EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual report 2014

An agency of the European Union

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Mission Statement

The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Guiding principles

We are strongly committed to public and animal health.

We make independent recommendations based on the best scientific evidence, using state-of-the-art knowledge and expertise in our field.

We support research and innovation to stimulate the development of better medicines.

We value the contribution of our partners and stakeholders to our work.

We assure continual improvement of our processes and procedures, in accordance with recognised quality standards.

We adhere to high standards of professional and personal integrity.

We communicate in an open, transparent manner with all of our partners, stakeholders and colleagues.

We promote the well-being, motivation and ongoing professional development of every member of the Agency.

Principal activities

Working with the Member States and the European Commission as partners in a European medicines regulatory network, the European Medicines Agency:

- provides independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines;
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the European Commission;
- implements measures for continuously monitoring and supervising the quality, safety and efficacy of all medicines authorised in the EU to ensure that their benefits outweigh their risks;
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines;
- recommends safe limits for residues of veterinary medicines used in food-producing animals, for the establishment of maximum residue limits by the European Commission;
- involves representatives of patients, healthcare professionals and other stakeholders in its work, to facilitate dialogue on issues of common interest;
- publishes impartial and comprehensible information about medicines and their use;
- develops best practice for medicines evaluation and supervision in Europe, and contributes alongside the Member States and the European Commission to the harmonisation of regulatory standards at the international level.

Legal role

The European Medicines Agency is the European Union (EU) body responsible for coordinating the scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

The Agency provides the Member States and the institutions of the EU the best-possible advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.

Foreword

by Professor Sir Kent Woods

Chair of the Management Board

For the European Medicines Agency, 2014 has been a particularly eventful and productive year. As this report describes, EMA in close collaboration with the European Union (EU) network of medicines regulatory agencies has continued to bring a high standard of science to bear on the assessment of pharmaceuticals. This is achieved through the work of its seven scientific committees, which are able to draw on experts in a wide range of disciplines from across the EU.

This collaborative effort across some 50 agencies and over 4,500 experts is a unique strength of the EU system for medicines regulation. During the year there were 390 scientific meetings in the agency attended by 7,300 delegates – an increase of 10% and 6% respectively over 2013. The network has actively embraced technology for remote working to improve its efficiency. In 2014 there were over 3,000 video-, tele- and web-conferences co-ordinated from EMA – an increase of 11% over the preceding year. This rising workload reflects both the increasing number of centrally authorised pharmaceuticals in the EU and the impact of recent legislation to strengthen the oversight of medicines, particularly in the field of pharmacovigilance.

In summer the agency moved into its new building at 30 Churchill Place. The relocation was the culmination of several years' planning for headquarters accommodation after the expiry of the Westferry Circus lease. The Management Board took a close interest in the appraisal of options to find the most cost-effective and adaptable solution for the needs of EMA over the next two decades. Construction and fitting out were completed within time and budget, allowing a smooth migration of staff from the old building to the new with minimal disruption of work. Feedback on the new working environment has been extremely positive. I would like to congratulate all who contributed to this excellent outcome.

It was my privilege to carry out the official opening of the new headquarters on 26th January 2015 in the presence of staff and distinguished guests – and to the accompaniment of the EMA choir. The date was significant as the 20th anniversary of EMA. This major milestone will also be marked by a scientific conference to be held in March 2015.

What matters for the citizens of Europe is not the building but what goes on inside it. I hope you will see from the contents of this report that EMA and the network together did much good work during 2014 to support human and veterinary health. On behalf of the Management Board I would like to acknowledge the commitment and skill of the many people who have contributed to those achievements during the year.

Introduction

by Andreas Pott Deputy Executive Director

and Professor Guido Rasi Principal Adviser in charge of Strategy

This past year - the 20th of the European Medicines Agency's existence - has been challenging and rewarding, in equal measure. The Agency operates in a fast-paced environment, and as in previous years, we have seen rapid changes in scientific development, legislation, business trends, globalisation, economic pressures and stakeholder involvement. Our environment is not only changing quickly but also getting ever more complex.

We strive to adapt to the complexity and new developments and so, in 2014, re-organised our processes and structures. The goal was to strengthen our support of the work of the scientific committees, improve knowledge sharing with the European medicines regulatory network and better meet the needs of our stakeholders.

Once again, the European medicines network was the source of the Agency's success. The EU network of medicines regulatory agencies makes available the members of the scientific committees and gives access to a pool of experts who participate in EMA's working parties and advisory groups. This allows the Agency to source the best-available scientific expertise for the regulation of medicines in the EU.

Undoubtedly, the main achievement of 2014 was the adoption of our policy on the publication of clinical data in October. This landmark policy sets a new standard for transparency in public health and pharmaceutical research and development. It is based on an extensive consultation and its adoption was particularly welcomed by the scientific community and broader society. We hope that this major initiative will strengthen public confidence and trust in the regulatory system that strives to protect and enhance public health.

Our legal framework continues to evolve. In 2014, we implemented more provisions from the pharmacovigilance legislation and supported Member States and the European Commission in the implementation of the Falsified Medicines Directive. We also worked to operationalise the new Clinical Trial Regulation, which came into force in June 2014 but will apply no earlier than 28 May 2016. Work will continue over the next years to fully implement this regulation that will transform the way clinical trials are approved and monitored by regulatory and ethics bodies in the European Union. In the area of veterinary medicines, the European Commission proposed a revision of the existing legal framework. We will assist the Commission with our expertise whenever needed to help improve the health and wellbeing of animals by stimulating the development and availability of veterinary medicines.

In 2014, it became clear that our focus of promoting the development of medicines to tackle unmet medical needs of patients was not in line with the more market-driven goal of developing bestselling blockbuster medicines. As a regulator, we have a dual function: as a gatekeeper who protects public and animal health by ensuring the safety and efficacy of medicines and as an enabler who supports research and innovation to stimulate the development of better medicines. In our enabling role, we looked at several initiatives to stimulate development, including adaptive pathways to marketing authorisation, which should help to accelerate patients' access to new medicines. We also strengthened our relationships with health technology assessment (HTA) bodies. This is critical to ensure that new approved medicines reach patients through the national health system of their countries.

The Agency's priority is to ensure the integrity of our scientific assessments of medicines. In November 2014, we published a revised policy on handling declarations of interests of scientific committee members and experts. This more robust policy aims to effectively restrict the involvement of experts with possible conflicts of interests in the Agency's work while maintaining EMA's ability to access the best available expertise.

Introduction

by Andreas Pott Deputy Executive Director

and Professor Guido Rasi Principal Adviser in charge of Strategy

Patients have always been at the heart of our work, and it is only through their engagement that we can achieve our ambitious goals. In 2014, we started a pilot project to involve patients in the assessment of the benefits and risks of medicines by our Committee for Medicinal Products for Human Use (CHMP). We are convinced that listening to patients enriches the scientific assessment and ensures that new medicines respond to their needs.

We continue to play a vital role in the global response to the threat of antimicrobial resistance. In 2014, we published recommendations on the use of antibiotics in animals and humans and a fourth report on sales of veterinary antimicrobials to promote the responsible use of antimicrobials.

Public health bodies were seriously challenged in 2014 with the outbreak of Ebola virus disease in West Africa. We played our part in the global response to this challenge by providing scientific and regulatory advice to pharmaceutical companies and by helping to speed up the development of Ebola treatments and vaccines. This emergency stressed once again the importance of regulators across the world working together to find solutions to limit the spread of disease, and protect and treat patients in a timely and coordinated manner.

In 2014, we also re-located the Agency to our new premises at 30 Churchill Place which are better equipped to facilitate our work. The move went very smoothly thanks to the hard work of all involved.

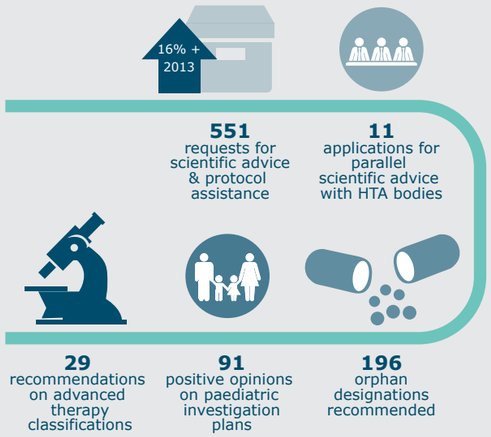
We are grateful for the achievements and dedication of the Agency's staff, of the members of all its scientific committees, the working parties and scientific advisory groups, the management Board, and all the national experts who together enable EMA to fulfil its mission to protect and promote public and animal health in the European Union.

1 | Key achievements in 2014

2014 was an exciting year for EMA. It was a very busy year and it has demonstrated once again that the environment in which the Agency operates is ever-changing, continuously presenting new challenges. The following highlights a few of the many projects, initiatives and achievements of 2014, focusing on those that have had or continue to have a profound effect on how the Agency operates.

HUMAN MEDICINES

RESEARCH & DEVELOPMENT



AUTHORISATION

new active substances **41** | positive opinions **82**

Highlights

17 orphan medicines | **1** stem cell therapy | **1** paediatric use

SAFETY MONITORING

471 periodic safety update reports assessed

18 referral procedures started

1.1 MILLION adverse reaction reports received

2030 signals reviewed → **34** signals validated → **7** changes to product information

Human medicines

EMA recommended 82 medicines for human use for marketing authorisation in 2014. Many of these medicines can treat diseases for which no treatments were previously available or bring added benefit to patients over existing therapies.

2014 saw the first recommendation of a medicine for the treatment of Duchenne muscular dystrophy as well as the first treatment for erythropoietic protoporphyria, a rare genetic disease which causes intolerance to light. The first therapy based on stem cells was also recommended in 2014.

In 2014, 17 medicines recommended for marketing authorisation were intended for the treatment of a rare disease, providing therapies for patients who often have few or no treatment options. This is the highest number of orphan designated medicines recommended for marketing authorisation in a year.

Increased use of EMA support tools

EMA's Committee for Medicinal Products for Human Use (CHMP) received more requests for scientific support in the early stages of medicine development than previous years. Almost 70% of applicants received scientific advice during the development phase of their medicine and this figure rises to 80% when it comes to innovative medicines.

Seven positive opinions were granted after an accelerated assessment in 2014. This mechanism aims to speed up the assessment of medicines that are expected to be of major benefit for public health.

EMA used the accelerated assessment tool for four new medicines for the treatment chronic hepatitis C virus (HCV) infection. These treatments have high cure rates and belong to a new generation of medicines that have recently reshaped the way patients with chronic HCV infection can be treated.

Veterinary medicines

In 2014, 20 new veterinary medicines were recommended for marketing authorisation. This is a significant increase compared to previous years which is due to the record number of initial marketing-authorisation applications received in 2013.

Amongst these medicines, 11 are for companion animals, including a range of vaccines for dogs, and nine are for food-producing animals, including poultry, pigs, cattle and sheep.

2014 saw the first vaccine against Schmallenberg virus in cattle and sheep to be recommended for authorisation at the European level, and the first recommendation of a marker vaccine for the immunisation of pigs against classical swine fever virus.

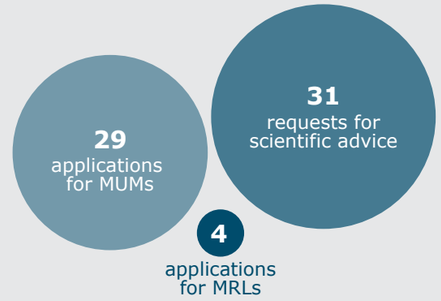
Increase in MUMS classifications

In 2014, the Committee for Medicinal Products for Veterinary Use (CVMP) received the highest number of requests in a year (29) for the classification of medicines for minor use minor species (MUMS)/limited market. Since its introduction in September 2009, the MUMS/limited market policy has successfully stimulated the development of new veterinary medicines for minor species and for rare diseases in major species, with almost 100 products classified so far.

While fewer applications for the establishment of maximum residue limits (MRLs) for new substances were received in 2014 compared to 2013, the continued submission of MRL applications indicates the ongoing interest of the animal health industry in developing new medicines for food-producing animals.

VETERINARY MEDICINES

RESEARCH & DEVELOPMENT



AUTHORISATION

12 new applications

20 positive opinions

SAFETY MONITORING

28 404 reports on suspected adverse reactions

158 periodic safety update reports submitted

7 referral procedures started

28 Jan — Minutes of CHMP, CVMP & CAT meetings are published for the first time

14 Feb — Dr Paula Salmikangas appointed as new chair of CAT

16 Feb — Dina Tsiambaou appointed as new Head of IT Development Department

11 Mar — Publication of first summary of a risk-management plan for a medicine

19 Mar — Launch of EMA's adaptive licensing pilot project

7 Apr — Sharing of full assessment reports of orphan medicines with Australian Therapeutic Goods Administration agreed

The Agency is committed to continuously extending its approach to transparency. There were three key developments in 2014 – the adoption of the EMA policy on the publication of clinical data, the extension of the European database of suspected adverse drug reactions, and the publication of the agendas and minutes for the meetings of all scientific committees.

Publication of clinical data

In 2014, EMA decided to publish the clinical reports that underpin the decision-making on medicines. The EMA Management Board's adoption of the landmark policy on the publication of clinical data for medicinal products for human use on 2 October 2014, was widely welcomed as a crucial advance in transparency and open access to published clinical trial data.

"The adoption of this policy sets a new standard for transparency in public health and pharmaceutical research and development. This unprecedented level of access to clinical reports will benefit patients, healthcare professionals, academia and industry,"
Guido Rasi, Principal Adviser in charge of Strategy

Under the policy, the Agency proactively publishes the clinical reports submitted as part of marketing-authorisation applications, regardless of whether an authorisation is granted. The policy allows identified individuals to download, save, and print clinical data for academic and non-commercial research purposes.

The adoption of the policy followed an extensive consultation with patients, healthcare professionals, academia, industry and other European entities, since it was first announced in 2012.

EMA expects the new policy to increase trust in its regulatory work as it will allow the general public to better understand the Agency's decision-making. The publication of clinical reports will also help to avoid duplication of clinical trials, foster innovation and encourage development of new medicines.

"We believe that patients have a right to know about the scientific basis for the approval and use of their medicines and that transparency of clinical trial data is therefore essential,"
Sergio Bonini, Hans-Georg Eichler, Guido Rasi, Noël Wathion in N Eng J Med 371; 26; 2452-2455, January 2014

The policy came into force on 1 January 2015. Once a medicine has received a marketing authorisation or when an application is withdrawn or a negative opinion issued, EMA will publish the supporting clinical reports.
For line extensions and additional indications of already approved medicines, the Agency will give access to clinical reports for applications submitted as of 1 July 2015 after a decision has been taken.

Clinical trial summary results in the EU Clinical Trials Register

Since July 2014, sponsors have been obliged to post clinical trial results in the European Clinical trials Database (EudraCT) and this information is made available to the public through the EU Clinical Trials Register. This is a separate initiative to the EMA's policy on the publication of clinical data for medicinal products for human use.

EudraCT is a database, hosted by EMA, and used by national competent authorities to enter information on clinical trials submitted by clinical trial sponsors, as well as information on clinical trials conducted outside the EU if they are included in a paediatric investigation plan (PIP).

A subset of the data contained in EudraCT is made available through the public website EU Clinical Trials Register, which the Agency manages on behalf of the EU. Information contained in EudraCT is also available through the World Health Organization (WHO) International Clinical Trials Registry Platform (WHO ICTRP). EudraCT has been recognised as a primary registry of WHO ICTRP.

At the end of 2014, summary results from a number of trials could already be viewed on the public website. A typical set of summary results provides information on the objectives of a given study, explains how it is designed and gives its main results and conclusions.

This new feature of EudraCT is another step towards increasing clinical trial transparency in Europe and allows sponsors to provide summary results of all interventional trials already published in the EU CTR.

European database of suspected adverse drug reactions

In October 2014, EMA expanded the publication of data from the European database of suspected adverse drug reactions to nationally authorised medicines (www.adrreports.eu).

This website was first launched in 2012 as part of the Agency's continuing efforts to ensure EU regulatory processes are transparent and open. Initially, this website provided public access to reports of suspected reactions to centrally authorised medicines. Due to the extension to nationally authorised medicines, European citizens can now obtain information on suspected adverse drug reactions of many more active substances contained in medicines approved in the European Union (EU).

The website contains a single report per medicine or active substance. Each report pulls together the total number of individual suspected side effect reports submitted to EudraVigilance, the EU adverse drug reaction collection and management system, by Member States and marketing-authorisation holders. These aggregated data can be viewed by age group, sex, type of suspected side effect and outcome.

The further roll-out of public access to suspected side effects related to all medicines available in the EU will occur gradually over the next few years.

Information on meetings of EMA's scientific committees

EMA now routinely publishes all agendas of its scientific committee meetings at the start of each meeting, and the minutes after their adoption, usually the following month. The minutes are a record of all of the topics discussed during the meetings of the committees.

In January 2014, the meeting minutes of the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Advanced Therapies (CAT) were published for the first time.

These publications are part of a major initiative to make the meetings of the Agency's seven scientific committees more transparent. This started with the Paediatric Committee (PDCO) in June 2012 and the Pharmacovigilance Risk Assessment Committee (PRAC) in July 2012, the Committee for Orphan Medicinal Products (COMP) in September 2012 and the Committee on Herbal Medicinal Products (HMPC) in September 2013.

16 Apr – EMA publishes implementation plan actions agreed with EU national competent authorities to address medication errors

8 May – Start of public consultation on best practice guidance on parallel scientific advice with health-technology-assessment bodies

14 May – EMA and US FDA joint proposal to facilitate clinical investigation of new medicines for Gaucher disease in children

14 May – EMA and European Chemicals Agency sign a memorandum of understanding

28 May – New Clinical Trial Regulation is published in Official Journal of the EU

5 Jun – Public consultation on European Medicines Agency's draft guide on monitoring of medical literature

12 Jun – Sir Kent Woods re-elected as chair of Management Board

1.3 | Implementation of new legislation

New legislation is a major driver for change, and implementation of new provisions into the Agency's operations is a continuing task. In 2014, the implementation of the pharmacovigilance legislation, the most substantial change in the Agency's legal framework since its establishment in 1995, remained a priority. The Agency also continued to work on the implementation of the falsified medicines directive and provided assistance to the European Commission in the revisions of the clinical trials legislation and of the legal framework for veterinary medicines.

Pharmacovigilance legislation

Two years after it came into effect, the pharmacovigilance legislation has already delivered major change in the way the safety of medicines is being monitored, which should lead to better public health. This is shown by strengthened clarity of roles and responsibilities of parties involved in pharmacovigilance activities in the EU, greater transparency of information about safety of medicines, improved timeliness and robustness of procedures as well as enhanced data collection instruments throughout a medicine's life cycle. Implementation continued in 2014 and important progress was made in a number of areas.

Pharmacovigilance fees

The pharmacovigilance fee Regulation was published in the Official Journal of the European Union on 27 June 2014 and has applied to procedures starting from 26 August 2014, although annual fees to support information technology systems and literature monitoring activities will not be levied until 2015.

The EU Pharmacovigilance legislation has been operational since July 2012 and foresees various information systems to enhance pharmacovigilance, particularly to support the collection, management and analysis of data, information and knowledge. These systems will contribute to public health through optimisation of the safe and effective use of medicines.

The pharmacovigilance fee Regulation now allows EMA to collect fees from marketing authorisation holders to finance these pharmacovigilance activities conducted at EU level for medicinal products for human use. The income is used to remunerate national competent authorities (NCAs) for the scientific assessment carried out by the rapporteurs of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and contributes to the pharmacovigilance costs of the Agency.

Once the Regulation has been in effect for a full year EMA will provide key performance indicators and cost information on these fees and fee-related activities in future annual activity reports and annual reports.

Literature monitoring

EMA launched a public consultation on its draft guide on the monitoring of medical literature for safety information and the entry of relevant information into the EudraVigilance database. Literature monitoring is a new responsibility for EMA aimed at improving safety monitoring of medicines. It will be provided as a service to industry who will no longer have to enter the literature cases into EudraVigilance.

Literature monitoring will be outsourced by EMA to a service provider. A public procurement procedure to select a provider with the necessary experience and knowledge in this area was launched in November 2014. A service provider is expected to be selected in early 2015.

Data submission for authorised medicines – Art. 57 database

Working closely with representatives of European pharmaceutical-industry associations through the Joint Implementation Working Group (IWG), the Agency published guidance and formats for a data maintenance submission process to help marketing authorisation holders to keep the information held on their medicines up-to-date. In July 2014, EMA started the review of quality and integrity of medicinal product information, and began to provide feedback to marketing authorisation holders by the end of the year.

PSUR repository

Preparations to establish a repository for periodic safety update reports and their assessment reports continued. The Agency built an IT system for the repository on the basis of requirements gathered together with the national competent authorities and pharmaceutical industry. User acceptance testing was completed in November 2014 and public release was scheduled for early January 2015.

Adverse drug reaction reporting and signal management

The new legislation foresees improvements to Eudravigilance, the EU adverse drug reaction collection and management system, to simplify reporting, enhance data quality and improve searching, analysis and tracking functionalities for better health protection.

A public consultation on the revision of the EudraVigilance Access Policy was held in 2014. The revision maintains the key principles established with the original version of the policy published in 2011, but takes into account the changes to the system of safety monitoring of medicines introduced by the pharmacovigilance legislation.

The Agency published a guide to support the implementation of a new international standard designed to improve the reporting of suspected side effects of medicine in Individual Case Safety Reports (ICSRs) by establishing the same reporting format across the world.

Falsified medicines

The Agency continued to support Member States and the European Commission in the implementation of the Falsified Medicines Directive (Directive 2011/62/EU)

The Directive introduces a new paradigm for global medicines regulation. It provides a clear basis and framework for strengthened international cooperation and dialogue on the supervision of active substances manufacturing, sharing of responsibilities with regulators outside the EU, and development of local supervision.

The Agency developed further guidance for good manufacturing practice (GMP) and good distribution practice (GDP) inspections and also supported the assessment of third countries for equivalent GMP requirements and supervision arrangements. By the end of 2014, four countries were listed by the European Commission as equivalent. Those countries no longer have to issue written confirmation per manufacturing site and per active substance that the site in question complies with GMP requirements.

Countries with equivalent GMP standards in relation to active substances

- Australia
- Japan
- Switzerland
- United States

A logo for online retailers of medicines

The Directive has introduced an obligatory logo that will allow patients and consumers to identify authorised online retailers of medicines providing authentic, authorised medicines. The logo will appear on the websites of legally operating online retailers of medicines in the EU. Clicking on the logo will link to the national regulatory authority websites, where all legally operating online retailers of medicines in their respective countries will be listed. The respective Implementing Regulation establishing the new logo entered into force in July 2014, and gave Member States and EMA until July 2015 to prepare for its application.

Clinical Trial Regulation

On 16 April 2014 the new EU Regulation on clinical trials on medicinal products for human use was adopted by the European Parliament and the Council of the EU prior to its publication in the Official Journal in May. This new piece of legislation supports the conduct of clinical trials in the EU, with the highest standards of safety for participants. Although the Regulation EU No. 536/2014 entered into force on 16 June 2014, it will not apply earlier than 28 May 2016 once a number of technical requirements (including the EU portal and EU database) have been implemented.

While authorisation and oversight of clinical trials remains the competence of EU Member States, EMA was tasked to develop and maintain a clinical trial portal and database to be used for the submission, authorisation and supervision of trials in the EU. The database will serve as the source of public information on all clinical trials conducted in the EU.

Following a public consultation in October, the functional specifications for the EU portal and EU database were agreed and published in December 2014.

In addition, the Agency committed to carry out a separate consultation on the transparency requirements of the Clinical Trial Regulation, which was under preparation by the end of the year.

Veterinary medicines legislation

On 10 September 2014 the European Commission adopted a proposal for a major evolution of the legal framework for the authorisation of veterinary medicines in the EU. The new rules proposed by the European Commission aim at improving the health and wellbeing of animals by stimulating the development and increasing the availability of veterinary medicines. The legislative proposal also tackles the growing concerns over antimicrobial resistance by proposing a series of tools to minimise the risks that may arise from the use of antibiotics, particularly in food-producing animals.

The Agency provided technical advice to the European Commission during the development of this proposal and welcomed its publication as the availability of veterinary medicines and the fight against antimicrobial resistance are two major EMA priorities.

24 Jun — European Commission launches logo for online retailers of medicines to protect patients from falsified medicines

27 Jun — Pharmacovigilance fee Regulation is published in Official Journal of the EU

21 Jul — Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) becomes mandatory for sponsors

24 Jul — Public consultation on rules of procedures for public hearings

31 Jul — Publication of first public summaries of Paediatric Committee evaluations of paediatric investigation plans

1.4 | Support to the European medicines regulatory network

The European medicines regulatory network is the cornerstone of the work and success of the Agency, with experts from national authorities carrying out the assessment of medicines on behalf of EMA. There has been a substantial increase in workload over the years. For the system to remain sustainable, and to be able to carry out the work to a high level of quality, it is essential that more and more national authorities participate in the assessment of medicines.

Efforts undertaken during the last few years are paying off. The number of national competent authorities involved in EMA procedures as rapporteurs or co-rapporteurs is increasing. In 2010, 16 Member States participated in the assessments as rapporteur or co-rapporteur, while in 2014 this number increased to 24. This is an important positive trend for the EU system. To ensure its continuation, EMA launched a number of initiatives in 2014 which aim to better support the assessment work of the many thousands of EU experts involved in the regulation of medicines.

EU Network Training Centre

In February 2014, EMA and the Heads of Medicines Agencies (HMA) kicked-off a project to establish an EU Network Training Centre (EU NTC), a central online platform for the exchange of information and regulatory and scientific training across the network.

This initiative aims to develop a training strategy for continuous professional development of staff from national competent authorities and EMA, in order to improve the quality, consistency and efficiency of the work of the network and promote harmonised application of the regulatory framework and guidelines.

The mandate, governance structure and vision of the EU NTC were adopted by EMA and HMA in 2014. The EU NTC is expected to offer personalised and modular curricula adapted to the diversity of training needs. It will provide access to different types of training materials and a variety of learning strategies, including face-to-face and online trainings.

In September 2014, over 60 participants from more than 20 national agencies met in London to agree on the scope and key priorities of the centre.

Multinational teams to assess medicines

Building on a successful pilot scheme, the Agency offered to the CHMP the option to form multinational co-rapporteur teams to assess initial marketing authorisations for medicines for human use. This initiative aims to make use of the best expertise across the EU for the assessment of a marketing authorisation application.

The pilot involved Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Poland and Sweden.

EMA is now exploring how the scheme can be extended to CHMP rapporteurship and to other EMA committees.

Data sharing

The Agency developed a 'dashboard' which provides user-friendly access to information on medicines evaluation procedures for human medicines to all national competent authorities.

These dashboards allow the generation of predefined reports, thus providing key information on past and ongoing procedures as well as on expected submissions of applications. The information includes the status of ongoing procedures, procedural timetables and rapporteurship involvement.

Further to a successful pilot phase on the use of the dashboards, all national competent authorities were invited to indicate whether they are interested in using this tool. As of December 2014, 74 users from 17 countries had registered.

Assistance to candidate countries

The coordination of activities in line with the framework of the Instrument for Pre-accession Assistance (IPA) was concluded in September 2014 and has seen the successful introduction of best practices and standard operating procedures in the fields of inspection and medicines evaluation for a number of the beneficiaries involved. The programme culminated in a successful conference in Belgrade, Serbia, dedicated to reinforcing communication with patients and healthcare professionals.

1.5 | International collaboration

The increasing complexity of globalised pharmaceutical development and manufacturing and the limited resources available to enforce standards leads to unique public health challenges that require a strategic international approach based on multilateral cooperation. International agreements are the basis for current change in the model of international collaboration, allowing not only sharing of information but also sharing of work.

The Agency has confidentiality agreements with the Therapeutic Goods Administration (TGA) in Australia, Health Canada (HC), the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the Food and Drug Administration (FDA) in the United States. There are almost daily interactions with these authorities, partly structured around clusters of activities (see box), partly ad-hoc.

In the framework of the Transatlantic Trade and Investment Partnership (TTIP), EMA supported the Commission, working together with the US Food and Drug Administration to establish the basis for mutual reliance on the outcomes of Good Manufacturing Practice (GMP) inspections carried out by regulatory authorities in both regions.

In April 2014, EMA and the Australian TGA agreed to strengthen collaboration by sharing the full assessment reports of marketing authorisation applications for orphan medicines, which are intended to treat rare diseases. If the same marketing-authorisation application is received in parallel by EMA and TGA, the two regulators have the possibility of scientific exchange to facilitate the evaluation of the medicine. Both regulators will still reach their own conclusions about the suitability of each medicine to be authorised in their respective markets.

EMA and the FDA released a draft joint proposal to facilitate the clinical investigation of new medicines for the treatment of Gaucher disease in children for public consultation in May 2014. The aim of the proposal is not only to facilitate a rapid and smooth agreement of an EMA Paediatric Investigation Plan and FDA Pediatric Study Plan, but also to address the feasibility of developing multiple medicines for a rare disease in a reduced timeframe and in a limited number of patients.

Clusters with regulatory partners

- Orphan medicines (with FDA)
- Paediatric medicines (with FDA, PMDA, TGA, HC)
- Vaccines (with FDA, HC)
- Oncology medicines (with FDA, PMDA, HC, TGA)
- Blood Products (with FDA, HC)
- Biosimilars (with FDA, PMDA, HC)
- Advanced Therapy Medicinal Products (with FDA, HC)
- Pharmacovigilance Cluster (with FDA, PMDA, HC)
- Pharmacogenomics Cluster (with FDA)
- Veterinary Medicinal Products Cluster (with FDA)

Working with multilateral coalitions

The International Conference on Harmonisation (ICH) is the longest-standing international forum in which the Agency participates. In 2014, EMA, as part of the Steering Committee, worked to reform ICH in terms of governance, new membership and funding. It also contributed to the development of a five-year strategic plan for future ICH activities.

The Agency took part in the International Pharmaceutical Regulators Forum (IPRF). Established in 2013, the IPRF was created as a protected space for discussion and promotion of harmonisation among regulatory authorities. Formal terms of reference were established in 2014, on the basis of the growing interaction between the members of IPRF.

EMA led an initiative on mapping of international activities, to support the work of a new interim International Coalition of Medicines Regulatory Authorities (ICMRA) formed in early 2014. In the margins of the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) held in Rio de Janeiro one of the first initiatives of ICMRA was to affirm the commitment of its members to work together and with the World Health Organization (WHO) to encourage the development and regulatory evaluation of medicines against the disease, in the face of the Ebola crisis.

EMA also started to work with the Bill and Melinda Gates Foundation to explore how its procedure supporting development of medicines for use outside the EU (Art. 58) could be better used to facilitate access to new medicines in developing countries.

Cooperation with WHO intensified during 2014, with heightened collaboration on combatting the Ebola crisis, addressing the challenges of antimicrobial resistance, cooperative GMP and GCP inspections and on the establishment of a framework for more effective exchange of adverse reaction reports.

In the veterinary domain, EMA provided strong support to the further development of the VICH Outreach Forum which aims to extend the uptake of VICH guidelines beyond member and observer countries.

European cooperation as a model for other regions

International regulators are looking to the European medicines regulatory network as a model for regional cooperation. In 2014, the African Union announced the creation of an African Medicines Agency modelled on the EMA concept. Similarly, the East African Community developed a decentralised authorisation model for five African countries, and Caribbean regulators launched a similar initiative in 2014. EMA supports these activities by providing guidance and input based on its 20 years of experience with a networking model covering both human and veterinary medicines.

A pilot programme allowing non-EU regulators to benefit from EU assessments of generic medicines in real time was launched in July 2014.

1 Aug — Relocation of the Agency to new premises

4 Aug — Public consultation on updates to policy on access to EudraVigilance

15 Aug — Ebola Expert group established

18 Aug — Manuel Ortigao appointed as new Head of Human Resources

1 Sep — Start of periodic-safety-update-report single assessment for nationally authorised medicines

1.6 | Communication with stakeholders

Throughout 2014, the Agency continuously developed and broadened its communication activities. Three key developments in this area are outlined below.

Creation of the Stakeholders and Communications Division

The Agency finalised the structure of the Stakeholders and Communication Division. The new division is responsible for ensuring that the Agency has a coherent, coordinated and consistent approach to stakeholder relations management and communication. The new division reflects the increasing demand for transparency and information, knowledge and data about medicines as well as an expectation from stakeholders that information is tailored to their needs.

The division manages relations with and provides information to patients and healthcare professionals, coordinates medicines information in the European medicines regulatory network and manages the Agency's online presence, external communication and press relations, as well as the EMA information centre. The division also manages relations with the pharmaceutical industry, and provides support to micro, small and medium-sized enterprises (SMEs) through its SME Office.

Public hearings

The pharmacovigilance legislation, which became operational in 2012, gave the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) the possibility of holding public hearings as part of certain safety reviews of medicines. In July 2014, the Agency launched a public consultation on its draft rules of procedures for public hearings. These rules of procedures describe the process and practical arrangements for the preparation, conduct and follow-up of these public hearings. The Agency received comments from a broad range of stakeholders and expects to publish the final rules in 2015

"Public hearings give EU citizens a voice in the evaluation of the safety of medicines and allow the PRAC to access perspectives, knowledge and insights into the way medicines are used on the ground that would not otherwise be available to the Committee,"
June Raine, Chair of the PRAC

The voice of patients and healthcare professionals in benefit-risk evaluations

In October 2014, EMA launched a pilot project to involve patients in the assessment of the benefits and risks of medicines in its Committee for Medicinal Products for Human Use (CHMP). This pilot project marks the next step to include patients' views and values in the assessment of medicines throughout their lifecycle.

"Involving patients in CHMP discussions brings the patients' voice into the decision-making process and ultimately contributes to the safe and rational use of medicines,"
Tomas Salmonson, Chair of the CHMP

As part of the pilot project, patients are invited to present their views on medicines under review for which there is an unmet medical need and where the CHMP is still undecided.

The pilot project is currently exploring how patients can be involved systematically and effectively in oral explanations at the CHMP and stems from a wider EMA strategy to better involve patients in Agency activities. The project is expected to run for at least one year to allow a full assessment of the feasibility of involving patients in CHMP oral explanations. A report on the experience gained will be presented to the CHMP at the end of the pilot phase.

EMA concluded a series of three workshops involving representatives of patients and healthcare professionals together with members of EMA scientific committees and other interested stakeholders. The initiative began in 2013 with a workshop that looked at how to involve patients in the evaluation of benefit-risk throughout the product lifecycle. This was followed by a workshop in February 2014 exploring methodologies and standards for the evaluation of benefit-risk. The final workshop held in September 2014 explored communication.

Finally, during the June 2014 workshop of the European Network of Paediatric Research at EMA, the ICAN Research (International Children's Advisory Network) was created, linking up existing European advisory groups of young people with established groups in North American into an international network for worldwide involvement of young people in research.

1.7 | Public health challenges

Antimicrobial resistance

The development of antimicrobial resistance, particularly resistance to antibacterials, is a major global public health concern. Infections by multidrug-resistant bacteria are estimated to cause 25,000 deaths in the European Union every year. Antimicrobial resistance is a problem both in humans and animals and resistance can also spread from animals to humans through the food chain or direct contact. Encouraging the appropriate use of antibiotics is key in the fight against antimicrobial resistance.

The Agency works in collaboration with its EU and international partners on a number of initiatives aiming to limit the development of antimicrobial resistance. In 2014, this included contributing to the European Commission's action plan against the rising threats from antimicrobial resistance, as well as global initiatives to combat antibiotic resistance, such as the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR).

A central pillar in EMA's strategy to help fight antimicrobial resistance in human medicine is the stimulation and facilitation of the development of innovative antibiotics. In 2014, EMA received more than 15 requests for scientific advice from several companies developing new antibiotics and EMA carried out a number of specific activities in the human and veterinary areas.

The Agency published the fourth report on sales of veterinary antimicrobials from the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) which is used by risk assessors and risk managers in Member States to inform antimicrobial policy and to promote the responsible use of antimicrobials. The report found that sales fell overall by 15% between 2010 and 2012 in Europe. For the 2012 data, 26 countries from the European Economic Area (EEA) submitted data on sales of antibiotics authorised in their territory, accounting for approximately 95% of the food-producing animal population in the region.

The Agency also published recommendations linked to the use of antibiotics in animals and humans and the impact on public health and animal health. This followed a request from the European Commission as part of its action plan against the rising threats from antimicrobial resistance and involved cooperation with European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA) as the other European Agencies involved in this area as well as extensive consultation with experts and stakeholders. The draft makes a number of recommendations to minimise the risk of transmission of resistance from animals to humans.

In July 2014, EMA published a concept paper on the use of aminoglycosides in animals in the EU and the development of resistance and impact on human and animal health.

Initiatives to facilitate the development of Ebola medicines

The 2014 outbreak of Ebola virus disease in West Africa is the largest and most complex Ebola outbreak to date. It is unprecedented in terms of scale and geographical spread of the disease. In responding to this emergency, the Agency worked together with regulatory authorities around the world to support the World Health Organization's response and to advise on possible pathways for the rapid development, evaluation and approval of medicines to fight Ebola.

In Europe, the Agency worked with the European Commission to facilitate information exchange between EU Member States and to coordinate approaches on prevention of and preparation for Ebola outbreaks.

EMA created of an ad-hoc task force of European experts with specialised knowledge in vaccines, infectious diseases and clinical trial design to contribute to the global response against Ebola.

A key area in 2014 was facilitating development of Ebola medicines and EMA active collaboration with pharmaceutical industry and researchers. The Agency put in place an accelerated scientific advice procedure for developers of Ebola medicines and vaccines and encouraged the use of the orphan designation.

In September 2014, EMA started to review available information on the various experimental Ebola treatments under development. The goal was to provide an overview of the current state of knowledge to support decision-making by health authorities. EMA published an interim assessment report in December 2014. At the time of its publication, there was not enough evidence yet for any of the experimental therapies to draw conclusions on their safety or efficacy. EMA continues this review and aims to provide the best possible overview of data on treatments for Ebola.

23 Sep — 10th anniversary of Committee on herbal medicinal products

1 Sep — Marie-Agnes Heine appointed as new Head of Communication Department

10 Sep — European Commission adopts proposals for new legislation for veterinary medicines

17 Sep — Workshop on benefit-risk communication with patients and healthcare professionals

26 Sep — Start of pilot project to involve patients in the assessment of the benefits and risks of medicines in its CHMP

30 Sep — Adoption of EU Telematics Strategy 2014-2016

1.8 | Facilitating early phases of development of medicines

The evolution of the development model for medicines, a better understanding of pathologies and the emergence of novel technologies offer new opportunities and challenges in bringing new medicines to patients.

In 2014, the Agency started a pilot project to explore the possibility of introducing a staggered approval of medicines. It also consolidated its collaboration with health technology assessment (HTA) bodies, key actors that inform decision-making for the reimbursement of medicines in the different Member States. Both initiatives aim to accelerate access to new medicines for patients.

In the veterinary domain, the Agency established the Ad Hoc expert group on veterinary novel therapies (ADVENT) which will produce guidance to assist applicants with bringing to market products that involve of the use of therapies and approaches that are new to veterinary medicine.

Launch of adaptive pathways pilot project

EMA launched the adaptive pathways pilot project in March 2014.

The concept of adaptive pathways foresees an early approval of a medicine for a restricted patient population based on small initial clinical studies. The first approval is followed by progressive adaptations of the marketing authorisation to expand access to the medicine to broader patient populations based on data gathered from its real world use and additional studies.

"The adaptive pathways approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks,"
Hans-Georg Eichler, EMA Senior Medical Officer

Adaptive pathways is particularly relevant for medicines with the potential to treat serious conditions with an unmet medical need, and may reduce the time to a medicine's approval or to its reimbursement for targeted patient groups.

In 2014, companies were invited to submit ongoing medicine development programmes for consideration as prospective pilot cases.

Discussions with applicants took place in a 'safe harbour' environment to allow free exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side.

In December 2014, EMA published a report on the first experiences and the next steps. As of December 2014, EMA received and assessed 34 applications, ten of which were selected for discussion with the applicant. Stage I of the pilot was expected to close on 28 February 2015. It is followed by in-depth, face-to-face meetings with the selected applicants in stage II.

Collaboration with health technology assessment (HTA) bodies

For a medicine to reach the market and benefit patients, companies must not only ensure that they meet the requirements of the regulators, but also more and more those of the HTA bodies in the Member States. EMA is strengthening its interaction with HTA bodies to enable innovation to reach patients in a timely manner.

Since the launch of a pilot project of parallel scientific advice with HTA bodies in 2010, EMA has received an increasing number of requests from pharmaceutical companies who wish to obtain simultaneous feedback from the two parties on their development plans for new medicines. The initiative aims to initiate early discussion and agreement on a development plan that generates data that both EMA and HTA bodies can use in their respective assessment, with the ultimate objective to shorten the time required for a medicine to reach patients. Thirty-five procedures have been conducted so far, one third of which were conducted in 2014. The requests covered a variety of therapeutic areas, including rare conditions.

In addition, EMA is involved in a European Commission-funded project which explores early dialogue between multiple HTA bodies and developers of medicines or medical devices. The project called SEED (Shaping European Early Dialogues) involves 7 development programmes for medicinal products; EMA is associated with three of these programmes, providing scientific advice.

In December 2014, EMA and the European Network for Health Technology Assessment (EUnetHTA), a network representing all organisations that produce or contribute to HTA in Europe, had their 9th joint meeting. EMA and EUnetHTA reviewed the progress made as part of their 3-year work plan adopted in November 2013. As part of their efforts to harmonise the advice given to companies on the development of a medicine, the two parties agreed that EMA will contribute to the development of EUnetHTA's disease-specific guideline on osteoarthritis.

In June 2014, EMA and EUnetHTA published the outcome of a joint initiative which aimed to make EMA's European Public assessment reports (EPARs) on medicines better usable by HTA bodies. As part of this project, EMA and EUnetHTA improved the structure and presentation of the key information presented in EPARs in order to increase clarity and transparency of the outcome of the scientific-review process. The outcomes of this project and of an analysis conducted subsequently were published in Value in Health, the Journal of The International Society For Pharmacoeconomics And Outcomes Research, in June 2014.

29 Oct
Revised overarching guideline on biosimilars published - Regulatory pathways

2 Oct
EMA policy on publication of clinical data for medicinal products for human use adopted

6 Oct
www.adrreports.eu extended to include information on suspected side effects of nationally authorised medicines

15 Oct
Publication of European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report on sales of veterinary antimicrobials

13 Nov
Judgement by European Union Civil Service Tribunal annuls appointment procedure of EMA Executive Director

12 Dec
CVMP adopts scientific opinion of the use of diclofenac in animals in EU and the risk to vultures

1.9 | Improving the way we work

2014 saw a number of improvements to streamline the way the Agency operates. A few highlights are outlined below.

Re-organisation of the Agency

Throughout 2014, the Agency continued the work started in 2013 to re-organise its processes and structures in order to better support the work of its scientific committees, share knowledge throughout the European medicines regulatory network and meet the needs of its various stakeholders. The ultimate aim of this exercise is to improve the efficiency and effectiveness of the Agency's operations so that it can continue to conduct its core business activities to the highest level of quality and consistency in a rapidly changing environment.

The re-organisation introduced a new operating model for how medicines are managed throughout their lifecycle at the Agency, as it separates scientific and procedure management.

The main change for applicants is a change in their focal point, as the old product team lead (PTL) concept has been replaced with two new roles:

- a Procedure Manager, or PM, to oversee all aspects of the management of specific procedures. Procedure Managers ensure regulatory consistency at EMA and are responsible for managing the regulatory process for each application. Procedure Managers provide guidance on regulatory procedural matters and serve as the primary contact point for applicants and experts from the national competent authorities in respect to their specific procedure.

- an EMA Product Lead, or EPL, to maintain oversight of a medicine as it moves through the different stages of its lifecycle. EPLs are responsible for the overall knowledge about a medicine and the wider context of a therapeutic area. They provide regulatory science input and facilitate discussions within and between EMA's scientific committees when needed.

Also as part of its reorganisation, the Agency revised its process for handling access-to-documents requests to provide a tailored service for requesters. Each request is now assigned to an EMA coordinator who liaises with the individuals to understand their needs. The Agency also released a practical guide detailing the process for requesting access to unpublished documents held by the Agency.

Updating EMA's declarations of interests policy

In November 2014, the Agency published its revised policy on handling declarations of interests of scientific committee members and experts. The revisions reflect a more balanced approach to handling declarations of interests and aims to effectively restrict the involvement of experts with possible conflicts of interests in the Agency's work while maintaining EMA's ability to access the best available expertise.

"The priority of EMA is to ensure that the integrity of our scientific assessments of medicines is not compromised by private interests in the pharmaceutical industry. The updated declarations of interests policy should now allow a level of involvement better tailored to the interest profile of each expert,"
Noël Wathion, EMA Chief Policy Adviser

The revised policy, which was endorsed by the Management Board in March 2014, includes a number of measures which better take into account the nature of the declared interest before determining the length of time any restrictions may apply:

- an executive role, or a lead role in the development of a medicine during previous employment with a pharmaceutical company now results in a lifetime non-involvement with the concerned company or product;

- for the majority of declared interests a three-year cooling-off period is foreseen. Restrictions to involvement decrease over time and make a distinction between current interests and interests within the last three years;

- for some interests, such as financial interests, there continues to be no cooling-off period required when the interest is no longer present.

All EMA scientific committee members and experts were required to submit their updated declarations of interests by the end of January 2015.

The new policy entered into force on 30 January 2015.

1.10 | Other developments

Decision of the Civil Service Tribunal

On 13 November 2014 the European Union Civil Service Tribunal gave a judgment that annulled, on formal grounds, the 2011 decision of the Agency's Management Board to appoint Guido Rasi as Executive Director of the Agency.

EMA Deputy Executive Director Andreas Pott took over responsibility for the management and operations of the Agency. Although the judgement had no immediate effect on EMA's day-to-day operations, the sudden loss of its Executive Director had an impact on many of the Agency's strategic initiatives. The lack of leadership to help shape the future in medicine regulation was felt by partners and stakeholders, both inside and outside the European Union.

Preparations for the launch of a new recruitment procedure were instigated by the end of 2014 and are expected to result in an appointment of the new Executive Director in the second half of 2015.

16 Dec — Establishment of ad hoc Working Group on Veterinary Novel Therapies (ADVENT)

16 Dec — Interim report on review of Ebola treatments under development

19 Dec — First stem-cell therapy recommended for approval in EU

19 Dec — Publication of scientific advice on the impact on public health and animal health of the use of antibiotics in animals

19 Dec — Revised framework of EMA interaction with patients, consumers and their organisations adopted

19 Dec — Functional specifications of a clinical trial portal and a database endorsed

19 Dec — EMA anti-fraud strategy adopted

Move to 30 Churchill Place

In August 2014, the Agency moved to its new offices at 30 Churchill Place in Canary Wharf, London.

The new premises occupy a total surface area of approximately 23,500 square metres and include six floors of offices as well as two floors of conference rooms to host the meetings of the Agency's seven committees, its working parties, and other groups organised each year with thousands of scientific experts from across the EU as well as other Agency stakeholders. It also includes a dedicated working area for industry.

The building includes many environmentally-friendly features, such as photovoltaic (or solar) cells and a 'green' roof to enhance biodiversity. It achieves a new standard for environmental performance and energy efficiency in London and the design was awarded a Building Research Establishment Environmental Assessment Methodology (BREEAM) 'excellent' rating.

30 Jun — Construction and fit-out completed

1 Jul — Formal access to new premises

Jul-Aug — Staff moves from former premises to Churchill Place

8-10 Jul — First committee meeting takes place at 30 Churchill Place (CVMP)

1 Aug — Formal change of address for EMA

2 | Advancing public and animal health in 2014

This chapter intends to provide engaging thoughts on topics of major importance in medicines and health in 2014. The essays introduce high-profile actors of the Agency and its stakeholders, and present their views on how to promote innovation in the European Union for the benefit of public health and bringing the patients' voice to the heart of scientific innovations.

2.1 | Promoting innovation in the European Union for the benefit of public health

Sabine Jülicher, Head of Medicinal Products Unit, European Commission's Health & Food Safety Directorate-General
Melanie Carr, Head of EMA's Corporate Stakeholders Department

Sabine Jülicher (left), Melanie Carr (right)

EMA and the European Commission recognise that innovation in healthcare is important for the health and well-being of citizens and patients through access to novel products, services and treatments that bring added benefit over existing therapies.

Academia, research centres, public-private partnerships and small companies lie at the heart of innovation; however the development of innovative medicines can be complex, costly and time-consuming and includes risks, which makes it particularly difficult for smaller actors to bring innovative products to the market.

The role of regulators is to safeguard public health by acting as gatekeepers—ensuring the safety and efficacy of medicines to be authorised—and, at the same time, to contribute to public health by acting as enablers for those products that bring substantial benefit to patients.

We have a responsibility to enable sponsors to develop innovative and promising products, whether the development originates in academia or the private sector. To achieve this, we need a regulatory system easy to access and navigate and we need to facilitate development and reinforce predictability wherever possible for the benefit of patients.

EMA is actively engaging with sponsors through scientific advice to optimise development programmes, and it is encouraging to see that sponsors, including SMEs, are using this valuable tool more and more often. EMA also has a dedicated forum for emerging therapies, the Innovation Task Force, to facilitate the informal exchange of information and the provision of guidance early in the development process. Academia and SMEs are the primary target of this platform and they represented 80% of the meetings that took place in 2014.

EMA and the European Commission are committed to promoting early dialogue with all key stakeholders, including medicines developers in the first instance, but also patients and healthcare professionals. Maximising the effective use of existing EU regulatory tools, such as accelerated assessment, the conditional marketing authorisation and compassionate use, is also essential to support the early engine of innovation and ultimately accelerating access to promising new medicines.

How to promote innovation for the benefit of patients in the European Union is a topic that has been widely discussed at various levels and in a number of fora, including by Member States, EMA, the Commission and the Council of the EU. Responding to these developments the Commission established a group of experts from Member States and EMA on 'Safe and Timely Access of Medicines for Patients' (STAMP) to explore ways to optimise the use of existing regulatory tools.

Our aim is to enable development of innovative medicines, but, first and foremost, to allow these innovations to be translated into concrete benefits for patients.

Here again, early dialogue between all the actors who have a role in determining patient access, as well as the ongoing European cooperation on health technology assessment which aims to promote more consistent approaches to HTA across the EU, should promote quicker access to medicines for the benefit of patients.

2.2 | Bringing patients' voices to the heart of scientific innovations

Yann Le Cam, Chief Executive Officer, EURORDIS
Hans-Georg Eichler, EMA Senior Medical Officer

When thinking about how we can make the medicines development and assessment journey patient-centric, several key milestones come to mind.

Right at the beginning of the process, patients should have a role in steering the industry's attention and investment towards those areas where they need new therapeutic options. A very early dialogue between patients groups and medicines developers, involving regulators and payers, on areas of unmet medical needs will help ensure that the new medicines coming to market respond to patients' needs, that time and money are not wasted, and that patients are not recruited into clinical trials unnecessarily.

The second key element is about making clinical development patient-relevant. Patients should be able to engage in a constructive dialogue with sponsors on all aspects related to the design of a clinical trial, in order to achieve an optimal development from a patient's perspective. This includes the choice of endpoints, the techniques to be used to measure these endpoints in a meaningful way, informed consent, the selection of centres, the recruitment of patients, the interpretation of data and the dissemination of results.

In particular, patients should inform the clinical development so that outcomes that are meaningful to them are included – and monitored – these are known as Patient Relevant Outcomes. Patients should also have a role in reporting additional information stemming from their day-to-day experience of living with their condition – these are Patient Reported Outcomes. For example, during the development of the first treatment for Sanfilippo A syndrome, a seriously debilitating and life-threatening genetic disease which causes a wide range of symptoms, parents observed an impact of the investigational treatment on the quality of sleep of their child (and their own quality of sleep) and a reduction of the hyperactivity which was of significant importance for their quality of life and that of their family. This was not initially identified as a key outcome. Regulators also have a role in making sure that medicines developers take these aspects into account when developing their medicines.

When it comes to assessing the benefits and risks of a new medicine, only patients can legitimately determine how much risk or harm they are willing to accept for a given benefit. As experts in their disease, they know better than anyone what benefits would make a real difference to their quality of life and which trade-offs between the benefits and the risks/uncertainty are acceptable.

There are more and more tools and pilot projects that allow patients to provide their input, preferences and choices in a timely manner, including parallel scientific advice with health technology assessment bodies, scientific advisory groups, adaptive pathways pilot project, involvement of patients in the benefit risk assessment pilot project and the European Commission-funded SEED project on early dialogue.

Recognition of patients' input as credible and representative, relies on valuing both individual and collective experiences. Regulators and patients have to work together to put in place the right methodologies to incorporate patients' views in the regulatory process; and mechanisms should be explored to allow patients groups to provide evidence-based, qualitative and quantitative opinions in an independent manner, so that their views are accepted by all the relevant actors and can have a real impact on decision-making.

Scientific innovation cannot be disconnected from access to medicines. If a scientific innovation only translates into an innovative medicine being approved and not into societal advancement reaching all patients who need to benefit from it in the EU, we would be failing in our primary mission and objective. A lifetime engagement with patients, together with all stakeholders who have a role in determining patient access, integrated all along the medicine development pathway is needed to facilitate availability of innovative medicines for patients in Europe.

"A very early dialogue between patients groups and medicines developers, involving regulators and payers, on areas of unmet medical needs will help ensure that the new medicines coming to market respond to patients' needs" - *Yann Le Cam*

Hans-Georg Eichler (left), Yann Le Cam (right)

3 | Key figures and recommendations in 2014

This chapter presents the main outcomes of the Agency's activities, including the most notable recommendations for approval for human and veterinary medicines, the most important safety reviews and a selection of concept papers, reflection papers and guidelines. This chapter also presents the key figures of the Agency's activities in 2014 and highlights the major trends and changes observed over the past years.

Supporting research and development

Promoting innovation and research in medicine development and accelerating patients' access to safe and effective medicines are key priorities of the Agency. The approach is to initiate early interaction and dialogue with developers to facilitate the process and help companies to abide by all regulatory criteria. These supporting activities are carried out through the Agency's scientific committees and through collaboration with HTA bodies and international partners.

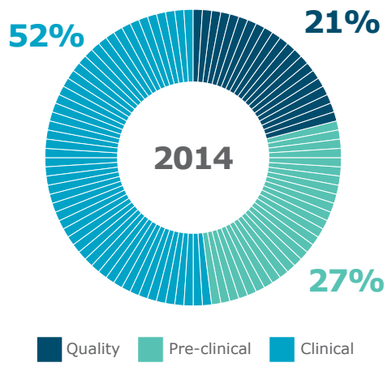
Scientific advice

The Agency provides scientific advice and protocol assistance to pharmaceutical companies and other sponsors during the research and development phase of medicinal products. Scientific advice is considered as one of the Agency's key tools to promote innovation and research and facilitate and improve earlier availability of medicinal products to patients and healthcare professionals.

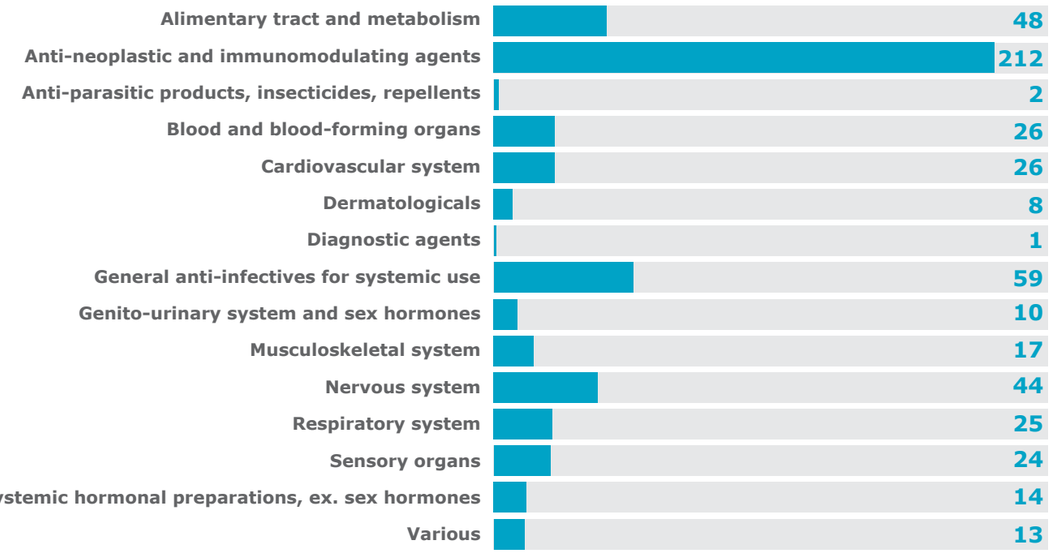
Highlights

- The overall number of scientific advice and protocol assistance requests rose by 16% compared to 2013.
- 11 applications for parallel scientific advice with HTA bodies were received compared to 7 in 2013.
- The number of requests for qualification opinions on the acceptability of using a new methodology during the development of a medicine also increased significantly from 15 in 2013 to 22 in 2014.

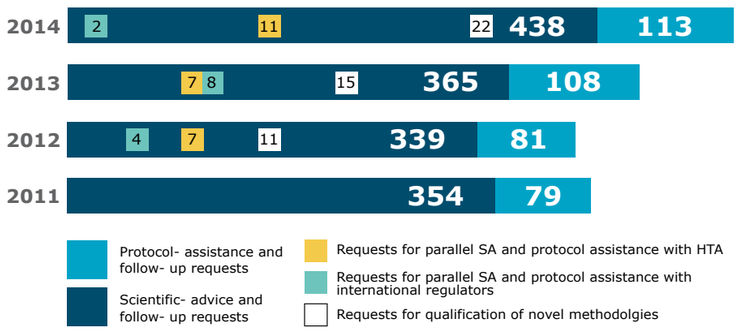
Scientific-advice requests by topic - 2014



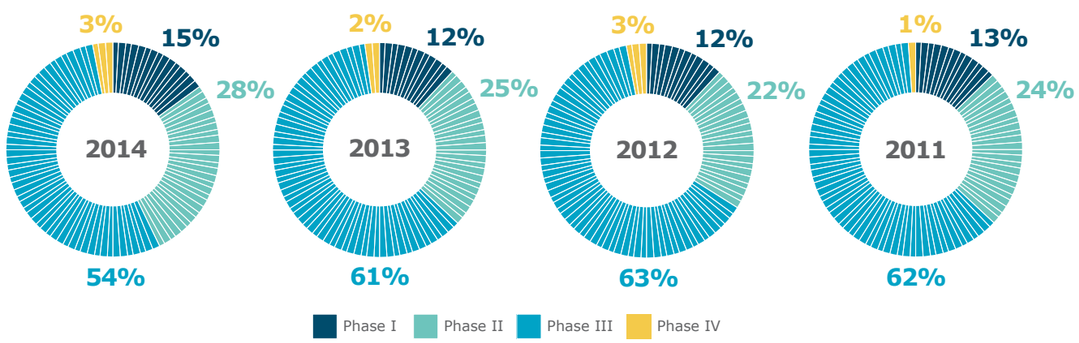
Scientific-advice requests by therapeutic area - 2014



Scientific-advice and protocol-assistance requests received



Clinical-trial phases of scientific advice requests



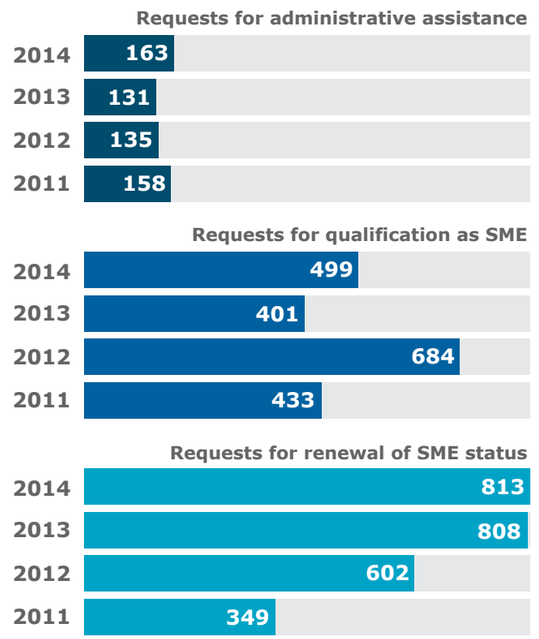
Support to small and medium-sized enterprises (SMEs)

SMEs are the driving force of the development of new medicinal products in Europe. The Agency promotes innovation and development of medicines by SMEs by giving active regulatory, financial and administrative support to these companies in the development of their medicines. The Agency's SME office provides advice and guidance, organises topical workshops and disseminates a dedicated newsletter to SMEs registered with EMA. These companies also have access to a number of fee incentives. Since 2014, EMA has expanded its range of incentives to include post-authorisation procedures.

Highlights

- 1301 active SMEs were registered with EMA at the end of 2014
- The SME office responded to 163 requests for direct assistance on administrative or regulatory aspects and organised 15 briefings to provide assistance to SMEs that are unfamiliar with the EU regulatory system.
- 7 applications for initial marketing authorisation were submitted by SMEs.
- 24% of all requests for scientific advice and protocol assistance received were submitted by SMEs.
- SMEs made 8 of the 22 requests for qualification of a new methodology to be used during the development of a medicine.

SME-related activities - requests received



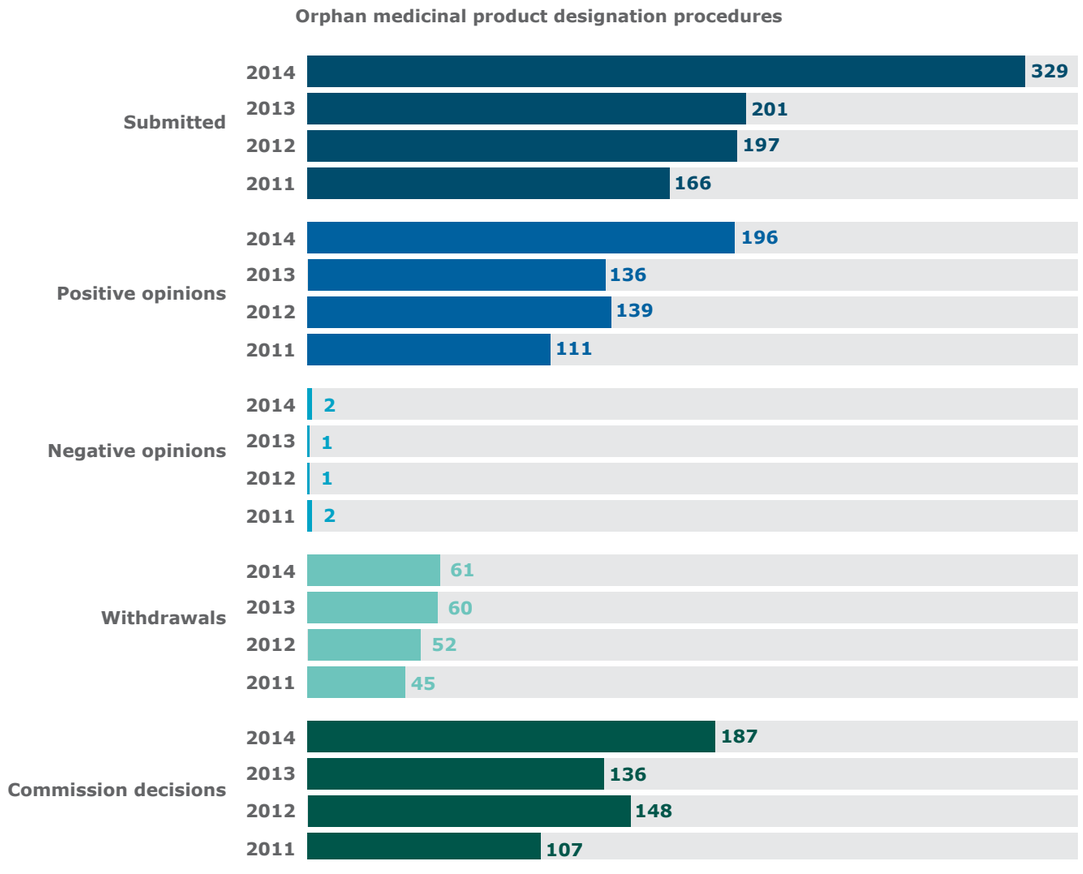
Orphan-medicine designation

Orphan medicines are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect not more than five in 10,000 people in the European Union. As it is often not profitable for companies to develop medicines for rare diseases, EMA provides incentives to the developers. The Agency's Committee for Orphan Medicinal Products (COMP) is responsible for reviewing orphan designation applications.

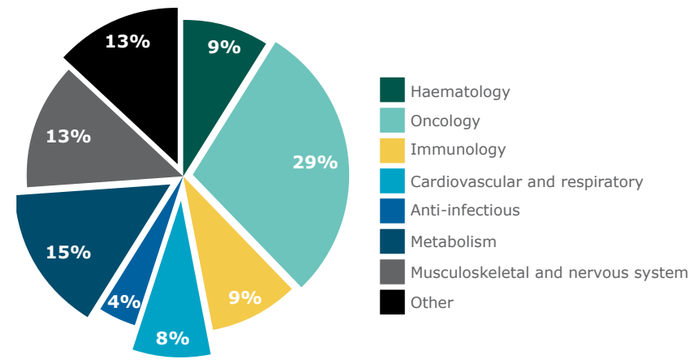
Highlights

- There was a 63% increase in the number of applications for orphan designations compared to the previous year.
- 2014 saw the highest number of orphan designations granted in a year since the EU Orphan Regulation came into force in 2000.
- 29% of opinions for orphan designation were for oncology products. This is the most represented therapeutic area.

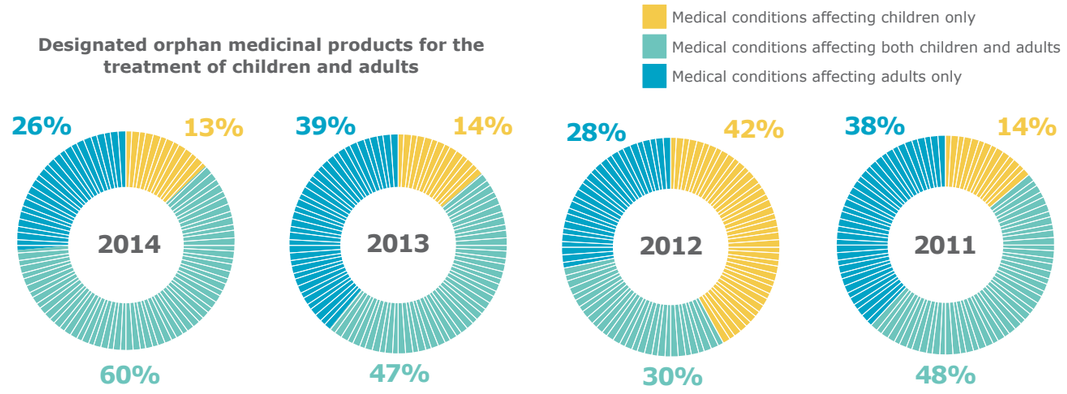
Orphan medicinal product designation procedures



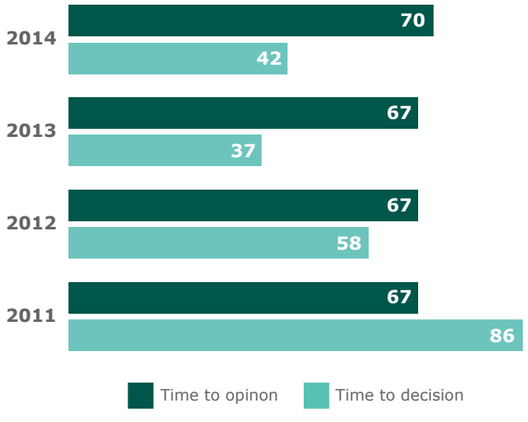
COMP opinions by therapeutic area - 2014



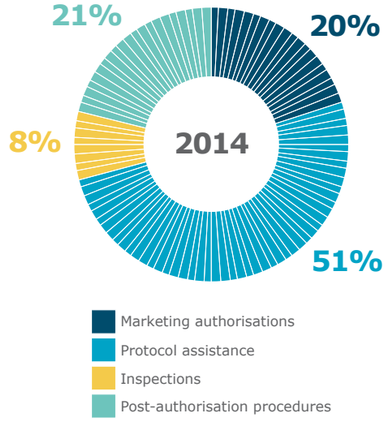
Designated orphan medicinal products for the treatment of children and adults



Average time for orphan designation procedures in days



Use of EU special contribution for orphan medicines - 2014



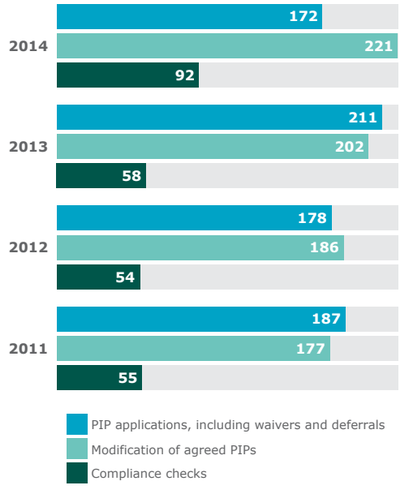
Medicines for children

This area includes the Agency's activities relating to the assessment, agreement, and verification of compliance with paediatric investigation plans (PIPs) and waivers by the Paediatric Committee (PDCO), and other activities mandated by the Paediatric Regulation such as the European Network of Paediatric Research Networks at EMA (Enpr-EMA).

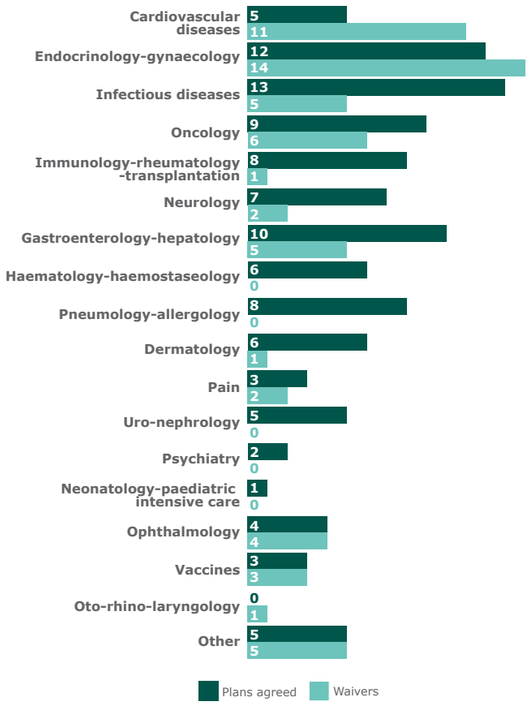
Highlights

- Following a peak in 2013, the number of first PIP/waiver applications was back to levels seen in 2012 and 2011.
- The number of modifications of agreed PIPs continues to grow at a steady rate, in line with the increasing number of initial PIPs now agreed (and not yet completed).
- The number of compliance checks increased by almost 60%, as most of the medicines submitted for marketing authorisation applications now have PIPs which require a check before the start of the assessment.

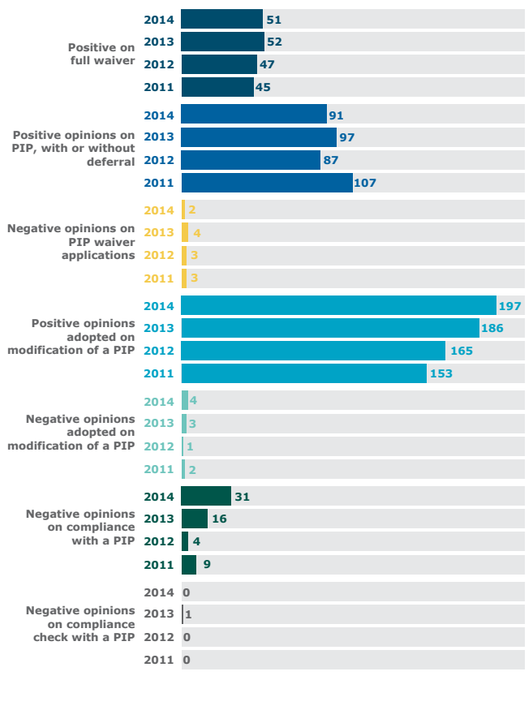
Paediatric and PIP applications received



Paediatric investigation plans agreed and waivers granted



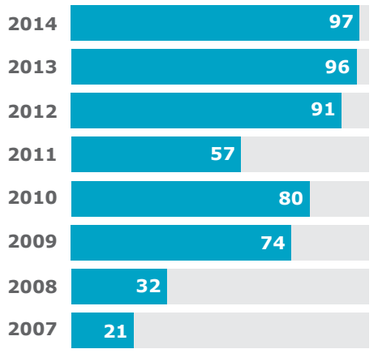
PDCO opinions by year



Paediatric use of centrally approved medicines - 2014

Impact of paediatric activities on centrally authorised medicines	total	of which PIP/ waiver-related
New paediatric indications for already authorised products	12	10
New products authorised including a paediatric indication	8	8
Paediatric use marketing authorisation granted	1	1
Other updates in the product information related to paediatric aspects	124	110
Product-specific waivers mentioned in the product information	26	26
Deferrals for completing paediatric studies mentioned in the product Information	27	27

Scientific advice procedures including paediatric questions



Assessment of paediatric studies by CHMP for centrally authorised products	2011	2012	2013	2014
Art 45 - Active substances assessed	55	0	0	2
Art 46 - Paediatric studies assessed	24	53	80	96

European Network of Paediatric Research Networks at EMA

Enpr-EMA is now fully operational. Three new networks joined in 2014, bringing the number of registered networks so far to a total of 44. Information about Enpr-EMA members is available in a fully searchable database established by the Agency in 2014.

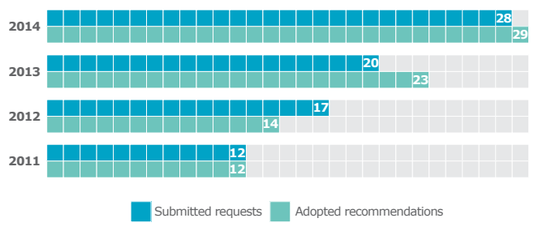
Advanced-therapy medicinal products

Advanced-therapy medicinal products (ATMPs) are made from genes, cells and engineered tissues. They may offer ground-breaking new treatment opportunities for many diseases and injuries. The Committee for Advanced Therapies (CAT) is the EMA committee responsible for assessing the quality, safety and efficacy of ATMPs. It prepares a draft opinion on each ATMP application before the CHMP adopts a final opinion for the medicine concerned. The CAT also participates in Agency procedures for the certification of quality and non-clinical data for small and medium-sized enterprises developing ATMPs, and for the provision of scientific recommendations on the classification of ATMPs.

Highlights

- There was a 26% increase in the number of recommendations on the classification of ATMPs.
- Two applications for marketing authorisation for ATMPs were received.
- Quality/non-clinical data for two ATMPs developed by SMEs were certified by the CAT.

Scientific recommendations on advanced therapy classification



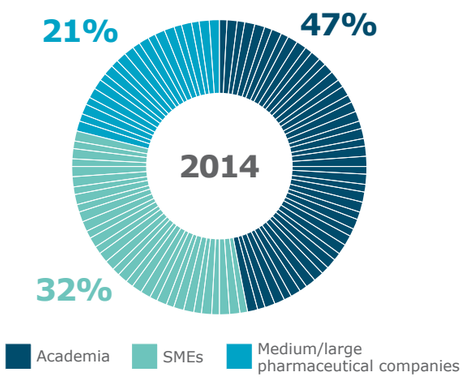
Innovation Task Force

The Innovation Task Force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. It provides a forum for early dialogue with applicants, in particular SMEs and academic sponsors, to proactively identify scientific, legal and regulatory issues related to emerging therapies and technologies.

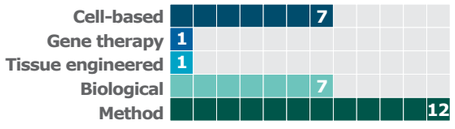
Highlights

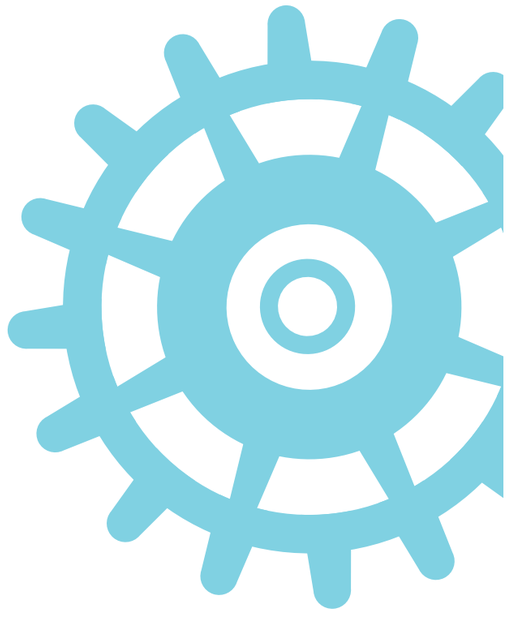
- 28 requests for early dialogue with the Innovation Task Force were received in 2014, a similar level to that in 2013.
- Almost one in two requests originated from academic sponsors.
- One in three requests concerned advanced therapy medicinal products (ATMPs).

ITF briefing meetings by type of requester - 2014



ITF briefing meetings by type of product - 2014





Key scientific guidelines

The Agency develops scientific guidelines to provide advice to applicants or marketing-authorisation holders, competent authorities and/or other interested parties on the best or the most appropriate way to fulfil the requirements laid down in the EU pharmaceutical legislation.

In 2014, the Agency developed new guidelines and revised existing guidance to reflect the latest scientific developments and experience gained in a number of areas. A selection is presented below.

Topic	Content
Biosimilars	A revised overarching guideline on biosimilars. The main change brought by this new guidance is the possibility for medicines developers to use a comparator authorised outside the European Economic Area (EEA) during the clinical investigation of a biosimilar. This new concept is expected to facilitate the global development of biosimilars and to avoid unnecessary repetition of clinical trials.
Guidance on parallel scientific advice with health technology assessment bodies	A best practice guidance on parallel scientific advice with health technology assessment bodies for public consultation. The draft guidance sets out the different phases of the process for EMA-HTA parallel scientific advice and highlights ideal timelines and actions for all parties, including HTA bodies, EMA and applicants undertaking a parallel advice procedure. It is intended to facilitate early dialogue between regulators, HTA bodies and medicines developers.
Use of pharmacogenomics in pharmacovigilance activities	A draft guideline for public consultation which addresses how pharmacogenomics can support pharmacovigilance activities and help optimise the use of medicines. The guideline describes how pharmacogenomics can be implemented in risk-management plans, risk-minimisation measures, signal detection and the benefit-risk evaluation of medicines with an established link between genetic features and efficacy and safety. The guideline also describes different types of genomic biomarkers that can be relevant for pharmacovigilance and provides examples.
Classification of advanced-therapy medicinal products	A revised reflection paper for public consultation on the classification of ATMPs to reflect the CAT's current position on how ATMPs should be classified. Based on examples, the revised paper clarifies the cases in which medicines can be classified as ATMPs and those in which they cannot. It also discusses borderline cases and areas where scientific knowledge is limited or evolving rapidly.
Inclusion of pharmacogenetic studies in revised ENCePP guideline	A revised guide on methodological standards in pharmacoepidemiology updated to include a new chapter on the design and analysis of pharmacogenetic studies. This new chapter provides an overview of all relevant methodological guidance for the conduct of pharmacogenetic studies, from the identification of genetic variants through to study design, data collection, analysis and reporting. The guidance was developed by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is coordinated by EMA.
Annual strain change of seasonal influenza vaccines	Updated guidance for annual strain change of seasonal influenza vaccines. The update ensures that EU requirements for the annual strain change reflect current knowledge, and are consistent with the approach taken by other regulatory authorities globally. It introduces an improved system that allows strengthened and sustainable monitoring of an influenza vaccine's performance over the years in a real-life setting.
New overarching guideline on influenza vaccines	The second and third module of a new overarching guideline for public consultation on the development of influenza vaccines. With these publications, EMA is now close to finalising the establishment of a revised regulatory framework which aims to facilitate the prompt assessment of new influenza vaccines.
Good pharmacoVigilance Practice (GVP)	GVP Module III – Pharmacovigilance inspections, GVP Module VI – Management and reporting of adverse reactions to medicinal products, GVP Module XVI– Risk minimisation measures - Selection of tools and effectiveness indicators and GVP Module V – Risk management systems were updated.

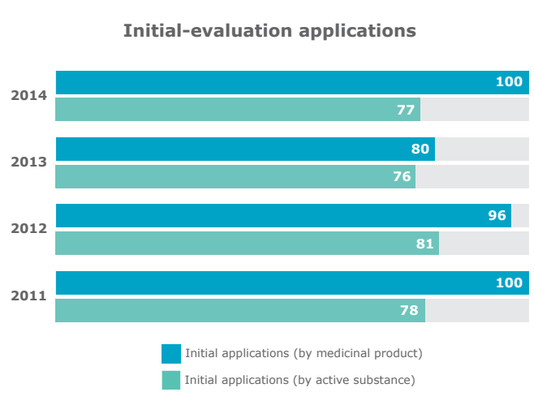
Recommendations for authorisation

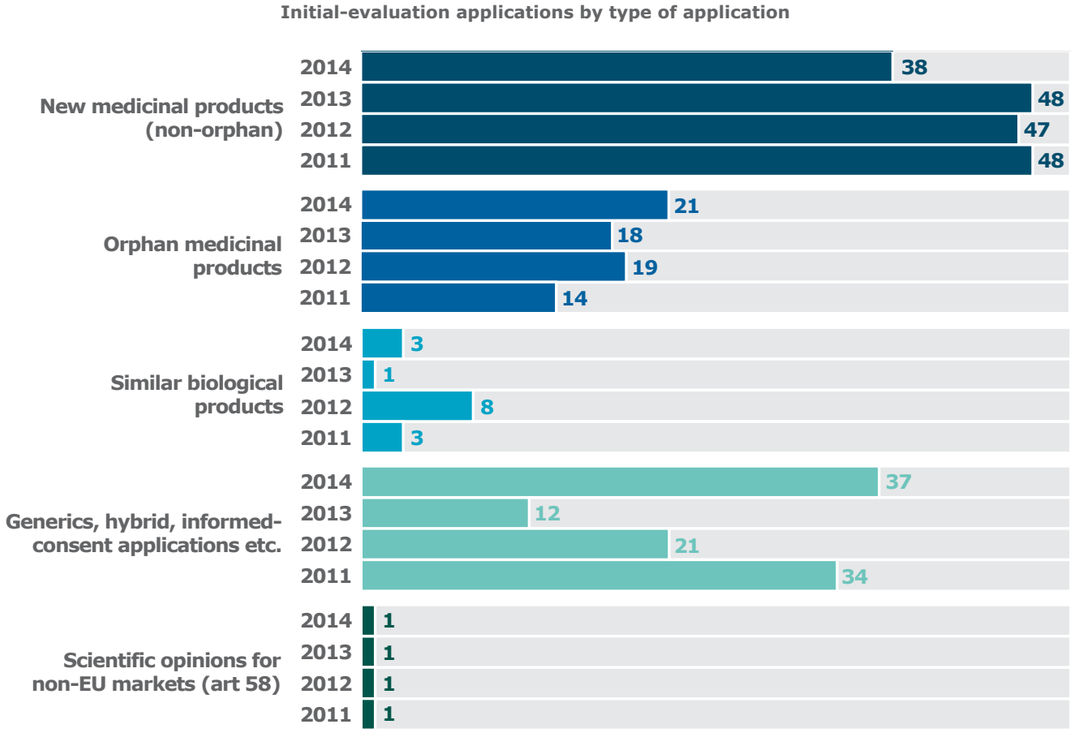
Applications for initial evaluation

Initial evaluation covers activities relating to the processing of marketing-authorisation applications for medicines, from pre-submission discussion with future applicants, through evaluation by the CHMP, to the granting of a marketing authorisation by the European Commission.

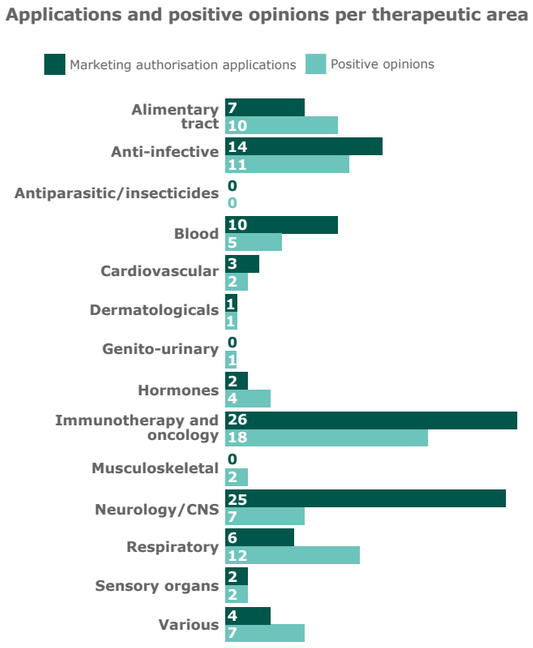
Highlights

- There was a slight increase in the overall number of applications for initial evaluation received in 2014 compared to 2013.
- The number of applications for orphan designated medicines increased slightly.
- 2014 saw a rise in the number of applications for generic medicines and hybrid applications.
- One application for the initial evaluation of an ATMP was received.
- One application for scientific opinion, in collaboration with the World Health Organization, for a medicine to be used exclusively in non-EU markets was received.



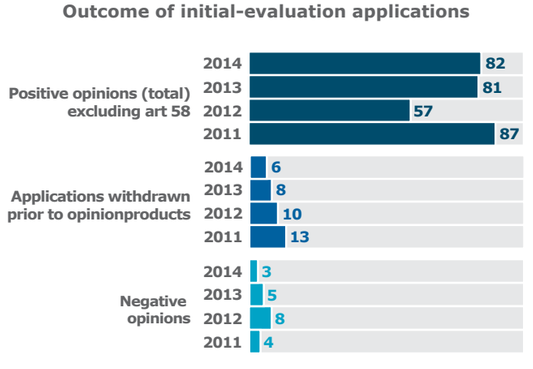


Outcome of initial evaluation

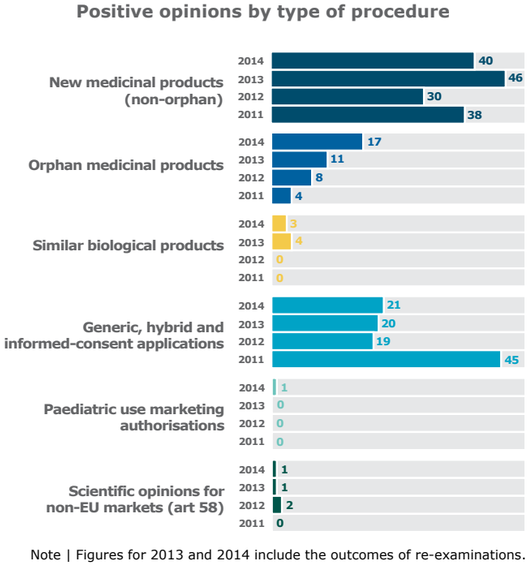


Highlights

- 82 medicines for human use were recommended for marketing authorisation in 2014 – one of which obtained a positive opinion after a re-examination procedure.
- One in two medicines that were granted a positive opinion contained a new active substance.
- Seven positive opinions were granted after an accelerated assessment.
- 70% of applicants received scientific advice during the development phase of their medicine and this figure rises to 80% when it comes to innovative medicines.
- 17 orphan designated medicines were recommended for marketing authorisation – the highest number in a year. Three of these medicines had their applications withdrawn by the sponsor prior to a final decision by the European Commission.
- 2014 saw the second recommendation for a paediatric-use marketing authorisation (PUMA). The first one was in 2011.
- One medicine was granted a positive scientific opinion for use exclusively in non-EU markets (not included in the 82 medicines).



Note | Figures for 2013 and 2014 include the outcomes of re-examinations. Article 58 applications are not included.



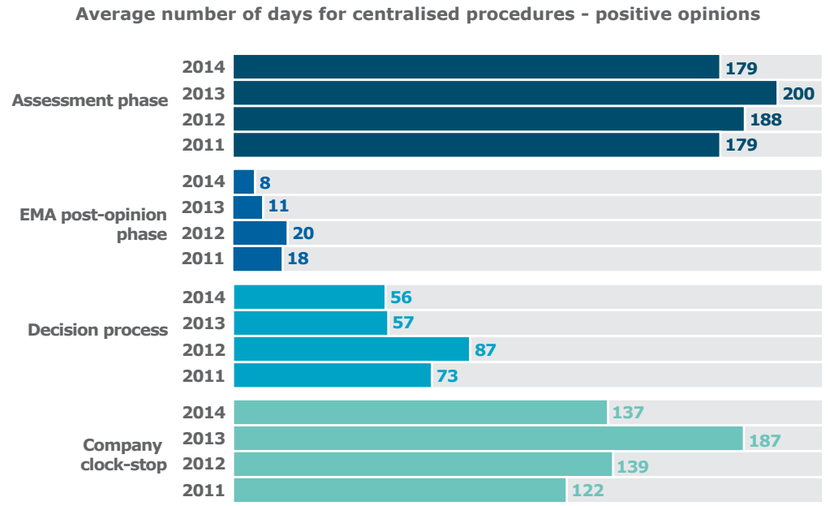
Note | Figures for 2013 and 2014 include the outcomes of re-examinations.

Recommendations of new medicines - Highlights of 2014

Medicine	What is it used for?	
Abasaglar/Abasria (insulin glargine)	Treatment of diabetes mellitus. Abasaglar is the first biosimilar insulin to be recommended for marketing authorisation in the EU.	
Cerdelga (eliglustat)	Treatment of adults with Gaucher disease type 1, a rare, debilitating and life-threatening genetic disease.	O
Daklinza (daclatasvir)	Used in combination with other medicines to treat chronic (long term) hepatitis C in adults.	A
Entyvio (vedolizumab)	Treatment of adult patients with ulcerative colitis or Crohn's disease.	
Exviera (dasabuvir)	Treatment of chronic hepatitis C virus in adults in combination with other medicines.	A
Gazyvaro (obinutuzumab)	Used with chlorambucil (another cancer medicine) to treat adult patients with previously untreated chronic lymphocytic leukaemia.	O
Harvoni (sofosbuvir / ledipasvir)	Treatment of chronic hepatitis C in adults.	A
Hemoprostol (misoprostol)	Treatment of post-partum haemorrhage due to uterine atony in situations where intravenous oxytocin is not available. Hemoprostol is intended exclusively for markets outside the European Union.	
Holoclar (*ex-vivo* expanded autologous human corneal epithelial cells containing stem cells)	Treatment for moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns to the eye in adults. Holoclar is the first advanced-therapy medicinal product (ATMP) containing stem cells to be recommended for approval in the EU.	O, C
Imbruvica (ibrutinib)	Treatment of two types of blood cancers: chronic lymphocytic leukaemia and mantle cell lymphoma.	O
Ketoconazole HRA (ketoconazole)	Treatment of Cushing's syndrome, a rare hormonal disorder.	O, A
Lynparza (olaparib)	'Maintenance' treatment of adult patients with high grade serous epithelial ovarian cancer, including cancer of the fallopian tubes and cancer of the peritoneum. Lynparza is the first medicine for ovarian cancer specifically targeting forms of the disease carrying a mutation of the BRCA gene.	O
Mekinist (trametinib)	Treatment of adults with melanoma (a type of skin cancer). Mekinist is the first MEK inhibitor to be recommended for marketing authorisation in the EU.	O
Mysimba (naltrexone / bupropion)	Weight management of overweight and obese adults. Mysimba is recommended for use in addition to reduced-calorie diet and physical activity.	
Ofev (nintedanib)	Treatment of idiopathic pulmonary fibrosis (IPF).	O, A
Scenesse (afamelanotide)	Prevention of phototoxicity in adults with erythropoietic protoporphyria (EPP), a rare genetic disease which causes intolerance to light.	O, E
Sylvant (siltuximab)	Treatment of multicentric Castleman's disease in adults who tested negative for the human immunodeficiency virus and the human herpesvirus-8 (HHV-8).	O, A
Translarna (ataluren)	Treatment of patients aged 5 years and older with Duchenne muscular dystrophy who are able to walk.	O, C
Viekirax (ombitasvir / paritaprevir / ritonavir)	Treatment of chronic hepatitis C in adults in combination with other medicines for chronic hepatitis C.	A
Zydelig (idelalisib)	Treatment of two types of blood cancer: chronic lymphocytic leukaemia and follicular lymphoma.	O

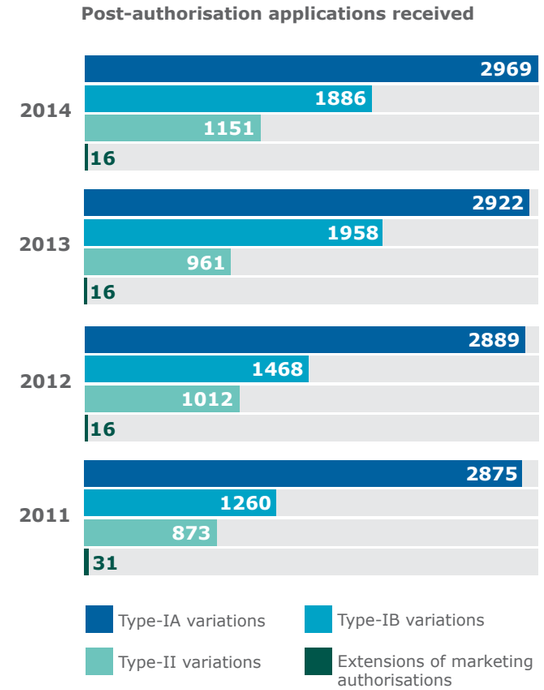
O: orphan designation | **A**: accelerated assessment | **C**: conditional approval | **E**: exceptional circumstances

Average assessment time



Post-authorisation activities (or variations/ changes to marketing authorisation)

Post-authorisation activities relate to variations, extensions of marketing authorisations and transfers of marketing authorisations.



Change in classification status

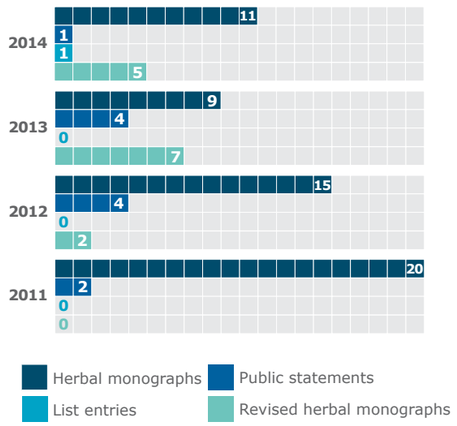
EllaOne (ulipristal acetate): the classification of the emergency contraceptive EllaOne was changed from prescription to non-prescription. This means that the medicine could be obtained without a prescription in the EU.

Herbal medicines

The Agency's Committee on Herbal Medicinal Products (HMPC) is responsible for preparing the Agency's opinions on herbal medicines. Aimed at promoting an increasingly harmonised process for licensing and information on herbal substances across the EU, the HMPC establishes European Union monographs (previously known as Community herbal monographs) for traditional and well-established herbal medicines, as well as a draft list of herbal substances, preparations and combinations thereof for use in traditional herbal medicines.

Highlights
- The assessment of 12 new herbal substances was completed in 2014, leading to the publication of 11 final European Union monographs and one final public statement.
- 12 draft monographs were released for public consultation.
- Five monographs were revised as part of a project aimed at systematically revising all adopted monographs started in 2012.

Herbal monographs and list of herbal substances, preparations and combinations thereof



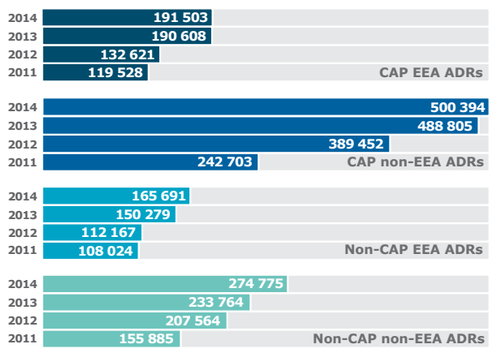
Safety monitoring activities

EudraVigilance – Adverse Drug Reactions

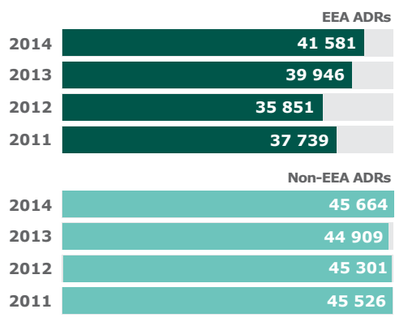
The Agency's main responsibilities in the safety monitoring of medicines include the coordination of the European pharmacovigilance system, the provision of information on the safe and effective use of medicines and the operation and maintenance of the EudraVigilance system. Both EMA and medicines regulatory authorities in Member States are required by legislation to continuously monitor the adverse drug reaction (ADR) data reported to EudraVigilance to determine whether there are new risks or known risks and whether those risks have an impact on the overall benefit-risk balance of a medicine.

Highlights
- More than 1.1 million ADR reports were entered into EudraVigilance in 2014, a 6.5% increase compared to 2013.
- Almost 38,000 reports originated from patients in the European Economic Area (EEA), a similar level to 2013.
- Increases in ADRs reports received were observed in particular in relation to non-centrally-authorised products, whether the reports came from countries of the EEA or from outside this area.
- The general increase in ADRs received over the years indicates an increased commitment of stakeholders to provide all available data.

EEA and non-EEA ADR reports received



ADR reports concerning investigational medicinal products for human use



Signal detection

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine element of pharmacovigilance and is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary. This usually takes the form of updates of the summary of product characteristics and the package leaflet.

Signals reviewed by EMA

Highlights
- In 2014, 2,030 potential signals were reviewed by EMA.
- Among these 2,030 potential signals, 34 were validated by EMA for further evaluation. In addition, 56 signals were detected and validated by Member States.
- Together, these 90 signals were subsequently prioritised and analysed by the PRAC.
- Approximately 40% of signals assessed by PRAC resulted in a recommendation for an update of the product information, including distribution of a Direct Healthcare Professional Communication (DHPC) on seven occasions to highlight important new safety information to prescribers.
- Approximately a third of these 90 signals were still under review by the PRAC at the end of 2014 as further data were required.
- The assessment of 18 signals was closed and routine pharmacovigilance recommended as follow-up.
- One signal resulted in a recommendation to update the Risk Management Plan (RMP), one signal will be further assessed through a Post-Authorisation Safety Study (PASS) and two signals were evaluated in a referral procedure.

Periodic safety update reports (PSURs)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at regular, predefined time points following a medicine's authorisation. PSURs summarise data on the benefits and risks of a medicine and take into consideration all studies carried out with this medicine (in authorised and unauthorised indications). In 2013, the Agency started the single assessment (PSUSAs) of PSURs, a deliverable of the 2010 pharmacovigilance legislation. The Agency is responsible for the procedures supporting the analysis of all reports on medicines that contain a particular active substance, on all types of marketing authorisations and on medicines authorised in more than one Member State.

Highlights
- 471 recommendations were issued by the PRAC based on the assessment of PSURs in 2014.
- Among these, 45 PSURs procedures included both centrally and nationally authorised medicines and were assessed together, as part of single assessments, because they contain the same active substance.

PSURs and PSUSAs finalised	2013	2014
PSURs stand-alone (CAPs only)	430	426
PSURs single assessment (CAPs and NAPs)	6	45
Total	**436**	**471**

Outcomes of PSURs and PSUSAs	2013	2014
Maintenance	360	389
CHMP variation	76	88
Suspension	0	0
Revocation	0	0
Total	**436**	**471**

Post-authorisation safety studies (PASS)

A PASS is a study that is carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. The European Medicines Agency's PRAC is responsible for assessing the protocols of imposed PASSs and their results.

	2014
PASS procedures (imposed)	32
PASS procedures (non-imposed)	3
PASS protocols	35
PASS interim reports	3
PASS final reports	5

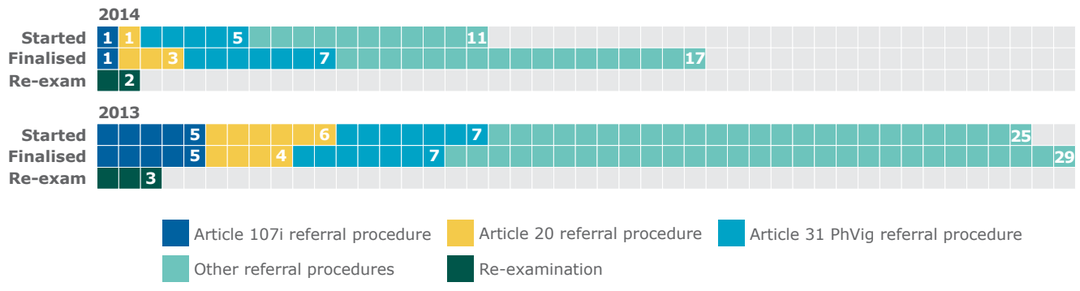
Referral procedures

Referral procedures are used to resolve concerns over the safety or benefit-risk balance of a medicine, or disagreements among Member States on the use of a medicine. In a referral, the Agency is requested to conduct, on behalf of the European Union, a scientific assessment of a particular medicine or class of medicines, to agree on a recommendation for the harmonised position across the EU. A recommendation subsequently results in a legally binding decision throughout the EU issued by the European Commission. In the case of nationally authorised products where there is a consensus from the CMDh, the decision is not submitted to the Commission.

Highlights

- 18 referral procedures started in 2014.
- Among these, seven were pharmacovigilance-related (under Articles 31, 20 and 107i).
- The remaining 11 referral procedures were initiated to address either efficacy or quality concerns with certain medicines, or a need for EU-wide harmonisation of product information, or were triggered by differences between the Member States in the mutual-recognition and decentralised procedures.

Arbitrations and referrals for human medicines



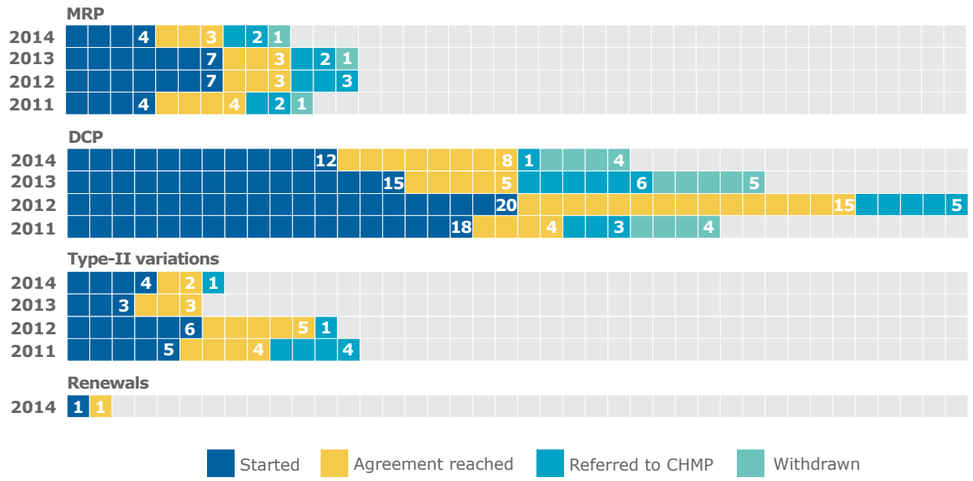
The Agency carried out a number of reviews in 2014.
Key recommendations are presented in the table below:

Medicine	Recommendation
Bromocriptine-containing medicines	Restrictions of the use of these medicines for preventing or stopping breast milk production. They should only be used orally in strengths up to 2.5mg to inhibit lactation when there are compelling medical reasons.
Caustinerf arsenical, Yranicid arsenical	Revocation of the marketing authorisations of these dental pastes due to concerns over the risk of genotoxic effects and cell death in tissues around the teeth.
Corlentor / Procoralan (ivabradine)	New warnings aimed at reducing the risk of heart problems, including heart attack and excessively low heart rate, in patients taking this medicine for angina. Ivabradine must not be prescribed together with medicines that reduce the heart rate (verapamil or diltiazem), and patients should be monitored for atrial fibrillation.
Diacerein-containing medicines	Restrictions to limit risks of severe diarrhoea and effects on the liver.
Domperidone-containing medicines	Restrictions of the use of the product to relieve of symptoms of nausea and vomiting, due to effects on the heart. Dose and length of treatment should be restricted and adjusted carefully to the patient's weight (in children). Products supplying a dose of 20 mg by mouth, and suppositories of 10 or 60 mg were withdrawn. Combination products with cinnarizine (an antihistamine) were also withdrawn.
Emergency contraceptives	Levonorgestrel and ulipristal remain suitable emergency contraceptives for all women, regardless of bodyweight. Data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight.
Iclusig (ponatinib)	Iclusig (ponatinib) Strengthened warnings aimed at minimising risk of blood clots and blockages in the arteries.
Linoladiol N and Linoladiol HN	Restrictions to the use. Linoladiol N cream is only to be used inside the vagina for treating postmenopausal women with vaginal atrophy due to a lack of the hormone estrogen, while Linoladiol HN cream is for postmenopausal women with mild, inflammatory skin conditions around the genital area.
Methysergide-containing medicines	Restriction of the use of the product to preventing severe intractable migraines and cluster headaches when standard medicines have failed, due to the risk of fibrosis.
Methadone medicinal products for oral use containing povidone	Suspension of the marketing authorisation of methadone oral solutions containing high molecular weight povidone because of the potential harm that could derive from misuse. Methadone tablets containing low molecular weight povidone should remain on the market with changes to the product information.
Polymyxin-containing medicines	Changes to the product information to ensure safe use of these antibiotics in the treatment of serious infections resistant to standard antibiotics.
Protelos / Osseor (strontium ranelate)	Further restrictions of use for women with osteoporosis who have heart or circulatory problems.
Renin-angiotensin system (RAS)	Restriction on combining different classes of medicines that act on the renin-angiotensin system (RAS), a hormone system that controls blood pressure and the volume of fluids in the body. This was due to an increased risk of hyperkalaemia, kidney damage or low blood pressure of the combination compared with using one class alone.
Testosterone-containing medicines	Update to product information and warnings that the lack of testosterone should be confirmed by signs, symptoms and laboratory tests before treating men with these medicines. No consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone.
Valproate medicines	Strengthened warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. Valproate should not be prescribed for epilepsy or bipolar disorder in women or in girls unless other treatments are ineffective or not tolerated. Valproate must not be used in the prevention of migraine in pregnant women.
Zolpidem-containing medicines	New warnings and a change to the posology and method of administration to minimise the known risk of reduced mental alertness and impaired ability to drive and use machinery the morning after use.

Mutual-recognition and decentralised procedures

The Agency provides secretarial support to the Co-ordination Group for Mutual-recognition and Decentralised Procedures – Human (CMDh) and its working parties, in accordance with the approved rules of procedure. The work of the CMDh is essential for the effective authorisation and maintenance of more than 90% of medicines entering the EU market. The mutual-recognition procedure (MRP) and the decentralised procedure (DCP) are the primary authorisation routes for generic applications within the EU.

Applications referred to CMDh



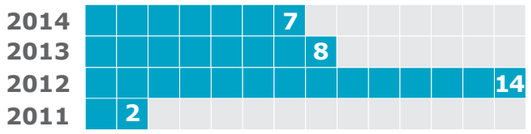
Work sharing for assessment of paediatric studies for nationally authorised products (or authorisation through DCPs/MRPs)

	2011		2012		2013		2014	
	submitted	reports published	submitted	reports published	submitted	reports published	submitted	reports published
Art 45* active substances	55	27	42	45	23	41	18	25
Art 46** paediatric substances	34	17	45	12	29	23	51	15

*Article 45 of the Paediatric Regulation requires marketing authorisation holders to submit any study in children, done or initiated with the authorised product before 2007, to EMA or the national competent authority, for evaluation and assessment. The CMDh coordinates this assessment, in subsequent batches, for approximately one thousand non-centralised products.

**Article 46 of the Paediatric Regulation requires marketing authorisation holders to submit any new study in children, which is sponsored by them, to EMA or national competent authority within 6 months of the completion of the study (regardless of whether the study is included in an agreed paediatric investigation plan or not).

Recommendations related to revised Variations Regulation



Activities supporting research and development

The Agency provides pre-authorisation support to medicines developers to promote innovation and research in order to facilitate the availability of safe and effective veterinary medicinal products. This is achieved by a number of activities and incentives offered to companies prior to submitting the application for marketing authorisation. These tools promote interaction and dialogue with the Agency from the very early stages of medicine development.

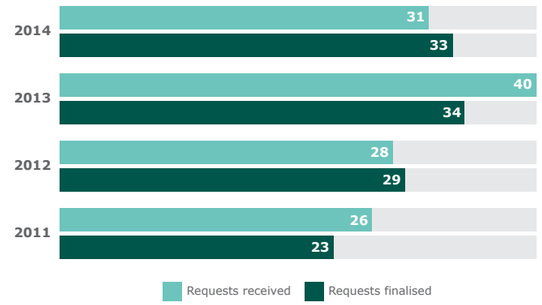
Scientific advice

Scientific advice is provided on any aspect of research and development relating to the quality, safety or efficacy of medicines for veterinary use, and to the establishment of maximum residue limits. Scientific advice is a means to facilitate and improve early availability of veterinary medicines.

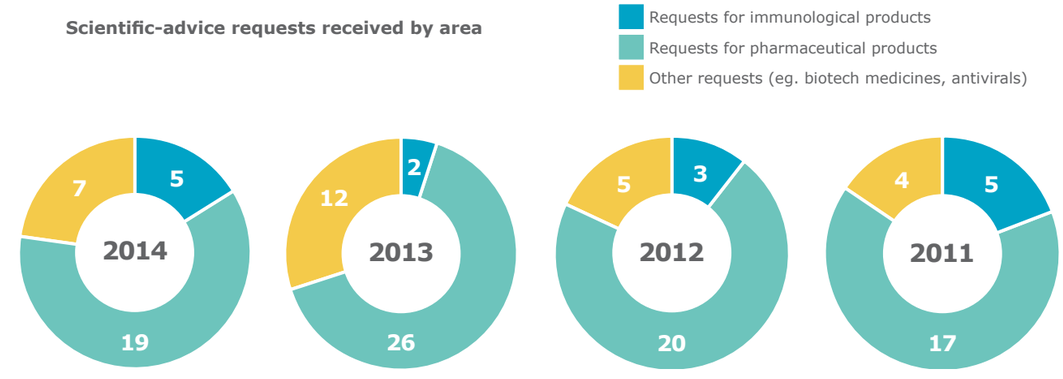
Highlights

- After a record number of requests for scientific advice received in 2013 (40), the number of requests received in 2014 was still high compared with previous years.

Scientific-advice requests received and finalised



Scientific-advice requests received by area



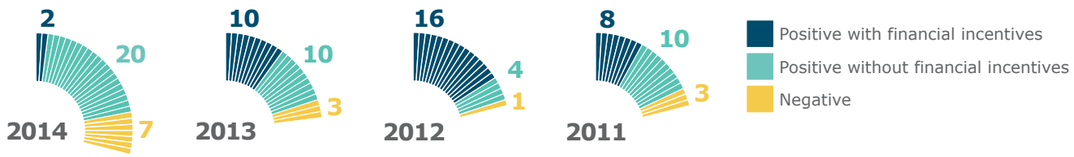
Minor Use Minor Species

The Agency's Minor Use Minor Species (MUMS) / limited market policy adopted in 2009 aims to assist companies with the submission of applications for products for limited markets. The goal is to stimulate development of new veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment.

Highlights

- 2014 saw the highest number of requests in a year for the classification of veterinary medicines intended for MUMS/limited market.
- Among the 29 requests, 22 were confirmed as MUMS, and benefited from reduced data requirements, two of which were also granted financial incentives such as access to free scientific advice and reduced application fees.
- The MUMS policy was revised in 2013/2014 to limit financial incentives to products indicated for food producing animals. This is in line with the direction from the EMA Management Board that publicly-funded support should be used in promoting the development of this class of product.

Outcomes of MUMS/limited market applications finalised



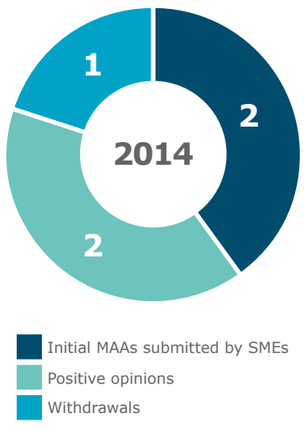
Support to small and medium-sized enterprises

The Agency put the SME initiative in place in December 2005 to promote innovation and development of medicines by SMEs. This initiative provides active regulatory, financial and administrative support to small and medium-sized companies in the development of their medicines. The support takes the form of individual guidance and more general advice through the SME user guide, topical workshops and a dedicated newsletter.

Highlights

- A total of 1301 SME companies were registered with EMA at the end of 2014.
- Among these, 5% are veterinary companies and 6% are companies developing products for both human and veterinary use.
- SMEs submitted two of the 12 applications for marketing authorisation for veterinary medicines received in 2014.
- They accounted for approximately one third of all requests for scientific advice received in the veterinary area.

SMEs and marketing authorisation applications



Innovation Task Force

The Innovation Task Force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. It provides a forum for early dialogue with applicants, in particular SMEs, to proactively identify scientific, legal and regulatory issues related with emerging therapies and technologies.

The scope of the European Medicines Agency's Innovation Task Force, which provides support to medicines innovation in EU, was extended to cover support to veterinary medicines during the early stages of their development in 2013.

Two ITF briefing meetings in relation to the development of veterinary medicines were held in 2014.

Key scientific guidelines

A number of guidelines and guidance documents were adopted for consultation or published during 2014. They relate to the quality, safety, environmental risk assessment and efficacy of medicines for veterinary use. They also include guidance documents for antimicrobial medicines in order to reduce as much as possible the risk of the development of antimicrobial resistance in animals and humans. Guidance documents from 2014 include:

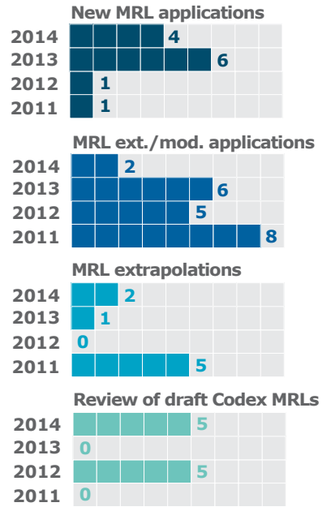
Guidelines and Working Documents	Description
Reflection paper on the use of pleuromutilins in food producing animals in the European Union: development of resistance and impact on human and animal health	This revised reflection paper has been developed to summarise current knowledge on resistance development related to this class of antibiotics and the potential impact of this resistance on animal and human health as detailed in a previous concept paper on the topic.
Concept paper proposing the development of a reflection paper on the use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health	This concept paper, released for public consultation, addresses the impact of use of aminoglycoside antibiotics in animals on public and animal health.
Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (NSAID)	The guideline was developed to provide clearer information and guidance on trial design and conduct, as well as on reporting standards for efficacy studies submitted in support of an application to authorise a new NSAID, or to vary the indications of an already authorised NSAID.
Draft reflection paper on anthelmintic resistance	This draft reflection paper, released for public consultation, has been developed to address the current views on issues in relation to anthelmintic resistance.
Draft guideline on demonstration of palatability of veterinary medicinal products. Adopted for consultation, July 2014	The draft guideline was developed to provide recommendations regarding the design, conduct, and evaluation of studies for the demonstration of palatability of veterinary medicinal products intended for oral individual or group animal treatment. It was released for public consultation.
Concept paper recommending the drafting of a new guideline on data requirements for the prevention of transmission of canine and feline vector-borne diseases	The draft guideline, released for public consultation, aims to provide guidance on the specific study design to demonstrate the prevention of transmission of vector-borne diseases, which is not available at present.
Revised guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicines	The guideline outlines the criteria for PBT/vPvB assessment for veterinary medicinal products and explains how these, under the guidance developed for industrial chemicals under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation, should be interpreted for veterinary medicinal products and what testing strategy should be followed to complete the PBT assessment as well as the approach for the assessment of veterinary medicinal products containing a PBT substance.
Guideline on data requirements for changes to the strain composition of authorised equine influenza vaccines in line with the OIE requirements	The guideline provides guidance on the data requirements to support modifications to authorised, equine influenza vaccines based on recommendations from the OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition.
Draft reflection paper on the replacement of cell lines used for the production of immunological veterinary medicinal products	This draft reflection paper, released for public consultation, has been developed to outline the data requirements for marketing authorisation holders to replace the cell line as host system for production of immunological veterinary medicinal products without significant changes to the production process and maintaining finished product specifications.
Draft reflection paper on the use of heat treatment to inactivate retrovirus RD114 in live immunological veterinary medicinal products	This draft reflection paper has been developed to outline the data requirements for marketing authorisation holders to introduce a heat treatment to inactivate retroviruses in the active substance for the production of live viral vaccines for immunological veterinary medicinal products and to show the absence of negative impact of this treatment on the immunological veterinary medicinal product.
Concept paper proposing for the revision of the CVMP guidelines on data requirements for veterinary medicinal products for minor use minor species (MUMS)	This concept paper, released for public consultation, outlines the intention for the review of the current MUMS guidelines in view of experience gained and also taking into account the latest revised policy, so that the available guidance is in line with current knowledge and best practice. In addition, further clarification to applicants in terms of applicability to particular products is intended.

Maximum residue limits

The use of veterinary medicines in food-producing animals may result in the presence of residues in foodstuffs obtained from treated animals. The Agency assesses and recommends maximum residue limits (MRLs) for pharmacologically active substances in veterinary medicinal products used to treat animals, to provide for the safe use of food-stuffs of animal origin, including meat, fish, milk, eggs and honey. The Agency also has this responsibility for pharmacologically active substances in biocidal products used in animal husbandry. The European Commission formally establishes the MRL status.

Highlights
- Four applications for the establishment of MRLs were received in 2014.
- The continued submission over the past years in applications for MRLs indicates the ongoing interest of the animal health industry in developing new products for food-producing animals.

Evaluation of maximum residue limits



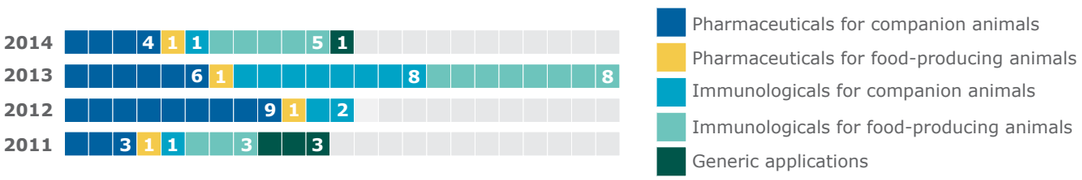
Authorisation activities

Initial evaluation

The initial evaluation phase covers activities relating to the processing of marketing authorisations for veterinary medicines, ranging from pre-submission meetings with future applicants, through evaluation by the Committee for Medicinal Products of Veterinary Use (CVMP) to the granting of marketing authorisation by the European Commission.

Highlights
- 12 applications for marketing authorisation were received in 2014, with similar numbers of pharmaceutical and immunological products.
- Seven of these medicines are intended for food-producing animals.
- Following previous trends, the majority of the pharmaceutical products are intended for companion animals and the majority of immunological products are intended for food-producing species.

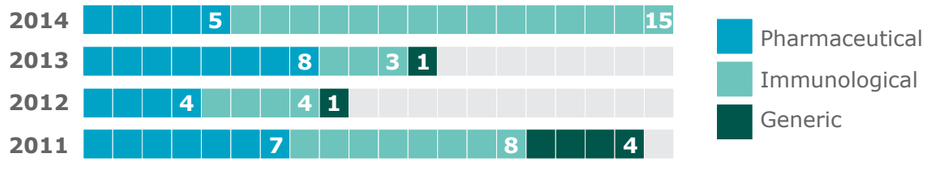
Applications for veterinary medicines received



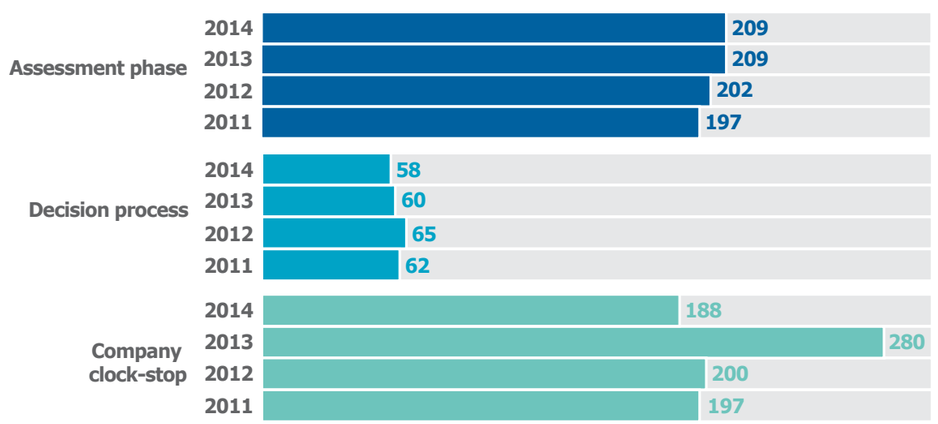
Recommendations for authorisation

Highlights
- 20 new veterinary medicines were recommended for marketing authorisation in 2014.
- This is an increase compared to previous years, which is due to the record number of applications submitted in 2013.
- The majority of opinions were for vaccines, seven being for companion animals, including a range of vaccines for dogs.
- Nine medicines were for food-producing animals including eight vaccines for poultry, pigs, cattle and sheep.
- Three medicines were for minor species or for rare diseases in major species, such as cattle or sheep.

Opinions for veterinary medicines adopted



Average number of days for centralised procedures



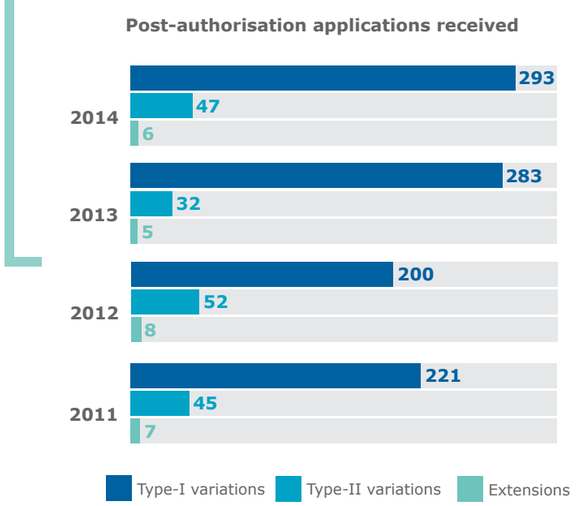
Recommendation of new medicines – Highlights of 2014

Veterinary medicine	What is it used for?	
Fungitraxx (itraconazole)	An antifungal medicine, available as a solution to be given by mouth, for the treatment of ornamental birds with two types of fungal infections of the respiratory tract (aspergillosis and candidiasis).	MUMS
Equisolon (prednisolone)	A corticosteroid, given as a powder by mouth, for the alleviation of clinical recurrent airway obstruction (RAO or heaves) in horses in combination with environmental control measures.	
Parvoduk	A vaccine used to protect Muscovy ducks against Muscovy duck parvovirosis and Derzsy's disease.	MUMS
Vectra Felis (dinotefuran, pyriproxyfen)	A spot-on treatment used on cats to treat and prevent flea infestations.	
ERYSENG	A vaccine used to protect male and female pigs against swine erysipelas caused by *Erysipelothrix rhusiopathiae* bacteria of specific types called serotype 1 and serotype 2.	
ERYSENG PARVO	A vaccine used to protect embryonic and foetal piglets against porcine parvovirus infection via the placenta, also used to protect male and female pigs against swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.	
OSURNIA (terbinafine, florfenicol and betamethasone acetate)	A gel to be given into the ear for dogs for treatment of short lived or recurrent ear infections due to *Staphylococcus pseudintermedius* and *Malassezia pachydermatitis*.	
Nobilis IB Primo QX	A vaccine used to protect chickens against viral infectious bronchitis caused by strains of infectious bronchitis virus known as QX-like variants, such as strain D388.	
Porcilis PCV M Hyo	A vaccine used to protect pigs against two separate infections, porcine circovirus and *Mycoplasma hyopneumoniae*.	
Bovela	A vaccine for active immunisation of pregnant cattle against bovine viral diarrhoea (BVD).	
NEXGARD SPECTRA (afoxolaner and milbemycin oxime)	Chewable tablets for dogs for treatment of flea, tick and gastrointestinal nematode infestations and prevention of heartworm disease.	
Suvaxyn CSF Marker	A vaccine for active immunisation of pigs to prevent mortality and reduce infection and disease caused by classical swine fever virus. This vaccine allows discrimination of vaccinated pigs from naturally infected pigs with classical swine fever virus using an appropriate serological test.	
Zulvac SBV	A vaccine for active immunisation of cattle and sheep to prevent viraemia associated with infection by Schmallenberg virus.	MUMS
Versican Plus L4	A vaccine used to protect dogs against leptospirosis.	
Versican Plus Pi	A vaccine used to protect dogs against infectious tracheobronchitis (kennel cough).	
Versican Plus Pi/L4	A vaccine used to protect dogs against infectious tracheobronchitis, and leptospirosis.	
Versican Plus Pi/L4R	A vaccine used to protect dogs against infectious tracheobronchitis, leptospirosis and rabies.	
Versican Plus DHPPi	A vaccine used to protect dogs against canine distemper, infectious hepatitis, infectious tracheobronchitis and parvovirus disease.	
Versican Plus DHPPi/L4R	A vaccine used to protect dogs against canine distemper, infectious hepatitis, infectious tracheobronchitis, parvovirus disease, leptospirosis and rabies.	
Versican Plus DHPPi/L4	A vaccine used to protect dogs against canine distemper, infectious hepatitis, infectious tracheobronchitis, parvovirus disease, and leptospirosis.	

MUMS | Minor Use Minor Species

Post-authorisation activities

Post-authorisation activities relate to variations, extensions of marketing authorisations and transfers of marketing authorisations.



Safety monitoring of medicines

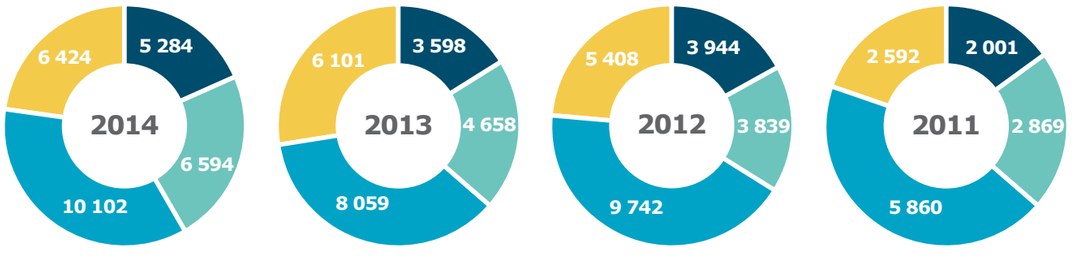
Pharmacovigilance covers activities relating to the detection, assessment, understanding and prevention of adverse events (AEs) or other drug-related problems. It aims at ensuring that post-authorisation monitoring and effective risk-management are continuously applied to veterinary medicines throughout the EU.

EudraVigilance

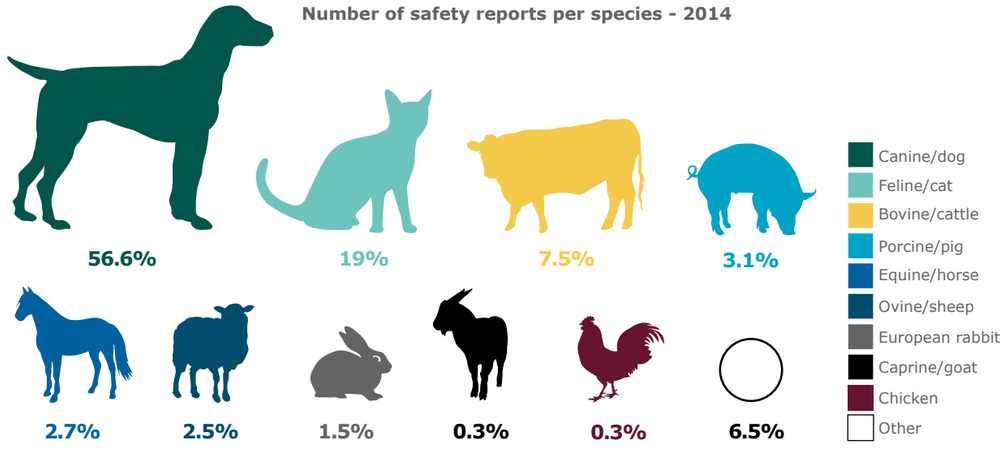
Highlights

- A general increase in the number of AE reports received in EudraVigilance was observed in 2014 with a 27% rise compared to 2013.
- Similarly to the human area, these trends reflect an increased commitment of stakeholders to provide all available data on medicines.

Reports on suspected adverse reations in animals and human reactions



Number of safety reports per species - 2014



Signal detection and management

All adverse effects within EudraVigilance Veterinary are analysed at 6-monthly or yearly intervals for statistically significant signals (signal detection) for each centrally authorised product.

This resulted in a total of 356 surveillance analyses during 2014, of which about 11% led to follow-up monitoring of potential signals at the next surveillance instance.

For six analyses it was recommended to ask the marketing authorisation holder for a cumulative review of the issues identified as part of the next periodic safety update report (PSUR).

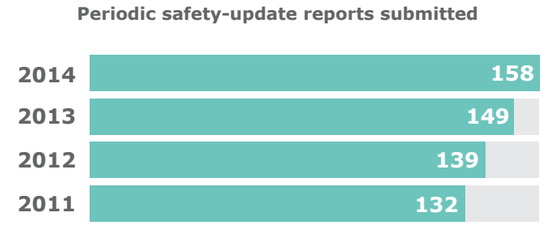
Periodic safety update reports (PSURs)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at predefined time points following a medicine's authorisation. PSURs summarise data on the benefits and risks of a medicine and include the results of all studies carried out with this medicine (in authorised and unauthorised indications).

Highlights

- The CVMP started the assessment of 158 PSURs in 2014. The increasing number of PSURs over the years reflects the progressive accumulation of products authorised through the centralised procedure.

Periodic safety-update reports submitted



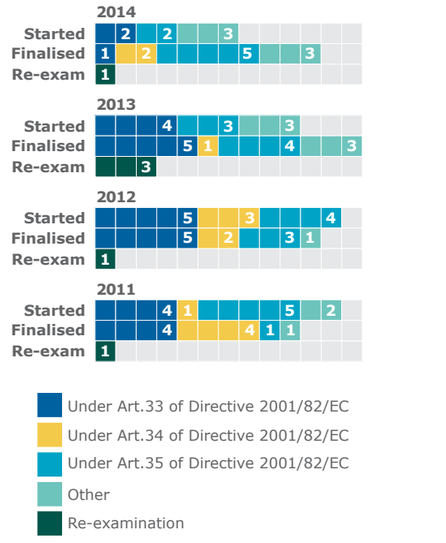
Referral and arbitration procedures

Arbitration procedures are used to resolve disagreements and address concerns raised by EU Member States. In a referral, the Agency is requested to conduct, on behalf of the EU, a scientific assessment of a particular medicine or class of medicines, to agree on a recommendation for a harmonised position across the EU.

Highlights

- Seven referral or arbitration procedures related to veterinary medicinal products started in 2014 and 11 procedures concluded.
- Of those started in 2014, four procedures concerned individual antimicrobials or classes of antimicrobials which reflect the continuous EU activities to ensure that such products are authorised with appropriate conditions of use, in order to reduce as much as possible the risk of antimicrobial resistance development.

Arbitrations and referrals for veterinary medicines



Notable referral or arbitration procedures started or concluded in 2014 are shown in the table below.

Medicine	Recommendation
All veterinary medicinal products containing colistin for oral administration	The aim of the referral was to consider measures needed to ensure the prudent use of colistin in food-producing animals across the EU and to minimise potential risks of antimicrobial resistance development. Recommendation on restricted indication, a limitation of the duration of treatment up to 7 days and warning sentences on prudent use for veterinary medicinal products containing colistin as a sole active substance for oral administration in food-producing animals.
All veterinary medicinal products containing gentamicin presented as solutions for injection to be administered in horses	Recommendation to harmonise indications and dosing regimens, thereby also addressing concerns on target animal safety for these veterinary medicinal products.
Baytril (2.5%; 5% and 10% injectable) and associated names, and related injectable veterinary medicines containing enrofloxacin	Recommendation to harmonise indications, dosage regimens, withdrawal periods, contraindications and special precautions for use.
All veterinary medicinal products containing tylosin to be administered orally via feed or the drinking water to pigs	Recommendation to delete an indication for swine dysentery caused by *Brachyspira hyodysenteriae* and to limit the maximum treatment duration to three weeks.

Scientific opinion

In 2014, the European Commission requested the CVMP to investigate whether the use of diclofenac in animals presents a risk to vultures and other necrophagous birds in Europe and, if a risk is identified, to provide an opinion on actions or mitigation measures that could be implemented to manage this risk effectively. The CVMP identified certain defined situations in which necrophagous bird species can be exposed to harmful levels of diclofenac in the EU, and considered a wide range of measures that could potentially minimise or eliminate this risk. In addition, the Committee assessed the practicality of these measures and their impact from the time of administering diclofenac to an animal through to consumption of the carcass by necrophagous birds.

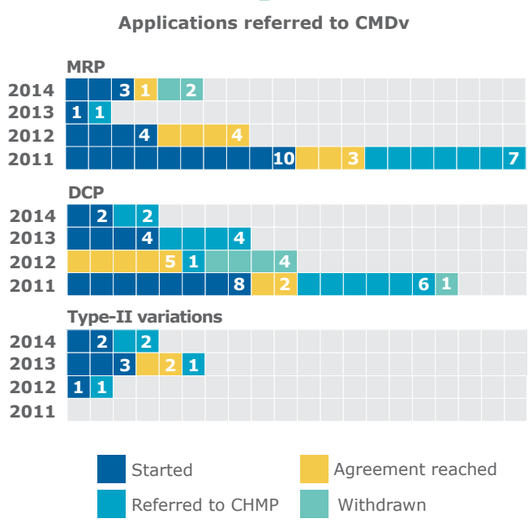
Joint recommendations

The Agency works with the European Commission and Member States in the framework of the European Commission's action plan against antimicrobial resistance. Following a request from the Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals in 2013, the Committee adopted answers to the three remaining questions in December 2014.

The advice included the classification of antibiotics according to their importance for human medicine, risk mitigation measures for antibiotics that are currently used in animals, including those that are critically important in human medicine, and recommendations regarding the authorisation of new veterinary antibiotics. The advice was prepared by the Antimicrobial Advice Ad Hoc Expert Group (AMEG), composed of representatives and experts from the CVMP and CHMP as well as the CVMP Antimicrobials Working Party and the CHMP Infectious Diseases Working Party, from the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control (ECDC) and the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA).

Mutual-recognition and decentralised procedures

The Agency provides secretarial support to the Co-ordination Group for Mutual-recognition and Decentralised Procedures – Veterinary (CMDv) and its working groups, in accordance with the approved rules of procedure. The work of the CMDv is essential for the effective authorisation and maintenance of veterinary medicines entering the EU market via the mutual-recognition procedure (MRP) and the decentralised procedure (DCP).



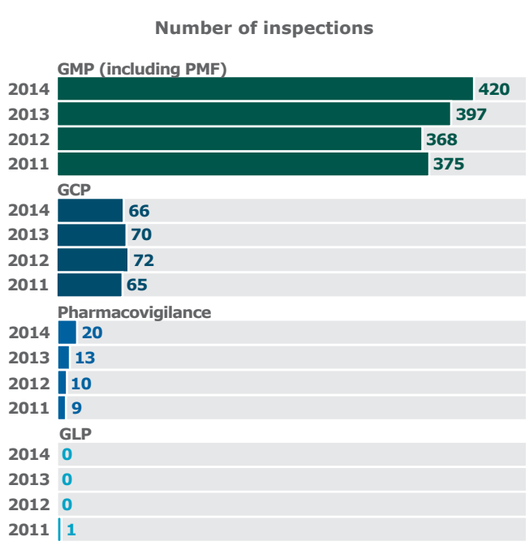
3.3 | Inspections and compliance

The Agency coordinates the verification of compliance with the principles of good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), good pharmacovigilance practice (GVP), and certain aspects of the supervision of authorised medicinal products in the European Union. The main verification tool are inspections requested by the CHMP or CVMP in connection with the assessment of marketing-authorisation applications and/or the assessment of matters referred to these committees in accordance with EU legislation.

The Agency also checks that the distribution of centrally authorised medicines from one Member State to another by a pharmaceutical company independent of the marketing authorisation holder is compliant with the rules. Finally, the Agency issues certificates to confirm the marketing-authorisation status of medicines that have either been authorised or for which an application for marketing authorisation has been submitted to the Agency.

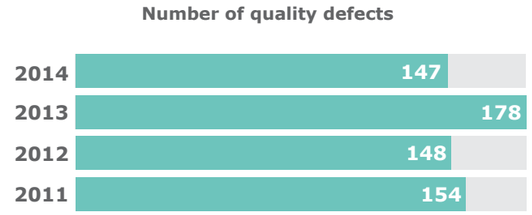
Inspections

As in previous years, the number of inspections increased in 2014, mainly due to the increase of GMP inspections, linked to the growing number of centrally authorised products and the increasing number of manufacturing sites located outside the EEA. There was also an increase in the number of pharmacovigilance inspections, mainly reflecting the evolving process of pharmacovigilance inspections as well as a number of cases where the CHMP and CVMP had requested additional inspections to investigate particular situations.



Number of quality defects reported

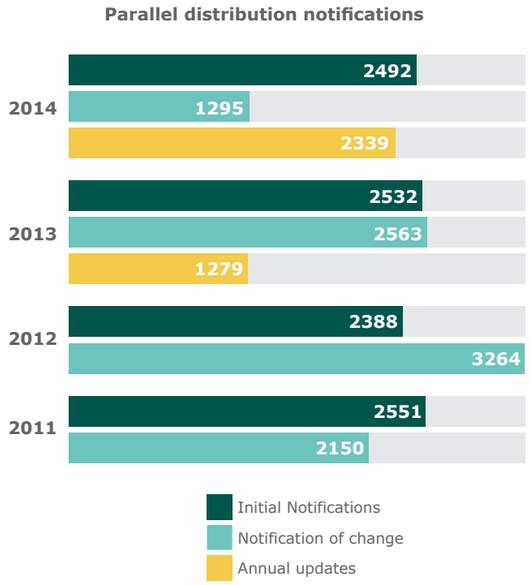
After a peak in 2013, the number of quality defects in 2014 is again in line with the numbers reported in previous years.



Breakdown of recalls (2014)

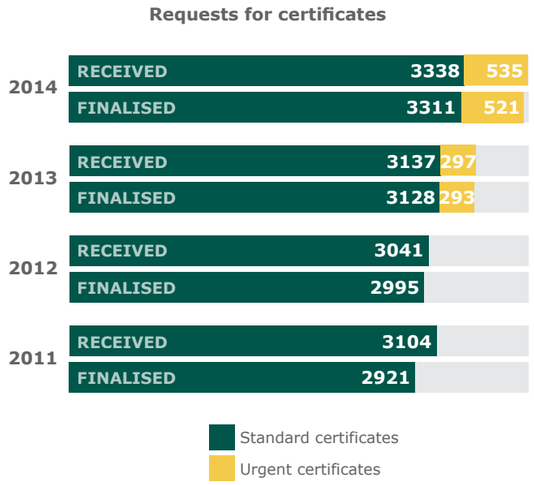
Recalls (total)	14
Class 1 recalls	2
Class 2 recalls	8
Class 3 recalls	4

Parallel distribution



The successful implementation of the annual update procedure in 2013 enabled companies to combine notifications of change into one annual update.

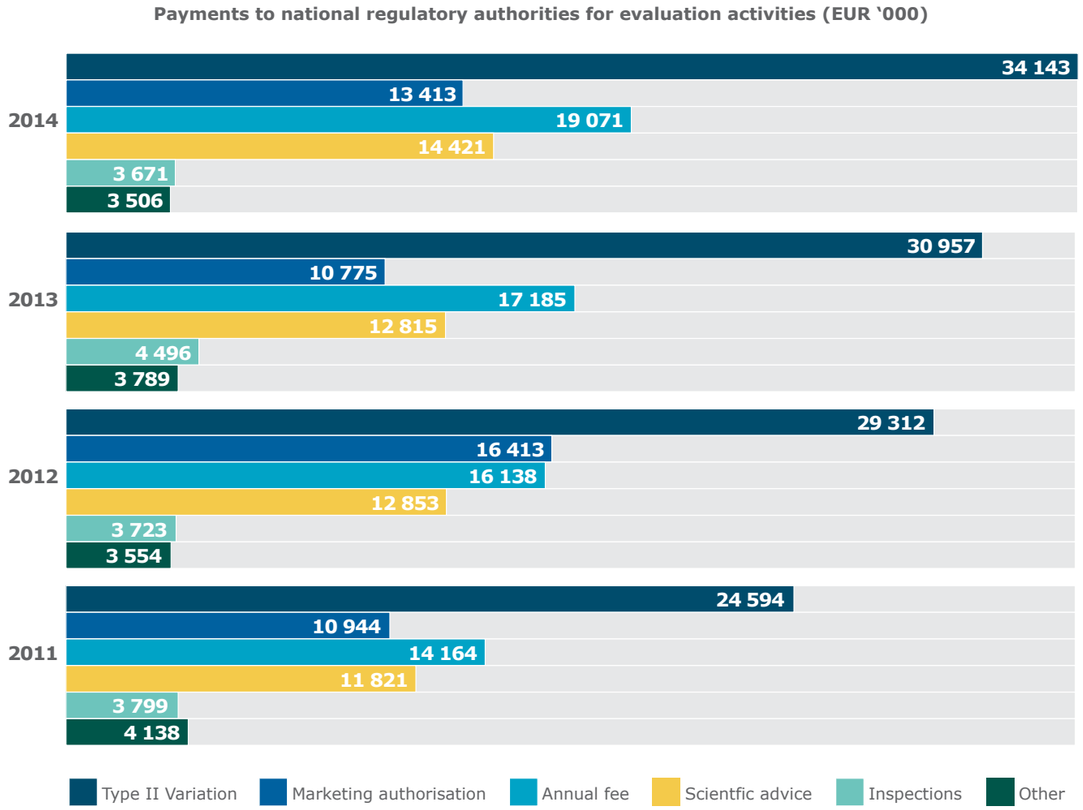
Certificates



Since 2013, a new procedure has allowed the processing of urgent requests for certificates.

3.4 | European medicines regulatory network

The European medicines regulatory network – a partnership between the European Medicines Agency, the European Commission and 50 medicines regulatory authorities in the European Union (EU) and the European Economic Area (EEA) – is the basis of the Agency's success. The network gives the Agency access to a pool of over 4,500 experts, allowing it to source the best-available scientific expertise for the regulation of medicines in the EU. Experts participate in the work of the Agency as members of its seven scientific committees, 26 working parties, 9 scientific advisory groups and a number of other ad-hoc advisory groups as well as part of the assessment teams carrying out the evaluation of medicines (see annexes for further information on these groups).



Meeting organisation

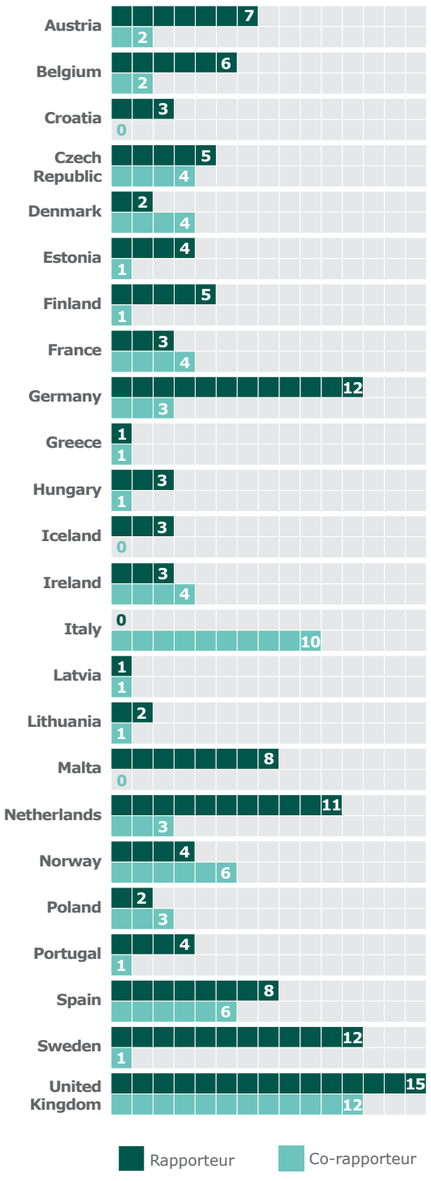
Support was provided to over 8,500 delegates attending meetings at EMA:

Total reimbursed meetings for 2014	397
Total virtual meetings for 2014 (Vitero and Adobe Connect)	1020
Total audio and video conferences for 2014	2195

Rapporteurships/co-rapporteurships

CHMP rapporteurships (including generics)

CHMP rapporteurship / co-rapporteurship - 2014



These figures relate to the appointments of rapporteurs and co-rapporteurs that occurred in 2014 for initial marketing authorisation applications, including generic medicines.

Multinational teams

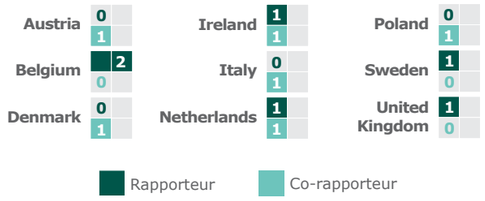
In some cases, the appointed CHMP co-rapporteur used a multinational team in the assessment of the initial application. Details on these multinational teams are provided in the table below.

	Appointed co-rapporteur	Assessors included in multinational teams
Austria	1	-
Cyprus	-	1
Estonia	1	-
Germany	2	4
Greece	1	-
Ireland	1	1
Portugal	1	1

CVMP rapporteurships

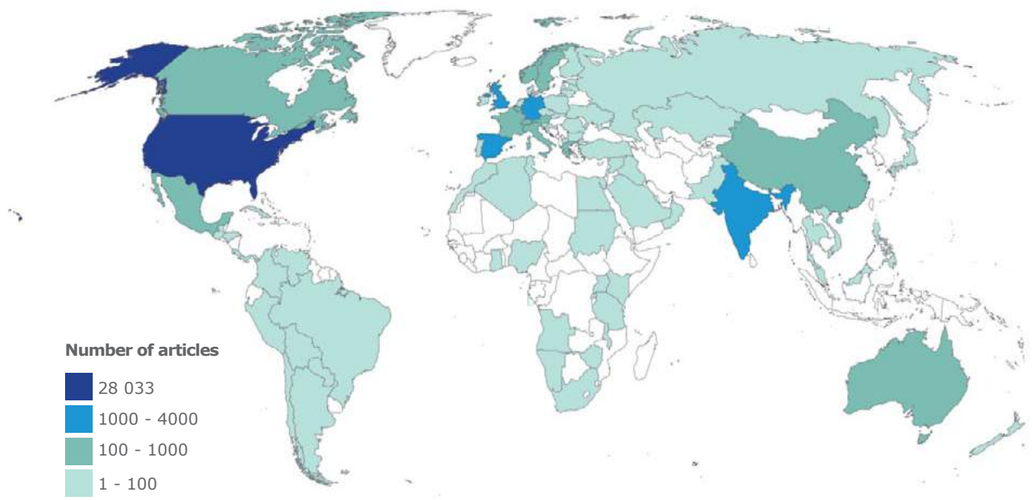
These figures relate to the appointment of rapporteurs and co-rapporteurs that occurred in 2014 in response to expressions of intent to submit initial marketing authorisation applications (including generic medicines, where applicable).

CVMP rapporteurship / co-rapporteurship - 2014



In 2014 EMA issued 91 press releases and published 103 news items.

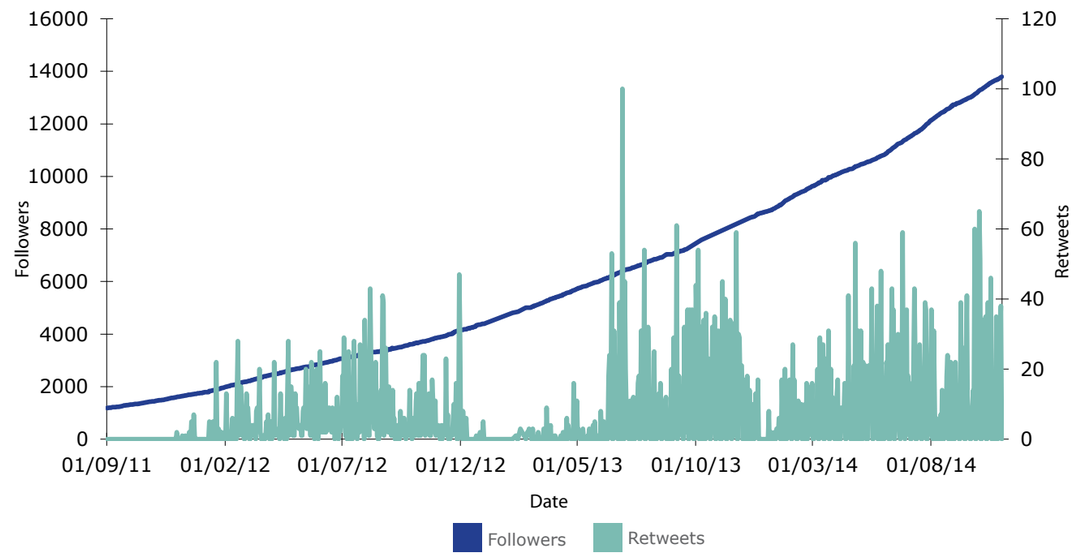
EMA in the media around the world



Social media

At the end of 2014 EMA had 14,789 followers on Twitter, an increase of 70% compared to 2013. The chart below shows the number of followers of **@EMA_news** and retweets since September 2011.

EMA Twitter followers and number of retweets



Access-to-documents requests

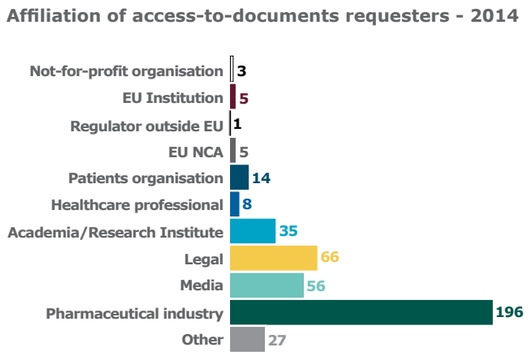
EU citizens have a right of access to documents held by EU Institutions, Bodies, Offices and Agencies. The European Medicines Agency grants this access according to the principles and further conditions as defined by Regulation (EC) No 1049/2001 and its policy on access to documents.

Highlights

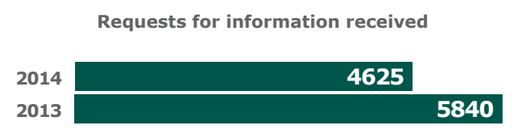
- EMA continued to grant access to documents pending three court cases, two of which were withdrawn in April 2014 whilst one is still on-going.
- However, in light of the restrictive interim orders issued by the General Court in 2013 and the findings by the Court of Justice in the appeal proceedings, EMA took particular care when assessing requests for access to documents similar to those which were the subject matter of the three Court cases.

Requests for access to documents in 2014	Initial requests	Confirmatory applications
Fully granted	229	25
Partially granted (with redactions)	15	2
Refused	70	14

Confirmatory applications can be submitted by requesters whose initial request for access to documents was refused. Confirmatory applications are submitted directly to the EMA Executive Director for reconsideration.

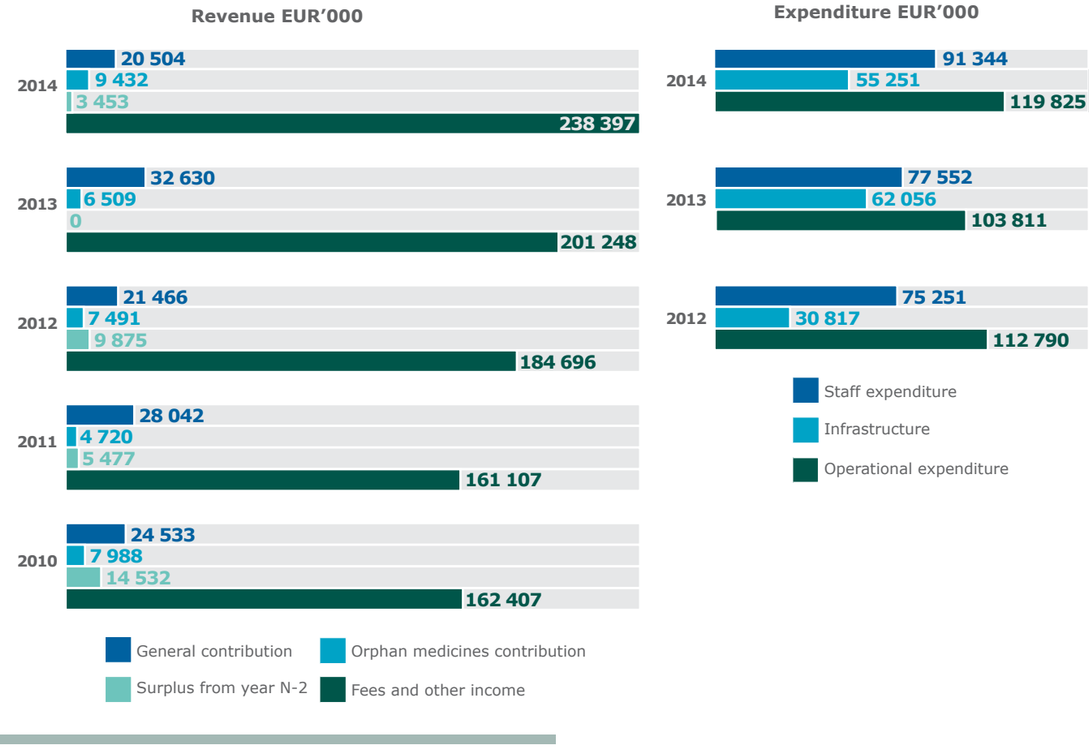


Requests for information



Budget Composition

The total budget of the Agency in 2014 was €282,424,000 representing a 12.3% increase compared to 2013, which is mainly due to the overall higher number of applications in 2014. The EU general contribution provided for 7.5% of the revenue in 2014 compared to 13.6% in 2013.



Environmental reporting

In August 2014, the Agency completed its move to 30 Churchill Place in Canary Wharf, London.

The building includes many environmentally-friendly features, such as photovoltaic (or solar) cells and a 'green' roof to enhance biodiversity.

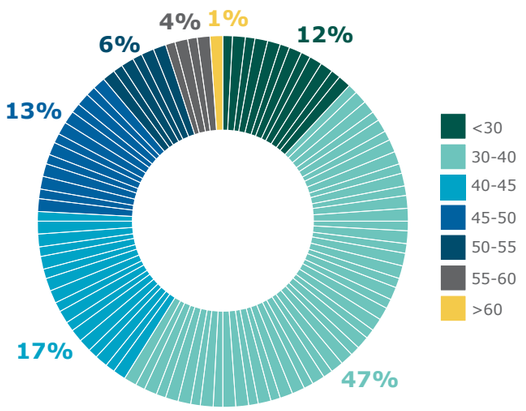
It achieves a new standard for environmental performance and energy efficiency in London and the design was awarded a Building Research Establishment Environmental Assessment Methodology (BREEAM) 'excellent' rating.

KPI	Description	Units	2012	2013	2014
Energy efficiency	*Electricity consumption*	KWh	3 414 782	3 406 245	3 069 676
Resource efficiency	*Water consumption*	m^3	3 053	5 130	2 585
	Paper consumption	metric tons	41	42	41
Waste management	*Recycled waste*	metric tons	63	67	53
	Non-recyclable waste	metric tons	88	87	59
Carbon footprint	*Greenhouse gas emissions*	tons CO_2e	2 618	2 679	2 601

Agency staff

	Men	Women	Total
Visiting experts	0	1	1
Trainees	9	39	48
National experts	12	16	28
Interim staff	4	34	38
Contract agents	26	118	144
Temporary agents	194	386	580
Total	245	594	839

Age range statistics



National origins of the Agency staff - 2014

Austria	1.91%
Belgium	2.86%
Bulgaria	1.91%
Croatia	0.6%
Cyprus	0.36%
Czech Republic	3.58%
Denmark	1.55%
Estonia	1.31%
Finland	1.19%
France	12.28%
Germany	6.67%
Greece	5.24%
Hungary	3.69%
Ireland	2.26%
Italy	12.16%
Latvia	1.07%
Lithuania	1.55%
Luxembourg	0%
Malta	0.12%
Netherlands	1.55%
Poland	6.32%
Portugal	5.84%
Romania	2.62%
Slovakia	2.74%
Slovenia	0.48%
Spain	10.25%
Sweden	2.38%
United Kingdom	7.03%
Other	0.48%

Annexes

Annex documents are available on the Agency's website (**www.ema.europa.eu**) via:
About us > How we work > Annual reports and work programmes

Annex 1	Members of the Management Board
Annex 2	Members of the Committee for Medicinal Products for Human Use
Annex 3	Members of the Pharmacovigilance Risk Assessment Committee
Annex 4	Members of the Committee for Medicinal Products for Veterinary Use
Annex 5	Members of the Committee on Orphan Medicinal Products
Annex 6	Members of the Committee on Herbal Medicinal Products
Annex 7	Members of the Committee for Advanced Therapies
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Annex 11	Opinions adopted by the Committee on Orphan Medicinal Products
Annex 12	European Union herbal monographs in 2014
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Annex 15	Arbitrations and referrals in 2014 – veterinary medicines
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Annex 17	European Medicines Agency Establishment Plan
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Annual report 2014