European Medicines Agency

EMEA/61492/2005/EN/Final

Tenth annual report of the

European Medicines Agency

2004

Adopted by the Management Board on 10 March 2005

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Contents

The annual report for 2004 is presented to the Management Board by the Executive Director in accordance with Article 64(3) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. It is forwarded to the European Parliament, Council, Commission and Member States. It is available in all official EU languages.

In accordance with the EMEA Financial Regulation, the Agency is required to publish an analysis and assessment of its annual activity report together with its annual report. The Agency will publish the required analysis and assessment on its website once it has been adopted by the Management Board.

Previous annual reports and other reference documents are available from the EMEA website:

www.emea.eu.int

This report covers activities of the EMEA in 2004. Chapter 1 sets out the activities of the EMEA within the European system. It includes the work of the Agency's Management Board, its partnership with national competent authorities and European institutions, and other general aspects of the EMEA, including transparency and the Agency's international activities.

The operational and technical work of the EMEA is reported in Chapter 2 on medicines for human use, Chapter 3 on veterinary medicines and Chapter 4 on inspection activities. Implementation of the EU telematics strategy, administration and other support activities are described in Chapters 5 and 6.

The report also summarises the operation of the decentralised (mutual recognition) procedure in accordance with Article 38(1) of Council Directive 2001/83/EC on the Community code relating to medicinal products for human use as amended by Directive 2004/27/EC and Article 42(1) of Council Directive 2001/82/EC as amended by Directive 2004/28/EC.

EMEA mission statement

The EMEA's Mission Statement is, in the context of a continuing globalisation, to protect and promote public and animal health by

developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription 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,

facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry, and

mobilising and coordinating scientific resources from throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programmes, to perform inspections for ensuring fundamental GXP provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals.

The European system offers two routes for authorisation of medicinal products. The EMEA plays a role in both procedures:

- The centralised procedure is compulsory for medicinal products derived from biotechnology and is available at the request of companies for other innovative new products. Applications are submitted directly to the EMEA. At the conclusion of the scientific evaluation, undertaken in 210 days within the Agency, the opinion of the scientific committee is transmitted to the European Commission to be transformed into a single market authorisation applying to the whole European Union.
- The decentralised procedure (or mutual recognition procedure) applies to the majority of conventional medicinal products and is based upon the principle of mutual recognition of national authorisations. It provides for the extension of marketing authorisations granted by one Member State to one or more other Member States identified by the applicant. Where the original national authorisation cannot be recognised, the points in dispute are submitted to the EMEA for arbitration. The opinion of the scientific committee is transmitted to the European Commission.

The European Commission adopts its decision with the assistance of a standing committee composed of representatives of the Member States.

Foreword by the Chairman of the Management Board

Hannes Wahlroos

I would like to begin by thanking the EMEA staff and scientific committees and working group members for the results achieved in 2004 in very challenging circumstances and at a time of many changes. I would also like to thank members of the Management Board for all the support given to me at the start of my Chairmanship in spring 2004. My particular thanks go to the Executive Director of the Agency and his staff for their support and cooperation on the work of the Management Board.

The year 2004 was the Agency's tenth year of operations. The past year also marked a milestone in the development of the EU pharmaceutical legislation and the enlargement of the EU.

The EU's revised pharmaceutical legislation and the expansion of the total number of Member States to 25 brought about changes to the composition of the Management Board. Every Member State now has one member on the Board. In addition to the members appointed by the European Commission and the European Parliament, the new Board will also have representatives from doctors' and patients' organisations. These new members had not yet been appointed by the end of the year. On behalf of the Management Board, therefore, I would like to extend a warm welcome to them in advance.

The EMEA Management Board's main duties are related to the management, monitoring and control of the Agency's operations and finances. In addition, the Board takes numerous decisions on Agency policies. In 2004, the Board approved the revised rules on access to EMEA documents and the EMEA Code of Conduct, which are binding on all who participate in the work of the Agency. Transparent and public rules of conduct reinforce the Agency's reliability in the eyes of the general public.

In 2004, the Management Board focused on the preparation of the EMEA Road Map to 2010. Following the approval of this long-term strategy in December 2004, the Agency's operations now and over the next few years will centre on its implementation. In this context, I would like to draw attention to an important issue in the Road Map, which will further improve the interests of EU citizens and patients by means of medicines control: the reinforcement of pharmacovigilance coordination.

The unexpected withdrawal of certain medicinal products last year demonstrates in a concrete way how vulnerable EU pharmacovigilance efforts still are. It is essential to improve EMEA coordination on the collection and evaluation of adverse effects data for medicinal products. It is also important to strengthen pharmacoepidemiological research in individual Member States and at EU level. Existing healthcare databases in Member States should also be used for pharmacovigilance purposes. In my capacity as Chairman of the Management Board, I have noticed that Member States have a strong will to implement these goals.

The EMEA's ten years of operations have proven that both EU citizens and the pharmaceutical industry benefit from centralised medicines control and supervision. This allows innovations of the pharmaceutical industry to reach healthcare services and patients in the EU market faster than before. I am confident that the next ten-year period will also prove to be a successful one for European cooperation.

Introduction by the Executive Director

Thomas Lönngren

In a year which saw the adoption of four important new pieces of EU pharmaceutical legislation as well as the single biggest expansion of the European Union in its history, the year 2004 was one characterised by change. It is, therefore, quite fitting that it was also the year in which the European Agency for the Evaluation of Medicinal Products changed its name to the European Medicines Agency.

I am pleased to report that the integration of the 10 new Member States into the European regulatory network was successful beyond all expectations – thanks to excellent preparatory work conducted in the years leading up to the EU enlargement. And while the growth of the European network to 28 EEA-EFTA countries, 42 national competent authorities and a pool of over 3 500 national experts certainly placed increased pressure on the EMEA in its role as coordinator, the Agency was able to cope without any major difficulty.

As a result of the enlargement and the new legislation, the Agency underwent some significant structural changes: the composition of the Management Board was amended to accommodate the new Member State representatives and the Agency's fourth scientific committee – the Committee on Herbal Medicinal Products (HMPC) – was created.

Management changes in 2004 included the implementation of an integrated management policy for the Agency, the extension of internal audits to include the functioning of the scientific committees, and the establishment of an Audit Advisory Committee. A major step towards improving the quality of the EU regulatory network as a whole was the agreement between the heads of regulatory agencies to introduce an EU benchmarking system.

On the international stage, there were two significant developments. Firstly, the conclusion and implementation of a confidentiality arrangement with the US Food and Drug Administration (FDA) creates enhanced cooperation between the two agencies, particularly on the provision of parallel scientific advice to companies developing new medicines. Secondly, a new legislative tool entered into force allowing the EMEA, in cooperation with the World Health Organization (WHO), to assess medicines for third-world countries.

As regards core operations, 2004 was an extremely active year for the EMEA. The volume of applications for scientific assessment of medicinal products for human use was substantially higher than in 2003, with 21 more applications for orphan medicine designation, 25 more requests for scientific advice and protocol assistance, 12 more applications for initial marketing evaluation, 8 more opinions on initial marketing evaluation, and 61 more post-authorisation opinions. The workload relating to medicinal products for veterinary use fell somewhat in comparison to 2003 but was, nonetheless, also substantial.

Overall performance for the year was very good, with regulatory timelines being met in almost all areas of activity. There were very few deviations from planned results, one notable exception being the slow implementation of EudraVigilance by Member States.

The safety of medicines was once again in the spotlight in 2004, with two major classes of nationally authorised medicinal products causing serious public concern – COX-2s and SSRIs – both of which the EMEA conducted safety reviews of. The safety of medicines is always a primary concern of the Agency, and work was begun in 2004 on developing a risk management strategy with the heads of

European medicines agencies, which, together with new legislative tools to strengthen safety controls, should yield improvements in this vitally important area.

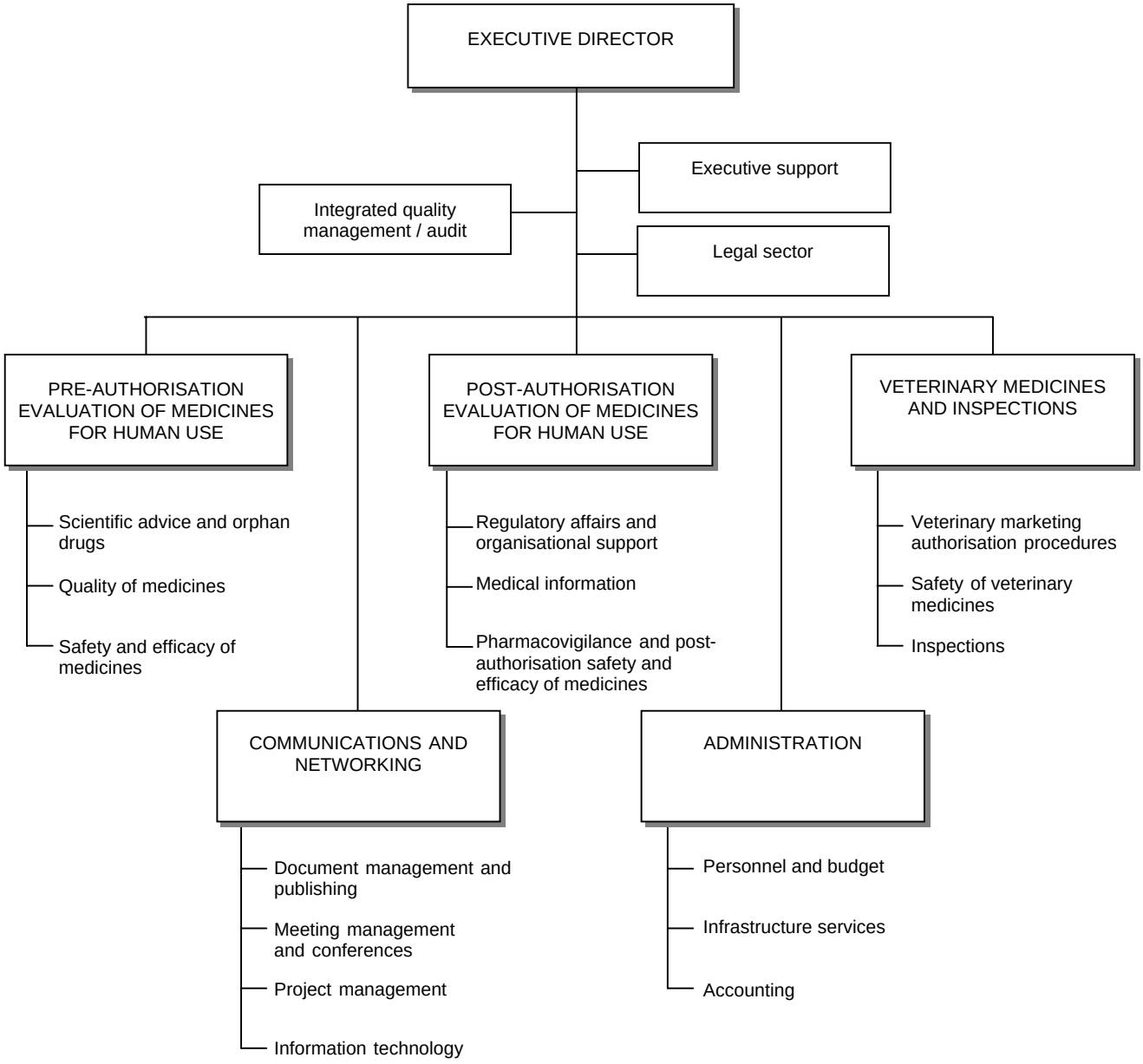
Another perennial focus area for the Agency is the availability of medicines for European citizens. By providing scientific advice, the Agency helps companies to research and develop new medicines and to further their scientific exploration in areas such as emerging therapies. In 2004, the provision of scientific advice and protocol assistance was up by approximately 25 % in comparison to 2003.

The EU enlargement, new scientific committee and new responsibilities of the EMEA arising from the parts of the new legislation that entered into force in 2004 generated a huge increase in the number of delegates and visitors coming to the Agency. Interaction with stakeholders – especially patients' organisations – was extensive during 2004. Good relations were maintained with Industry, academia and other stakeholders, while cooperation with and support from the European Commission and Parliament were also extremely good. As in previous years, the scientific support given to the EMEA by the national competent authorities was excellent. The engaged involvement and intensive cooperation of so many partners, stakeholders and other interested parties contributed greatly to the success of the Agency's operations in 2004.

Much effort was devoted in 2004 to the establishment of a long-term vision and implementation strategy for the Agency. The resulting EMEA Road Map to 2010 sets out a clear strategy for implementing the provisions of the revised legislation and also establishes a series of concrete actions the Agency and its partners can take to further strengthen the regulation of medicines in Europe, for the benefit of all its citizens.

In brief, 2004 was a year of change, a year of hard work, but also a year of significant achievement. My deepest personal thanks go to all of the Agency's staff and to all those in the European network who contributed to this, the 10th successful year of operation of the EMEA.

Structure of the EMEA



1 EMEA in the European system

1.1 Management Board

The composition of the Management Board changed in May 2004 with the entry into force of Regulation (EC) No 726/2004[1]. The Board now has one representative per Member State (and no longer two), two representatives of the European Parliament, two representatives of the European Commission and, for the first time, two representatives of patients' organisations and one representative each of doctors' and veterinarians' organisations.

The Management Board met for the first time in its new configuration on 24 May 2004 at an extraordinary meeting. The Board elected Hannes Wahlroos as its chairman and re-elected Jytte Lyngvig as vice-chairman. In line with its new responsibilities, the Board was consulted on the nominations for the Agency's Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP).

The Board discussed matters relating to the new pharmaceutical legislation and its impact on the role and operations of the Agency, as well as the 'European Medicines Agency Road Map to 2010' long-term strategy. The Board heard regular progress reports on the EU telematics strategy.

The Management Board met 5 times in 2004:

11 March 2004

- Approved the 'European Medicines Agency Road Map to 2010' consultation paper for release for public consultation
- Adopted new policy on the handling of declarations of interests, and agreed to the publication of the declarations of interests of scientific committee members on the EMEA website

24 May 2004 — Extraordinary meeting

- Elected Hannes Wahlroos (Finland) as chairman of the Board and re-elected Jytte Lyngvig (Denmark) as vice-chairman
- Approved nominations from Member States for new composition of the CHMP and CVMP

10 June 2004

- Adopted new financial regulation and implementing rules for the Agency
- Approved a proposal to publish the name of active substances, orphan condition and name of sponsor for all designated orphan drugs submitted for marketing authorisation

[1] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

30 September 2004

- Discussed large number of contributions received from patients' and healthcare professionals' groups, the pharmaceutical industry, national competent authorities, national health ministries, European institutions and others as part of the 'Road Map to 2010' consultation process

- Revised the rules on public access to EMEA documents

16 December 2004

- Endorsed the 'Road Map to 2010' long-term strategy

- Adopted 2005 work programme and budget totalling € 110 160 000, together with an establishment plan requesting 379 temporary-agent posts for 2005

1.2 Implementation of the review of the European system

Following a comprehensive review of the EU's pharmaceutical legislative framework, which started in July 2001, the new European pharmaceutical legislation was published in the Official Journal of the European Union on 30 April 2004.

The new legislative framework consists of:

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

- Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products.

- Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

Title IV of the new Regulation entered into force on 20 May 2004. The remaining provisions will come into force 18 months later, on 20 November 2005. The revised legislative package has significant impact on the Agency. It introduces new responsibilities and a new administrative structure for the Agency.

Elements of the new legislation which came into force in 2004 include:

- Change to the name of the Agency: The EMEA changed its official title from 'European Agency for the Evaluation of Medicinal Products' to 'European Medicines Agency'

- Change to the composition of the Management Board, CHMP and CVMP
- Creation of scientific advisory groups to assist the committees in their work
- Creation of a new EMEA scientific committee: the Committee on Herbal Medicinal Products (HMPC)
- Reinforced role for the Agency in the provision of scientific advice to companies
- Provision for the CHMP to give scientific opinions in the context of cooperation with the WHO for the use of medicines outside the EU

Preparations started for the full application of all provisions by 20 November 2005. Important areas of the remaining provisions include: the implementation of conditional marketing authorisation and accelerated review procedures for the authorisation of medicinal products; expanded scope of the centralised procedure to include mandatory application to the EMEA for evaluation of medicinal products for HIV/AIDS, cancer, neurodegenerative diseases and diabetes; new pharmacovigilance and surveillance tools to increase the safety of medicines; greater emphasis on transparency, communication and the provision of information.

1.3 A long-term strategy for the EMEA

At the beginning of 2004, the EMEA launched an exercise to create a new long-term strategy for the Agency that would contribute to better protection and promotion of public and animal health, improve the regulatory environment for medicinal products, and help to stimulate innovation, research and development in the EU.

In April, the EMEA released for public consultation a discussion paper entitled 'The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future'.

The three-month consultation period that followed generated feedback from some 65 contributors, including EU institutions, national health authorities, patients' groups, professional healthcare organisations, pharmaceutical companies, trade associations, academics and other interested parties. The comments received were taken into account in the final, revised version of the Road Map, which was approved by the EMEA Management Board in December 2004.

Involving its partners and stakeholders in this consultation process allowed the EMEA to achieve a broad consensus on the best way forward for the Agency in an operating environment characterised by significant political, institutional, legislative and scientific developments.

The resulting long-term strategy is one that takes a realistic view of the challenges facing the Agency and the EU regulatory system as a whole, while offering viable proposals as to how those challenges can be met.

By implementing the detailed actions set out in the Road Map – beginning in 2005 – the Agency will be working to maintain and further strengthen its position as a regulatory authority that is public-health oriented, science-driven, transparent in the way it operates, and committed to applying good administrative practices.

The ultimate objective of the Road Map exercise is to ensure that, building on the achievements of its first 10 years, the EMEA adequately prepares the ground for further success in the future.

1.4 European medicines network

Useful websites:	
Heads of Medicines Agencies–Human	*http://heads.medagencies.org*
Heads of Medicines Agencies–Veterinary	*http://www.hevra.org*
European product index (mutual recognition procedure)	*http://heads.medagencies.com/mrindex/index.html*

The EMEA operates in partnership with the national competent authorities for human and veterinary medicinal products in the Member States and the EEA-EFTA countries Iceland, Liechtenstein and Norway. The authorities make scientific resources available in the form of a network of more than 3 500 European experts who assist the Agency in the performance of its scientific tasks.

The EU enlargement in May 2004, with the accession of 10 new Member States, had a significant impact on the EU, its institutions and agencies. The network within which the EMEA operates increased from 27 to 42 national competent authorities. With the additional national competent authorities of the new Member States and a larger number of European experts, the EMEA is now required to operate in and manage an increasingly complex system. This has been addressed by the Road Map, in which proposals have been made concerning the future cooperation of the network.

The EMEA compensates the national competent authorities for the provision of scientific services. In 2004, total compensation was € 32 233 000 — about one third of the Agency's total budget.

In 2004, work continued towards establishing common costing methodologies for calculating the cost of scientific services provided by the national competent authorities to the EMEA.

With a view to ensuring the quality and consistency of regulatory practices, a benchmarking exercise based on ISO 9004:2000 was started in 2004, involving the EMEA and national competent authorities. The aim of this benchmarking system is to contribute to the development of a world-class regulatory system for medicinal products, based on a network of agencies operating to best-practice standards.

The EMEA participated in all meetings of the Heads of Medicines Agencies organised during the Irish and Dutch EU presidencies in 2004. Topics included risk management strategies, pharmacovigilance and the implementation of the European telematics strategy.

1.5 Transparency and communication

EMEA general information service:	*info@emea.eu.int*

The Agency continually reviews its transparency policy with a view to increasing access to information and improving understanding of how it operates.

The Management Board adopted new rules on access to EMEA documents at its March 2004 meeting. Similar rules were adopted by all EU agencies to bring them in line with other EU institutions. The new rules clarify procedures relating to the release of documents originating from a third party and

allocate responsibility for the handling of confirmatory applications[1] specifically to the Executive Director.

A new policy and procedure on the handling of conflicts of interests of scientific committee members and experts was adopted in March 2004. As part of this, the Board and committees agreed to the publication of the declarations of interests of the members of the Agency's scientific committees on the EMEA website.

The EMEA Code of Conduct was revised in 2004 in order to clarify the meaning of some sections. The code ensures that a consistent standard of professional conduct applies to all parties associated with the EMEA's work and responsibilities. The code provides specific guidance on conflicts of interests and the declaration of those interests, on confidentiality and discretion, and on good administrative practices.

In 2004, the Agency began to implement a series of transparency policy measures adopted by the Management Board in October 2003. Good progress was made on 8 of the 12 sets of recommendations proposed; most notably, the EMEA began publishing 'question and answer' documents for patients, healthcare professionals, the general public and the media relating to situations where there are public health concerns. The Agency also began, in July 2004, publishing the name of the active substance (international non-proprietary name, or INN), the orphan condition and the name of the sponsor for all designated orphan drugs submitted for marketing authorisation, in order to improve transparency with regard to orphan medicinal products.

A further outcome of the review on transparency policy measures was the development of a 'Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework'. The paper was released for external consultation in September 2004 and aims at putting in place a transparent process for the development, consultation, finalisation and implementation of pharmaceutical guidelines.

The EMEA is actively engaged in a dialogue with its stakeholders, i.e. patients, healthcare professionals, academia, learned societies and the pharmaceutical industry.

The Agency consulted with its stakeholders on a number of issues during 2004. It held a public consultation exercise relating to the EMEA Road Map to 2010 discussion paper and a consultation on recommendations for better provision of information to patients. The EMEA/CHMP Working Party with Patients' Organisations reviewed the comments and contributions received following the release for consultation of the paper 'Recommendations and proposals for action' (CPMP/5819/04) in April 2004. The outcome of the consultation exercise was discussed during a workshop held at the EMEA in December 2004.

[1] Applications to the EMEA which request that its refusal of an initial application for access to documents be reconsidered.

1.6 EU institutions, agencies and international partners

Useful websites:	
International Conference on Harmonisation	*http://www.ich.org*
International Cooperation on Harmonisation (Veterinary)	*http://vich.eudra.org*
World Health Organization	*http://www.who.int*

The EMEA cooperates closely with other scientific and regulatory institutions and agencies in the public health arena at European Union level. The Agency also contributes to, and participates in, a number of multilateral forums, and has close relations with a number of non-EU competent authorities.

EU institutions and other agencies

The primary institutional partner of the EMEA is the European Commission, in particular the Directorate-General for Enterprise and Industry. The EMEA also works closely with the Directorates-General for Health and Consumer Protection and for Research.

During 2004, the EMEA participated in all meetings of the Commission's Pharmaceutical Committees for human and veterinary medicines and of the working groups established by the Pharmaceutical Committees.

The EMEA continued its interaction with the European Parliament, in particular with the Committee on the Environment, Public Health and Food Safety. The Executive Director answered questions of the Committee members during the annual hearing in November 2004.

In addition to its ongoing work with the Commission services in 2004, the EMEA cooperated with other EU agencies, most notably the European Food Safety Authority (EFSA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). First contacts were established during 2004 with the new European Centre for Disease Prevention and Control (ECDC).

International partners

The Agency remained committed to and participated in the two international conferences on harmonisation of technical requirements for the registration of human and veterinary pharmaceuticals (ICH and VICH respectively) in 2004.

Cooperation between the EMEA and the World Health Organization (WHO) was strengthened during 2004. EMEA and WHO representatives participated in each other's meetings to discuss matters of global significance, such as tropical diseases, influenza pandemics, pharmacovigilance and consultations on international non-proprietary names (INNs). In addition, the EMEA participated in the eleventh International Conference of Drug Regulatory Authorities (ICDRA), in Madrid. The ICDRA promotes worldwide collaboration between regulatory authorities for medicinal products.

The Agency also participated in international activities of the Codex Alimentarius, the World Organisation for Animal Health (OIE) and the European Directorate for the Quality of Medicines (EDQM)/European Pharmacopoeia.

EU-US FDA confidentiality arrangements

Bilateral relations with non-EU competent authorities also continued in 2004, in particular with regard to the implementation of the EU-US FDA confidentiality arrangements signed by the European Commission, EMEA and FDA in September 2003.

The implementation plan for the confidentiality arrangement, detailing the information and documents the two agencies will exchange and the process for monitoring the implementation of the plan itself, was published in October 2004.

A key part of the plan is a pilot programme under which companies can request parallel scientific advice from the two agencies. The programme focuses primarily on important breakthrough drugs, and includes a mechanism for the EMEA, FDA and companies to exchange views on scientific issues during the development phase of new medicinal products.

1.7 Corporate governance – Integrated management system

Management and internal control systems are part of EMEA corporate governance and are consolidated in an integrated management system at the EMEA.

The control framework of the Agency changed significantly with the adoption of the new EMEA quality policy and new internal control standards. The Management Board adopted the EMEA quality policy in March 2004, with a revision in June 2004. The policy aims to assist the effective planning, operation and control of processes within the Agency, and to continually improve its interaction with partners in the European network.

New internal control standards were adopted in December 2004. The standards define the management rules all services must follow in their management of resources. They are intended to guarantee a consistent level of internal control of all business activities throughout the Agency, whether their financial impact is direct or indirect.

The Internal Audit Function of the Agency was formalised in 2004. It has an advisory function for integrated quality management at the Agency. It also ensures the Agency's risk management and liaises with the European Commission's Internal Audit Service.

A provisional Audit Advisory Committee was established in September 2004 with a number of external and internal members. The task of the Committee is to advise the Executive Director on the outcome of audit reports issued by the Court of Auditors, the Internal Audit Service of the European Commission, the IQM/Audit function of the Agency and any other external audit organisation.

The programme of internal audits continued in 2004, including audits of the Committee for Medicinal Products for Human Use, the Committee for Medicinal Products for Veterinary Use and the Committee on Orphan Medicinal Products. In addition, a management audit based on ISO 9004:2000 was conducted.

1.8 Organisational changes to the Agency

The internal structures of the EMEA were reorganised in 2004 with the creation of three horizontal services reporting to the Executive Director: an Executive Support Sector, a Legal Affairs Sector and the formalisation of the Integrated Quality Management/Internal Audit Function (see above).

The Executive Support Sector addresses, in particular, the need for improved relations with external partners and the provision of support for the Agency's management activities.

The Legal Affairs Sector brings together the legal resources of the Agency into one specialised group in response to the increasing demand for legal services.

The new EU pharmaceutical legislation gives the Agency a greater mandate for the provision of information to patients and healthcare professionals. In light of this, the EMEA created a new Sector for Medical Information. The new sector is responsible for the provision of information that is easily understandable and accessible for patients and healthcare professionals.

2 Medicines for human use

Overview

Unit for the pre-authorisation evaluation of medicines for human use

Head of Unit	Patrick LE COURTOIS
Head of Sector for scientific advice and orphan drugs	Agnès SAINT-RAYMOND
Acting Deputy Head of Sector for scientific advice and orphan drugs	Spiros VAMVAKAS (from mid-October 2004)
Head of Sector for quality of medicines	John PURVES
Head of Sector for safety and efficacy of medicines	Isabelle MOULON (until mid-October 2004)
Acting Head of Sector for safety and efficacy of medicines	Agnès SAINT-RAYMOND (from mid-October 2004)
Deputy Head of Sector for safety and efficacy of medicines	Marisa PAPALUCA AMATI

Unit for the post-authorisation evaluation of medicines for human use

Head of Unit	Noël WATHION
Head of Sector for regulatory affairs and organisational support	Tony HUMPHREYS
Head of Sector for pharmacovigilance and post-authorisation safety and efficacy of medicines	Panos TSINTIS
Deputy Head of Sector for pharmacovigilance and post-authorisation safety and efficacy of medicines	Sabine BROSCH
Head of Sector for medical information	Isabelle MOULON

See Annexes 2, 4 and 5 for members of committees, working parties and ad hoc groups.

Medicines for human use – Highlights in 2004

- The new EU Member States were successfully integrated in the scientific committees dealing with medicines for human use and in the activities of the Agency. Support was provided through scientific and regulatory training for committee members, experts and assessors.

- The organisational and structural changes to the Agency and its scientific committees following the entry into force of Title IV of Regulation (EC) No 726/2004 were successfully implemented.

- The steady increase in the number of requests for scientific advice and protocol assistance reflects the efforts of the EMEA to encourage the systematic use of these procedures. The Agency finalised the procedures well within the defined time limits. Discussions were ongoing to bring about further development and improvements in the services provided. As part of the confidentiality arrangements with the US FDA, a pilot scheme was launched to give parallel scientific advice.

- The total number of new applications for marketing authorisation received in 2004 was higher than initially planned, particularly for those concerning non-orphan products. This reflects the upward trend in the number of applications that has been experienced since the shortfall in 2002, with the highest number of active substances in the past five years. All procedures were completed within the legal timelines, with summaries of opinion published at the same time as the opinions. EPARs were made public in all official languages within four weeks of the European Commission adopting its decision.

- Likewise, the total number of variation applications exceeded the forecast figure, although a significant increase in the number of major variations had been expected, following the entry into force in 2003 of the new Regulation on variations[1], which altered the categorisation of some variations. All variation procedures were handled within the legal timeframes.

- The Agency's processes in relation to human medicines were further improved as a consequence of successful implementation of several short-term improvements, mainly stemming from the audit of the former CPMP conducted in 2003. This should result in increased regulatory and scientific consistency of the outcome of scientific evaluations from 2005 onwards.

- The EMEA risk management strategy was further developed, in particular through the implementation of a newly established procedure for the handling of safety concerns, both pre- and post-authorisation, for centrally processed applications. In addition, the EMEA contributed to the work undertaken at the level of the Heads of Medicines Agencies on further development of the European Risk Management Strategy. As a joint effort, a revised mandate of the Pharmacovigilance Working Party was agreed upon.

- Major work was undertaken in 2004 in relation to the further development and implementation of the EudraVigilance project. Although the implementation rate at the level of Member States and pharmaceutical industry has remained low, the EMEA took several initiatives in 2004 to stimulate electronic reporting of individual case safety reports (ICSRs). The positive effects of such initiatives should become visible from 2005 onwards.

[1] Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93.

- New procedures for plasma master files (PMFs) and vaccine antigen master files (VAMFs) were implemented in 2004 and paved the way for the submission of the first PMFs.

- Applications for medicinal products under development for the treatment of rare diseases to be designated as orphans increased again in number. The duration of the procedure was maintained well within the official timeframe.

- Work continued on the development of a regulatory and scientific environment for emerging and new technologies and therapies, and on contributing to new areas of legislation to address products for paediatric use, tissue engineered products and other public health areas such as influenza pandemic preparedness.

- A programme of ongoing quality improvements in the scientific and regulatory operations of the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Orphan Medicinal Products (COMP) was put in place and initiated.

- New scientific advisory groups were set up to replace the former therapeutic advisory groups as a result of the entry into force of Title IV of Regulation (EC) No 726/2004. These groups continue to bring additional expertise into the European regulatory system.

- The EMEA/CHMP Working Group with Patients' Organisations finalised its 'Recommendations and proposals for action' after extensive consultation. This exercise was conducted in a most transparent manner, with the recommendations being discussed and finalised at a workshop in which all organisations that had commented were invited to participate.

2.1 Orphan medicinal products

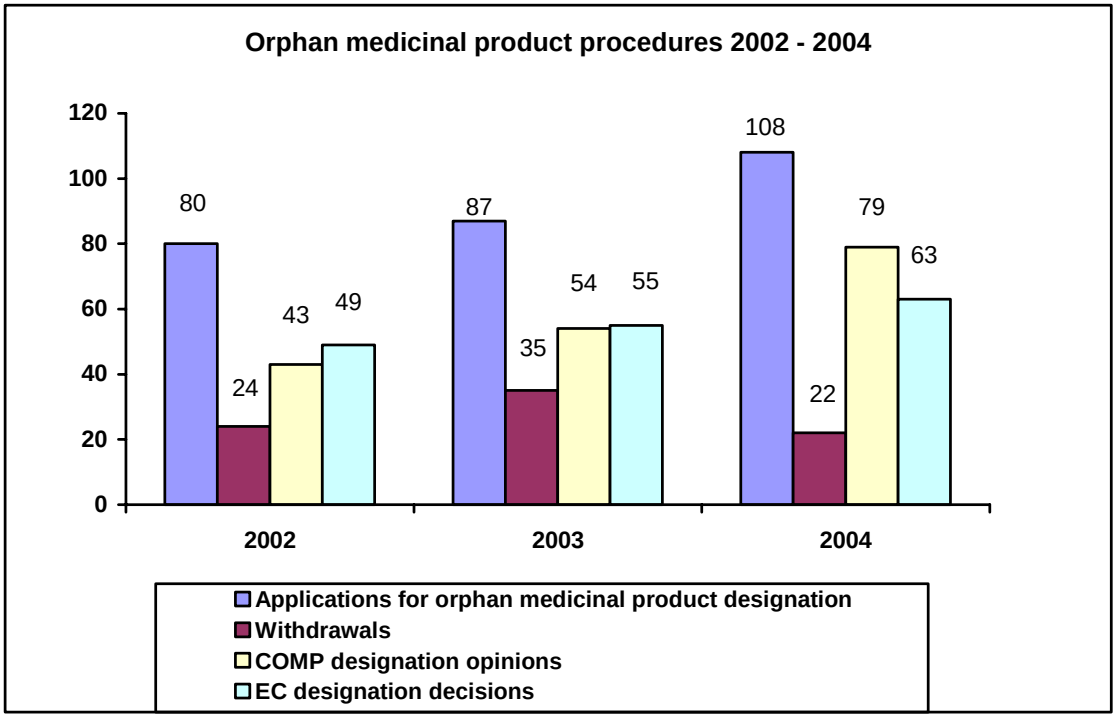
Orphan medicinal products are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect not more than five in 10 000 people in the European Union.

An EU special contribution – the orphan medicinal products fund – is provided to create incentives for sponsors intending to develop such medicinal products, which otherwise might not be developed.

The fund supports new marketing authorisation applications for orphan medicinal products, as well as protocol assistance and post-authorisation activities relating to these medicines.

Applications for orphan medicinal product designation are reviewed by the EMEA, through its Committee on Orphan Medicinal Products (COMP).

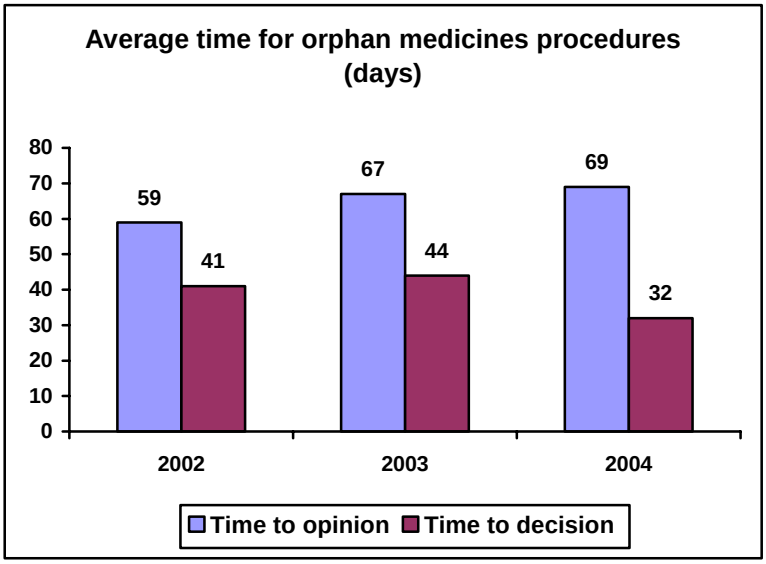
Helping to bring medicines for rare diseases to the market



The COMP adopted 75 positive opinions on orphan medicinal product designation in 2004. This is the highest number of positive opinions adopted in any year since orphan medicinal product legislation was implemented in 2000.

The COMP adopted 4 negative opinions in 2004. The number of applications for orphan medicinal product designation withdrawn by sponsors in 2004 was 22. This number is lower than in previous years, possibly reflecting a better understanding among sponsors of the procedure and criteria for orphan designation.

In 2004, the duration of the overall designation process, from validation by the EMEA through to Commission Decision, averaged 101 days; well within the 120-day legislative timeframe. On average, the COMP reached an opinion within 69 days and the Commission adopted a decision within 32 days.



Transparency

Summaries of COMP opinions are published on the EMEA website once a decision on designation has been taken. This initiative started in 2002, and the Agency is now preparing summaries for medicinal products designated in previous years.

Since July 2004, additional details of COMP opinions have been published in the COMP press release. These details include the name of the medicinal product, the orphan indication and the name of the sponsor.

Improved transparency for orphan drugs

A further new transparency initiative started in September 2004: COMP press releases and CHMP monthly reports now list all designated orphan medicinal products that have been the subject of a marketing authorisation application submitted since July 2003.

Pre-submission meetings

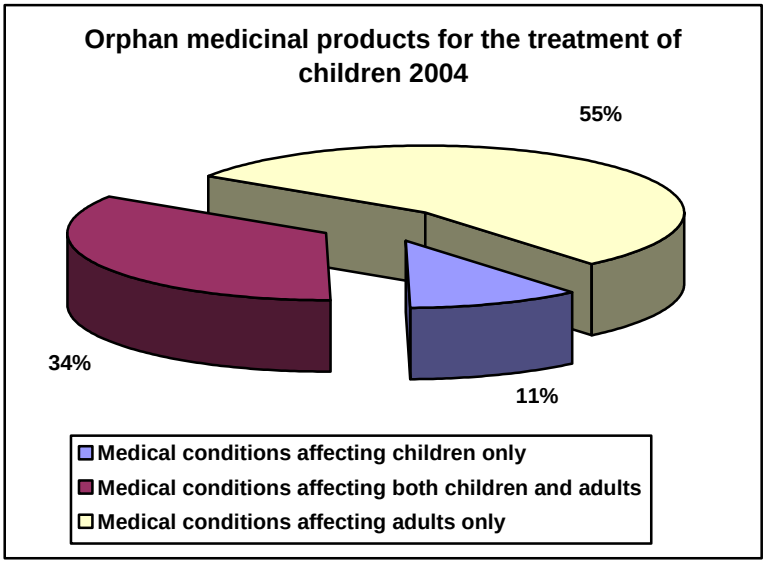
The EMEA offers to hold pre-submission meetings with sponsors who intend to submit an application for orphan designation. In 2004, the number of pre-submission meetings held was 65.

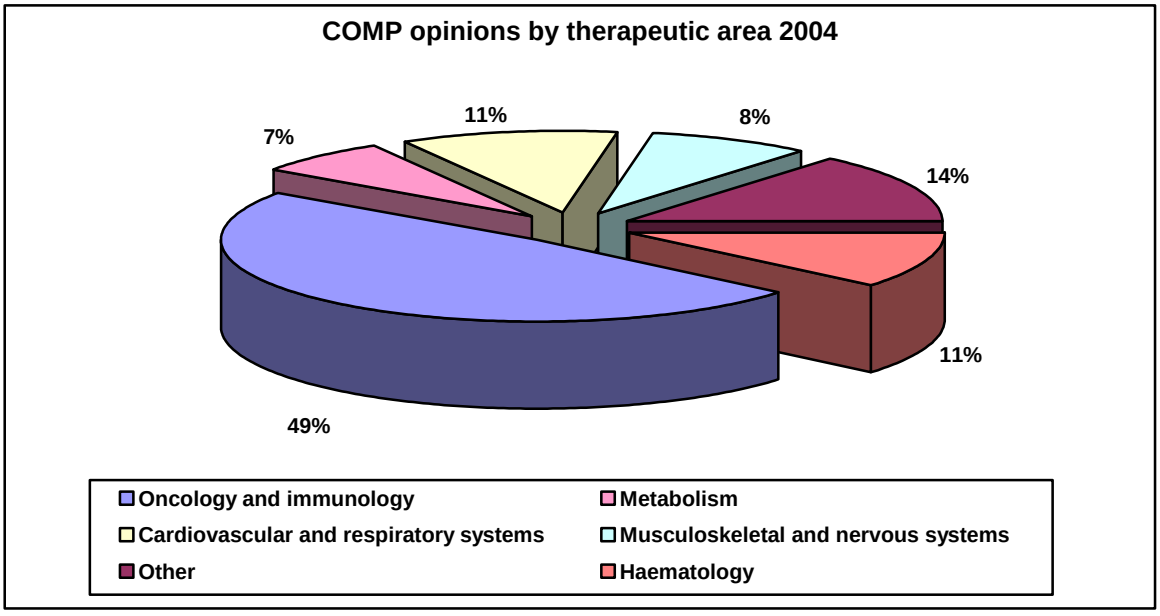
Those applications for which a pre-submission meeting was held were of higher quality, as measured by time to validation, which was 30 % shorter on average than for applications for which no pre-submission discussion took place.

A total of 108 applications for orphan product designation were received in 2004, which is a 24 % increase compared to the 87 received in 2003. There has been an increase in the number of applications during each of the past five years.

Three of the orphan product designation applications received in 2004 were from sponsors established in the new Member States.

Almost half of the orphan medicinal products designated in 2004 are indicated for conditions that affect children.





The EMEA regularly reviews annual reports for designated orphan medicinal products. These reports provide updates on the development of designated orphan products prior to submission of an application for a marketing authorisation. 126 annual reports were reviewed and reported to the COMP in 2004.

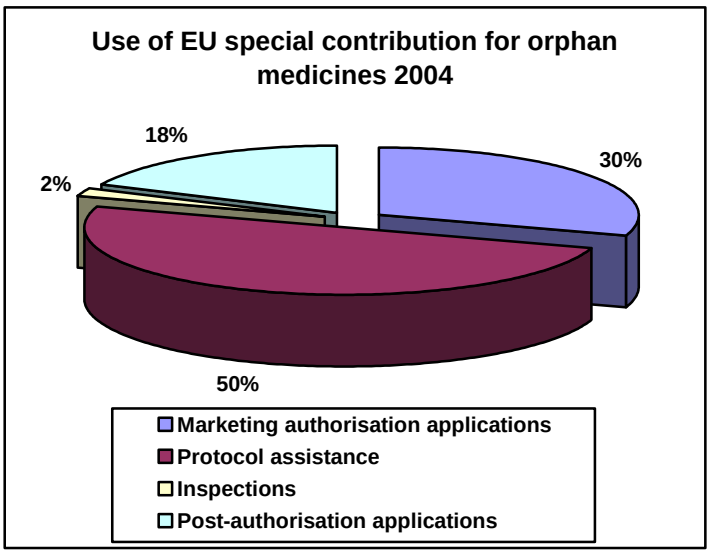
Support to sponsors

The EMEA provides special support to small and medium-sized enterprises (SMEs). Assistance with translation of the indication and active substance name is offered to those SMEs which encounter difficulties in doing so themselves.

In 2004, further assistance to sponsors was provided in a number of cases by conducting pre-submission teleconferences to spare them the travel costs associated with pre-submission meetings.

EU special contribution

Sponsors of designated orphan medicinal products are entitled to reductions on fees levied by the EMEA for protocol assistance, marketing authorisation applications and other regulatory procedures. A special contribution ('orphan drug fund') is allocated each year by the European Parliament and the Council for these reductions. The EU special contribution in 2004 amounted to € 4 million, most of which contributed towards reduced fees for marketing authorisation applications and for protocol assistance.



The fee reduction policy applicable to designated orphan medicinal products during 2004 remained unchanged since 2002 and was as follows:

100 % fee reduction for protocol assistance

50 % fee reduction for inspections

50 % fee reduction for new applications for a marketing authorisation in the centralised procedure

50 % fee reduction for post-authorisation activities and annual fees

2.2 Scientific advice and protocol assistance

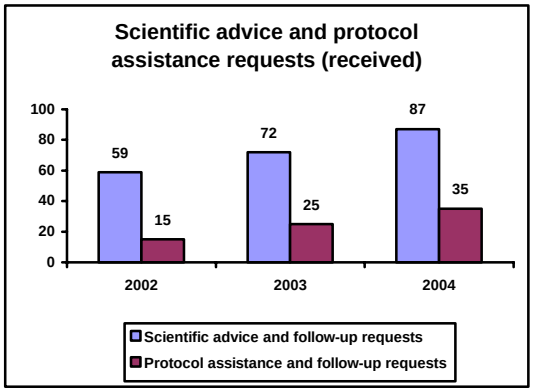
The provision of scientific advice is a priority area for the EMEA as it benefits companies developing new medicinal products and thus contributes to the availability of innovative medicines for EU citizens.

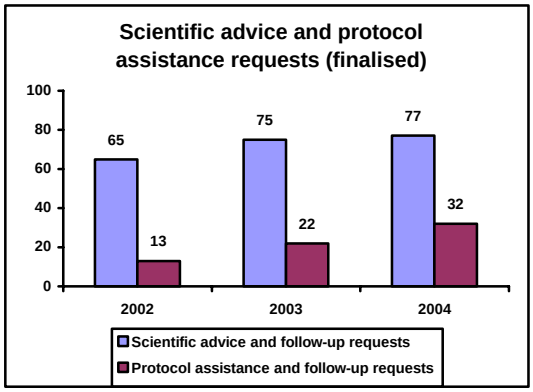
The EMEA provides companies with scientific advice on specific questions relating to the quality, safety or efficacy of their medicinal products. Such questions usually arise during the research and development phase. In the case of sponsors developing designated orphan medicinal products, the scientific advice provided by the Agency is referred to as protocol assistance and is offered free of charge.

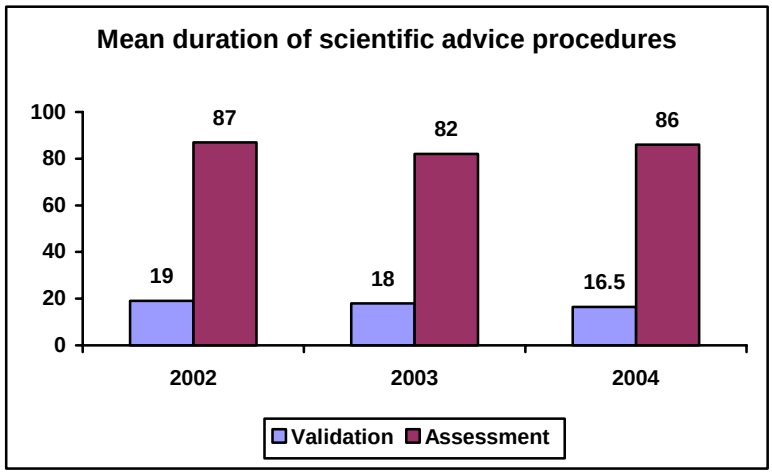
Scientific advice (SA) activity increased in 2004. A total of 87 requests were received and 77 were finalised.

The total number of requests for protocol assistance (PA) was 35, of which 32 were finalised. This represents a 40 % increase in activity when compared to 2003, and indicates that companies developing medicines for rare diseases have a high level of interest in receiving support and advice during the research and development phase.

The average duration of the procedures was 86 days in 2004. Including validation time, the overall procedure took 102 days on average.

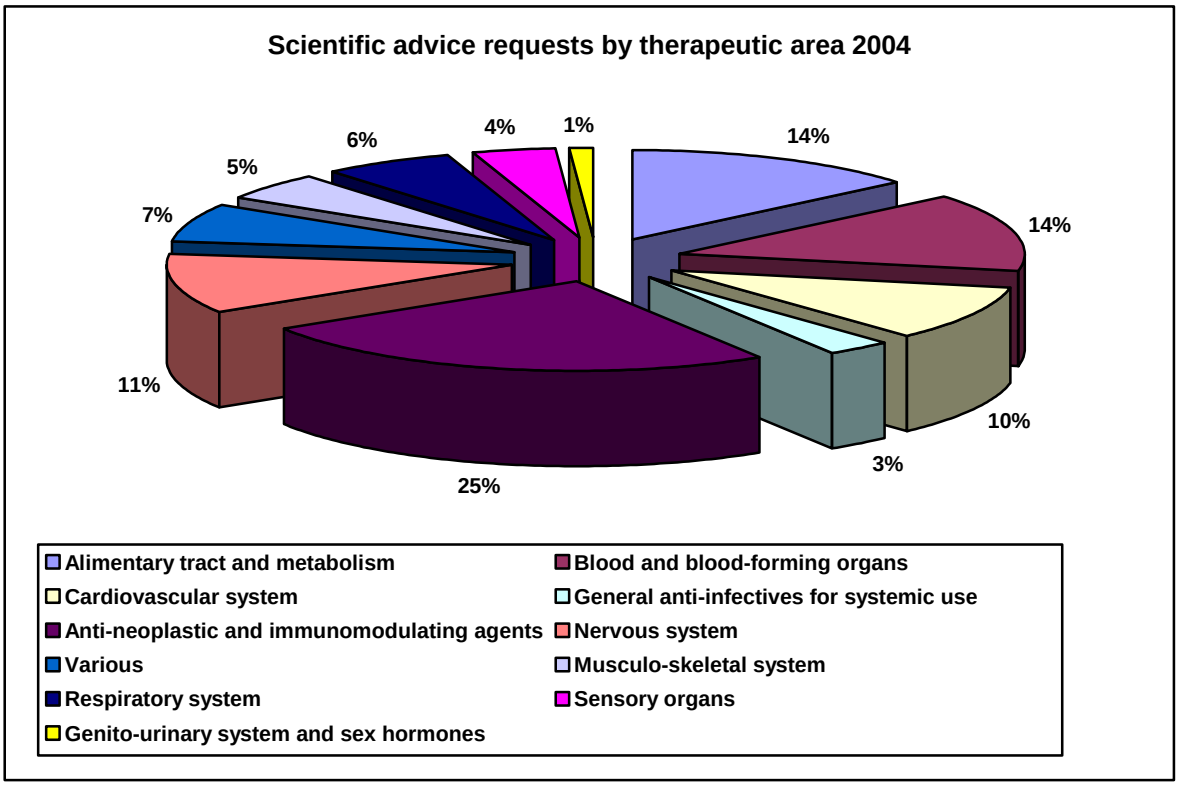


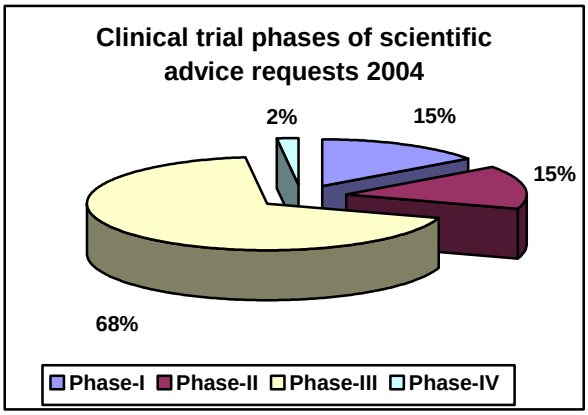


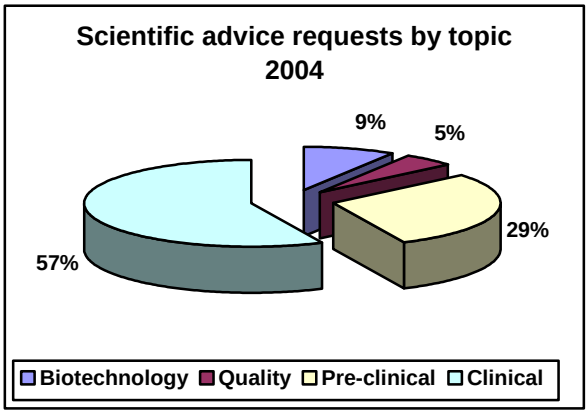


Out of the overall requests for scientific advice received in 2004, 23 related to the field of cancer, 7 to the field of diabetes, 4 to the field of neurodegenerative diseases and 1 to the field of HIV/AIDS.

Five requests for scientific advice in 2004 were for products relating to new and emerging therapies and technologies.





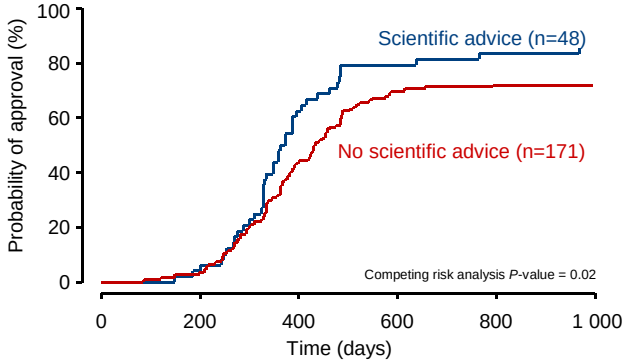


Of the requests for scientific advice and protocol assistance finalised in 2004, two thirds related to clinical aspects of the development of medicinal products. Of these, phase-I clinical trials represented 15 %, compared to 18 % the year before, and 68 % related to phase-III trials.

Impact of scientific advice

The impact of scientific advice on the outcome of the scientific evaluation at the marketing authorisation stage has been assessed. In 2004, 8 (22 %) out of 37 applications for marketing authorisation that had an outcome in the centralised procedure received prior scientific advice. Six (75 %) of these received a positive CHMP opinion, indicating that, while SA/PA is no guarantee of a positive outcome, it appears to have a favourable influence. This has been the overall experience since 1998.

Impact of scientific advice (n=48) on proportion of approvals over time



Organisation of scientific advice at the Agency

As a consequence of the new legislation, the Scientific Advice Working Group became a standing working party of the CHMP in May 2004. In addition, the composition of the new Scientific Advice Working Party (SAWP) was expanded from 18 to 21 members. 18 of the 21 members are appointed by the CHMP and 3 members are appointed by the COMP.

The new pharmaceutical legislation also gives the Executive Director, in liaison with the Committee for Medicinal Products for Human Use (CHMP), the responsibility of setting up the administrative structures and procedures allowing the development of scientific advice for companies and sponsors.

Pre-submission meetings are offered to companies before they submit requests for SA/PA, during which the EMEA can provide regulatory information and scientific support on how to submit their requests, the required information and the most suitable format. In 2004, the number of pre-submission meetings held for scientific advice procedures was 40, with a further 20 pre-submission meetings held for protocol assistance procedures.

Improvements to consistency of advice provided

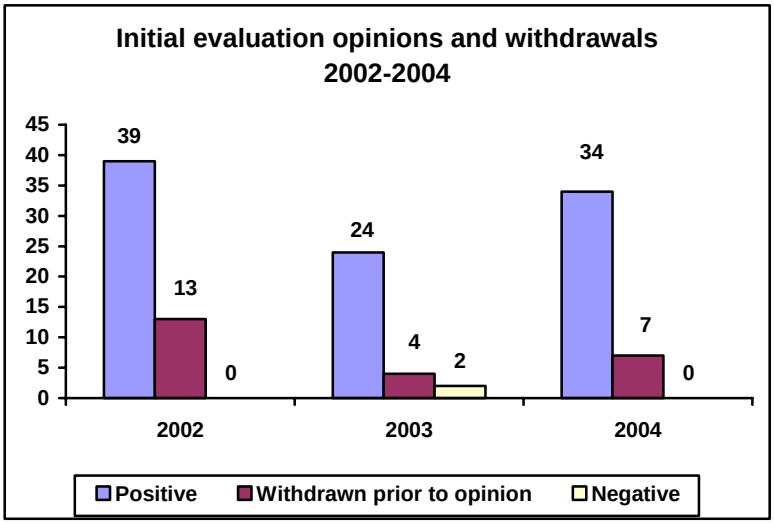
In 2004, further progress was made on establishing a scientific and regulatory ‘memory’ database to enhance the consistency of the advice the Agency provides. A systematic in-house peer-review system was also developed to help ensure a high level of continuity, consistency and quality of finalised SA/PA letters adopted by the CHMP.

EMEA-US FDA parallel scientific advice

In 2004, as an initial trial, there was an exchange of information with the US Food and Drug Administration regarding 4 scientific advice procedures in the context of the EU-FDA confidentiality arrangements. The scope was to explore the possibility of developing a parallel scientific advice procedure, where the two agencies would evaluate advice requests within the same timelines and discuss them together. Following the positive outcome of this initial trial, a formal pilot phase will be starting in January 2005, as outlined in the document jointly agreed during the EMEA and FDA bilateral meeting on 17 September 2004. The pilot phase will last one year, after which the experience and value of the programme will be reassessed. So far, 15 companies, mainly EU-based, have contacted the EMEA expressing interest in the procedure.

2.3 Initial evaluation

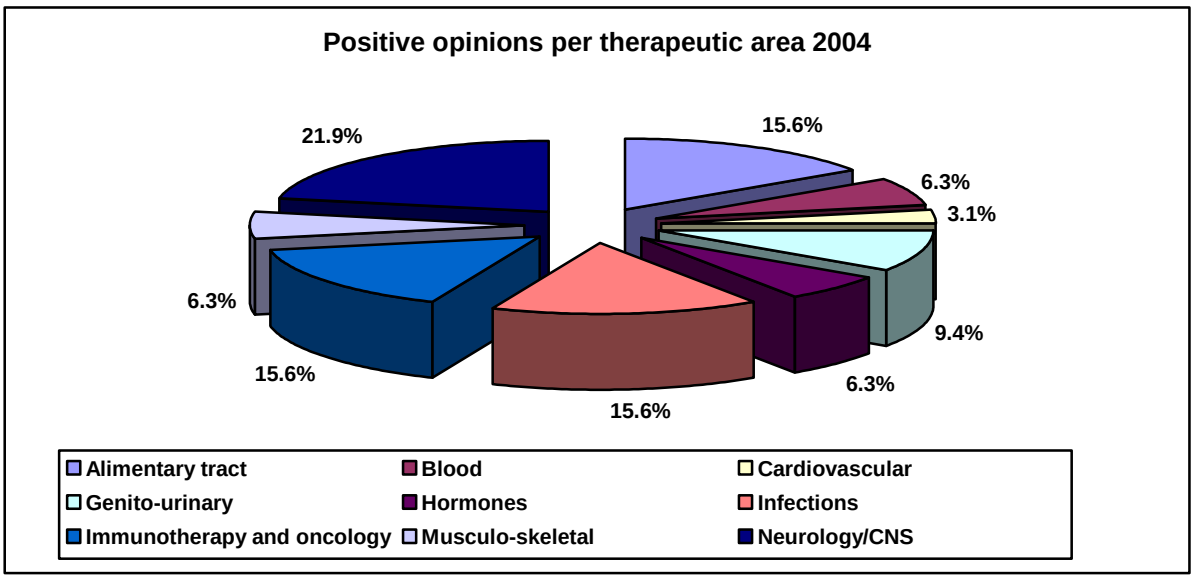
The EMEA, through its Committee for Medicinal Products for Human Use (CHMP), conducts a thorough scientific evaluation of all new applications for marketing authorisation concerning medicinal products for human use submitted through the Community or 'centralised' procedure. This evaluation process determines whether a product for which a marketing authorisation is sought satisfies the quality, safety and efficacy requirements set out in EU legislation. If so, the CHMP adopts a positive opinion that is reflected in a European Public Assessment Report and makes a recommendation to the European Commission that a marketing authorisation be granted for that product. The evaluation process serves to ensure that medicinal products reaching the EU marketplace have a favourable risk/benefit balance for patients.



In 2004, a total of 34 marketing authorisation applications received a positive opinion from the EMEA. This figure includes 6 positive opinions for designated orphan medicinal products, and relates to a total of 29 new active substances. There were no negative opinions given in 2004. Seven applications were withdrawn by applicants prior to an opinion being given.

The new products that received a positive opinion in 2004 will benefit patients in the following areas:

- Cancer (5 new products)
- HIV/AIDS (3 new combinations of products)
- Rare metabolic diseases affecting the blood or the cardiovascular system in neonates (5 products)
- Neuropsychiatric disorders, such as epilepsy, depression, Parkinson's disease or severe pain (7 products)
- Osteoporosis
- Psoriasis



Of the medicinal products having received a positive opinion, some were more notable in terms of therapeutic progress:

- The CHMP reviewed and gave a positive opinion for the first proteosome inhibitor, which is indicated for the treatment of a form of cancer of the blood

- The CHMP recommended a marketing authorisation for a monoclonal antibody that binds to the epidermal growth factor receptor associated with the growth of many cancers

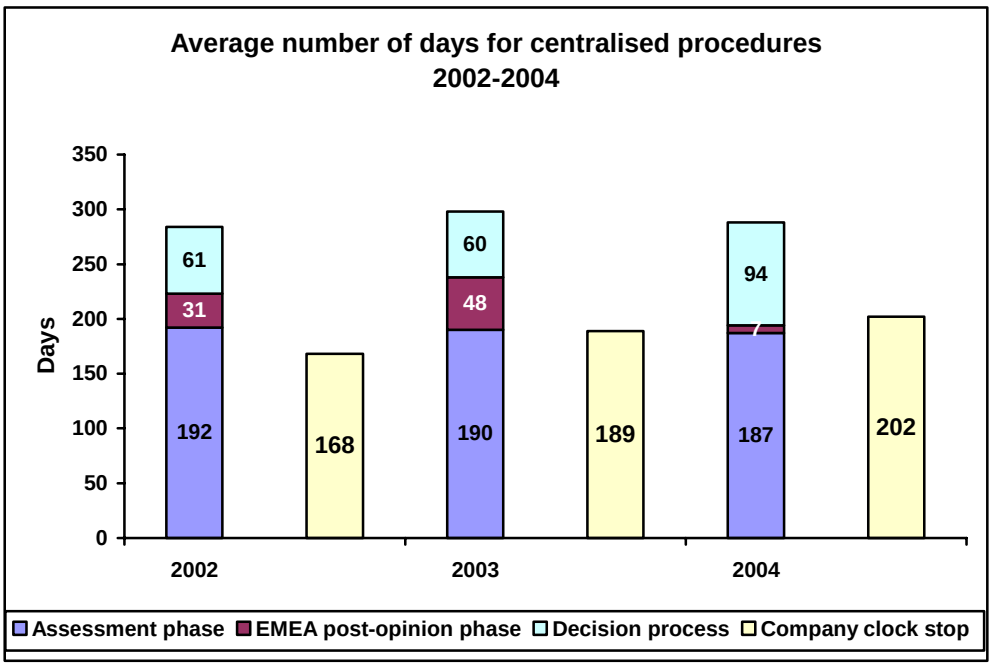
- The CHMP recommended approval of an anti-cancer drug that targets folate-dependent reactions that are essential for cell proliferation. It became the first product approved by the Agency that plays a role in the treatment of malignant pleural mesothelioma, a rare form of cancer

- An antibody that targets vascular endothelial growth factor received a positive opinion. This improves the treatment options of metastatic carcinoma of the colon or rectum, a leading cause of death in the EU

In 2004, the regulatory time for proceeding through the centralised procedure remained stable, at an average of 288 days, including 187 days for assessment. The time taken by companies to answer questions relating to deficiencies in their applications (referred to as ‘clock stop’) increased. For half of the applications, the clock stop was over 200 days, while for others it was shorter — in a number of cases, as short as 50 or 60 days.

Transparency

Once an opinion has been given, the Agency posts a summary of opinion on its website. A European public assessment report (EPAR) is published once the Commission has adopted a final marketing authorisation decision. Due to an increase in the workload and the implementation of a new publishing process, EPARs were published within three to four weeks after the Commission decisions.



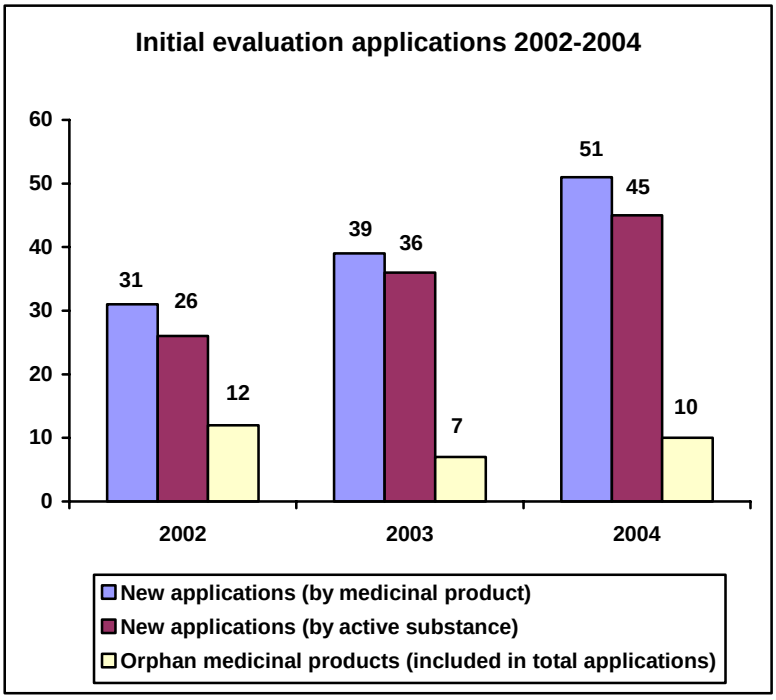
Level of applications

After two years of decline, 2004 saw a recovery in the number of applications submitted to the EMEA for products containing new active substances.

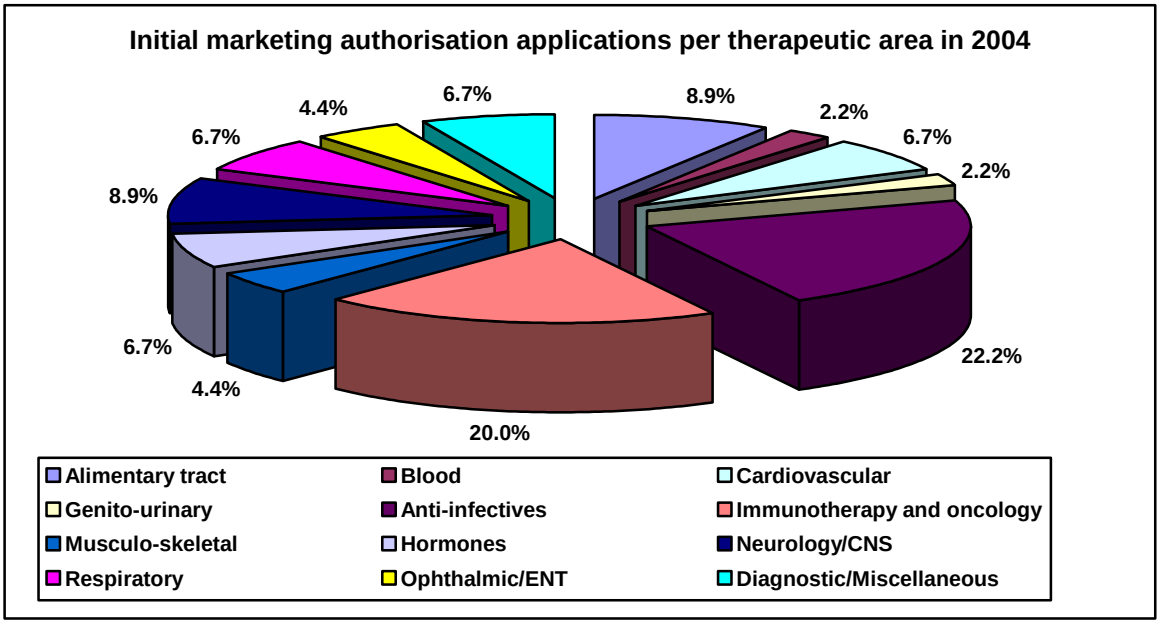
In 2004, a total of 51 new applications for marketing authorisation were received under the centralised procedure. This number is 31 % higher than the figure for 2003, and 27.5 % higher than the forecast number of 40. Predictions for 2005-2006 indicate a relatively stable level of applications.

This total includes 3 applications for biosimilar products and 6 multiple applications. The number of applications for orphan medicinal products remained relatively stable in 2004, with 10 applications.

The total number of active substances in applications submitted was 45 – the highest number seen in the past five years.



The three therapeutic areas where the number of applications was highest are oncology, HIV and diabetes. Registration through the centralised procedure will be mandatory for these therapeutic areas from the end of 2005.



Plasma master files (PMF) and vaccine antigen master files (VAMF)

Eight applications were received in 2004 for PMFs. One PMF was finalised. No applications were received for VAMFs.

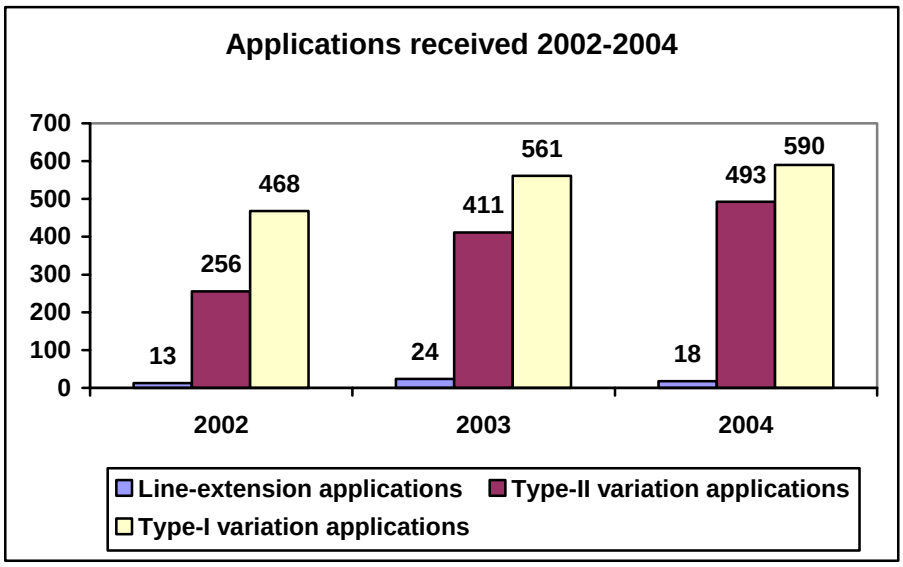
2.4 Post-authorisation activities

All changes that are made to the terms of authorisation of a centrally authorised medicinal product throughout its life have to be approved by the Community. A wide range of changes are possible to alter or improve the medicinal product. Marketing authorisation holders may want to add new treatment options or introduce additional warnings or contraindications, or they may wish to change the manufacturing process.

Post-authorisation activities relate to variations, line extensions, renewals and transfers of marketing authorisation. Variations to marketing authorisations can be either minor (type-IA or IB) or major (type-II) changes.

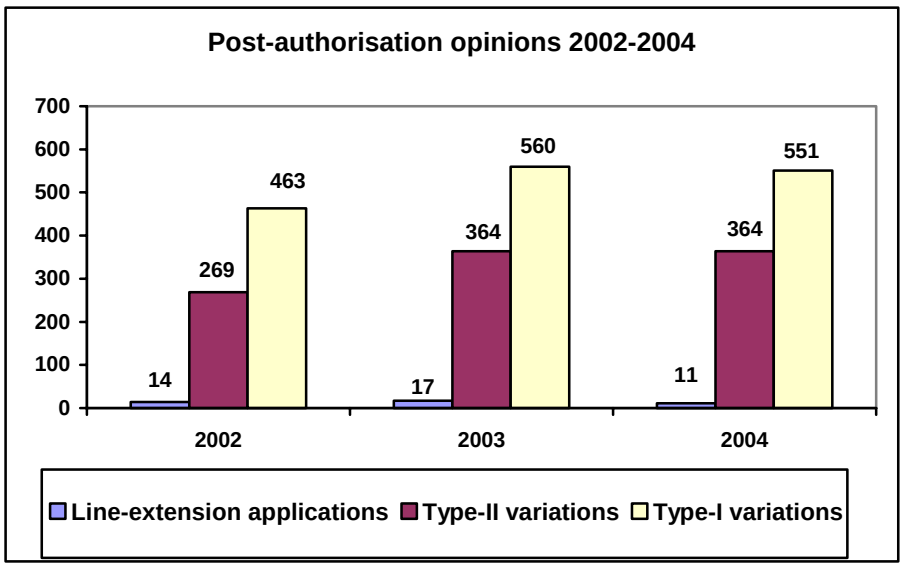
Number of variation applications in excess of 1 000 for the first time

As a consequence of the increasing number of centrally authorised products, the number of applications for variations to marketing authorisations increased once more in 2004. For the first time, the total number, including type-I and II variations and line extensions, was over one thousand (1 101).



The implementation of new Community legislation in October 2003 split type-I variations into type-IA and type-IB variations, and also converted about 25 % of the former quality-related type-I variations into type-II variations.

Of all type-II variation opinions adopted in 2004, 5.3 % related to extension of indication, 46.3 % related to changes in the SPC and 48.4 % related to quality.



Significant variations/new treatment options for patients suffering from cancer

Several medicinal products already authorised through the centralised procedure for cancer treatment had their indications extended to include new treatment options for patients suffering from breast cancer, ovarian cancer or (non-small cell) lung cancer. Other medicinal products were approved for use in combination with other chemotherapy to treat metastatic breast cancer, non-Hodgkins lymphoma and metastatic prostate cancer.

Significant variations/new treatment options for patients suffering from HIV/AIDS

In the anti-HIV area, several variations were implemented in 2004 to add important safety information to relevant SPCs. This included 'class labellings' for all antiretroviral medicinal products with regard to liver impairment and immune reactivation syndrome, and a statement on mitochondrial toxicity in children with postnatal or *in utero* exposure to nucleotide and nucleoside analogues. Information on the high rate of virological failure and emergence of resistance at an early stage with some triple combinations was added to relevant product information. To simplify dosing and aid compliance, a once-daily regimen was introduced for a medicinal product in this class.

Significant variations/new treatment options for patients suffering from diabetes

Two medicinal products already authorised through the centralised procedure for the treatment of diabetes had their use extended to include new combination regimens for diabetes.

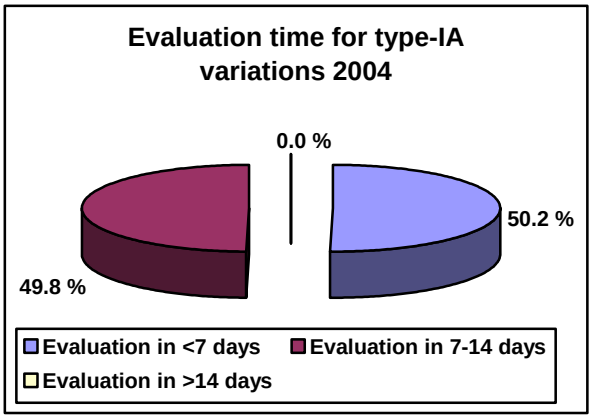
Significant variations/new treatment options for patients suffering from neurodegenerative diseases

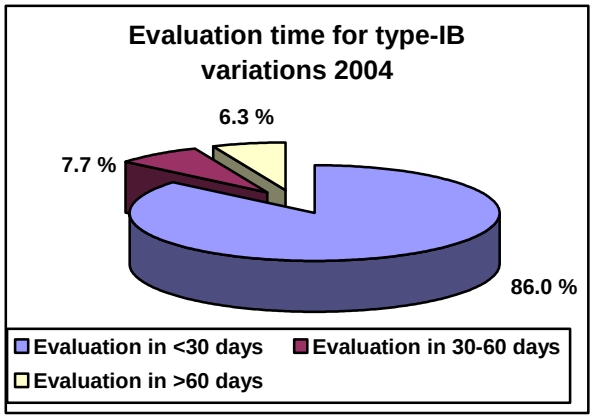
The suspension of a medicinal product used to treat patients suffering from Parkinson's disease was lifted in 2004, based on new data evaluated by the CHMP.

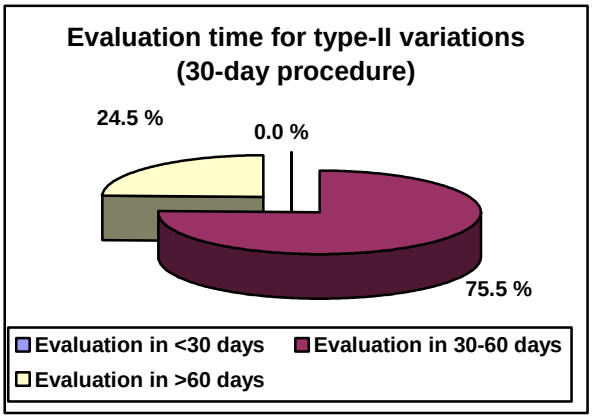
Significant line extension applications approved in 2004 to include child populations

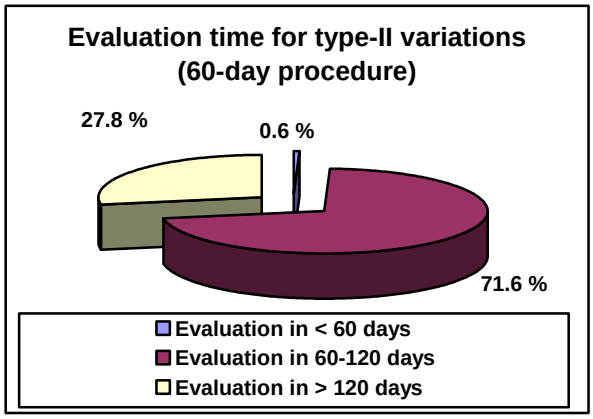
In 2004, several marketing authorisations were extended in order to provide more treatment options for children. One product can now be used to treat children over 3 years of age suffering from hepatitis C, in combination with an antiviral medicine. A hepatitis A and B vaccine had its use extended to children aged 1 to 5 years. The use of a pneumococcal vaccine was extended to include the age range 2 to 5 years and a new treatment option for children under 6 suffering from haemophilia A was made available.

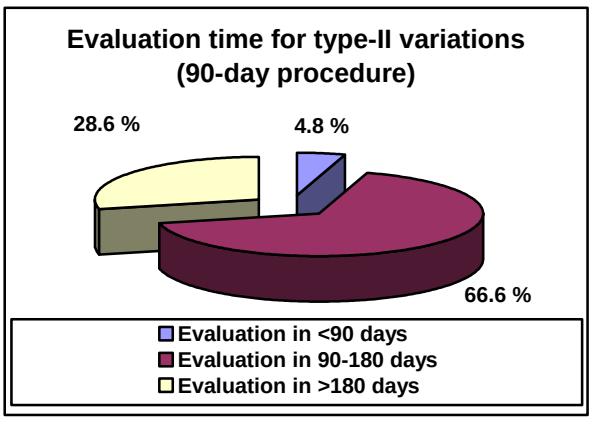
The evaluation of variations was carried out within the legally defined time limits.











2.5 Pharmacovigilance and maintenance activities

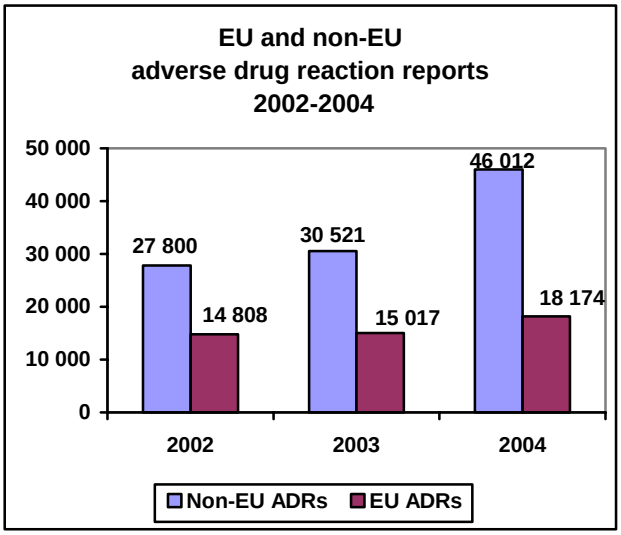
Useful website:

EudraVigilance *http://eudravigilance.emea.eu.int*

Pharmacovigilance involves a process of continuous monitoring of medicinal products on the market. Its aim is to identify and report any potential safety issues relating to medicines and to prevent adverse drug reactions. The collection and exchange of such information between marketing authorisation holders, sponsors of clinical trials and regulators allows rapid and appropriate responses to be made in order to afford the best protection to users of medicinal products.

Pharmacovigilance is a priority area for the EMEA, and its activities in this field include collecting and reviewing adverse drug reaction reports and periodic safety update reports, managing electronic collection and reporting systems, and issuing safety recommendations to healthcare professionals.

The Agency received a total of 64 186[1] adverse drug reaction reports (ADRs) during 2004 for centrally authorised products from EU national competent authorities and marketing authorisation holders. This represents an overall 41 % increase in the level of reporting. 18 174 reports were received from EU sources and 46 012 were from outside the EU.

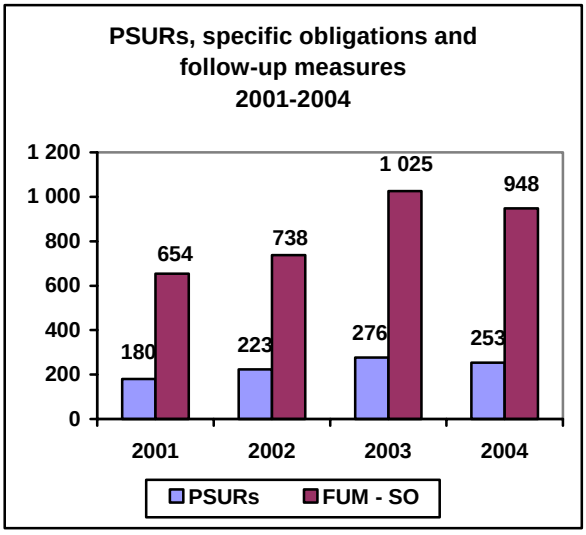


253 periodic safety update reports (PSURs) were reviewed in 2004. Marketing authorisation holders are required to submit a PSUR at regular intervals or upon request. The PSUR records all adverse drug reactions reported worldwide during a defined time interval, together with all other emerging information relevant to safety, including proposals for safety-related action, where necessary.

In addition, the Agency receives data to address post-authorisation commitments (specific obligations and follow-up measures) for centrally authorised products. The workload arising from the handling of periodic safety updates, follow-up measures and specific obligations decreased slightly compared to 2003, owing partly to a decrease in the number of marketing authorisation applications received at the EMEA in the years 2002 and 2003.

The Agency received 948 post-authorisation commitments made up of follow-up measures and specific obligations in 2004.

[1] This figure refers to all reports received either on paper or electronically by the Agency.



Rapid procedure for updating product information

The Agency completed 2 urgent safety restriction (USR) procedures for centrally authorised products during 2004, introducing warnings into the marketing authorisation of the two medicinal products.

A USR procedure is a rapid, 24-hour regulatory process used to change the product information provided to prescribers and users of a medicine. The Agency communicates the finalisation of a USR procedure and the new safety recommendations to healthcare professionals and patients by issuing an EMEA public statement. In addition, following the finalisation of the USR, it is common for the company concerned to inform healthcare professionals by means of a 'Dear Doctor' letter in all EU countries where the medicine is marketed. This rapid USR procedure is followed by a formal variation to the marketing authorisation of the medicine.

Information on USRs can be found on the EMEA website at:
http://www.emea.eu.int/htms/human/drugalert/drugalert.htm

Two major safety reviews

Two major safety reviews involving two classes of medicines were initiated in 2004. One of these related to SSRI (serotonin selective reuptake inhibitor) and SNRI (serotonin-norepinephrine reuptake inhibitor) products, in particular regarding the use of these products in children and adolescents.

The other safety review related to the class of COX-2 inhibitor medicines. Following the worldwide withdrawal of Vioxx in September 2004, the CHMP began a review of all aspects of cardiovascular safety of COX-2 inhibitors at the request of the Commission.

Further details on both procedures can be found in section 2.6.

EudraVigilance

EudraVigilance is the EU's data processing network and management system for monitoring adverse drug reactions. Collecting, processing and analysing data in one repository is one of the prerequisites for efficiently supporting the pharmacovigilance activities and risk management strategy of the EU.

The EMEA component of the EudraVigilance project proceeded as planned in 2004. EudraVigilance version 7.0 was launched in May 2004, including a Clinical Trial module (EVCTM) to support the electronic reporting of suspected unexpected serious adverse reactions (SUSARs) occurring during clinical trials.

In addition, a special web-based tool designed to support electronic reporting by small and medium-sized enterprises and non-commercial sponsors of clinical trials was released in 2004. Furthermore, a large-scale training programme was developed by the EMEA and launched in May 2004 to provide training to the Agency's business partners (national competent authorities and pharmaceutical companies).

Implementation status

Progress with the implementation of the electronic transmission of individual case safety reports (ICSRs) was delayed at the level of the national competent authorities and pharmaceutical companies. With the introduction of the new EU legislation, however, and in accordance with Article 24 of Regulation (EC) No 726/2004, save in exceptional circumstances, adverse drug reactions will have to be transmitted electronically as of 20 November 2005 onwards.

In total, 61 518 ICSRs were reported electronically to EudraVigilance in 2004, referring both to reports for centrally authorised medicinal products as well as those authorised through the mutual recognition and national procedures.

The number of SUSARs received electronically was 7 984, of which 3 746 were from EU sources and 4 238 from outside the EU.

Two national competent authorities and 21 pharmaceutical companies implemented the electronic transmission of ICSRs during 2004. This brings the total to 5 national competent authorities and 39 pharmaceutical companies in production with EudraVigilance at the end of 2004.

To speed up the implementation of EudraVigilance, the EMEA took additional initiatives. One-day individual implementation meetings were organised with each national competent authority to achieve better and more robust planning. Furthermore, an Ad hoc Expert Working Group was established to look at policy, compliance and regulatory aspects resulting from first experience with electronic reporting.

The new Member State authorities were connected to the EudraVigilance Gateway and are actively involved in the joint implementation activities at Community level. The Czech Republic was the first of the new Member States to transmit data to EudraVigilance.

Risk management strategy

The EMEA contributed to the further development of the European risk management strategy and further developed the Agency's component thereof.

Initiatives undertaken in 2004 mainly related to the areas of risk identification and risk evaluation: in the field of risk identification through the further development and implementation of EudraVigilance; in the area of risk assessment by looking at a more proactive conduct of pharmacovigilance. The EMEA started the implementation of the newly established procedure for the handling of safety concerns in relation to centrally processed applications in April 2004, with a pilot phase based on selected medicines undergoing evaluation for marketing authorisation.

Under this procedure, there is a case-by-case decision on whether the handling of safety concerns for a medicine, both pre- and post-authorisation, requires additional scientific input. The CHMP can request the involvement of the Pharmacovigilance Working Party and, in cases where specialised scientific input is needed, it can draw additional expertise from a pool of pharmacovigilance experts. Upon request from the EMEA, national competent authorities have nominated more than 100 specialised experts in the areas of pharmacovigilance, pharmacoepidemiology, epidemiology, emerging therapies (such as gene therapy) and risk communication. The procedure will be revised based on experience gained from the pilot phase in time for the introduction of the new Community legislation in November 2005.

In 2005, new Community legislation will introduce a requirement for risk management plans in relation to certain medicines with important (established or potential) risks. In anticipation, some marketing authorisation holders (MAHs) already submitted risk management plans for review by the CHMP during 2004, and several meetings with MAHs for centrally authorised products were held in 2004, mainly to discuss risk management concepts. This should facilitate the future introduction of risk management plans as foreseen in the new Community legislation and compliance with the ICH E2E concept of pharmacovigilance planning.

2.6 Arbitration and Community referrals

Arbitration procedures (either under Article 29 of Directive 2001/83/EC or Article 6(12) of Commission Regulation (EC) No 1084/2003) are initiated because of disagreement between Member States in the framework of the mutual recognition procedure.

Referral procedures under Article 30 of Directive 2001/83/EC are mainly initiated in order to obtain harmonisation within the Community of the conditions of authorisation for products already authorised by the Member States.

Referral procedures under Articles 31, 36 and 37 of Directive 2001/83/EC are mainly initiated in cases involving the interests of the Community or concerns relating to the protection of public health.

Referral procedures under Article 18 of Regulation (EEC) No 2309/93 are initiated in cases where there is a safety concern relating to a centrally authorised product.

Referrals concluded

The CHMP gave 2 opinions on referrals under Article 29 and 2 opinions on referrals under Article 30. Three Article 6(12) referrals were withdrawn. Details of these can be found in Annex 13.

The CHMP adopted an opinion on a referral under Article 31 regarding paroxetine-containing medicines in April 2004. The referral was initiated because of safety concerns relating to potential risk of emotional changes and withdrawal reactions associated with the use of paroxetine. The Committee concluded that the benefit-risk balance of paroxetine remains positive, but that changes to the product information should be introduced, especially with regard to warnings of suicide-related behaviour in children and adolescents.

Following the paroxetine referral, the Committee conducted a review of data available for the whole class of SSRI (serotonin selective reuptake inhibitor) and SNRI (serotonin-norepinephrine reuptake inhibitor) products at the request of the European Commission. At an extraordinary meeting in December 2004, the CHMP concluded, on the basis of the available evidence, that there are public health concerns in relation to the safe use of these medicinal products in children and adolescents with depression, anxiety and related conditions, irrespective of the therapeutic indication. Following this, the European Commission asked the CHMP to carry out a further review at Community level.

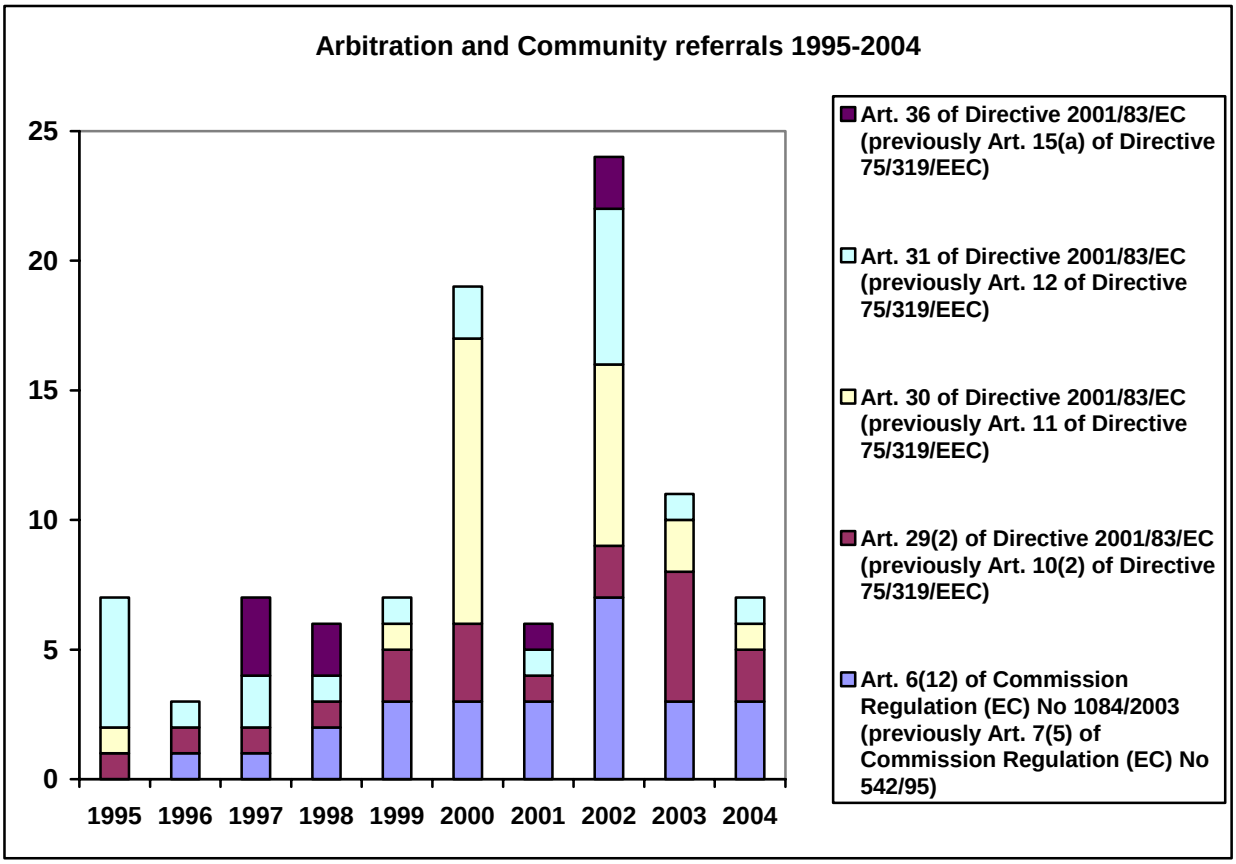
Referrals started

A new referral procedure under Article 31 (Article 18 for centrally authorised products) was started for all COX-2 inhibitor medicines available in the EU in October 2004, due to concerns over cardiovascular safety. During the procedure, new clinical trials data for the COX-2 inhibitor celecoxib became available, indicating an increased cardiovascular risk. Following this, the EMEA decided to expedite the review of COX-2 inhibitors in the context of the ongoing procedure.

The Agency also received 6 referrals under Articles 29 and 30. There were no referral procedures under Articles 36 or 37.

Public information on arbitration and referral procedures was made available by the EMEA upon finalisation of the procedures by the European Commission. In addition, the EMEA released advice to healthcare professionals and patients in the form of question and answer documents accompanying the EMEA public statements, in line with the Agency's policy for increased transparency towards the public.

Work relating to the improvement of various aspects of the management of referral procedures, which started in 2003, continued throughout 2004. Draft guidance documents were developed, including external guidance that will become publicly available in 2005.



Details of all referrals are given in Annex 13.

2.7 Regulatory guidance

Regulatory and procedural guidance or advice is provided to the pharmaceutical industry during the lifecycle of medicinal products, starting from pre-submission meetings with applicants through to annual meetings with marketing authorisation holders (MAHs).

Guidance documents focusing on the key steps of the centralised procedure are continuously developed and updated by the EMEA. In addition, regulatory and procedural guidance is provided to the CHMP, HMPC and COMP, and to their related working parties and ad hoc groups.

Activities in relation to the key steps of the centralised procedure

- 'Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community'. This document provides the procedures to implement Article 58 of Regulation (EC) No 726/2004 and was released for external consultation in November 2004. Article 58 of the Regulation responds to the need to give scientific assistance to non-member countries in the context of cooperation with the WHO whilst at the same time allowing rapid access to important new medicines for those countries.

- Revision 4 of the 'Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure' (CPMP/328/98, Rev 4) was released for external consultation in September 2004.

- In 2004, the CHMP/EMEA initiated a revision of the European Commission Summary of Product Characteristics (SPC) Guideline, and agreement on sections 4.1 and 5.1 was reached. The other sections of the guideline were reviewed in 2004 and it is expected that the European Commission will publish an amended version in the first quarter of 2005.

- Assessment report templates to harmonise and facilitate the assessment review by the CHMP during the evaluation of the dossier pre-/post-authorisation were updated to take into consideration the changes of the European pharmaceutical legislation, especially Annex 1 of Directive 2001/83/EC.

New regulatory framework

As the Agency prepares to receive applications in relation to emerging therapies and new technologies, a new regulatory framework needs to be developed.

Biosimilar products

In June 2003, the European pharmaceutical law introduced a legal framework for marketing authorisations for products similar to biological products that were already authorised — so-called biosimilar products. This legislation is particularly relevant for biotechnology-derived products, which means that there is likely to be an increasing number of such applications in the coming years.

The CHMP reviewed its guidance on comparability of medicinal products and focused on new guidelines specifically addressing biosimilar products. An overarching guideline on the general principle was issued for consultation in November 2004, along with concept papers on the requirements for different types of products.

Plasma master files, vaccine antigen master files and medical devices containing biotechnology and blood-derived medicinal products

Following adoption of the guidelines on data requirements and procedures for the evaluation and certification of plasma master files (PMFs) and vaccine antigen master files (VAMFs) in February 2004, the EMEA made further progress on the implementation of Commission Directive 2003/63/EC providing the legal basis for the submission of PMFs and VAMFs. A standard operating procedure for coordination of PMF inspections and a guideline on PMF/VAMF '2nd step' were developed and published in 2004. The 'second step', following the PMF/VAMF evaluation and certification, sets out how the competent authorities that will grant or have granted a marketing authorisation will take into account the certification, re-certification or variation of the PMF/VAMF relating to the medicinal products concerned.

Activities in relation to new and emerging therapies

In the EMEA Road Map, the Agency has developed a strategy that will help to stimulate innovation and research in the EU pharmaceutical, biotechnology and healthcare industries for the development of medicinal products. The reinforcement of the partnership between EU regulatory authorities will lead to the establishment of a network of excellence. Greater collaboration with non-EU authorities and increased dialogue with health organisations, academia and learned societies should facilitate a consistent regulatory approach for new technologies. Legislative provisions implementing special measures for innovative medicines, technologies and therapies will help to provide more rapid access to medicines without compromising the safety of patients. The EMEA is participating in ongoing discussions with DG Research to establish a European Technology Platform for Innovative Medicines. The contributions that industry associations are making to this technology platform will help to find solutions to clear bottlenecks during the development of new medicines.

2.8 Management and organisation of EMEA scientific committees for human medicines

The Committee for Medicinal Products for Human Use (CHMP), the Committee on Orphan Medicinal Products (COMP) and the Committee on Herbal Medicinal Products (HMPC) are responsible for formulating the Agency's opinions on all questions concerning medicinal products for human use.

Committee for Medicinal Products for Human Use (CHMP)

Following the entry into force of parts of the new pharmaceutical legislation in May 2004, the Committee for Medicinal Products for Human Use (CHMP) replaced the Committee for Proprietary Medicinal Products (CPMP). The first meeting of the new Committee, which for the first time included representatives from the 10 new EU Member States as full members, took place from 1–3 June 2004. The Committee re-elected Dr Daniel Brasseur as chairman and Dr Eric Abadie as vice-chairman. The new Rules of Procedure were discussed and adopted in July 2004.

The Committee is composed of one member and one alternate per Member State, in addition to one member and one alternate each from Iceland and Norway. The composition of the CHMP was announced on 1 June 2004, following the conclusion of a Management Board consultation procedure.

The new legislation gives the CHMP the possibility of appointing up to five additional members to gain additional expertise in particular scientific areas. The Committee elected five new members, who joined in September 2004.

The Committee held 11 plenary meetings in 2004. In addition, an extraordinary meeting was held in December in order to discuss safety concerns relating to SSRIs and SNRIs (see section 2.5).

Working parties of the CHMP

The work of the CHMP is supported by a number of working parties, composed of European experts selected from a list maintained by the EMEA. The working parties are involved, according to their specific area of responsibility, in the development and revision of scientific guidelines and in the provision of recommendations and advice on medicinal products for which applications are made for orphan drug designation, scientific advice, protocol assistance, marketing authorisation or post-authorisation activities.

Following the implementation of Title IV of Regulation (EC) No 726/2004, the mandates of the new CHMP working parties were updated to include an increased supportive role for the assessment of new applications, in accordance with the new pharmaceutical legislation.

By the end of 2004, the following standing working parties supported the work of the CHMP:

- Scientific Advice Working Party
- Biotechnology Working Party
- Pharmacovigilance Working Party
- Joint CHMP/CVMP Quality Working Party
- Safety Working Party
- Efficacy Working Party
- Blood Products Working Party
- Vaccine Working Party
- Gene Therapy Working Party
- Pharmacogenetics Working Party

Four temporary working parties also supported the work of the CHMP:

- Paediatric Working Party
- (Pre-)Clinical Working Party on Comparability of Biotechnology Products
- EMEA/CHMP Working Group with Patients' Organisations
- (Invented) Name Review Group

Creation of scientific advisory groups

In addition to the standing and temporary working parties, the CHMP has created scientific advisory groups (SAGs). The role of these groups is to advise the CHMP on specific questions addressed to them by the Committee. The Committee, while taking into account the position expressed by the SAG, remains responsible for its final opinion. An overarching document describing the mandate, objectives and rules of procedure for CHMP scientific advisory groups was adopted by the Committee. Rules of procedure for individual SAGs will follow, based on this document.

The Oncology SAG, SAG on Diagnostics and SAG on Anti-infectives were the first SAGs created by the Committee. The establishment of SAGs for HIV/viral diseases, endocrinology/diabetes, CNS/psychiatry and cardiology is planned for 2005.

See Annex 2 for information on working parties and scientific advisory groups.

Scientific guidance

The development and revision of scientific guidelines is a particularly important aspect of the work of the working parties as they contain guidance on specific scientific issues and are based on the most up-to-date scientific knowledge available, providing essential information to be taken into account in the research and development of new medicines. Often, such guidelines are developed as a result of the EU's cooperation with Japan, the US and other international partners on the harmonisation of regulatory requirements for medicinal products, particularly through the International Conference on Harmonisation (ICH), and thus reflect a harmonised approach.

The CHMP working parties and groups have, over time, developed positions on a wide range of topics, including variant Creutzfeldt-Jakob disease (vCJD), viral safety, influenza pandemic, new technologies and therapies, etc. Experts in each of the areas covered have kept these topics under review and produced updated position papers periodically, to reflect the current state of knowledge. These experts and the EMEA secretariat will continue work in these and other new areas, such as cell therapy and tissue engineering, in 2005.

See Annex 12 for full list of guidelines.

Management and organisation of the Committee on Orphan Medicinal Products (COMP)

The Committee on Orphan Medicinal Products is responsible for reviewing applications for 'orphan medicinal product' designation.

In May 2004, the composition of the COMP increased to 31 members as the Committee welcomed members from the 10 new EU Member States. The new COMP members brought new expertise to the Committee in the areas of paediatrics, genetics and oncology.

The Committee met 11 times in 2004. To further improve its scientific assessment procedures, the COMP continued to actively involve experts in the designation process, with 41 experts being consulted on specific applications in 2004.

Two working parties and one ad hoc group assist the Committee:

- COMP Working Group with Interested Parties

- COMP Biotechnology Working Group

- Ad hoc Working Group on Prevalence

Establishment of the Committee on Herbal Medicinal Products (HMPC)

The year 2004 saw the establishment of a new scientific committee at the EMEA, following the entry into force of Title IV of Regulation (EC) No 726/2004 and the Directive on Herbal Medicinal Products.

The Committee on Herbal Medicinal Products (HMPC) held its inaugural meeting on 23 September 2004. This Committee will provide the Member States and the European institutions with the best-possible scientific opinion on questions relating to herbal medicinal products. It will help to harmonise procedures and provisions concerning herbal medicinal products laid down in the Member States and help to further integrate herbal medicinal products in the European regulatory framework.

The new legislation introduced a simplified registration procedure for traditional herbal medicinal products.

Major tasks of the HMPC: preparatory work for the establishment of a draft list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products; the elaboration of Community herbal monographs for herbal medicinal products with a well-established use and for traditional herbal medicinal products.

The HMPC met twice in 2004 and set up temporary working groups to review and update available guidance that was adopted by the Herbal Medicinal Products Working Party (HMPWP) between 1997 and 2004, and to identify the need for additional guidance in the quality, safety and efficacy fields or on organisational matters.

Herbal Medicinal Products Working Party

The HMPWP continued its work in 2004 until the inauguration of the HMPC in September 2004. All working documents adopted by the HMPWP are listed in Annex 12.

2.9 Improvement of the Agency's structures and procedures for human medicines

As part of the Agency's efforts to improve its structures and procedures, and as a follow-up to an audit of the former CPMP held in 2003, an EMEA action plan for the improvement of the Agency's core procedures and CHMP activities was developed. Implementation of the plan, which also considered the impact of the EU enlargement in May 2004 and the need to prepare for future revisions of pharmaceutical legislation, started in early 2004.

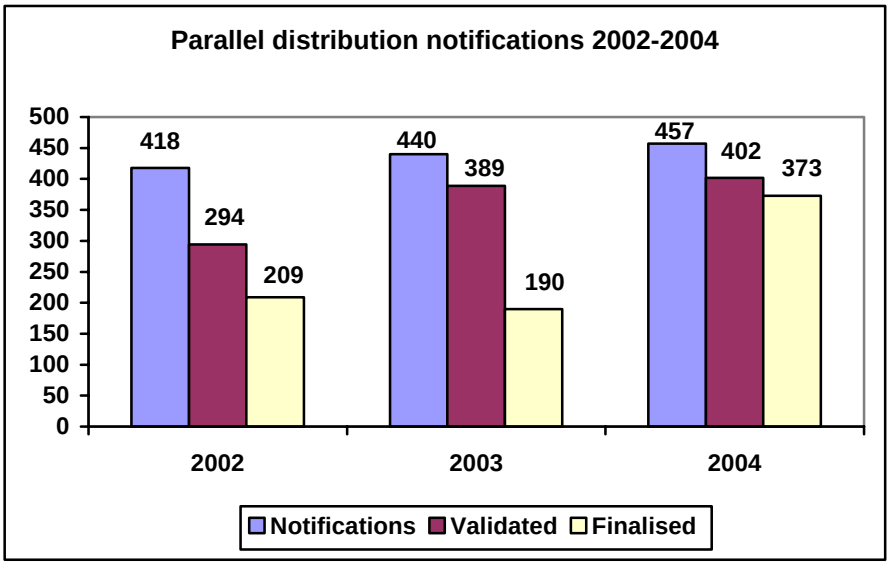
Work is still ongoing on the implementation of this action plan, although, overall, good progress has been made. Actions have focused on revision and strengthening of the quality assurance system, establishing clear roles and tasks for the working parties, and revising the policy on the handling of conflicts of interests. In addition, guidance documents on how to further improve the centralised procedure and the functioning of the CHMP and its working parties have been drafted, finalised or are still being discussed at Committee level.

The existing procedures were updated to take account of the consequences of the EU enlargement and the revision of the pharmaceutical legislation.

2.10 Parallel distribution

A Community marketing authorisation is valid throughout the EU and a centrally authorised medicinal product is by definition identical in all Member States. Products placed on the market in one Member State can be marketed in any other part of the Community by a 'parallel distributor' independent of the marketing authorisation holder. Typically, this is done to benefit from price differentials. The EMEA checks compliance of such products distributed in parallel with the appropriate terms of the Community marketing authorisation.

In 2004, the EMEA validated 402 initial parallel distribution notifications and finalised 373 initial notifications. The Agency finalised 340 notifications of change.



The parallel distribution activity was marked by two major changes in 2004:

The enlargement of the European Union made it necessary to implement the Specific Mechanism in the existing notification procedure. In addition, the notification of the parallel distribution of centrally authorised medicinal products to the EMEA became mandatory on 20 May 2004, in accordance with Title IV of Regulation (EC) No 726/2004.

To prepare for these changes, the notification procedure was changed to take into account feedback received from parallel distributors. These changes should increase the process efficiency and lead to shorter timelines. The EMEA agreed with the European Association of Euro-Pharmaceutical Companies (EAEPC) to put in place a joint performance indicator exercise to monitor the operation of the procedure. In 2004, the EMEA also published guidance for parallel distributors.

2.11 Mutual recognition facilitation group

Websites:

Heads of Medicines Agencies–Human *http://heads.medagencies.org*

European product index *http://heads.medagencies.org/mrindex/index.html*

The Mutual Recognition Facilitation Group (MRFG) reports to the Heads of Medicines Agencies–Human. The group is made up of delegates from the EU, Iceland and Norway, and meets at the EMEA to coordinate Member States' positions on topics relating to the mutual recognition procedure (MRP). Observers from the European Commission and from accession countries also participate in the monthly meetings.

The MRFG also, on request, provides procedural and regulatory advice and develops general guidance papers, which it publishes on the MRFG website.

The MRFG met 11 times in 2004. Caitríona Fisher chaired the meetings during the Irish EU presidency and Truus Janse-de Hoog chaired the meetings during the Dutch EU presidency. Two informal meetings were held in 2004, in Dublin and Scheveningen. The enlargement of the European Union on 1 May 2004 and the preparation for the implementation of the new Community legislation were permanent items on the MRFG agenda.

The number of new applications for the mutual recognition procedure in 2004 increased compared to 2003. In addition, there was an increase in the number of arbitrations of new applications compared to previous years. Statistical information on applications under the mutual recognition procedure is provided by the EMEA and presented in the monthly MRFG press releases.

Mutual recognition procedure	Total submitted in 2004*	Under evaluation in 2004*	Ended positively in 2004*	Referrals started in 2004
New applications	935	285	760	9
Type-IA variations	3 472	130	3 240	N/A
Type-IB variations	2 128	54	1 998	N/A
Type-II variations	1 402	233	1 083	0

*The numbers include multiple procedures as stated at 31 December 2004.

The EMEA/MRFG secretariat can be contacted by e-mail to: mrp@emea.eu.int

3 Veterinary medicines

Unit for veterinary medicines and inspections	
Head of Unit	Peter JONES
Head of Sector for veterinary marketing authorisation procedures	Jill ASHLEY-SMITH
Deputy Head of Sector for veterinary marketing authorisation procedures	Melanie LEIVERS
Head of Sector for safety of veterinary medicines	Kornelia GREIN
Head of Sector for inspections	Emer COOKE

The annual report for inspection activities is given in Chapter 4.

See Annex 3 for members of the committee, working parties and ad hoc groups.

Medicines for veterinary use – Highlights in 2004

- The CVMP adopted its 'Position paper regarding availability of products for minor uses and minor species' (EMEA/CVMP/477/03/Final) detailing the strategy to be taken in advancing the greater availability of medicines in the veterinary sector. Many of the recommendations are now in the process of being implemented.

- EudraVigilance in the veterinary sector for electronic reporting of adverse reactions became fully operational on 1 January 2005.

- The CVMP's preparation for enlargement of the European Union proved more than adequate, with the restructuring of the Committee in accordance with the revised pharmaceutical legislation taking place smoothly and without any difficulty. In addition, a new Scientific Advice Working Party was created, and its mandate and work objectives agreed by the CVMP.

- Initiatives to acquaint and train assessors and other regulatory staff with new environmental safety testing requirements were begun.

- The Scientific Advisory Group on Antimicrobials was created as planned, and its mandate and work objectives agreed and formalised by the CVMP.

- There was 100 % adherence to regulatory timelines for all activities relating to applications for centralised procedures and MRL applications.

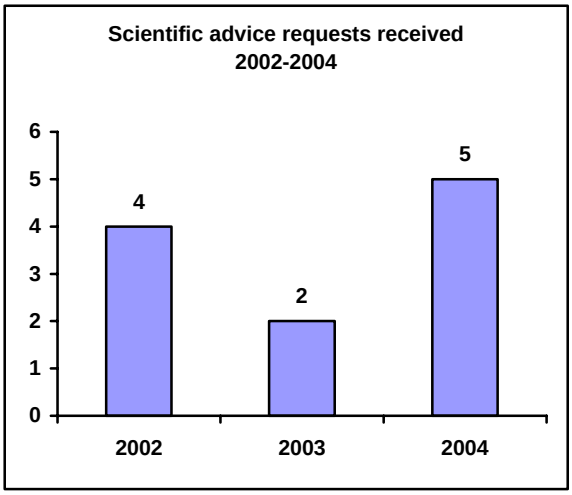
- Good progress was achieved on improving the quality and consistency of scientific assessment reports, with a revision of the assessor guideline and the initiation of a scientific memory database for centralised procedures.

- A CVMP audit was completed in October 2004 and four 'opportunities for improvement' resulted; action plans addressing the concerns highlighted were finalised and submitted to the EMEA IQM team.

3.1 Scientific advice

Improving the availability of medicinal products is one of the core objectives of the EMEA. By providing scientific advice to companies developing new medicinal products, the EMEA helps to increase the likelihood of those products being granted a marketing authorisation, and thus helps to bring the products to market more quickly.

Five applications for scientific advice were received in 2004. One application involved collaboration with the Food and Drug Administration (FDA) on a parallel protocol assistance procedure, which was also subject to a follow-up procedure. This was the first time that such dialogue had occurred for a veterinary scientific advice procedure.



Following an exchange of views with IFAH-Europe in 2004, the procedure and guidance for prospective applicants to request scientific advice has been considerably amended, which appears to be resulting in more applications. The Management Board also approved the provision of free scientific advice to companies developing products for minor uses and minor species.

Scientific Advice Working Party

A new working party was created in 2004, following the entry into force of Title IV of Regulation (EC) No 726/2004: the Scientific Advice Working Party, responsible for all requests for scientific advice relating to product development. The first meeting took place in September 2004. The mandate and work plan for the new group were published. The standard operating procedure (SOP) and web guidance document were revised considerably, taking into account comments received from interested parties.

3.2 Initial evaluation

The EMEA promotes public and animal health by reviewing new applications for authorisation of medicinal products in a timely and efficient manner, thus contributing to the provision of new and safe treatment options.

An initial evaluation is conducted by the EMEA to assess the quality, safety and efficacy of every new veterinary product that is subject to the Community or centralised procedure. Following this initial evaluation, the Committee for Medicinal Products for Veterinary Use (CVMP) adopts an opinion on whether the product should receive a marketing authorisation.

The CVMP adopted 10 positive opinions for veterinary medicines, including 8 vaccines. There were no negative opinions and 1 application was withdrawn prior to opinion.

The year's most notable evaluations concerned:

- An equine vaccine for immunisation against *Streptococcus equi* for the condition of strangles — a most debilitating disease that affects horses, characterised by high fever, coughing and difficulty in swallowing due to swelling of the mandibular lymph nodes

- A new vaccine (the only one available) for active immunisation of dogs against *Babesia canis* and *Babesia rossi* to reduce severity of clinical signs associated with acute babesiosis and the anaemia that ensues following a heterologous challenge infection

- A new non-steroidal anti-inflammatory medicinal product (NSAID) belonging to the coxib group, which acts by selective inhibition of cyclooxygenase-2 (COX-2) medicated protaglandin synthesis, for relief of pain and inflammation associated with osteoarthritis in dogs

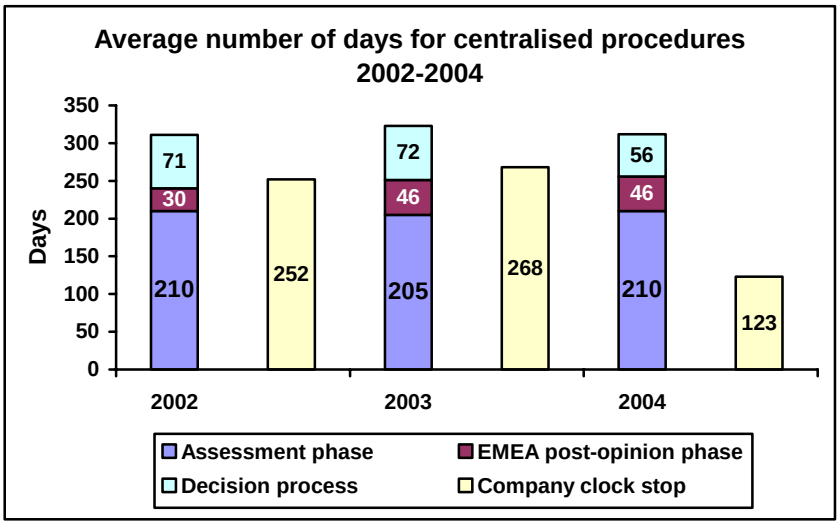
- A range of vaccines for cats, containing live and inactivated components in various valency combinations, allowing veterinarians to adapt the vaccination programme to the needs of individual cats, for active immunisation of:

    - Feline viral rhinotracheitis
    - Calcivirus infection
    - *Chlamydophilia felis* infection
    - Feline panleucopenia
    - Feline leukaemia

    These vaccines contain no adjuvant and should result in less injection-site reactions in vaccinated cats

See Annex 10 for a detailed list of opinions adopted.

The CVMP took an average of 210 days for assessment of those new applications which received a Commission decision in 2004.

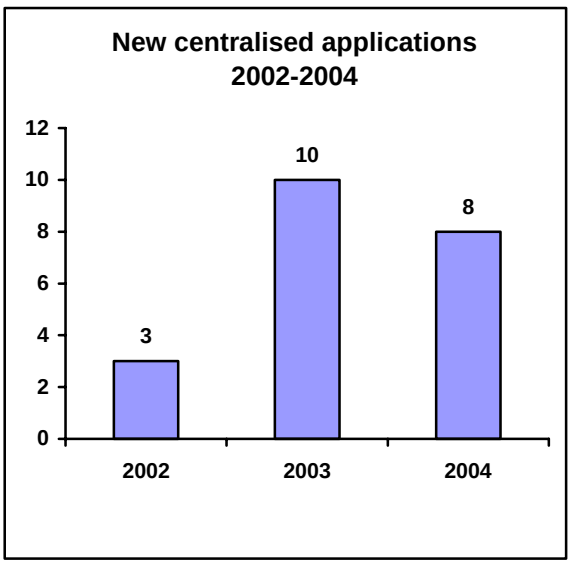


Transparency

Summaries of opinion for initial centralised applications are published at the time of adoption by the CVMP. European Public Assessment Reports are published as soon as possible after receipt of the respective Commission Decision in line with the procedure for human medicines.

Level of applications

Companies submitted 8 new applications for veterinary medicines in 2004, of which 4 were for immunologicals and 4 were for pharmaceuticals, including 1 generic. Five of the applications were for companion animals and 3 for food-producing animals, namely horses.



There was a shortfall of 3 applications from the 11 forecast for the year. It remains challenging to accurately predict the number of applications to be received, despite forecasts supplied by Industry, as there is, unfortunately, little intelligence available in the veterinary sector regarding new products in the development pipeline.

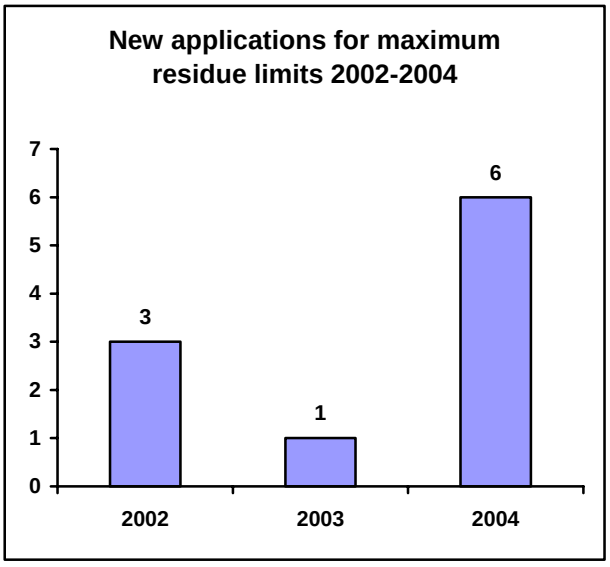
Greater level of satisfaction with the quality of dossiers

CVMP rapporteurs, co-rapporteurs and EMEA project managers reported (in the joint EMEA/IFAH-Europe survey on the centralised procedure) a much greater level of satisfaction with the quality of dossiers submitted than was reported in the previous survey, in which the outcome had already been regarded as very positive. This indicates that there were fewer premature applications. Part 4 of the dossier, regarding efficacy, has been identified as the area where quality of the dossier could be further improved; it is the part of the dossier which results in most questions to the applicant at day 120 of the procedure. In some cases where the applicant has been unable to address these questions and the dossier was heading for a negative opinion, this has led to the withdrawal of the application.

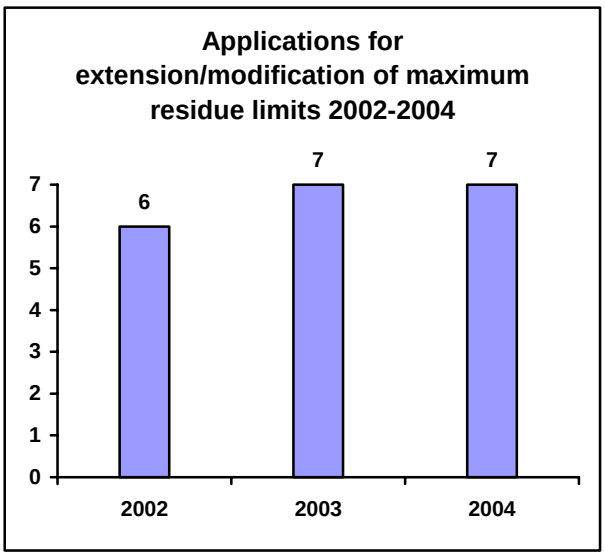
3.3 Maximum residue limits

If food animals are treated with medicines, residues may remain in the food produced by or from them. Consumers expect that residues be avoided as far as possible, and, where not possible, that they be safe. To obtain a marketing authorisation for a veterinary medicinal product intended for use in food-producing species, so-called maximum residue limits (MRLs) for all pharmacologically active substances must be established in advance for the animal species concerned and for its relevant tissues or products, e.g. meat, milk, honey etc. An MRL is the safe level of residue in food that can be consumed by a person every day over a lifetime without it causing a harmful effect.

In 2004, the EMEA received 6 new applications for new MRLs. This is an increase of 5 over the previous year, and reflects the continuing emergence of new active substances for food-producing animals. Such substances are evolving partly through the development of new products, while others are old molecules for which no MRLs had previously been established or which had previously not been used as veterinary medicines. The CVMP took an average of 108 days for assessment of new MRLs.



Seven applications for extension or modification of MRLs were submitted in 2004. This is a shortfall of 3 in comparison with the forecast of 10 MRL applications, and means the number remains at the same level as in 2003.



MRL summary opinions are published following their adoption by the CVMP. Summary reports are published on the EMEA website within 14 days of publication in the Official Journal of a Commission Regulation amending the Annexes to Council Regulation (EEC) No 2377/90.

Cooperation with EFSA

2004 saw the first cooperation with the European Food Safety Authority (EFSA), involving the establishment of maximum residue limits for Lasalocid sodium (coccidiostat) for chicken and game birds, which was also evaluated in 2004 by EFSA for approval as a feed additive. This cooperation follows a new legal provision of Article 59 of Regulation (EC) No 726/2004, which lays down provisions to avoid conflicts between scientific opinions of different Community bodies.

See Annex 10 for a detailed list of opinions adopted.

Establishment of maximum residue limits for old substances

At the beginning of 2004 there were 3 ‘old’ substances remaining for which MRLs had not been entirely completed: altrenogest, flugestone acetate and norgestomet. Old substances are those which were on the market prior to the entry into force of Regulation (EEC) No 2377/90 and for which there are still some outstanding issues to address. Altrenogest received a positive opinion to establish final MRLs in June 2004. Flugestone acetate and norgestomet were placed in Annex III of Regulation (EEC) No 2377/90 in 2003, with provisional MRLs expiring in 2008. The work for final MRLs for these two substances is well underway and is likely to be completed in 2005.

3.4 Availability of medicines for minor use and minor species

The EMEA and CVMP continued to advance the course of greater medicines availability for minor uses and minor species. The Committee adopted its key position paper in June 2004 setting out to further define the problem and offering solutions to try and resolve matters from a regulatory perspective. In its strategic action plan detailed in the paper, the Agency and Committee are exploring such possibilities as provisional authorisations, adaptation of data requirements, further possibilities for extrapolation of MRLs, and the provision of assistance by the Agency to companies wanting to authorise such products. The Committee also finalised its proposals to the Commission for a list of essential products for equidae that can be authorised without MRLs providing six-month statutory withdrawal periods are applied.

Following a decision of the Management Board in 2003, a 12-month pilot project was launched, in May 2004, to grant free scientific advice to any sponsor seeking to develop veterinary medicinal products for food-producing animals that fall under the minor uses and minor species scheme.

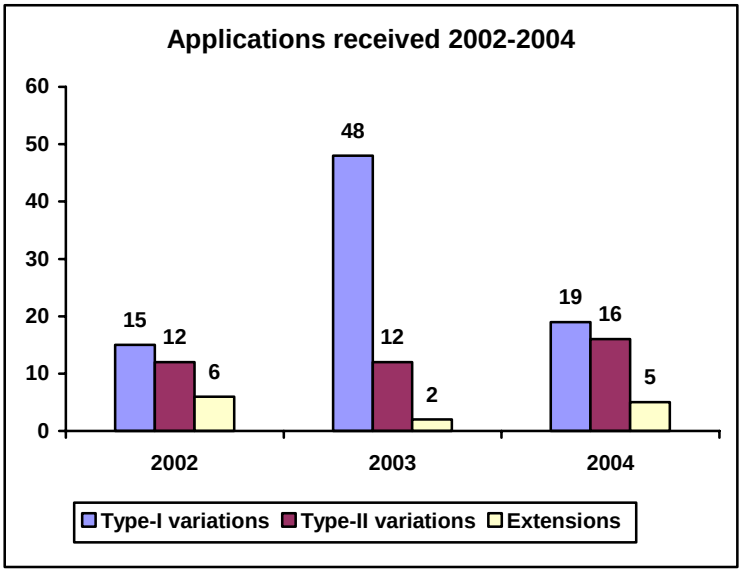
Progress continued in extrapolating major species MRLs to minor uses. MRLs established for cattle were extrapolated for three substances; in one case to goats, in a second case to sheep and in a third case to all mammalian species.

3.5 Post-authorisation activities

All changes that are made to the terms of authorisation of a centrally authorised medicinal product throughout its life have to be approved by the Community. Marketing authorisation holders may want to change the manufacturing process, alter or improve the medicinal product, or introduce additional warnings and contraindications.

Post-authorisation activities relate to variations, line extensions and transfers of marketing authorisation. Variations to marketing authorisations can involve either minor (type-IA or IB) or major (type-II) changes.

The EMEA received a total of 19 type-I variation applications (14 type-IA and 5 type-IB) — less than half of the original 40 forecast. This was compensated for by a higher number of type-II variations. Whereas 12 type-II variations had been forecast, the EMEA actually received 16, of which 12 concerned pharmaceuticals and 4 concerned vaccines.



Five applications for extension to the original marketing authorisation were received in 2004, exceeding the initial forecast of 3 applications. Three of those 5 concerned vaccines and 2 concerned pharmaceuticals.

3.6 Pharmacovigilance and maintenance activities

This includes activities relating to pharmacovigilance information (periodic safety update reports), follow-up measures, specific obligations, annual re-assessments (annual reports) and renewal applications.

Pharmacovigilance is a priority area for the Agency and, as a consequence, the EMEA will continue and further strengthen its efforts in order to ensure the safe use of products licensed in accordance with the centralised procedure.

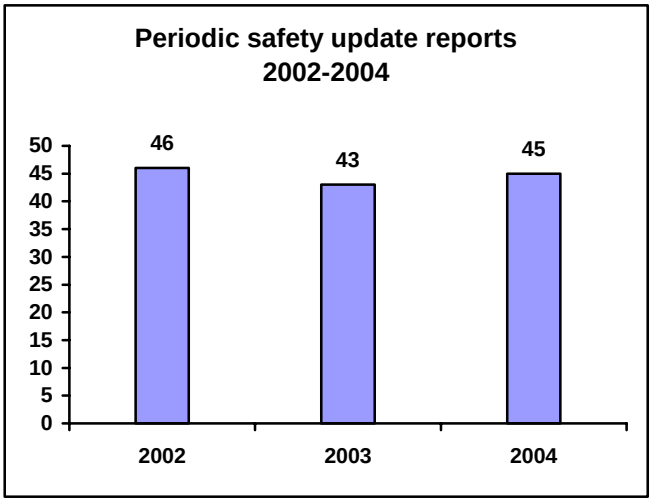
Annual reports for 32 products were prepared in 2004, each of which is prepared in cooperation with a rapporteur and co-rapporteur, and adopted by the CVMP.

Seven applications for renewal of marketing authorisations were received in 2004. One product was not renewed and, therefore, its marketing authorisation expired in 2004.

Pharmacovigilance for veterinary medicines has continued to be a very high priority for the veterinary secretariat, which seeks to drive forward initiatives for optimising adverse event reporting and risk management of medicinal products in the post-authorisation phase.

Forty-five periodic safety update reports (PSURs) were received as forecast and were reviewed by the CVMP based on in-depth reviews provided by the rapporteur. In no case did such reviews lead to a call for changes to the summary of product characteristics (SPC) or product label/leaflet.

The CVMP Pharmacovigilance Working Party continues to advise the Committee on pharmacovigilance issues and, in 2004, reviewed even more issues relating to the safety of nationally approved products, underlining the benefits of the good working relationship that exists between the EMEA, CVMP and Member States with regard to ensuring adequate safety monitoring of products in the market place.



In order to support initiatives promoting pharmacovigilance in the EU, with particular focus on providing support to the new Member States, a common reporting form for reporting suspected adverse reactions to veterinary medicinal products by veterinarians and other veterinary health professionals was developed by the CVMP Pharmacovigilance Working Party for use in all EU Member States, and was released for consultation by the CVMP in October 2004. This common

reporting form aims to ensure consistency of collected information and to foster a common understanding of adverse reaction reporting by practising veterinarians throughout the EU.

The CVMP adopted its 'Guideline on harmonising the approach to causality assessment for adverse reactions' in order to ensure greater consistency throughout the EU in reporting adverse events by all parties involved.

The objective of introducing greater consistency in the triggering of investigations following receipt of pharmacovigilance reporting has been progressed by the release for consultation of a guideline by the CVMP on this topic in June 2004.

Initiatives to improve veterinary pharmacovigilance

The development of a CVMP simple guide to veterinary pharmacovigilance in the EU was started in 2004, following consultation on a concept paper. The objective of the guide is to inform veterinarians and other animal-health professionals about the pharmacovigilance system for veterinary medicinal products in the EU and to stimulate their cooperation on the reporting of adverse drug reactions (ADRs). The guide also advises on how to report ADRs. It is expected that this initiative will increase the number of reports produced and, subsequently, strengthen the basis for evaluating the safety of authorised veterinary medicinal products.

The implementation of CVMP recommendations on more effective and adequate reporting of ADRs for veterinary medicines in the EU continued, following on from progress achieved in 2003. In addition, the EMEA was pleased to support the launch of the IFAH-Europe Good Veterinary Pharmacovigilance Practice Guide, produced by Industry to encourage further advances in the consistent reporting of ADRs throughout the Community.

European surveillance strategy

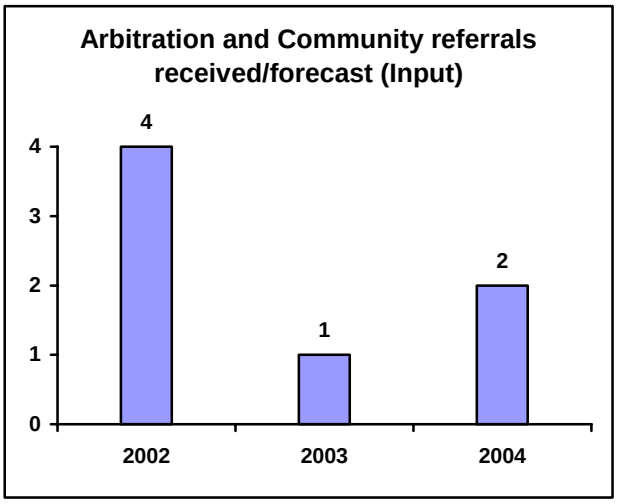
In 2004, the EMEA and the CVMP, together with the Heads of Medicines Agencies–Veterinary, started the European surveillance strategy — an initiative intended to foster collaboration and support between Member States on the conduct of good pharmacovigilance practices.

EudraVigilance

The revised EudraVigilance Veterinary test system was available from early September 2004, with the production system becoming available on 18 October 2004 — well before 1 January 2005, the date for implementation of electronic reporting agreed with the Member States' Heads of Veterinary Regulatory Authorities.

3.7 Arbitration and Community referrals

Arbitration procedures are initiated because of disagreement between Member States in the framework of the mutual recognition procedure (Article 33 of Directive 2001/82/EC). Referrals are initiated either in order to obtain harmonisation within the Community of the conditions of authorisation for products already authorised by the Member States (Article 34 of Directive 2001/82/EC), or in cases involving the interests of the Community or concerns relating to the protection of human or animal health or the environment (Articles 35 and 40 of Directive 2001/82/EC).



In 2004, 2 referrals were received; no arbitration was submitted.

One referral concerned the harmonisation of withdrawal periods, which differed significantly between the marketing authorisations in the different Member States, for Dectomax 1 % injectable solution (doramectin) — an endectocide injectable product for sheep. The CVMP agreed to set a harmonised withdrawal period, which is now adopted throughout the Community.

The other referral concerned the veterinary medicinal product Micotil 300 (tilmicosin). The referral was initiated to investigate concerns regarding user safety, in the interest of the Community, following an accidental human fatality resulting from use of this product during the treatment of animals earlier in 2004. The CVMP decided that the benefits of using Micotil outweighed the risks, but, in order to mitigate such risks, required additional precautions and warnings to be included on the SPC and label.

See also Annex 13.

3.8 Regulatory guidance

EU institutions and regulatory authorities

The EMEA actively contributed to the public consultation on proposals to replace the existing Regulation on the establishment of maximum residue limits.

Interested parties

Relationships with interested parties continued to flourish in 2004. Two Infodays took place, in June and December 2004, held together with Industry. There were also regular bilateral meetings between the EMEA and the secretaries of various interested parties.

A new task for the EMEA stemming from the new Community legislation is to improve and optimise contacts with its various stakeholders to facilitate dialogue and communication. In line with this new responsibility, the CVMP adopted the position paper 'Procedure to be followed to facilitate communication and dialogue between the CVMP and interested parties'.

3.9 Management and organisation of the CVMP

The Committee for Medicinal Products for Veterinary Use (CVMP) is responsible for formulating the Agency's scientific opinions regarding the quality, safety and efficacy of medicinal products for veterinary use and the establishment of maximum residue limits.

Important responsibilities of the CVMP include the preparation of regulatory guidelines for the veterinary pharmaceuticals industry as well as the provision of assistance to companies researching and developing new veterinary medicines.

After the EU enlargement on 1 May 2004, the CVMP met for the first time with members from the new Member States. Following entry into force of Title IV of Regulation (EC) No 726/2004 on 20 May 2004, a new Committee structure came into effect from June 2004 with one member per country. The Committee now has one member from each of the 25 EU Member States and one member each from Iceland and Norway. Each Committee member has an alternate.

The new Regulation gives the Committee the possibility of nominating up to five co-opted members, when necessary, to gain additional expertise in a particular scientific area. The CVMP nominated additional members as follows: one expert on quality aspects of biotechnology products; three experts on clinical medicine (one for companion animals, one for large animals and one for intensive production, with a focus on poultry); and one expert on safety and risk assessment. These nominations for co-opted members were confirmed in all but one discipline, intensive production, by the end of 2004.

In 2004, the CVMP met 11 times and held 2 informal meetings. Issues discussed included: enlargement of the EU and implementation of the new legislation; integration of the new members; the new Committee structure; quality and integrity of scientific assessments; and improvements called for following an audit of the Committee in October 2004.

Working parties

The work of the CVMP is supported by a number of working parties, composed of European experts selected from a list maintained by the EMEA. They are involved, according to their specific area of responsibility, in the development and revision of guidelines and in the provision of recommendations and advice on medicinal products for which applications are made for scientific advice, marketing authorisation or post-authorisation activities. Recommendations and advice provided include general public-health issues relating to veterinary medicinal products.

The CVMP established the following standing and temporary working parties to assist its scientific assessment activities:

Standing working parties

- Efficacy Working Party
- Immunological Working Party
- Pharmacovigilance Working Party
- Joint CHMP/CVMP Quality Working Party
- Safety Working Party
- Scientific Advice Working Party

Temporary working party

- Environmental Risk Assessment

Scientific Advisory Group on Antimicrobials

The CVMP created a Scientific Advisory Group on Antimicrobials in 2004. The role of this group is to advise the CVMP on specific scientific questions addressed to it.

See Annex 3 for details of working parties and scientific advisory groups.

Scientific guidance

The development and revision of scientific guidelines is a particularly important aspect of the work of the working parties as they contain guidance on specific scientific issues and are based on the most up-to-date scientific knowledge available, providing essential information to be taken into account in the research and development of new medicines. Often, such guidelines are developed as a result of the EU's cooperation with Japan, the US and other international partners on the harmonisation of regulatory requirements for medicinal products, particularly through the VICH conference, and thus reflect a harmonised approach.

See Annex 10 for details of guidance documents.

3.10 Improving the Agency's structures and procedures for veterinary medicines

The Agency continually strives to improve the structures and procedures of the scientific evaluation of medicinal products. In this context, the CVMP, its processes, records and working practices were audited in October 2004. Based on the findings of the audit, an action plan was developed to implement the opportunities for improvement identified.

Other activities in 2004 focused on the quality and consistency of CVMP assessments for centrally authorised products.

3.11 Veterinary mutual recognition facilitation group

Useful website:	
Heads of Medicines Agencies–Veterinary	*http://www.hevra.org*

The Veterinary Mutual Recognition Facilitation Group (VMRFG) met at the EMEA every month (except August) in 2004, under the chairmanship of the Irish and Dutch EU presidencies. Two informal meetings were held in 2004: one in Cork, in May, under the Irish presidency, and one in Rotterdam, in November, under the Dutch presidency. The EMEA provided full secretariat and administrative support to the group.

Ninety-four mutual recognition procedures were completed in 2004. Ten Member States acted as reference Member State in these procedures, compared with 9 in 2003.

Integration of the new EU Member States

From 1 May 2004, the 10 new EU Member States were able to participate at the VMRFG meetings as full members of the group. An observer for the veterinary authority of one EEA-EFTA state participated in plenary sessions.

Prior to May 2004, the new Member States participated voluntarily in simplified mutual recognition procedures under the Collaboration Agreement between Veterinary Drug Registration Institutions (CAVDRI) of European Union Associated Countries.

In 2004, the VMRFG provided answers to a wide range of questions from both Member States and Industry on a number of different regulatory issues. The group also adopted and revised a number of documents on the management of procedures. Considerable effort was made to prepare for the significant changes associated with the new legislation, which will come into full effect on 20 November 2005.

VMRFG members met with interested parties from the animal health industry 5 times during 2004, in February, April, June, September and December. Representatives attended from the VMRFG, IFAH-Europe and the European Group for Generic Veterinary Products (EGGVP). An oral report on the activities of the VMRFG was provided at each CVMP meeting in 2004.

4 Inspections

Head of Sector	Emer COOKE
Working parties and ad hoc groups	
Ad hoc Meeting of GMP Inspection Services	Emer COOKE (chair)
Ad hoc Meeting of GCP Inspection Services	Fergus SWEENEY (chair)

Inspections – Highlights in 2004

- Despite initial delays, the preparatory work for effective operation of the Japan-EU mutual recognition agreement (MRA) was successfully concluded, allowing the operational phase of the agreement to come into force on 29 May 2004.

- The EMEA provided support for the implementation of the Clinical Trials Directive, ensuring the successful rollout of the European clinical trials database (EudraCT) in line with the legal deadline of 1 May 2004.

- All requests for GMP, GCP (including pharmacovigilance) and GLP inspections relating to applications for products through the centralised procedure were successfully coordinated and managed within the timeframes laid down in Community law and to the standards required in the Agency's quality management system.

- Inspections of blood establishments to support certification of plasma master files (PMF) were initiated in the second half of 2004 and a new procedure was developed and published.

- The first steps in the review of the sampling and testing programme were agreed, including revised objectives for the programme, principles for new testing arrangements, and greater transparency measures.

- The EMEA took over responsibility for publication of the compilation of Community procedures for GMP inspectorates and developed a revised procedure for development of EU pharmaceutical guidelines, which takes into account new calls for transparency.

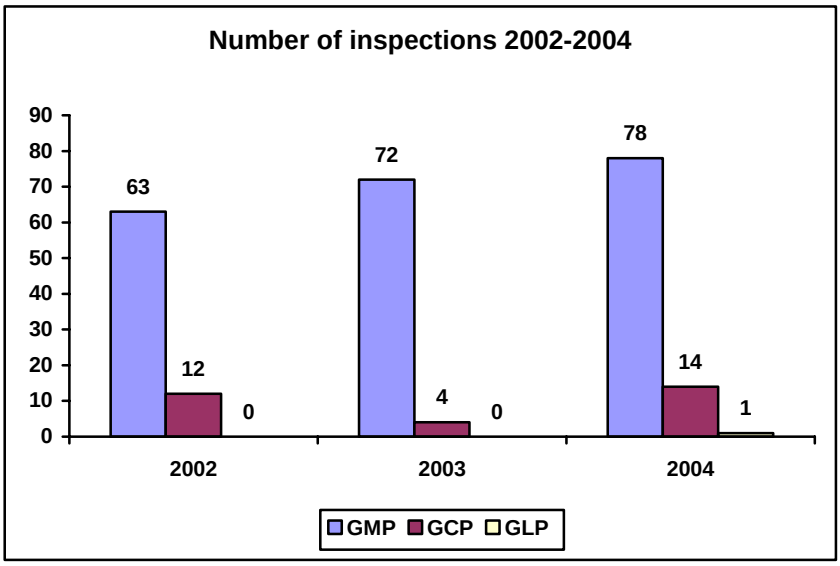
- PAT team — a European team of GMP inspectors and quality assessors — was established to address matters relating to the implementation of process analytical technology (PAT) by manufacturers, and a training session for assessors and inspectors was organised in September with the support of the Swedish Medical Products Agency.

4.1 Inspections

The EMEA coordinates the verification of compliance with the principles of good manufacturing practice (GMP), good clinical practice (GCP) and good laboratory practice (GLP), and with certain aspects of the supervision of authorised medicinal products in use in the EU, through inspections requested by the CHMP or CVMP in connection with the assessment of marketing authorisation applications and/or the assessment of matters referred to these committees in accordance with Community legislation.

These inspections may be necessary to verify specific aspects of the clinical or laboratory testing or manufacture and control of the product and/or to ensure compliance with GMP, GCP or GLP and quality assurance systems. Similarly, the EMEA coordinates pharmacovigilance inspections requested by the scientific committees and inspections of blood establishments within the plasma master file (PMF) certification framework.

Communication and action by Member States in response to suspected quality defects relating to centrally authorised medicines are also coordinated by the EMEA.



Good manufacturing practice (GMP) activities

GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.

Requests for GMP inspection increased by 8 % relative to 2003, mainly due to a large number of re-inspections which fell due and the impact of inspections in the context of the PMF certification scheme.

Seventy-eight GMP inspections were requested in 2004; 40 % of these related to requests for re-inspection of sites already inspected two to three years previously.

Inspections of blood establishments to support certification of PMFs were initiated in the second half of 2004 and a total of 15 inspections were carried out in this context, involving 27 blood establishment sites. A new 'Procedure for coordinating pre-approval inspections in the context of plasma master file certification' (SOP/INSP/2009) was developed, agreed and published on the EMEA website.

The quality and safety of products derived from human plasma rely both on the source plasma material and the further manufacturing processes. This means that the collection, testing, storage and transportation of human plasma are major factors in the quality assurance of the manufacture of plasma-derived products. Collection of human plasma for further manufacturing, as well as storage, testing and transportation, is subject to periodic inspections in order to ensure the expected product quality.

Good clinical practice (GCP) activities

GCP ensures that ethical and scientific standards for designing, conducting, recording and reporting clinical trials are adhered to. It protects the rights, integrity and confidentiality of the trial's subjects and ensures that data and reported results are credible and accurate.

Fourteen GCP inspections were requested in 2004. This more than triples the number requested in 2003 and results from an increase in the number of applications, the impact of applications for biosimilar medicinal products, and a number of inspections for pharmacovigilance purposes.

Good laboratory practice (GLP) activities

The principles of GLP define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.

One GLP inspection was requested in 2004.

A new procedure for requesting and reporting GLP inspections for centralised applications came into effect on 15 August 2004. The procedure describes the coordination of GLP inspections of the non-clinical safety, toxicological and pharmacological studies proposed in human and veterinary applications for marketing authorisations under the centralised system.

Product defects and deviations

In order to protect public and animal health, it may become necessary to implement urgent measures such as the recall of one or more batches of a medicinal product during its marketing period. Every holder of a manufacturing authorisation is required to implement an effective procedure for the recall of defective products. The authorisation holder is required to notify the EMEA of any defect or abnormal restriction of a centrally authorised medicinal product that could result in a recall.

As expected, the workload in dealing with product defects and deviations increased, mainly due to the greater number of centrally authorised products on the market and a growing awareness of Industry's responsibilities to keep the EMEA informed.

The EMEA received 38 quality defect reports concerning human medicinal products and 2 defect reports for veterinary medicinal products. For 10 of these defect reports a recall was necessary; the remainder were classified as minor.

The majority of recalls were initiated by the marketing authorisation holder and were in response to problems such as the presence of particulate matter, raised impurity levels, sterility failures, dissolution test failures and unsatisfactory inspection reports.

Meetings and other activities

The EMEA chaired and organised 4 meetings each for the Ad hoc GMP and GCP Inspectors Groups in 2004. These two groups contribute to the harmonisation of inspection-related procedures across the EU and develop guidance documents.

The Agency also provides secretarial support to the Joint CHMP/CVMP Quality Working Party (QWP) that continued with the development of EU quality guidelines, support to ICH, and cooperation with the European Directorate for the Quality of Medicines (EDQM).

The EMEA continually supported the Commission and the Member States with the implementation of Directive 2001/20/EC on clinical trials through the activities of the ad hoc meetings of GCP and GMP inspection services, through participation in working groups of the Commission, and through support to the implementation of European databases for clinical trials.

The first steps towards implementation of the confidentiality arrangements with the FDA took place in the second half of 2004 and included both routine exchanges of information on inspections performed and ad hoc exchanges on a number of inspection-related issues.

One joint meeting of the QWP and ad hoc GMP inspectors took place, building on cooperation between assessors and inspectors on quality-related matters. In addition, a training meeting for GCP inspectors was organised in Lisbon, focusing also on cooperation, bioequivalence studies and GCP/GMP interfaces.

An EMEA PAT team was created in January 2004 to review the implications of PAT with a view to ensuring that the European regulatory framework and the authorities are prepared for and adequately equipped to conduct thorough and effective evaluations of PAT-based submissions. PAT is a system for designing, analysing and controlling manufacturing through the timely measurement (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (= identifying and monitoring factors that affect product quality). The PAT team held 5 meetings in 2004 and established contacts with 3 pharmaceutical companies.

New responsibilities under the revised legislation

Following the adoption of the revised pharmaceutical legislation, work on a number of guidance documents relating to the new GMP requirements for active substances was begun.

The Ad hoc GMP Inspectors Group was appointed as the Telematics Implementation Group (TIG) for the Community GMP database in May 2004, and a preliminary implementation plan was drawn up. Two meetings with representatives from Member States were organised to identify existing systems.

4.2 Mutual recognition agreements

Mutual recognition agreements (MRAs) between the European Community (EC) and partner (third) countries include specific annexes regarding medicinal products and GMP. They allow EU Member States and the MRA partner to mutually recognise the conclusions of inspections of manufacturers carried out by the respective inspection services of the other party and the manufacturers' certification of the conformity of each batch to its specifications without re-control at import. The EMEA is responsible for the implementation and the operational aspects of these MRAs. MRAs with Australia, New Zealand, Switzerland, Canada and Japan are currently operational, but with slightly different provisions as to scope and applicability.

EC-Japan MRA

Despite initial delays, the preparatory work for effective operation of the Japan-EU MRA was successfully concluded through a series of visits and inspections allowing the operational phase of the agreement to come into force on 29 May 2004. Sterile medicinal products and some biological medicinal products are excluded from the scope. The agreement covers medicinal products for human use only.

EC-Canada MRA

Health Canada initiated assessments of Hungary and the Czech Republic following successful pre-MRA visits coordinated by the Commission as part of the extension of the MRA to cover new Member States.

Apart from the MRAs with Canada and the US, as of 1 May 2004, all MRAs now apply in all 25 Member States. MRA partners have agreed to work on harmonisation of operational aspects across the different agreements. Discussions to harmonise the certificate of GMP compliance of a manufacturer and maintenance programmes were initiated in 2004. The batch certificate format has been adapted to include investigational medicinal products and active substances. Work is ongoing with respect to harmonised rapid alert procedures and annual reporting provisions.

Mutual recognition agreement (MRA) implementation status and coverage

MRA	Implementation status	Coverage
European Community – Australia	Human medicinal products: 1 January 1999 Veterinary medicinal products: 1 June 2001	Human and veterinary medicinal products Official batch release excluded
European Community – Canada	Operational since 1 February 2003	Human and veterinary medicinal products Veterinary immunologicals and vaccines excluded
European Community – Japan	Operational since 29 May 2004	Human medicinal products only Currently excludes active substances, investigational medicinal products, medicinal gases Official batch release excluded
European Community – New Zealand	Human medicinal products: 1 January 1999 Veterinary medicinal products: 1 June 2002	Human and veterinary medicinal products Official batch release excluded

European Community – Switzerland	1 June 2002	Human and veterinary medicinal products and recognition of official batch control of biologicals
European Community – United States	Not in operation. Transitional period ended. No decision on formal extension of the transitional period has been taken	Human and veterinary medicinal products Official batch release excluded

4.3 Sampling and testing

The objectives of the sampling and testing programme, derived from the legal requirements, are to supervise the quality of centrally authorised medicinal products placed on the market and to check compliance of these with their authorised specifications. Sampling from the market in different countries is carried out by national inspectorates and testing is performed by Official Medicines Control Laboratories coordinated through the EDQM (European Directorate for the Quality of Medicines). A selection of centrally authorised products is included in each annual programme.

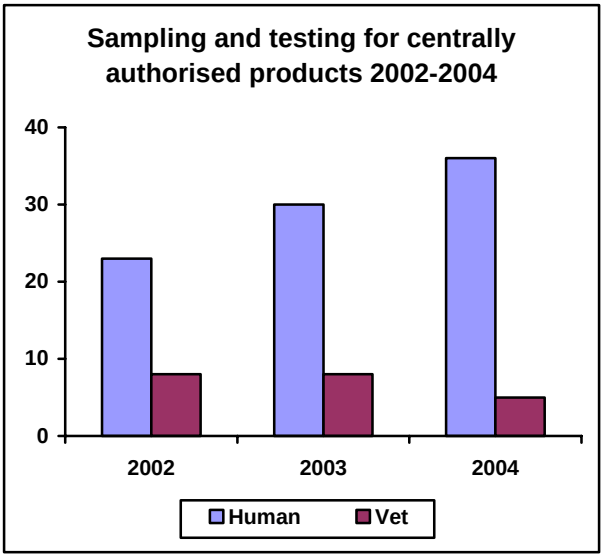
The Agency carried out sampling and testing activities as planned. The sampling and testing programme underwent a comprehensive review following the outcome of a seminar held in September 2003. The overall objectives were revised and published and a new testing scheme was agreed in principle. Special attention was paid to improving communication between the stakeholders and to increasing transparency and understanding.

Forty-one products were included within the scope of the programme of sampling and testing of centrally authorised products performed by the Network of Official Medicines Control Laboratories. This represents an increase of 10 % over 2003.

At the time of writing of this report, testing was completed and results reported for 31 products. The remaining 10 reports are in the process of finalisation and expected by the end of April 2005. The majority (>90 %) of results received show that the products were of high quality and complied with their authorised specifications. Results requiring further investigation were found for 3 of the 31 products. In one case, a confirmed out-of-specification result for one parameter (pH) was found. This is still under investigation to see if it is an isolated incident. Two further test results were identified with apparent out-of-specification results. However, these were due to difficulties with method transfer, rather than actual problems with the products. Method transfer problems occur in particular when the description of testing procedures by the companies is not sufficiently detailed. In line with the procedure, the results were provided to the (co-)rapporteurs to consider and subsequently to make recommendations for follow-up actions, i.e. specific investigation, inspections or variations.

New Member States took part in the testing part of the programme from May 2004 onwards, as samples of certain products had already been taken from the market prior to accession.

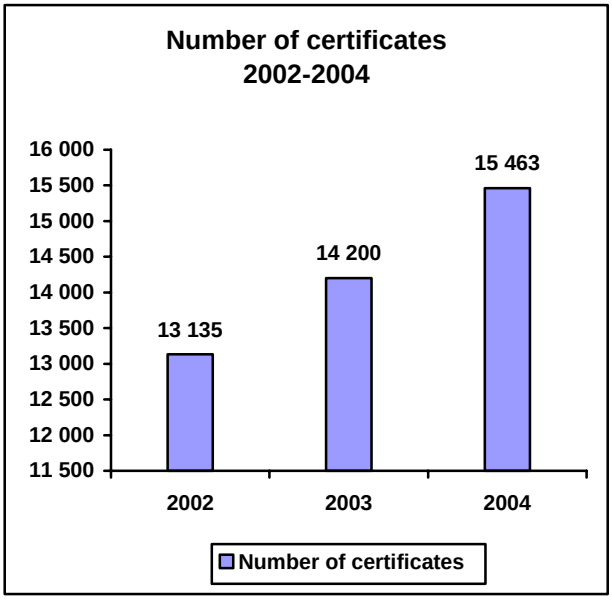
After a one-year period of implementation, changes have been introduced to the pilot procedure for follow-up of test results to streamline the reporting structures. In 2004, annual reports of the sampling and testing results were produced for the first time, starting with the 2003 programme.



4.4 Certificates of a medicinal product

The purpose of the EMEA certificates of medicinal products scheme is to support the work of health authorities outside the European Union, in particular in developing countries. EMEA certificates are issued by the EMEA, on behalf of the European Commission, to confirm the marketing authorisation status of either products authorised by the European Commission through the centralised procedure or products for which a centralised application has been submitted to EMEA. The certificates also confirm the Good Manufacturing Practice (GMP) compliance status of the manufacturing site(s) producing the medicinal product bulk pharmaceutical form. Authorities in developing countries can rely on centralised assessments to support marketing in their countries, thus facilitating access to these medicines and avoiding the need for costly and duplicative assessment work.

The number of requests for EMEA certificates continued to increase in 2004 due to the high number of new applications for centralised marketing authorisation received in 2003.



5 EU telematics strategy

The European Union telematics strategy for pharmaceuticals is agreed between Member States, the EMEA and the European Commission, and aims to increase efficiency, enhance transparency and provide support for the procedures set out in European legislation. The strategy is to concentrate on a small number of projects with high European added value.

Overall, substantial progress was made on implementing the telematics strategy during the year, with projects being delivered in line with expectations. The main achievements are described briefly in the table below.

Initiatives	Achievements
EudraNet	• EudraNet II in operation by May 2004 • All new Member States connected by 1 April 2004 • 85 % of all national competent aurthorities were connected to EudraNet II at the end of 2004
EuroPharm	• User requirements for the database were drawn up in line with additional requirements resulting from the terms of Regulation (EC) No 726/2004, G10 recommendations and Council conclusions • A first iteration forming the basis of the first production system — restricted to data on products that have been approved using the centralised procedure — was completed and demonstrated at the end of 2004 • Two exercises ultimately aimed at enabling the automatic transfer of data between competent authorities and EU Telematiics systems were initiated
EudraVigilance	• A pilot data-warehousing and business intelligence system was put in place • The first production version of EudraVigilance Veterinary was released at the end of 2004
Electronic submission	• A test implementation of an eCTD review system across the EU regulatory community for pharmaceuticals resulted in a decision to extend the requirements-gathering phase by a further 12 months • The contract for building the Product Information Management (PIM) system was placed following completion of a specification exercise • Two standards for electronic information exchange (the EU Module 1 Specification and the Application Form Specification) were adopted
Clinical trials databases	• Both the phase-1 registration system (known as EudraCT) and the EudraVigilance Clinical Trials Module were successfully deployed
GMP database	• This is a new requirement, on which specification work was initiated
Horizontal telematics services	• Security: security policies were proposed for adoption • Infrastructure: the initial environments were put in place • Business continuity: a second data room was established and disaster recovery sites identified

6 Support activities

6.1 Administration

Activities in the administration area relate to a number of functions, including managing and administering staff and seconded personnel, conducting recruitment procedures, and managing revenue, expenditure and accounts according to existing rules and regulations, as well as providing and running the necessary infrastructure services for effective functioning of the Agency.

The main achievements in 2004 included:

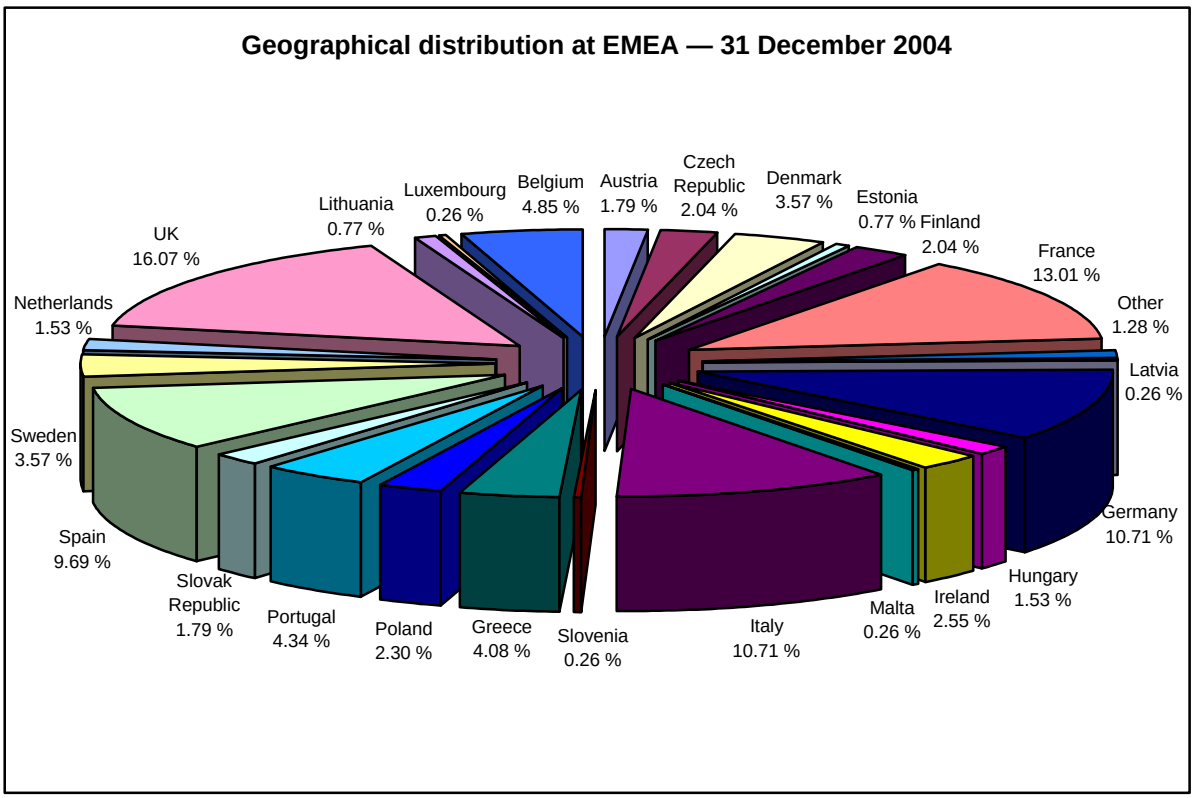
- Implementation of the new staff regulations
- Implementation of the new EMEA Financial Regulation, with revision of procedures
- Implementation of an improved activity-based budgeting database and budgetary planning
- Integration of delegates from the new Member States
- Implementation of new and modified accounting practices in line with the reform of the Commission
- Refurbishment of parts of the EMEA offices to accommodate new staff, telematics projects, and delegates and experts from the new Member States

Personnel

On 1 May 2004, the new 'Regulations and Rules applicable to officials and other servants of the European Communities' entered into force. Following this, a new career structure was implemented, as were changes to grading and allowances etc., which are being applied to existing staff and new recruits.

Recruitment of new staff continued — particularly from the new Member States. By the end of 2004, almost 10 % of the total of 335 EMEA staff members were nationals of one of the 10 new Member States.

A total of 27 recruitment procedures were carried out in 2004. Recruitment planning was put in place so that units can better plan recruitment needs and to enable more efficient organisation of selection procedures.



In line with the Agency's continuous drive for excellence, the availability of training was increased, with the aim of achieving up to 5 days of training per staff member per year. Training profiles were proposed for a range of job profiles at all levels within the Agency. Once finalised, these training profiles will help to establish a common competency standard among EMEA staff. A training tender was concluded which put framework contracts in place for future training needs.

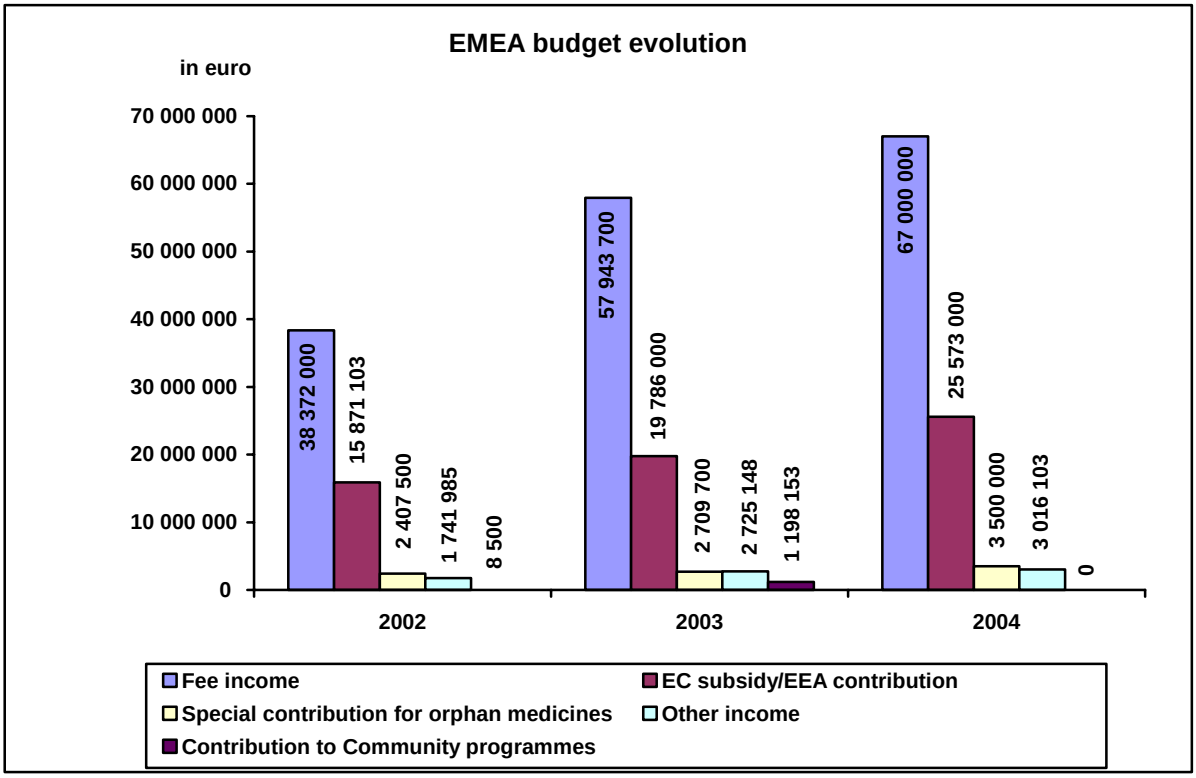
Budget

The new EMEA Financial Regulation was implemented with the agreement of the European Commission, the favourable opinion of the Court of Auditors and approval of the EMEA Management Board. All relevant staff were trained on the changes introduced.

The new Financial Regulation allows the Agency to build up a reserve from positive balance out-turns. Surpluses in one budget year are returned to the Commission, where they are earmarked to compensate for shortfalls in fee income in following budget years. This helps to enhance the financial stability of the Agency.

For the first time, the discharge for the implementation of the 2002 budget was given to the Executive Director by the European Parliament. In previous years, discharge was given by the Agency's Management Board.

A system of activity-based budgeting was developed, with details included in the budget reports to the Management Board and to the budgetary authority. A revised template was introduced to facilitate the collection of relevant data. The EMEA coordinated and chaired meetings of the Costing Group. The task of this group is to establish, together with the Member States, a cost-based reimbursement system for rapporteurship.

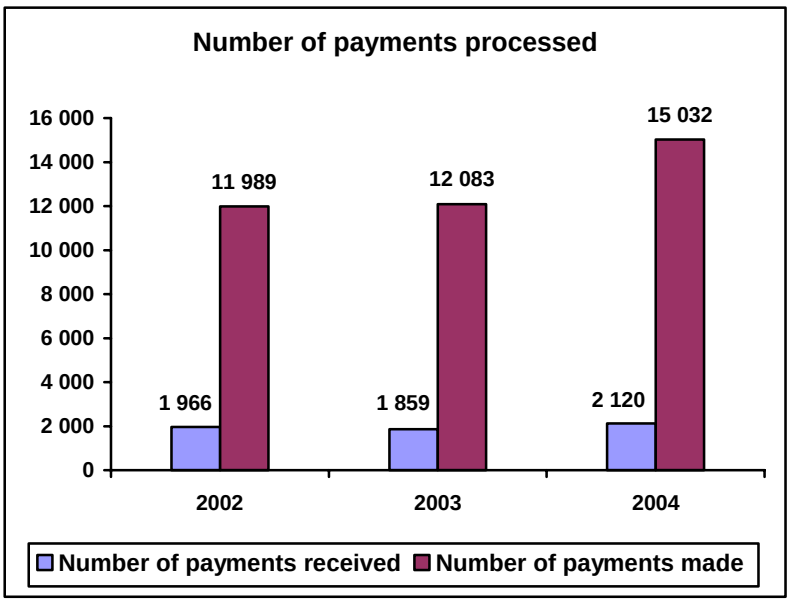


Accounts

The accounts sector maintains the accounts, makes payments and collects revenue in accordance with the procedures laid down in the Financial Regulation. It manages efficiently the cash resources of the Agency, maintains the Agency's relationship with its banks, and provides accurate and timely financial information to management.

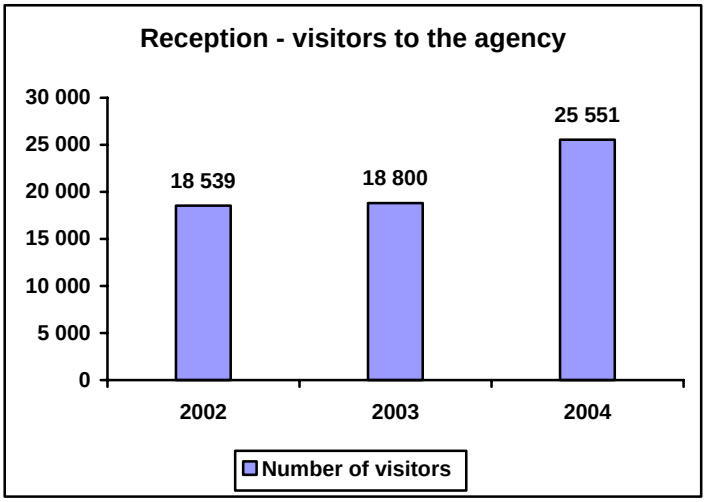
Meeting reimbursements increased by 38 % — due to EU enlargement — with a corresponding increase in the recording of new third parties. The volume of the third parties' database grew significantly in 2004, with over 1 000 parties added. The database now totals approximately 5 000 records.

An inventory accounting system was implemented and all data, including tangible and intangible assets, were uploaded to the system. The business objects reporting tool was also installed so that standard financial reports on asset purchases and depreciation could be produced.



Infrastructure

In 2004, the Agency had a record 25 551 visitors. This is a 36 % increase compared to the previous year.



Parts of the Agency were refurbished in 2004. In light of the steady growth of the Agency, a new floor providing office space for EMEA staff was fitted out in 2004.

In order to accommodate delegates from the 10 new Member States following enlargement, the EMEA reorganised and refurbished the delegates' offices.

The Agency continued to work on a business continuity plan, which sets out the overall business continuity and disaster recovery planning and arrangements to be implemented over a number of years. In this context, the EMEA signed a contract in order to be supplied with a 50-desk disaster static recovery suite.

A procurement plan for the whole Agency was compiled, providing a framework for tenders launched over the course of the year. Calls for tenders were published in the Official Journal of the European Union and, also, on the EMEA website.

6.2 Information technology at the EMEA

The smooth operation of EMEA internal information technology systems is critical to the Agency's ability to perform its tasks.

The IT sector provides reliable and robust IT services to EMEA staff, delegates and all users of pan-European systems. It provides efficient support and helpdesk services to the Agency's corporate users. The IT sector also ensures archiving and back-up of data, and maintains a high level of security and confidentiality for all data held on EMEA systems. In addition, the sector constantly introduces new services and improvements to the infrastructure as required from business and users alike, taking into account prevailing technological trends to ensure that infrastructure and facilities are moving with the times.

2004 was a very successful year for the IT sector from both operational and project-delivery points of view. A 99.5 % availability of IT services was achieved and key projects were delivered on time and within budget.

A commitment was made in 2003 to implement a large number of projects in 2004. Many of these projects were big and involved development and deployment through collaboration with the EMEA Human and Veterinary Units. The effective coordination, management and resourcing of these projects led to their successful delivery.

A selection of corporate projects in 2004:

- The Meeting Management System (MMS) was upgraded, including a new range of services. This has radically improved the EMEA's ability to arrange all meetings and conferences

- The Experts database, comprising more than 3 500 European experts, was upgraded. The new version of the database was made available to all national competent authorities. This allows more efficient coordination of the network

- The EMEA, together with the Inspections Telematics Implementation Group, began to work on the deployment of an inspections database which comprises information about all inspections activities carried out in the European system

- Conception, elaboration and early construction phases of a scientific advice database were completed in 2004

- EDMS, the Agency's electronic document management system, was successfully launched in September 2004

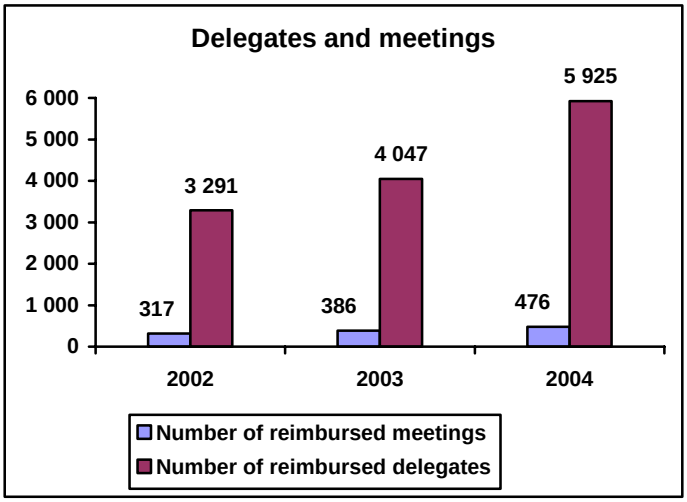
See Annex 8 for key internal IT projects and operational activities undertaken and delivered.

6.3 Meeting management and conferences

The EMEA ensures efficient support for the meetings it organises, providing facilities and services, and constantly improves the resources available. The Agency assists delegates with logistics and practical arrangements. This includes the organisation of meetings, travel and hotel arrangements for delegates and hosts, reception of visitors, the reimbursement of delegates' expenses and the payment of suppliers' invoices, as well as the preparation and follow-up of meeting room facilities.

The enlargement of the European Union to 25 Member States on 1 May 2004 and the entry into force of the new pharmaceutical legislation, which introduced a fourth scientific committee and new scientific groups, led to a considerable increase in the number of meetings organised, in the number of meeting days, and in the number of delegates to be reimbursed.

The number of meetings and meeting days increased by 24 % compared to the previous year, including extraordinary Management Board and CHMP meetings in May and September respectively, as well as new Committee on Herbal Medicinal Products (HMPC) meetings from September 2004 onwards.



A total of 5 925 delegate visits were reimbursed, leading to a 47 % increase in expenditure in 2004. This was due partly to the increased number of meetings and partly to the reimbursement of meeting expenses for representatives from the new Member States.

A further 40 % increase in the number of travel and hotel bookings for reimbursed delegates occurred, as well as a 20 % increase in hotel booking requirements for non-reimbursed delegates.

The provision of interpretation was reviewed and tailored to real needs, and thus interpretation days were reduced by 68 % compared to the previous year.

Participation in the development of the third phase of an automated meetings management system (MMS) to manage the meeting process as a whole was effective. The MMS includes an Experts database and enables the automation of many administrative documents, such as invitations, participation lists and reimbursement forms, and the setting up of a tracking system for hotel and travel details.

6.4 Document management and publishing

The Agency ensures full compliance with all regulatory and quality requirements in the areas of document and records management. This includes: ensuring best practice in document and records management; verifying the quality of all published documents; and verifying the accuracy of translations.

In view of the growing use of electronic documents, their publication on the Internet, new legislation on access to documents, the role of the Agency as a medicinal information provider, and requirements for document and records management under ISO 9000, the Agency has refocused its activities on the entire lifecycle of documents and, consequently, has adapted its approach to records management.

Documentum, the electronic document management system, was successfully rolled out throughout the Agency during 2004.

As a result of the enlargement and the increased number of documents being posted on the EMEA website, the number of external requests for information increased by 50 % over the previous year.

Translations

With the enlargement of the European Union in 2004, the number of official EU languages increased from 11 to 20. This, together with the automatic extension of European Commission decisions granting marketing authorisations for medicinal products to the 10 new Member States on the date of accession, and the implicit requirement that product information be available in all official languages of the European Union, increased the volume of translation work substantially.

The EMEA set up a 'pre-accession linguistic review process' for 199 human and 41 veterinary centrally authorised products in the 9 new EU languages. This was to enable a more phased approach and address potential public health concerns.

Annexes

1. **Members of the Management Board**
2. **Members of the Committee for Medicinal Products for Human Use (CHMP)**
3. **Members of the Committee for Medicinal Products for Veterinary Use (CVMP)**
4. **Members of the Committee on Orphan Medicinal Products (COMP)**
5. **Members of the Committee on Herbal Medicinal Products (HMPC)**
6. **National competent authority partners**
7. **EMEA budget summaries 2003-2005**
8. **IT projects and operational activities**
9. **CHMP opinions in 2004 on medicinal products for human use**
10. **CVMP opinions in 2004 on medicinal products for veterinary use**
11. **COMP opinions in 2004 on designation of orphan medicinal products**
12. **EMEA guidelines in 2004**
13. **Arbitration and Community referrals overview 2004**
14. **EMEA contact points and reference documents**

Annex 1
Members of the Management Board

Chair: Hannes WAHLROOS
EMEA contact: Martin HARVEY ALLCHURCH

Members

European Parliament	Gianmartino BENZI, José-Luis VALVERDE LÓPEZ
European Commission	Horst REICHENBACH, Fernand SAUER (*Alternates:* Paul WEISSENBERG, Patricia BRUNKO)
Belgium	Johan van CALSTER, André PAUWELS
Czech Republic	Milan ŠMÍD (*Alternate:* Alfred HERA)
Denmark	Jytte LYNGVIG *(vice-chairman)* (*Alternate:* Paul SCHÜDER)
Germany	Walter SCHWERDTFEGER (*Alternate:* Ilse-Dore SCHÜTT)
Estonia	Kristin RAUDSEPP (*Alternate:* Alar IRS)
Greece	Dimitrios VAGIONAS (*Alternate:* Vassilis KONTOZAMANIS)
Spain	Val DIEZ[1] (*Alternate:* José MARTINEZ OLMOS)
France	Philippe DUNETON (*Alternate:* Jean MARIMBERT)
Ireland	Pat O'MAHONY (*Alternate:* Joan GILVARRY)
Italy	Nello MARTINI (*Alternate:* Silvia FABIANI)
Cyprus	Panayiota KOKKINOU (*Alternate:* Louis PANAYI)
Latvia	Jānis OZOLINŠ (*Alternate:* Inguna ADOVICA)
Lithuania	Vytautas BASYS (*Alternate:* Juozas JOKIMAS)
Luxembourg	Mariette BACKES-LIES (*Alternate:* Claude A HEMMER)
Hungary	Tamás L PAÁL (*Alternate:* Beatrix HORVÁTH)
Malta	Patricia VELLA BONANNO (*Alternate:* Kenneth MIFSUD)
Netherlands	Aginus A W KALIS (*Alternate:* Pim KAPITEIN)
Austria	Robert SCHLÖGEL (*Alternate:* Christian KALCHER)
Poland	Piotr BLASZCZYK (*Alternate:* Jacek SPLAWINSKI)
Portugal	Rui dos SANTOS IVO
Slovenia	Stanislav PRIMOŽIČ (*Alternate:* Vesna KOBLAR)
Slovakia	Ľudevít MARTINEC (*Alternate:* Stanislava GAJDOŠOVÁ)
Finland	Hannes Wahlroos (*Alternate:* Pekka JÄRVINEN)
Sweden	Gunar ALVÁN (*Alternate:* Anders BROSTRÖM)
United Kingdom	Kent WOODS (*Alternate:* Steve DEAN)

Observers

Iceland	Ingolf J PETERSEN (*Alternate:* Rannveig GUNNARSDÓTTIR)
Liechtenstein	Brigitte BATLINER (*Alternate:* Peter MALIN)
Norway	Gro Ramsten WESENBERG (*Alternate:* Hans HALSE)

[1] Replaced Carlos LENS CABRERA as of June 2004 meeting.

Annex 2
Members of the Committee for Medicinal Products for Human Use

Chair: Daniel BRASSEUR
EMEA contact: Anthony HUMPHREYS

Members

- Eric ABADIE (France) *(vice-chairman)*
  Alternate: Jean-Hugues TROUVIN
- János BORVENDEG (Hungary)
  Alternate: Agnes GYURASICS
- Gonzalo CALVO ROJAS (Spain)
  Alternate: Fernando DE ANDRES-TRELLES
- Nikolaos DRAKOULIS (Greece)
  Alternate: Michalis AVGERINOS
- Jacqueline GENOUX-HAMES (Luxembourg)
- Manfred HAASE[1] (Germany) *(co-opted)*
- Ian HUDSON (United Kingdom)
  Alternate: Julia DUNNE
- Arthur ISSEYEGH (Cyprus)
  Alternate: Panayiota KOKKINOU
- Raul KIIVET (Estonia)
  Alternate: Alar IRS
- Gottfried KREUTZ (Germany)
  Alternate: Karl BROICH[2]
- Pekka KURKI[1] (Finland) *(co-opted)*
- Metoda LIPNIK-STANGELJ (Slovenia)
  Alternate: Barbara RAZINGER-MIHOVEC
- David LYONS (Ireland)
  Alternate: Patrick SALMON
- Romaldas MACIULAITIS (Lithuania)
  Alternate: Mykolas MAURICAS
- Ján MAZÁG[3] (Slovakia)
  Alternate: Leila FARAH
- Pieter NEELS[4] (Belgium)
  Alternate: Bruno FLAMION[5]
- Giuseppe NISTICÒ (Italy)
  Alternate: Pasqualino ROSSI
- Sif ORMARSDÓTTIR (Iceland)
  Alternate: Magnús JÓHANNSSON
- Michał PIROŻYŃSKI (Poland)
  Alternate: Piotr SIEDLECKI
- Heribert PITTNER (Austria)
  Alternate: Josef SUKO
- Ingemar PERSSON[1] (Sweden) *(co-opted)*
- Juris POKROTNIEKS (Latvia)
  Alternate: Indulis PURVINS
- Jean-Louis ROBERT[1] (Luxembourg)
  (co-opted)
- Frances ROTBLAT[1] (United Kingdom)
  (co-opted)
- Tomas SALMONSON (Sweden)
  Alternate: Per NILSSON
- Beatriz SILVA LIMA (Portugal)
  Alternate: Cristina SAMPAIO
- Eva SKOVLUND (Norway)
  Alternate: Liv MATHIESEN
- Milan ŠMÍD (Czech Republic)
- Steffen THIRSTRUP[6] (Denmark)
  Alternate: Jens ERSBØLL[7]
- Markku TOIVONEN (Finland)
  Alternate: Riita TOKOLA[8]
- Patricia VELLA BONANNO[9] (Malta)
  Alternate: John Joseph BORG[10]
- Barbara VAN ZWIETEN-BOOT (Netherlands)
  Alternate: Frits LEKKERKERKER

[1] Joined from September 2004 meeting.
[2] Replaced Manfred HAASE as of September 2004 meeting.
[3] Replaced Pavel ŠVEC as of July 2004 meeting.
[4] Replaced Daniel BRASSEUR as of June 2004 meeting.
[5] Replaced Pieter NEELS as of June 2004 meeting.
[6] Replaced Jens ERSBØLL as of November 2004 meeting.
[7] Replaced Steffen THIRSTRUP as of November 2004 meeting.
[8] Replaced Pekka KURKI as of September 2004 meeting.
[9] Replaced Helen VELLA as of July 2004 meeting.
[10] Replaced Patricia VELLA BONANNO as of November 2004 meeting.

Biotechnology Working Party
Chair: Jean-Hugues TROUVIN
EMEA contact: John PURVES

Blood Products Working Party
(formerly Blood Products Working Group)
Chair: Manfred HAASE
EMEA contact: John PURVES

Efficacy Working Party
Chair: Barbara VAN ZWIETEN-BOOT
EMEA contact: Agnès SAINT-RAYMOND

Herbal Medicinal Products Working Party
Chair: Konstantin KELLER
EMEA contact: Anthony HUMPHREYS

Pharmacovigilance Working Party

Chair: Anne CASTOT (acting)
EMEA contact: Panos TSINTIS

Safety Working Party
Chair: Beatriz SILVA LIMA
EMEA contact: Agnès SAINT-RAYMOND

Joint CHMP/CVMP Quality Working Party
Chair: Jean-Louis ROBERT
EMEA contact: Emer COOKE

Scientific Advice Working Party
(formerly Scientific Advice Working Group)
Chair: Markku TOIVONEN
EMEA contact: Agnès SAINT-RAYMOND

Cell Therapy Working Party
(formerly Ad hoc Expert Group on Cell Therapy)
Chair: Pekka KURKI

Biosimilar Medicinal Products Working Party
(formerly Ad hoc Working Group on (Pre-) Clinical Comparability of Biotechnology Products)
Chair: Pekka KURKI
EMEA contact: Marisa PAPALUCA AMATI

Gene Therapy Working Party
(formerly Ad hoc Expert Group on Gene Therapy)
Chair: Klaus CICHUTEK
EMEA contact: Marisa PAPALUCA AMATI

Paediatric Working Party
(formerly Paediatric Expert Group)

Chair: Daniel BRASSEUR
EMEA contact: Agnès SAINT-RAYMOND

Pharmacogenetics Working Party
(formerly Ad hoc Expert Group on Pharmacogenetics)
Chair: Eric ABADIE
EMEA contact: Marisa PAPALUCA AMATI

Vaccine Working Party
(formerly Vaccine Expert Group)
Chair: Roland DOBBELAER
EMEA contact: John PURVES

Scientific Advisory Group on Anti-infectives
(formerly Therapeutic Advisory Group on Anti-infectives)
Chair: Bjarne ORSKOV LINDHARDT
EMEA contact: Agnès SAINT-RAYMOND

Scientific Advisory Group on Diagnostics
(formerly Therapeutic Advisory Group on Diagnostics)
Chair: To be appointed
EMEA contact: Agnès SAINT-RAYMOND

Scientific Advisory Group on Oncology
(formerly Therapeutic Advisory Group on Oncology)
Chair: Michel MARTY
EMEA contact: Agnès SAINT-RAYMOND

Working Group with Patients' Organisations
Chair: Frits LEKKERKERKER/Noël WATHION
EMEA contact: Isabelle MOULON

EMEA contact: John PURVES

Annex 3
Members of the Committee for Medicinal Products for Veterinary Use

Chair: Gérard MOULIN
EMEA contact: Peter JONES

Members

- Birgit AASMÄE (Estonia)
  Alternate: Helen MAHLA
- Margarita ARBOIX (Spain)
  Alternate: Ricardo de la FUENTE LÓPEZ
- Gabriel BEECHINOR (Ireland)
- Rory BREATHNACH (Irland) *(co-opted)*
- Ivo CLAASEN (Netherlands) *(co-opted)*
- Johannes DICHTL (Austria)
  Alternate: Jean-Pierre BINDER
- Peter EKSTRÖM (Sweden) *(co-opted)*
- Christian FRIIS (Denmark) *(co-opted)*
- Judita HEDEROVÁ (Slovakia)
- Alfred HERA (Czech Republic)
  Alternate: Jiří BUREŠ
- Anja HOLM (Denmark)
  Alternate: Lotte Winther
- Tonje HØY (Norway)
  Alternate: Hanne BERGENDAHL
- Arvils JAKOVSKIS (Latvia)
- Laimi JODKONIS (Lithuania)
  Alternate: Juozas JOKIMAS
- Eva JOHNSSON (Sweden)
  Alternate: Henrik HOLST
- Liisa KAARTINEN (Finland)
  Alternate: Kristina LEHMANN
- Reinhard KROKER (Germany)
  Alternate: Manfred MOOS
- Katarzyna KRZYŻAŃSKA (Poland)
  Alternate: Roman LECHOWKSI
- Ioannis MALEMIS (Greece)
  Alternate: Orestis PAPADOPOULOS
- Eduardo MARQUES-FONTES (Portugal)
  Alternate: Leonor Maria MEISEL
- Kenneth MIFSUD (Malta)
  Alternate: Joseph VELLA
- John O'BRIEN (United Kingdom)
  Alternate: Martin ILOTT
- Sigurður ÖRN HANSSON (Iceland)
  Alternate: Halldór RUNÓLFSSON
- Johannes PETRUS HOOGLAND (Netherlands) *(vice-chairman)*
- Jean-Claude ROUBY (France)
  Alternate: Michael HOLZHAUSER-ALBERTI
- Tibor SOÓS (Hungary)
  Alternate: Gábor KULCSÁR
- Stane SRCIC (Slovenia)
  Alternate: Blanka EMERSIC
- Katia STEPHANIDOU (Cyprus)
  Alternate: Phedias LOUCAIDES
- Maria TOLLIS (Italy)
  Alternate: Virgilio DONINI
- Bruno URBAIN (Belgium)
  Alternate: Lionel LAURIER
- Marc WIRTOR (Luxembourg)
  Alternate: Maurice HOLPER

Working parties and ad hoc groups

Efficacy Working Party
Chair: Michael HOLZHAUSER-ALBERTI
EMEA contact: Jill ASHLEY-SMITH

Immunologicals Working Party
Chair: Jean-Claude ROUBY
EMEA contact: Jill ASHLEY-SMITH

Pharmacovigilance Working Party
Chair: Cornelia IBRAHIM
EMEA contact: Kornelia GREIN

Joint CHMP/CVMP Quality Working Party
Chair: Jean-Louis ROBERT
EMEA contact: Emer COOKE

Safety Working Party
Chair: Christian FRIIS
EMEA contact: Kornelia GREIN

Scientific Advice Working Party
Chair: Reinhard KROKER
EMEA contact: Jill ASHLEY-SMITH

Scientific Advisory Group on Antimicrobials
Chair: Liisa KAARTINEN
EMEA contact: Kornelia GREIN

Environmental Risk Assessment (temporary working party)
Chair: Hans HOOGLAND
EMEA contact: Kornelia GREIN

Annex 4
Members of the Committee on Orphan Medicinal Products

Chair: Josep TORRENT-FARNELL
EMEA contact: Agnès SAINT-RAYMOND

Members

- Eric ABADIE (EMEA representative)
- Gianmartino BENZI (EMEA representative)
- Heidrun BOSCH TRABERG (Denmark)
- Birthe BYSKOV HOLM (patients' organisation representative)
- Yann LE CAM (patients' organisation representative) *(vice-chairman)*
- Judit EGGENHOFER (Hungary)
- Rembert ELBERS (Germany)
- Emmanuel HÉRON (France)
- Joseph GIGLIO (Malta)
- Lars GRAMSTAD (Norway)
- Bernd JILMA (Austria)
- Alistair KENT (patients' organisation representative)
- Ioannis KKOLOS (Cyprus)
- Kateřina KUBÁČKOVÁ (Czech Republic)
- Magdaléna KUŽELOVÁ (Slovakia)
- André LHOIR (Belgium)
- David LYONS (EMEA representative)
- Henri METZ (Luxembourg)
- Greg MARKEY[1] (United Kingdom)
- Martin MOŽINA (Slovenia)
- José Félix OLALLA MARAÑÓN (Spain)
- Kristina PAVLOVSKA (Latvia)
- Veijo SAANO (Finland)
- Patrick SALMON[2] (Ireland)
- Harrie J J SEEVERENS (Netherlands)
- George STATHOPOULOS (Greece)
- Domenica TARUSCIO (Italy)
- Sigurður B THORSTEINSSON (Iceland)
- Vallo TILLMANN (Estonia)
- José Manuel TOSCANO RICO (Portugal)
- Algirdas UTKUS (Lithuania)
- Kerstin WESTERMARK (Sweden)
- Jolanta WIECKOWSKA (Poland)

[1] Replaced Rashmi SHAH as of December 2004 meeting.
[2] Replaced George SHORTEN as of December 2004 meeting.

Ad hoc Biotechnology Working Group
Chair: Harrie SEEVERENS/Jean-Hugues TROUVIN
EMEA contact: Spiros VAMVAKAS

Prevalence Ad hoc Working Group
Chair: Kalle HOPPU
EMEA contact: Spiros VAMVAKAS

Working Group with Interested Parties
Chair: Yann LE CAM/Agnès SAINT-RAYMOND
EMEA contact: Spiros VAMVAKAS

Annex 5
Members of the Committee on Herbal Medicinal Products

Chair: Konstantin KELLER
EMEA contact: Anthony HUMPHREYS

Members

- Linda ANDERSON (United Kingdom)
  Alternate: Sue HARRIS
- Mariette BACKES-LIES (Luxembourg)
  Alternate: Jacqueline GENOUX-HAMES
- Steffen BAGER (Denmark)
  Alternate: Kristine HVOLBY
- Zsuzsanna BIRÓ-SÁNDOR (Hungary)
  Alternate: Gyöngyi BACS
- Per CLAESON (Sweden)
  Alternate: Ubonwan CLAESON
- Christian CUSCHIERI (Malta)
  Alternate: Caroline ATTARD
- Dairíne DEMPSEY (Ireland)
  Alternate: Elaine BRESLIN
- Wojciech DYMOWSKI (Poland)
  Alternate: Elżbieta WOJTASIK
- Anna-Liisa ENKOVAARA (Finland)
  Alternate: Sari KOSKI
- Emiel VAN GALEN (Netherlands)
  Alternate: Burt H KROES
- Gloria GARCÍA LORENTE (Spain)
  Alternate: Adela VELÁZQUEZ
- Catherine HARVALA (Greece)
  Alternate: Foteini TZAVELLA
- Marie HEROUTOVÁ (Czech Republic)
- Thorbjörg KJARTANDSDÓTTIR (Iceland)
  Alternate: Kristín INGÓLFSDÓTTIR
- Andrea KUPKOVÁ (Slovakia)
  Alternate: Ľudmila ŠTRBOVÁ
- Audronis LUKOSIUS (Lithuania)
- Steinar MADSEN (Norway)
  Alternate: Gro FOSSUM
- Ana Paula MARTINS (Portugal)
  Alternate: Maria Helena PINTO FERREIRA
- Aleš MLINARIC (Slovenia)
  Alternate: Barbara RAZINGER-MIHOVEC
- Dailonis PAKALNS (Latvia)
  Alternate: Dace KALKE
- Heribert PITTNER (Austria) *(vice-chairman)*
  Alternate: Wolfgang KUBELKA
- Klaus REH (Germany)
  Alternate: Christine WERNER
- Marie SAARSOO (Estonia)
  Alternate: Ain RAAL
- Antoine SAWAYA (France)
  Alternate: Jacqueline VIGUET POUPELLOZ
- Vittorio SILANO (Italy)
  Alternate: Marisa DELBÓ
- Panayiotis TRIANTAFYLLIS (Cyprus)
  Alternate: Maria STAVROU
- Arnold J VLIETINCK (Belgium)
  Alternate: Heidi NEEF

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

BELGIUM

Johan van CALSTER
Generaal Adviseur
Federale Overheidsdienst Volksgezondheid,
Veiligheid van de Voedselketen
Directoraat-Generaal Bescherming
Volksgezondheid en Leefmilieu
Geneesmiddelen - DGG
33 Bischoffsheimlaan
Building Amazone
B – 1000 Brussel
Tel. (32-2) 210 94 46
Fax (32-2) 227 55 54
E-mail: johan.vancalster@health.fgov.be
Internet: http://www.afigp.fgov.bek

CZECH REPUBLIC

Milan ŠMÍD
Director
Státní ústav pro kontrolu léčiv
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Annex 7
EMEA budget summaries 2003–2005

The summarised comparative budget statements for 2003 to 2005 are as follows:

(Amounts expressed in euro)

	2003[1] (31.12.2003)		2004[2] (31.12.2004)		2005[3] (16.12.2004)	
Revenue						
Fees	56 742 000	67.41 %	67 000 000	67.60 %	77 455 000	70.31 %
General EU contribution	12 300 000	14.61 %	17 000 000	17.16 %	17 900 000	16.25 %
Special EU contribution for IT telematics strategy	7 000 000	8.32 %	7 500 000	7.57 %	7 500 000	6.81 %
Special EU contribution for orphan medicinal products	3 100 000	3.68 %	4 000 000	4.04 %	3 700 000	3.36 %
Contribution from EEA	558 000	0.66 %	573 000	0.58 %	530 000	0.48 %
Contribution from EU programmes (PERF)	1 530 000	1.82 %	p.m.	0.00 %	p.m.	0.00 %
Other	2 949 000	3.50 %	3 016 103	3.05 %	3 075 000	2.79 %
TOTAL REVENUE	**84 179 000**	**100.00 %**	**99 089 103**	**100.00 %**	**110 160 000**	**100.00 %**

Expenditure						
Staff						
Salaries	27 352 500	32.49 %	31 766 000	32.06 %	35 876 000	32.57 %
Interim and other support persons	1 845 000	2.19 %	2 087 000	2.11 %	2 695 000	2.45 %
Other staff-related expenditure	2 355 500	2.80 %	2 211 000	2.23 %	2 759 000	2.50 %
Total title 1	*31 553 000*	*37.48 %*	*36 064 000*	*36.40 %*	*41 330 000*	*37.52 %*
Building/equipment						
Rent/charges	5 686 000	6.76 %	5 651 000	5.70 %	8 698 000	7.90 %
Expenditure on data processing	9 517 000	11.31 %	14 015 000	14.15 %	8 931 000	8.10 %
Other capital expenditure	1 959 000	2.33 %	1 530 000	1.54 %	2 023 000	1.84 %
Postage and communications	418 000	0.50 %	427 000	0.43 %	580 000	0.53 %
Other administrative expenditure	2 075 000	2.46 %	2 371 000	2.39 %	4 030 000	3.66 %
Total title 2	*19 655 000*	*23.35 %*	*23 994 000*	*24.21 %*	*24 262 000*	*22.03 %*
Operational expenditure						
Meetings	3 946 800	4.70 %	5 354 000	5.40 %	7 439 000	6.75 %
Evaluations	26 810 800	31.85 %	32 223 000	32.52 %	35 673 000	32.38 %
Translation	701 000	0.83 %	1 176 000	1.19 %	1 001 000	0.91 %
Studies and consultants	27 000	0.03 %	100 000	0.10 %	200 000	0.18 %
Publications	78 000	0.09 %	178 000	0.18 %	255 000	0.23 %
EU programmes	1 407 400	1.67 %	103	0.00 %	p.m.	0.00 %
Total title 3	*32 971 000*	*39.17 %*	*39 031 103*	*39.39 %*	*44 568 000*	*40.45 %*
TOTAL EXPENDITURE	**84 179 000**	**100.00 %**	**99 089 103**	**100.00 %**	**110 160 000**	**100.00 %**

Notes

(1) Final appropriations for the 2003 budget.

(2) Final appropriations for the 2004 budget.

(3) Budget for 2005 as adopted by the Management Board on 16.12.2004.

Annex 8
IT projects and operational activities

Service or project	Description of measure	Details of progress
Corporate service availability	To achieve 99.5 % availability for all IT services supporting the corporate activities of the EMEA	IT maintained high service levels throughout 2004, achieving more than 99.5 % availability to corporate users
Corporate helpdesk	To provide help and support between the hours of 08h30 and 18h00, five days a week	IT provided support and helpdesk services to the EMEA's corporate users to a high and professional level. This was one of the key components helping the Sector achieve availability targets of 99.5 %
Archiving and back-up of data	To ensure the timely back-up and archiving of the EMEA data, including off-site disaster recovery scenarios	Back-up copies of all EMEA data are held in secure off-site locations. Systems and procedures are fully in place for the timely back-up and archiving of the EMEA data
Security	To maintain the highest levels of security and confidentiality for all data held on EMEA systems	Centrally within the EMEA and between EMEA and NCAs all aspects of security services and communications have been implemented. For example, within the EMEA, the implementation of an extensive firewall combined with the segmented 3-tier architecture ensures high levels of protection
Data centre	To implement a new data centre at the EMEA with full switched back-up capability to the existing computer room	A new data centre was constructed in 2004 with storage mirroring capability and critical redundant services deployed, combined with the implementation of a new LAN with sophisticated data switching equipment at the EMEA. Also delivered was the implementation of web, application and database servers in the data centre for key EU telematics and corporate applications (see 3-tier architecture)
Storage capability in the data centre	To ensure that the Agency's processing and storage capabilities are aligned to its business workload	Having implemented 2 large data storage arrays in the new EMEA data centre, IT has ensured that the Agency's processing and storage capabilities are aligned to its workload for the next 5 years
3-tier architecture	Implementation of 3-tier architecture with appropriate security and interface to Internet services for internal and remote services	Having completed the implementation of the data centre, the EMEA 3-tier architecture was implemented in 2004 with fully integrated security as the foundation platform for all new applications

Service or project	Description of measure	Details of progress
Training	To promote internal awareness of IT and training on EMEA-specific systems amongst EMEA staff and delegates	IT training was provided to all EMEA staff on a regular basis. In 2004, a wide range of user, technical and NCA training was successfully provided to EMEA staff and delegates alike. Specific training on all aspects of Eudranet was given to Eudranet NCA delegates at the EMEA
Second and third-level support	To ensure that the help and support available to EMEA staff, delegates and users of EU telematics systems is in line with the Agency's operating requirements	The dedicated range of services provided to EMEA staff, delegates and users of EU telematics systems from the applications themselves to the three levels of helpdesk support services ensure these systems are in line with the Agency's operating requirements
Meetings management system (MMS)	To maintain the MMS and implement a range of new services in MMS Phase III	A comprehensive upgrade to the MMS was delivered both on time and within budget. This was developed in direct consultation with the EMEA's Conferences Sector and radically improved their ability to arrange all EMEA meetings and conferences
Eudra Common Directory (ECD)	To implement one common and standard directory of all parties involved in the EU pharmaceutical regulatory process	This project was successfully launched in 2004, providing EMEA users with a directory (ECD) based on LDAP. ECD will be used by many applications that require directory information, starting first of all with MMS Phase III
Experts	To upgrade the Experts database and make it available to all NCAs	The IT development team provided a new version of the Experts database in 2004
Inspections	To deploy the inspections database	The IT development team started work on the inception phase of this project with the Inspections TIG. Work on the elaboration and construction phases will continue in 2005
EDMS	To take over the final stages of the EDMS pre-production application, prepare it for the move into operation and operate the application when in production	IT deployed a support team to prepare for the handover of EDMS into production. The Sector also completed a 'system health-check' to finalise relevant aspects of configuration, operational support and delivery of services. EDMS was successfully launched in September 2004 with an integrated helpdesk support service
Scientific advice	To deploy a scientific advice database	The IT development team completed the conception, elaboration and early construction phases of this project with input from the EMEA scientific advice experts

Service or project	Description of measure	Details of progress
Videoconferencing and audiovisual	Implement videoconferencing and web-streaming services for EMEA/NCA meetings	IT completed testing of IP-based videoconferencing over the Internet successfully and used it in several Eudranet TIG meetings. Visual recording of meetings for archiving and broadcasting purposes was set up using Internet/web-based technology

Annex 9
CHMP opinions in 2004 on medicinal products for human use

Centralised applications – Positive opinions

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ ATC code ▪ Summary of indication	**EMEA/CHMP** ▪ Validation ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Opinion received ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Velcade ▪ bortezomib ▪ Part B	Millennium Pharmaceuticals Ltd	▪ L01XX32 ▪ Treatment of patients with refractory multiple myeloma	▪ 24.02.2003 ▪ 21.01.2004 ▪ 183 days ▪ 148 days	▪ 30.01.2004 ▪ 26.04.2004 ▪ 28.04.2004 ▪ OJ C 172, 02.07.2004, p. 4
▪ Lysodren[#] ▪ mitotane ▪ Part B	Laboratoire HRA Pharma	▪ L01XX23 ▪ Symptomatic treatment of advanced adrenal cortical carcinoma	▪ 18.11.2002 ▪ 21.01.2004 ▪ 194 days ▪ 236 days	▪ 30.01.2004 ▪ 28.04.2004 ▪ 30.04.2004 ▪ OJ C 172, 02.07.2004, p. 4
▪ Abilify ▪ aripiprazole ▪ Part B	Otsuka Pharmaceuticals Europe Ltd	▪ N05AX12 ▪ Treatment of schizophrenia	▪ 24.12.2001 ▪ 26.02.2004 ▪ 217 days ▪ 577 days	▪ 04.03.2004 ▪ 04.06.2004 ▪ 08.06.2004 ▪ OJ C 166, 25.06.2004, p. 2
▪ Levemir ▪ insulin detemir ▪ Part A	Novo Nordisk A/S	▪ A10AE (pending) ▪ Treatment of diabetes mellitus	▪ 18.11.2002 ▪ 26.02.2004 ▪ 181 days ▪ 284 days	▪ 04.03.2004 ▪ 01.06.2004 ▪ 04.06.2004 ▪ OJ C 166, 25.06.2004, p. 2
▪ TachoSil ▪ Human Fibrinogen + Human Thrombin ▪ Part B	Nycomed Austria GmbH	▪ B02BC ▪ Supportive treatment in surgery for improvement of haemostasis	▪ 22.07.2002 ▪ 26.02.2004 ▪ 228 days ▪ 356 days	▪ 10.03.2004 ▪ 08.06.2004 ▪ 11.06.2004 ▪ OJ C 166, 25.06.2004, p. 2
▪ Yentreve ▪ duloxetine ▪ Part B	Eli Lilly Nederland B.V.	▪ Pending ▪ Treatment of stress urinary incontinence in women	▪ 24.02.2003 ▪ 24.03.2004 ▪ 182 days ▪ 213 days	▪ 05.05.2004 ▪ 11.08.2004 ▪ 13.08.2004 ▪ OJ C 215, 27.08.2004, p. 7
▪ Ariclaim ▪ duloxetine ▪ Part B	Boehringer Ingelheim International GmbH	▪ Pending ▪ Treatment of stress urinary incontinence in women	▪ 23.06.2003 ▪ 24.03.2004 ▪ 60 days ▪ 173 days	▪ 23.03.2004 ▪ 11.08.2004 ▪ 13.08.2004 ▪ OJ C 215, 27.08.2004, p. 7

[#] Denotes an orphan medicinal product designated under Regulation (EC) No 121/2000.

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CHMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Lyrica ▪ pregabalin ▪ Part B	Pfizer Limited	▪ N03A (pending) ▪ Treatment of peripheral neuropathic pain in adults; and treatment of epilepsy as adjunctive therapy in adults with partial seizures	▪ 24.03.2003 ▪ 24.03.2004 ▪ 172 days ▪ 153 days	▪ 31.03.2004 ▪ 06.07.2004 ▪ 08.07.2004 ▪ OJ C 194, 30.07.2004, p. 2
▪ Telzir ▪ fosamprenavir ▪ Part B	Glaxo Group	▪ J05AE07 ▪ Treatment of HIV-1 infected adults with low-dose ritonavir in combination with other anti-retroviral products	▪ 20.01.2003 ▪ 24.03.2004 ▪ 177 days ▪ 207 days	▪ 29.03.2004 ▪ 12.07.2004 ▪ 14.07.2004 ▪ OJ C 194, 30.07.2004, p. 2
▪ Erbitux ▪ cetuximab ▪ Part A	Merck KGaA	▪ L01XC06 ▪ Treatment of patients with EGFR-expressing metastatic colorectal cancer in combination with irinotecan after failure of irinotecan-containing therapy	▪ 21.07.2003 ▪ 24.03.2004 ▪ 175 days ▪ 61 days	▪ 29.03.2004 ▪ 29.06.2004 ▪ 01.07.2004 ▪ OJ C 194, 30.07.2004, p. 2
▪ Pedea[#] ▪ ibuprofen ▪ Part B	Orphan Europe SARL	▪ C01EB16 ▪ Treatment of a haemodynamic-ally significant patent ductus arteriosus in pre-term newborn infants less than 34 weeks of gestational age	▪ 21.07.2003 ▪ 22.04.2004 ▪ 148 days ▪ 61 days	▪ 27.04.2004 ▪ 29.07.2004 ▪ 02.08.2004 ▪ OJ C 215, 27.08.2004, p. 7
▪ Apidra ▪ insulin glulisine ▪ Part A	Aventis Pharma Deutschland GmbH	▪ A10AB (pending) ▪ Treatment of diabetes mellitus	▪ 23.06.2003 ▪ 03.06.2004 ▪ 184 days ▪ 162 days	▪ 08.06.2004 ▪ 27.09.2004 ▪ 29.09.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Osseor ▪ strontium ranelate ▪ Part B	Les Laboratoires Servier	▪ M05BX03 ▪ Treatment of postmenopausal osteoporosis to reduce the risk of fracture	▪ 21.07.2003 ▪ 23.06.2004 ▪ 184 days ▪ 154 days	▪ 25.06.2004 ▪ 21.09.2004 ▪ 23.09.2004 ▪ OJ C 266, 29.10.2004, p. 5

[#] Denotes an orphan medicinal product designated under Regulation (EC) No 121/2000.

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CHMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Alimta ▪ pemetrexed ▪ Part B	Eli Lilly Nederland B.V.	▪ L01BA04 ▪ Treatment of malignant pleural mesothelioma in combination with cisplatin and of non-small cell lung cancer after prior chemotherapy	▪ 18.08.2003 ▪ 23.06.2004 ▪ 201 days ▪ 108 days	▪ 25.06.2004 ▪ 20.09.2004 ▪ 22.09.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Angiox ▪ bivalirudin ▪ Part B	The Medicine Company	▪ B01A (pending) ▪ Anticoagulant in patients undergoing percutaneous coronary intervention (PCI)	▪ 18.08.2003 ▪ 23.06.2004 ▪ 181 days ▪ 129 days	▪ 25.06.2004 ▪ 20.09.2004 ▪ 22.09.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Protelos ▪ strontium ranelate ▪ Part B	Les Laboratoires Servier	▪ M05BX03 ▪ Treatment of postmenopausal osteoporosis to reduce the risk of fracture	▪ 21.07.2003 ▪ 23.06.2004 ▪ 184 days ▪ 154 days	▪ 25.06.2004 ▪ 21.09.2004 ▪ 23.09.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Wilzin[#] ▪ zinc acetate ▪ Part B	Orphan Europe SARL	▪ A16AX05 ▪ Treatment of Wilson's disease	▪ 24.03.2003 ▪ 23.06.2004 ▪ 188 days ▪ 269 days	▪ 25.06.2004 ▪ 13.10.2004 ▪ 18.10.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Raptiva ▪ efalizumab ▪ Part A	Serono Europe Ltd	▪ L04AA21 ▪ Treatment of patients with moderate to severe plaque psoriasis	▪ 24.02.2003 ▪ 23.06.2004 ▪ 183 days ▪ 303 days	▪ 28.06.2004 ▪ 20.09.2004 ▪ 22.09.2004 ▪ OJ C 266, 29.10.2004, p. 5
▪ Emselex ▪ darifenacin ▪ Part B	Novartis Europharm Ltd	▪ G04BD10 ▪ Treatment of overactive bladder	▪ 23.06.2003 ▪ 29.07.2004 ▪ 181 days ▪ 221 days	▪ 04.08.2004 ▪ 22.10.2004 ▪ 26.10.2004 ▪ OJ C 289, 26.11.2004, p. 7
▪ Parareg ▪ cinacalcet ▪ Part B	Amgen Europe B.V.	▪ H05BX01 ▪ Treatment of hyperpara-thyroidism in patients with end-stage renal disease on haemodialysis and of hyper-calcaemia in patients with parathyroid carcinoma	▪ 27.10.2003 ▪ 29.07.2004 ▪ 196 days ▪ 80 days	▪ 08.04.2004 ▪ 22.10.2004 ▪ 26.10.2004 ▪ OJ C 289, 26.11.2004, p. 7

[#] Denotes an orphan medicinal product designated under Regulation (EC) No 121/2000.

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CHMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Mimpara ▪ cinacalcet ▪ Part B	Amgen Europe B.V.	▪ H05BX01 ▪ Treatment of hyperpara-thyroidism in patients with end-stage renal disease on haemodialysis and of hyper-calcaemia in patients with parathyroid carcinoma	▪ 27.10.2003 ▪ 29.07.2004 ▪ 196 days ▪ 80 days	▪ 04.08.2004 ▪ 22.10.2004 ▪ 26.10.2004 ▪ OJ C 289, 26.11.2004, p. 7
▪ Xagrid[#] ▪ anagrelide ▪ Part B	Shire Pharmaceutical Contracts Ltd	▪ B01AC14 ▪ Reduction of elevated platelet counts in at-risk essential thrombo-cythaemia patients who are intolerant to or not satisfactorily treated with their current therapy	▪ 22.04.2002 ▪ 29.07.2004 ▪ 181 days ▪ 271 days	▪ 05.08.2004 ▪ 16.11.2004 ▪ 18.11.2004 ▪ OJ C 320, 24.12.2004, p. 23
▪ Cymbalta ▪ duloxetine ▪ Part B	Eli Lilly Nederland B.V.	▪ Pending ▪ Treatment of major depressive episodes	▪ 27.10.2003 ▪ 16.09.2004 ▪ 210 days ▪ 113 days	▪ 22.09.2004 ▪ 17.12.2004 ▪ 22.12.2004 ▪ OJ C 23, 28.01.2005, p. 2
▪ Xeristar ▪ duloxetine ▪ Part B	Boehringer Ingelheim International GmbH	▪ Pending ▪ Treatment of major depressive episodes	▪ 27.10.2003 ▪ 16.09.2004 ▪ 210 days ▪ 113 days	▪ 22.09.2004 ▪ 17.12.2004 ▪ 22.12.2004 ▪ OJ C 23, 28.01.2005, p. 2
▪ Kivexa ▪ Abacavir+ lamivudine ▪ Part B	Glaxo Group	▪ J05AF30 ▪ Treatment of HIV-1 infected adults and adolescents from 12 years in combination with other anti-retroviral products	▪ 22.12.2003 ▪ 16.09.2004 ▪ 175 days ▪ 118 days	▪ 20.09.2004 ▪ 17.12.2004 ▪ 22.12.2004 ▪ OJ C 23, 28.01.2005, p. 2

[#] Denotes an orphan medicinal product designated under Regulation (EC) No 121/2000.

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CHMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Quintanrix ▪ comb. Vaccine ▪ Part A	GlaxoSmithKline Biologicals	▪ JO7CA10 ▪ Active immunisation of infants against diphtheria, tetanus, pertussis, hepatitis B and diseases caused by *Haemophilus influenzae* type b	▪ 23.06.2003 ▪ 21.10.2004 ▪ 215 days ▪ 297 days	▪ 27.10.2004 ▪ ……. ▪ ……. ▪ …….
▪ Fendrix ▪ Hepatitis B virus surface antigen (rDNA) (S protein) ▪ Part A	GlaxoSmithKline Biologicals SA	▪ JO7AP ▪ Active immuni-sation against hepatitis B virus infection	▪ 26.05.2003 ▪ 21.10.2004 ▪ 168 days ▪ 363 days	▪ 17.12.2004 ▪ 02.02.2005 ▪ ……. ▪ …….
▪ Avastin ▪ bevacizumab ▪ Part A	Roche Registration Ltd	▪ L01XC07 ▪ Treatment of metastatic carcinoma of the colon or rectum in combination with other intravenous antitumour agents	▪ 22.12.2003 ▪ 21.10.2004 ▪ 202 days ▪ 100 days	▪ 03.11.2004 ▪ 12.01.2005 ▪ 14.01.2005 ▪ OJ C 23, 28.01.2005, p. 2
▪ Truvada ▪ emtricitabine + tenofovir disoproxil fumarate ▪ Part B	Gilead Science International Limited	▪ J05AF30 ▪ Treatment of HIV-1 infected adults in combination with other anti-retroviral products	▪ 29.03.2004 ▪ 18.11.2004 ▪ 182 days ▪ 52 days	▪ 30.11.2004 ▪ ……. ▪ ……. ▪ …….
▪ Prialt[#] ▪ ziconotide ▪ Part B	Elan Pharma International Ltd	▪ N02BG08 ▪ Treatment of severe, chronic pain in patients requiring intrathecal (IT) analgesia	▪ 26.05.2003 ▪ 18.11.2004 ▪ 196 days ▪ 346 days	▪ 23.11.2004 ▪ 21.02.2005 ▪ ……. ▪ …….
▪ Orfadin[#] ▪ nitisinone ▪ Part B	Swedish Orphan International AB	▪ A16AX04 ▪ Treatment of hereditary tyrosinemia type 1	▪ 21.07.2003 ▪ 18.11.2004 ▪ 197 days ▪ 289 days	▪ 23.11.2004 ▪ 21.02.2005 ▪ ……. ▪ …….

[#] Denotes an orphan medicinal product designated under Regulation (EC) No 121/2000.

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CHMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Azilect ▪ rasagiline ▪ Part B	Teva Pharma GmbH	▪ N04BD02 ▪ Treatment of idiopathic Parkinson's disease (PD) in patients with end-of-dose fluctuations	▪ 27.10.2003 ▪ 18.11.2004 ▪ 208 days ▪ 180 days	▪ 25.11.2004 ▪ 21.02.2005 ▪ ……. ▪ …….
▪ Aloxi ▪ palonosetron ▪ Part B	Helsinn Birex Pharmaceuticals Ltd	▪ Pending ▪ Prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy	▪ 18.08.2003 ▪ 15.12.2004 ▪ 206 days ▪ 279 days	▪ 08.02.2005 ▪ ……. ▪ ……. ▪ …….
▪ Zonegran ▪ zonisamide ▪ Part B	Elan Pharma International Ltd	▪ N03AX15 ▪ Adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation	▪ 24.11.2003 ▪ 15.12.2004 ▪ 202 days ▪ 185 days	▪ 02.02.2005 ▪ ……. ▪ ……. ▪ …….

Centralised applications – Negative opinions

There were no negative CHMP opinions in 2004.

Annex 10
CVMP opinions in 2004 on medicinal products for veterinary use

Centralised applications – Positive opinions

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Target species ▪ Summary of indication	**EMEA/CVMP** ▪ Validation ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Opinion received ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Equilis Strep E ▪ Vaccine ▪ Part A	Intervet International	▪ Horses ▪ Vaccine against Streptococcus Equi	▪ 12.11.2002 ▪ 10.02.2004 ▪ 210 days ▪ 243 days	▪ 31.03.2004 ▪ 07.05.2004 ▪ 11.05.2004 ▪ OJ C 172, 2.7.2004, p.6
▪ Virbagen Omega ▪ Felin Interferon ▪ Part A - Extension	Virbac S.A.	▪ Cat ▪ Reduce mortality and clinical signs of canine parvovirosis	▪ 25.03.2003 ▪ 14.04.2004 ▪ 210 days ▪ 141 days	▪ 03.06.2004 ▪ 29.07.2004 ▪ 02.08.2004 ▪ OJ C 215, 27.8.2004, p.10
▪ Aivlosin ▪ Acetylisovaleryl -tylosintartrate ▪ Part B	Eco Animal Health	▪ Pigs ▪ Prevention and treatment of Swine Enzotic Pneumonia	▪ 12.03.2003 ▪ 12.05.2004 ▪ 210 days ▪ 64 days	▪ 28.06.2004 ▪ 09.09.2004 ▪ 13.09.2004 ▪ OJ C 237, 24.9.2003, p.6
▪ Nobivac Piro ▪ Vaccine ▪ Part B	Intervet International	▪ Dogs ▪ Vaccine against Babesios	▪ 16.09.2003 ▪ 12.05.2004 ▪ 210 days ▪ 29 days	▪ 28.06.2004 ▪ 02.09.2004 ▪ 06.09.2004 ▪ OJ C 237, 24.9.2003, p.6
▪ Previcox ▪ Firocoxib ▪ Part B	Merial	▪ Dogs ▪ Pain and inflammation	▪ 17.03.2003 ▪ 16.06.2004 ▪ 210 days ▪ 155 days	▪ 27.07.2004 ▪ 13.09.2004 ▪ 15.09.2004 ▪ OJ C 237, 24.9.2003, p.6
▪ Purevax RCPCh FeLV ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panlecopenia, Leukaemia	▪ 15.10.2003 ▪ 10.11.2004 ▪ 203 days ▪ 155 days	▪ ……. ▪ ……. ▪ ……. ▪ …….
▪ Purevax RCPCh ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panlecopenia, Leukaemia	▪ 18.11.2003 ▪ 10.11.2004 ▪ 203 days ▪ 120 days	▪ ……. ▪ ……. ▪ ……. ▪ …….
▪ Purevax RCP FeLV ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panlecopenia, Leukaemia	▪ 18.11.2003 ▪ 10.11.2004 ▪ 203 days ▪ 120 days	▪ ……. ▪ ……. ▪ ……. ▪ …….

Product ▪ Brand name ▪ INN ▪ Part A or B	**Marketing authorisation holder**	**Therapeutic area** ▪ Summary of indication	**EMEA/CVMP** ▪ Opinion ▪ Active time ▪ Clock stop	**European Commission** ▪ Date of decision ▪ Notification ▪ Official Journal
▪ Purevax RCP ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panleucopenia, Leukaemia	▪ 16.12.2003 ▪ 10.11.2004 ▪ 203 days ▪ 92 days	▪ ……. ▪ ……. ▪ ……. ▪ …….
▪ Purevax RC ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panleucopenia, Leukaemia	▪ 16.12.2003 ▪ 10.11.2004 ▪ 203 days ▪ 92 days	▪ ……. ▪ ……. ▪ ……. ▪ …….
▪ Purevax RCCh ▪ Vaccine ▪ Part A	Merial	▪ Cats ▪ Rhinotracheitis, Calicivirus, Chlamydia felis, Panleucopenia, Leukaemia	▪ 13.01.2004 ▪ 10.11.2004 ▪ 203 days ▪ 64 days	▪ ……. ▪ ……. ▪ ……. ▪ …….
▪ Metacam 20mg/ml solution for injection ▪ Meloxicam ▪ Part B – Extension	Boehringer Ingelheim Vetmedica	▪ Horses ▪ Alleviation of pain and inflammation in both acute and chronic musculo-skeletal disorders	▪ 05.05.2004 ▪ 10.11.2004 ▪ 160 days ▪ 29 days	▪ 16.12.2004 ▪ ……. ▪ ……. ▪ …….
▪ Eurifel FeLV ▪ Live Vaccine ▪ Part A - Extension	Merial	▪ Cats ▪ Feline leukaemia	▪ 07.04.2004 ▪ 08.12.2004 ▪ 177 days ▪ 58 days	▪ ……. ▪ ……. ▪ ……. ▪ …….

Centralised applications – Negative opinions

There were no negative CVMP opinions in 2004.

Establishment of maximum residue limits for new substances

Substance INN	Therapeutic area ▪ Target species	EMEA/CVMP ▪ Validation ▪ Opinion ▪ Active time ▪ Clock stop	European Commission ▪ Opinion received ▪ Date of regulation ▪ Official Journal
Diclaruzil (extension)	▪ All ruminants, porcine	▪ 17.10.2003 ▪ 14.01.2004 ▪ 90 days ▪ 0 days	▪ 12.02.2004 ▪ …… ▪ ……
Tulathromycin	▪ Bovine, porcine	▪ 09.08.2001 ▪ 14.01.2004 ▪ 244 days ▪ 631 days	▪ 12.02.2004 ▪ 12.06.2004 ▪ OJ L 211, 12.06.2004, p. 5
Sodium Salicylate (extension)	▪ Extension to oral use	▪ 14.11.2003 ▪ 11.02.2004 ▪ 90 days ▪ 0 days	▪ 09.03.2004 ▪ 29.10.2004 ▪ OJ L 326, 29.10.2004, p. 21
Fenvalerate	▪ Cattle	▪ 13.07.2001 ▪ 17.03.2004 ▪ 177 days ▪ 801 days	▪ 15.04.2004 ▪ 29.10.2004 ▪ OJ L 326, 29.10.2004, p. 21
Beclometasone dipropionate	▪ Horses	▪ 18.03.2004 ▪ 16.06.2004 ▪ 90 days ▪ 0 days	▪ 09.07.2004 ▪ …… ▪ ……
Moxidectin (extension)	▪ Milk	▪ 18.03.2004 ▪ 14.07.2004 ▪ 118 days ▪ 0 days	▪ 06.08.2004 ▪ …… ▪ ……
Toltrazuril (extension)	▪ Cows	▪ 18.03.2004 ▪ 16.06.2004 ▪ 90 days ▪ 0 days	▪ 09.07.2004 ▪ …… ▪ ……
Acetylisolvalerytylosin (extension)	▪ Poultry	▪ 15.04.2004 ▪ 14.07.2004 ▪ 90 days ▪ 0 days	▪ 06.08.2004 ▪ …… ▪ ……
Bituminosulfonate (extension)	▪ All mammalian food-producing	▪ 10.06.2004 ▪ 07.09.2004 ▪ 89 days ▪ 0 days	▪ 05.10.2004 ▪ …… ▪ ……
Lasalocid sodium	▪ Chicken and game birds	▪ 12.02.2004 ▪ 13.10.2004 ▪ 120 days ▪ 124 days	▪ 11.11.2004 ▪ …… ▪ ……
Carprofen (extension)	▪ Bovine milk	▪ 12.08.2004 ▪ 10.11.2004 ▪ 90 days ▪ 0 days	▪ 10.12.2004 ▪ …… ▪ ……
Ivermectin (modification)	▪ Cattle	▪ 06.04.2003 ▪ 10.11.2004 ▪ 118 days ▪ 467 days	▪ 10.12.2004 ▪ …… ▪ ……

Annex 11
COMP opinions in 2004 on designation of orphan medicinal products

Positive COMP designation opinions

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Opinion received ▪ Date of decision
Human Monoclonal Hepatitis B Immunoglobulins	ICON Clinical Research (UK) Ltd	Prevention of hepatitis B re-infection following liver transplantation	▪ 23.10.2003 ▪ 10.11.2003 ▪ 14.01.2004 ▪ 65 days	▪ 21.01.2004 ▪ 23.02.2004
LF 16-0687 Ms (Common)/N-3[[4-(aminoiminomethyl) benzoyl]amino]propyl]-1-[[2,4—dichloro-3-[[2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulphonyl]-(2S)-2-pyrrolidinecarboxa-mide, di(methanesulfonate)	Laboratoires Fournier	Treatment of moderate and severe traumatic brain injury	▪ 27.02.2003 ▪ 02.05.2003 ▪ 14.01.2004 ▪ 257 days (including appeal procedure)	▪ 21.01.2004 ▪ 23.02.2004
Treosulfan	medac Gesellschaft für klinische Spezialpräparate mbH	Conditioning treatment prior to haematopoietic progenitor cell transplantation	▪ 20.10.2003 ▪ 10.11.2003 ▪ 14.01.2004 ▪ 65 days	▪ 21.01.2004 ▪ 23.02.2004
Adeno-associated viral vector expressing lipoproprotein lipase	Mr Aart Brouwer	Treatment of lipoprotein lipase deficiency	▪ 03.12.2003 ▪ 19.12.2003 ▪ 05.02.2004 ▪ 48 days	▪ 11.02.2004 ▪ 08.03.2004
Idebenone	Promedipharm GmbH	Treatment of Friedreich's ataxia	▪ 01.12.2003 ▪ 19.12.2003 ▪ 05.02.2004 ▪ 48 days	▪ 11.02.2004 ▪ 08.03.2004
Ethanol (96 per cent) (gel for injection)	Orfagen	Treatment of congenital lymphatic malformations	▪ 14.11.2003 ▪ 19.12.2003 ▪ 05.02.2004 ▪ 48 days	▪ 11.02.2004 ▪ 08.03.2004
Anti-epithelial cell adhesion molecule/anti-CD3 monoclonal antibody	Fresenius Biotech GmbH	Treatment of ovarian cancer	▪ 01.12.2003 ▪ 19.12.2003 ▪ 05.02.2004 ▪ 48 days	▪ 11.02.2004 ▪ 08.03.2004
3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione	Gregory Fryer Associates Ltd	Treatment of myelodysplastic syndromes	▪ 04.12.2003 ▪ 19.12.2003 ▪ 05.02.2004 ▪ 48 days ▪	▪ 11.02.2004 ▪ 08.03.2004
Ethanol (96 per cent) (gel for injection)	Orfagen	Treatment of congenital venous malformations	▪ 22.10.2003 ▪ 10.11.2003 ▪ 05.02.2004 ▪ 87 days	▪ 11.02.2004 ▪ 08.03.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
Treprostinil sodium (inhalation use)	LungRx Limited	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	▪ 05.01.2004 ▪ 19.01.2004 ▪ 16.03.2004 ▪ 57 days	▪ 23.03.2004 ▪ 14.04.2004
2-Methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-phenol	Dr David Chaplin	Treatment of anaplastic thyroid cancer	▪ 24.10.2003 ▪ 19.12.2003 ▪ 08.03.2004 ▪ 80 days	▪ 19.03.2004 ▪ 14.04.2004
Human monoclonal antibody against CD4	Genmab A/S	Treatment of cutaneous T-cell lymphoma	▪ 10.12.2003 ▪ 19.01.2003 ▪ 16.03.2004 ▪ 57 days	▪ 23.03.2004 ▪ 14.04.2004
Vascular endothelial growth factor-D gene in an adenoviral vector for use with a collagen collar	Ark Therapeutics Ltd	Prevention of stenosis in synthetic grafts used in haemodialysis	▪ 30.01.2004 ▪ 16.02.2004 ▪ 26.04.2004 ▪ 70 days	▪ 29.04.2004 ▪ 08.06.2004
(2-aminoethyl) carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxy benzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt	Novartis Europharm Limited	Treatment of functional gastro-entero-pancreatic endocrine tumours	▪ 05.01.2004 ▪ 19.01.2004 ▪ 14.04.2004 ▪ 86 days	▪ 20.04.2004 ▪ 08.06.2004
Tetrahydrobiopterin	Dr Gertrud Thormann	Treatment of hyperphenylalaninemia	▪ 18.11.2003 ▪ 16.02.2004 ▪ 14.04.2004 ▪ 58 days	▪ 20.04.2004 ▪ 08.06.2004
Ciclosporin	Allergan Pharmaceuticals Ireland	Treatment of Atopic Keratoconjunctivitis	▪ 03.12.2003 ▪ 19.12.2003 ▪ 08.03.2004 ▪ 79 days	▪ 19.03.2004 ▪ 14.04.2004
5'-CTG CCA CGT TCT CCT GC-(2' methoxy)A-(2' methoxy)C-(2' methoxy)C-3'	PPD Global Ltd	Treatment of Myasthenia Gravis	▪ 30.01.2004 ▪ 19.03.2004 ▪ 14.05.2004 ▪ 56 days	▪ 25.05.2004 ▪ 21.06.2004
Aztreonam lysinate (inhalation use)	MoRa Pharm GmbH	Treatment of gram negative bacterial lung infection in cystic fibrosis	▪ 05.01.2004 ▪ 19.03.2004 ▪ 14.05.2004 ▪ 56 days	▪ 25.05.2004 ▪ 21.06.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
Muramyl Tripeptide Phosphatidyl Ethanolamine	Immuno-Designed Molecules SA	Treatment of osteosarcoma	▪ 03.03.2004 ▪ 19.03.2004 ▪ 14.05.2004 ▪ 56 days	▪ 25.05.2004 ▪ 21.06.2004
Suberolylanilide Hydroxamic acid	Stringer Consultancy Services Ltd	Treatment of cutaneous T-cell lymphoma	▪ 05.01.2004 ▪ 19.03.2004 ▪ 14.05.2004 ▪ 56 days	▪ 25.05.2004 ▪ 21.06.2004
HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor	CellCure ApS	Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients	▪ 30.01.2004 ▪ 16.02.2004 ▪ 14.05.2004 ▪ 88 days	▪ 25.05.2004 ▪ 21.06.2004
Defibrotide	Gentium S.p.A.	Prevention of hepatic veno-occlusive disease	▪ 01.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
Mepolizumab	SmithKline Beecham plc	Treatment of hypereosinephilic syndrome	▪ 02.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
Midostaurin	Novartis Europharm Limited	Treatment of acute myeloid leukaemia	▪ 05.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
Sinapultide, dipalmitoylphosphatidylcholine, palmitoyloleoy phosphatidylglycerol and palmitic acid	GMG BioBusiness Ltd	Treatment of respiratory distress syndrome in premature neonates of less then 37 weeks of gestational age	▪ 04.03.2004 ▪ 19.03.2004 ▪ 16.06.2004 ▪ 89 days	▪ 25.06.2004 ▪ 29.07.2004
Sinapultide, dipalmitoylphosphatidylcholine, palmitoyloleoy phosphatidylglycerol and palmitic acid	GMG BioBusiness Ltd	Prevention of respiratory distress syndrome in premature neonates of less than 32 weeks of gestational age	▪ 04.03.2004 ▪ 19.03.2004 ▪ 16.06.2004 ▪ 89 days	▪ 25.06.2004 ▪ 29.07.2004
Porfimer sodium (for use with photodynamic therapy)	Axcan Pharma International BV	Treatment of cholangiocarcinoma	▪ 01.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 29.07.2004 ▪ 29.07.2004
Ciclosporin (inhalation use)	PARI Aerosol Research Institute	Treatment of graft rejection after lung transplantation	▪ 18.03.2004 ▪ 19.03.2004 ▪ 16.06.2004 ▪ 89 days	▪ 25.06.2004 ▪ 29.07.2004
Ciclosporin (inhalation use)	PARI Aerosol Research Institute	Prevention of graft rejection after lung transplantation	▪ 01.03.2004 ▪ 19.03.2004 ▪ 16.06.2004 ▪ 89 days	▪ 25.06.2004 ▪ 29.07.2004
Sorafenib tosylate	Bayer Healthcare AG	Treatment of renal cell carcinoma	▪ 06.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
(R, S)-3-(bromomethyl)-3-butanol-1-yl-disphosphate	Innate Pharma	Treatment of renal cell carcinoma	▪ 06.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
Acetylsalicylic acid	Bayer Vital GmbH	Treatment of polycythemia vera	▪ 11.03.2004 ▪ 26.04.2004 ▪ 1.6.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
Defibrotide	Gentium S.p.A.	Treatment of hepatic veno-occlusive disease	▪ 01.04.2004 ▪ 26.04.2004 ▪ 16.06.2004 ▪ 51 days	▪ 25.06.2004 ▪ 29.07.2004
5,10-methylene-tetrahydrofolic acid	Interface International Consultancy Ltd	Treatment of pancreatic cancer in combination with 5-fluorouracil	▪ 19.05.2004 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
Pancreatic enzymes (cross-linked enzyme crystal lipase, protease, amylase)	Dr Falk Pharma GmbH	Treatment of malabsorption due to exocrine pancreatic enzyme insufficiency	▪ 02.08.2002 ▪ 26.04.2004 ▪ 22.07.2004 ▪ 88 days	▪ 09.08.2004 ▪ 02.09.2004
Heparin-Sodium	Prof. Dr W Seeger	Treatment of idiopathic pulmonary fibrosis	▪ 08.04.2004 ▪ 26.04.2004 ▪ 22.07.2004 ▪ 88 days	▪ 09.08.2004 ▪ 02.09.2004
Anti-epidermal growth factor receptor antibody h-R3	Oncoscience AG	Treatment of glioma	▪ 24.05.2004 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
Sodium dichloroacetate	EBD Group	Treatment of systemic monochloroacetate poisoning	▪ 01.10.2003 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
HLA-B27-derived peptide (amino acid 125-138)	Lynkeus BioTech GmbH	Treatment of autoimmune uveitis	▪ 19.05.2004 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
Homoharringtonine	Stragen France SAS	Treatment of chronic myeloid leukaemia	▪ 26.05.2004 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
Recombinant human interleukin-21	Novo Nordisk A/S	Treatment of renal cell carcinoma	▪ 14.05.2004 ▪ 14.06.2004 ▪ 22.07.2004 ▪ 39 days	▪ 09.08.2004 ▪ 02.09.2004
1, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11-tetraazacyclotetradecane	Orphix Consulting GmbH	Treatment to mobilise progenitor cells prior to stem-cell transplantation	▪ 23.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 20.10.2004
Homoharringtonine	Stragen France SAS	Treatment of acute myeloid leukaemia	▪ 29.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 20.10.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
Dexamethasone sodium phosphate encapsulated in human erythrocytes	Dideco S.p.A.	Treatment of cystic fibrosis	▪ 24.05.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 20.10.2004
Recombinant human insulin-like growth factor-I/recombinant human insulin-like growth factor binding protein-3	Dr Geoffrey Allan	Treatment of Type-B extreme insulin resistance syndrome	▪ 05.04.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 20.10.2004
Deferoxamine mesilate	Neuraxo Biotec GmbH	Treatment of traumatic spinal cord injury	▪ 03.03.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 560 days	▪ 30.09.2004 ▪ 20.10.2004
Rufinamide	Eisai Limited	Treatment of Lennox-Gastaut Syndrome	▪ 25.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 20.10.2004
Biotinylated anti-tenascin monoclonal antibody for use with 90-Yttrium	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.	Treatment of glioma	▪ 28.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 20.10.2004
Deuterium oxide	BDD Berolina Drug Development GmbH	Treatment of pancreatic cancer	▪ 26.05.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 20.10.2004
Adeno-associated viral vector containing the human gamma-sarcoglycan gene	Généthon	Treatment of gamma-sarcoglycanopathies	▪ 23.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 21.10.2004
Sitaxsentan sodium	PPD Global Ltd	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	▪ 06.04.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 21.10.2004
Recombinant human insulin-like growth factor-I/recombinant human insulin-like growth factor binding protein-3	Dr Geoffrey Allan	Treatment of Type-A extreme insulin resistance syndrome	▪ 05.04.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 21.10.2004
Recombinant human insulin-like growth factor-I/recombinant human insulin-like growth factor binding protein-3	Dr Geoffrey Allan	Treatment of Leprechaunism	▪ 05.04.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 21.10.2004
Recombinant human insulin-like growth factor-I/recombinant human insulin-like growth factor binding protein-3	Dr Geoffrey Allan	Treatment of Rabson-Mendenhall syndrome	▪ 05.04.2004 ▪ 14.06.2004 ▪ 09.09.2004 ▪ 88 days	▪ 23.09.2004 ▪ 21.10.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
Doxorubicine polyisohexylcyanoacrylate nanoparticles	Bioalliance Pharma SA	Treatment of hepatocellular carcinoma	▪ 25.06.2004 ▪ 12.07.2004 ▪ 09.09.2004 ▪ 60 days	▪ 23.09.2004 ▪ 21.10.2004
Pirfenidone	Uppsala Medical Information System AB	Treatment of idiopathic pulmonary fibrosis	▪ 28.07.2004 ▪ 16.08.2004 ▪ 07.10.2004 ▪ 53 days	▪ 15.10.2004 ▪ 16.11.2004
Aplidine	Pharma Mar SA Sociedad Unipersonal	Treatment of multiple myeloma	▪ 22.06.2004 ▪ 12.07.2004 ▪ 07.10.2004 ▪ 88 days	▪ 15.10.2004 ▪ 16.11.2004
Alpha-1 antitrypsin (inhalation use)	BCG (Europe) Ltd	Treatment of emphysema secondary to congenital alpha-1-antitrypsin deficiency	▪ 28.07.2004 ▪ 16.08.2004 ▪ 07.10.2004 ▪ 53 days	▪ 15.10.2004 ▪ 16.11.2004
Alpha-1 antitrypsin (inhalation use)	BCG (Europe) Ltd	Treatment of cystic fibrosis	▪ 28.07.2004 ▪ 16.08.2004 ▪ 07.10.2004 ▪ 53 days	▪ 15.10.2004 ▪ 16.11.2004
N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole	AB Science	Treatment of Mastocytosis	▪ 30.07.2004 ▪ 16.08.2004 ▪ 07.10.2004 ▪ 53 days	▪ 15.10.2004 ▪ 16.11.2004
Valproic Acid, Sodium	G2M Cancer Drug AG	Treatment of familial adenomatous polyposis	▪ 29.07.2004 ▪ 16.08.2004 ▪ 07.10.2004 ▪ 53 days	▪ 22.10.2004 ▪ 30.11.2004
Sabarubicin	Menarini Ricerche S.p.A.	Treatment of small cell lung cancer	▪ 29.07.2004 ▪ 16.08.2004 ▪ 11.11.2004 ▪ 88 days	▪ 19.11.2004 ▪ 21.12.2004
17-allylamino-17-demethoxygeldanamycin	Wainwright Associates Ltd	Treatment of multiple myeloma	▪ 25.08.2004 ▪ 10.09.2004 ▪ 11.11.2004 ▪ 63 days	▪ 19.11.2004 ▪ 21.12.2004
Val-Leu-Gln-Glu-Leu-Asn-Val-Thr-Val (Pr1 nanopeptide, sequence 169-177, of proteinase 3)	Accelsiors CRO & Consultancy Services GmbH	Treatment of myelodyplastic syndromes	▪ 30.07.2004 ▪ 16.08.2004 ▪ 11.11.2004 ▪ 88 days	▪ 19.11.2004 ▪ 21.12.2004
Val-Leu-Gln-Glu-Leu-Asn-Val-Thr-Val (Pr1 nanopeptide, sequence 169-177, of proteinase 3)	Accelsiors CRO & Consultancy Services GmbH	Treatment of chronic myeloid leukaemia	▪ 30.07.2004 ▪ 16.08.2004 ▪ 11.11.2004 ▪ 88 days	▪ 19.11.2004 ▪ 21.12.2004
Val-Leu-Gln-Glu-Leu-Asn-Val-Thr-Val (Pr1 nanopeptide, sequence 169-177, of proteinase 3)	Accelsiors CRO & Consultancy Services GmbH	Treatment of acute myeloid leukaemia	▪ 30.07.2004 ▪ 16.08.2004 ▪ 11.11.2004 ▪ 88 days	▪ 19.11.2004 ▪ 21.12.2004

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Date of decision
Recombinant histidine-tagged idiotype immunoglobulin Fab fragment of clonal B-cell receptors	CellGenix Technologie Transfer GmbH	Treatment of multiple myeloma	▪ 25.08.2004 ▪ 10.09.2004 ▪ 11.11.2004 ▪ 63 days	▪ 19.11.2004 ▪ 21.12.2004
Recombinant histidine-tagged idiotype immunoglobulin Fab fragment of clonal B-cell receptors	CellGenix Technologie Transfer GmbH	Treatment of follicular lymphoma	▪ 25.08.2004 ▪ 10.09.2004 ▪ 11.11.2004 ▪ 63 days	▪ 19.11.2004 ▪ 23.12.2004
Recombinant histidine-tagged idiotype immunoglobulin Fab fragment of clonal B-cell receptors	CellGenix Technology Transfer GmbH	Treatment of mantle cell lymphoma	▪ 25.08.2004 ▪ 10.09.2004 ▪ 11.11.2004 ▪ 63 days	▪ 19.11.2004 ▪ 21.12.0004
N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole	AB Science	Treatment of malignant gastro-intestinal stromal tumours	▪ 30.07.2004 ▪ 16.08.2004 ▪ 16.11.2004 ▪ 93 days	▪ 19.11.2004 ▪ 21.12.2004
Recombinant human alpha-Mannosidase	HemeBiotech A/S	Treatment of alpha-Mannosidosis	▪ 27.09.2004 ▪ 18.10.2004 ▪ 08.12.2004 ▪ 52 days	▪ 22.12.2004 ▪ 26.01.2005
L-Asparaginase	medac Gesellschaft für klinische Spezialpräparate mbH	Treatment of acute lymphoblastic leukaemia	▪ 30.07.2004 ▪ 10.09.2004 ▪ 08.12.2004 ▪ 90 days	▪ 22.12.2004 ▪ 26.01.2005
Acetylcysteine	Zambon Group S.p.A.	Treatment of idiopathic pulmonary fibrosis	▪ 29.09.2004 ▪ 18.10.2004 ▪ 08.12.2004 ▪ 52 days	▪ 22.12.2004 ▪ 26.01.2005
17-allylamino-17-demethoxygeldanamycin	Wainwright Associates Ltd	Treatment of chronic myeloid leukaemia	▪ 30.09.2004 ▪ 18.10.2004 ▪ 08.12.2004 ▪ 90 days	▪ 22.12.2004 ▪ 26.01.2005
Recombinant human bile salt-stimulated lipase	Arexis AB	Treatment of cystic fibrosis	▪ 25.03.2004 ▪ 10.09.2004 ▪ 08.12.2004 ▪ 90 days	▪ 22.12.2004 ▪ 26.01.2005

Negative COMP designation opinions

Product INN	Sponsor	Summary of indication	EMEA/COMP ▪ Submission ▪ Start date ▪ Opinion ▪ Active time	European Commission ▪ Opinion received ▪ Date of decision
Histamine dihydrochloride	Maxim Pharmaceuticals Europe Ltd	Treatment of malignant melanoma	▪ 02/10/2003 ▪ 17/10/2003 ▪ 14/01/2004 ▪ 92 days	▪ 25/06/2004 ▪ 24/08/2004
Midazolam hydrochloride	Special Products Ltd	Treatment of status epilepticus	▪ 03/04/2003 ▪ 02/05/2003 ▪ 30/07/2003 ▪ 90 days	▪ 26/11/2003 ▪ 01/03/2004

Annex 12
Guidelines and working documents in 2004

General guidelines

Reference number	Document title	Status
EMEA/P/24143/04	Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework	Released for consultation in September 2004

Committee for Medicinal Products for Human Use (CHMP)

Reference number	Document title	Status
EMEA/CHMP/5579/04	Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community	Released for consultation in October 2004

CHMP Invented Name Review Group

Reference number	Document title	Status
(CPMP/328/98, Rev 4)	Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure	Released for consultation in September 2004

CHMP Biotechnology Working Party

Reference number	Document title	Status
EMEA/CPMP/BWP/125/04	Guideline on epidemiological data on blood transmissible infections	Released for consultation in January 2004
EMEA/CPMP/BWP/4663/03	Guideline on requirements for plasma master file (PMF) certification	Adopted in February 2004
EMEA/CPMP/BWP/3794/03	Guideline on the scientific data requirements for a plasma master file (PMF)	Adopted in February 2004
EMEA/CPMP/BWP/4548/03	Guideline on requirements for vaccine antigen master file (VAMF) certification	Adopted in February 2004
EMEA/CPMP/BWP/3734/03	Guideline on the scientific data requirements for a vaccine antigen master file (VAMF)	Adopted in December 2003

Reference number	Document title	Status
EMEA/CPMP/BWP/1104/04	EU recommendations for the influenza vaccine composition for the season 2004/2005	Adopted in April 2004
EMEA/CPMP/BWP/2879/02 revision 1	CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products	Adopted in June 2004
EMEA/410/01 Revision 3	Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products	Released for consultation in June 2004
EMEA/CHMP/BWP/27/04	First cases of BSE in USA and Canada: Risk assessment of ruminant materials originating from USA and Canada	Adopted in July 2004
EMEA/CHMP/BWP/5180/03	Guideline on assessing the risk for virus transmission - New Chapter 6 of the note for guidance on plasma-derived medicinal products	Adopted in October 2004
EMEA/CHMP/BWP/64/04	Concept paper on the need to revise the guideline on production and quality control of monoclonal antibodies (3AB4A, Revision December 1994)	Released for consultation in October 2004

CHMP Blood Products Working Party

Reference number	Document title	Status
CPMP/BPWG/3732/02	Core SPC for human tick-borne encephalitis immunoglobulin for intramuscular use	Adopted in March 2004
CPMP/BPWG/3730/02	Core SPC for human tetanus immunoglobulin for intramuscular use	Adopted in March 2004
CPMP/BPWG/3728/02	Core SPC for human rabies immunoglobulin for intramuscular use	Adopted in March 2004
CPMP/BPWG/859/95 rev. 2	Core SPC for human normal immunoglobulin for intravenous administration (IVIg) - Revision 2	Adopted in July 2004
CPMP/BPWG/2048/01	Core SPC for human plasma-derived coagulation factor VII products	Adopted in July 2004
CPMP/BPWG/153/00	Core SPC for plasma-derived fibrin sealant/haemostatic products	Adopted in July 2004
CPMP/BPWG/1089/00	Guideline on the clinical investigation of plasma-derived fibrin sealant/haemostatic products	Adopted in July 2004
CPMP/BPWG/278/02	Core SPC for human plasma-derived von Willebrand factor	Released for consultation in October 2004
CPMP/BPWG/3735/02	Core SPC for human prothrombin complex products	Adopted in October 2004

CHMP Vaccine Working Party

Reference number	Document title	Status
CPMP/VEG/4717/03	Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application	Adopted in March 2004
CPMP/VEG/1194/04	EMEA public statement on thiomersal in vaccines for human use	Adopted in March 2004
CPMP/VEG/4986/03	Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure	Adopted in March 2004
CHMP/VEG/1820/04	Concept paper on the development of a Committee for Human Medicinal Products (CHMP) - Revised guideline on clinical evaluation of new vaccine	Adopted in June 2004
CPMP/VEG/17/03/04	Guideline on adjuvants in vaccines	Released for consultation in March 2004

CHMP Efficacy Working Party

Reference number	Document title	Status
(CPMP/EWP/6235/04)	Concept paper on the development of a CPMP points to consider on clinical investigation of medicinal products for the prophylaxis of venous thromboembolism in non-surgical patients	Adopted in February 2004
(CPMP/EWP/6172/03)	Concept paper on the development of a CPMP points to consider on clinical investigation of medicinal products for the treatment of chronic hepatitis B	Adopted in February 2004
(CPMP/EWP/438/04)	Concept paper on the development of a CPMP points to consider on clinical investigation of medicinal products for the treatment of psoriatic arthropathy	Adopted in February 2004
(CPMP/EWP/422/04)	Concept paper on the development of a CPMP points to consider on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (JIA)	Adopted in February 2004
(CHMP/EWP/5872/03)	Concept paper on the development of a CHMP guideline on data monitoring committee (DMC)	Adopted in February 2004
(CPMP/EWP/4937/03)	Concept paper on the development of a CPMP points to consider on investigations of medicinal products for the treatment of chemotherapy-induced nausea and vomiting	Adopted in March 2004

Reference number	Document title	Status
(CHMP/EWP/1470/04)	Concept paper on the development of a CHMP note for guidance on the need for regulatory guidance in the evaluation of medicinal products for the secondary cardiovascular prevention	Adopted in June 2004
(CHMP/EWP/1738/04)	Recommendation on the need for revision of the CPMP points to consider on HRT	Adopted in June 2004
(CHMP/EWP/1068/04)	Recommendation on the need for revision of the note for guidance on evaluation of anticancer medicinal products in man	Adopted in July 2004
(CHMP/EWP/104288/2004)	Recommendation on the need for revision of the CHMP note for guidance on clinical trials with haemopoietic growth factors for the prophylaxis of infection following melosuppressive or myeloablative therapy	Adopted in October 2004
(CHMP/EWP/106094/04)	Recommendation on the need for revision of the note for guidance on clinical investigation of medicinal products for the treatment of multiple sclerosis	Adopted in October 2004
(CHMP/EWP/139565/2004)	Recommendation for revision of the points to consider on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome	Adopted in November 2004
(CPMP/EWP/2339/02)	Draft note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function	Released for consultation in February 2004
(CPMP/EWP/2158/99)	Draft CPMP points to consider on the choice of non-inferiority margin	Released for consultation in February 2004
(CPMP/EWP/252/03)	Draft CPMP points to consider on clinical investigation of medicinal products for the treatment of neuropathic pain	Released for consultation in February 2004
(CHMP/EWP/519/98 rev. 1)	Note for guidance on clinical investigation of steroid contraceptives in women	Released for consultation in June 2004
(CHMP/EWP/5872/03)	Guideline on data monitoring committee (DMC)	Released for consultation in October 2004
(CHMP/EWP/139391/2004)	Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products	Released for consultation in November 2004
(CHMP/EWP/3635/03)	Guideline on clinical investigation of medicinal products for the treatment of social anxiety disorder (SAD)	Released for consultation in November 2004

Reference number	Document title	Status
(CPMP/EWP/4151/00)	Points to consider on the requirements for clinical documentation for orally inhaled products (OIP)	Adopted in April 2004
(CPMP/558/95 rev. 1)	Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections	Adopted in April 2004
(CHMP/EWP/225/02)	Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function	Adopted in June 2004
(CHMP/EWP/238/95 rev. 2)	Note for guidance on clinical investigation of medicinal products in the treatment of hypertension	Adopted in June 2004
(CHMP/EWP/2998/03)	Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications	Adopted in June 2004
(CPMP/EWP/2986/03)	Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure – addendum on acute cardiac failure	Adopted in July 2004
(CPMP/EWP/3020/03)	Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders	Adopted in July 2004
(CHMP/EWP/2455/02)	Note for guidance on the clinical development of medicinal products for the treatment of allergic rhino-conjunctivitis	Adopted in October 2004
(CHMP/EWP/2454/02)	Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis	Adopted in November 2004
(CHMP/EWP/252/03)	Guideline on clinical investigation of medicinal products intended for the treatment of neuropathic pain	Adopted in November 2004

CHMP Pharmacovigilance Working Party

Reference number	Document title	Status
CPMP/ICH/5716/03	Note for guidance on planning of pharmacovigilance activities	

CHMP Safety Working Party

Reference number	Document title	Status
CPMP/SWP/4447/00	Guideline on environmental risk assessments for pharmaceuticals	Re-release for consultation expected in 4th quarter 2004 or 1st quarter 2005

Reference number	Document title	Status
CPMP/SWP/5199/02	Guideline on the limits for genotoxic impurities	Finalisation expected in 1st quarter 2005
CPMP/SWP/1094/04	Guideline on the evaluation of control samples for toxicokinetic parameters in toxicology studies: checking for contamination with the test substance	Re-release for consultation expected in 1st quarter 2005
CPMP/SWP/799/95	Guideline on the non-clinical documentation for mixed marketing authorisation applications	Finalisation expected in 2nd quarter 2005
EMEA/CHMP/SWP/149188/2004	Guideline on the need for pre-clinical testing of human pharmaceuticals in juvenile animals	Release for consultation expected in 1st quarter 2005
EMEA/CHMP/SWP/94227/2004	Guideline on investigation of dependence potential of medicinal products	Release for consultation expected in 1st quarter 2005
	Guideline on the non-clinical development of fixed combinations of medicinal products	Release for consultation expected in 3rd quarter 2005
EMEA/CHMP/SWP/5382/2003	Guideline on the non-clinical testing for inadvertent germline transmission of gene transfer vectors	Release for consultation expected in 2nd quarter 2005
EMEA/CHMP/SWP/178958/2004	Guideline on drug-induced hepatotoxicity	Release for consultation expected in 3rd quarter 2005
CPMP/SWP/QWP/4446/00	Guideline on specification limits for residues of metal catalysts in medicinal products	Re-release for consultation expected in 1st quarter 2005
	Guideline on risk assessment of medicinal products on human reproductive and development toxicities: from data to labelling	Release for consultation expected in 3rd quarter 2005
	Guideline on the assessment of carcinogenic and mutagenic potential of anti-HIV medicinal products	Release for consultation expected in 3rd quarter 2005
	Guideline on the investigation of mitochondrial toxicity of HIV-therapeutics in vitro	Release for consultation expected in 3rd quarter 2005
CPMP/SWP/2592/02 Rev 1	CHMP SWP conclusions and recommendations on the use of genetically modified animal models for carcinogenicity testing	Revision adopted in June 2004
CPMP/SWP/2599/02 Rev 1	Position paper on the non-clinical safety studies to support clinical trials, with a single low dose of a compound	Revision adopted in June 2004
CHMP/ICH/423/02 Revised	ICH S7B – The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals	SWP contribution

Reference number	Document title	Status
	ICH S8 – Immunotoxicology studies	SWP contribution
	ICH Q5E – Comparability of biotechnological and biological products subject to changes in their manufacturing process	SWP contribution

CHMP Scientific Advice Working Party

No guidelines released or adopted.

CVMP Environmental Risk Assessment (Temporary Working Party)

Reference number	Document title	Status
CVMP/VICH/790/03	Guideline on environmental impact assessments for veterinary medicinal products (VMPs) – Phase II	Adopted in November 2004

CVMP Efficacy Working Party

Reference number	Document title	Status
EMEA/CVMP/625/03	Guideline – Specific efficacy requirements for ectoparasiticides in cattle	Adopted in July 2004
EMEA/CVMP/384/04	Concept paper – Revision of the guideline for fixed-combination products	Adopted in April 2004
EMEA/CVMP/638/04	Concept paper – SPC guidance to minimise the development of anthelmintic resistance	Adopted in July 2004
EMEA/CVMP/546/04	Comments on draft WAAVP guidelines on ectoparasiticites	Adopted in June 2004

CVMP Immunologicals Working Party

Reference number	Document title	Status
EMEA/CVMP/865/03	Position paper on the data requirements for removing the target animal batch safety test for immunological veterinary medicinal products in the EU	Adopted in July 2004
EMEA/CVMP/775/02	Position paper on requirements for vaccines against foot-and-mouth disease	Adopted in June 2004
EMEA/CVMP/004/04	Guideline on live recombinant vector vaccines for veterinary use	Adopted in December 2004

Reference number	Document title	Status
EMEA/CVMP/018/04	Concept paper on the need to revise the note for guidance on requirements for combined vaccines	Adopted in December 2004

CVMP General

Reference number	Document title	Status
CVMP/VICH/644/01-FINAL	VICH Topic GL27: Guidance on pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance	Adopted in January 2004

CVMP Safety Working Party

Reference number	Document title	Status
CVMP/VICH/467/03-FINAL	VICH Topic GL36 – Safety of veterinary drugs in human food: General approach to establish a microbiological ADI	Adopted in June 2004
CVMP/VICH/468/03-FINAL	VICH Topic GL37 – Safety of veterinary drugs in human food: Repeat-dose (chronic) toxicity testing	Adopted in June 2004
EMEA/CVMP/542/03-FINAL	Injection-site residues	Adopted in October 2004
EMEA/CVMP/543/03-CONSULTATION	User-safety for pharmaceutical veterinary medicinal products	Consultation ended in October 2004

Joint CHMP/CVMP Quality Working Party

Reference number	Document title	Status
EMEA/CVMP/373/04 CPMP/QWP/576/96-rev.1	Guideline on stability testing for applications for variations to a marketing authorisation	Consultation ended in October 2004
EMEA/CVMP/205/04 CPMP/QWP/4359/03	Guideline on plastic primary packaging materials	Consultation ended in August 2004
EMEA/CVMP/134/02 CPMP/QWP/227/02	Guideline on active substance master file procedure	Adopted by CPMP/CVMP in January/February 2004
EMEA/CVMP/1069/02 CPMP/QWP/297/97-Rev.1	Guideline on summary of requirements for active substances in the quality part of the dossier	Adopted by CPMP/CVMP in June 2004
EMEA/CVMP/540/03	Guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water	Adopted by CVMP in July 2004

Reference number	Document title	Status
EMEA/CVMP/541/03	Guideline on the chemistry of new active substances	Adopted by CVMP in May 2004
EMEA/CVMP/395/03 CHMP/QWP/2054/03 (Annex II to CHMP/QWP/848/99 & EMEA/CVMP/395/03)	Annex II to Note for guidance on process validation: non-standard processes	Adopted by CVMP/CHMP in May/July 2004
EMEA/CVMP/059/04	Position paper on control of impurities of pharmacopoeial substances: Compliance with the European Pharmacopoeia general monograph 'Substances for pharmaceutical use' and general chapter 'Control of impurities in substances for pharmaceutical use'	Adopted by CVMP in March 2004
CVMP/VICH/810/04-CONSULTATION	VICH Topic GL39 – Specifications: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: Chemical substances	Consultation ends in February 2005
CVMP/VICH/811/04-CONSULTATION	VICH Topic GL40 – Specifications: Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products	Consultation ends in February 2005

CVMP Scientific Advice Working Party

Reference number	Document title	Status
SOP/V/4016	Scientific advice to be given by the CVMP for veterinary medicinal products	
EMEA/CVMP/854/02-Rev.1	EMEA guidance for companies requesting scientific advice	

CVMP Pharmacovigilance Working Party

Reference number	Document title	Status
EMEA/CVMP/556/04	Additional lists for use with EudraVigilance Veterinary	Adopted in December 2004
EMEA/CVMP/413/99-FINAL-Rev.1	VEDDRA list of clinical terms for reporting animal adverse reactions to veterinary medicines	Adopted in October 2004
EMEA/CVMP/553/03	List of breeds and species for electronic reporting of adverse reactions in veterinary pharmacovigilance	Adopted in April 2004, updated in September 2004

Reference number	Document title	Status
EMEA/CVMP/065/03	Data elements for the electronic submission of adverse reaction reports related to veterinary medicinal products authorised in the EEA	Version 2.1.1 adopted in July 2004
EMEA/CVMP/280/04	EudraVigilance Veterinary XML-schema definition (XSD)	Version 2.1.1 adopted in July 2004
EMEA/CVMP/552/03-FINAL	Causality assessment for adverse reactions to veterinary medicinal products	Adopted in April 2004
EMEA/CVMP/345/98-Rev.1	Procedures for competent authorities for pharmacovigilance information for veterinary medicinal products	Adopted in April 2004
EMEA/CVMP/891/04	VEDDRA list of clinical terms for reporting suspected adverse reactions in human beings to veterinary products	Consultation ends in April 2005
EMEA/CVMP/893/04	An EU veterinary suspected adverse reaction report form for veterinarians and health professionals	Consultation ends in April 2005
EMEA/CVMP/900/03	Mechanisms to Trigger Investigations of the Safety of Veterinary Medicinal Products by EU Competent Authorities	Consultation ended in December 2004
EMEA/CVMP/557/04	Concept paper for a simple guide to veterinary pharmacovigilance	Consultation ended in August 2004
EMEA/CVMP/183/96-Rev.1	Pharmacovigilance of veterinary medicinal products	Consultation ended in September 2004

Committee on Orphan Medicinal Products (COMP)

Reference number	Document title	Status
EMEA/35607/03	Note for sponsors on the enlargement of the European Union	Published in February 2004
ENTR/6283/00 Rev 2	Guideline on format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another	Revision 2 finalised in July 2004
COMP/1527/03	Draft guidance on the elements required to support the medical plausibility and assumption of significant benefit for an orphan designation	Released for consultation in September 2004

EMEA Herbal Medicinal Products Working Party[1]

Reference number	Document title	Status
HMPWP/1417/02	Final proposal for a core-data* on *Menthae piperitae aetheroleum* (peppermint oil)	Adopted in February 2004
HMPWP/243/03	Final proposal for a core-data* on *Primulae radix* (primula root)	Adopted in February 2004
HMPWP/341/03	Final proposal for a core-data* on *Salicis cortex* (willow bark)	Adopted in February 2004
HMPWP/343/03	Final proposal for a core-data* on *Thymi herba* (thyme herb)	Adopted in February 2004
HMPWP/337/03	Final position paper* on the use of herbal medicinal products containing methyleugenol	Adopted in February 2004
HMPWP/338/03	Final position paper* on the use of herbal medicinal products containing estragole	Adopted in February 2004
HMPWP/1156/03	Final concept paper* on the implementation of different levels of scientific evidence in core-data	Adopted in February 2004
HMPWP/41/01 rev 3	SOP* on recording of core-data for herbal drugs/herbal-drug preparations	Adopted in February 2004
HMPWP/345/03	Final position statement* on *Chamomilla*-containing herbal medicinal products	Adopted in April 2004
EMEA/18123/00 rev 5	Compilation* of general quality questions answered by the HMPWP	Adopted in June 2004
HMPWP/60/04	Position paper* on laxative bulk producers and the risk of interaction with drugs known to inhibit gastrointestinal propulsive motility	Adopted in June 2004
HMPWP/37/04	Final position paper* on the allergenic potency of herbal medicinal products containing soya or peanut protein	Adopted in June 2004
HMPWP/37/04	Draft position paper* on the allergenic potency of herbal medicinal products containing soya or peanut protein	Released for consultation in March 2004

[1] The EMEA Herbal Medicinal Products Working Party (HMPWP) was succeeded by the Committee on Herbal Medicinal Products (HMPC).

* The views presented in this document are those of the HMPWP, which was created as a forum for exchange of experience in the field of herbal medicinal products. This document was released for the purpose of transparency and has no legal force with respect to Directive 2001/83/EC.

Reference number	Document title	Status
HMPWP/52/04	Draft position paper* on the use of herbal medicinal products containing pulegone and menthofuran	Released for consultation in April 2004

Committee on Herbal Medicinal Products (HMPC)

No guidelines released or adopted.

* The views presented in this document are those of the HMPWP, which was created as a forum for exchange of experience in the field of herbal medicinal products. This document was released for the purpose of transparency and has no legal force with respect to Directive 2001/83/EC.

Annex 13
Arbitration and Community referrals overview 2004

Referrals made to the CHMP

Type of referral	Date of CHMP opinion	International non-proprietary name (INN)
Article 29	January 2004	Amlodipine maleate
Article 30	January 2004	Simvastatin
Article 30	March 2004	Gemfibrozil
Article 31	April 2004	Paroxetine
Article 29	December 2004	Gadoteric acid

Referrals made to the CVMP

Community harmonisation and pharmacovigilance referrals

Type of referral	Date of CVMP opinion	International non-proprietary name (INN)
Article 34	07.09.2004	Dectomax
Article 35	09.12.2004	Micotil

Annex 14
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 the 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:	Panos TSINTIS Direct telephone: (44-20) 75 23 71 08 E-mail: panos.tsintis@emea.eu.int
For matters relating to pharmacovigilance for medicinal products for veterinary use:	Barbara FREISCHEM Direct telephone: (44-20) 74 18 85 81 E-mail: barbara.freischem@emea.eu.int
For product defect and other quality-related matters:	E-mail: qualitydefects@emea.eu.int Fax: (44-20) 74 18 85 90 Out of hours telephone: (44-7880) 55 06 97

Certificates of a medicinal product

The EMEA issues certificates of a medicinal product in conformity with the arrangements laid down by the World Health Organization. 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:	E-mail: certificate@emea.eu.int Fax: (44-20) 74 18 85 95

EMEA PMF/VAMF certificates

The EMEA issues plasma master file (PMF) and vaccine antigen master file (VAMF) certificates of a medicinal product in conformity with the arrangements laid down by Community legislation. The EMEA PMF/VAMF certification process is an assessment of the PMF/VAMF application dossier. The certificate of compliance is valid throughout the European Community.

For enquiries concerning PMF certificates:	Silvia DOMINGO Direct telephone: (44-20) 74 18 85 52 Fax: (44-20) 74 18 85 45 E-mail: silvia.domingo@emea.eu.int
For enquiries concerning VAMF certificates:	Ragini SHIVJI Direct telephone: (44-20) 75 23 71 47 Fax: (44-20) 74 18 85 45 E-mail: ragini.shivji@emea.eu.int

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:

- on the Internet at: www.emea.eu.int
- by e-mail request to: info@emea.eu.int
- by fax to: (44-20) 74 18 86 70
- by writing to:
  EMEA Documentation service
  European Medicines Agency
  7 Westferry Circus
  Canary Wharf
  UK – London E14 4HB

European experts list

Approximately 3 500 European experts are used by the EMEA in its scientific evaluation work. The list of these experts is available for examination on request at the EMEA offices.

Requests should be sent in writing to the EMEA or by e-mail to: europeanexperts@emea.eu.int

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