points

Pharmacovigilance and product defect reporting
The constant monitoring of the safety of medicines after authorisation ('pharmacovigilance') is an important part of the work of the national competent authorities and EMEA. The EMEA receives safety reports from within the EU and outside concerning centrally authorised medicinal products and coordinates action relating to the safety and quality of medicinal products.

For matters relating to pharmacovigilance for medicinal products for human use	*Contact point* **Noël WATHION** Direct telephone (44-20) 74 18 85 92 E-mail: noel.wathion@emea.eudra.org
For matters relating to pharmacovigilance for medicinal products for veterinary use	*Contact point* **Jos OLAERTS** Direct telephone (44-20) 74 18 86 24 E-mail: jos.olaerts@emea.eudra.org
For product defect and other quality-related matters	*Contact point* **Stephen FAIRCHILD** Fax number for defective product rapid alerts (44-20) 74 18 85 90 E-mail: stephen.fairchild@emea.eudra.org

Certificates of a medicinal product
The EMEA issues certificates of a medicinal product in conformity with the arrangements laid down by the World Health Organisation. These certify the marketing authorisation and good manufacturing status of medicinal products in the EU and are intended for use in support of marketing authorisation applications in and export to non-EU countries.

For enquiries concerning certificates for centrally authorised medicines for human or veterinary use	*Contact point* **Jonna SUNELL-HUET** Direct telephone (44-20) 74 18 84 65 E-mail: certificate@emea.eudra.org

Documentation services
A wide range of documents has now been published by the EMEA, including press releases, general information documents, annual reports and work programmes. These and other documents are available either on the Internet at **http://www.eudra.org/emea.html** or by writing to:

Subscription Service, European Agency for the Evaluation of Medicinal Products
7 Westferry Circus, Canary Wharf,
London E14 4HB
UK

A subscription service is available for all EMEA public documents, distributing documents electronically or in paper form.

Further information can be obtained from the above address or from

Contact point
Iro MAVROPOULOS
Direct telephone (44-20) 74 18 85 82
E-mail: subscriptions@emea.eudra.org

Requests for general information packs should be sent to

Contact point
Amanda BOSWORTH
Direct telephone (44-20) 74 18 84 08
E-mail: amanda.bosworth@emea. eudra.org

Media and press contacts
Representatives of the media should contact the following people for information:

For matters concerning medicinal products for human use

Contact points
Rolf BASS
Direct telephone (44-20) 74 18 84 11
E-mail: rolf.bass@emea.eudra.org

Noël WATHION
Direct telephone (44-20) 74 18 85 92
E-mail: noel.wathion@emea.eudra.org

For matters concerning medicinal products for veterinary use

Contact point
Peter JONES
Direct telephone (44-20) 74 18 84 13
E-mail: peter.jones@emea.eudra.org

For general information on any other matter

Contact points
Martin HARVEY
Direct telephone (44-20) 74 18 84 27
E-mail: martin.harvey@emea.eudra.org

Antoine CUVILLIER
Direct telephone (44-20) 74 18 84 28
E-mail: antoine.cuvillier@emea. eudra.org

EU official publications

- Council Regulation (EEC) No 2309/93 as amended (OJ L 214, 24.8.1993, p. 1)
- Council Regulation (EEC) No 2377/90 as amended (OJ L 224, 18.8.1990, p. 1)
- Council Directive 75/319/EEC as amended (OJ L 147, 9.6.1975, p. 13)
- Council Directive 81/851/EEC as amended (OJ L 317, 6.11.1981, p. 1)
- Council Regulation (EC) No 2743/98 (OJ L 345, 19.12.1998, p. 3)
- EMEA budget statement for the financial year 1999, including final appropriations for 1998 and outturn for 1997 (OJ L 58, 5.3.1999, p. 1)

The texts of these and other provisions are available in the series *Rules governing medicinal products in the European Community*. These publications, along with copies of the Official Journal, are available from:

Office for Official Publications of the European Communities
2, rue de Mercier
L - 2985 Luxembourg

and also on the EudraLex Internet site at **http://dg3.eudra.org/eudralex/index.htm**

EMEA documents

- First General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1995 (ISBN 92-827-7491-0, Office for Official Publications of the EU)
- Second General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1996 (ISBN 92-9155-002-7, Office for Official Publications of the EU)
- Third General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1997 (ISBN 92-9155-010-8, Office for Official Publications of the EU)
- Fourth General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1998 (ISBN 92-9155-018-3, Office for Official Publications of the EU)
- Statement of principles governing the partnership between the national competent authorities and the EMEA (EMEA/MB/013/97)
- Financial Regulation applicable to the budget of the EMEA (EMEA/MB/011/97)
- Decision of the Executive Director of 3 December 1997 on rules on access to documents of the EMEA(EDIR/016/1997)
- Decision of the Executive Director of 1 June 1999 on cooperation with the European Anti-Fraud Office (OLAF) (EDIR/006/1999)
- Catalogue of EMEA public documents (updated monthly)
- EMEA Code of Conduct (EMEA/D/37674/99)

These and other documents are available either on the Internet at **http://www.eudra.org/emea.html** or by writing to:

Sector for Document Management and Publishing
European Agency for the Evaluation of Medicinal Products
7 Westferry Circus
Canary Wharf
London E14 4HB
UK

Annex 2: EMEA budgets for 1997 to 1999

The summarised comparative budget statements for 1997 to 1999 are given below. For the sake of clarity, all amounts are expressed in euro although the single currency has only been in operation since 1 January 1999.

	1997[1] (4.12.1996)		1998[1] (3.12.1997)		1999[2] (1.12.1999)	
Expenditure						
Staff						
salaries	9 051 341	*33.47%*	12 743 000	*39.95%*	16 172 000	*37.92%*
interim and other support persons	977 998	*3.62%*	620 000	*1.94%*	1 183 000	*2.77%*
other staff-related expenditure	1 140 312	*4.22%*	1 010 000	*3.17%*	1 161 000	*2.72%*
total title 1	**11 169 651**	**41.31%**	**14 373 000**	**45.06%**	**18 516 000**	**43.41%**
Building/equipment						
rent/charges	1 859 982	*6.87%*	2 080 000	*6.52%*	2 167 450	*5.08%*
expenditure on data processing	1 769 987	*6.54%*	954 000	*2.99%*	883 000	*2.07%*
other capital expenditure	439 811	*1.62%*	165 000	*0.52%*	2 008 280	*4.71%*
postage and communications	463 346	*1.71%*	410 000	*1.29%*	378 000	*0.89%*
other administrative expenditure	968 037	*3.58%*	922 000	*2.89%*	1 214 270	*2.85%*
total title 2	**5 501 163**	**20.34%**	**4 531 000**	**14.20%**	**6 651 000**	**15.60%**
Operational expenditure						
meetings	1 986 442	*7.34%*	2 487 000	*7.80%*	3 284 000	*7.70%*
evaluations	6 700 000	*24.77%*	9 800 000	*30.72%*	13 894 000	*32.58%*
translation	1 200 000	*4.44%*	584 000	*1.83%*	--	*0%*
studies and consultants	243 782	*0.90%*	105 000	*0.33%*	95 000	*0.22%*
publications	242 216	*0.90%*	20 000	*0.06%*	210 000	*0.49%*
total title 3	**10 372 440**	**38.35%**	**12 996 000**	**40.74%**	**17 483 000**	**40.99%**
TOTAL EXPENDITURE	**27 043 254**	**100%**	**31 900 000**	**100%**	**42 650 000**	**100%**
Revenue						
fees	12 944 000	*47.85%*	17 030 000	*53.39%*	27 550 000	*64.60%*
EU contribution	13 546 000	*50.01%*	14 000 000	*43.89%*	13 000 000	*30.48%*
other	552 087	*2.04%*	870 000	*2.72%*	2 100 000	*4.92%*
TOTAL REVENUE	**27 043 254**	**100%**	**31 900 000**	**100%**	**42 650 000**	**100%**

Notes

(1) 1997 and 1998 budgets: outturn figures. (2) 1999 budget: final appropriations.

Annex 3: Members of the Management Board

Chairman	Strachan HEPPELL

Members

European Parliament	Gianmartino BENZI, Dietrich HENSCHLER *Alternates:* Dame Rosalinde HURLEY, Jean-Pierre REYNIER
European Commission	Jörn KECK, Joachim HEINE *Alternates:* Paul WEISSENBERG, Alejandro CHECCHI LANG
Belgique/België	André PAUWELS, Frans GOSSELINCKX[1]
Danmark	Ib VALSBORG, Ib Bo LUMHOLTZ
Deutschland	Hermann Josef PABEL, Gerhard Josef KOTHMANN
Ελλάδα/Greece	Haralampos MOUTSOPOULOS[2], Nikolaos KOKKOLIS
España	María Theresa PAGÉS JIMÉNEZ[3], Mariano BITRIÁN CALVO[4]
France	Philippe DUNETON[5], Jacques BOISSEAU
Ireland	Tom MOONEY, John COSTELLOE
Italia	Nello MARTINI, Romano MARABELLI *(Vice-chairman)*
Luxembourg	Mariette BACKES-LIES
Nederlands	André BROEKMANS, Frits PLUIMERS[6]
Österreich	Alexander JENTZSCH, Ernst LUSZCZAK
Portugal	José António ARANDA da SILVA, Maria Armanda MIRANDA
Suomi/Finland	Kimmo LEPPO, Hannes WAHLROOS
Sverige	Birgitta BRATTHALL, Anders BROSTRÖM
United Kingdom	Keith JONES, Michael RUTTER

Observers

Ísland	Rannveig GUNNARSDÓTTIR, Ingolf PETERSEN[7]
Norge/Noreg	Andreas DISEN[8], Gro Ramsten WESENBERG[9]

1 Replaced Michel CHOJNOWSKI as of the 1 December 1999 meeting.
2 Replaced Gerasimos KAVVADIAS as of the 1 December 1999 meeting.
3 Replaced Federico PLAZA PIÑOL as of the 2 June 1999 meeting.
4 Replaced Quintiliano PÉREZ BONILLA as of the 2 June 1999 meeting.
5 Replaced Jean-René BRUNETIÈRE as of the 2 June 1999 meeting.
6 Replaced Constand VAN DER MEIJS as of the 1 December 1999 meeting.
7 Replaced Einar MAGNUSSON as of the 29 September 1999 meeting.
8 Replaced Harold HAUGE as of the 2 June 1999 meeting.
9 Replaced Olav ROKSVAAG as of the 29 September 1999 meeting.

Annex 4: Members of the Committee for Proprietary Medicinal Products[1]

- Jean-Michel ALEXANDRE (France), *Chairman*

- Eric ABADIE (France)
- Eva ALHAVA (Suomi/Finland)
- Fernando de ANDRES-TRELLES (España)
- Cristina AVENDAÑO (España)[2]
- Michalis AVGERINOS (Ελλάδα/Greece)
- Daniel BRASSEUR (Belgique/België)
- Hans van BRONSWIJK (Nederlands)
- Geert DE GREEF (Belgique/België)
- Jens ERSBØLL (Danmark)[3]
- Silvio GARATTINI (Italia)
- Rogério GASPAR (Portugal)
- Jacqueline GENOUX-HAMES (Luxembourg)
- Willem van der GIESEN (Nederlands)
- Manfred HAASE (Deutschland)
- Alfred HILDEBRANDT (Deutschland)
- David JEFFERYS (United Kingdom)
- Gorm JENSEN (Danmark)
- David LYONS (Ireland)
- Per NILSSON (Sverige)[4]
- Jean-Louis ROBERT (Luxembourg)
- Tomas SALMONSON (Sverige)[5]
- Cristina SAMPAIO (Portugal)
- Mary TEELING (Ireland), *Vice-chairman*
- Markku TOIVONEN (Suomi/Finland)
- Jean-Hugues TROUVIN (France)
- Guiseppe VICARI (Italia)
- Patrick WALLER (United Kingdom)
- Hans WINKLER (Österreich)
- Christa WIRTHUMER-HOCHE (Österreich)
- Julia YOTAKI (Ελλάδα/Greece)

Observers

- Magnús JÓHANNSSON (Ísland)
- Lars GRAMSTAD (Norge/Noreg)
- Tove KARLSUD (Norge/Noreg)[6]
- Sigurdur THORSTEINSSON (Ísland)

1 The country of the nominating Member State is given for information purposes only.
2 Replaced José Félix OLALLA MARAÑÓN as of the October 1999 meeting.
3 Replaced Ib Bo LUMHOLTZ as of the January 1999 meeting.
4 Replaced Bo ODLIND as of the December 1999 meeting.
5 Replaced Per SJÖBERG as of the December 1999 meeting.
6 Replaced Gro RAMSTEN WESENBERG as of the November 1999 meeting.

Annex 5: Members of the Committee for Veterinary Medicinal Products[1]

- Reinhard KROKER (Deutschland), *Chairman*

- Margarita ARBOIX (España)[2]
- Gabriel BEECHINOR (Ireland), *Vice-chairman*
- Rory BREATHNACH (Ireland)[3]
- Gabriella CONTI (Italia)
- Luis CORBALAN (España)
- Steve DEAN (United Kingdom)[4]
- Johannes DICHTL (Österreich)
- Sabine EGLIT (Deutschland)
- Françoise FALIZE (Belgique/België)
- Christian FRIIS (Danmark)
- Helle HARTMANN FRIES (Danmark)
- Christos HIMONAS (Ελλάδα/Greece)
- Johannes HOOGLAND (Nederlands)
- Albert HUBERTY (Luxembourg)
- Liisa KAARTINEN (Suomi/Finland)
- Herman LENSING (Nederlands)
- Jan LUTHMAN (Sverige)
- Agostino MACRI (Italia)
- Ioannis MALEMIS (Ελλάδα/Greece)
- Manfred MOOS (Deutschland)
- Gérard MOULIN (France)
- John O'BRIEN (United Kingdom)
- Eugen OBERMAYR (Österreich)
- Paul-Pierre PASTORET (Belgique/België)
- Margarida PRATAS (Portugal)
- Jean-Claude ROUBY (France)[5]
- Liisa SIHVONEN (Suomi/Finland)[6]
- Carlos SINOGAS (Portugal)
- Annika WENNBERG (Sverige)
- Marc WIRTOR (Luxembourg)

Observers

- Hanne BERGENDAHL (Norge/Noreg)
- Tonje HØY (Norge/Noreg)
- Sigurdur ÖRN HANSSON (Ísland)
- Halldór RUNÓLFSSON (Ísland)

1 The country of the nominating Member State is given for information purposes only.
2 Replaced Odon SOBRINO as of the October 1999 meeting.
3 Replaced Cyril O'SULLIVAN as of the May 1999 meeting.
4 Replaced Michael RUTTER as of the August 1999 meeting.
5 Replaced Jacques BOISSEAU as of the April 1999 meeting.
6 Replaced Satu PYÖRÄLÄ as of the February 1999 meeting.

Annex 6: National competent authority partners

Further information on the national competent authorities is also available on the national authorities' Internet sites: **http://heads.medagencies.org** and **http://www.hevra.org**

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Annex 7: CPMP opinions in 1999 on medicinal products for human use

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Triacelluvax bacterial combination Vaccine Part A	Chiron S.P.A IT	JO7AJ Active immunisation of children against diphtheria, tetanus and pertussis	Suspension for injection Diphtheria toxoid ≥ 30IU Tetanus toxoid ≥ 40IU Pertussis toxoid 5µg FHA 2.5µg Pertactin 2.5µg 9 Presentations	20.06.97 23.07.98 188 Days 209 Days	08.10.98 11.01.99 14.01.99 OJ No. C 24 of 29.01.99, p. 23
Infergen interferon alfacon-1 Part A	Yamanouchi Europe B.V Japan	L03 Treatment of chronic hepatitis C	Solution for injection 9 µg 3 Presentations	25.07.97 23.07.98 182 Days 181 Days	03.12.98 01.02.99 04.02.99 OJ No. C 56 of 26.02.99, p. 8
Micardis telmisartan Part B	Boehringer Ingelheim International GmbH DE	C09CA07 Treatment of essential hypertension	Tablet 40 mg, 80 mg 8 Presentations	24.10.97 23.07.98 188 Days 84 Days	05.10.98 16.12.98 21.12.98 OJ No. C 24 of 29.01.99, p. 23
Pritor telmisartan Part B	Glaxo Wellcome UK	C09CA07 Treatment of essential hypertension	Tablet 40 mg, 80 mg 10 Presentations	24.10.97 23.07.98 188 Days 84 Days	20.09.98 11.12.98 16.12.98 OJ No. C 411 of 31.12.98, p. 9
Telmisartan Boehringer Ingelheim telmisartan Part B	Boehringer Ingelheim International GmbH DE	C09CA07 Treatment of essential hypertension	Tablet 40 mg, 80 mg 8 Presentations	24.10.97 23.07.98 188 Days 84 Days	05.10.98 16.12.98 21.12.98 OJ No. C 24 of 29.01.99, p. 23
Karvezide irbesartan / hydrochloro-thiazide Part B	Bristol-Myers Squibb Pharma EEIG USA	C09DA Treatment of essential hypertension	Tablet 150/12,5 mg, 300/12,5 mg 6 Presentations	19.12.97 23.07.98 153 Days 63 Days	21.08.98 16.10.98 21.10.98 OJ No. C 367 of 27.11.98, p. 21
CoAprovel irbesartan / hydrochloro-thiazide Part B	Sanofi Pharma Bristol-Myers Squibb SNC FR	C09DA Treatment of essential hypertension	Tablet 150/12,5 mg, 300/12,5 mg 6 Presentations	19.12.97 23.07.98 153 Days 63 Days	21.08.98 15.10.98 21.10.98 OJ No. C 367 of 27.11.98, p. 21
Forcaltonin recombinant salmon calcitonin Part A	Unigene UK	H05BA01 Paget's disease and hypercalcaemia of malignancy	Solution for injection 50 IU/0.5 ml, 100 IU/ml 2 Presentations	26.09.97 17.09.98 210 Days 147 Days	20.10.98 11.01.99 15.01.99 OJ No. C.24 of 29.01.99, p. 23
Prometax rivastigmine Part B	Novartis Europharm CH	N06DA03 Symptomatic treatment of mild to moderate severe Alzheimer Dementia	Hard capsule 1.5 mg, 3 mg 4.5 mg, 6 mg 12 Presentations	24.07.98 17.09.98 53 Days 0 Days	01.10.98 04.12.98 09.12.98 OJ No. C 411 of 31.12.98, p. 9

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Emadine emedastine Part B	Alcon Laboratories Ltd USA	S01GX Treatment of seasonal allergic conjuctivitis	Eye drops solution 0.05 % 2 Presentations	19.12.97 22.10.98 182 Days 127 Days	02.12.98 27.01.99 29.01.99 OJ No. C. 56 of 26.02.99, p. 8
Temodal temozolomide Part B	SP Europe USA	L01AX03 Indicated in the treatment of patients with recurrent malignant glioma	Hard capsule 5 mg, 20 mg 100 mg, 250 mg 8 Presentations	30.01.98 22.10.98 203 Days 60 Days	25.11.98 26.01.99 28.01.99 OJ No. C. 56 of 26.02.99, p. 8
Zaleplon Wyeth Medica Ireland zaleplon Part B	Wyeth USA	N05CF03 Short term treatment of insomnia	Hard capsule 5 mg, 10 mg 6 Presentations	30.01.98 19.11.98 182 Days 113 Days	13.01.99 12.03.99 18.03.99 OJ No. C 84 of 26.03.99, p. 3
Sonata zaleplon Part B	Wyeth USA	N05CF03 Short term treatment of insomnia	Hard capsule 5 mg, 10 mg 6 Presentations	30.01.98 19.11.98 182 Days 113 Days	13.01.99 12.03.99 18.03.99 OJ No. C 84 of 26.03.99, p. 3
Beromun tasonermin Part A	Boehringer Ingelheim International GmbH DE	L03AA Adjunct therapy to surgery for irresectable soft tissue sarcoma of the limbs, to prevent or delay amputation	Powder and solvent for solution for infusion 1 mg 1 Presentation	24.10.97 19.11.98 188 Days 204 Days	15.01.99 13.04.99 15.04.99 OJ No. C 119 of 30.04.99, p. 8
Zenapax daclizumab Part A	Roche Registration Ltd CH	L04AA08 Prophylaxis of acute renal transplant rejection	Concentrate for solution for infusion 5 mg/ml 2 Presentations	26.09.97 16.11.98 205 Days 214 Days	22.12.98 26.02.99 03.03.99 OJ No. C 84 of 26.03.99, p. 3
Cetrotide cetrorelix Part B	Asta Medica DE	G03X Prevention of premature ovulation in patients undergoing fertilisation treatment	Powder and solvent for solution for injection 0.25 mg, 3 mg 3 Presentations	27.02.98 17.12.98 173 Days 121 Days	19.01.99 13.04.99 15.04.99 OJ No. C 119 of 30.04.99, p. 8
Refacto moroctocog alfa Part A	Genetics Institute USA	B02BD02 Control and prevention of haemorrhagic episodes	Powder and solvent for solution for injection 250 IU, 500 IU, 1000 IU 3 Presentations	27.02.98 17.12.98 146 Days 148 Days	03.02.99 13.04.99 15.04.99 OJ No. C 119 of 30.04.99, p. 8
Regranex becaplermin Part A	Janssen-Cilag International B.V. BE	D03 X06 To promote healing of full thickness diabetic ulcers	Gel 100 µg/g 1 Presentation	21.11.97 17.12.98 188 Days 203 Days	28.01.99 29.03.99 29.03.99 OJ No. C 119 of 30.04.99, p. 8
Procomvax haemophilus b conjugate and hepatitis B vaccine Part A	Pasteur Merieux MSD FR	J07CA Immunisation against Haemophilus influenzae type B and infection by hepatitis B virus in infants	Suspension for injection Haemophilus influenzae type B 7.5 µg N. meningitidis OMPC 125 µg Recombinant Hepatitis B surface Antigen 5 µg 1 Presentation	27.02.98 27.01.99 175 Days 153 Days	03.03.99 07.05.99 14.05.99 OJ No. C 180 of 25.06.99, p. 2

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Paxene paclitaxel Part B	Norton Health Care Ltd UK	L01CD01 Treatment of advanced AIDS-related Kaposi's sarcoma	Concentrate for solution for infusion 6 mg/ml 2 Presentations	21.11.97 27.01.99 179 Days 251 Days	10.05.99 19.07.99 21.07.99 OJ No. C 242 of 27.08.99, p. 3
Rotashield rotavirus vaccine Part B	Wyeth-Lederle Vaccines S.A. USA	J07BH Immunisation against gastroenteritis caused by rotavirus serotypes 1, 2, 3 and 4 in infants	Powder and solvent for oral suspension 1.0 x 10^5 pfu of rotavirus serotypes 1, 2, 3 and 4 1 Presentation	25.07.97 27.01.99 175 Days 393 Days	05.03.99 07.05.99 14.05.99 OJ No. C 148 of 28.05.99, p. 5
Ferriprox deferiprone Part B	Apotex CA	V03AC Second line treatment of iron overload in thalassemia	Film-coated tablet 500 mg 1 Presentation	27.02.98 27.01.99 175 Days 160 Days	24.03.99 25.08.99 02.09.99 OJ No. C 270 of 24.09.99, p. 2
Integrilin eptifibatide Part B	SP Europe USA	B01AC16 Prevention of new myocardial infarction	Solution for infusion 0.75 mg/ml, 2 mg/ml 2 Presentations	30.01.98 24.02.99 173 Days 216 Days	30.03.99 01.07.99 09.07.99 OJ No. C 218 of 30.07.99, p. 7
Rebetol ribavirin Part B	SP Europe USA	J05AB04 Treatment in combination with interferon alpha 2b of chronic hepatitis C	Hard capsule 200 mg 2 Presentations	26.06.98 24.02.99 185 Days 57 Days	19.03.99 07.05.99 17.05.99 OJ No. C 180 of 25.06.99, p. 2
Cotronak ribavirin Part B	SP Europe USA	J05AB04 Treatment in combination with interferon alpha 2b of chronic hepatitis C	Hard capsule 200 mg 2 Presentations	26.06.98 24.02.99 185 Days 57 Days	19.03.99 07.05.99 17.05.99 OJ No. C 148 of 28.05.99, p. 5
Sustiva efavirenz Part B	Merck Sharpe & Dohme USA	JO5AG03 Combination therapy of HIV-1 infected patients	Hard capsule 50 mg, 100 mg 200 mg 4 Presentations	24.07.98 24.02.99 183 Days 27 Days	28.03.99 28.05.99 07.06.99 OJ No. C 180 of 25.06.99, p. 3
Stocrin efavirenz Part B	DuPont Pharmaceuticals USA	JO5AG03 Combination therapy of HIV-1 infected patients	Hard capsule 50 mg, 100 mg 200 mg 4 Presentations	24.07.98 24.02.99 183 Days 27 Days	28.03.99 28.05.99 07.06.99 OJ No. C 180 of 25.06.99, p. 3
Ziagen abacavir Part B	Glaxo Wellcome UK	JO5AFO6 Combination therapy of HIV-1 infected patients	Film coated tablet, Oral solution 300 mg, 20 mg/ml 2 Presentations	24.07.98 25.03.99 172 Days 66 Days	24.07.99 08.07.99 12.07.99 OJ No. C 218 of 30.07.99, p. 7
Zeffix lamivudine Part B	Glaxo Wellcome UK	JO5AF05 Treatment of chronic hepatitis B	Film coated tablet, Oral solution 100 mg, 5mg/ml 3 Presentations	24.04.98 22.04.99 201 Days 160 Days	26.05.99 29.07.99 05.08.99 OJ No. C 242 of 27.08.99, p. 3

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Vitravene fomivirsen Part B	Ciba Vision CH	S01AD Local treatment of CMV retinitis in patients with AIDS	Solution for injection 6.6 mg/ml 1 Presentation	29.05.98 22.04.99 141 Days 154 Days	26.05.99 29.07.99 05.08.99 OJ No. C 242 of 27.08.99, p. 3
Arava leflunomide Part B	Hoechst Marion Roussel Deutschland GmbH DE	ATC under consideration Treatment of active rheumatoid arthritis	Film coated tablet 10 mg, 20 mg, 100 mg 9 Presentations	27.02.98 20.05.99 186 Days 259 Days	22.06.99 02.09.99 07.09.99 OJ No. C 270 of 24.09.99, p. 2
Remicade infliximab Part A	Centocor B.V. NL	L04AA12 Treatment of Crohn's disease	Powder for solution for infusion 100 mg 1 Presentation	27.03.98 20.05.99 185 Days 259 Days	23.06.99 13.08.99 25.08.99 OJ No. C 270 of 24.09.99, p. 2
Synagis palivizumab Part A	Abbott USA	ATC under consideration Prevention of serious lower respiratory tract disease	Powder and solvent for solution for injection 50 mg, 100 mg 2 Presentations	21.08.98 20.05.99 174 Days 95 Days	22.06.99 13.08.99 25.08.99 OJ No. C 270 of 24.09.99, p. 2
Novorapid insulin aspart Part A	Novo Nordisk DK	A10AB05 Treatment of diabetes mellitus	Solution for injection 100 U/ml 5 Presentations	18.09.98 20.05.99 213 Days 28 Days	28.06.99 07.09.99 15.09.99 OJ No. C 270 of 24.09.99, p. 2
Ammonaps phenylbutyrate Part B	Orphan Europe FR	A16AX03 Adjunctive therapy in the chronic management of urea cycle disorders	Tablet, Granule 500 mg, 940 mg/g 4 Presentations	30.01.98 29.07.99 189 Days 481 Days	08.09.99 08.12.99
Tikosyn dofetilide Part B	Pfizer Ltd USA	C01BD04 Antiarrhythmic agent	Hard capsule 125 µg, 250 µg. 500 µg 15 Presentations	27.03.98 29.07.99 179 Days 333 Days	09.09.99 29.11.99
Thyrogen thyrotropin alfa Part A	Genzyme B.V NL	V04CJ01 Detection of thyroid cancer	Powder for solution for injection 0.9 mg 2 Presentations	19.12.97 29.07.99 208 Days 373 Days	01.09.99
Tractocile atosiban Part B	Ferring AB SE	not yet available Preterm birth	Solution for injection, Concentrate for solution for infusion 7.5 mg/ml 2 Presentations	24.07.98 23.09.99 186 Days 234 Days	25.10.99
Renagel sevelamer Part B	Genzyme B.V NL	V03AE02 Control of hyperphosphataemia in adult patients on haemodialysis	Hard capsule 403 mg 4 Presentations	24.07.98 23.09.98 199 Days 213 Days	29.10.99

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Alfatronol interferon alpha-2b Part A	SP Europe USA	L03AB05 Treatment of chronic hepatitis B and C, Hairy Cell Leukaemia, chronic Myelogenous Leukaemia, Multiple Myeloma, Follicular Lymphoma, Carcinoid Tumors and Malignant Melanoma	Powder and solvent for solution for injection, Solution for injection 1 MIU/ml, 3 MIU/ml, 5 MIU/ml, 6 MIU/ml 10 MIU/ml, 15 MIU/ml 18 MIU/ml, 25 MIU/ml 30 MIU/ml, 50 MIU/ml 39 Presentations	26.03.99 21.10.99 108 Days 98 Days	13.12.99
Virtron interferon alpha-2b Part A	SP Europe USA	L03AB05 Treatment of chronic hepatitis B and C	Powder and solvent for solution for injection, Solution for injection 1 MIU/ml, 3 MIU/ml, 5 MIU/ml, 6 MIU/ml 10 MIU/ml, 15 MIU/ml 25 MIU/ml, 30 MIU/ml 37 Presentations	26.03.99 21.10.99 108 Days 98 Days	13.12.99
Zyprexa Velotab olanzapine Part B	Eli Lilly USA	NO5AH03 Antipsychotic	Orodispersible tablet 5 mg, 10 mg, 15 mg, 20 mg 4 Presentations	23.4.99 21.10.99 117 Days 63 Days	22.11.99
Enbrel etanercept Part A	Wyeth Europa Ltd USA	L04AA11 Treatment of active rheumatoid arthritis	Powder and solvent for solution for injection 25 mg 1 Presentation	20.11.98 18.11.99 213 Days 146 Days	29.11.99
Azopt brinzolamide Part B	Alcon Laboratories Ltd USA	S01EC Treatment of elevated intraocular pressure in ocular hypertension and open-angle glaucoma	Eye drops, Suspension 10 mg/ml 2 Presentations	18.12.98 18.11.99 178 Days 154 Days	07.01.00

Annex 8: CVMP opinions in 1999 on medicinal products for veterinary use

Centralised applications

Product - Brandname - INN - Part A/B	**Company** - Name - Origin	**Therapeutic area** - ATC - Indication	**Presentation** - Form - Dosage - Number of presentations	**EMEA/CPMP** - Validation - Opinion - Active time - Clock stop	**Commission** - Opinion received - Date of Decision - Notification - Official Journal
Econor Valnemulin Part B	Novartis UK	Pigs Prevention and treatment of dysentery and treatment and control of enzootic pneumonia	50% microgranules/ 1% and 10% premix various 7	18.06.97 14.10.98 210 days 274 days	13.11.98 12.03.99 16.03.99 OJ No. C 84 of 26.03.99
Quadrisol Vedaprofen Part B extension	Intervet International NL	Dogs Control of inflammation	Gel 5mg/ml 2	12.11.97 14.10.98 210 days 126 days	13.11.98 15.02.99 24.02.99 OJ No. C 84 of 26.03.99
Locatim (previously Serinucoli) Oral colostrum based immuno-globin Part A	Biokema EEA	Calves Colostrum based immunoglobin	Oral solution 60 ml 1	18.06.97 09.12.98 209 days 330 days	11.01.99 29.03.99 28.04.99 OJ No. C 148 of 28.05.99
HESKA PERIOceutic Doxycycline Part B	Heska USA	Dogs Periodontal disease	Solution - 2	11.03.98 12.05.99 182 days 281 days	11.06.99 15.09.99 23.09.99 OJ No. C 311 of 29.10.99
Halocur Halofuginone Part B	Hoechst Roussel Vet FR	Bovine Crypto-sporidiosis in calves	Oral solution 0.05g/100ml 1	10.12.96 16.06.99 210 days 708 days	16.07.99 29.10.99 09.11.99 OJ No. C 339 of 26.11.99
Dicural Difloxacin Part B extension	Fort Dodge Animal Health NL	Dogs Antibacterial for systematic use	Coated tablets 15, 50, 100 & 150mg 1	03.03.98 14.07.99 183 days 316 days	13.08.99 16.11.99
Quadrisol Vedaprofen Part B extension	Intervet International NL	Horses Relief of pain associated with colic	Solution for injection 50mg/ml 1	12.11.97 14.07.99 204 days 407 days	13.08.99 16.11.99
Oxyglobin Haemoglobin Part B	Biopure Corporation USA	Dogs Anaemia	Intravenous infusion 130mg/ml 1	12.05.98 14.07.99 210 days 218 days	13.08.99
Eurifel Live vaccine Part A	Merial FR	Cats Vaccine against feline leukaemis	Pellet and diluent 1mg 3	12.01.99 08.12.99 182 days 120 days	
Rabigen SAG2 Live vaccine Part A	Virbac FR	Foxes Vaccine against rabies	Liquid within a blister pack Live attenuated SAG2 strain, minimum of $8\log_{10}$CCID50* per dose 3	23.03.99 08.12.99 196 days 428 days	
Incurin Oestriol Part B	Intervet International NL	Dogs Hormone dependent urinary incontinence	Scored tablets 1mg 1	14.07.99 08.12.99 210 days 302 days	

Establishment of Maximum residue limits for new substances

Substance - INN	**Therapeutic area** - Target species	**EMEA/CVMP** - Validation - Opinion - Active time - Clockstop	**Commission** - Sent to Commission - Date of Regulation - Official Journal
Thiamphenicol (extension)	Porcine, Ovine, Fish, Turkeys	15.05.98 09.09.98 117 days 0	08.10.98 16.04.99 OJ No. L 102 of 17.04.99
Cefquinome (extension)	Porcine	14.05.97 08.04.98 188 days 141 days	08.05.98 05.05.99 OJ No. L 118 of 06.05.99
Cypermethrin (extension)	Fish	29.07.96 06.05.98 162 days 483 days	05.06.98 05.05.99 OJ No. L 118 of 06.05.99
Carazolol (extension)	Bovine	12.06.96 06.05.98 185 days 507 days	05.06.98 05.05.99 OJ No. L 118 of 06.05.99
Danofloxacin (extension)	Porcine	25.07.97 10.06.98 183 days 137 days	10.07.98 05.05.99 OJ No. L 118 of 06.05.99
Praziquantel (extension)	Sheep milk	14.07.98 11.11.98 120 days 0	10.12.98 11.05.99 OJ No. L 122 of 12.05.99
Difloxacin (extension)	Bovine & Porcine	14.07.98 11.11.98 120 days 0	10.12.98 11.05.99 OJ No. L 122 of 12.05.99
Diflubenzuron	Salmonidae	23.03.98 11.11.98 107 days 0	10.12.98 11.05.99 OJ No. L 122 of 12.05.99
Halofuginone	Bovine	10.12.96 11.11.98 197 days 505 days	10.12.98 11.05.99 OJ No. L 122 of 12.05.99
Danofloxacin (extension)	Bovine	19.05.98 09.12.98 113 days 0	08.01.99 11.05.99 OJ No. L 122 of 12.05.99
Emamectin	Fish	18.05.98 13.01.99 200 days 40 days	12.02.99 09.09.99 OJ No. L 240 of 10.09.99
Teflubenzuron	Fish	20.01.97 13.01.99 79 days 510 days	12.02.99 09.09.99 OJ No. L 240 of 10.09.99
Cefquinome (extension)	Porcine	14.05.97 13.01.99 69 days 352 days	12.02.99 09.09.99 OJ No. 240 of 10.09.99

Substance - INN	**Therapeutic area** - Target species	**EMEA/CVMP** - Validation - Opinion - Active time - Clockstop	**Commission** - Sent to Commission - Date of Regulation - Official Journal
Florfenicol (extension)	Porcine	15.12.98 14.04.99 120 days 0	12.05.99 10.09.99 OJ No. L 241 of 11.09.99
Moxidectin (extension)	Equidae	09.04.07 14.04.99 174 days 561 days	12.05.99 10.09.99 OJ No. L 241 of 11.09.99
Danofloxacin (extension)	Pigs	25.07.97 14.04.99 241 days 387 days	12.05.99 10.09.99 OJ No. L 241 of 11.09.99
Eprinomectin (modification)	Bovine	19.06.98 14.10.98 114 days 0	13.11.98 10.09.99 OJ No. L 241 of 11.09.99
Dicyclanil	Ovine	25.02.97 17.02.99 191 days 797 days	12.03.99 11.11.99 OJ No. L 290 of 12.11.99
Tosylchloramide sodium	Fin fish	20.10.98 17.02.99 103 days 0	12.03.99 10.11.99 OJ No. L 288 of 11.11.99
Meloxicam	Bovine	28.03.96 17.02.99 301 days 755 days	12.03.99 11.11.99 OJ No. L 290 of 12.11.99
Amitraz (extension)	Bees	12.03.97 17.02.99 200 days 507 days	12.03.99 11.11.99 OJ No. L 290 of 12.11.99
Flubendazole (extension)	Turkey	17.11.98 17.03.99 120 days 0	13.04.99 10.11.99 OJ No. L 288 of 11.11.99
Florfenicol (extension)	Chicken	17.11.98 17.03.99 120 days 0	13.04.99 10.11.99 OJ No. L 288 of 11.11.99
Spiramycin (extension)	Porcine	22.02.99 16.06.99 114 days 0	15.07.99 08.12.99 OJ No. L 315 of 09.12.99
Diflubenzuron	Atlantic salmon	23.03.98 16.06.99 185 days 265 days	15.07.99 08.12.99 OJ No. L 315 of 09.12.99
Toltrazuril (extension)	Porcine	16.02.99 16.06.99 120 days 0	15.07.99 08.12.99 OJ No. L 315 of 09.12.99

Substance - INN	**Therapeutic area** - Target species	**EMEA/CVMP** - Validation - Opinion - Active time - Clockstop	**Commission** - Sent to Commission - Date of Regulation - Official Journal
Tilmicosin (extension)	Bovine milk	22.02.99 16.06.99 114 days 0	15.07.99 08.12.99 OJ No. L 315 of 09.12.99
Carazolol (extension)	Bovine	12.06.96 14.04.99 270 days 884 days	12.05.99 - -
N-Methyl-pyrrolidone	Bovine, Swine & Ovine	12.01.99 12.05.99 112 days 0	10.06.99 - -
Meloxicam (modification)	Bovine	16.03.99 14.07.99 120 days 0	12.08.99 - -
Meloxicam (extension)	Milk	16.03.99 14.07.99 120 days 0	12.08.99 - -
Bismuth Subnitrate (extension)	Bovine	18.06.99 13.10.99 113 days 0	12.11.99 - -
Tilmicosin (extension)	Rabbits	16.07.99 13.10.99 86 days 0	12.11.99 - -
Flumequin (extension)	Bovine milk & Turkeys	27.07.99 10.11.99 89 days 0	09.12.99 - -
Rafoxanide	Bovine & Ovine	11.02.97 14.07.99 193 days 690 days	12.08.99 - -
Doramectin (extension)	Reindeer	11.12.97 14.07.99 203 days 377 days	12.08.99 - -
Abamectin (modification)	Ovine	23.04.99 18.08.99 115 days 0	31.08.99 - -
Acetyl isovaleryl tylosin tartrate	Porcine	18.10.95 13.10.99 195 days 1247 days	12.11.99 - -
Methylprednisolone	Bovine	13.07.99 13.10.99 92 days 0	12.11.99 - -

Annex 9: EMEA guidelines in 1999

CPMP Biotechnology Working Party

Reference number	Guidelines	Status
CPMP/BWP/1230/98 Rev.	Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products	*Adopted in April 1999*
CPMP/BWP/328/99	Annex of development pharmaceuticals for biologicals	*Released for consultation in March 1999*
CPMP/BWP/305/99	Explanatory Note: The expiry date of products incorporating plasma-derived products as stabilisers or excipients: Addendum to Note for guidance on plasma-derived medicinal products	*Released for consultation in March 1999*
CPMP/BWP/3088/99	Revision of Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer material products	*Released for consultation in December 1999*

CPMP Blood and Plasma Working Group

Reference number	Guidelines	Status
CPMP/BPWG/575/99	Clinical investigation of human anti-D immunoglobulin and human anti-D immunoglobulin for intravenous use	*Released for consultation in June 1999*
CPMP/BPWG/388/95 rev. 1	Clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)	*Released for consultation in June 1999*
CPMP/BPWG/198/95 rev. 1	Clinical investigation of plasma derived factor VIII and IX products	*Released for consultation in June 1999*
CPMP/BPWG/1561/99	Clinical investigation of recombinant factor VIII and IX products	*Released for consultation in June 1999*
CPMP/BPWG/574/99	Core SPC for human anti-D immunoglobulin and human anti-D immunoglobulin for intravenous use	*Released for consultation in June 1999*
CPMP/BPWG/859/95 rev. 1	Core SPC for human normal immunoglobulin for intravenous administration (IVIg)	*Released for consultation in June 1999*
CPMP/BPWG/1619/99	Core SPC for human plasma derived and recombinant coagulation factor VIII products	*Released for consultation in June 1999*
CPMP/BPWG/1625/99	Core SPC for human plasma derived and recombinant coagulation factor IX products	*Released for consultation in June 1999*
CPMP/PhVWP/BPWG/2231/99	Core SPC for human albumin	*Released for consultation in December 1999*

CPMP Efficacy Working Party

Reference number	Points to consider	Status
CPMP/EWP/863/98	Helicobacter pylori eradication therapy wording in selected SPC sections	*Adopted in September 1999*
CPMP/EWP/707/98	Clinical investigation of medicinal products for prophylactic management of intra- and post-operative venous thrombo-embolic risk	*Released for consultation in February 1999*
CPMP/EWP/570/98	Clinical investigation of medicinal products for treatment of unstable angina pectoris (UAP) or non-Q-wave myocardial infarction	*Released for consultation in February 1999*
CPMP/EWP/197/99	Endpoints in clinical studies with haematopoietic growth factors for mobilisation of stemcells	*Released for consultation in July 1999*
CPMP/EWP/565/98	Clinical investigation of medicinal products for amyotrophic lateral sclerosis (ALS)	*Released for consultation in September 1999*
CPMP/EWP/482/99	Biostatistical/methodological issues: Superiority, non-inferiority and equivalence	*Released for consultation in September 1999*
CPMP/EWP/2655/99	Pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products	*Released for consultation in December 1999*
Reference number	Guidelines	Status
CPMP/EWP/463/97	Clinical investigation of new vaccines	*Adopted in May 1999*
CPMP/EWP/280/96	Modified release oral and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation)	*Adopted in July 1999*
CPMP/1697/98	Summary of Product Characteristics (SPC)	*Adopted in October 1999*
CPMP/EWP/235/98, rev. 1	Clinical investigation of medicinal products for treatment of cardiac failure	*Adopted in December 1999*
CPMP/EWP/563/98	Clinical investigation of medicinal products for treatment of venous thrombo-embolic disease	*Adopted in December 1999*
CPMP/EWP/519/97	Clinical investigation of steroid contraceptives in women	*Released for consultation in April 1999*
CPMP/ICH/364/96 (E10)	Choice of control group in clinical trials	*Released for consultation in June 1999*
CPMP/EWP/561/98	Clinical investigation of medicinal products for treatment of multiple sclerosis	*Released for consultation in July 1999*
CPMP/EWP/552/95, rev. 1	Involutional osteoporosis in women	*Released for consultation in September 1999*
CPMP/ICH/2711/99 (E11)	Clinical investigation of medicinal products in the paediatric population	*Released for consultation in October 1999*
CPMP/EWP/566/98	Clinical investigation of medicinal products for treatment of epileptic disorder	*Released for consultation in October 1999*
CPMP/ICH/2887/99	The Common Technical Document for the registration of pharmaceutical for human use - efficacy - table of content	*Released for consultation in November 1999*
CPMP/EWP/567/99	Clinical investigation of medicinal products for the treatment of bipolar disorder	*Released for consultation in December 1999*

CPMP Pharmacovigilance Working Party

Reference number	Guidelines	Status
CPMP/PhVWP/108/99 corr.	Notice to marketing authorisation holders (for inclusion in Volume 9 of the Rules Governing Medicinal Products for Human Use)	*Adopted in January 1999*
CPMP/PhVWP/175/95 Rev.1	Procedure for competent authorities on the undertaking of pharmacovigilance activities	*Adopted in February 1999*
CPMP/PhVWP/005/96 Rev. 1	Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in human pharmacovigilance	*Adopted in July 1999*
CxMP/PhVWP/2056/99	Electronic exchange of pharmacovigilance information for human and veterinary medicinal products in the European Union	*Adopted in July 1999*
CPMP/PhVWP/2058/99	Joint pilot plan for the implementation of the electronic transmission of individual case safety reports between the EMEA, national competent authorities and the pharmaceutical industry	*Adopted in July 1999*

CPMP Safety Working Party

Reference number	Guidelines	Status
CPMP/ICH/2887/99	The Common Technical Document for the registration of pharmaceutical for human use - safety - table of content	*Released for consultation in November 1999*
CPMP/SWP/1042/99	Revised Note for guidance on repeated dose toxicity	*Released for consultation in December 1999*

EMEA Working Party on Herbal Medicinal Products

Reference number	Draft proposals	Status
(EMEA/HMPWG/15/99)	Note for guidance on fixed combinations of herbal medicinal products with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data	*Revised in January 1999*

CVMP Efficacy Working Party

Reference number	Guidelines	Status
CVMP/VICH/839/99	Anthelmintics: Specific recommendations for bovines	*Adopted in December 1999*
CVMP/VICH/840/99	Anthelmintics: Specific recommendations for ovines	*Adopted in December 1999*
CVMP/VICH/841/99	Anthelmintics: Specific recommendations for caprines	*Adopted in December 1999*
CVMP/VICH/832/99	Efficacy on Anthelmintics: general requirements	*Adopted in December 1999*
EMEA/CVMP/133/99	Conduct of pharmacokinetic studies in animals	*Released for consultation in March 1999*
EMEA/CVMP/344/99	Conduct of efficacy studies for intramammary products for use in cattle	*Released for consultation in June 1999*

CVMP Efficacy Working Party, continued

Reference number	Guidelines	Status
CVMP/VICH/833/99	Efficacy on Anthelmintics: specific requirements for equines	*Released for consultation in December 1999*
CVMP/VICH/834/99	Efficacy on Anthelmintics: specific requirements for swine	*Released for consultation in December 1999*
CVMP/VICH/835/99	Efficacy on Anthelmintics: specific requirements for canine	*Released for consultation in December 1999*

CVMP Safety Working Party

Reference number	Guidelines	Status
EMEA/CVMP/276/99	Assessment of the effect of antimicrobial substances on dairy starter cultures	*Released for consultation in May 1999*

CVMP Pharmacovigilance Working Party

Reference number	Guidelines	Status
EMEA/CVMP/141/98	Revised rapid alert system in veterinary pharmacovigilance	*Adopted in February 1999*
EMEA/CVMP/143/99	Conduct of pharmacovigilance for veterinary medicinal products authorised through the mutual recognition procedure	*Adopted in March 1999*
EMEA/CVMP/345/98	Procedure for competent authorities for pharmacovigilance information of veterinary medicinal products	*Adopted in May 1999*
EMEA/CVMP/141/98-Rev.2	Revised rapid alert system and non-urgent information system in veterinary pharmacovigilance	*Adopted in August 1999*
EMEA/CVMP/143/99 -Rev.1	Conduct of pharmacovigilance for veterinary medicinal products authorised through the mutual recognition procedure	*Adopted in August 1999*
EMEA/CxMP/PhVWP/2056/99	Electronic exchange of pharmacovigilance information for human and veterinary medicinal products in the European Union	*Adopted in August 1999*
EMEA/CVMP/044/99	Conduct of post-marketing surveillance studies of veterinary medicinal products	*Released for consultation in February 1999*

CVMP Immunologicals Working Party

Reference number	Guidelines	Status
EMEA/CVMP/145/97-Revision	Minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products	*Adopted in June 1999*
EMEA/IWP/52/97	Requirements for combined veterinary vaccines	*Released for consultation in March 1999*
EMEA/CVMP/682/99	Duration of protection achieved by veterinary vaccines	*Released for consultation in October 1999*

Joint CPMP/CVMP Quality Working Party

Reference number	Document title	Status
CPMP/QWP/054/98	Annex to Note for guidance on development pharmaceutics (CPMP/QWP/155/96): Decision trees for selection of sterilisation methods	*Adopted in February 1999*
CPMP/QWP/8567/99	Explanatory note on the operation of two-year transition period for application of Note for guidance on residual solvents to marketed products	*Adopted in March 1999*
CPMP/QWP/604/96	Note For guidance on quality of modified release products: A. oral dosage forms; B. and transdermal dosage forms; Section I (Quality).	*Adopted in July 1999*
CPMP/ICH/367/96	Note for guidance on specifications - Test procedures and acceptance criteria for new drug substances and new drug products - chemical substances	*Adopted in November 1999*
CPMP/QWP/848/96 EMEA/CVMP/598/99	Note for guidance on process validation	*Released for consultation in September 1999*
CPMP/ICH/2736/99	Note for guidance on stability testing of new drug substances and products Step 2 document	*Released for consultation in November 1999*
CPMP/ICH/2737/99	Note for guidance on impurities testing: impurities in new drug substances	*Released for consultation in November 1999*
CPMP/ICH/2738/99	Draft Note For guidance on impurities in new medicinal products	*Released for consultation in November 1999*
CPMP/ICH/2887/99	The Common Technical Document for the registration of pharmaceutical for human use - quality - table of content	*Released for consultation in November 1999*
CVMP/004/98	Note for guidance: Excipients in the dossier for application for marketing authorisation for veterinary medicinal products	*Adopted in February 99*
CVMP/VICH/899/99	Stability testing guidelines: New drug substances and products	*Adopted in June 1999*
CVMP/VICH/900/99	Stability testing requirements for new dosage forms	*Adopted in June 1999*
CVMP/VICH/901/99	Guideline for the photostability testing of new drug substances and products	*Adopted in June 1999*
CVMP/315/98	Note for guidance on development pharmaceutics for veterinary medicinal products	*Adopted in August 1999*
CVMP/VICH/836/99	Stability testing for medicated premixes	*Adopted in December 1999*
CVMP/VICH/837/99	Impurities in new veterinary drug substances	*Adopted in December 1999*
CVMP/VICH/838/99	Impurities in new veterinary medicinal products	*Adopted in December 1999*
CVMP/065/99	Annex to Note for guidance: Development harmaceutics for veterinary medicinal products: Decision trees for the selection of sterilisation methods	*Released for consultation in February 1999*

Joint CPMP/CVMP Quality Working Party, continued

Reference number	Document title	Status
CVMP/198/99	Note for Guidance on the maximum shelf life for sterile veterinary medicinal products after first opening or following reconstitution	*Released for consultation in April 1999*
CVMP/VICH/502/99	Impurities: Residual solvents	*Released for consultation in June 1999*
CVMP/VICH/501/99	Stability testing of biotechnological/ biological veterinary medicinal products	*Released for consultation in June 1999*
CVMP/422/99	Note for guidance: Definition of storage conditions for veterinary pharmaceutical products in the product particulars	*Released for consultation in August 1999*
CVMP/846/99	Stability testing of existing active substances and related finished products	*Released for consultation in December 1999*

Ad hoc GMP and GCP Inspectors Working Groups

Reference number	Document title	Status
GMP EMEA/INS/GMP/546/98	Harmonised format for inspection reports for use by Community inspectorates	*Finalised and approved by the Pharmaceutical Committee*
GMP III/5643/98	Harmonised format for manufacturing authorisations for use by EU competent authorities	*Finalised and approved by the Pharmaceutical Committee*
GMP EMEA/T/4527/99	Guideline on responsibilities and enforcement measures in respect of verifying and ensuring GMP compliance	*Finalised in September 1999*
GMP III/5581/99	GMP Guide on validation master plan, design qualification, installation and operational qualification	*Released for consultation in October 1999*
GMP EMEA/INS/478/98	GMP Guide on certification by a qualified person and batch release of medicinal products	*Released for consultation in November 1999*