European Medicines Agency

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The European Medicines Agency in 2006

Summary of the twelfth annual report of the EMEA

This document provides a summary of the EMEA annual report for 2006. The full EMEA annual report for 2006 was adopted by the Management Board on 8 March 2007, and is available on the EMEA website:

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EMEA MISSION STATEMENT

The EMEA's mission 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.
- 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 decisions 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

I would like to begin by congratulating the Executive Director, his staff, the scientific committees and all working parties for their outstanding performance in 2006. The results presented in the annual report 2006 document that the Agency's preparatory work to implement the new legal provisions has fully paid off: the Agency has demonstrated that it adapted successfully to the new regulatory framework and was able to run new and existing procedures successfully and efficiently. This success has been recognised by all of the Agency's stakeholders.

2006 was also the first full year in which the Management Board operated in its full composition. The presence of representatives from patients', doctors' and veterinarians' organisations, who joined the Board in September 2005, has added a new dimension to how the Board operates, and their experience and expertise has made an invaluable contribution to the Board's functioning. By saying this I would also like to take this opportunity to thank all the Board members for their contributions to the work of the Board.

The changes brought about by the revised pharmaceutical legislation had a fundamental impact on the structure and organisation of the Management Board. The members have therefore started to look at new ways to improve the Board's involvement in the work of the Agency and its strategic decision-taking. As part of this, an ad hoc working group was created to re-define the Management Board's role and responsibilities.

The Board has been closely following the Agency's achievements in 2006. The EMEA has made considerable efforts to increase its outreach to patients and healthcare professionals by providing them more and better information about medicines, most notably with the launch of the EudraPharm database, and by encouraging their participation the Agency's work. I am convinced that the efforts made will help to secure and build up public confidence in the Agency's actions in relation to medicinal products.

The Agency has continued its contribution to the promotion of research and development in Europe. The scientific advice procedure has been improved and is used increasingly by sponsors of medicinal products. In addition, the Agency made a successful start with the SME Office, which provides assistance to small and medium-sized enterprises involved in the development of medicines in Europe. Finally, the EMEA was an important contributor for the development of strategic research agendas for both human and veterinary medicinal products within the 7th Framework Programme, the EU's chief instrument for funding scientific research and technological development over the period 2007 to 2013.

Continuing its preparedness efforts for pandemic influenza, the Agency has achieved several milestones in 2006 related to both human and animal health. The Board encourages the Agency to continue its good work and to remain alert in view of the threat levels.

At the end of 2006, new European legislation aimed at promoting the development of medicines for children was adopted. The EMEA has worked hard in 2006 to prepare the ground for ensuring the smooth implementation of this new piece of legislation.

Before I come to the end, I would like to commemorate our dear friend and Management Board colleague, Professor Gianmartino Benzi, who passed away in November 2006. His spirit, his enthusiasm and his contributions to the work of the European Medicines Agency are greatly missed.

INTRODUCTION BY THE EXECUTIVE DIRECTOR

Thomas Lönngren

It is once again my pleasure to introduce to you our report on the activities and achievements of the European Medicines Agency in the past year. And 2006 was indeed a year with plenty to report on.

This was the first full year of operation of the new pharmaceutical legislation introduced in the European Union in November 2005, under which the EMEA assumed new responsibilities and saw the scope of its tasks greatly extended.

Despite the operational challenges and increased workload this entailed, the Agency was able to achieve all the main objectives it had set itself for the year, and once more delivered good performance results across the entire spectrum of its activities.

To pick out just a few notable achievements in core business areas:

- There were more positive opinions in favour of new medicines for human use than in any previous year, contributing to the availability of 51 new medicines, 11 of which are intended for the treatment of rare diseases.
- The CVMP adopted positive opinions on the authorisation of 13 new veterinary medicines for treatment of a number of conditions in chickens, cats and dogs.
- The Agency managed record numbers of initial marketing-authorisation applications and post-authorisation variation applications, and of requests for scientific advice, parallel-distribution notifications and certificates.
- The scientific committees were able to speed up the average assessment time for several key procedures, including initial evaluations, orphan designations and scientific advice, thus helping to accelerate the development and availability of new medicines.

In addition to the good performance in core operational areas, the EMEA also made a strong contribution to a number of important European public-health initiatives, such as pandemic-influenza preparedness, the European paediatric initiative, the European risk-management strategy, provision of better information for patients, and tackling antimicrobial resistance to veterinary medicines in food-producing animals.

We also contributed towards stimulating research and development of new medicines through our involvement in the Innovative Medicines Initiative and the European Technology Platform for Global Animal Health, but in particular through the dedicated support provided to small and medium-sized companies by our SME Office, which, in its first year of operation, generated even greater interest than had been expected.

Further progress was made in other areas too, notably our transparency, information and communication initiatives, preparations for the accession to the EU of Bulgaria and Romania, arrangements for the participation of Croatia and Turkey in EMEA activities, and international cooperation with our scientific and regulatory partners at the European and global levels.

As always, I am grateful to the national competent authorities for the scientific resources they have made available to the EMEA. I am also grateful the European Commission and the European Parliament for their continuous support to the EMEA and its mission for public and animal health over the past year. The successes we were able to achieve were due to the smooth operation of the European network as a whole, and in particular to the outstanding work of our scientific committees, working parties and secretariat personnel.

1. PRIORITIES IN 2006

1.1 Improving the safety of medicines

Improving the safety of medicines for human and veterinary use was once again a focus of the Agency's efforts in 2006, with considerable success being achieved in this priority area.

European Risk-Management Strategy (ERMS) for medicines for human use

The EMEA and national competent authorities made further progress with the European Risk-Management Strategy for human medicines, particularly in the areas highlighted below.

- Monitoring the new legal tools relating to risk-management, in particular risk-management plans.
- Speeding up electronic reporting by all involved parties and discussing ways to improve the quality of the data submitted.
- Preparing for the establishment of the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) – a network of academic centres for intensive drug monitoring.
- Reinforcing the scientific expertise of the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) by co-opting 8 specialised experts.
- Preparing guidance on paediatric pharmacovigilance.
- Preparing guidance on pharmacovigilance for vaccines.

EudraVigilance Veterinary

EudraVigilance Veterinary became the main reporting tool for suspected adverse reactions used by national competent authorities in 2006. Marketing-authorisation holders started reporting electronically and implementation plans for full electronic reporting were being finalised by major veterinary pharmaceutical companies. Procedures for reporting into EudraVigilance Veterinary were considerably enhanced during the year.

In order to further progress the direct electronic reporting of adverse reactions into the EudraVigilance Veterinary database, a simplified electronic reporting tool was made available, designed particularly for use by smaller companies in the veterinary industry.

Other initiatives for improving the safety of veterinary medicines included:

- Developing an action plan for better harmonisation and work-sharing between authorities in the European Surveillance Strategy (ESS) for veterinary medicines.
- Revising the mandate of the Agency's Pharmacovigilance Working Party for medicines for veterinary use, making it the core scientific group for monitoring pharmacovigilance matters relating to veterinary medicinal products authorised in the EU.
- Preparing guidance for marketing-authorisation holders and applicants on pharmacovigilance systems to put in place, and guidance for regulatory authorities on the assessment of periodic safety-update reports. Simple guidance was also finalised for veterinarians concerning the reporting of adverse reactions.

1.2 Improving access to medicines and stimulating R&D

Implementing the new framework for scientific advice

In July 2006, the Agency implemented a new framework for the provision of scientific advice. The new framework helps to manage an increasing workload and the new legal requirements in relation to medicines for human use. Main initiatives of this new framework:

- Four additional members were appointed to the Scientific Advice Working Party (SAWP), and its meetings were extended to three days, allowing more meetings to be held with applicant companies for discussions.
- The scientific-advice procedure was streamlined to allow finalisation within 40 days (up to a maximum of 70 days), whereas the previous procedure could take up to 100 days.
- Coordinators and their assessors/experts are now systematically involved in the planning/pre-submission phase of all scientific-advice procedures.

First year of the EMEA SME Office: supporting innovation among Europe's SMEs

On 15 December 2005, the EMEA launched an 'SME Office' to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs), with the aim of promoting innovation and the development of new human and veterinary medicinal products by SMEs.

In the SME Office's first year of operation:

- Companies' interest in the SME initiative exceeded expectations.
- Over 145 companies, including 6 veterinary companies, submitted applications for SME status to the Agency.
- 117 companies from 17 countries across the EU were assigned SME status, including an encouragingly high number of micro enterprises (24%), many of which were university spin-off companies.
- The SME Office provided regulatory assistance to 14 companies.
- 23 SMEs requested scientific advice and a total of €1.4 million in SME fee reductions was processed for scientific advice.
- 8 companies submitted marketing-authorisation applications.
- €1 million in fees for marketing-authorisation applications and inspections was deferred.

Contributing to the Innovative Medicines Initiative

The EMEA contributed to the preparatory steps of the Innovative Medicines Initiative through its participation in workshops and frequent dialogue with the European Commission Directorate-General for Research. In addition, the Agency made proposals for topics of public-health interest, such as pharmacovigilance, to be included in the project. As a complementary action, the Agency's Committee for Medicinal Products for Human Use established a think-tank on innovation, which is expected to report in 2007 on its meetings with pharmaceutical companies and academic groups.

Stimulating availability of veterinary medicines for rare uses and species

The EMEA continued its work on improving the availability of medicines. In particular, major progress was made on adapting the data requirements for products for minor uses and minor species. The Committee for Medicinal Products for Veterinary Use (CVMP) finalised guidelines for quality-, safety- and efficacy-testing of such products, and published for consultation a similar guideline regarding immunological products. Further work is being done to better define minor uses and limited

markets, in order to facilitate use of the guidelines and to allow for a harmonised implementation across the EU.

The CVMP continued to extrapolate maximum residue limits (MRLs) to further species, at the request of companies concerned. This required no fee or formal application, provided the scientific criteria allowing such extrapolations were met.

Free scientific advice for minor uses and minor species

In December 2006, the EMEA Management Board further extended the pilot scheme for free scientific advice for veterinary medicines for minor uses and minor species. The scheme is part of the Agency's strategy to improve the availability of such medicines.

Contributing to the European Technology Platform for Global Animal Health

The Agency is part of the Steering Council of the European Technology Platform for Global Animal Health and assisted in finalising its Strategic Research Agenda aimed at promoting access to the market for innovative products for animal health, including those for limited markets. The Agency subsequently accepted a place in the coordination group set up to convert those parts of the agenda dealing with regulatory issues into an action plan.

1.3 Information and communication

The increasing importance of the Agency's role in the provision of high-quality information to patients and healthcare professionals led to a number of initiatives in the area of information and communication in 2006, as briefly outlined below.

Efforts to improve public access to information about medicines

As part of its implementation of EU pharmaceutical legislation, the EMEA launched a first version of EudraPharm – a new medicines-information database for the EU – on 6 December 2006. The launch of the database is a first step towards providing public access to comprehensive and up-to-date information about all authorised medicines in the European Union.

In February 2006, the Agency began publishing summaries of European public assessment reports (EPARs) that are specially written to be understandable by patients and members of the general public. As part of its commitment to providing useful and comprehensible information about the medicines the Agency evaluates, all EPARs for newly authorised medicines are now accompanied by a so-called 'summary for the public'. In addition, a project has also been running to prepare such summaries for products approved prior to 2006. By the end of 2006, 160 EPAR summaries had been published.

The Agency systematically provided comprehensive information in the form of press releases and question-and-answer documents to explain scientific opinions in a number of areas, including the safety of medicines, new types of applications, new technological advances and the approval procedure for pandemic flu vaccines, as well as general question-and-answer documents to help with communication on subjects such as compassionate use or generic and biosimilar medicines.

Efforts to improve transparency of regulatory activity

After consulting its stakeholders, the EMEA put in place procedures to publish information on the withdrawal of applications prior to opinion and on the refusal of marketing authorisations. Question-and-answer documents are now systematically published to give relevant information at the time of

withdrawal or refusal of applications. In 2006, information on 14 withdrawals and 7 refusals was published.

Efforts to improve interaction with patients

A new working party – the EMEA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) – was established to provide recommendations to the Agency and its scientific committees on all matters of interest to patients. The PCWP will build on the work already undertaken by the former EMEA/CHMP Working Group with Patients' and Consumers' Organisations.

Keen interest expressed by patients' and consumers' organisations

Almost forty organisations representing patients and consumers answered the Agency's call in 2006 for expressions of interest in becoming involved in EMEA activities, of which 16 met the EMEA eligibility criteria and were placed on a public list on the Agency's website, which will be updated regularly.

Efforts to improve interaction with healthcare professionals

Another new group – the EMEA/CHMP Working Group with Healthcare Professionals' Organisations' – was created in December to make recommendations and proposals for developing a framework of interaction with organisations representing healthcare professionals.

Information and communication on veterinary topics

In the veterinary sphere, the EMEA held a very successful Infoday with IFAH-Europe, in November, at which a number of topics were intensely debated, including benefit–risk assessment, user-safety guidelines and environmental-risk assessment.

A focus-group meeting was held with members of the Committee for Medicinal Products for Veterinary Use, industry and national competent authorities to agree on the implementation of practical measures to promote the prudent use of fluoroquinolones in food-producing species.

1.4 European medicines network

Sharing expertise and competence-development in the network

The EMEA and national competent authorities of the EU Member States carried out a number of actions aimed at strengthening the European medicines network – one of the Executive Director's priorities for 2006. These focused on improving the safety of medicines, increasing the availability of new medicines, and enhancing scientific competence within the network.

The Agency organised a number of conferences, workshops and training sessions for assessors and inspectors, designed to share competencies and strengthen cooperation among the network of European experts. Areas covered relating to medicines for human use included the use of biomarkers in medicines development, slowing the progression of neurodegenerative diseases, investigation of medicinal products in children and neonates, and obesity in children. Areas relating to veterinary medicines included the establishment of acceptable daily intakes for the purpose of setting maximum residue limits and withdrawal periods, and efficacy of veterinary medicinal products.

1.5 Better medicines for children

The EMEA contributed towards the preparation of the new Paediatric Regulation[2], which was published in December 2006. The European Commission Directorate-General for Enterprise and the EMEA published a joint Priority Action Plan in July 2006 for implementation of the regulation, and a dedicated task-force was set up within the Agency to manage this plan.

To prepare a strategy for establishing a pan-European paediatric-research network, the EMEA met with existing networks in the EU. The Agency also attended meetings with the European Commission Directorate-General for Research to prepare the funding of research on off-patent medicines.

Other initiatives included the Agency's contribution to establishing recommendations on the ethics of clinical trials in children and to a workshop on medicines for neonates, which allowed the Agency to establish contacts with representatives of patients' organisations and learned societies.

1.6 Pandemic-influenza preparedness

Continuing its activities in the area of pandemic-influenza preparedness, the EMEA: developed a pandemic-influenza crisis-management plan; held a meeting of the Joint EMEA-Industry Task-Force; strengthened contacts with the European Commission Directorate-General for Health and Consumer Protection and with the European Centre for Disease Prevention and Control; had regular communications with the US Food and Drug Administration (FDA) to discuss issues of common interest.

Positive opinion for first pandemic-influenza 'mock-up' vaccine

The EMEA adopted the first positive opinion for a pandemic-influenza 'mock-up' vaccine in December 2006. A mock-up vaccine is not intended for use outside a declared pandemic-influenza situation, but can be used to speed up the availability of a final vaccine in the event of a pandemic, once the pandemic strain has been identified.

Two avian-influenza vaccines approved

The Agency issued positive opinions on authorisation under exceptional circumstances of two avian-influenza vaccines for birds, following accelerated assessment by the CVMP. This prompt action, together with accelerated decision-making procedures by the European Commission, enabled authorised vaccines of high quality to be made available for use across the EU at a time of increased risk of avian-influenza occurrence in the autumn of 2006.

Pharmacovigilance activities

Recommendations for a core pharmacovigilance plan for pandemic-influenza vaccines were developed and approved in 2006. These recommendations are to be included in the risk-management plans of all pandemic-influenza vaccines. In addition, the EMEA worked on the development of a pharmacovigilance strategy for antivirals in case of a pandemic-influenza outbreak, taking into account the initiatives taken at industry level.

[2] Regulation (EC) No 1901/2006 on medicinal products for paediatric use.

1.7 Tackling antimicrobial resistance

One of the main policy issues tackled by the CVMP during 2006 was limiting the impact on public and animal health of the development of antimicrobial resistance caused by the use of veterinary medicinal products.

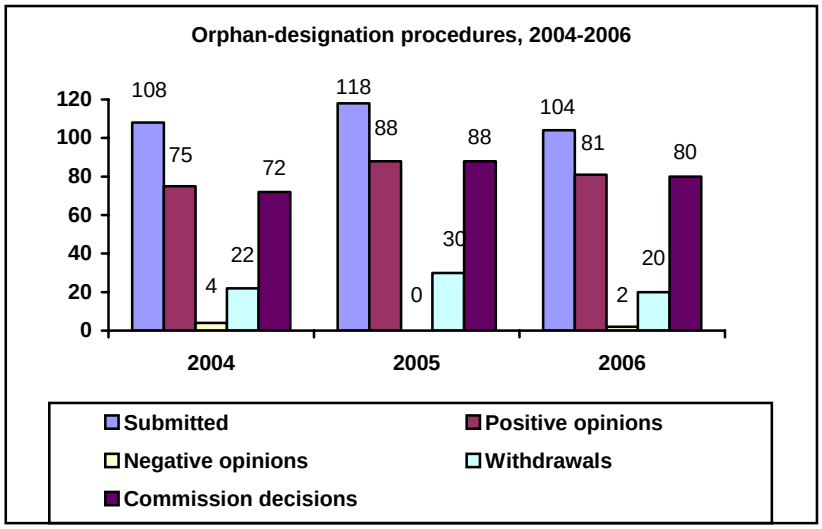
Based on the recommendations of its Scientific Advisory Group on Antimicrobials (SAGAM), the CVMP:

- Adopted a new strategy on antimicrobials for the years ahead.
- Adopted a reflection paper on the use of quinolones and fluoroquinolones in the EU, critically reviewing recent data on their use and potential impact on human and animal health.
- Proposed risk-management actions, including a recommendation for harmonised prudent-use guidance in the product literature of all (fluoro)quinolone-containing veterinary medicines for food-producing animals.

2. MEDICINES FOR HUMAN USE

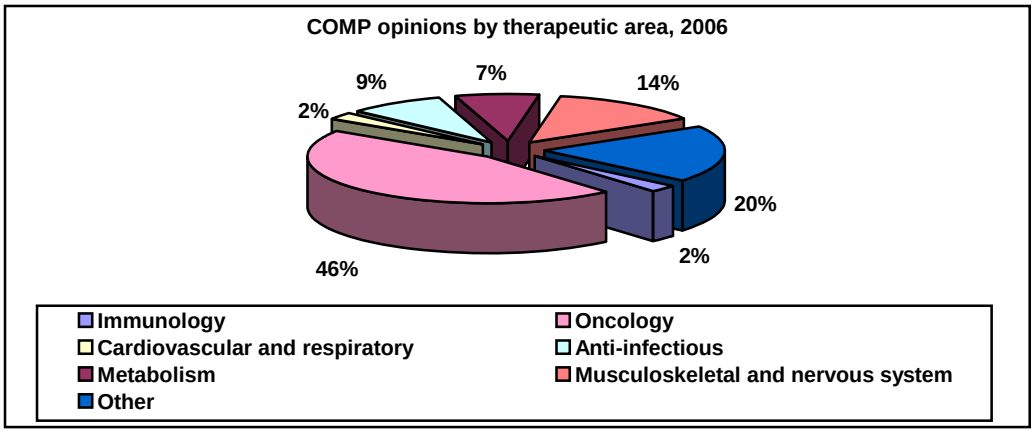
2.1 Orphan designation

For the third consecutive year, more than one hundred applications were received for the designation of orphan medicinal products: a total of 104 applications were submitted. The Committee for Orphan Medicinal Products (COMP) adopted 81 positive opinions. The number of withdrawn applications (20) was the lowest in the past 6 years.



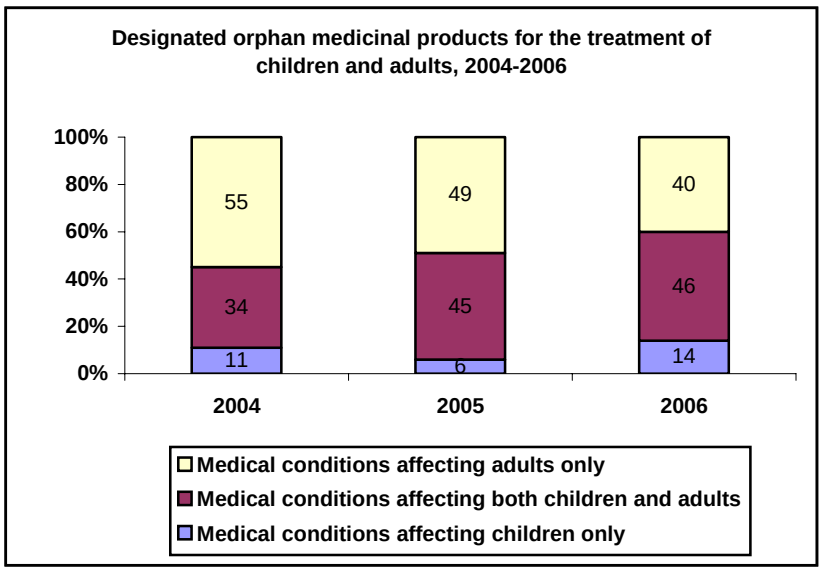
Cancer still the main therapeutic area concerned

As in previous years, there were more positive opinions on orphan designation for cancer treatments than in any other therapeutic area.



More than half of orphan-designated medicines are for treatment of children

Sixty percent of orphan products designated in 2006 were for conditions that affect children, including 14% intended exclusively for paediatric use.



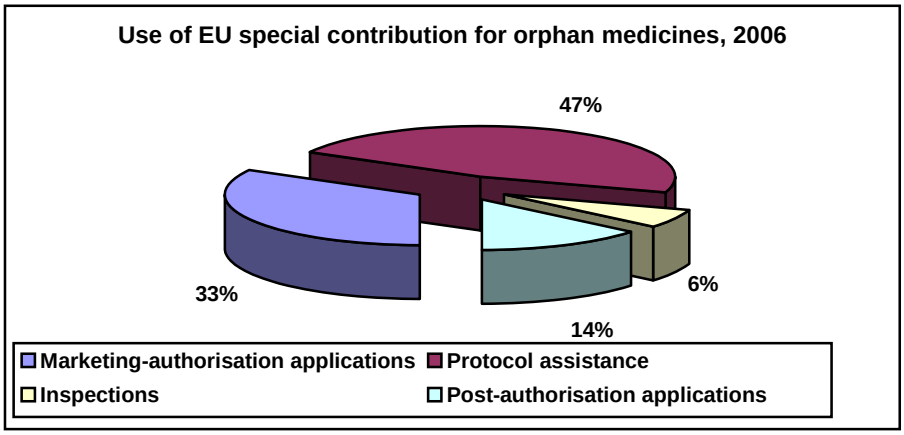
Faster processing of orphan designations

The Agency managed to further reduce the average processing time for designation procedures to 57 days – the shortest average time since the start of the procedure, in the year 2000.

Special financial support from the EU budget

A total of €6.7 million was granted to fund fee reductions for orphan medicines in 2006, primarily from the EU special contribution.

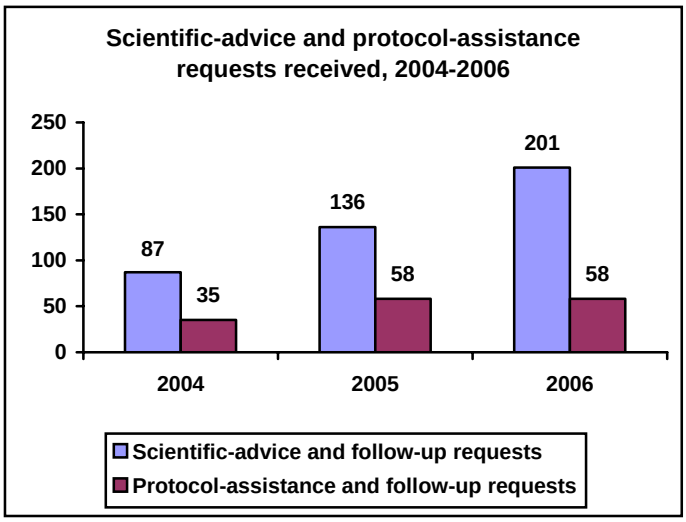
The Agency's policy on fee reductions for orphan medicines was amended in 2006 to take into account the increasing number of fee-reduction requests being received. The main change to the policy concerned a re-focusing of incentives on support for protocol assistance and other pre-authorisation assistance.



2.2 Scientific advice and protocol assistance

Number of requests for scientific advice continues to rise

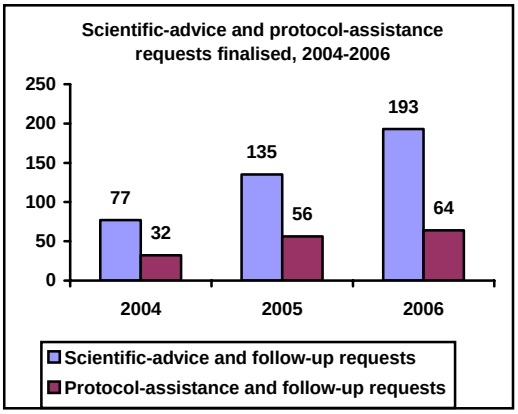
A further increase in the number of requests for scientific advice was registered in 2006, with 33% more requests received than in 2005, indicating that interest in this assistance from the EMEA remains high.

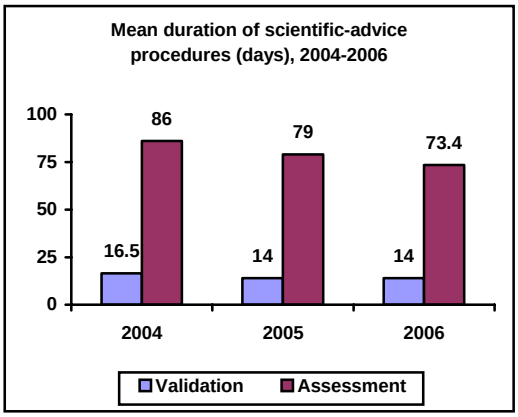


More procedures finalised, in shorter time

A total of 257 scientific-advice, protocol-assistance and follow-up requests were finalised in 2006, compared to 191 in 2005.

Thanks to the newly streamlined procedure, the SAWP was able to complete these scientific-advice procedures more quickly than in previous years.





Cancer and nervous system still the predominant therapeutic areas concerned

The highest numbers of requests received concerned medicinal products for conditions related to cancer or the nervous system, with those relating to the alimentary tract and metabolism forming the third most-represented therapeutic area.

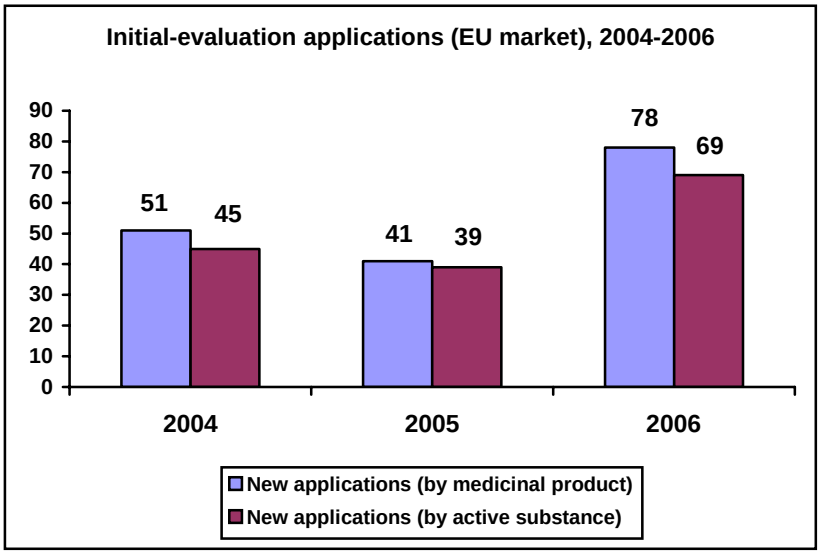
Scientific advice increasingly sought for gene and cell-therapy products

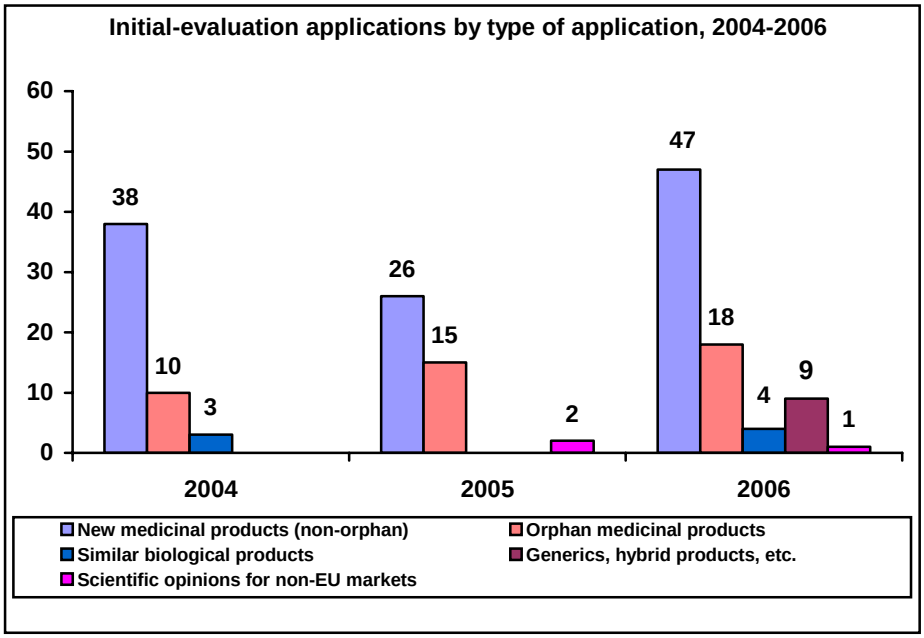
More scientific advice and protocol assistance was provided in relation to gene and cell-therapy products than in previous years, reflecting progress made in the field. The number of requests is expected to continue to grow as more marketing-authorisation applications are submitted.

2.3 Initial evaluation

New applications in 2006

The Agency received 79 applications for initial marketing authorisation in 2006, including one concerning a medicinal product intended exclusively for use outside the EU.



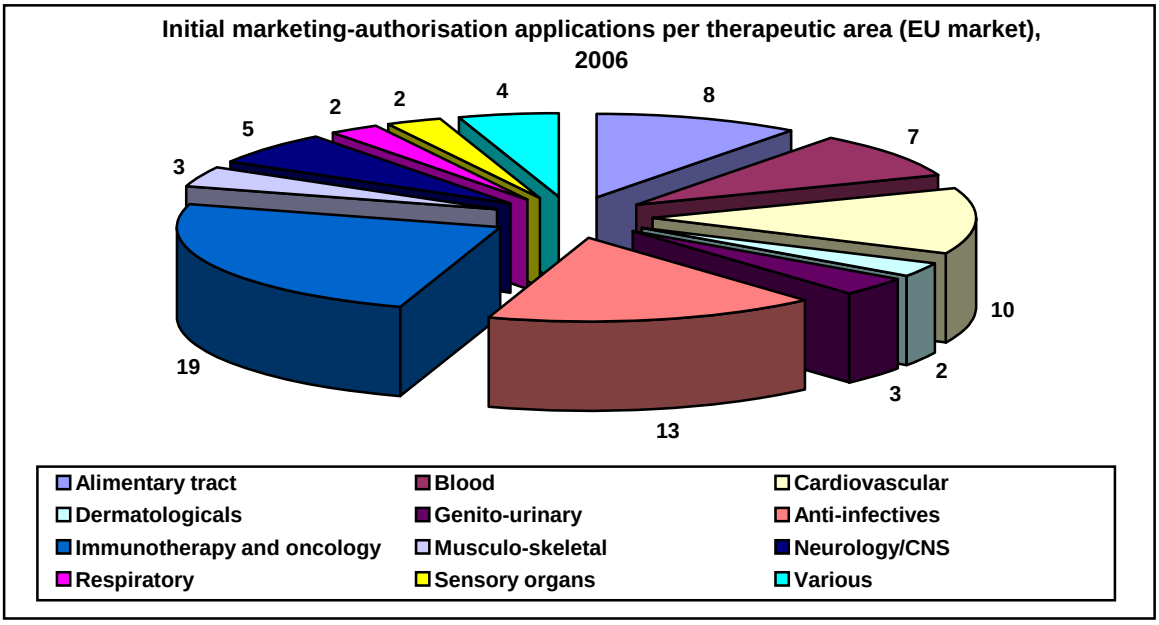


New dossiers concerning generics and novel aspects of pharmaceutical development

A new development in 2006 was the receipt of the first applications for generics of centrally authorised products whose 10-year data-exclusivity period has ended: three such applications were received. Although these generic medicines are not innovative, they are considered to represent an important contribution to public health in the EU.

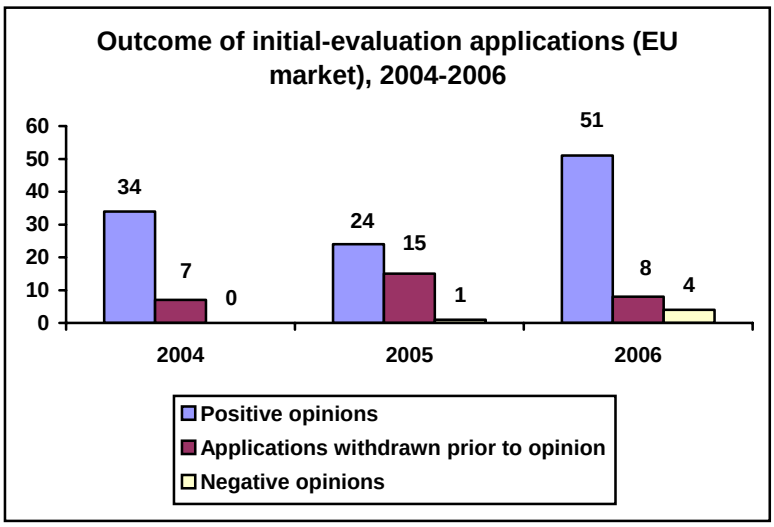
Therapeutic areas concerned: cancer still dominates

Applications for new products for use in the treatment of cancer once again represented the highest proportion by therapeutic area in 2006. Anti-infectives, which include medicines for the treatment of HIV/AIDS infections, and cardiovascular products were the two next most-represented therapeutic groups, overtaking alimentary-tract and central-nervous-system treatments that held these positions in 2005.



Opinions adopted in 2006

The CHMP adopted 51 positive opinions and 4 negative opinions on initial marketing-authorisation applications evaluated in 2006. Eight applications were withdrawn by applicants before an opinion could be adopted.



Europe first to approve biosimilars

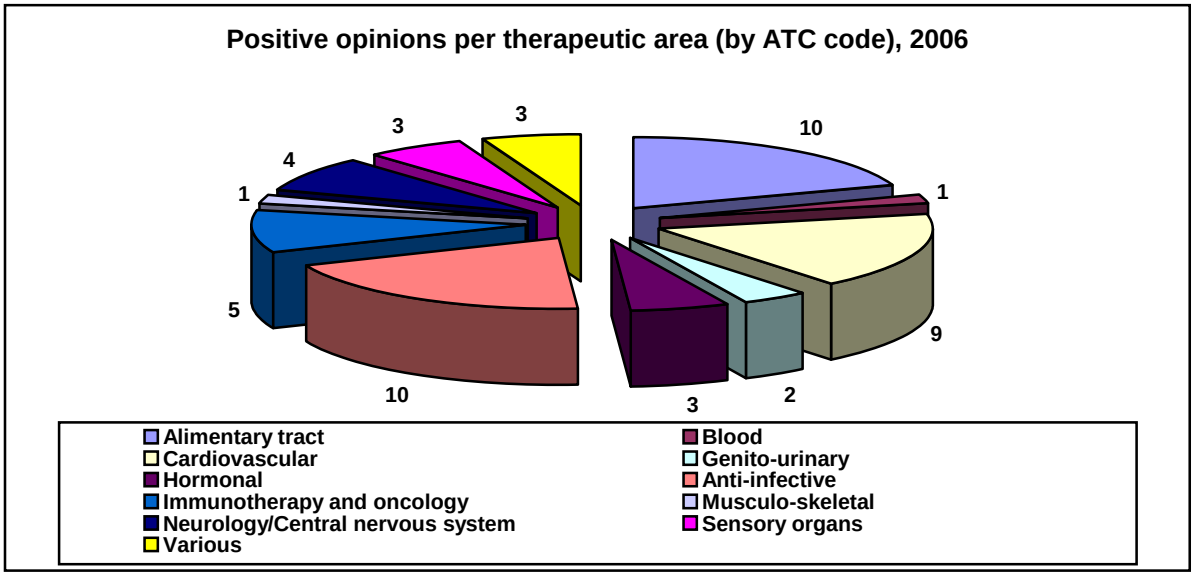
Among the positive opinions adopted, 11 concerned new orphan products and 2 concerned similar biological (biosimilar) products containing human DNA-recombinant growth hormone. The approval of biosimilar products places Europe at the forefront of medicines regulation in this area and represents an important contribution to public health in the EU.

Use of special authorisation procedures

The CHMP adopted positive opinions in 3 conditional-approval procedures (concerning products for treatment of cancer, epilepsy and HIV infection) and approved a further 3 products under exceptional circumstances (concerning 1 product for cancer, 1 for an enzyme-deficiency disease, and 1 pandemic-influenza mock-up vaccine). No opinions were adopted on products evaluated through compassionate-use or accelerated-assessment procedures.

Anti-infectives once again among the most-represented therapeutic areas

More positive opinions were adopted in respect of anti-infectives and alimentary-tract products than other types, with those relating to the cardiovascular system forming the third major group.



Public-health benefits of medicines recommended for approval in 2006

Medicinal products of notable public-health interest that received a positive opinion from the CHMP in 2006 included:

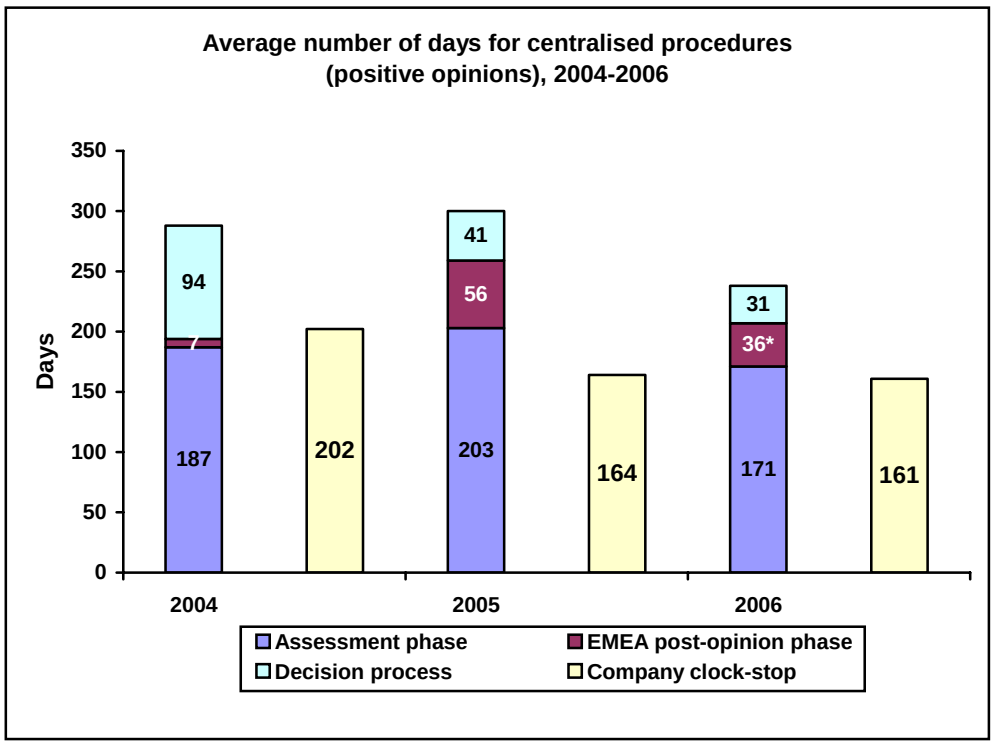
- The first medicinal product produced by transgenic biotechnology in animals: a copy of the human protein that prevents blood-clots, extracted from the milk of goats which have had a gene inserted that enables them to produce the human protein.
- The first vaccine against human papilloma virus – a widespread cause of genital infections that can lead to cervical cancer.
- The first pandemic-influenza mock-up vaccine, containing the reverse genetic H5N1 strain. (A mock-up pandemic vaccine is not intended for stockpiling, but can be used to speed up the availability of a final vaccine in the event of a pandemic, once the pandemic strain has been identified.)
- Targeted agents for renal cancer, leukaemia and pancreatic cancer, intended for conditions where there has been a high unmet need.
- Products for rare forms of epilepsy in children, such as Lennox-Gastaut and Dravet's syndrome.
- A new treatment option for type-2 diabetes mellitus, introducing a new class of medicinal products called incretin mimetics.
- An enzyme-replacement treatment for Pompe disease.
- A medicine for smoking cessation.
- A medicine for opioid-dependency-substitution treatment.

Increasing availability of medicines for rare diseases

By the end of 2006, a total of 31 orphan medicinal products had been granted a centralised marketing authorisation by the European Commission since the entry into force of the European orphan medicines legislation (in 2000). These products potentially benefit some 1.6 million European patients suffering from 24 different rare conditions.

Applications processed more quickly

The average overall time required for approval of a marketing-authorisation application decreased significantly in 2006, with marked reductions compared to 2005 in the average times for the assessment, post-opinion and decision phases of the procedure. A further improvement was also registered in the average clock-stop time required by applicant companies.



* The 36-day EMEA post-opinion phase in 2006 accounts for the Agency's processing time as well as the time required by applicants and Member States to carry out their post-opinion translation checks.

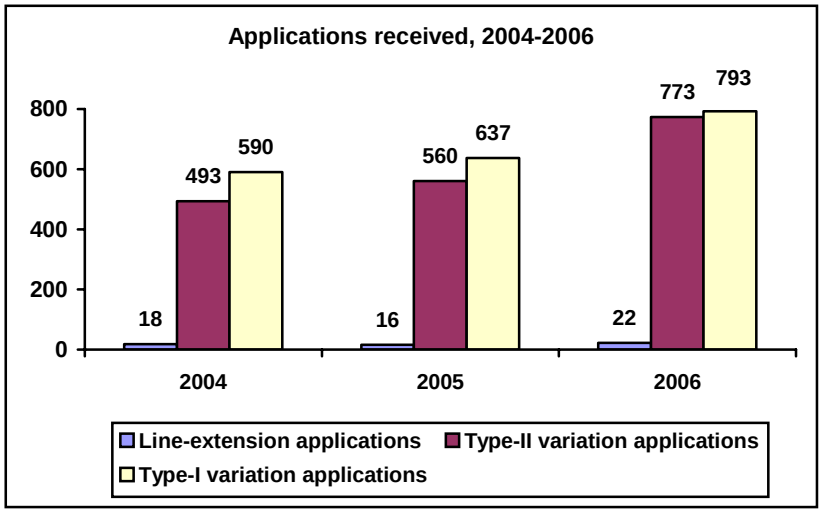
2.4 Post-authorisation activities

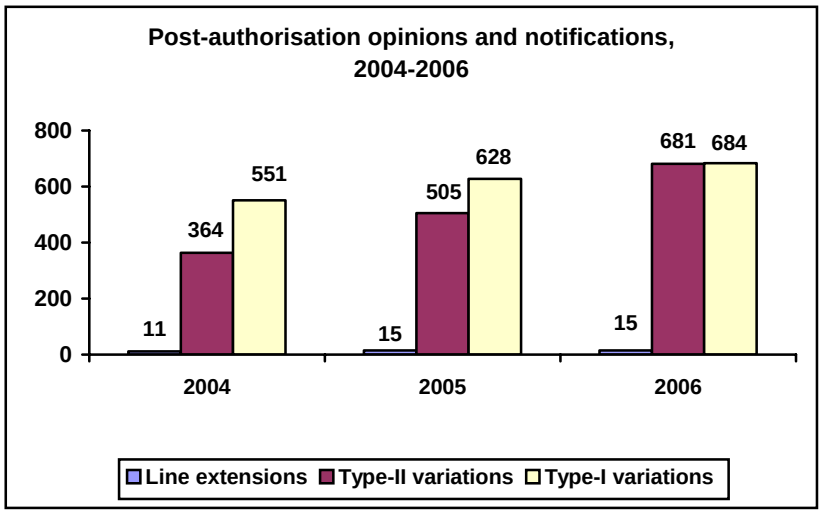
Number of variation applications up by almost one third

A total of 1,588 applications for variations and line extensions were received in 2006 – an increase of 31% over the total received in 2005.

The number of post-authorisation opinions adopted was also significantly higher (20%) than in the previous year. In particular, the total number of type-II variations (including extensions of indication) finalised during 2006 was 35% greater. Of the 681 such opinions adopted, 60% related to safety and efficacy, and 40% related to quality changes.

The total number of type-I variations handled during the year represents a 9% increase compared to the previous year.





New indications broaden scope of existing medicines

A particularly high number of extensions of indication – 41 (46% more than in 2005) – were introduced in 2006, providing additional treatment options for patients.

The majority of new indications related to medicinal products approved for the treatment of various forms of cancer. Several extensions of indication were also granted for the diagnosis or treatment of central-nervous-system disorders, diabetes and a range of diseases.

Contra-indications, class labelling and warnings

Of the post-authorisation opinions adopted in 2006 for type-II variations, 79 related to special warnings and precautions for use. Six new contra-indications were also adopted, for medicinal products used in fields such as depression, diabetes and infectious diseases.

Warnings and contra-indications were added for the classes of medicinal products (class labelling) below:

- New contra-indication for the use of PDE-5 inhibitors in patients suffering from vision loss in one eye because of non-arteritic anterior ischemic optic neuropathy.

- New warning for HIV products relating to the possible risk of osteonecrosis associated with their use.
- New warning for glitazones relating to the possible risk of macular oedema associated with their use in diabetic patients.
- New warning for biphosphonates relating to the possible risk of osteonecrosis of the jaw associated with their use.
- Alleviation of contra-indications and concomitant strengthening of warnings for beta-interferon-containing medicinal products used in the treatment of multiple sclerosis.

2.5 Safety of medicines for human use

Major safety reviews

The EMEA dealt with a number of major safety issues in 2006, involving both centrally and non-centrally authorised medicines for human use. Notably, the Agency finalised safety reviews of:

- The cardiovascular safety of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) stemming from new clinical and pharmacoepidemiological study data. The CHMP concluded that it cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment. However, these medicinal products are important treatments for arthritis and other painful conditions, and the overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information.
- Centrally authorised tacrolimus-containing medicinal products (Protopic and Protopy), in relation to a potential risk of skin cancer and lymphoma. The CHMP concluded that the benefits associated with the use of these dermatological medicinal products outweigh the risks, but that they should be used with greater caution in order to reduce potential risks of skin cancer and lymphoma as far as possible. The same review was conducted for non-centrally authorised pimecrolimus-containing medicinal products (Elidel) under Article 31 of Directive 2001/83/EC, with the same outcome.
- Centrally authorised recombinant hepatitis B vaccines (HBVAXPRO and Procomvax), in relation to the efficacy of the vaccines. The CHMP concluded that these medicinal products continue to offer effective protection against hepatitis B, but recommended some changes to the prescribing information.
- A centrally authorised perflutren-containing microspheres medicinal product (Optison), further to the suspension of a manufacturing authorisation due to concerns over compliance with good manufacturing practice (GMP). The marketing-authorisation holder and the manufacturer are currently undertaking an extensive corrective-action plan to restore GMP compliance at the site of manufacture, and the matter is under close monitoring by the CHMP.

Implementation and further development of risk-management plans

The concept of risk-management plans (RMPs) was fully implemented in 2006 as part of the new legislative provisions of Regulation (EC) No 726/2004.

The Agency reviewed 80% of the RMPs submitted as part of new applications. Most of those not reviewed related to active substances whose safety profile was well known. Risk-management input was also provided in the early phase of the evaluation of new applications, through the peer-review process at CHMP level.

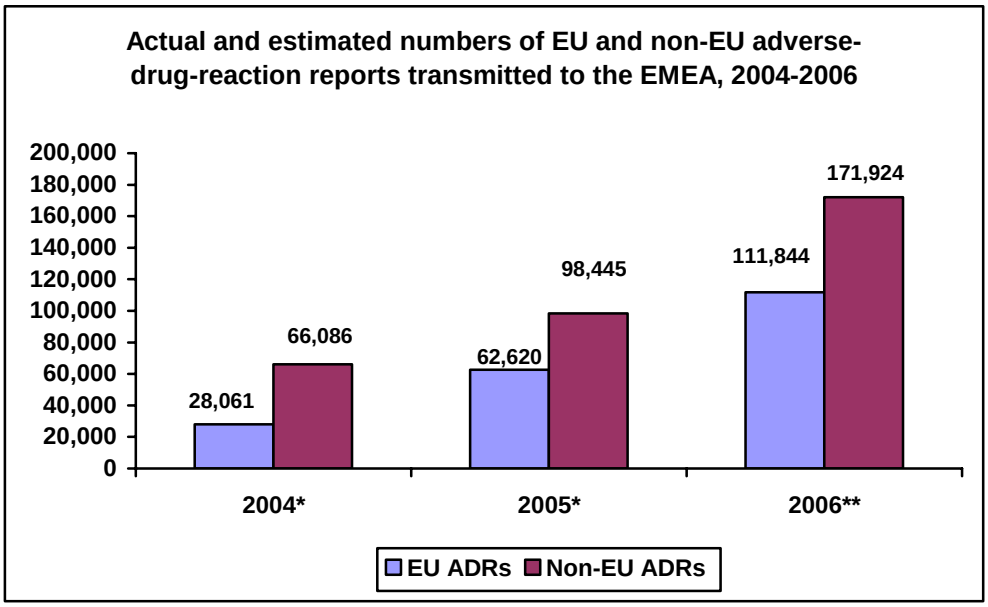
In order to review the experience gained with risk-management plans to date, and to introduce further improvements, a Review and Learning Project was set up, involving the EMEA, CHMP, PhVWP and CMD(h).

Detection of pharmacovigilance signals

The availability of an adequate pharmacovigilance-signals-detection system is important to the Agency's efforts for monitoring the safety of medicines. In 2006, the list of products reviewed by the Agency for detection of pharmacovigilance signals was extended to include medicinal products submitted for authorisation under the centralised procedure but not yet authorised.

Further progress with EudraVigilance

The good progress observed in 2005 with EudraVigilance continued in 2006. By the end of the year, a total of 26 national competent authorities (NCAs) were reporting electronically to EudraVigilance, as were 201 marketing-authorisation holders. More than 95% of marketing-authorisation holders of centrally authorised products are now in production with the system. At the end of 2006, EudraVigilance contained a total of 677,976 individual-case-safety reports (ICSRs), corresponding to 409,138 individual cases.



* The figures for 2004 and 2005 have been revised to taken into account the reports submitted for non-centrally authorised products.

** A new method has been used as of 2006 to present the number of ICSRs received/expected over time.

Further progress was made with regard to signal-detection in EudraVigilance through: implementing a new data-analysis system; drafting guidance on the use of statistical signal-detection methods in the data-analysis system; and initiatives undertaken to address identified problems in relation to compliance with expedited reporting and the quality of the submitted data.

EudraVigilance and clinical trials

By the end of the year, 161 sponsors of clinical trials being conducted in the European Economic Area were reporting suspected unexpected serious adverse reactions to the EudraVigilance Clinical Trial Module (EVCTM). To date, a total of 53,642 ICSRs, corresponding to 26,997 individual cases, have been transmitted to EVCTM.

2.6 Arbitration, Community referrals and 'opinions on any scientific matter'

Substantial increase in arbitration and referral activity in 2006

The number of procedures for arbitrations, referrals and Article 5(3) opinions started in 2006 was 79% greater than in 2005. The number of such procedures finalised in 2006 was also greater, with a total of 32 opinions being adopted. These included the first 'opinions on any scientific matter', under Article 5(3) of Regulation (EC) No 726/2004.

Procedure type	2004		2005		2006	
	Started	Finalised	Started	Finalised	Started	Finalised
Article 6(12) of Commission Regulation (EC) No 1084/2003	3	0	3	1	0	2
Article 6(13) of Commission Regulation (EC) No 1084/2003	0	0	4	0	0	4
Article 29 of Directive 2001/83/EC	2	2	7	5	20	12
Article 30 of Directive 2001/83/EC	1	2	3	0	1	4
Article 31 of Directive 2001/83/EC	1	1	2	0	3	1
Article 36 of Directive 2001/83/EC	0	0	0	0	7	7
Article 5(3) of Regulation (EC) No 726/2004	0	0	0	0	3	2
Totals:	**7**	**5**	**19**	**6**	**34**	**32**

2.7 Herbal medicines

Community herbal monographs

The Committee on Herbal Medicinal Products (HMPC) finalised Community herbal monographs in 2006 for valerian root, linseed, ispaghula husk, ispaghula seed, psyllium seed, senna pods, senna leaf, frangula bark and aloes (cape and barbados). These monographs were released for public consultation prior to being finalised.

The HMPC also released for public consultation 5 new draft Community herbal monographs, for aniseed, anis oil, bitter fennel fruit, sweet fennel fruit and bitter-fennel-fruit oil.

Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products

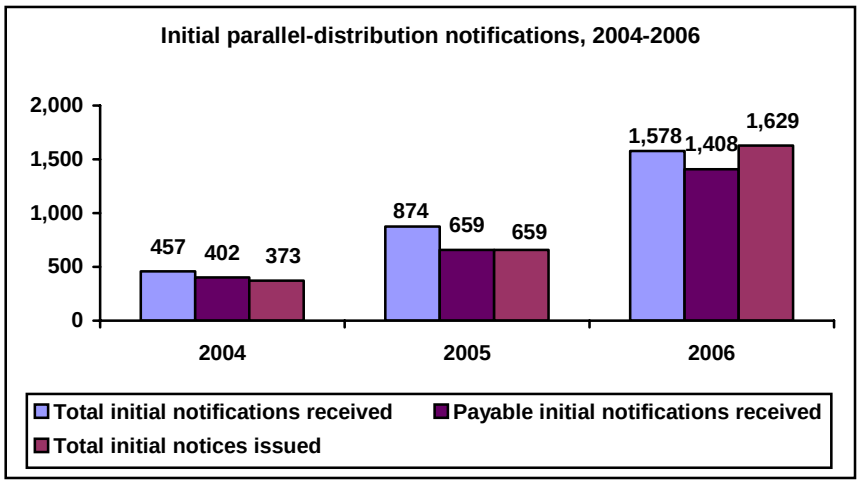
The Committee released for public consultation 2 new draft entries to the Community list, for bitter fennel fruit and sweet fennel fruit.

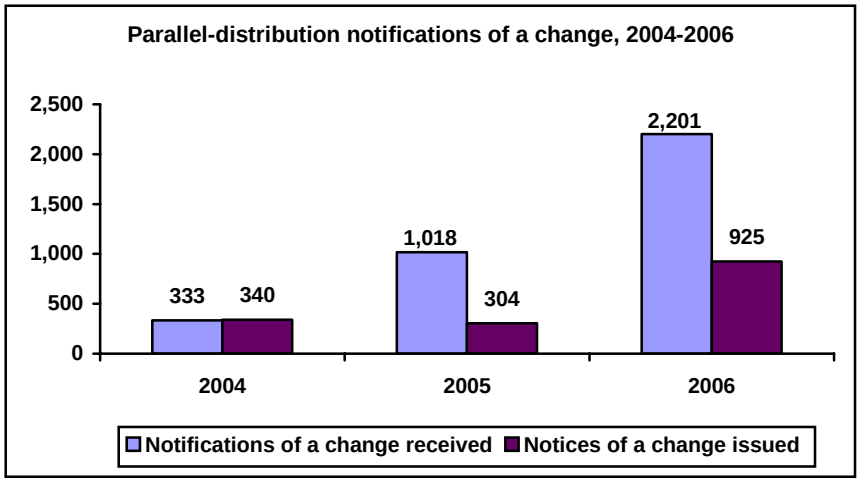
In December 2006, the HMPC presented to the European Commission a comprehensive overview of its activities and achievements since its establishment in September 2004. This overview is intended to support the Commission with the preparation of its report to the European Parliament and to the Council concerning the application of the relevant legislative provisions relating to traditional herbal medicinal products.

2.8 Parallel distribution

The number of initial parallel-distribution notifications received in 2006 was 1,408 (113% more than in 2005). This high number of notifications was attributable to: new parallel distributors starting this activity; parallel distributors complying with the mandatory notification procedure; recently authorised medicinal products entering the parallel-distribution chain; and enlargement by existing parallel distributors of their range of products.

In addition to initial notifications, the Agency received 2,201 notifications of a change, representing a 120% increase compared to 2005 (1,018). This was due to the frequent update of the Annexes to the Community marketing authorisations of parallel-distributed products and to other changes proposed by parallel distributors (e.g. addition of countries of origin).

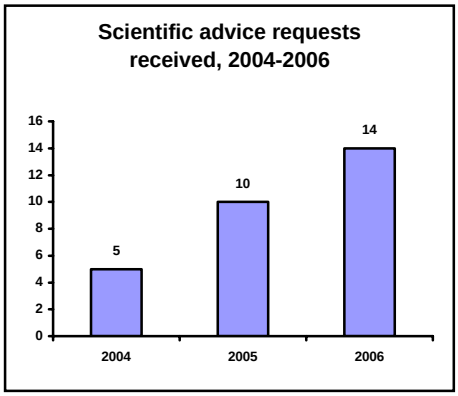




3. MEDICINES FOR VETERINARY USE

3.1 Scientific advice

Scientific-advice activity increased noticeably in 2006: 14 requests for scientific advice were received (2 more than the forecast and 4 more than were received in 2005).

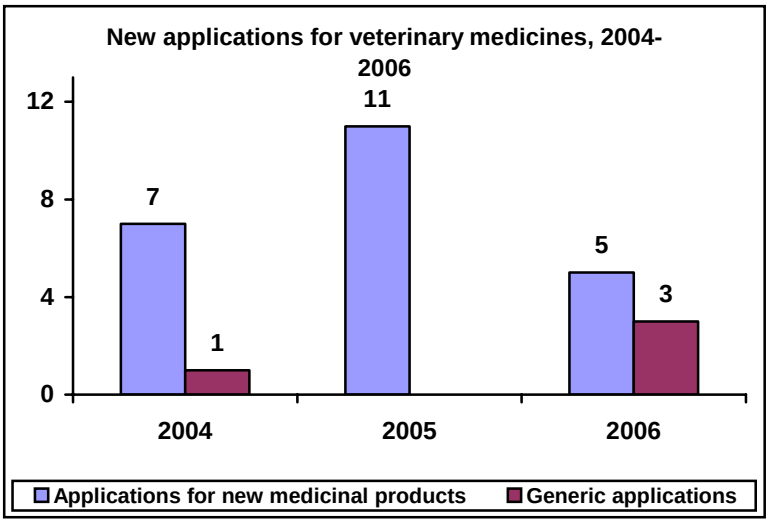


The average time required to finalise procedures for provision of scientific advice in 2006 was 55 days.

Three scientific-advice requests were deemed eligible in 2006 for free advice under the provisions of the scheme for minor uses and minor species. These related to an antimicrobial for turkeys and gamebirds (pheasants), a live vaccine for wild rabbits, and development of a vaccine for sheep, goats and cattle.

3.2 Initial evaluation

Eight initial marketing-authorisation applications were received, 5 of which were for pharmaceuticals and 3 for immunologicals. The 5 pharmaceutical applications, 3 of which were generic applications, concerned medicinal products for dogs, while the 3 immunological applications concerned medicines for chickens principally.



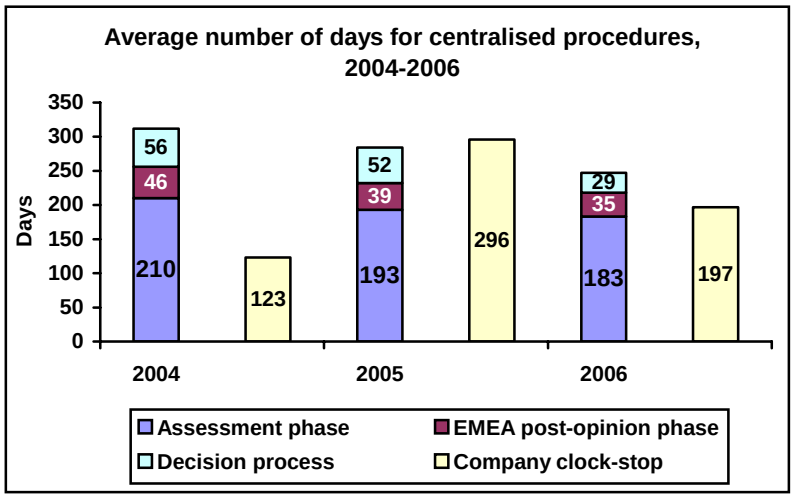
In 2006, the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a total of 13 positive opinions for initial marketing-authorisation applications. There was 1 negative opinion (which was confirmed following a re-examination) for an antimicrobial for treatment of specific skin and soft-tissue infections and specific acute infections of the upper respiratory tract and the urinary tract in cats and dogs.

Veterinary medicinal products that received a positive opinion in 2006 included:

- Two vaccines for chickens, against avian influenza, which were evaluated on an accelerated timetable with opinions adopted in 79 days, taking into account the epidemiological situation within the EU. These led to authorisations under exceptional circumstances and are subject to specific obligations and follow-up measures, including enhanced pharmacovigilance measures, to ensure the safe use of these products.
- Two ectoparasiticides for treatment and prevention of flea and tick infestations in dogs.
- One ectoparasiticide for treatment and prevention of flea infestations in cats.
- One medicinal oxygen intended for oxygen supplementation and as a carrier gas during inhalation anaesthesia.
- One steroid for treatment of inflammatory and pruritic dermatoses in dogs.
- One product for treatment of benign prostatic hypertrophy in dogs.
- One product for treatment of overweight and obese dogs.
- One cephalosporin for treatment of specific skin, soft-tissue and urinary-tract infections in cats and dogs.
- One product for treatment and prevention of emesis in dogs.

Average assessment time quicker than in 2005

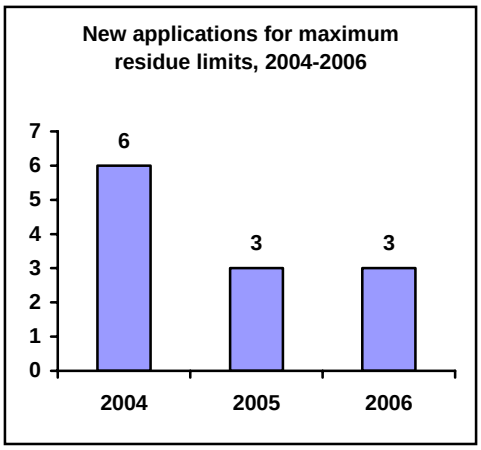
All initial evaluations were carried out within the 210-day regulatory time limit. For those new applications for which the Commission delivered a decision in 2006, the average CVMP assessment time was 183 days – noticeably shorter than the average of 193 days in 2005, partly due to the accelerated assessment of avian-influenza-vaccine applications.

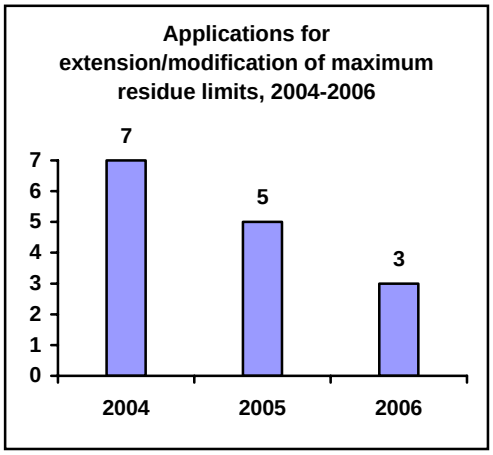


3.3 Maximum residue limits

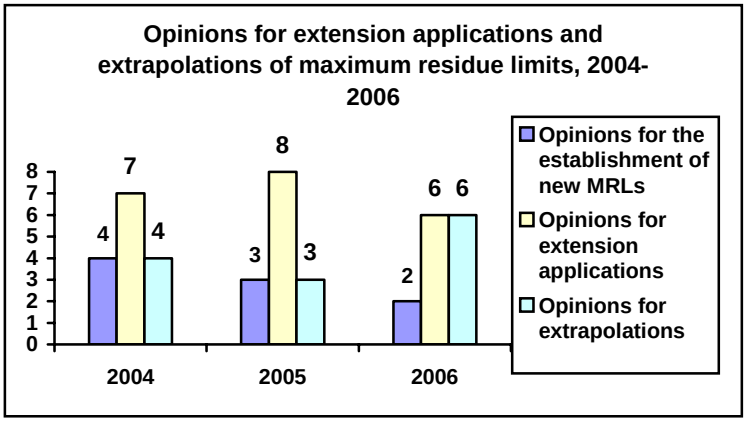
Fewer maximum-residue-limit applications submitted than expected

In 2006, the EMEA received and validated 3 new applications for maximum residue limits (MRLs) – the same number as in 2005, and 2 fewer than were forecast for the year. The small number of new MRL applications is consistent with the comparatively greater interest currently seen for the development of new veterinary medicines for companion animals than for food-producing animals.





There was also a shortfall in the number of applications submitted for extension or modification of MRLs, with only 3 of the forecast 7 being submitted.

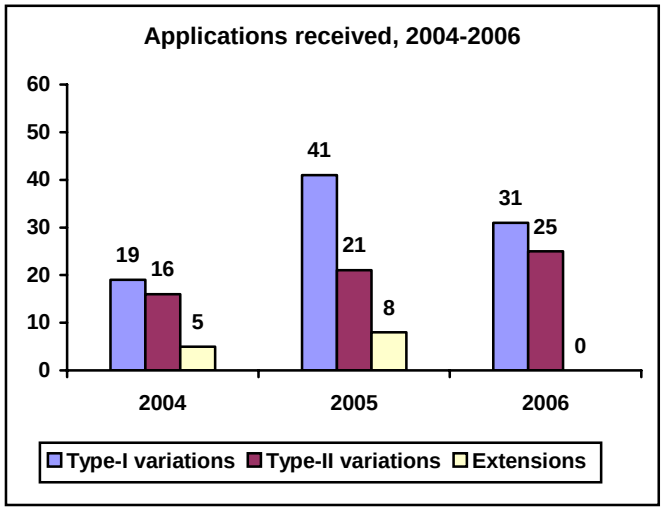


All applications for new MRLs and for extension or modification of existing MRLs were processed within the 120-day legal timeframe.

In the context of its efforts to improve availability of medicines for minor uses and minor species, the EMEA's proposal for a list of essential substances for the treatment of certain indications in equidae with no MRL but with a withdrawal period of at least six months was approved by the Commission.

3.4 Post-authorisation activities

The overall number of applications for variations to marketing authorisations received in 2006 was lower than in 2005, despite the greater number of centrally authorised products on the market.



There were 25 applications relating to the more complex type-II variations. Of these, 14 concerned pharmaceutical products and 11 concerned immunological products. Nine of the variations concerning pharmaceuticals related to changes in quality and 5 related to clinical changes. All variations concerning immunologicals related to quality changes.

All variation applications were evaluated within the regulatory time limits.

3.5 Safety of medicines for veterinary use

Pharmacovigilance in the veterinary sector in the EU is undergoing changes triggered by the new legislation. The electronic exchange of pharmacovigilance information within the EU is improving, as are active surveillance, harmonisation and risk-management.

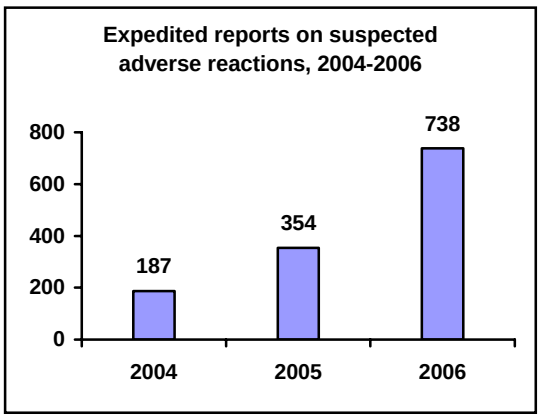
Marked increase in expedited reporting of suspected adverse reactions

For centrally authorised veterinary products, a total of 738 expedited spontaneous reports of suspected adverse reactions were reported within the 15-day legal timeframe in 2006.

This is a considerable increase – more than twice the number received in 2005 – and would appear to result from efforts to promote awareness of expedited reporting.

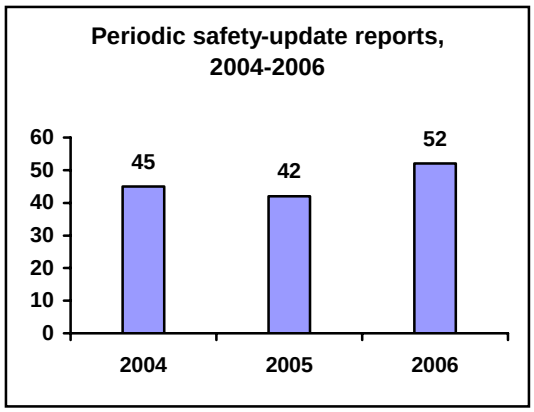
Of the 738 reports received:

- 638 related to suspected adverse reactions in animals and 100 to reactions in humans.
- 53 related to food-producing animals (mainly cattle, pigs and horses), following treatment of 2,251 animals, of which 559 showed suspected adverse reactions.
- 380 related to suspected adverse reactions in dogs.
- 200 related to suspected adverse reactions in cats.
- 300 originated within the EU.



Review of PSURs

Fifty-two periodic safety-update reports (PSURs) were received in 2006 for centrally authorised products. Following its review of these reports, the CVMP recommended in 7 cases that variations be submitted for the products concerned, mainly concerning the addition of new adverse-reaction information to the product literature.



First Article 78 procedure

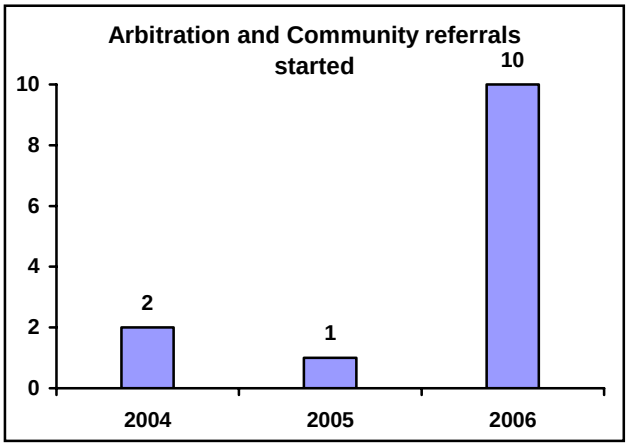
Following a request for consideration from a Member State, the CVMP recommended that new precautionary measures concerning user safety be added to the product literature of 21 veterinary medicinal products containing alpha2-adrenoreceptor agonists. This was the first procedure conducted under the new pharmacovigilance provision of Article 78 of Directive 2001/82/EC, as amended.

Confirmation of CVMP opinion on veterinary Cox-2s and NSAIDs

The CVMP further reviewed the safety of Cox-2 inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) for use in veterinary medicine as a result of the conclusion of the review of concerns related to human use of these substances. The Committee reconfirmed its previous conclusion that no action was required regarding concerns of possible cardiovascular effects and skin reactions for this class of medicines.

3.6 Arbitration and Community referrals

A total of 10 referrals were made to the CVMP in 2006 in the framework of the mutual-recognition procedure.



Four of the referrals related to the demonstration of efficacy and concerned pharmaceuticals. Six related to safety issues or benefit/risk evaluation, of which 3 were for pharmaceuticals and 3 were for vaccines.

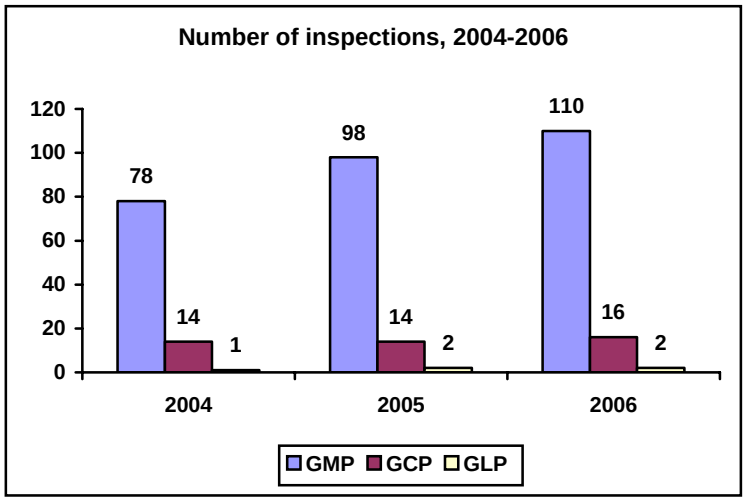
Referral procedures concluded in 2006

The CVMP completed the assessment and issued opinions in 4 referral procedures, 3 of which started in 2006 and 1 in 2005.

4. INSPECTIONS

4.1 GMP, GCP, pharmacovigilance and GLP inspections

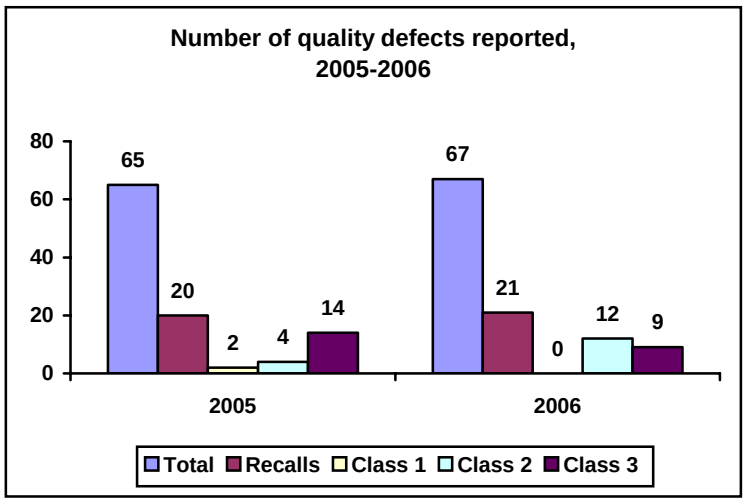
The EMEA continued to support all Member States on good-manufacturing-practice (GMP), good-clinical-practice (GCP), good-laboratory-practice (GLP) and pharmacovigilance inspection procedures. Support was provided primarily through the ad hoc GMP and GCP inspectors' meetings, which focused on harmonisation of procedures and interpretation of related requirements.



All inspections were completed within the legal timeframes and to the standards required by the Agency's quality-management system.

Product defects and deviations

In 2006, the EMEA received 64 quality-defect reports concerning human medicinal products and 3 quality-defect reports concerning veterinary medicinal products. Of these, 21 resulted in a product recall (19 human medicines and 2 veterinary medicines); the remainder of the defects reported were classified as minor.

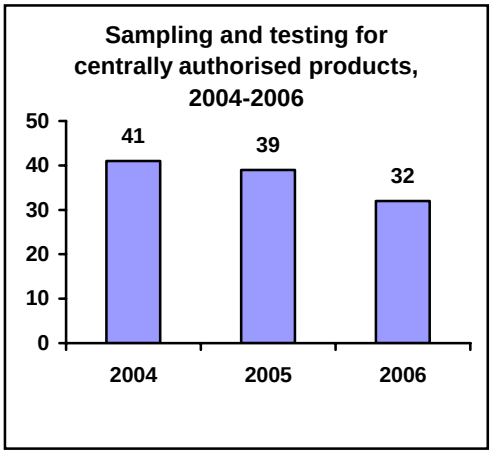


None of the 21 recalls were classified as ‘class 1’ recalls, which relate to defects that are potentially life-threatening or could cause serious risk to health. Twelve of the recalls were ‘class 2’ recalls, which relate to defects that could cause illness or mistreatment, and the remaining 9 were classified as ‘class 3’ recalls, which are not associated with serious public-health hazards.

An analysis of all defects reported during 2005 was completed and published.

4.2 Sampling and testing

The 2006 programme for sampling and testing included 32 centrally authorised products.



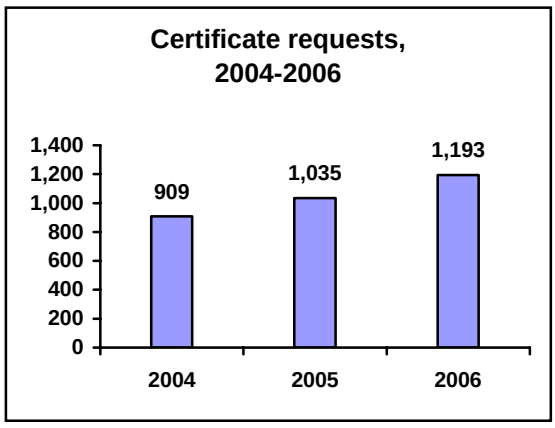
Testing results showed that the majority of the products were of high quality. However, 2 products were found not to comply with their authorised specifications. In one case, this resulted in the recall of a batch of the product. Results requiring further investigation were found in 18 products. The investigations revealed some regulatory and scientific discrepancies, which were mainly addressed through amendment of the testing documentation by the Marketing-authorisation holders concerned.

Work continued on improving the operation of the sampling-and-testing programme. Procedures for ad hoc or emergency testing of centrally authorised products and for handling out-of-specification results were finalised and adopted.

4.3 Certificates of a medicinal product

Main developments in 2006

- The number of certificate requests continued to climb, with 15% more being received than in 2005.
- The year saw two firsts: the first certificates issued within the context of cooperation with the World Health Organization, and the first certificates provided free of charge to small and medium-sized enterprises.
- A meeting with stakeholders held early in the year confirmed the successful removal of the legalisation step previously performed by the European Commission’s UK representation.
- A new system of revenue (invoicing) was introduced and implemented successfully.


Certificate requests,
2004-2006
1,400
1,200
1,000
800
600
400
200
0
909
1,035
1,193
2004
2005
2006

5. EU TELEMATICS STRATEGY

The Agency is responsible 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.

Project status at the end of 2006

- EudraNet (secure communication between stakeholders in the European Medicines Regulatory Network). The network is in place, connecting regulatory authorities in the European Economic Area, including the two new EU Member States, Bulgaria and Romania.
- EudraVigilance (web-based information system to support the pharmacovigilance obligations laid down by Community legislation). The base system is in place. Work is required in order to complete the data warehouse and business intelligence functionality, sophisticated signal detection, signal tracking, and implementation of the access policies with regard to all stakeholders.
- EudraPharm (database of medicinal products authorised in the European Union to support regulatory activities and to make information on medicinal products available to the public). The base system is in place. Work is required to implement extended search, technical structuring of the content, incorporation of data from national competent authorities, and a multilingual approach.
- EudraCT (database of information on the content, commencement and termination of clinical trials in the EU). The base system is in place. Requests for enhancements have been received.
- PIM (Product Information Management – a process that supports the electronic exchange of product information between applicants and the EMEA, as well as the review of this information). The system for the centralised procedure is nearly complete, with adjustments for post-authorisation procedures being planned for early 2007. Thereafter, subject to budgetary capacity, it is hoped to extend the system to the decentralised and mutual-recognition procedures.
- EudraGMP (EU database of manufacturing authorisations and of certificates of good manufacturing practice). The core system was in testing as at the end of 2006. Enhancements to permit semi-automatic batch upload are planned for 2007. Further requests for enhancements have been received.
- EU Telematics Controlled Terms (a central hub providing agreed and authoritative look-up information for medicinal products in as many EU/EEA languages as possible). Planning of development work on a production system, following two successful prototypes in 2006, was ongoing at the end of the year.

6. MANAGING THE AGENCY

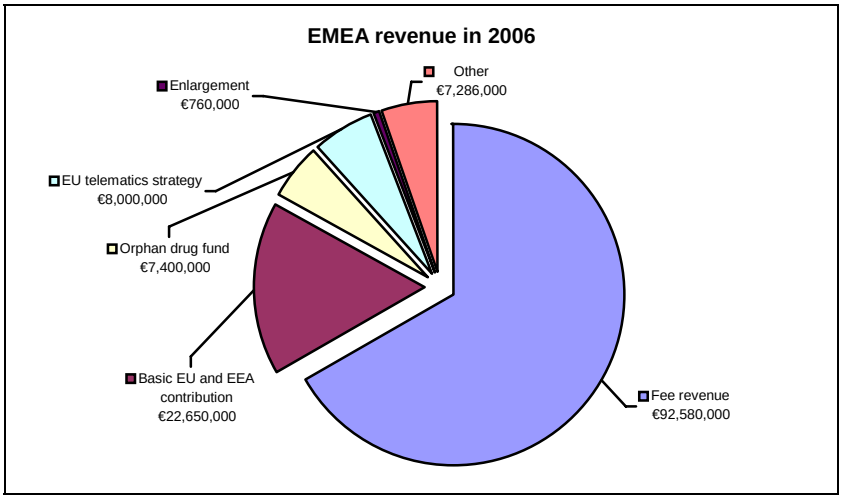
6.1 Management Board

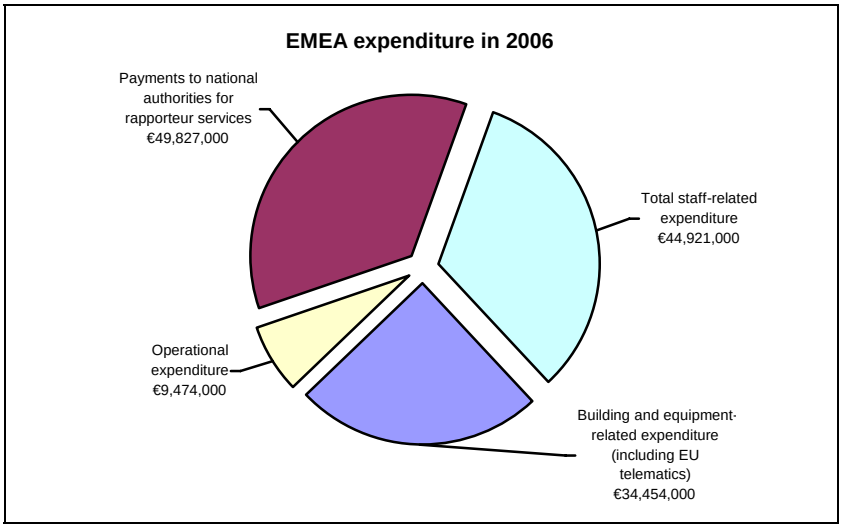
The EMEA Management Board met four times in 2006, under chairman Hannes Wahlroos, from Finland, and vice-chairman Jytte Lyngvig, from Denmark.

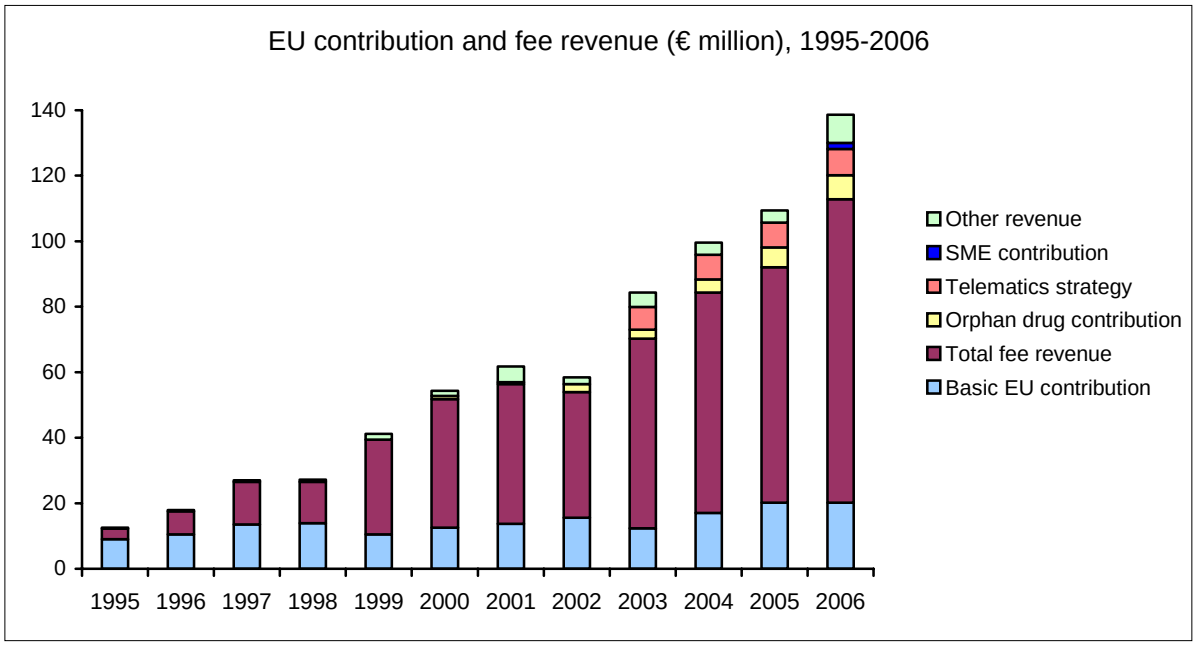
Highlights of the Management Board's work in 2006 included

- Adoption of several proposals for greater transparency.
- Extension of the pilot programme free scientific advice for veterinary medicines for minor uses and minor species for another year, with a view to stimulating development of medicines for limited markets.
- Constitution of a working group on roles and responsibilities of the Management Board, following calls for more involvement and engagement of the Board members in the work of the Agency.
- Adoption of the Agency's work programme, establishment plan and budget for 2007.

Revenue and expenditure in 2006







6.2 Integrated quality-management at the Agency

Management and internal-control systems are part of EMEA governance and are consolidated in an integrated management system at the Agency. Continuous improvement of its processes, working together with its partners and stakeholders, is inherent to the integrated management system. Reviewing business processes to rationalise them and make them more efficient and less time-consuming, while improving or at least maintaining the quality of the work undertaken, was emphasised in 2006 at all levels of the EMEA's operations.

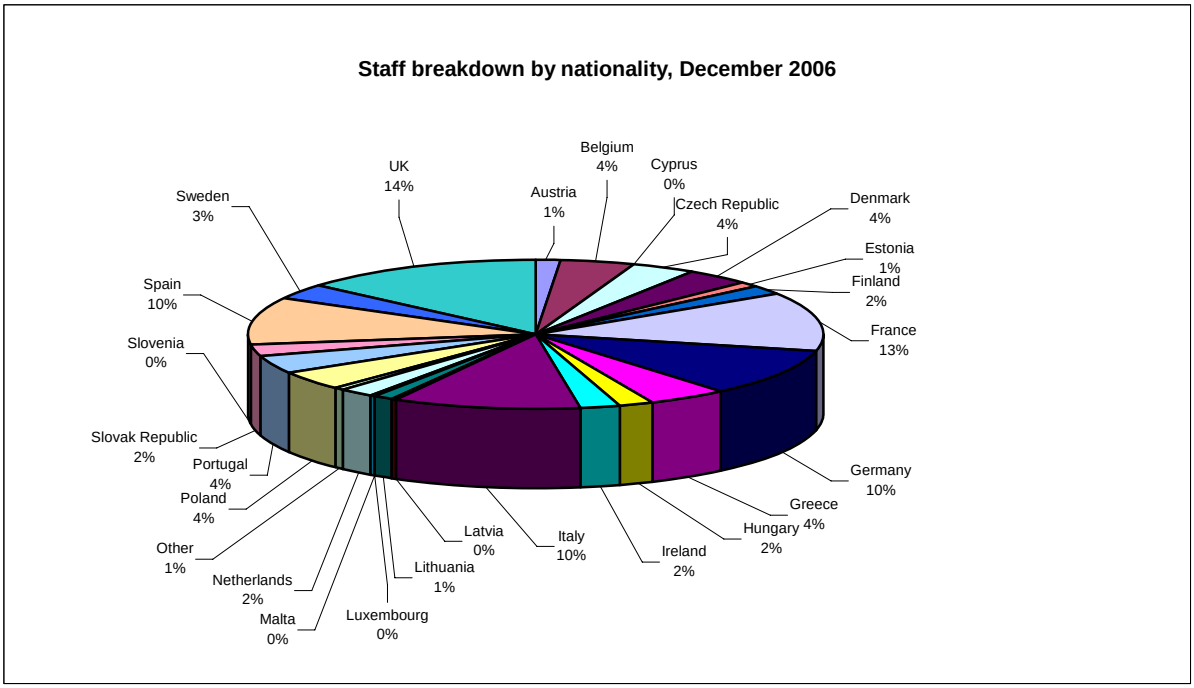
An annual management review was conducted, aimed at ensuring that management tools are effective and suitable. This included a review of results from: risk-management, internal and external audits; self-assessments related to internal control standards; self-assessments as part of the Benchmarking of European Medicines Agencies (BEMA); the environmental analysis 2006; and the 2006 staff-motivation survey. The decisions and actions arising from the management review are incorporated in planning directives, annual work programme and budget.

The Audit Advisory Committee, whose external members were selected by tender, is reinforcing the integrated management and internal-audit system.

6.3 Personnel

By the end of 2006, the Agency employed a total of 497 staff. In addition, about 45 people worked at the Agency on a contractual basis, mainly on IT projects.

There is a balanced geographical representation of EU Member State nationalities among the EMEA staff, with emphasis being made in recent years on recruiting from the new EU accession countries.



Much effort was placed on competence-development in 2006. There was a substantial increase (of €150,000) in the training budget, the range of professional-training opportunities was extended, and, for each staff member, a 'training profile' was developed to serve as a competence-development guideline for the coming years.