European Medicines Agency

EMEA/81246/2006

Summary of the annual report of the European Medicines Agency 2005

This document provides a summary of the Agency's annual report for 2005, adopted by the Management Board on 9 March 2006.

The full annual report 2005 in English can be found on the Agency's website: www.emea.eu.int

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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[1] provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals.

Routes for authorisation of medicinal products in the European system:

- The centralised procedure is compulsory for all medicinal products for human and animal use derived from biotechnology processes. The same applies to all human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative disorders and for all designated orphan medicines intended for the treatment of rare diseases. Similarly, all veterinary medicines intended for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals have to go through the centralised procedure. For medicinal products that do not fall under any of the above-mentioned categories companies can submit an application for a centralised marketing authorisation to the EMEA, provided the medicinal product constitutes a significant therapeutic, scientific or technical innovation or the product is in any other respect in the interest of patient or animal health.

  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 valid throughout the whole European Union.

- The decentralised procedure and the mutual recognition procedure apply to the majority of conventional medicinal products. Both procedures are based upon the principle of recognition of national authorisations. They 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.

[1] GXP means 'good clinical practice' (GCP), 'good manufacturing practice' (GMP) and 'good laboratory practice' (GLP) collectively.

FOREWORD BY THE CHAIRMAN OF THE MANAGEMENT BOARD

Professor Hannes Wahlroos

The 11th year of operation of the European Medicines Agency (EMEA) was eventful. The reform of EU pharmaceutical legislation, implementation of the EMEA's Road Map to 2010 and dealing with pharmacovigilance issues required alertness, steadfastness and commitment to the important task of promoting public health.

The results presented in this Annual Report prove that the EMEA ably faced up to its many challenges in 2005. On behalf of the Management Board, therefore, I would like to thank the personnel of the EMEA for their important input in promoting European regulation in the field of pharmaceuticals. I would also like to thank the secretariat of the Management Board for their constructive and outstanding collaboration throughout the year. In addition, I would like to thank the Member States' competent authorities, which, together with the EMEA, form the core regulatory network for medicinal products. This close-knit network has been strengthened in recent years. In years to come, the EMEA will need further top-quality expertise and will be increasingly reliant on the Member States and their authorities to offer this.

Ultimate responsibility for the Agency's operational work rests with the Executive Director. Thomas Lönngren was unanimously appointed by the Management Board to serve in this demanding post for another five-year period, from 2006 to 2010. It is a pleasure for me, at this point, to congratulate him and wish him every success in his further term of office.

On behalf of the Management Board, I would like to emphasise a couple of events that took place last year. An important step forward was made in improving the usability of data relating to the safety of medicines. By the end of the year, the majority of the Member States' authorities were submitting their adverse drug reaction reports electronically to the Agency. This development will greatly enhance the ability of the EMEA to evaluate the safety of medicines.

The membership of the Management Board finally reached its full complement during the year under review, as new representatives of patients' organisations and doctors' and veterinarians' associations appointed by the Council of Ministers joined in the work. I am confident that, as a result, the broadened outlook of the Management Board will have a favourable impact on our work.

The EMEA will assume an active role in precautionary measures against pandemic influenza. The measures already taken to expedite the assessment procedures for vaccines and conventional medicines have been welcomed and are necessary. The information updates published on the EMEA website relating to these issues have been acclaimed as extremely useful.

The Management Board has been closely following the progress of the European innovation and technology platform, especially in the area of veterinary medicines. The Agency is involved in the steering group of the platform, and there are therefore good opportunities to influence and improve the development and availability of veterinary medicines.

At the end of 2005, the European Commission set up the Pharmaceutical Forum, a discussion platform for topics like pricing and reimbursement of medicines, relative effectiveness of medicinal products and drug information in Europe. The EMEA will be involved in the issues of relative effectiveness and provision of information to patients.

The Year 2005 was a very promising beginning for the second decade of the EMEA.

INTRODUCTION BY THE EXECUTIVE DIRECTOR

Thomas Lönngren

As anticipated, 2005 was quite an extraordinary year for the European Medicines Agency.

It began with celebrations to mark an important milestone in the history of the EMEA: its tenth anniversary. The generous birthday tributes paid to the Agency by so many of its partners and stakeholders were a welcome endorsement of its efforts to maintain and further develop an effective regulatory environment for medicines in the EU.

Now, with a decade of very solid progress behind it, and a good long-term plan in place to guide its forward evolution, the Agency is in better shape than ever to pursue its mission for the protection and promotion of health in Europe.

Those ten years of continuous growth and consolidation gave the Agency the experience and confidence it needed to meet the greatest challenge it has had to face so far: the full entry into force of the revised EU pharmaceutical legislation, in November 2005.

Thanks to the excellent planning and preparations put in place during the run-up to that date, the Agency was able to successfully implement all relevant provisions and guidelines stemming from the new legislation.

As a result, the Agency was immediately able to embrace its new responsibilities and begin offering an extended range of services in support of European efforts to bring innovative new medicines to the market. Achievements of particular note include:

- the successful launch of the Agency's SME Office, which provides specific assistance to the smaller companies that are so often at the cutting edge of medicinal technologies development;
- the implementation of procedures for greater (and in some cases free) provision of early-stage scientific advice to companies developing 'breakthrough' medicines;
- the introduction of new measures to accelerate the assessment of medicines that are of critical importance to public health.

While the Agency devoted great energy in 2005 to setting up these and other initiatives under its extended mandate, it also focused on improving its core scientific activities, particularly in the area of pharmacovigilance, which resulted in more efficient and effective practices for safeguarding the quality, safety and efficacy of authorised medicinal products.

Improvements to scientific and other business practices helped the Agency to deliver very good performance results for the year. The overall volume of pre- and post-authorisation applications received was high, but the Agency was able to handle its tasks successfully. The Agency also made significant contributions to wider European public-health activities, most notably with regard to pandemic-influenza preparedness, and the preparation of new legislation on medicines for children and advanced therapies.

All of these achievements in 2005 would not have been possible without the dedicated cooperation and support the Agency received from the European Parliament, the European Commission, the national medicines authorities and all of the Agency's partners throughout Europe, all of whom I thank for their invaluable help. I am particularly grateful for the excellent participation of our partners from the new Member States, in what was the first full year of operation in a European Union of 25 nations.

Lastly, I extend my wholehearted thanks to all EMEA staff, whose tireless efforts throughout this challenging year resulted in such a positive outcome for the Agency. I know I can rely on your continuing commitment as we bring the EMEA forward into its second decade.

1 IMPLEMENTATION OF THE REVISED LEGISLATION

On 20 November 2005, the Agency welcomed the full entry into force of Regulation (EC) No 726/2004[2], which heralds a more robust, modern and effective regulatory framework for pharmaceuticals in Europe. The new legal basis puts the Agency in a stronger position to fulfil its public and animal health mandate. It enables the Agency to strike the right balance between encouraging research and development of new medicines and strengthening their surveillance, giving patients access to much-needed new, safe and innovative medicines.

The Regulation also gives the EMEA important new responsibilities, in particular for the provision of better information about medicines to patients, consumers and healthcare professionals, and for strengthening the provision of scientific advice to companies. It significantly extends the scope of the centralised procedure for medicines for human use, giving the Agency responsibility for the evaluation and supervision of:

- Biotechnology medicines
- New medicines for the treatment of HIV/AIDS
- New medicines for the treatment of cancer
- New medicines for the treatment of diabetes
- New medicines for the treatment of neurodegenerative disorders
- Designated orphan medicinal products.

The scope of medicines for which the centralised procedure is optional has been broadened to allow for certain circumstances of expected benefit to public health, and now also includes self-medication products and generic medicines.

In the area of veterinary medicines, the Agency is responsible for all medicinal products derived from biotechnology or intended primarily for use as performance enhancers to promote growth of or to increase yield from treated animals. The centralised procedure is optional for immunological veterinary medicines for animal diseases that are subject to Community prophylactic measures.

The Regulation introduces, under specific conditions, new accelerated assessment and conditional marketing authorisation procedures, which help to ensure that patients have timely access to innovative medicines. At the same time, it provides new tools for strengthened protection of public health. These include risk-management plans, the collection of specific pharmacovigilance data from targeted groups of patients, and new possibilities for pharmacovigilance inspections and inspection of active substances.

During 2005, the Agency provided guidance in preparation for the entry into force of the revised legislation. This included drawing up guidelines for the new procedures, as well as contributing to the update of existing guidance documents, for both human and veterinary medicines, such as the good manufacturing practice (GMP) guide and the Notice to Applicants.

Notification to the EMEA became mandatory following the implementation of the revised pharmaceutical legislation. This led to a doubling of parallel distribution notifications submitted to the EMEA in 2005. In addition to these notifications, the Agency received over 1,000 notifications of changes. Because of this unexpected important increase in workload, delays in the procedure were encountered during 2005, but, due to a temporary increase in staff and improved efficiency of the process, the delays were partially reduced by the end of the year.

The implementation of the new pharmaceutical legislation was a success thanks to the joint efforts of the EMEA, its scientific committees and their working parties, the national competent authorities and

[2] OJ L 136, 30.04.2004, p. 1.

the European Commission, as well as interested parties, who provided valuable feedback during the public consultation on guidelines and procedures.

2 IMPLEMENTATION OF THE ROAD MAP

In the beginning of 2005, the Agency published its long-term strategy, the 'European Medicines Agency Road Map to 2010: Preparing the Ground for the Future'. The strategy aims to contribute to better protection and promotion of public and animal health, to improve the regulatory environment for medicinal products, and to stimulate innovation, research and development in the EU.

Road Map actions implemented during 2005 related to:

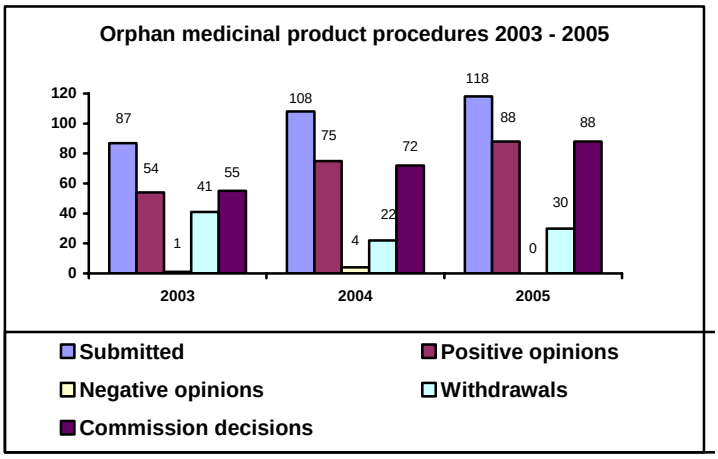
- Strengthening the quality-assurance system of scientific assessments by adopting a procedure for pilot peer reviews during the initial assessment phase of marketing authorisation applications
- Supporting applicants in the development of new therapeutic approaches and technologies
- Strengthening the Agency's interaction with European industry associations representing the innovative, generic and self-medication industries
- Strengthening interaction with patients' and consumers' organisations
- Developing a European Risk Management Strategy (ERMS) for safer medicines
- Addressing antimicrobial resistance by progressing a new strategy on risk management and risk assessment for antimicrobials in veterinary medicinal products
- Ensuring adequacy of environmental risk assessment by developing guidance to help applicants prepare the environmental risk assessment part of marketing-authorisation applications for veterinary medicines.

3 EVALUATION OF MEDICINES

3.1 Medicines for human use

3.1.1 Orphan designation

The Committee for Orphan Medicinal Products (COMP) adopted 88 positive opinions on designation of orphan medicines in 2005 — the highest number since the entry into force of EU legislation on orphan medicines (Regulation (EC) No 141/2000) in 2000.



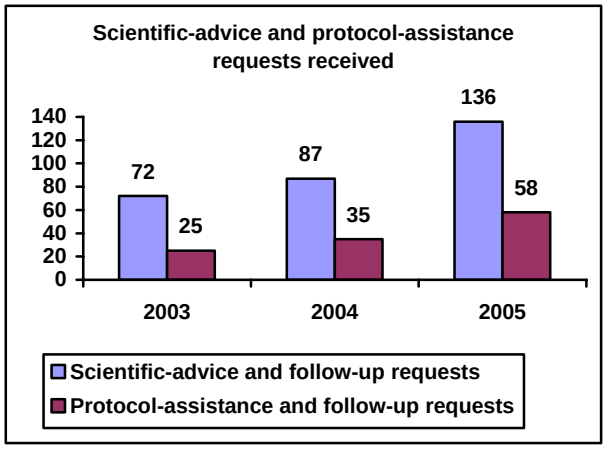
Designations were for products covering a wide range of therapeutic areas, but the largest number of them related to products for the treatment of cancer.

As the EU institutions progressed their discussions in 2005 on new EU legislation on medicines for children, over half of the designation opinions in 2005 were for conditions that affect children.

3.1.2 Scientific advice and protocol assistance

Major increase in requests for scientific advice

There was a substantial increase in the number of requests for scientific advice and protocol assistance in 2005 — up 60% on the number received in 2004.

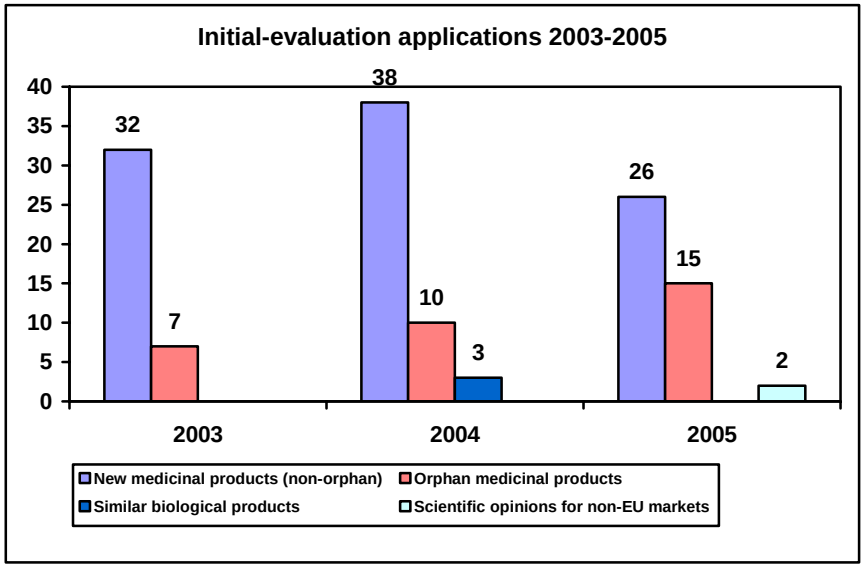


Some streamlining of the scientific advice procedure meant that, despite the increase in requests, the Agency was able to deliver more and faster scientific advice in 2005 than in previous years.

3.1.3 Initial evaluation

New applications in 2005

The Agency received 41 applications for initial marketing authorisation in 2005: 15 of these were applications for designated orphan medicinal products. An additional 2 were applications for opinions in the context of cooperation with the World Health Organization (WHO) for medicinal products intended exclusively for markets outside of the EU.



Opinions in 2005

The CHMP adopted 24 positive opinions and 1 negative opinion in 2005 on products intended for the European market. A further 15 applications were withdrawn prior to opinion.

Public health impact of opinions in 2005

Of the medicinal products intended for the European market for which a positive opinion was adopted:

- 2 are for use in cancer therapy, including the treatment of lung cancer — one of the highest causes of cancer-related deaths in the EU
- 7 are anti-infectives, of which 2 are for the treatment of HIV and AIDS
- 4 are for the treatment of metabolic disorders, of which 1 offers a new route of administration for diabetes patients by allowing insulin to be delivered via the lungs
- 5 are for the treatment of diseases of the central nervous system and sensory organs
- 6 are for the diagnosis or treatment of cardiovascular or pulmonary diseases.

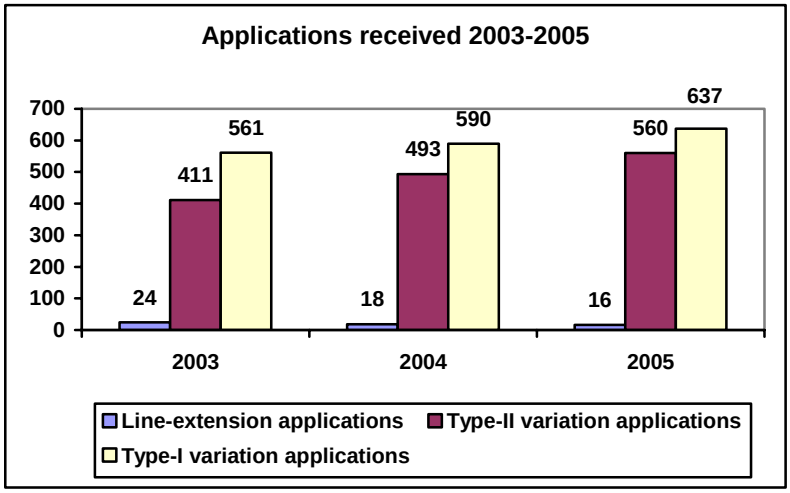
Of these 24 products, 3 are designated orphan medicinal products.

The CHMP also gave its first scientific opinions in the context of cooperation with the World Health Organization (WHO) on medicines intended exclusively for use in countries outside of the EU. The opinions concerned 2 medicinal products for the treatment of HIV.

3.1.4 Post-authorisation activities

Variations in 2005

The number of applications for variations to marketing authorisations increased once again in 2005. A total of 1,213 applications were received, which represents a 10% increase compared to 2004.



There was a similar increase in the number of finalised post-authorisation procedures, particularly those for type-II variations. Altogether, more than 1,000 post-authorisation procedures were finalised in 2005, including 628 notifications for type-I variations, 505 opinions for type-II variations (50% relating to safety and efficacy, and 50% relating to quality changes) and 15 opinions for line extensions.

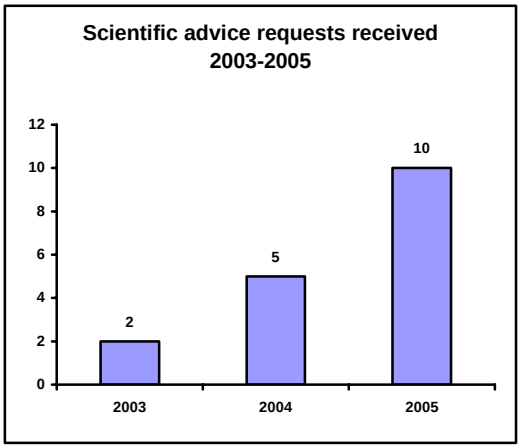
Public health impact of post-authorisation activities

- *New indications:* A total of 28 extensions of indications were introduced, a large number of which related to new treatment options for previously approved medicines in the area of cancer. There were also new indications in the area of diabetes, cardiovascular, neurodegenerative and rheumatoid diseases.
- *Contra-indications and warnings:* A total of 5 new contra-indications were introduced for 11 medicinal products used in the fields of HIV, immunosuppression, osteoporosis and metabolic diseases. In addition, there were 74 type-II variations relating to special warnings and precautions for use. Several class-labelling procedures were performed for HIV products. A class-labelling procedure was also conducted in relation to the use of epoetins in cancer patients, and another one in relation to dental, periodontal and psychiatric disorders possibly associated with the use of peginterferon alfa.
- *Extensions of use for children:* 4 products had their use extended to include the treatment of children. The medicines involved are an antiviral for the prevention of influenza, an antibacterial for a range of infections, an anti-epileptic and a product used in the treatment of leukaemia.

3.2 Medicines for veterinary use

3.2.1 Scientific advice

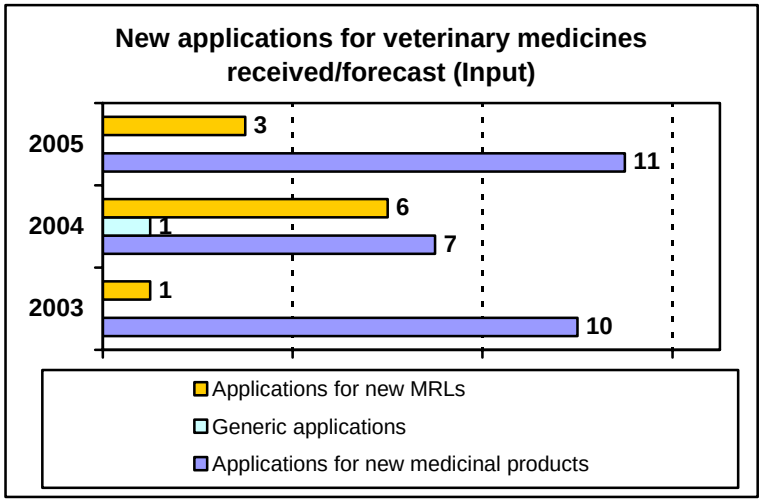
Scientific advice activities increased significantly in 2005: 10 requests for scientific advice were received. Two scientific advice requests received in 2005 were eligible for free advice under the pilot scheme for free scientific advice for veterinary medicines for minor uses and minor species (MUMS).



3.2.2 Initial evaluation

Level of applications

Eleven initial marketing authorisation applications were received, 10 of which were for pharmaceuticals and 1 for an immunological. The majority of applications concerned medicinal products for single, companion-animal species (dogs or cats only); 1 was for dogs, cats and horses; 1 was for use in food-producing animals (pigs).



Opinions in 2005

In 2005, the CVMP adopted a total of 5 positive opinions for initial marketing authorisation applications. There were no negative opinions. One application was withdrawn prior to opinion.

Among the 5 positive opinions were:

- 1 for a third-generation cephalosporin used to treat bacterial infections in pigs
- 1 for a novel combination endoparasiticide to treat roundworms and tapeworms in cats
- 3 vaccines for horses, against equine influenza and tetanus.

3.2.3 Maximum residue limits

In 2005, the EMEA received and validated 3 new applications for maximum residue limits (MRLs). Five applications for extension or modification of MRLs were submitted in 2005.

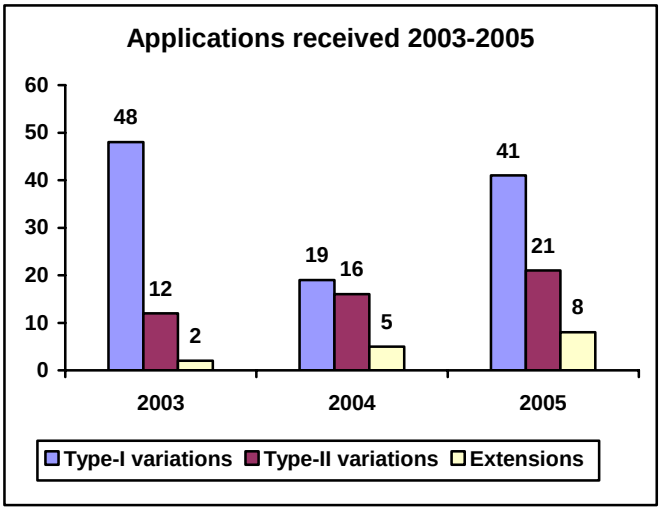
The CVMP gave 3 positive opinions for the establishment of MRLs and 8 opinions for the extension of existing MRLs to other species. In addition, the Committee gave 3 opinions for the extrapolation of existing MRLs to further species, in line with its policy on availability of veterinary medicines.

3.2.4 Post-authorisation activities

A total of 41 type-I variation applications were received, relating to 14 type-IA and 27 type-IB variations.

Twenty-one applications received related to the more complex type-II variations. Of these, 14 applications were for immunologicals, and concerned quality changes; 7 were for pharmaceuticals, with 4 concerning clinical changes and 3 concerning quality changes.

Eight applications for extension of a marketing authorisation were received: 6 related to pharmaceuticals and 2 to immunologicals. While the majority of these concerned new pharmaceutical forms, 2 concerned new target species.



4 SAFETY OF MEDICINES

Safety of medicines for human and veterinary use continued to be a top priority for the EMEA in 2005. The new legislation contains new tools to reinforce the Agency's capacity to ensure the safety of medicines, especially new pharmacovigilance obligations on companies and new provisions for submission of risk management plans.

4.1 Medicines for human use

The Agency dealt with a number of major safety issues in 2005, involving both centrally and non-centrally authorised medicines for human use, including:

- Conclusion of the safety review of COX-2 inhibitors
- Safety review of non-steroidal anti-inflammatory drugs (NSAIDs)
- Conclusion of the safety review of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants
- Suspension of a centrally authorised hexavalent vaccine due to concerns over the level of long-term protection offered by one of its components

- Initiation of a safety review for dermatological medicinal products containing tacrolimus or pimecrolimus, following concerns of potential cancer risks for patients
- Initiation of a review of mifepristone-containing medicinal products (Mifegyne) due to safety and efficacy concerns.

Risk management strategy

The Agency made good progress with national competent authorities in further developing and implementing the 2003 European risk management strategy (ERMS) that looks at how to better identify and manage safety issues. An action plan to further progress the European risk management strategy (ERMS) was published in May 2005, covering a number of key aspects including:

- Implementation of additional tools provided by the revised EU pharmaceutical legislation for monitoring the safety of medicines
- Initiatives in the areas of risk detection, risk assessment, risk minimisation and risk communication
- Strengthening the EU pharmacovigilance system to make the best use of the scientific resources and expertise available at EU level.

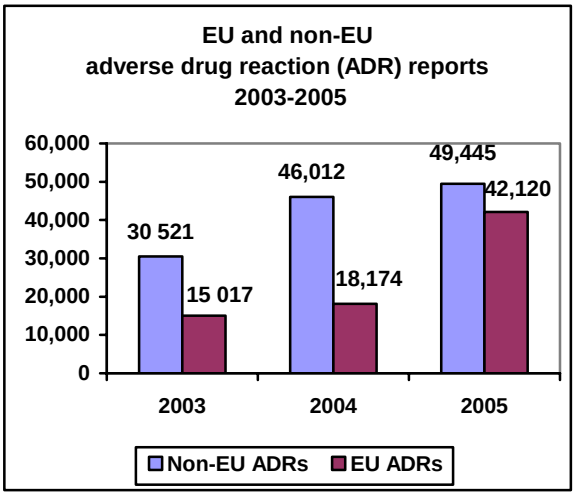
A special group (ERMS facilitation group) was set up to oversee the delivery of these key objectives through the development of a rolling work plan for 2005-2007. The group will provide progress reports to the EMEA Management Board and to the group of heads of national medicines agencies.

Risk management plans

As part of the revised pharmaceutical legislation, all new applications for marketing authorisation and applications for major changes to existing authorisations must be accompanied by a risk management plan. Work began in 2005 on implementing this new provision, which will require plans to identify any known or potential risks associated with the medicinal product concerned. The plans will allow the proactive implementation of risk minimisation measures and other pharmacovigilance activities.

Pharmacovigilance

Electronic reporting into the EudraVigilance database became mandatory in November 2005. The number of adverse drug reaction (ADR) reports for centrally authorised medicinal products received by the EMEA in 2005 was significantly greater than in previous years.



Good progress with EudraVigilance

Good progress was made with the implementation of EudraVigilance in 2005, with 23 national competent authorities and 105 marketing authorisation holders reporting electronically to the EudraVigilance Post-Authorisation Module (EVPM). These stakeholders reported electronically a total of 144,786 individual case safety reports (ICSRs) originating from within and outside the EU. Thereof, 73,198 ICSRs were received electronically for CAPs corresponding to 80% of the total adverse reaction reports received for CAPs in 2005.

In addition, 67 sponsors conducting clinical trials within the European Economic Area (EEA) were reporting suspected unexpected serious adverse reactions (SUSARs) to the EudraVigilance Clinical Trial Module (EVCTM). A total of 34,352 ICSRs relating to SUSARs were received.

The recommendations by the ad hoc working group to look at policy, compliance and regulatory aspects relating to EudraVigilance were adopted by the Heads of Medicines Agencies and the EMEA Management Board. The Agency established a EudraVigilance Steering Committee, which defines policies of implementation and access to EudraVigilance, and a EudraVigilance Expert Working Group, addressing all practical and operational aspects of implementation involving all stakeholders.

Strengthened procedures for detection of pharmacovigilance signals

The EMEA put in place procedures to reinforce detection of pharmacovigilance signals for centrally authorised products during 2005, allowing the Agency to take appropriate action earlier. A total of 880 suspected signals, concerning 87 products, were detected and investigated. When appropriate, further follow-up was undertaken to inform the Rapporteur and to assess the need for the collection of additional data from the marketing authorisation holders or the amendment of the product information via a type-II variation.

4.2 Medicines for veterinary use

In 2005, the EMEA received a total of 354 expedited spontaneous reports of suspected serious adverse reactions to centrally authorised veterinary medicines in animals or humans. This number includes reports originating in the EU and in countries outside the EU, such as the United States.

Of these, 305 reports related to suspected adverse reactions in animals, with a single report relating to one or more animals. Suspected adverse reactions in dogs and cats were most frequently reported. Only 32 reports related to food-producing animals. Altogether, 238 deaths in animals were reported.

Adverse reactions in human beings following exposure to a veterinary medicinal product were reported in 49 cases during 2005, none of which resulted in fatality.

Safety reviews

The Agency looked again at the safety of Micotil, following a request by the European Commission to take into account new information. On the basis of this, the Committee for Medicinal Products for Veterinary Use (CVMP) gave more guidance on advisable treatment in the case of accidental human injection.

Following on from the developments in human medicines, the Committee reviewed the safety of COX-2 inhibitors and NSAIDs used in animals, looking in particular at potential exposure of consumers. The Committee concluded in November 2005 that, based on the available evidence, no action to protect consumer safety or animal safety was necessary.

Improving veterinary pharmacovigilance

Pharmacovigilance in the veterinary sector was a top priority for the EMEA in 2005. A number of important actions were carried out, aimed at improving electronic reporting of post-authorisation

safety information, improving the exchange of safety information within the EU, and ensuring adequate surveillance and harmonised action.

The CVMP prepared a simple guide on veterinary pharmacovigilance, targeted primarily at veterinarians, in order to encourage reporting of adverse drug reactions.

The Agency also developed guidelines and concept papers designed to improve the consistency of safety data assessments.

Working with national competent authorities

The European Surveillance Strategy (ESS), which focuses on improved cooperation between all EU competent authorities and the EMEA in the field of pharmacovigilance for veterinary medicinal products, was revived, with the EMEA Secretariat now as a partner.

Good progress with EudraVigilance Veterinary

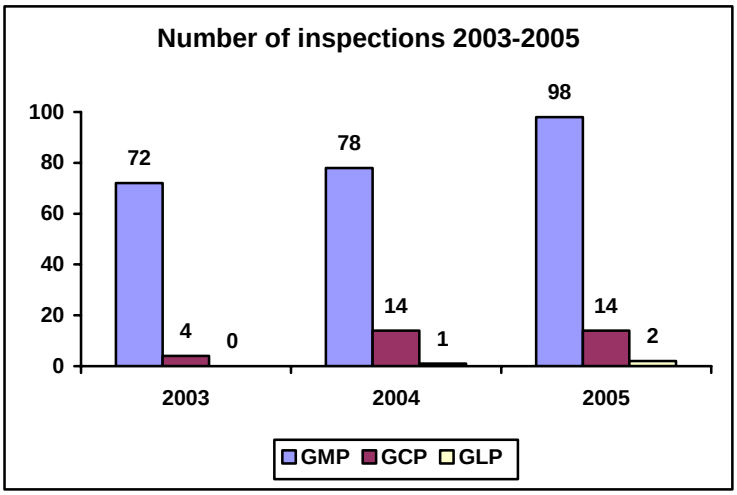
By the end of 2005, the majority of EU Member States were reporting electronically to the EudraVigilance Veterinary database, launched in October 2004; the remaining Member States are set to follow suit shortly.

Electronic reporting of adverse reactions is now mandatory. In 2005, the Agency discussed implementation plans for electronic reporting with major partners in the veterinary pharmaceutical industry. To address the specific needs of smaller companies, an additional, simple electronic reporting form was developed for use at Member State level by smaller marketing authorisation holders.

5 INSPECTIONS

5.1 GMP, GCP, GLP inspections

The EMEA coordinated and managed requests for 98 good manufacturing practice (GMP) and plasma master file inspections, 14 good clinical practice (GCP) and pharmacovigilance inspections, and 2 good laboratory practice (GLP) inspections during 2005, representing a total increase of 23% relative to 2004. By August 2005, 500 GMP inspections had been completed since the start of the operation of the centralised procedure.



5.2 Product defects and deviations

The EMEA received 65 quality-defect reports concerning human medicinal products and 3 quality-defect reports for veterinary medicinal products. Twenty-two of these defect reports resulted in a product recall (20 related to human medicinal products and 2 related to veterinary medicinal products); the remainder were classified as minor.

Two out of the 22 recalls were classified as 'Class 1' recalls, i.e. relating to defects, which are potentially life-threatening or could cause serious risks to health. Six recalls were 'Class 2' recalls, i.e. relating to defects which could cause illness or mistreatment. The majority of recalls (14) were classified as 'Class 3' recalls, which are not associated with serious public health hazards.

5.3 Sampling and testing

Thirty-nine medicinal products were included within the scope of the 2005 programme of sampling and testing of centrally authorised products. The majority of results show that the products were of high quality and complied with their specifications. Results requiring further investigation were found in 8 of the 39 products.

None of these concerned out-of-specification results. The investigations revealed some regulatory and scientific discrepancies, which were mainly addressed through amendment of the testing documentation by the marketing authorisation holders concerned.

5.4 Certificates of a medicinal product

The EMEA issues certificates of medicinal products to confirm the marketing authorisation status of products that have been authorised through the centralised procedure, or of products for which a centralised marketing authorisation application has been submitted to the EMEA.

The number of issued certificates continued to increase, and certificate number 100,000 was issued (for an AIDS product) in August 2005. Despite the increasing number of requests, the average issuing time has remained within procedural limits. This has been achieved by rationalisation of human resources and further process automation.

6 ENCOURAGING RESEARCH AND DEVELOPMENT OF MEDICINES

Competitiveness of the European pharmaceutical industry in the context of the 'Lisbon Agenda' remains high on the political agenda. While EMEA is not directly involved in this process, it does contribute to encouraging research and development in the pharmaceutical industry, ultimately improving access of patients to new and important medicines.

A new strategy for providing scientific advice

The revised EU pharmaceutical legislation gives the Agency a greater mandate to provide scientific advice, and gives the Executive Director direct responsibility for establishing efficient structures for its provision — particularly with regard to advice for the development of new therapies.

Working together with the CHMP, Scientific Advice Working Party and interested parties, the Executive Director proposed a new strategy and procedure, for which a 2-month public consultation exercise was launched in September 2005.

The strategy includes earlier and more frequent involvement of experts particularly on rare diseases and new therapies. Broader advice e.g. on non-product related issues will now be offered, and, in

parallel, workshops and think-tank meetings will create opportunities for increased awareness and dialogue with specific experts.

New regulatory tools for the evaluation of medicines

The new legislation gives the Agency new tools, aimed at fostering innovative medicines and therapies and providing for faster access of patients to medicines. These include accelerated assessment, conditional marketing authorisation, and opinions on compassionate use of medicines.

Also introduced by the new legislation is a new procedure, which enables the CHMP to give scientific opinions in the context of cooperation with the World Health Organization (WHO) for medicinal products used in markets outside of the European Union.

New therapies

EMEA supports applicants in the development of new therapeutic approaches and technologies. New opportunities for early informal discussions in the form of briefing meetings were introduced and a pilot procedure established to facilitate the evaluation of whether emerging approaches can be considered as medicinal products and thus have access to the centralised procedure. A think-tank group was established to consider innovative methods for drug development and to assess hurdles that may be encountered by pharmaceutical companies researching or developing such methods.

Availability of veterinary medicines

The EMEA continued efforts to address the shortage of essential medicines to the veterinary practitioner particularly for minor uses and minor species (MUMS), focusing in particular on the implementation of recommendations of the position paper regarding availability of products for minor uses and minor species.

The CVMP launched a public consultation for a number of guidelines proposing the adaptation of data requirements for the testing of veterinary medicines for minor uses and minor species regarding quality, safety, including maximum residue limits (MRLs), and efficacy, while ensuring public health.

The EMEA Management Board extended a pilot scheme to provide free scientific advice and protocol assistance to companies willing to develop medicines for MUMS. While only few scientific advice applications for MUMS products have been received since the scheme was introduced in October 2003, industry have confirmed high interest. The scheme will only become fully operational once the guidelines on adaptation of data requirements become available.

Another initiative aimed in particular at encouraging the development of medicines for minor species in the important livestock sector is the extrapolation of MRLs from major to minor species. The CVMP continued to extrapolate MRLs upon requests from companies in 2005 for substances important for therapy in minor species. The extrapolations are carried out without specific applications or payment of fees, provided the criteria detailed in the relevant CVMP guideline are met, thus ensuring consumer safety.

The CVMP, in consultation with the Federation of Veterinarians in Europe, prepared a proposal for a list of essential substances for the treatment of horses following the request from the European Commission. The list was submitted to the Commission in May 2005 to serve as basis for a list of essential substances, which is provided for by the new legislation . Once adopted products containing the listed substances can be used by veterinarians for the treatment of horses under the conditions of the ‘cascade principle’ providing a minimum 6-month withdrawal period is applied.

Dealing with R&D bottlenecks

In addition to its own internal activities, the EMEA also cooperated in 2005 with the European Commission Directorate-General for Research in the context of the ‘Innovative Medicines Initiative’ of the 7th Framework Programme for research, technological development and demonstration activities (2007-2013).

Contributions were made to the Innovative Medicines Initiative (IMI), the development of the European Technology Platform on Global Animal Health (ETPGAH), and the establishment of priorities for rare diseases.

7 SUPPORT TO SMALL AND MEDIUM-SIZED ENTERPRISES

An important new task of the revised legislation is the provision of assistance to small and medium-sized enterprises (SMEs) involved in the development of pharmaceuticals in the European Union.

With the aim of promoting innovation and the development of new medicinal products by micro, small and medium-sized enterprises, the Agency launched the 'SME Office', dedicated to addressing the particular needs of smaller companies, following the entry into force of the new SME Regulation[3] to implement provisions relating to incentives for SMEs in the new EU pharmaceutical legislation.

The SME Office has the sole remit of offering assistance to SMEs. The SME Office aims to facilitate communication with SMEs through dedicated personnel within the Agency who respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs.

The incentives offered by the SME Regulation apply equally to the human and veterinary sectors, and include:

- Administrative and procedural assistance from the SME Office at the Agency
- Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits
- Fee exemptions for certain administrative services of the EMEA
- Deferral of the fee payable for an application for marketing authorisation or related inspection
- Conditional fee exemption where scientific advice is followed and a marketing-authorisation application is not successful
- Assistance with translations of the product-information documents submitted in the application for a marketing authorisation.

A survey of SMEs was carried out in 2005 to understand their specific needs and expectations, and a first meeting with SME stakeholder organisations was held to discuss the results.

The EMEA received the first requests for SME status following the entry into force of the SME Regulation, and processed them.

8 HERBAL MEDICINES

The year 2005 was the first full year of operation of the Committee on Herbal Medicinal Products (HMPC), following its inaugural meeting in September 2004.

The Committee focused on work to establish the necessary procedures for conducting its business. This included the finalisation of the structure of the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products and the template for Community herbal monographs and the organisation of training sessions for EU assessors.

The Committee released for public consultation the first draft Community herbal monographs — for Valerian root, Psyllium seed, Linseed, Ispaghula husk and Ispaghula seed. A Community herbal monograph comprises the HMPC's scientific opinion on a given herbal medicinal product, based on

[3] Commission Regulation (EC) No 2049/2005, OJ L329, 16.12.2005, p. 4.

its evaluation of available scientific data (well-established use) or on the historic use of that product in the European Community (traditional use).

The Committee released for public consultation draft entries to the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' for Valerian root and Linseed. Herbal medicinal products entered into the Community list fulfil certain criteria, such as having been in medicinal use for a sufficiently long time, and are considered not to be harmful under normal conditions of use.

9 INFORMATION AND COMMUNICATION

The EMEA has a major role, reinforced by the new pharmaceutical legislation, in the provision of information to patients and healthcare professionals. A new Medical Information sector became fully operational in September 2005 and assumed responsibilities for interaction with patients' and healthcare professionals' organisations and for activities associated with the provision of product-related information.

Working through the EMEA/CHMP Working Group with Patients' and Consumers' Organisations (the Agency's platform for interaction with patients and consumers), a set of recommendations was published in March 2005 relating to: transparency and dissemination of information; product information; pharmacovigilance; and interaction between the EMEA and patients' organisations. The recommendations were the outcome of an extensive external consultation exercise with the Agency's partners and stakeholders. Some of the recommendations were implemented in 2005, including one for new product-information templates which allow better information to be provided for patients and which are tested for readability.

The EMEA Management Board adopted criteria in September 2005 for the participation of patients' or consumers' organisations in EMEA activities. In order to allow the development of these activities within a broader and more structured environment, the Management Board adopted, in December 2005, a 'Framework of Interaction' between the EMEA and patients' and consumers' organisations.

The new pharmaceutical legislation also gives the Agency new tasks to improve product-related information. These include the publication of a summary of the European public assessment report (EPAR) in a manner that is easily understandable to the public, the publication of withdrawals of marketing-authorisation applications prior to an opinion, and the publication of refusals of marketing authorisations.

An important aspect of information and communication is the provision of safety-related information to patients and healthcare professionals. A number of 'Dear Doctor Letters' were agreed by the CHMP, in addition to public statements. Question-and-answer documents were prepared systematically for all major safety issues involving centrally authorised products. A new initiative in 2005 was the publication of summaries of certain post-authorisation opinions, namely opinions on extension of indications and on the addition of new contra-indications or warnings.

To further improve the management of translations, the Management Board adopted a revised EMEA translation policy in September 2005. This policy put in place a framework for the checking of translations of product information by the national competent authorities, and set up a financial compensation scheme. Finally, in view of the next phase of EU enlargement, the EMEA completed preparations for pre-accession linguistic check activities for Bulgaria and Romania, to be launched in January 2006.

Following a period of external consultation with stakeholders, the Agency finalised and published a procedure for the development of pharmaceutical guidelines and related documents, proposing a consistent and transparent approach to their development, consultation and publication.

10 CONTRIBUTION TO EU PUBLIC HEALTH STRATEGIES

Pandemic influenza preparedness

The Agency released the 'EMEA pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals' for consultation in 2005.

EMEA has worked on its pandemic influenza preparedness since 2003 and has put in place an innovative and proactive approach for the accelerated assessment and approval of new vaccines against a pandemic influenza.

This European approach uses a 'core dossier' that allows the completion of the evaluation and approval of an application based on a mock-up vaccine (with an influenza virus strain similar to the pandemic strain) before the outbreak of a pandemic. In the event of a pandemic, the actual influenza strain is submitted as a variation to the core dossier. The evaluation period for the pandemic variation is then expected to be very short, typically less than one week.

Incentives, including fee waivers for scientific advice, were introduced in 2005 to encourage companies to use the core-dossier approach. The CHMP also made a commitment to accelerate the scientific evaluation of applications for scientific advice and for marketing authorisation relating to core dossiers for pandemic-influenza vaccines.

The first submission of a core dossier was made in December 2005, and discussions on a number of other submissions were under way at the year's end.

In addition to its activities relating to development of a pandemic influenza vaccine, the EMEA also looked at antivirals and issued guidelines in October 2005 on the use of these medicines in the event of a pandemic.

Medicines for paediatric use

Preparatory work for implementation of the future regulation on medicinal products for paediatric use was initiated in conjunction with the CHMP Paediatric Working Party. In addition, the EMEA set up an initiative reminding all marketing authorisation holders of their obligation to submit existing data not yet submitted to the competent authorities, in particular data relating to paediatric use of authorised medicines. This initiative runs in parallel to a similar one initiated by Member States through the Mutual Recognition Facilitation Group.

Advanced therapies

The Agency contributed to the development of a proposed regulation on advanced therapies. It provided support to the European Commission with the technical requirements for such products, and will continue to do so as necessary during the Council and European Parliament consultation process.

11 PREPARATION FOR NEW TYPES OF APPLICATIONS

The revised pharmaceutical legislation opens the way for new types of applications to be made to the Agency.

- *Similar biological medicinal products:* An overarching guideline on similar biological medicines was finalised in November 2005. Together with this key document, a further 6 draft guidelines on specific types of products were released for consultation in the first half of the year. As part of the consultation process, a major public conference was organised in December 2005, with the participation of industry, regulators, academia, healthcare professionals and patients. The new CHMP Working Party on Similar Biological Medicinal Products was established in 2005.

- *Generic medicines:* Detailed guidance was published and existing guidance updated in 2005 concerning all aspects relating to the submission to the EMEA and assessment by the CHMP of generic medicines.

- *Compassionate use*: A guideline was drafted in preparation for the submission of any request by Member States for CHMP opinions.

- *Self-medication medicines:* Amendments were proposed in 2005 to existing Commission guidance on the supply of non-prescription medicines, in particular relating to use of the centralised procedure for self-medication medicines. A reflection paper to highlight patients' benefits in this new area was issued. A number of meetings were held with companies ahead of possible future applications.

12 COORDINATION GROUPS FOR THE MUTUAL RECOGNITION PROCEDURE AND THE DECENTRALISED PROCEDURE

The Mutual Recognition Facilitation Group (MRFG) and the Veterinary Mutual Recognition Facilitation Group (VMRFG), which coordinated and facilitated the operations of the mutual recognition procedure for human and veterinary medicinal products respectively over the past ten years, both held their final meetings in October 2005.

In November 2005, the MRFG was replaced by the 'Coordination Group for Mutual Recognition and Decentralised Procedures-Human', or 'CMD(h)' and the VMRFG was replaced by the 'Coordination Group for Mutual Recognition and Decentralised Procedures—Veterinary', or 'CMD(v)'. The new groups are set up under the revised EU pharmaceutical legislation to examine any question relating to the marketing of a medicinal product for human or veterinary use in two or more Member States, in accordance with the mutual recognition procedure (MRP) or the new decentralised procedure (DCP).

A sub-group with representatives from the CMD(h), CHMP, the EMEA and the European Commission was created to lay down a list of human medicinal products for which a harmonised SPC should be drawn up. A similar sub-group was created of CMD(v) representatives, an observer of the Commission and the EMEA to draw up such a list for veterinary medicinal products.

The EMEA provided full secretariat and administrative support to the work of the two coordination groups.

13 EU TELEMATICS STRATEGY AND INFORMATION TECHNOLOGY

The Agency was given responsibility for implementing the EU telematics strategy agreed by the European Commission, Member States and the EMEA. This covers a large number of projects, which are essentially designed to increase efficiency of the European medicines network, to provide better information to patients and users of medicinal products, and to contribute to the safe and effective use of these products.

- The first production version the Community database for medicinal products was delivered in line with the planned specifications and made available to regulatory authorities. It presents key data relating to medicinal products authorised via the centralised procedure and has multiple-field search functionality that allows searching by product name, active substance etc.

- First production versions of the EudraVigilance datawarehouse and pharmacointelligence tools were delivered for testing. These tools enable the analysis of safety data of medicines against complex criteria to highlight potential trends for further investigation in the context of the assurance of product safety.

- The first production version of the product information management (PIM) review system for regulatory authorities and the first production version of the PIM light-authoring tool for applicants were ready, enabling formal delivery very early in 2006. PIM enables the management and exchange of product information (summary of product characteristics, package leaflet and labelling) by all parties involved in the evaluation process for the centralised procedure.

- Work on the completion of phase 2a of EudraCT, the European Clinical Trails registration database, was delayed due to unforeseen difficulties with the final steps of the upgrade to version 3.0.0.

- EudraGMP: Work on the development of this system, the Community database of manufacturing authorisations and of certificates of good manufacturing practice, began. An initial prototype was demonstrated to the responsible implementation group in December.

14 MANAGING THE AGENCY

EMEA Management Board

Meeting four times in 2005, the EMEA Management Board:

- Welcomed two representatives of patients', one representative of doctors' and one representative of veterinarians' organisations as members of the Board

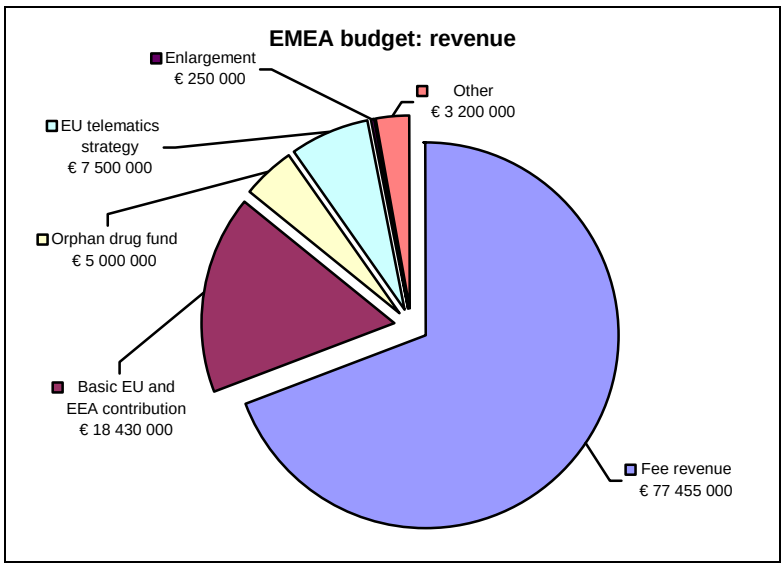
- Welcomed observers from Bulgaria and Romania

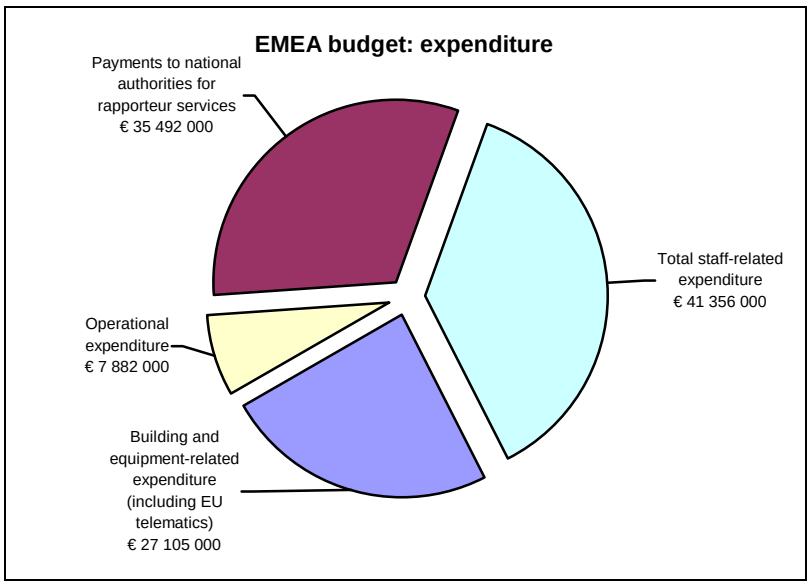
- Reappointed Thomas Lönngren as Executive Director of the EMEA

- Adopted strengthened rules on the handling of conflicts of interest of committee members and experts

- Introduced revised fee implementing rules providing, in particular, for graduations in the fee levels payable for certain new types of applications

- Approved a total budget of EUR 111,935,000 for 2005 (a 12% increase compared to the previous year), together with an establishment plan bringing the Agency's total number of temporary-agent posts to 379.





Integrated quality management system

Management and internal-control systems are part of EMEA corporate governance and are consolidated in an integrated management system at the EMEA. In 2005 this included the annual management review, which aims to ensure that management tools are effective and suitable in relation to the Agency's needs, and a self-assessment carried out in the context of the EU benchmarking system in order to improve the EMEA management system. The Agency made continuous improvements to its processes and interfaces with partners in the European network and ensures the logistics of the benchmarking of medicines agencies of 28 EU/EEA countries.

Personnel management

Following the entry into force of new 'Regulations and Rules applicable to officials and other servants of the European Communities', the EMEA prepared a series of implementing rules for adoption by the Management Board.

Taking into account the greater scientific role of the Agency, stemming from the revised EU pharmaceutical legislation and the Road Map, the Agency started the implementation of training profiles for all EMEA staff. The training profiles aim for a continuous system of competence development and help to identify outstanding training needs.