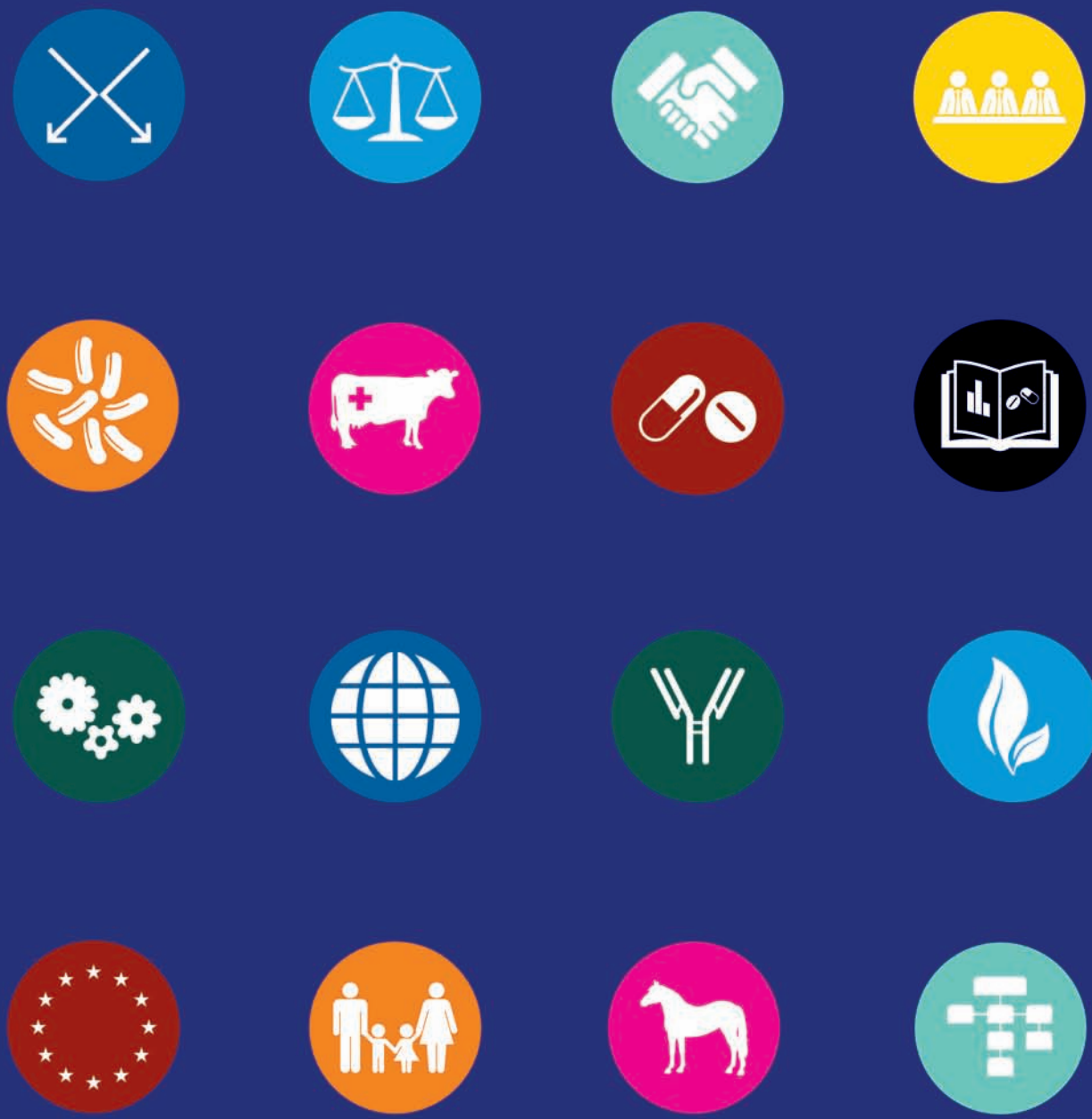
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual report 2013



An agency of the European Union

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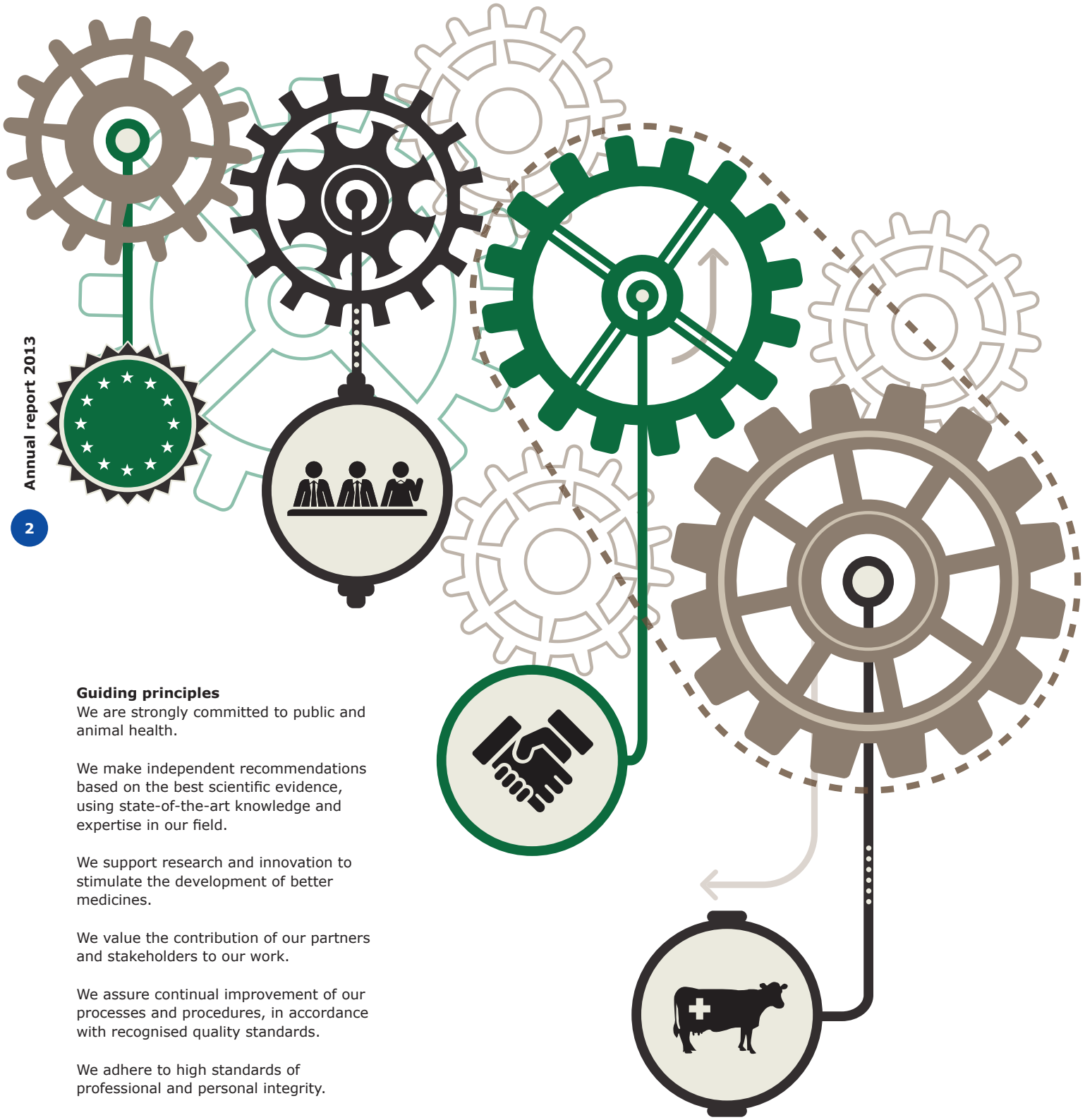
Mission statement

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;

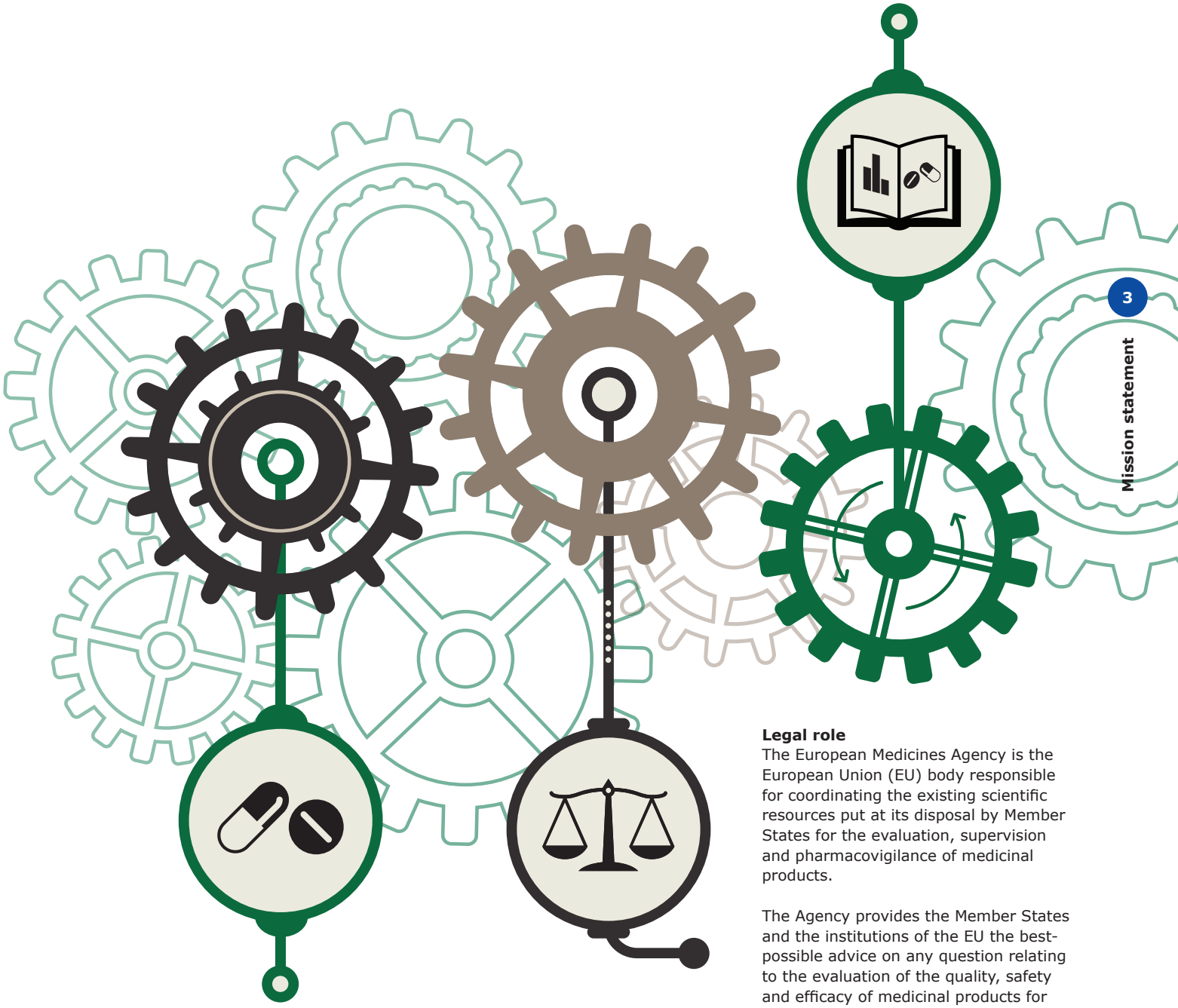
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines;

- 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 existing 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

I am pleased to introduce the 2013 annual report, which describes the many and varied activities of the European Medicines Agency during the year. Much has been accomplished at a time of active therapeutic innovation and evolving EU medicines legislation. Close co-operation between the EMA, national competent authorities and European Commission is a critical success factor. This was well shown by the implementation during 2013 of the new requirements of the Falsified Medicines Directive for active pharmaceutical ingredients – on time and without disturbance of pharmaceutical supply.

The report includes three contributions jointly written by national experts and EMA staff illustrating the Agency's engagement in science, medicines and health. An active programme of scientific advice during product development supports innovative methods and increases the likelihood that regulatory requirements will be met by products with novel modes of action, to the benefit of future patients. Such contacts also help to keep regulatory science in step with new knowledge. For veterinary medicines there are particular challenges arising from the nature of the market – there needs to be a well-informed dialogue between regulators and industry to which veterinarians and the public contribute. The same theme of active engagement between regulators, industry, prescribers and public emerges clearly in the account of the work of the Pharmacovigilance and Risk Assessment Committee (PRAC), set up in 2012 under the new pharmacovigilance legislation.

The continuing impact of that new legislation is shown by some key statistics. In 2013, over a million suspected adverse drug reactions (ADRs) were reported to the EudraVigilance system hosted by the EMA – an increase of 26% over 2012. ADR reports from patients within the European Economic Area increased by 62% in 2013 compared with 2012. Chapter 4 includes a summary of the distillation of this huge data resource into new knowledge of the benefit-risk relationship for marketed medicines and the communication of that knowledge to prescribers and patients.

Equally impressive is the diversity of innovative products assessed for market authorisation during 2013. These include pharmaceuticals directed towards some difficult clinical problems, for example multidrug resistant tuberculosis and several types of cancer. The continuing movement towards highly targeted biological medicines is clear, followed now by several biosimilar molecules being brought forward for market authorisation.

On behalf of the Management Board, I would like to thank the Agency staff and the many external experts from across Europe who have made possible the programme of work set out here. Through the networked model, the very best expertise can be brought to bear on the scientific challenges and opportunities of pharmaceutical regulation, for the benefit of public and animal health.

Introduction

by Professor Guido Rasi

Executive Director

The year 2013 has yet again demonstrated that the environment in which the EMA operates is rapidly changing. In fact, it has shown us if anything that the rate of change is accelerating. We see this trend in all aspects of our work, whether they are new scientific developments, business trends, globalisation, economic pressures or legislative changes. And we don't expect this trend to stop or even to slow down anytime soon.

Our legal framework is ever-changing. While we are still implementing provisions from the new pharmacovigilance legislation, we have started the implementation of the Falsified Medicines Directive. New pieces of legislation, such as on clinical trials or medical devices, are in the final stages of legislative decision-making in the European Parliament and the Council and will have further implications on the operations of the EMA.

Medical research is rapidly changing. New development methods, the possibilities offered by personalised medicines or the prospects of making full use of the power of data – all of this underlines that the anticipated paradigm shift in pharmaceutical research and development is now becoming a reality.

It is the duty of regulators to be prepared for these changes so that we can support new development approaches which have real potential to increase the success rate in medicines development and speed up access of patients to new medicines. This was one of the drivers behind the re-organisation of the Agency in 2013.

We created four new divisions with responsibilities right through the lifecycle of a medicine for human use from development to use in patients. Along with these organisational changes comes a new operating model for how medicines are managed through their entire lifecycle at the Agency, as well as dedicated structures to support early dialogue with medicines developers, and research and development.

The ultimate aim of this exercise is to give our scientific committees the best possible support, alongside the expertise from the national agencies, to help them keep delivering high-quality, consistent opinions on medicines in these rapidly changing times. Their expertise is the bedrock on which the success of the European medicines regulatory network as a whole is built.

Looking back at 2013 would not be complete without reflecting on our initiative to proactively give access to clinical trial data. I have said that the question is not 'if' but 'how' we are going to make the data we hold as part of marketing authorisations submitted to the EMA available. We remain committed to this aim and we are encouraged by the many comments we have received from our stakeholders that show that there is broad support for our plans to allow access to these data. It is particularly encouraging that an increasing number of stakeholders, including the vast majority of pharmaceutical industries, now recognise that clinical study reports do not generally contain commercially confidential information. We have also seen that there is a need for further analysis and clarifications of certain aspects. That's why we will continue working with all our stakeholders to achieve a broad consensus for our policy.

Patients are at the heart of everything we do and the year 2013 saw a significant new dimension in the Agency's engagement with them, in particular thanks to the new routes to incorporate their views and preferences into the decision-making process brought by the pharmacovigilance legislation. We owe these new platforms for dialogue and participation to the patients who have demonstrated over many years how valuable their input in our decision-making is.

I am grateful for the hard work and the 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 enable the EMA to fulfil its mission. It gives me great pleasure to present our joint achievements in protecting and promoting public and animal health in the European Union.

1 | The Agency in 2013

2013 was an exciting year for the European Medicines Agency (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 chapter highlights a few of the many projects, initiatives and achievements of 2013, focusing on those that have had or continue to have a profound effect on how the Agency operates.

1.1 | Implementation of new legislation – integrating new tasks

Implementing the pharmacovigilance legislation
The new pharmacovigilance legislation brought about the biggest change to the legal framework for human medicines since the creation of the Agency in 1995. It established a new, seventh scientific Committee, the Pharmacovigilance Risk Assessment Committee (PRAC) at the Agency and led to a greater involvement of the Agency and the PRAC within the European medicines regulatory network to support pharmacovigilance for nationally authorised products, while underpinning the critical role of the national competent authorities.

In its first full year of operation, the PRAC worked to enhance public-health protection by proactively monitoring the safety of medicines and making recommendations to manage and minimise their risks from the granting of marketing authorisation and throughout their lifecycle. This included a number of milestone recommendations on the safe and effective use of some widely-used medicines, ensuring that doctors and patients have the best information to take appropriate healthcare decisions. Details of the PRAC's work are provided in Chapters 3 and 4 of this annual report.

"Since establishing the new Pharmacovigilance Risk Assessment Committee, the Committee has proactively grasped the opportunities of the new pharmacovigilance legislation to strengthen European drug safety. By involving patients and healthcare professionals in our decision-making, strengthening the science base of risk assessment, and working transparently, we have made great strides towards a new era in protecting public health."
June Raine, Chair of the PRAC

The Agency and the national medicines agencies spearheaded a successful campaign to explain the objectives of additional monitoring and the meaning of the inverted black triangle which is now displayed in package leaflets and in information for healthcare professionals for certain medicines.

This campaign followed the selection of the inverted black triangle by the European Commission in April 2013 as a symbol to identify medicines that are under additional monitoring. The black triangle was selected on the basis of a recommendation by the EMA that was made in cooperation with the patients and healthcare professionals represented in the Patients' and Consumers' Working Party and the Healthcare Professionals' Working Group.

The EMA now coordinates the maintenance and publishes a monthly updated list of medicines subject to additional monitoring that should be identified by the symbol.

Despite the progress made in the implementation of the pharmacovigilance legislation, the absence of pharmacovigilance fees for pharmacovigilance activities means that a number of specific measures from the new legislation have yet to be delivered, for example EMA literature monitoring, the EU Medicines Web-portal, public hearings and a repository of periodic safety update reports (PSURs) to allow centralised submission to the EMA. PSUR assessments by the PRAC for nationally authorised products that are on the market in more than one Member State have also been postponed because of the current absence of financial compensation for work undertaken by the PRAC. Such assessments continue for the time being at national level. A new fee regulation covering pharmacovigilance activities is expected to be in place in the course of 2014.

15 Jan

Advisory groups on access to clinical trial data start their work

15 Jan

eSubmission web client goes live for all applications for human medicines

21 Jan

Framework for a close collaboration with Israel in place

4 Feb

Three actions for annulment against EMA decisions to release non-clinical and clinical documents lodged by two pharmaceutical companies to the General Court in Luxembourg

Implementing the Falsified Medicines Directive

The Falsified Medicines Directive entered into force on 1 January 2013. This new piece of legislation is a necessary response to the public health threat of falsified medicines and the need to strengthen the supply chain in response to globalisation of manufacturing and the increasing number of actors involved.

The Agency plays a key role in assisting the European Commission and the Member States and in facilitating the implementation of the Directive, in the coordination of inspections in third countries and continued development of EudraGMDP.

"The Falsified Medicines Directive opens the way to 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 local regulators and development of local supervision."

Emer Cooke, EMA Head of International Affairs

The new Directive introduced new requirements for the importation of active substances. From July 2013, all active substances manufactured outside the EU and imported into the EU must be accompanied by a written confirmation from the regulatory authority of the exporting country. These statements are issued per manufacturing site and per active substance and ensure that standards of good manufacturing practice (GMP) equivalent to those in force in the EU are upheld. A number of countries including India and China are issuing written confirmations.

Exporting countries with an 'equivalent' regulatory framework do not need to issue these written confirmations. The regulatory frameworks of countries applying for 'equivalent' status are assessed by the European Commission, together with the Agency and Member States. By the end of 2013, Switzerland, Australia, Japan and the United States were listed.

There was concern that the new provisions in relation to active substance importation may lead to shortages. However, by year-end, no risk of shortage due to the requirements of the Directive was reported either by EU competent authorities or by the pharmaceutical industry.

The Commission, the Agency and the Member States all made a big effort to effectively communicate the new EU legislation requirements to authorities in the major exporting countries. As part of this, the Agency, cooperating closely with the Commission and Member States, led a risk-assessment process, to identify priority active substances for which manufacturers in third countries may need to be inspected in order to avoid shortages and to coordinate the necessary inspections. The methodology developed by the Agency was rolled out to Member States and was also used to assess the risk of shortages for non-centralised medicinal products. In addition, a group with the participation of the Commission and some key Member States was created by the Agency to monitor sites at risk and to coordinate the necessary inspections.

Other key deliverables achieved in 2013 included:

- extension and update of the EudraGMDP database with modules for distribution authorisation; good distribution practice (GDP) certificates; active pharmaceutical ingredients (API) manufacturers, importers and distributors registration;
- creation of harmonised and agreed templates for the activities listed above;
- adoption of a revised GDP guideline, which was finalised and published by the European Commission.

The implementation of the Falsified Medicines Directive continues in 2014.

1 Mar

Workshop on medication errors calls for coordinated EU approach

15 Mar

Renewal of confidentiality arrangement with Canada

2 Apr

Agneta Brandt joins as new Head of Infrastructure Services

15 Apr

EMA and EFSA give joint advice on risk to consumers of phenylbutazone detected in horsemeat

1.2 | Reorganisation of the EMA – reshaping for the future

In September 2013 the Agency launched a new organisational structure designed to fundamentally reorganise the Agency's operations in order to enable it to better support its public- and animal-health mission, and its role as part of the European medicines regulatory network.

The new structure reflects a renewed focus on three key elements:

- better support to the scientific work of the EMA committees;
- better sharing of knowledge and information the Agency holds throughout the European medicines regulatory network;
- improved partner and stakeholder relations.

The reorganisation introduces a new operating model for how medicines are managed throughout their entire lifecycle at the Agency, with separation of scientific and procedure management. With the increasing number and complexity of applications being handled by the Agency's committees, this is intended to reinforce the robustness and quality of the Agency's output and allow development of greater specialist skills to respond and support the work of the committees.

At its core, the new structure has four divisions with responsibilities right through the lifecycle of a medicine for human use, from development to use in patients. Those are:

- Human Medicines Research and Development Support Division;
- Human Medicines Evaluation Division;
- Procedure Management and Business Support Division;
- Inspections and Human Medicines Pharmacovigilance Division.

Veterinary medicines are managed through a single division that has been refocused to deal solely with veterinary medicines and animal health. Information technology and administration continue to be managed through separate divisions.

A new Stakeholders and Communication Division is created to provide improved coordination of the Agency's relations with stakeholders, in particular patients, healthcare professionals and industry associations, provide specific support for small and medium-sized enterprises, and act as a dedicated communication service.

"These changes reshape the EMA so that it is ready to handle future challenges and seize opportunities."

Guido Rasi, EMA Executive Director

The new organisational structure is underpinned by advisory functions, which provide advice to the Executive Director and the Agency on operational and scientific issues in their fields of expertise. In addition to the existing functions of Senior Medical Officer, International Affairs, Audit and the Legal Department, this also includes the newly created roles of Chief Policy Adviser and Head of Programme Design Board.

The organisational changes were the result of a comprehensive review of the Agency's operating processes. Reengineering of these processes is expected to be finalised over the course of 2014.

18 Apr

Upgrade of EudraGMDP database to include information related to the distribution of medicines

25 Apr

First list of medicines under additional monitoring published

30 Apr

General Court of the EU gives interim measures in court cases against AbbVie and Intermune ordering the Agency not to disclose certain documents

7 Jun

EMA and EUnetHTA review progress of their cooperation

1.3 | Access to clinical trial data – at the forefront of a global debate

2013 saw the European Medicines Agency at the centre of a lively global debate on open access to clinical trial data. The Agency's announcement at the end of 2012 on the development of a policy for the proactive release of clinical trial data submitted by applicants as part of a marketing authorisation application was a catalyst for various similar initiatives from other organisations, such as other regulators, the pharmaceutical industry, healthcare payer bodies and academic centres.

From the start, the Agency took an inclusive and considered approach to developing its policy, based on listening to and respecting the views and concerns brought forward by all stakeholders and European bodies.

Building on the views, interests and concerns brought forward during a workshop held at the end of 2012 to discuss the practical and policy issues that needed to be addressed before the Agency can begin to release these complex data, the EMA issued a call for nominations to join five advisory groups to provide the Agency with more feedback on:

- ensuring the protection of patient confidentiality;
- identifying appropriate and efficient formats to share and process clinical trial data;
- developing rules of engagement for access to clinical trial data;
- applying good analysis practice;
- legal aspects.

More than 200 people from all stakeholder groups applied to participate in one or more of the five advisory groups. The groups met between January and April 2013, with meetings taking place via teleconference. Advice from all five groups was published at the end of April and taken into account by the Agency in the development of the draft policy.

On 30 June 2013, the EMA published the draft of its policy on publication and access to clinical-trial data for a three-month public consultation.

The public consultation on the policy generated input from an unprecedented range of stakeholders. By 30 September 2013, the EMA had received over 1,000 comments from more than 150 individuals and organisations representing patients, healthcare professionals, the pharmaceutical industry, researchers, transparency campaigners, academic and public institutions, health technology assessment bodies and a range of others. Many of the comments came from individual citizens who expressed their support for the Agency's initiative to increase transparency and availability of clinical trial data.

A thorough review and analysis of all comments received showed that there was broad support for the Agency's plans to allow access to clinical trial data submitted as part of marketing authorisation applications, but they also highlighted that there is a need for further analysis and clarification of certain aspects.

"We live in an era where the public legitimately demand transparency and openness of information to allow them to scrutinise the relationship between regulators and the regulated."
Guido Rasi, EMA Executive Director

The Agency therefore announced that it would continue to work with stakeholders, including industry, academia and civil society organisations, to further clarify and fine-tune the proposed policy to achieve the broadest possible consensus. This also allows the Agency to take into account the impact of other developments at a European level, such as the progress in the pending court cases and the ongoing discussions on the new European clinical trials legislation.

Further work on the policy is guided by a set of key principles that were agreed with the Agency's Management Board on 12 December 2013, which include among others a stepwise approach for implementation with, as a first step, preparation for the

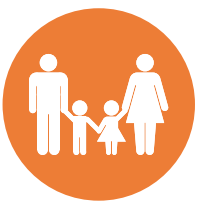
16 Jun

Stefano Marino joins as new Head of Legal Service

18 Jun

Policy on MUMS / limited-market revised

24 Jun



European Commission publishes report on the first five years of the EU paediatric regulation

28 Jun

CHMP recommends approval of first two monoclonal-antibody biosimilars

publication of clinical study reports, and the development of a methodology for de-identification of patients.

The Agency has welcomed the public debate on its initiative and the unprecedented level of interest from all levels of society and it continues to reiterate its firm commitment to pursuing the objective of transparency of clinical trial data for the benefit of public health and society.

30 Jun

Draft policy on publication and access to clinical trial data released for public consultation

30 Jul

CVMP gives advice on use of colistin and tigecycline in animals

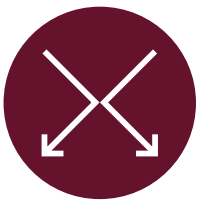
1 Jul

Croatia becomes new member of the European medicines regulatory network

2 Jul

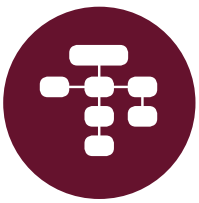
Imported active substances need written confirmation to guarantee GMP standards

6 Sep



Workshop on conflicts of interests

16 Sep



New organisational structure revealed

1.4 | Collaboration with HTA bodies – a rapidly evolving relationship

For a new medicine to reach the market and benefit patients, companies must not only ensure that they meet requirements of the regulators, but also more and more those of health technology assessment bodies (HTAs) bodies in the Member States. The EMA recognises that close collaboration with them is critical to allow new medicines to reach patients, and cooperation with HTAs intensified markedly in 2013.

"A strong interaction between regulators and health technology assessment bodies is critical to enable innovation to reach patients, and ultimately for the benefit of public health."
Guido Rasi, EMA Executive Director

Among the milestones achieved in 2013 was the publication of the first joint work plan with EUnetHTA, a network of European health technology assessment organisations. The three-year work plan outlines the following key areas for collaboration:

- exchange on the development of scientific and methodological guidelines to facilitate clinical-trial design that can generate data relevant for both benefit-risk and relative effectiveness assessments;
- developing approaches for collection of post-authorisation data to support activities of both medicines regulatory authorities and HTA bodies;
- orphan medicinal products, exploring ways of sharing information for the common benefit of patients affected by rare diseases and the financial sustainability of the healthcare systems;
- scientific advice / early dialogue with sponsors, involving medicines regulators and HTA bodies.

Since 2010, the EMA has put in place a pilot project of parallel scientific advice with HTA bodies that allows developers to receive simultaneous feedback from both regulators and HTA bodies on their development plans for new medicines. The EMA, with the support of the national competent authorities, has so far conducted 25 parallel scientific advice procedures, with several HTA bodies taking part in this pilot project. Among the companies participating in this pilot were large pharmaceutical companies but also small and medium-sized enterprises.

The experience gained so far has clearly underlined the need to initiate early dialogue between medicines developers, the EMA and HTA bodies to discuss and agree on a development plan that generates data that both parties can use to determine a medicine's benefit-risk balance and value.

A workshop hosted by the EMA to look at the need for, and the current use of, parallel scientific advice from regulatory and HTA bodies during the medicine development process brought together over 280 representatives from the European Commission, European regulators, HTA bodies from 12 European Union countries, EUnetHTA, the pharmaceutical industry, payers, patients, healthcare professionals and academics, as well as representatives from the Agency's scientific committees and its Scientific Advice Working Party.

"Simultaneous feedback will ultimately lead to better advice for companies, to help them meet the requirements of all stakeholders and consequently increase predictability."
Tomas Salmonson, Chair of the CHMP

Following the workshop, the EMA is now developing guidance for EMA-HTA parallel scientific advice, which is expected to be released for public consultation in 2014.

11 Oct

Update of EudraCT enabling sponsors to include clinical trial results summaries

14 Oct

Workshop on prevention of product shortages

15 Oct

Report on sales of veterinary antimicrobials in 25 countries in 2011 published

17 Oct

Workshop on the clinical investigation of new medicines for the treatment of multiple sclerosis

1.5 | Other highlights

Antimicrobial resistance
The increasing levels of resistance to antibiotics in humans and animals are of concern to public health authorities worldwide. There are a number of initiatives aiming to tackle this problem across Europe.

In 2013, the Agency contributed 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). In addition, specific activities were undertaken both in the human and veterinary areas.

- To stimulate drug development in the area of antimicrobials, the Agency outlined in a guidance document for the industry a new approach facilitating the development of antibacterial agents targeted against multidrug-resistant pathogens where patients have very limited or no remaining treatment options. A workshop entitled 'Best use of medicines legislation to bring new antibiotics to patients and combat the resistance problem' was also organised, in collaboration with the Commission, to discuss regulatory options to foster the development and approval of new antibacterials for human use and actions to increase appropriate use of antibiotics.
- Encouraging the appropriate use of antibiotics is key in the fight against antimicrobial resistance. In this area, the Agency published the third 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 the responsible use of antimicrobials.
- The Agency also provided the first piece of advice related to the use of specific antimicrobials in animals and the potential impact of this use on human health and animal health, in response to a request from the European Commission.
- In addition, several guidance documents on antimicrobial medicines, which are detailed in the chapter 'Significant recommendations in 2013' of this annual report, were developed to promote the appropriate use of veterinary medicines and a consistent assessment of the public-health risk related to antimicrobial resistance.

31 Oct

Amendments to the pharmacovigilance legislation enter into force

8 Nov

Workshop on 'Best use of medicines legislation to bring new antibiotics to patients and combat the resistance problem'

8 Nov

Briefing meetings of the Innovation Task Force open for veterinary medicines

19 Nov

EMA and EUnetHTA agree joint work plan

26 Nov

EMA-HTA workshop on parallel scientific advice in drug development

Conflicts of interests

The management of conflicts of interests was again an important topic for the Agency in 2013. Over the last few years, the EMA has taken comprehensive steps to strengthen its handling of conflicts of interests. This was acknowledged by both the European Parliament and the European Court of Auditors, which found that, despite highlighting some areas for further improvement, the Agency now has some of the most advanced policies and procedures among EU agencies for declaring, assessing and managing potential conflicts of interests.

With strengthened procedures in operation, it became clear that the main challenge is how to achieve the right balance between ensuring the impartiality and independence of experts involved in the Agency's work, versus the need to secure the best possible scientific expertise to continually deliver high-quality scientific assessments.

On 6 September 2013 the Agency hosted a workshop entitled 'Best expertise vs conflicts of interests: striking the right balance'. The aim of this workshop was to elicit the views and concerns from academia, patient organisations, committee representatives, non-governmental organisations, the pharmaceutical industry and the scientific media on the Agency's current conflicts-of-interests policy.

The feedback received from stakeholders during the workshop was analysed carefully and used to inform the Agency as it entered the next revision cycle of its policy. Following this analysis, principles on which to revise the Agency's policy were developed and agreed by the Management Board at its December 2013 meeting.

Medication errors

Medication errors are a new area of activity for the European medicines regulatory network. Since July 2012, the EU pharmacovigilance legislation requires reporting of all suspected adverse drug reactions resulting from medication errors to EudraVigilance, the EU database of adverse drug reactions.

In February 2013, the EMA held a workshop on medication errors, bringing together some 240 participants representing various stakeholder groups. The aim of the workshop was to gather the available expertise in this area and to take stock of current best practice.

Six key recommendations resulted from the discussions, which are being prioritised by the Agency in collaboration with the European Commission and the European medicines regulatory network by considering their potential benefit for public health and the resource implications in Member States and at EU level.

28 Nov

Vice-President of the Court of Justice sets aside order for interim measures and refers Abbvie and Intermune court cases back to the General Court

17 Dec

Meeting agendas of all scientific committees are now published

18 Dec

EMA and FDA launch joint generic medicines application inspections initiative

18 Dec

Statements of non-compliance with GMP now publicly available in EudraGMDP

2 | Advancing public and animal health in 2013

This chapter intends to provide engaging thoughts on three topics of major importance in science, health and medicines in 2013. The three essays introduce high-profile actors of the Agency and their views on topics such as best evidence, access to innovative treatments and the issue of antimicrobial resistance. This chapter is articulated around the 'three pillars' on which all of the Agency's work is based:

Science

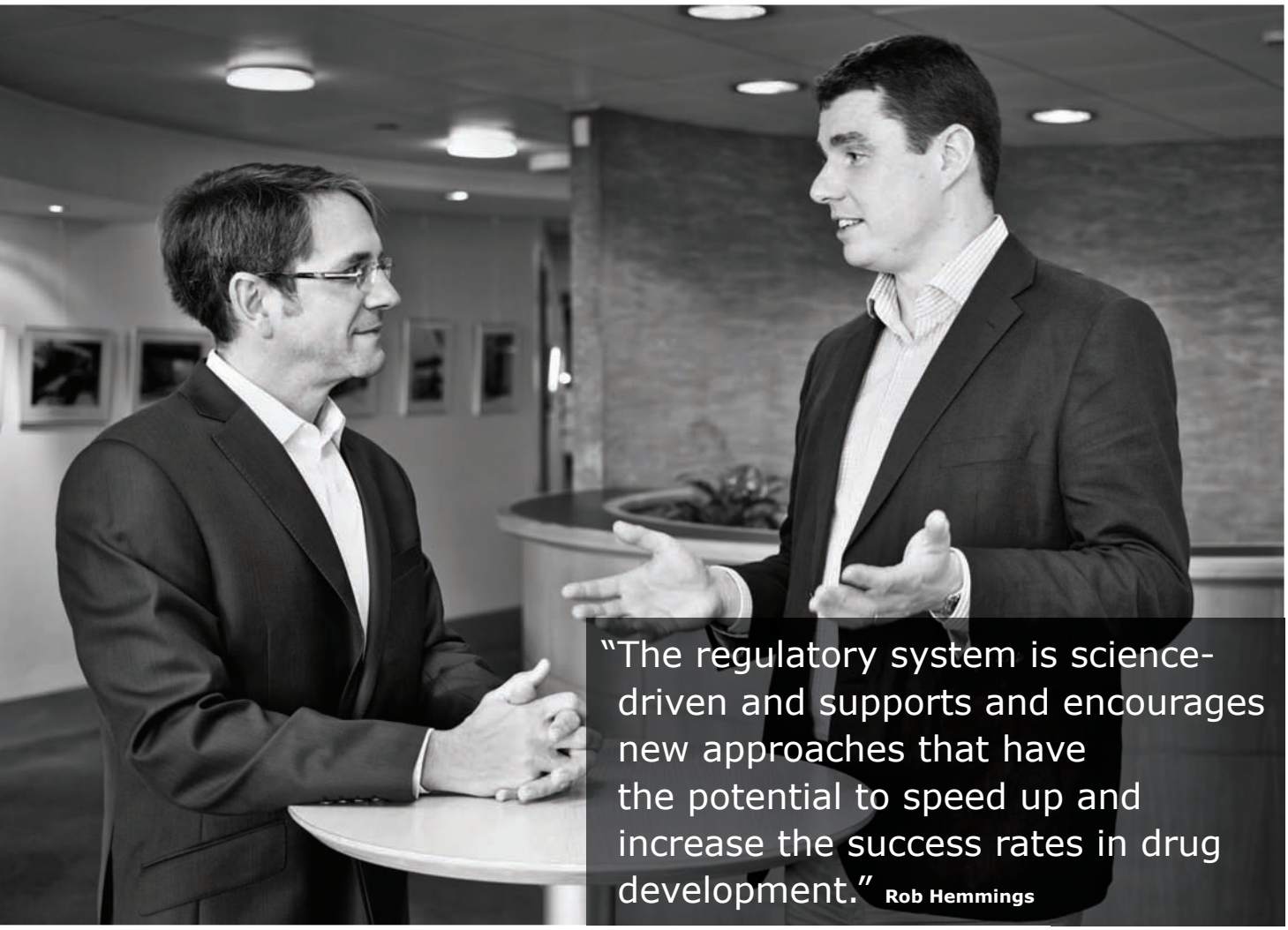
Representing the scientific expertise that guides the Agency in all of its regulatory decision-making.

Medicines

Representing the Agency's focus on assessing and monitoring medicines to ensure their quality, safety and efficacy.

Health

Representing the purpose for which the Agency was created, namely to protect and improve public and animal health.



Spiros Vamvakas (left), Rob Hemmings (right)

2.1 Science

Supporting new approaches to medicines development

Rob Hemmings, Chair of the Scientific Advice Working Party
Spiros Vamvakas, EMA Head of Scientific Advice

Today more than ever before there is an opportunity for a paradigm shift in drug development. Medicines developers have never had better tools to assist them in their development programmes, from the sequencing of the genome, through physiology-based models, to novel methods for clinical trial simulation and design.

When we started the qualification of novel methodologies five years ago, we wanted to send a clear message to the outside world that the regulatory system is science-driven and supports and encourages new approaches that have the potential to speed up and increase the success rates in drug development.

Not only are new tools available, but the regulatory system has never been more open to discussing how novel methods may be incorporated into medicines development and licensing.

In 2013, we issued the first qualification opinion on a statistical methodology for the quantification of dose-response and the selection of the best dose range of a medicine during the development programme; this is an example of science-driven, intelligent methodology that can increase the efficiency and the success rate of drug development.

We also qualified last year the first simulation tool for Alzheimer's disease clinical trials, which brought together various datasets to create a model of the disease. In the treatment of Alzheimer's disease, we have observed repeated failures of clinical trials over the past 10 years. Now science has shown that structural and biological changes associated with the disease start to occur as early as 10 to 20 years prior to the emergence of the clinical symptoms, and that certain therapeutic treatments may be more effective at early stage rather than later in the illness. Lately, we have issued a number of qualification opinions for biomarkers that help identify and select patients at the pre-dementia stage of the disease. Today, we accept that clinical programmes may include only this population of patients based on the use of such biomarkers. These approaches will change the conduct of clinical trials and ultimately the landscape of Alzheimer's disease treatment.

These are examples of important steps on the path to change. We hope that in a few years' time it will be the norm to design a clinical trial based on simulations of design properties under different scenarios. This should increase the likelihood that each trial is fit for purpose, testing the optimal dose range in the right patients.

Indeed, we are today in a better position to rationally identify patients who are most likely to best respond to a treatment using molecular biology and other tools. In scientific advice procedures we see more and more companies doing this before conducting the main clinical trials. As an example, in 2013 the Agency recommended for marketing authorisation a medicine for use in a very small subset of non-small cell lung cancer patients who have a specific mutation. The medicine targets exactly this mutation and the response rate in this population is close to 60%.

The Agency's scientific advice procedure is a platform where all these new approaches are discussed with medicines developers. The Agency approaches these discussions as both an enabler and a gatekeeper of medicines development, and welcomes and supports these changes that will contribute to better development programmes and better medicines for the benefit of public health.

2.2 Medicines

Veterinary medicines – increasing availability throughout the European Union

David Mackay, EMA Head of Veterinary Medicines Division
Jean-Pierre Orand, Head of HMA Veterinary Task Force on the Implementation of Legislation

The lack of availability of certain veterinary medicines in the European Union, for example those aimed at minor species or smaller markets, presents a clear challenge for the protection of animal health. Without appropriate options to prevent or treat the full range of conditions that affect animals comes also a risk to human health, through the possible transmission of infectious diseases such as influenza or diseases transmitted to man from food-producing animals or their products. In this context, the anticipated proposals from the European Commission for a revision of legislation governing veterinary medicinal products that are expected to be published in 2014 represent an exceptional opportunity for improvement.

The veterinary pharmaceutical industry as a whole has a turnover roughly equivalent to one blockbuster medicine in the human domain. This small market size, even for products which are widely used, implies challenges in terms of attracting investment, and can make it difficult for companies to make many of their products economically viable once on the market. This is especially true for medicines aimed at minor use in major species or for minor species (MUMS). Here, improving data protection could stimulate research for new medicines or for investing in research to extend existing products for use in new species. Any new framework needs to strike a balance between ensuring high standards in terms of protecting public and animal health while recognising the particular nature of the veterinary domain. More generally, there is a need to move towards the creation of a genuine single market in the EU for veterinary medicines. There needs to be a move away from the current situation where there is a lack of harmonisation between countries, for example concerning indications or withdrawal periods for the same veterinary medicine when marketed in different parts of the EU, as this is very difficult to understand for veterinarians and the general public. A way needs to be found to ensure that, in future, the conditions of use of a medicine are harmonised, whichever path to authorisation is taken. A genuine single market would also require the progressive harmonisation of existing authorisations of medicines throughout the EU.

Another challenge is to make the veterinary sector more attractive to innovation. There is currently no clearly defined regulatory pathway to authorisation for very innovative medicines such as cytokines, nanomedicines or stem cell treatments, contrary to human medicines where there is a specific framework for advanced therapies. Defining a regulatory path for advanced veterinary therapies, without introducing disproportionate or inflexible requirements, would act as an incentive for industry to invest in this field, for the benefit of animal health.

Finally, regulators would benefit from new tools to minimise the risks to human health that may arise from the use of antimicrobials in veterinary medicines through the development of resistance to antibiotics. A clear legal basis is required to take into account the particular benefit/risk assessment that relates to antibiotics, due to their potential impact on human health. The legislation needs to also take into account that the continued availability of appropriate antibiotics is essential both for public and animal health, as healthy food only comes from healthy animals. Future legislation therefore needs to provide predictability in terms of the controls that are appropriate for safe use of existing antibiotics, and also on what would be the expectations in terms of demonstrating a positive benefit-risk balance for bringing a new antibiotic to the veterinary market.

Experience has shown that all stakeholders need to be actively engaged for measures to promote availability to be successful, from the European medicines regulatory network (i.e. the European Commission together with national competent authorities and the European Medicines Agency) to the animal health industry and veterinarians, but also the general public. In this context, the Agency and the Heads of Medicines Agencies in the veterinary sector will contribute to the reflection, paying particular attention to the need to preserve the sustainability of the network of expertise they have built together.

Jean-Pierre Orand (left), David Mackay (right)

Fergus Sweeney (left), June Raine (right)

2.3 Health

Engagement of patients and healthcare professionals for safer use of medicines

June Raine, Chair of the Pharmacovigilance Risk Assessment Committee
Fergus Sweeney, EMA Head of the Inspections and Human Medicines Pharmacovigilance Division

The year 2013 has seen a significant new dimension in the Agency's engagement with patients and healthcare professionals in its scientific and public health work. The new European pharmacovigilance legislation opened new opportunities for involvement of civil society by providing new routes to incorporate the public's views and preferences into the regulatory decision-making process.

Engagement is at the core of increasing public confidence. Public participation in decision making and enhancing public knowledge and understanding of regulatory decisions contributes to building trust and confidence in the whole medicines regulatory system. This interaction enriches the scientific assessment and gives valuable insight into the way medicines are used on the ground and into perceptions of risks among patients and the general public.

The Agency recognises the importance of listening. Throughout the European Union, patients can now report suspected adverse drug reactions at national level. Following the entry into force of the new pharmacovigilance legislation, the number of reports submitted to the Agency that originate from patients rose by 62%. These spontaneous reports are particularly valuable to ensure rapid detection of new and changing safety issues, particularly those issues of greatest concern to patients.

Representatives of patients and healthcare professionals are fully involved in the assessment of safety issues related to medicines through their membership of the PRAC, the EMA's dedicated committee for pharmacovigilance. They bring the extensive knowledge and views of their wider community and associations alongside their own experience and expertise. Specialist clinical advice is added through scientific advisory groups. When we conducted the review of a lipid-lowering medicine for example, advice provided by a group of experts in the treatment of lipid disorders was extremely useful and helped us to reposition the use of that medicine in the context of current therapeutics.

The new legislation also enabled us to actively invite all stakeholders to take part in the evaluation process by sending us relevant data in order to facilitate prompt and efficient processing of their concerns. We used this new tool as part of the emergency safety review of a nutrition fluid for premature infants. The contributions received gave important perspectives on the medicine's risks and appropriate risk management, taking into account the role of the medicine in healthcare.

Engaging with patients and healthcare professionals also means testing with them that the recommendation we provide is feasible and understandable and therefore effective. We systematically involve them in the review of our safety communications. Their participation was particularly helpful during the review of combined hormonal contraceptives, to shape the right message in our various communication documents, including a checklist for healthcare professionals, a patient leaflet and a patient alert card, and to disseminate this new information. In addition to these activities, the Agency also relies on the recommendations of the Patients' and Consumers' Working Party and the Healthcare Professionals' Working Party on matters of interest to them such as transparency or new routes to engage civil society; for example we actively consulted them when we introduced the black symbol to flag new medicines that are being monitored more closely in the EU.

The experience of 2013 underlined that patients and healthcare professionals have a critical role in helping regulators reach their goal of a common understanding of the acceptable level of risk and a clear way of communicating that to the public. People measure risk differently depending on the disease that affects them and a number of other factors. We need to hear from patients to understand this. Public hearings, another new tool provided by the legislation, will be a key addition to our strategy for achieving this. Patients and all other stakeholders will have the opportunity to shape how this tool will work to add greatest value when proposed rules of procedure are released for public consultation in 2014.

3 | Significant recommendations in 2013

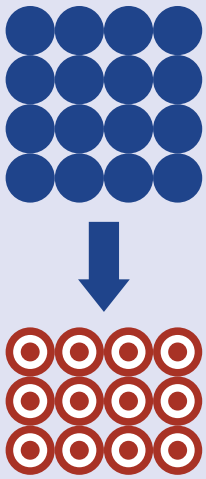
This chapter presents the main outcomes of the Agency's activities. These include the most notable recommendations for approval issued by the Agency in 2013 for human and veterinary medicines. Recommendations for both new medicines and line extensions are highlighted.

This chapter also describes the most important safety reviews related to human and veterinary medicines that the Agency finalised in 2013, and their outcomes.

Finally, a selection of concept papers, reflection papers, joint recommendations and guidelines is included in this chapter.

3.1 | Human medicines

Recommendations for approval
The Committee for Medicinal Products for Human Use (CHMP) recommended a total of 81 new medicines for marketing authorisation in 2013.



In 2013, 16 new medicines for the treatment of cancer were recommended for marketing authorisation, of which 12 contain a new active substance. Most of these medicines are considered to be targeted therapies, designed to block the growth and spread of cancer by interfering with specific molecules involved in tumour growth, or act on the patient's immune system.

Particularly noteworthy in the other therapeutic areas, is the recommendation of three medicines for the treatment of multidrug-resistant tuberculosis, an orphan indication associated with a very high mortality rate and whose burden has rapidly increased in recent years in the absence of new treatment options.

In 2013, the CHMP recommended the approval of four new medicines for use in patients infected with human immunodeficiency virus (HIV), all of which contain a new active substance, and five medicines for the treatment of type 2 diabetes, four of which contain a new active substance.

Of note, the CHMP recommended conditional marketing authorisations for five medicines and approval under exceptional circumstances for four medicines. Conditional marketing authorisations and approval under exceptional circumstances are intended to support market access of medicines that address previously unmet medical needs or have other relevant benefits for patient care or public health. Among the 81 medicines recommended for marketing authorisation, several medicines are particularly noteworthy because of their impact on public health or their innovative approach.

In the treatment of cancer, the most notable medicines include the following:

- **Bosulif** (bosutinib) for the treatment of chronic myelogenous leukaemia (CML). Bosulif is a designated orphan medicine. It is a protein kinase inhibitor which acts by inhibiting the abnormal Bcr-Abl kinase that promotes CML. Bosulif was granted conditional marketing authorisation.

- **Cometriq** (cabozantinib) for the treatment of medullary thyroid cancer, a rare type of thyroid cancer that cannot be removed by surgery or that has spread to other parts of the body. The medicine inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cometriq has an orphan designation. It was granted conditional marketing authorisation.

- **Erivedge** (vismodegib) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy. The medicine acts by blocking specific genes involved in proliferation, survival and differentiation of cells. Erivedge was granted conditional marketing authorisation.

- **Kadcyla** (trastuzumab emtansine) for use in patients with advanced or metastatic breast cancer that overexpress HER2, a protein present at the surface of the cancer cells. Kadcyla is the second antibody-drug conjugate which has been approved for marketing authorisation so far. The medicine combines an antibody and an active substance. The antibody can direct the medicine to the protein HER2, allowing a selective delivery of the active substance to cancer cells.

- **Pomalidomide Celgene** (pomalidomide) for the treatment of multiple myeloma, a rare and incurable cancer of the bone marrow. The medicine is for use in patients who have failed at least two prior therapies and for whom very limited treatment options are available. When used in combination with dexamethasone, Pomalidomide Celgene stimulates the patient's immune system to attack cancerous cells and stops the formation of blood vessels supplying these cells. Due to its teratogenic profile, the risk management plan for Pomalidomide Celgene was extensively discussed with patients, including victims of thalidomide, another compound with a similar chemical structure.

- **Provenge**, an advanced-therapy medicinal product (ATMP) for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated. Metastatic prostate cancer is the leading cause of prostate cancer-

related death and the disease cannot be cured by currently available therapies. Provenge is a cellular immunotherapy designed to induce an immune response against prostate cancer cells.

- **Tafinlar** (dabrafenib) for the treatment of adult patients with advanced (unresectable or metastatic) melanoma expressing a BRAF V600 gene mutation. Tafinlar is a targeted therapy meaning that it is designed to block the growth and spread of cancer by interfering with specific molecules involved in tumor growth. Mutations of the protein kinase BRAF have been identified in about half of all patients with metastatic melanoma, with the BRAF V600E mutation found in about 80% to 90% of these. By blocking the action of this abnormal protein, BRAF inhibitors such as Tafinlar help slow down the growth and spread of tumours bearing the BRAF V600 mutation. Tafinlar is the second BRAF inhibitor to be recommended for marketing authorisation in the EU.

For the treatment or prevention of infectious disease, the following medicines are particularly noteworthy:

- **Deltyba** (delamanid), the second treatment in 2013 that was recommended for the treatment of adult patients with pulmonary infections due to multidrug-resistant tuberculosis when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability. Deltyba was granted a conditional marketing authorisation.

- **Imvanex** (modified Vaccinia Ankara virus) for the active immunisation against smallpox in adults. Imvanex was granted approval under exceptional circumstances.

- **Sirturo** (bedaquiline) for use as part of a combination therapy for pulmonary multidrug-resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Multidrug-resistant tuberculosis is an orphan indication in the EU associated with a very high mortality rate and whose burden has rapidly increased in recent years in the absence of new treatment options. Similarly to Deltyba, Sirturo could contribute to responding to the high unmet medical need for new treatment options for this indication. Sirturo was also granted conditional marketing authorisation.

- **Sovaldi** (sofosbuvir) for use in combination with other medicines for the treatment of chronic (long-term) hepatitis C in adults. Sovaldi is the first representative of a new class of antivirals that act as inhibitors of an essential enzyme of the hepatitis C virus (HCV), the NS5B ribonucleic acid polymerase. This medicine provides the first interferon-free treatment option for chronic hepatitis C. Interferon-based therapies are associated with potentially serious side effects, which are sometimes difficult to manage and also make a considerable proportion of HCV patients ineligible for therapy. For these patients, there is a clear unmet medical need for new HCV treatment regimens.

- **Tivicay** (dolutegravir) for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral medicines. Tivicay has demonstrated its efficacy in previously untreated patients as well as patients with advanced treatment histories and resistant to multiple classes of HIV medicines. It demonstrated a high barrier to resistance, meaning that it is less prone to resistance development. The medicine blocks an enzyme called integrase, which is involved in the reproduction of HIV, and therefore slows down the spread of infection.

- **Tritanrix HB** for immunisation against diphtheria, tetanus, pertussis and hepatitis B in infants from six weeks onwards. The CHMP adopted a scientific opinion for Tritanrix HB in the framework of Article 58 of Regulation (EC) No 726/2004. Medicines eligible for this procedure are used to prevent or treat

diseases of major public health interest. Tritanrix HB is no longer used in the EU and its EU marketing authorisation ceased to be valid at the end of 2013. The request was submitted to the EMA by the applicant under Article 58 in order to avoid an interruption in the availability of the vaccine outside the EU, where it is still used in several countries.

Medicines for other therapeutic areas included the following:

- **Cholic Acid FGK** (cholic acid) for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or a-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7a-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults. Cholic acid FGK has an orphan designation. It was granted approval under exceptional circumstances.

- **Defitelio** (defibrotide) for the treatment of severe veno-occlusive disease in patients undergoing haematopoietic stem-cell transplantation. Defitelio has an orphan designation. Its mechanism of action has not been fully elucidated. Defitelio was granted approval under exceptional circumstances.

- **Inflectra and Remsima** (infliximab), the first two monoclonal-antibody biosimilars. Remsima and Infectra are similar to the biological medicine Remicade, a monoclonal antibody that has been authorised in the EU since 1999. These medicines mark the first time that the biosimilar concept has been successfully applied to such structurally complex molecules. Remsima and Inflectra are recommended for authorisation in the same indications as Remicade, covering a range of auto-immune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

- **Jetrea** (ocriplasmin) for the treatment of adults with vitreomacular traction (VMT), an eye condition which can cause severe visual disturbance. Jetrea represents the first medicinal option for patients suffering from this condition. The only active treatment option currently available for VMT is surgery (vitrectomy), which often implies for the post-vitrectomy patient to undergo a period of four to six weeks without being able to work or live normally.

- **Lojuxta** (lomitapide) as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low-density lipoprotein apheresis in adult patients with homozygous familial hypercholesterolaemia. The medicine acts by inhibiting microsomal transfer protein which is responsible for binding and shuttling lipids between membranes. Lojuxta was granted approval under exceptional circumstances.

- **Maci** (matrix-induced autologous chondrocyte implantation), an advanced-therapy medicinal product (ATMP), for the repair of symptomatic, full-thickness cartilage defects of the knee of 3-20 cm^2 in skeletally mature adult patients. Maci is the first combined tissue-engineered medicine authorised across the EU. Maci uses a scaffold formed of porcine collagen on which autologous chondrocytes are seeded. The benefit of autologous chondrocyte implantation over other restoration techniques is that larger lesions can be treated.

- **Nuedexta** (dextromethorphan hydrobromide and quinidine sulphate) for the treatment of pseudobulbar affect in adults, a medical condition in which patients experience sudden and uncontrollable bouts of laughing or crying unrelated or disproportionate to their emotional state. Nuedexta is the first treatment approved for pseudobulbar affect in the European Union. Although pseudobulbar affect is a non-life-threatening condition, it can have a significant impact on an individual's ability to interact normally in society and on their relationship with others.

Compassionate-use programmes
The Agency's CHMP gave two opinions on the use of new medicines in a compassionate-use programme. Such programmes, set up at the national level, are intended to give patients with a life-threatening, long-lasting or seriously disabling disease who have no available treatment options access to medicines that are still under development and that have not yet been authorised. These medicines are:

- **Sofosbuvir** for chronic (long-term) hepatitis C virus infection in combination with other agents could be given specifically for patients before or after liver transplantation. The CHMP's opinion on this compassionate-use programme was issued one month before the medicine was recommended for marketing authorisation.

- **Daclatasvir** in combination with sofosbuvir in the treatment of chronic (long-term) hepatitis C virus infection.

Extensions of existing indications
A total of 18 extensions of marketing authorisations were finalised in 2013.

The most noteworthy medicines that had their indications extended to include new populations of patients, including paediatric indications, in 2013:

- **Abraxane**: extension of the therapeutic indication to include pancreatic cancer, the fifth leading cause of cancer-related death. The medicine was already approved for the treatment of metastatic breast cancer.

- **Pegasys**: extension of the therapeutic indication to include paediatric patients of five years of age and older with HCV, in addition to adult patients.

- **Humira**: extension of the therapeutic indication to include children and adolescents aged 2 to 17 years with polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

- **Revlimid**: extension of the therapeutic indication to include patients with myelodysplastic syndromes. The medicine was already authorised for the treatment of multiple myeloma.

- **Glivec**: extension of the therapeutic indication to include paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

- **Prezista**: extension of the therapeutic indication to include the treatment of HIV-1 infected paediatric patients from the age of 12 years and at least 40kg body weight.

- **Zonegran**: extension of the therapeutic indication to include asthmatic adolescents and children aged six years and above.

- **Votubia**: change to the indication for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), extending the use to younger children.

- **Vepacel**: extension of the therapeutic indication to include active immunisation against H5N1 subtype of influenza A virus in children from the age of six months onwards.

- **Pandemic Influenza Vaccine H5N1 Baxter**: extension of the therapeutic indication to include pandemic influenza vaccination of children and adolescents from the age of 6 months onwards.

Safety reviews
The Agency carried out a number of safety reviews in 2013. The most notable recommendations issued include:

- Suspension of the marketing authorisations of **Tredaptive, Pelzont** and **Trevaclyn** (nicotinic acid / laropiprant) because new data showed that the use of these medicines with a statin had no significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin therapy alone, and that they did cause side effects of their own; these medicines were used to treat adults with dyslipidaemia.

- Restriction of the indications for **ergot derivatives** which should no longer be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications.

- Confirmation of positive benefit-risk balance for **intravenous iron-containing medicines** in the treatment of iron deficiency and anaemia associated with low iron levels, provided that adequate measures are taken to ensure the early detection and effective management of allergic reactions that may occur.

- Risk-minimisation measures for **diclofenac** containing medicines The same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied to diclofenac.

- Because of a risk of liver toxicity, restriction of the use of oral **flupirtine** medicines and suppositories to the treatment of acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids. In addition, there are new contraindications and advice to healthcare professionals.

- A series of risk-minimisation measures to address safety concerns with **codeine**-containing medicines when used for the management of pain in children, including restricting the use of these medicines to the treatment of acute moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen. New contraindications and warnings are also recommended.

- Confirmation of a positive benefit-risk balance of **Diane 35** (cyproterone acetate 2 mg / ethinylestradiol 35 micrograms) and its generics, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. New contraindications, warnings to patients and healthcare professionals and further pharmacovigilance activities were recommended, as were educational materials for prescribers and patients to raise awareness of the risks, signs and symptoms of thromboembolism.

- Confirmation of positive benefit-risk balance for **combined hormonal contraceptives** (CHCs) in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of venous thromboembolism with all CHCs is small. The review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care. The product information of CHCs will be updated to help women make informed decisions about their choice of contraception together with their healthcare professional.

- Conclusion that there are no new concerns for **GLP-1-based diabetes therapies**. The review of all available non-clinical and clinical data did not confirm concerns over an increased risk of pancreatic adverse events with these medicines.

- Suspension of the marketing authorisation of **Numeta G13%E**, an intravenous nutrition preparation for premature babies, because of a risk of hypermagnesaemia. Numeta G13%E will remain suspended until a reformulated preparation is made available. The benefit-risk balance of Numeta G16%E, another nutrition preparation which is used in full-term newborns and children up to two years, remains positive, provided that healthcare professionals monitor their patients' blood magnesium levels before and after giving the preparation.

- Restriction of the use of **hydroxyethyl-starch solutions** (HES) which should no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and raised mortality.

- Recommendations to help minimise the risk of blood clots obstructing arteries or veins in patients taking the leukaemia medicine **Iclusig**.

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 2013, the Agency developed new guidelines and revised existing guidance in order to reflect the latest scientific developments and experience gained in a number of areas. Below is a selection of this work. In the area of similar biological medicines (also known as '**biosimilars**'), the Agency pursued in 2013 the revision of its three overarching guidelines on this type of medicines, which started with the revision of a guideline addressing the quality issues related to biosimilar development in 2012. In 2013, the Agency released the following:

- A revised overarching guideline on similar biological medicines for public consultation which describes the concept of similar biological medicines and outlines the general principles to be applied; the revision also covers global development aspects, including the choice of the reference product when conducting non-clinical and clinical studies.

- A revised overarching guideline addressing the clinical and non-clinical issues related to similar biological products containing biotechnology-derived proteins as the active substance, for public consultation.

These overarching guidelines are complemented by product-specific biosimilar guidelines. In 2013, the Agency released a revised guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins (LMWHs), for public consultation.

In the area of **nanomedicines**, the Agency completed a series of four reflection papers in 2013. They are intended to provide guidance to sponsors developing medicines in this emerging scientific area and include the following:

- A joint EMA/Japanese Ministry of Health, Labour and Welfare (MHLW) reflection paper on the development of block-copolymer-micelle medicinal products, released for public consultation.

- A final reflection paper on general issues for consideration regarding the parenteral administration of coated nanomedicines.

- A final reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product.

- A draft reflection paper on the data requirements for intravenous iron-based nanocolloidal products developed with reference to an innovator medicine, released for public consultation.

In the area of **demonstration of bioequivalence studies**, the Agency released for the first time product-specific guidance on the demonstration of bioequivalence for 16 active substances for public consultation. The aim of this guidance is to enable a consistent approach to the assessment of applications supported by bioequivalence data, particularly generic applications, across all authorisation routes, i.e. centralised, decentralised, mutual-recognition and national authorisation procedures. This was only the first wave of such product-specific guidance. The Agency intends to continue developing this type of guidance with another wave planned in 2014.

In the area of **quality by design**, the EMA, in collaboration with the U.S. FDA, published two joint question-and-answer documents that provide guidance on specific aspects of the concept. This guidance was developed as part of a three-year EMA/FDA pilot programme for the parallel assessment of certain quality or chemistry manufacturing and control (CMC) sections of applications that are relevant to quality by design.

Other important and noteworthy new guidance documents published by the Agency in 2013:

- A final addendum to the guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections, which outlines a new approach facilitating the development of agents targeted against multidrug-resistant pathogens where patients have very limited or no remaining treatment options.

- A final revised guideline on the evaluation of anticancer medicines, which includes guidance on the use of biomarkers as an integrated part of the development of medicines, combination-therapy studies and the choice of endpoints in confirmatory trials.

- The first guideline in the European Union on clinical investigation of medicines for the treatment of lupus erythematosus, for public consultation.

- A final revised guideline on clinical investigation of medicines for the treatment of major depressive disorder, which addresses the specific issues related to patients who only respond partially to treatment and who are considered treatment-resistant, and provides recommendations on how to investigate medicines in these two patient populations.

- A revised guideline on the clinical development of medicines intended for the treatment of pain, for public consultation, which defines models of nociceptive and neuropathic pain that can be used for medicine development, as well as models of mixed pain.

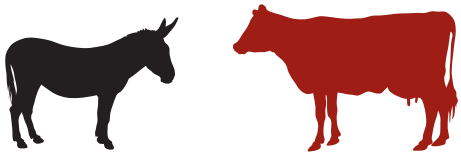
- A revised guideline on the clinical development of medicines for the treatment of human-immunodeficiency-virus (HIV) infection, for public consultation, which takes into account the recent change in the landscape of HIV treatment and provides a new definition of populations included in clinical trials.

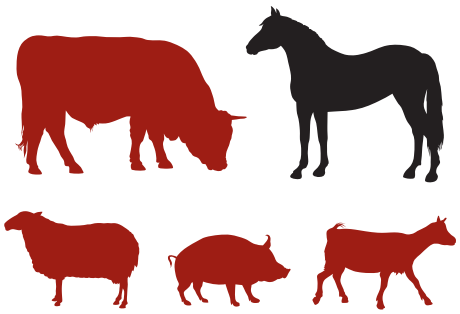
- A reflection paper on the use of medicines to prevent the transmission of HIV, released for public consultation.

- A concept paper on the need to revise the guideline on medicines for the treatment of Alzheimer's disease and other dementias, for public consultation, which outlines how recent progress in understanding the neurobiology and pathophysiology of the disease and recent developments on new diagnostic criteria and biomarkers have had an impact on recent and future clinical-trial protocols, and which discusses the elements to consider as part of the revision of the current guideline.

- New and updated modules and chapters of the 'Good pharmacoVigilance practice' (GVP) guidline were made available, including on vaccine vigilance, on periodic safety update reports, on safety communications and on additional monitoring of medicines.

3.2 | Veterinary medicines





Recommendations for approvals
The Committee for Medicinal Products for Veterinary Use (CVMP) issued 12 positive opinions in 2013 for new veterinary medicines, of which three were for immunological products for food-producing species, eight related to pharmaceuticals intended for companion animals and one was a generic pharmaceutical intended for both food-producing and non-food-producing species. The majority of the medicines aimed at companion animals were antiparasital products for cats and dogs.

- **Aftovaxpur DOE**, a vaccine for use in response to outbreaks of foot-and-mouth disease (FMD). The vaccine is intended for active immunisation of cattle and sheep from two months of age and pigs from ten weeks of age to reduce clinical signs of the disease. While some FMD vaccines had previously obtained a marketing authorisation at the national level, Aftovaxpur DOE was the first FMD vaccine to be recommended for use across all EU Member States. It was also the first vaccine using the full multi-strain dossier approach, a concept which was established in 2010 to allow the swift availability of suitable vaccines in case of outbreaks of major livestock diseases, as it allows for the most effective strain combination to be selected.

- **Ecoporc Shiga**, a vaccine for the active immunisation of piglets from the age of four days to reduce the mortality and clinical signs of oedema disease, which leads to fluids accumulating in the tissues of the stomach and gut. The disease is caused by Stx2e, a toxin produced by *Escherichia coli* bacteria.

- **Equilis West Nile**, a vaccine for the active immunisation of horses from six months of age against West Nile virus to reduce clinical signs of disease and lesions in the brain and to reduce viraemia. West Nile virus is an infection that is transmitted by mosquitoes and can cause severe disease and fatal brain infections in infected horses.

- **Oncept IL-2**, an immunotherapy product to be used in cats with fibrosarcoma, a type of aggressive tumour that affects the soft tissues. It is used in combination with surgery and radiotherapy to reduce the risk of, and delay, the tumour coming back.

- **ProZinc** (insulin human), indicated for the treatment of diabetes mellitus in cats. It is meant to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

- **Apoquel** (oclacitinib maleate), to be used in dogs to treat pruritus (itching) associated with allergic dermatitis (inflammation of the skin). It is also used in dogs to treat atopic dermatitis.

- **Trifexis** (spinosad / milbemycin oxime), indicated for the treatment and prevention of flea infestations in dogs when there is also a need to prevent heartworm disease (roundworms that infect the heart and blood vessels and are transmitted by mosquitoes) and/or to treat gut infections by other types of worms (the nematodes hookworm, roundworm and whipworm).

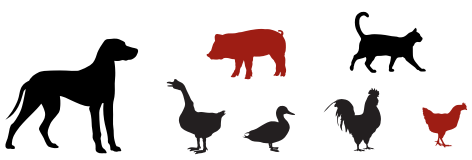
- **Vectra 3D** (dinotefuran/pyriproxyfen/permethrin), a spot-on solution for dogs, intended for the treatment and prevention of infestations by fleas and ticks. Vectra 3D is also intended for the prevention of bites from sand flies, mosquitoes and stable flies.

- **Broadline** (fipronil/eprinomectin/praziquantel/S-methoprene), a spot-on solution intended for cats with existing, or at risk from, mixed parasitic infections.

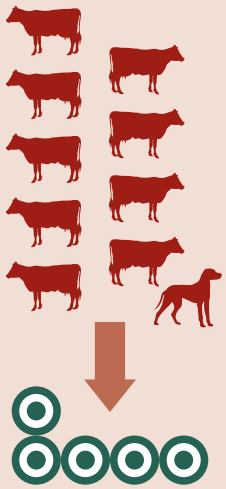
- **Bravecto** (fluralaner), chewable tablets indicated for the treatment of flea and tick infestations in dogs.

- **NexGard** (afoxolaner), chewable tablets indicated for the treatment of flea and tick infestations in dogs.

- **Meloxidolor** (meloxicam), an anti-inflammatory and antirheumatic generic for dogs, cats, cattle, pigs and horses. The benefits of Meloxidolor are the alleviation of inflammation and relief of pain.



Safety reviews



In 2013, the CVMP started nine referral or arbitration procedures related to veterinary medicinal products for food-producing animals and one arbitration related to a veterinary medicinal product for companion animals. Half of these procedures were initiated to assess a potential serious risk to the environment linked to the use of veterinary medicines.

Among the most noteworthy procedures started in 2013 were the following:

- Veterinary medicines containing **altrenogest** to be administered orally to pigs and horses. The aim of the referral is to consider the potential serious risk to the environment from the use of these products.

- Veterinary medicines containing **tylosin** to be administered orally via feed or drinking water to pigs. The aim of the referral is to consider the treatment durations and whether these veterinary medicines are still effective for the treatment of swine dysentery (caused by *Brachyspira hyodysenteriae*).

The CVMP concluded 13 referral or arbitration procedures in 2013. The most notable were the following:

- Recommendation on harmonised indications, dosage regimens and withdrawal periods for chickens and turkeys for veterinary medicinal products containing **enrofloxacin**, to be administered via the drinking water to chickens and/or turkeys.

- Recommendation on harmonised withdrawal periods and environmental risk-mitigation measures for veterinary medicinal products containing **doramectin**, to be administered to food-producing animals.

Joint recommendations

In 2013, several joint recommendations involving the EMA, its scientific committees and other EU agencies were defined for major public-health issues stemming from the veterinary field:

- In April 2013, the EMA worked with the European Food Safety Authority (EFSA) to produce a joint statement on the presence of residues of phenylbutazone in horsemeat, concluding that the illegal presence of residues of **phenylbutazone** in horsemeat is of low concern for consumers due to the low likelihood of exposure and the overall low likelihood of toxic effects.

- The CVMP, together with the CHMP, EFSA and the European Centre for Disease Prevention and Control (ECDC) provided advice to the European Commission, in July 2013, on the impact on public health and on animal health of the use of the antibiotics **colistin** and **tigecycline** in animals. This was the first response to a series of four questions raised by the Commission in a request to the Agency related to the use of antimicrobials in animals and the potential impact of this use on human and animal health.

Guidelines

A number of guidelines and guidance documents were adopted for consultation or published during 2013. They relate to the quality, safety, environmental risk assessment and efficacy of medicines for veterinary use.

The CVMP also adopted several guidance documents for antimicrobial medicines, particularly to ensure that these medicines are appropriately used, in order to reduce as much as possible the risk of development of antimicrobial resistance in animals and humans. Guidance in this area included the following:

- Concept paper on the development of a guideline on antimicrobial risk assessment. The guideline aims

to provide a basis for transparent and consistent assessment of the public-health risk related to animicrobial resistance to be applied by both companies and regulatory bodies. Adopted for consultation in January 2013.

- Draft reflection paper on the risk of antimicrobial resistance transfer from companion animals. Adopted for consultation in October 2013.

- 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. Adopted in November 2013.

- Guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances. Adopted for consultation in May 2013.

In the area of pharmacovigilance, the CVMP adopted several guidance documents, including the following:

- Reflection paper on pharmacovigilance communication concerning veterinary medicinal products. Adopted in December 2013.

- Draft recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products. Adopted for consultation in December 2013.

Other guidance documents:

- Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products. Published in July 2013.

- Reflection paper on injection-site residues. Adopted for consultation in October 2013.

- Concept paper on assessing the toxicological risk to humans and the environment of veterinary pharmaceuticals in groundwater. Adopted for consultation in April 2013.

- The CVMP adopted a concept paper, developed in coordination with relevant CHMP and CVMP working parties, on the review and update of EMA guidelines to implement best practice with regard to '3Rs' (replacement, refinement and reduction) in animal testing. Adopted for consultation in December 2013.

4 | Key figures in 2013

This chapter presents the key figures of the Agency's activities in 2013 through five topics. It also highlights the major trends and changes observed over the past few years.

- **Human medicines**
- **Veterinary medicines**
- **Inspections and compliance**
- **The European medicines regulatory network**
- **Administrative aspects**

Human medicines in 2013

Research and development

473
overall number of scientific advice and protocol assistance requests received in 2013

12.6%↑
increase compared with 2012

7
applications for parallel advice with health technology assessment bodies

136
orphan designations granted

97
positive opinions on paediatric investigation plans

23
recommendations on advanced therapy classifications

64%↑
increase compared with 2012

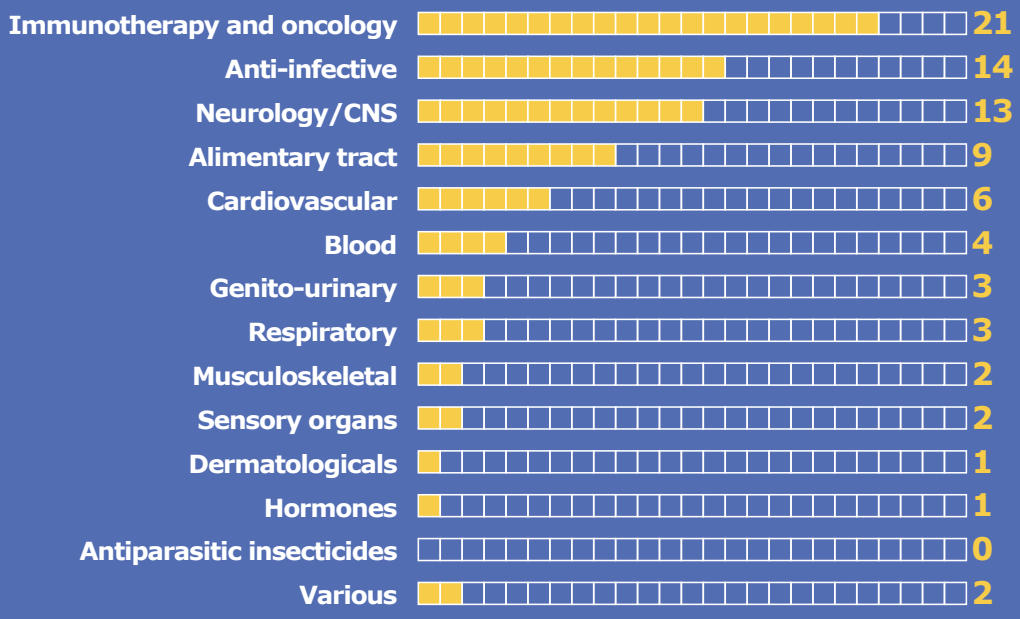
Authorisation phase

81
medicines recommended for marketing authorisation

2
advanced therapies

11
orphan medicines

2
biosimilar monoclonal antibodies



Safety monitoring

1,000,000+
ADR reports received in 2013

26.3%↑
increase compared with 2012

100
signals prioritised and analysed by the PRAC

43
referral procedures started

4.1 | Human medicines

4.1.1 Activities supporting research and development

The Agency provides pre-authorisation support to medicines developers to promote innovation and research and facilitate the availability of safe and effective medicinal products to patients and health-care professionals. This is achieved by a number of activities and incentives offered to companies prior to submission of the application for marketing authorisation. These tools promote interaction and dialogue with the Agency from the very early stages of medicine development. The assistance and support is provided by the Agency through its scientific committees as well as in collaboration with HTA bodies and international partners.

Scientific advice

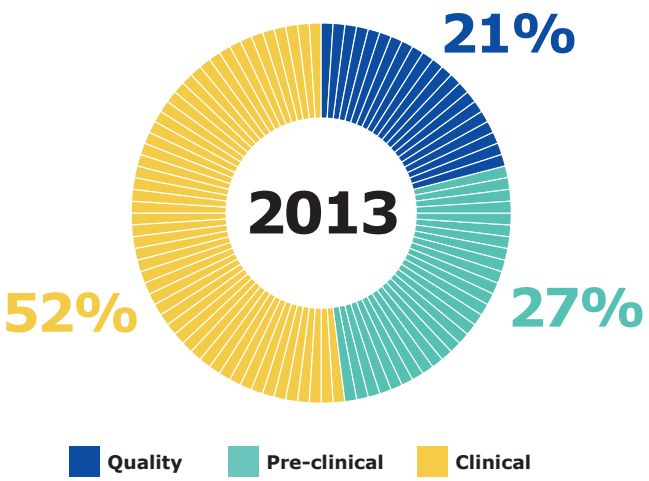
The Agency provides scientific advice and protocol assistance to sponsors during the research and development phase of medicinal products. Scientific advice is considered as one of the Agency's key tools to promote innovation and research and facilitate and improve earlier availability of medicinal products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

The overall number of scientific-advice and protocol-assistance requests received in 2013 was 473, a 12.6% increase compared with 2012.

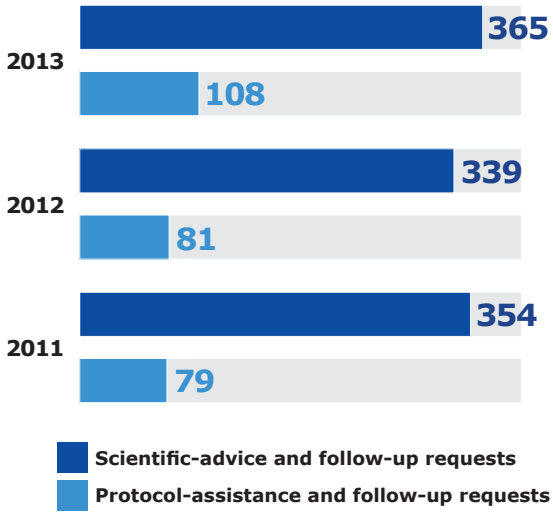
Among these requests, the Agency received seven applications for parallel advice with health technology assessment (HTA) bodies, the same number as in 2012, and six applications for parallel advice with the United States Food and Drug Administration (U.S. FDA).

As part of this activity, the Agency also received three requests for qualification opinions on the acceptability of using a new methodology in the context of research and development. There were also 12 requests for qualification advice on protocols or methods that are intended to develop a novel method with the aim of moving towards qualification.

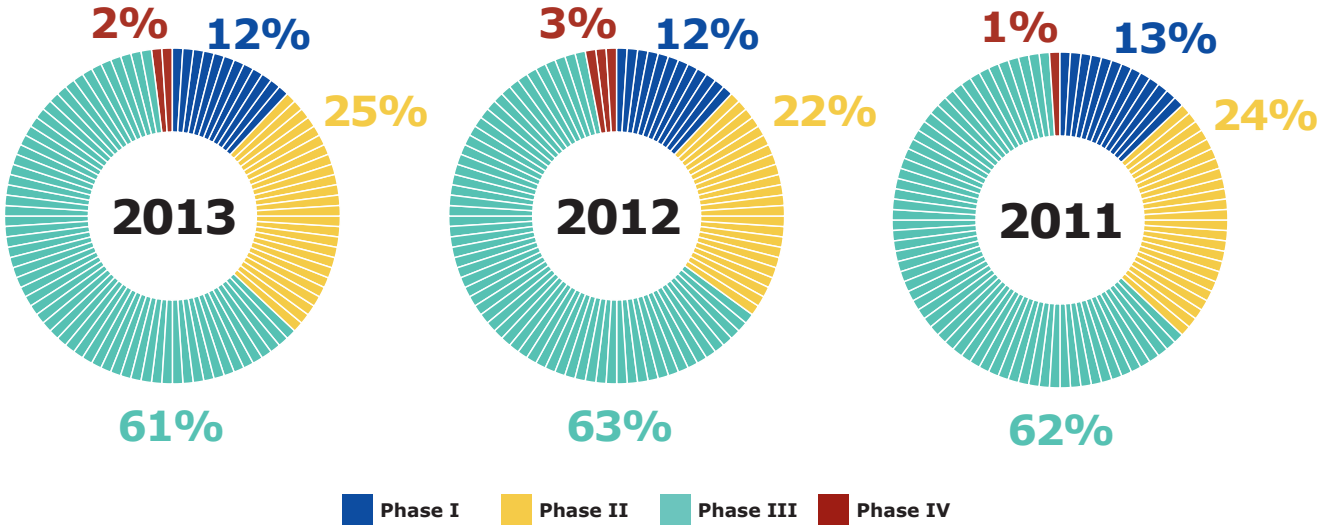
Scientific-advice requests by topic (2013)



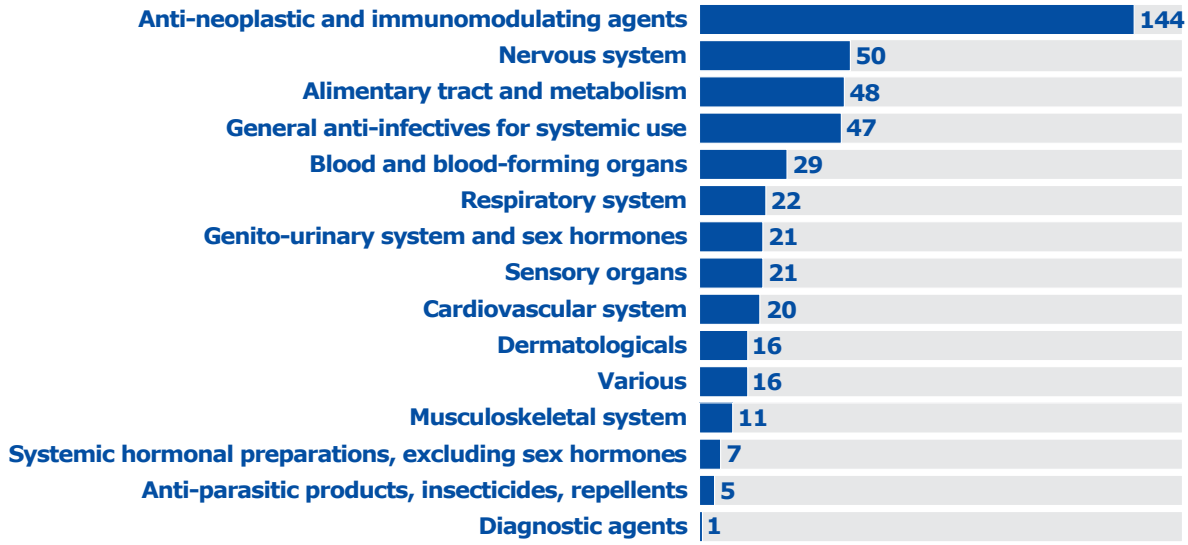
Scientific-advice and protocol-assistance requests received



Clinical-trial phases of scientific-advice requests



Scientific-advice requests by therapeutic area (2013)



Support to small and medium-sized enterprises

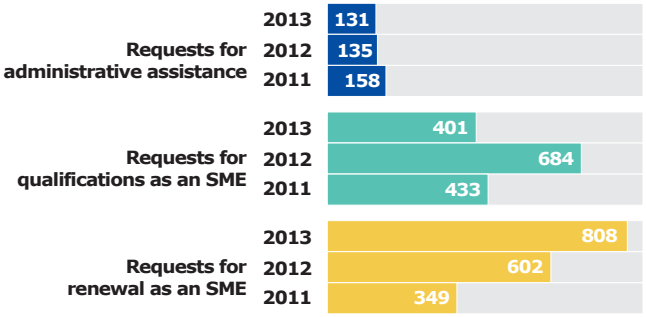
The Agency put the SME initiative in place in December 2005 to promote innovation and development of medicines by SMEs. This initiative provides active regulatory, financial and administrative support to these companies in the development of their medicines. The support takes the form of individual guidance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

In 2013, the number of companies assigned SME status by the Agency increased by 14.6% in comparison with 2012, with a cumulative total of 1,258 active SMEs registered at the end of the year.

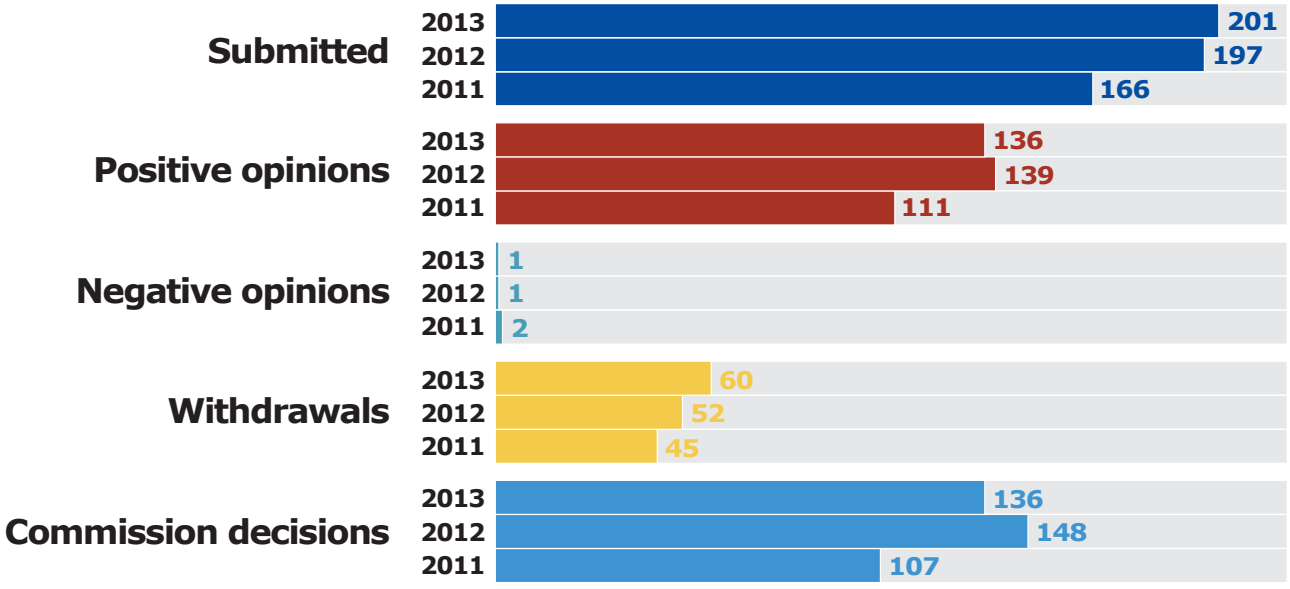
SMEs accounted for 24% of the requests for scientific advice received and 45% of the requests for protocol assistance received in 2013.

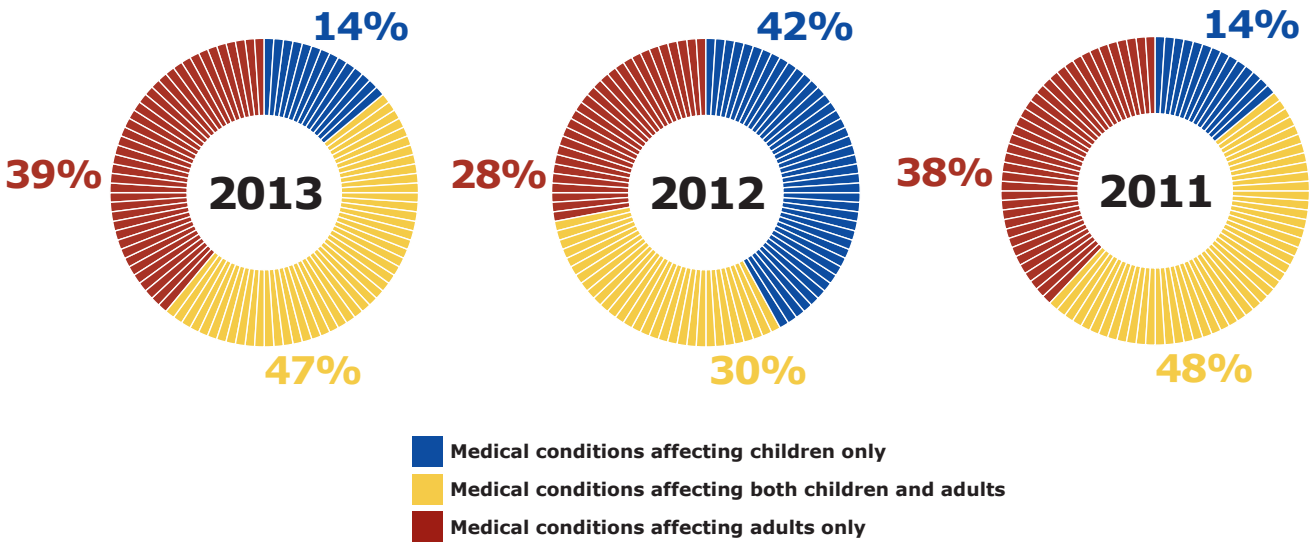
Two of the three requests for qualification opinions submitted to the Agency in 2013 and one in two requests for qualification-advice procedures were submitted by SMEs.

SME-related activites - requests received



Orphan-medicinal-product-designation procedures





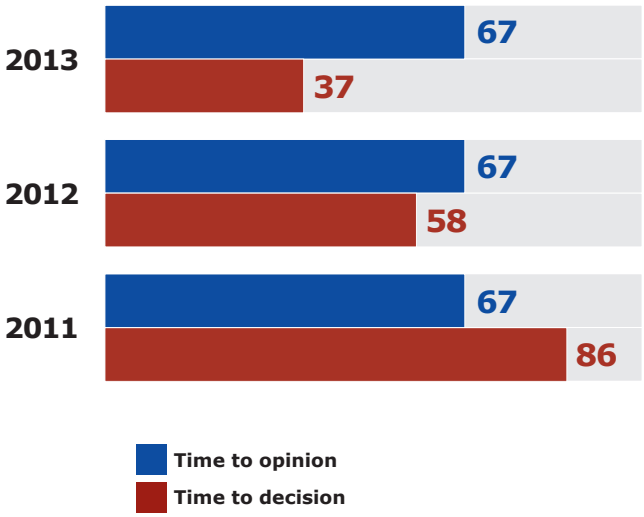
Orphan-medicine designation

Orphan medicines are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union, or where for economic reasons such medicines would not be developed without incentives.

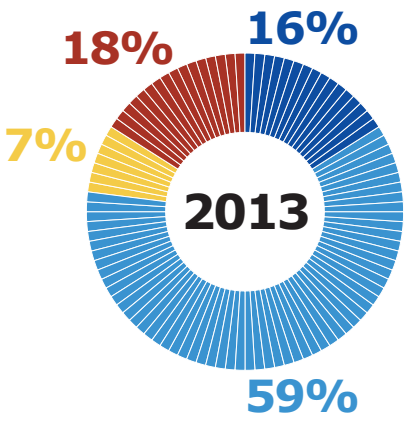
The number of applications for orphan designation remained at a stable, high level. A higher proportion of orphan-designated medicines were intended for use by both children and adults (47% in 2013 versus 30% in 2012), while the number of medicines intended for children only decreased (14% versus 42%), compared with 2012.

Similarly to previous years, the most-represented therapeutic area is cancer, with 29% of opinions for orphan designation being for oncology products.

Average time for orphan-designation procedures in days



Use of EU special contibution for orphan medicines (2013)



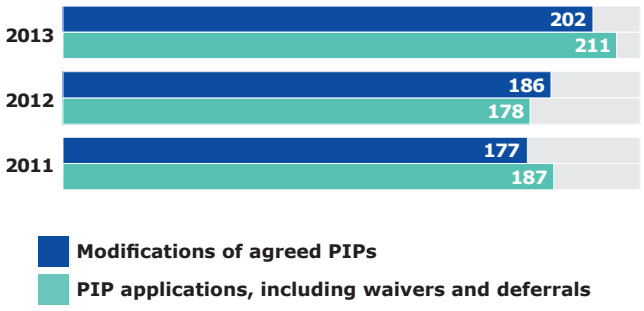
Medicines for children

This area covers the Agency's activities relating to the assessment and agreement of, and verification of compliance with, paediatric investigation plans (PIPs) and waivers by the Paediatric Committee (PDCO).

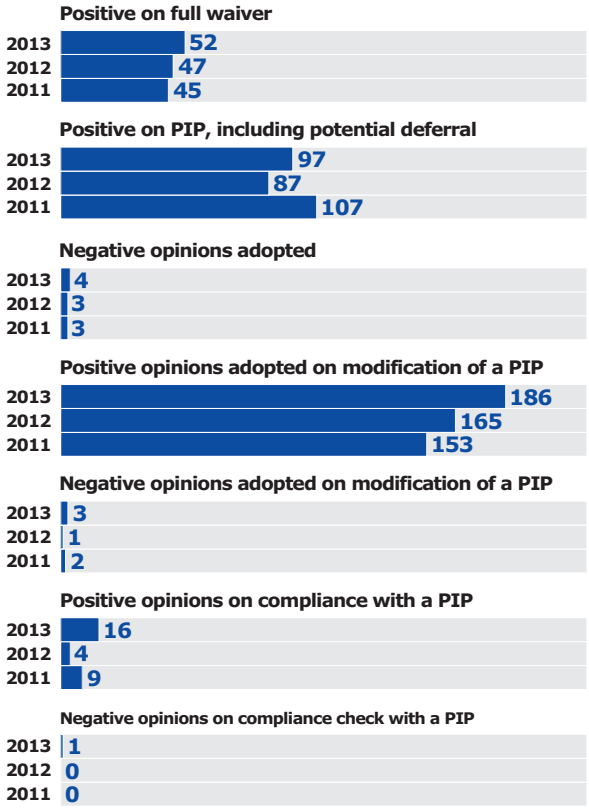
There was an 18.5% increase in the number of PIP applications, including waivers and deferrals, received in 2013 compared with 2012, and an 8.6% increase in the number of modifications of agreed PIPs received.

The PDCO conducted 64 PIP compliance checks in 2013.

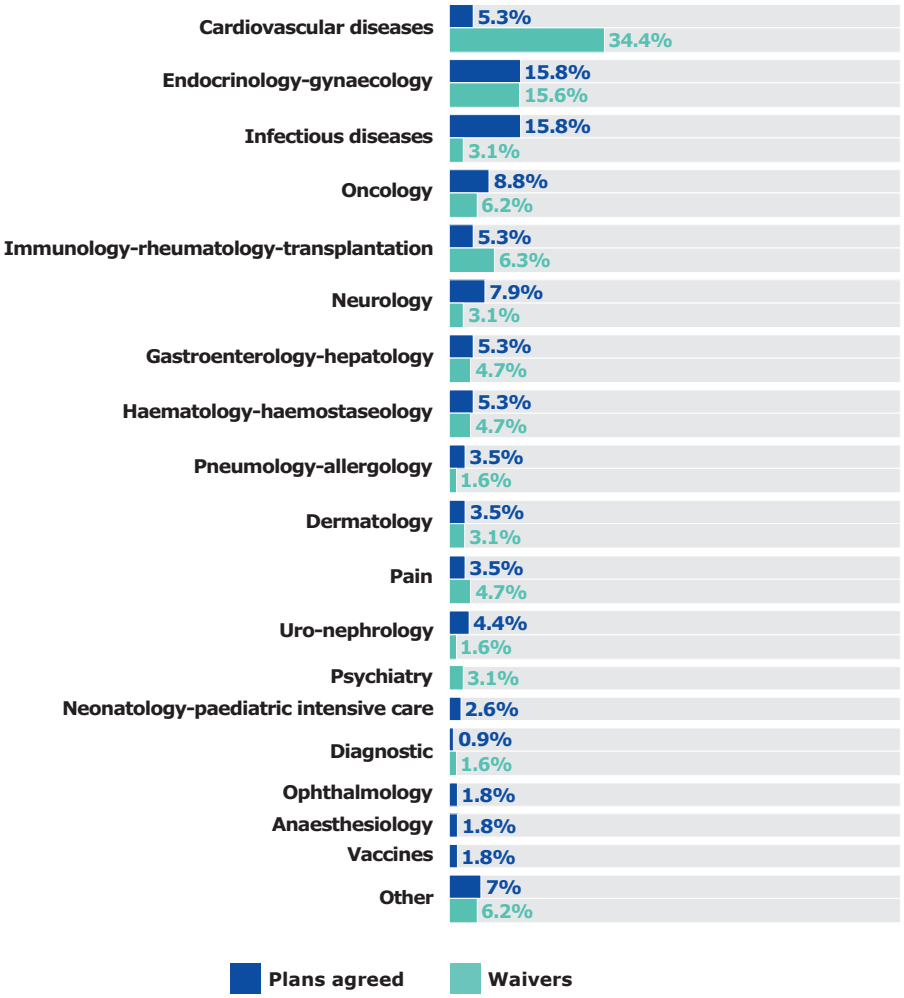
Paediatric and PIP applications received



PDCO opinions



Paediatric investigation plans agreed and waivers granted (2013)



Advanced-therapy medicinal products

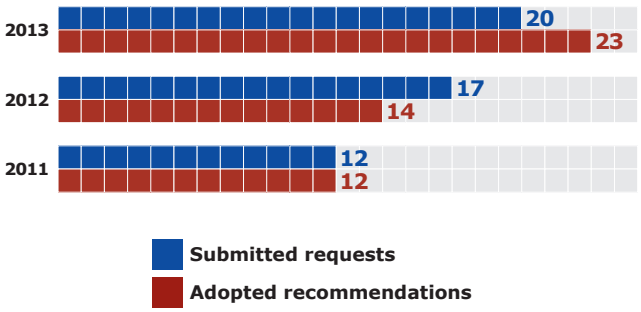
Advanced-therapy medicinal products (ATMPs) are derived from genes, tissues and cells. They may offer ground-breaking new treatment opportunities for many diseases and injuries. The Committee for Advanced Therapies (CAT) is the committee at the European Medicines Agency responsible for assessing the 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 prepared two positive draft opinions for initial marketing-authorisation applications for ATMPs in 2013.

The Committee adopted 23 recommendations on ATMP classifications, a 64% increase over 2012. The CAT received three requests for certification of quality and non-clinical data from SMEs developing ATMPs, leading to a total of five requests received since the CAT was established in 2009. The certification procedure is an opportunity for SMEs to get an assessment of the data they have generated and check that they are on the right track for successful development.

The Committee recommended issuing the first certification of non-clinical data for an ATMP in 2013.

Scientific recommendation on advanced-therapy classification



Innovation Task Force

The Innovation Task Force 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 of emerging therapies and technologies.

A total of 27 requests for early dialogue with the Innovation Task Force were received in 2013.
The outcomes of these requests were:

- 15 briefing meetings between the sponsors and experts from the European medicines regulatory network;
- eight briefing meetings addressed internally or re-directed to other procedures;
- four that did not go ahead.

4.1.2 Recommendations for authorisation

Applications for initial evaluation

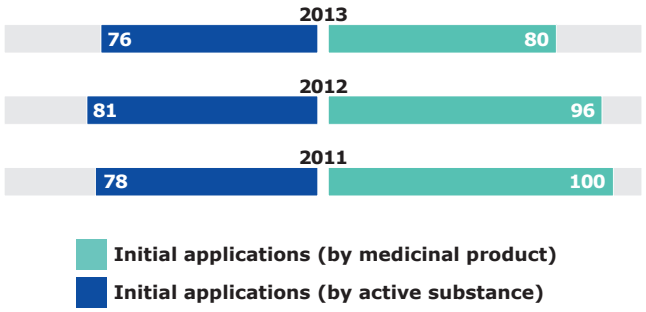
Initial evaluation covers activities relating to the assessment of marketing-authorisation applications for medicines, from pre-submission discussion with future applicants, through evaluation by the CHMP, to the granting of a marketing authorisation by the European Commission.

There was a slight decrease in the total number of applications for initial evaluation received in 2013 compared with 2012 (80 versus 96). However, the number of medicines containing a new active substance has continuously increased for the last three years.

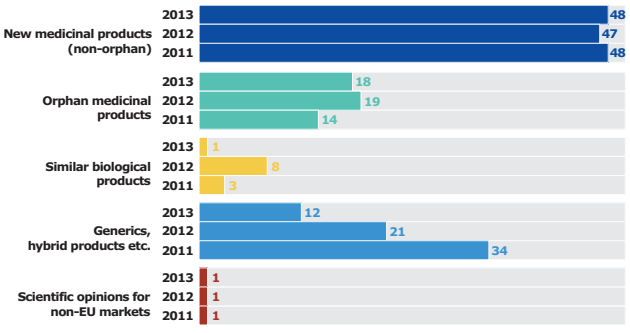
While the number of applications for new non-orphan and orphan medicines remains stable, the number of applications for generics and hybrid products decreased by 43%, in line with the trends of previous years. Several factors explain this tendency, including a note from the European Commission which clarifies the criteria that should be applied when dealing with submission of duplicate or multiple applications (which apply to generic products) and which may have led to more applications for generics being submitted nationally rather than centrally.

In 2013, five initial marketing-authorisation applications were submitted by SMEs, including one application for an orphan-designated medicine.

Initial-evaluation applications



Initial-evaluation applications by type of application



Outcome of initial evaluation

In 2013, the Agency's CHMP issued 79 initial positive opinions recommending marketing authorisation for new medicines.

Ten re-examinations were requested in 2013 and, following these re-examination procedures, two initial negative opinions were transformed into positive opinions (one recommending a conditional marketing authorisation and one recommending an approval under exceptional circumstances).

This leads to a total of 81 medicines recommended for marketing authorisation, including five opinions for conditional marketing authorisation and four opinions for approval under exceptional circumstances. A total of 37 medicines contained a new active substance.

Five medicines were recommended for marketing authorisation after accelerated assessment (in 2013, eight requests for accelerated assessment were accepted by the Agency and four were rejected.)
The number of recommendations for marketing authorisations of medicines intended for the treatment of rare diseases is steadily increasing.

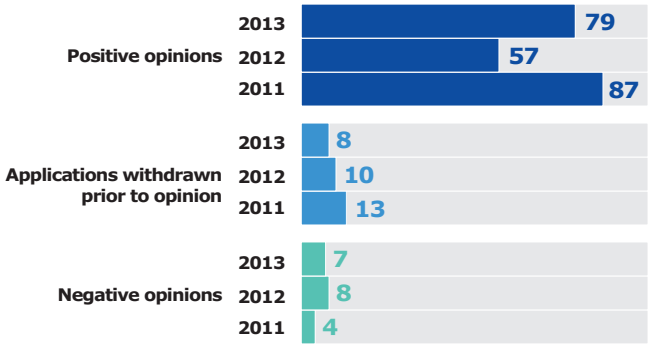
Two new ATMPs were recommended for approval in 2013, bringing to four the total number of ATMPs recommended for approval by the CHMP since the legislation on advanced therapies became operational in 2009.

2013 also saw the first two positive opinions for marketing authorisations of biosimilar monoclonal antibodies, successfully applying the biosimilar concept to such structurally complex substances.

11 of the 81 medicines recommended for marketing authorisation in 2013 were from SMEs.
One in every two applicants received scientific advice from the Agency's CHMP during the development phase of their medicine.

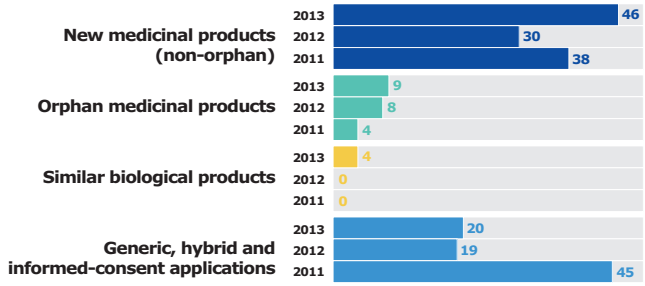
In addition, the Agency's CHMP adopted a scientific opinion, in cooperation with the World Health Organization (WHO), on a medicinal product that is intended exclusively for markets outside of the EU, in the framework of Article 58 of Regulation (EC) No 726/2004.

Outcome of initial-evaluation applications



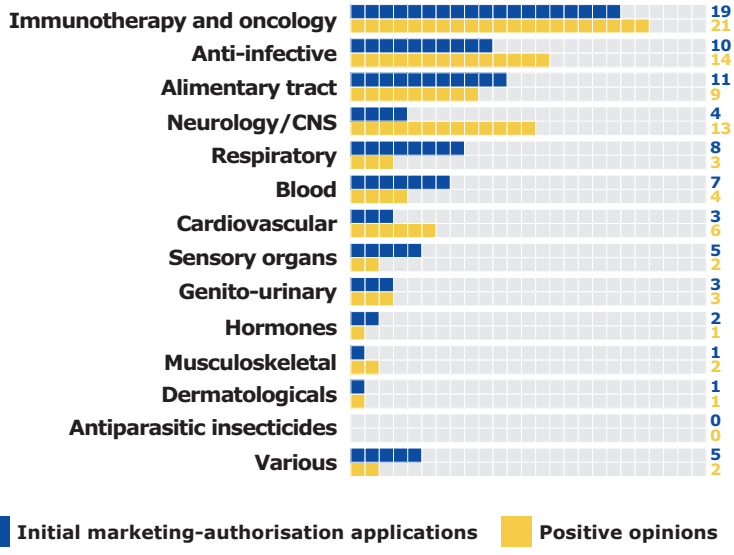
The figures in the chart above do not include the outcomes of re-examinations.

Positive opinions by type of procedure



The figures in the chart above do not include the outcomes of re-examinations.

Applications and positive opinions per therapeutic area

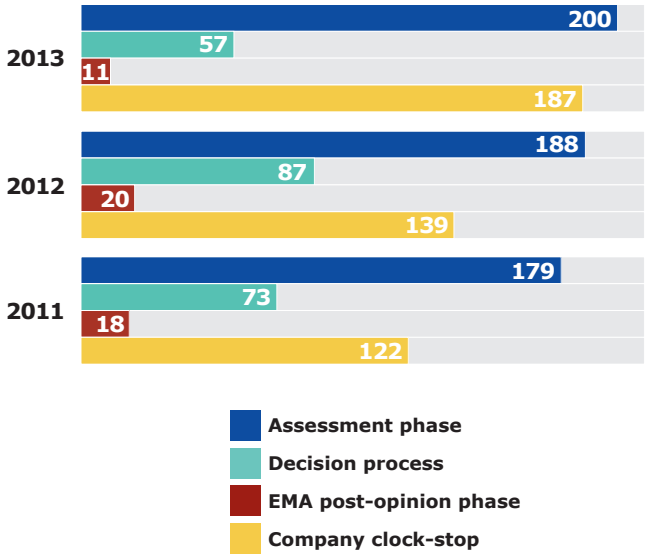


Average assessment time

An increase in the Agency's average assessment time of initial-evaluation applications was observed in 2012 and 2013. This increase reflects the recent change in the distribution of applications: a decrease in the number of generic and hybrid applications and an increase in the number of applications for medicines with orphan designation and for biosimilars. As expected, a similar trend has been observed for company clock-stops, which are on average longer, due to more complex applications under evaluation, requiring requests for supplemental information and scrutiny of additional data.

There was a 45% decrease in 2013 compared to 2012 in the average time for the EMA post-opinion phase. This is due to a change in the procedure: all opinions are now transmitted electronically to the European Commission.

Average number of days for centralised procedures - positive opinions

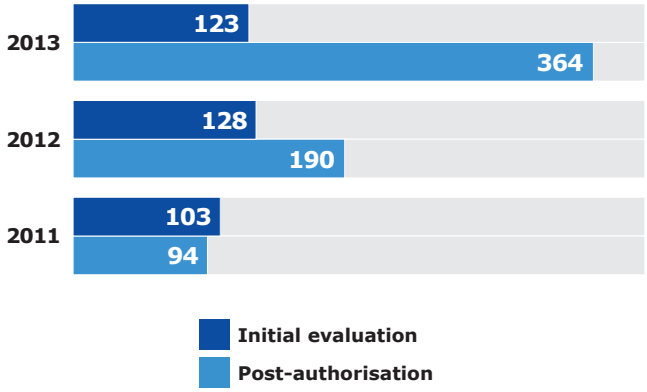


Risk-management plans

Companies submit a risk-management plan (RMP) to the Agency at the time of application for a marketing authorisation. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

While the number of risk-management plans as part of the initial authorisation of medicines was stable in 2013, there was an almost two-fold increase in the number of risk-management plans modified or updated post authorisation, highlighting the effects of the new European pharmacovigilance legislation.

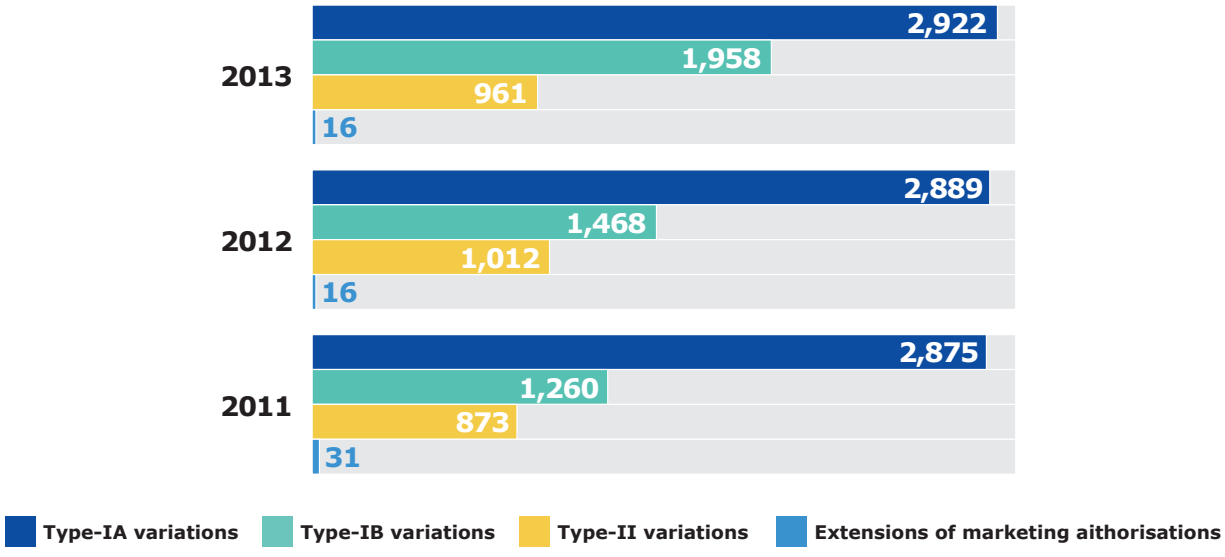
Peer-reviewed risk-management plans



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

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

Post-authorisation applications received



4.1.3 Herbal medicines

The Agency's Committee on Herbal Medicinal Products (HMPC) establishes 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.

In 2013, the HMPC finalised the assessment of 13 new Community herbal monographs, leading to the publication of 9 final monographs and 4 final public statements. The Committee also released 14 draft monographs for public consultation.

The Committee revised 7 adopted monographs, continuing the initiative started in the previous year to systematically revise its adopted monographs with a view to looking at the consistency of the assessments in the therapeutic areas where several monographs have been established since 2004.

4.1.4 Safety-monitoring activities

EudraVigilance – adverse drug reactions

Both the 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.

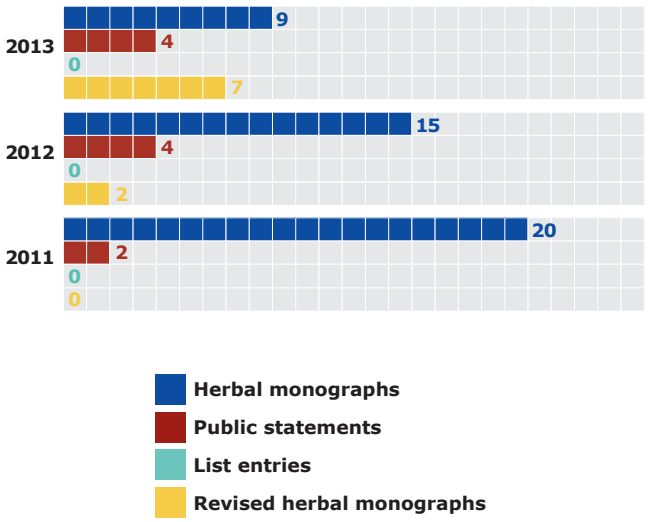
More than one million ADRs were reported to EudraVigilance in 2013, an increase of 26.3% compared with 2012.

There were particularly important increases in the number of reports coming from countries of the European Economic Area (EEA), both for centrally authorised products (CAPs; 43.7% increase) and non-centrally authorised products (non-CAPs; 33.9%).

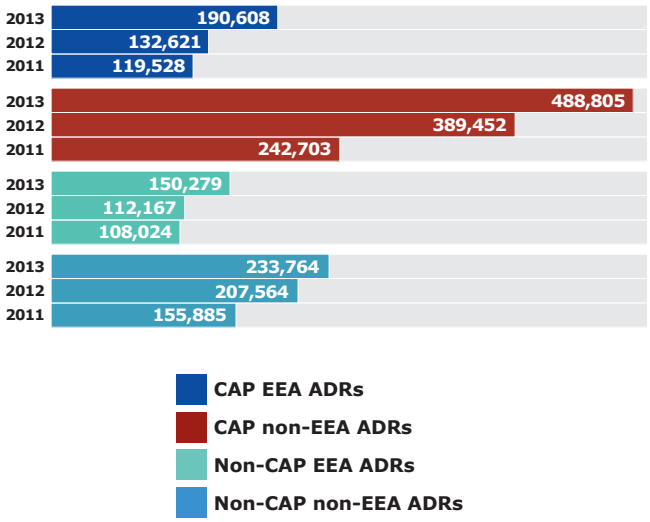
Of note, during the year following the entry into force of the new pharmacovigilance legislation, the number of reports that originated from patients in the EEA rose by 62%.

The general increase in ADRs indicates an increased commitment of stakeholders to provide all available data.

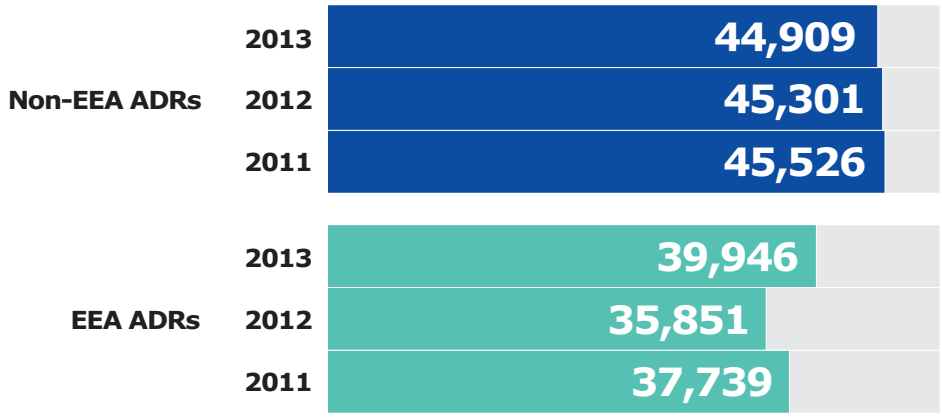
Herbal monographs and list of herbal substances, preparations and combinations thereof



EEA and non-EEA ADR reports received

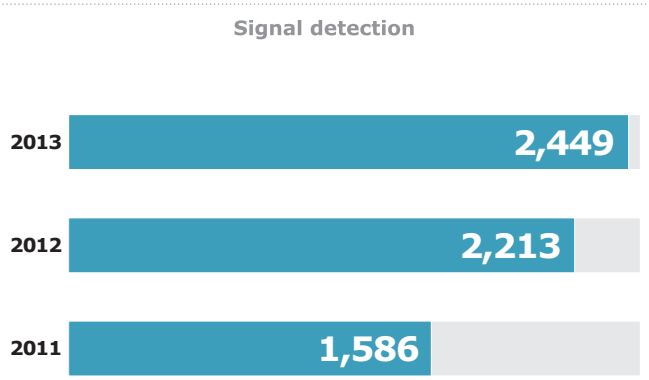


ADR reports concerning investigational medicinal products for human use



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.



1,000,000+

ADR reports received in 2013

2,449

potential signals reviewed by EMA's signal-validation team

43

signals validated by the EMA and analysed by the PRAC

In 2013, 43 signals were detected and validated by the EMA and 57 signals were detected and validated by Member States. Among the 43 signals raised by the EMA, two had been under monitoring by the signal-validation team at the Agency in 2012, eight were prompted by the scientific literature and five by information received from other regulatory authorities.

21 of the 43 signals validated by the EMA led to a recommendation for changes to the product information, either directly (n=7) or following a cumulative review (n=14), providing information to patients and healthcare professionals on the safe use of these products. For four signals, this also included the distribution of direct healthcare professional communications (DHPCs) to increase awareness about the new safety information.

The evaluation of 14 signals following the recommendation for a cumulative review was ongoing at the end of 2013. The evaluation of seven signals was closed with no further regulatory action required, with the routine pharmacovigilance activities deemed satisfactory for further follow-up of these signals. One signal led to a formal evaluation of the benefit-risk balance via an Article 31 referral.

Periodic safety-update reviews (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, defined time points following a medicine's authorisation. Since 2013, the Agency started the single assessment of PSURs, a deliverable of the 2010 pharmacovigilance legislation, which has given the Agency the responsibility to analyse all reports for medicines containing a particular active substance, for all types of marketing authorisation and for medicines authorised in more than one Member State.

In 2013, the PRAC issued 436 recommendations based on the assessment of PSURs, including four PSURs single assessments. This figure represents the number of procedures per active substance, and not by medicinal product.

4.1.5 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 total of 43 referral procedures started in 2013 and 45 were finalised.

With the implementation of the pharmacovigilance legislation, centrally authorised and nationally authorised products can now be reviewed in a single procedure, which has led to changes in the overall numbers of referrals.

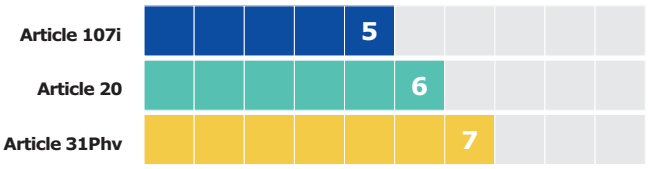
Among the 43 referral procedures started in 2013, 25 were initiated to address either efficacy or quality concerns with certain medicines, or a need for EU-wide harmonisation of product information, or were triggered by differences between the Member States in the mutual-recognition and decentralised procedures.

The other 18 referral procedures were pharmacovigilance-related (under Articles 31, 20 and 107i) and presented a large proportion of the overall workload of the PRAC in its first full year of operations.

PRAC outcomes of PSURs

Maintenance	360
CHMP variation	76
Suspension	0
Revocation	0
Total outcomes	436

Pharmacovigilance-related referral procedures started (2013)



4.1.6 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 subgroups/working groups, 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.

7 MRP and 15 DCP initial applications and 3 applications for type-II variations were referred to the CMDh in 2013.

Agreement was reached for 3 MRP and 5 DCP referrals (1 of the 3 MRP and 2 of the 5 DCP referrals were referred to the CMDh in 2012) and for 3 referrals for type-II variations.

2 MRPs and 6 DCPs were referred to the CHMP for the adoption of an EU-wide scientific opinion under Article 29(4) of Directive 2001/83/EC (1 of the 2 MRP and 3 of the 6 DCP referrals were referred to the CMDh in 2012). No applications for a type-II variation under Article 13 of Commission Regulation (EC) No 1234/2008 were referred to the CHMP in 2013.

With regard to work-sharing for the assessment of paediatric studies submitted according to Articles 45 and 46 of the Paediatric Regulation, 23 active substances under Article 45 and 29 submissions of paediatric studies under Article 46 were processed. 41 public assessment reports according to Article 45 and 23 public assessment reports according to Article 46 were published on the CMDh website.

With regard to the revised Variations Regulation, the CMDh gave recommendations on 14 requests for recommendation according to Article 5.

A full report on the CMDh activities is available on the website of the Heads of Medicines Agencies (www.hma.eu).

Veterinary medicines in 2013

Research and development

40
scientific-advice applications received in 2013

43% ↑
increase compared with 2012

23
applications received for designation of minor-use minor-species (MUMS) classification

7 ↑
applications for maximum residue limits (MRLs) received for a new substance in 2013

Authorisation phase

23
applications for initial evaluation of new veterinary products received by CVMP in 2013

x2
increase compared with 2012

12 →
medicines recommended by the CVMP for marketing authorisation

3
for immunological products for food-producing species

8
relating to pharmaceuticals intended for companion animals

1
generic pharmaceutical intended for both food-producing and non-producing species

Safety monitoring

22,326
reports on suspected adverse reactions in relation to a veterinary medicine

60.1%
of reports concerned dogs

10
referrals or arbitration procedures related to veterinary medicinal products started

9
food-producing animals

1
companion animals

4.2 | Veterinary medicines

4.2.1 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.

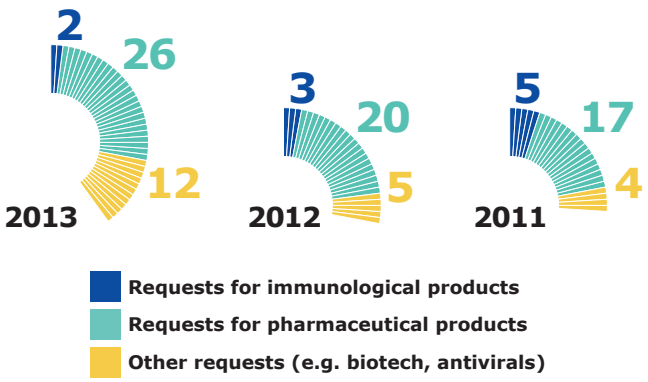
Scientific advice

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 considered as a means to facilitate and improve early availability of veterinary medicines.

The number of applications submitted for scientific advice in the veterinary field showed a sharp increase, with 40 requests received in 2013, representing a 43% rise compared to 2012. 26 of these applications concerned pharmaceutical products (+30%), and 12 concerned other products such as biotech products and antivirals (meaning more than a two-fold increase). The Agency expects this trend for an increasing proportion of requests to relate to new animal-health technologies to continue.

The Agency finalised 34 requests for scientific advice, representing an overall growth of 17%.

Scientific-advice requests received by area

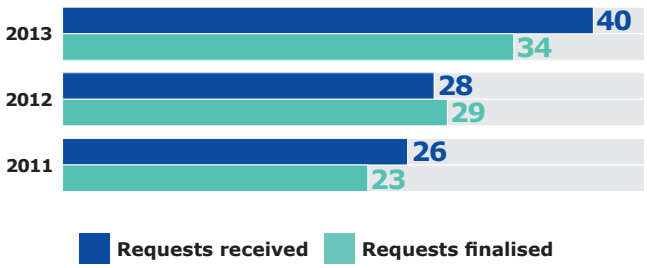


Minor use, minor species (MUMS) / limited-market classification

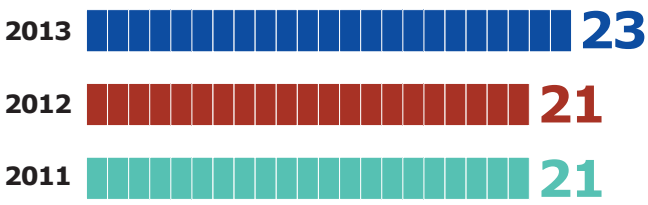
The Agency formalised in 2009 its minor use, minor species (MUMS) / limited-market policy, which aims to assist applicants with submitting applications for products for limited markets, in order to stimulate development of new veterinary medicines for minor species, and for rare diseases in major species which would otherwise not be developed in the current market conditions.

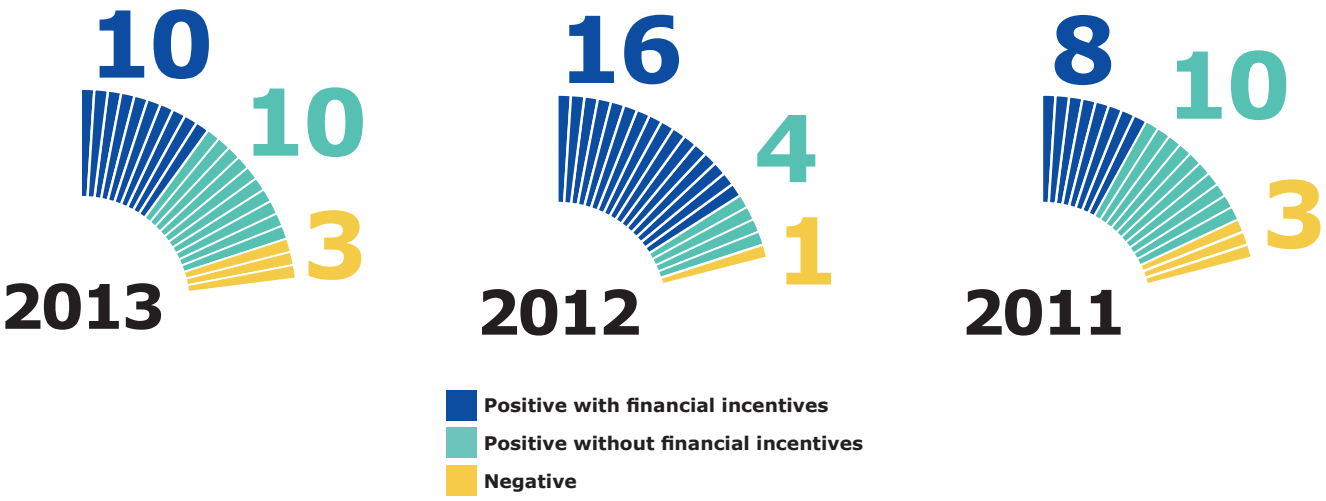
In 2013, the number of requests to the CVMP for classification as MUMS remained in line with previous years, with 23 applications received. Of these, 20 were confirmed as MUMS, and therefore benefitted from reduced data requirements for applications for MUMS products specified in CVMP guidelines, and half were also granted financial incentives such as access to free scientific advice and reduced application fees. Following a review of the type of MUMS products that had received financial support since 2009, the MUMS policy was revised during 2013 to limit financial incentives to products indicated for food-producing animals, in line with the direction from the EMA Management Board that this was the category of animal most deserving of publicly funded support.

Scientific-advice requests received and finalised



Number of applications for designation of MUMS





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 these 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.

At the end of 2013, out of the 1,258 companies registered as SMEs with the EMA, 4% (52 companies) were developing products for veterinary use and 6% (77 companies) were developing products for both human and veterinary use.

In the veterinary field, 39% of registered companies were micro-sized (with fewer than 10 staff), 32% were small, and 29% medium-sized. The average headcount of these companies was 43 and their average turnover was €8.7 million. The highest proportion of companies were based in the United Kingdom, Spain, France and Germany.

Two marketing-authorisation applications were submitted by SMEs in the veterinary field in 2013.

More information on the activities of the SME office in 2013 can be found in Section 4.1.1 of this annual report.

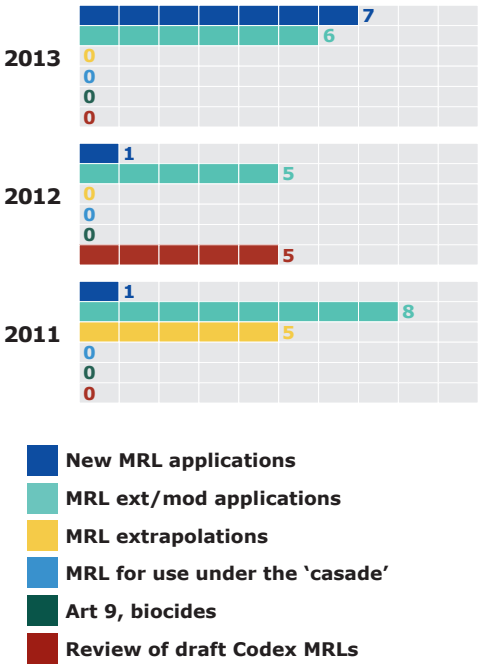
Innovation Task Force

The scope of the European Medicines Agency's Innovation Task Force, which provides support to medicines innovation in the EU, was extended to cover support to veterinary medicines during the early stages of their development in 2013. Specific steps have been defined for applicants developing veterinary medicines who wish to request briefing meetings. More information on the activities of the Innovation Task Force in 2013 can be found in Section 4.1.1 of this annual report.

4.2.2 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 establishes maximum residue limits (MRLs) for pharmacologically active substances in veterinary medicinal products used to treat animals, to provide for the safe use of foodstuffs of animal origin, including meat, fish, milk, eggs and honey. The Agency also has the responsibility to establish MRLs for pharmacologically active substances in biocidal products used in animal husbandry.

Applications for the establishment of MRLs



Seven applications for maximum residue limits were received for new substances in 2013. This is a sharp increase compared to 2011 and 2012, where only one application was received per year. There was a continuing interest in extending MRLs to other species, thereby increasing the potential availability of veterinary medicines for a wider range of species.

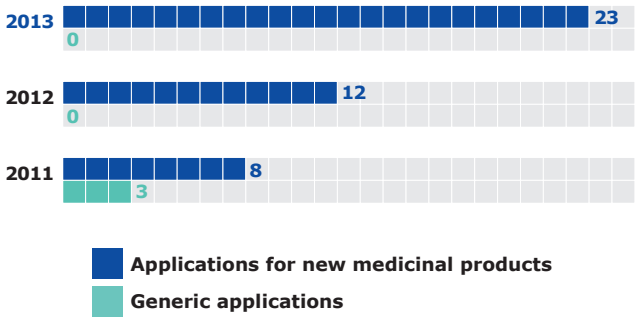
4.2.3 Authorisation activities

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 for Veterinary Use (CVMP) to the granting of marketing authorisation by the European Commission.

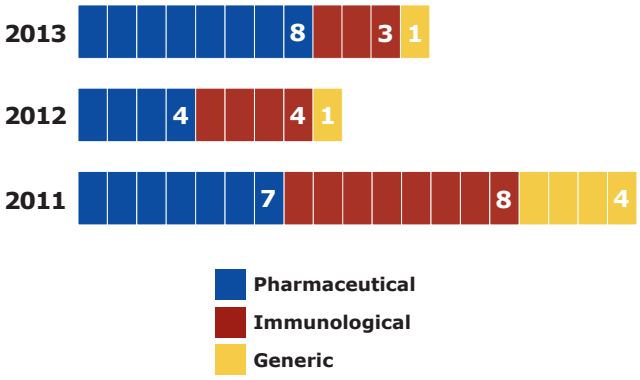
The CVMP received 23 applications for the initial evaluation of new veterinary products in 2013, which marks a two-fold increase compared to 2012. Almost 70% of the applications submitted were for immunologicals. 14 of the 23 applications were for companion animals. This increase was due to receipt of applications for a range of related vaccines, on top of the trend for a gradual increase in the number of applications received in recent years.

Applications for initial evaluations



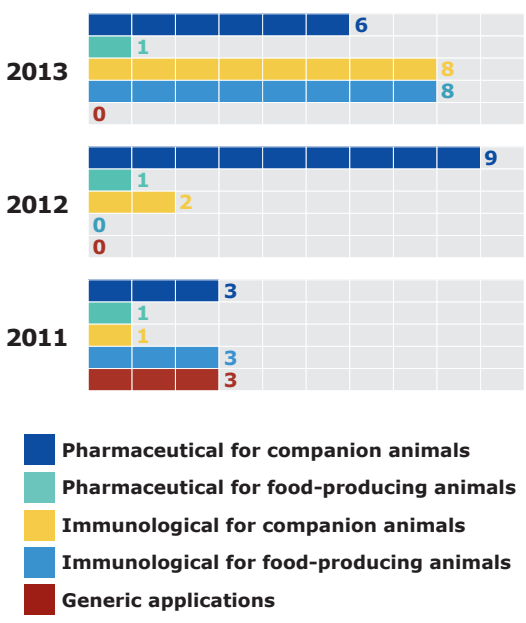
In 2013, the CVMP gave 12 positive opinions for new veterinary medicines, of which three were for immunological products for food-producing species, eight related to pharmaceuticals intended for companion animals and one was a generic pharmaceutical intended for both food-producing and non-food-producing species. The majority of the medicines aimed at companion animals were paraciticidal products for cats and dogs.

Opinions for veterinary medicines adopted

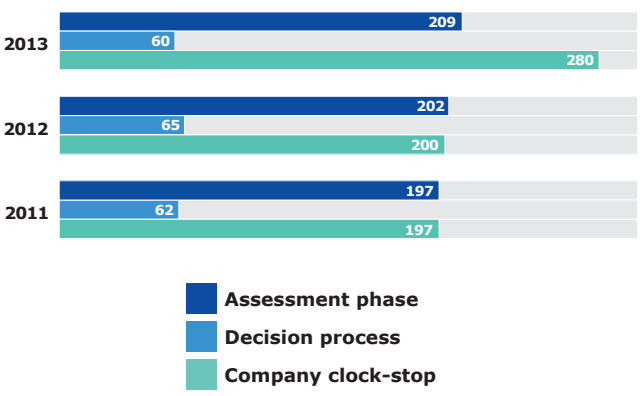


The average number of days for the centralised procedure remained stable, with an average of 269 days in total for the assessment phase and the decision process. The company clock-stop represented 280 days on average, compared with 200 days in 2012. It is not yet possible to determine if this increase in the time taken for companies to respond to issues raised during assessment is a trend or if it merely reflects the particular products assessed during 2013. The slight increase in assessment time by the Agency (209 days compared to 202 days in 2012) arose only due to the fact that no assessments ran to an accelerated timeline in 2013, as compared to one in 2012 and three in 2011.

Applications for veterinary medicines received



Average number of days for centralised procedures

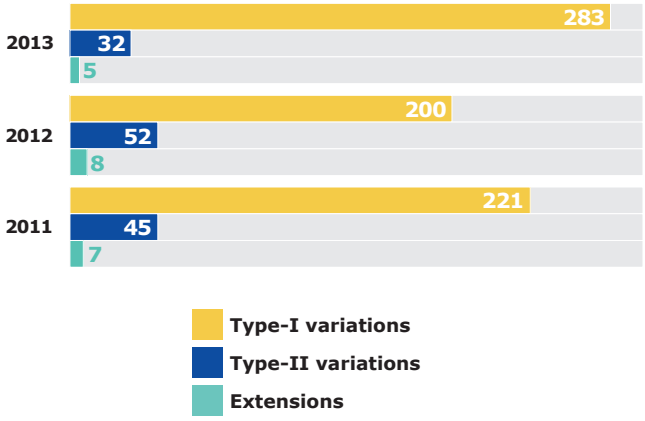


Post-authorisation activities

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

In 2013, the CVMP received 315 applications to vary the terms of a marketing authorisation and 5 applications for an extension of a marketing authorisation. An increase in type-I and a decrease in type-II variations were seen in 2013, resulting from an amendment of the variation regulations.

Post-authorisation applications received



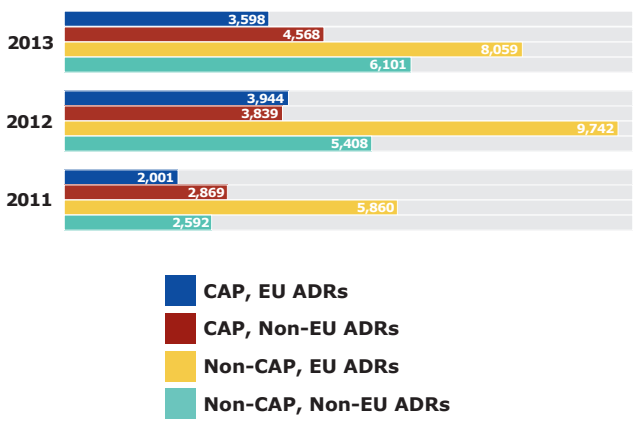
4.2.4 Safety monitoring of medicines

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.

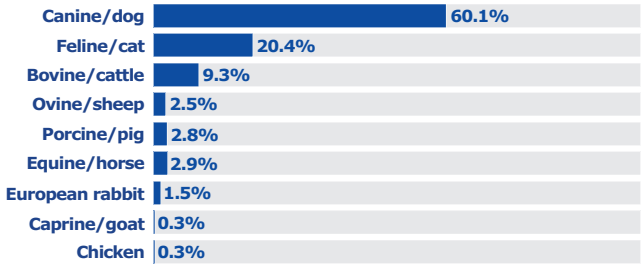
Eudravigilance – VET: adverse events

In 2013, the total number of AEs reached 22,326. This figure is in line with 2012, where there had been a significant increase in the number of reports linked to an increased commitment of stakeholders to provide all available data. The proportion of reports of reactions in dogs increased to represent 60.1% of the total of cases, compared to 47.9% in 2012.

Reports on suspected adverse reactions in animals and human reactions



Reports per species in EudraVigilance Veterinary (2013)



Signal detection and management

The totality of the AEs within EudraVigilance Veterinary are analysed at 3-monthly, 6-monthly or yearly intervals for statistically significant signals (signal detection) for each centrally authorised product. This resulted in a total of 470 surveillance analyses during 2013, of which about 12% led to follow-up monitoring of potential signals at the next surveillance instance or a request to the company for a cumulative review at the next PSUR.

Periodic safety-update reviews (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 defined 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 the authorised and unauthorised indications).

The CVMP assessed 149 PSURs in 2013, the increasing number reflecting the progressive accumulation of products authorised through the centralised procedure.

Periodic safety-update reports finalised

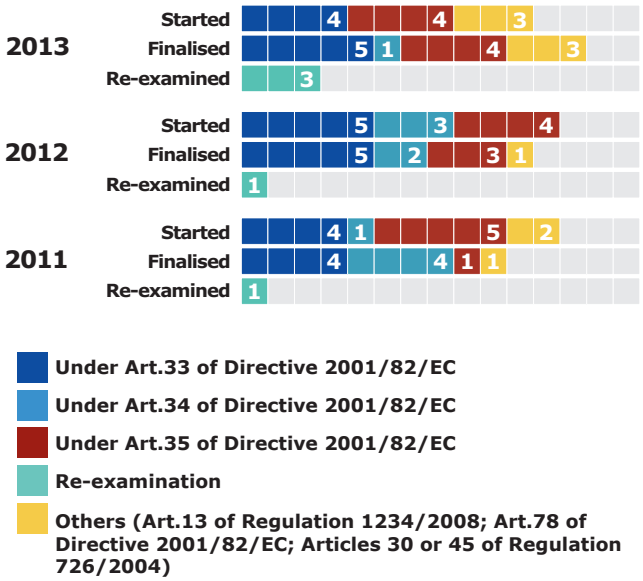
4.2.5 Referral and arbitration procedures

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.

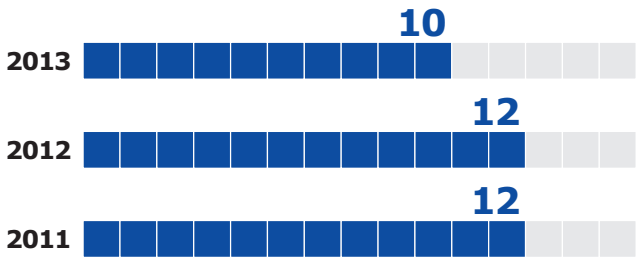
In 2013, the CVMP started nine referral or arbitration procedures related to veterinary medicinal products for food-producing animals and one arbitration related to a veterinary medicinal product for companion animals. Half of these procedures were initiated to assess a potential serious risk to the environment linked to the use of veterinary medicines.

The CVMP finalised 13 arbitration and referral procedures and carried out three re-examination procedures.

Arbitrations and referrals for veterinary medicines



Arbitration and referrals received



4.2.6 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).

- 218 MRPs/DCPs were finalised in 2013, which is the same number as in 2012. However, there was a shift towards the use of the MRP compared to the greater use of the DCP in 2012. This may reflect that marketing-authorisation holders are expanding existing product ranges into new markets rather than submitting entirely new applications. As in recent years, approximately 80% of the total MRPs/DPCs in 2013 were abridged applications under Article 13 of Directive 2001/82/EC, most of them generics.

- Five initial applications and 3 type-II variations (primarily to add indications) were referred to the CMDv in 2013, which equates to 2.5% of the MRPs/DCPs and a 20% decrease in the number of referrals compared to 2012. 70% of the referrals to the CMDv ended in disagreement and were further referred to the CVMP for final arbitration. The CVMP accepted 100% of the procedures referred by the CMDv and the final outcome was that 80% of these referrals were overruled, i.e. the concerns of the referring Member State(s) were not upheld or could be managed through risk-mitigation measures. Compared to 2012, the predominant ground for referral shifted from bioequivalence to environmental risk assessment, which may, in part, reflect the greater proportion of referred products indicated for use in food-producing species, particularly antiparasitics.

- The CMDv handled approximately 52 workshared variations – an increase of 50% from 2012. In August 2013 the scope of the Variations' Regulation was expanded to include purely national marketing authorisations and therefore it is expected that the number of worksharing procedures will continue to increase. The area of variations remains a focal point in the work of the CMDv.

- The CMDv working groups were active in the areas of validation, borderline products, improvement of DCP, packaging and update of guidance documents.

4.3 | 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 use in the European Union. It does this through inspections requested by the CHMP or CVMP in connection with the assessment of marketing-authorisation applications and/or the assessment of matters referred to these committees in accordance with EU legislation.

The Agency also checks compliance of parallel distribution of centrally authorised medicines that are distributed from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder. 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.

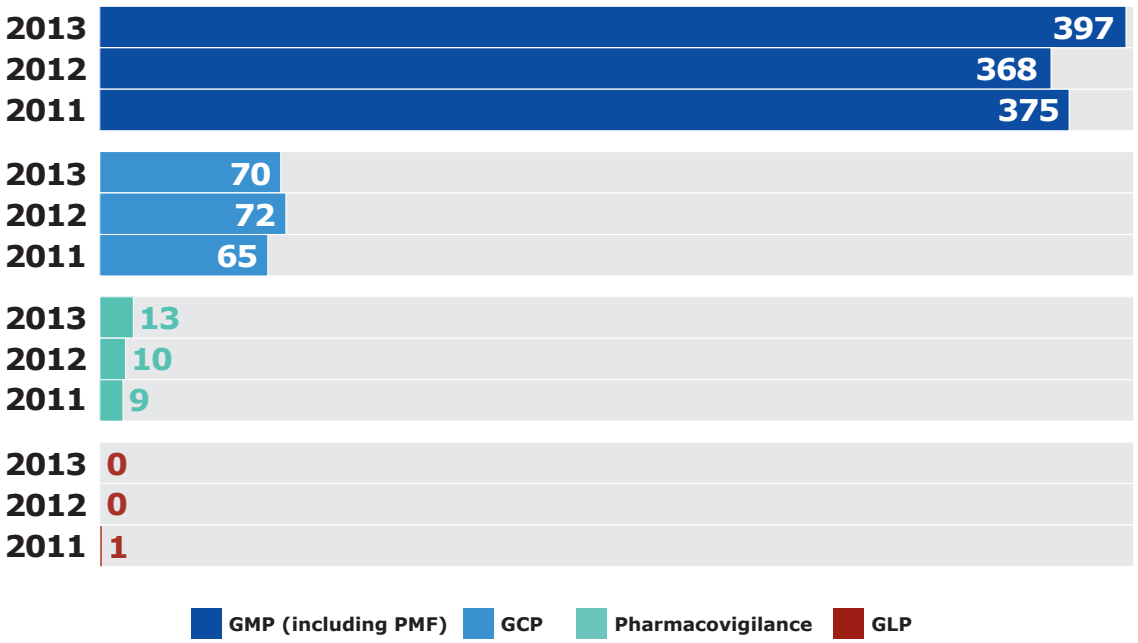
Inspections

The total number of inspections increased in 2013, 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.

These inspections were requested by the EMA committees, and many take place outside of the EEA since national authorities coordinate the large majority of inspections within the EEA as part of their supervisory role:

- 21 and 49 GCP-related inspections were respectively conducted in EEA and non-EEA countries;
- 11 and 2 pharmacovigilance-related inspections were respectively conducted in EEA and non-EEA countries;
- 6 and 391 GMP-related inspections were respectively conducted in EEA and non-EEA countries.

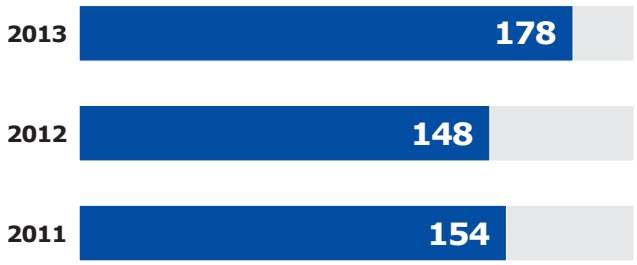
Number of inspections



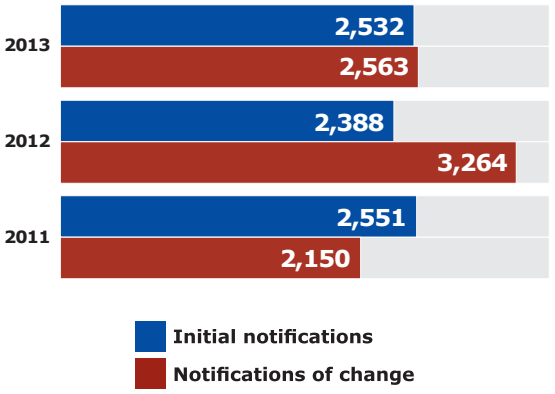
Number of quality defects
There has been a progressive increase in the number of quality defects over the years. Causes for this increase are multifactorial and the Agency is studying the root causes in order to draw general lessons from these incidents which can be used to further improve the quality of medicines.

Parallel distribution
In May 2013, a new procedure – the annual update notification – was introduced and the Agency received 1,205 notifications, of which 652 were processed.

Number of quality defects



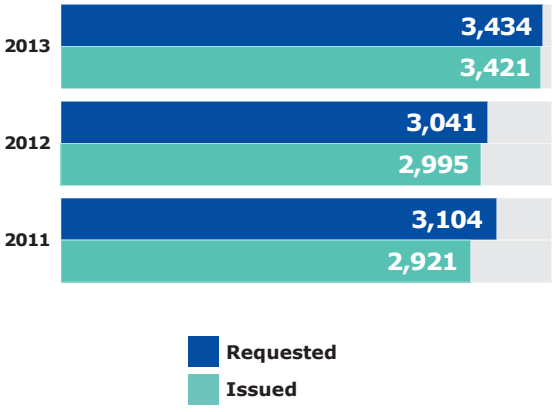
Parallel-distribution notifications



Quality defects and recalls (2013)

Quality defects reported	178
Recalls (total)	19
Class 1 recalls	5
Class 2 recalls	10
Class 3 recalls	4

Certificates



Certificates
A new procedure was developed to handle urgent certificates. The Agency received 297 requests and issued 293 urgent certificates.

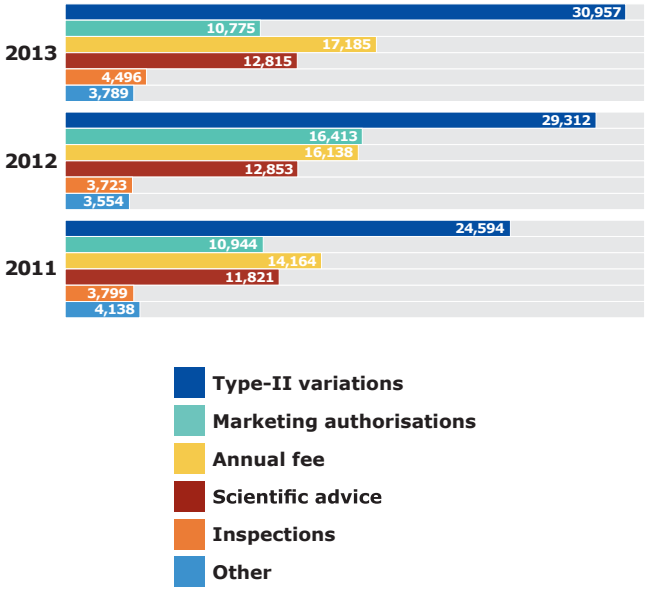
4.4 | The European medicines regulatory network

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 members of the assessment teams carrying out the evaluation of medicines.

Payment to national competent authorities for evaluation activities

The overall payment to national competent authorities (NCAs) remained stable in 2013 compared to 2012. There was a decrease in marketing-authorisation-related payments to national competent authorities in 2013 compared with 2012 due to the decrease in the number of initial applications received.

Payment to NCAs for evaluation activities (EUR '000)

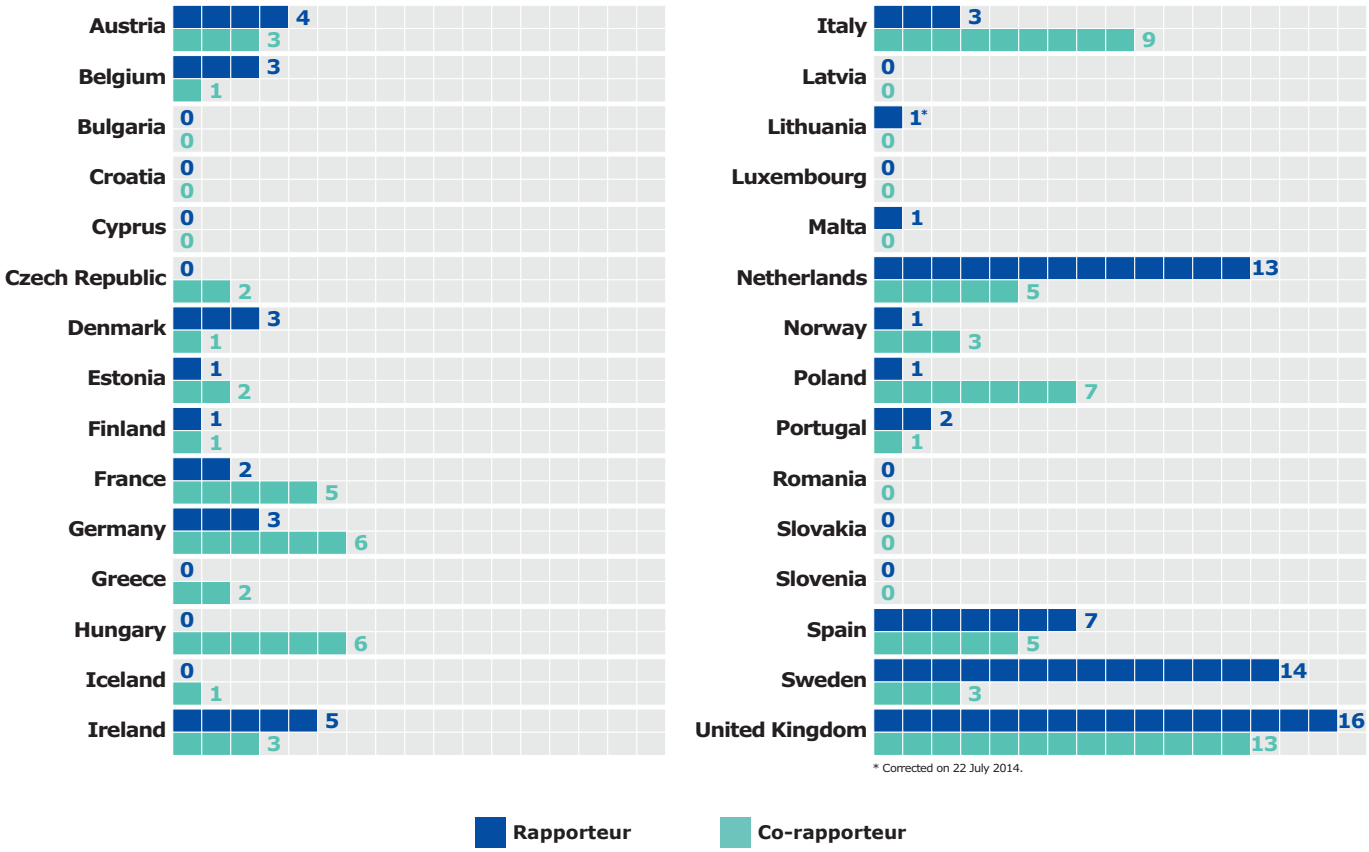


Rapporteurships/co-rapporteurships

Some of the EMA's committees appoint a member to lead each scientific assessment, who is referred to as the rapporteur for the procedure. The rapporteur works to an agreed timetable and prepares an assessment report for the committee. For certain procedures, the committee also appoints a co-rapporteur to consider the matter in parallel to, and independently from, the rapporteur. The rapporteur and co-rapporteur are supported by an assessment team to provide the necessary expertise and resources. Rapporteurs and assessment teams are selected based on criteria aimed at ensuring the high quality of scientific assessments and an effective use of resources.

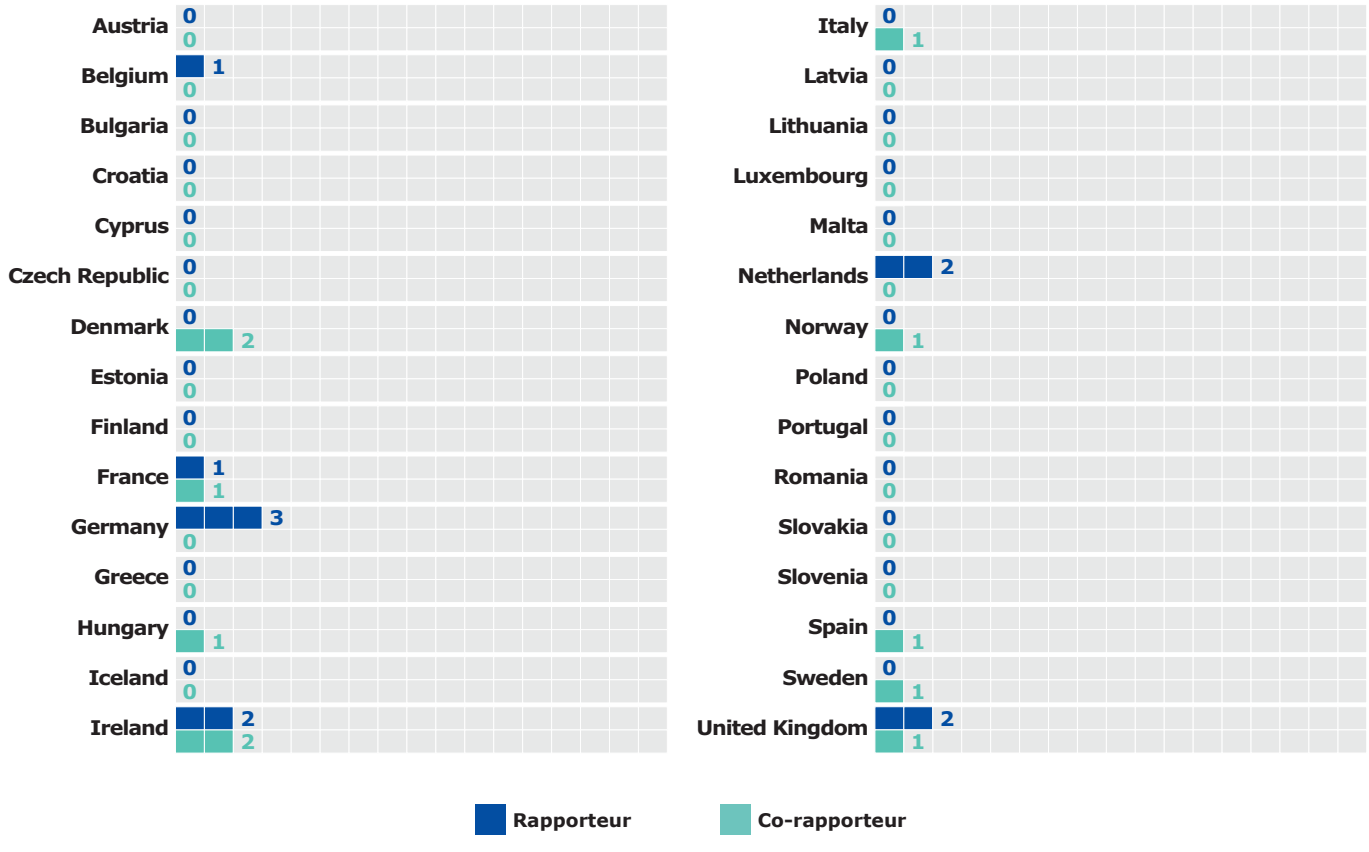
Opposite is an overview of the rapporteurships/co-rapporteurships of the CHMP and the CVMP, the two committees that are responsible for providing recommendations on marketing authorisation for medicines.

CHMP rapporteurships/co-rapporteurships (2013)



* Corrected on 22 July 2014.

CVMP rapporteurships/co-rapporteurships (2013)



4.5 | Administrative aspects

Access-to-document requests

EU citizens have a right to access 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.

While complying with the initial halt imposed by the interim rulings of the General Court on the release of clinical study reports, in 2013 the Agency received 293 requests for access to documents and released a total of 311,481 pages in response to requests.

The graph below shows the affiliation of the requester by request.

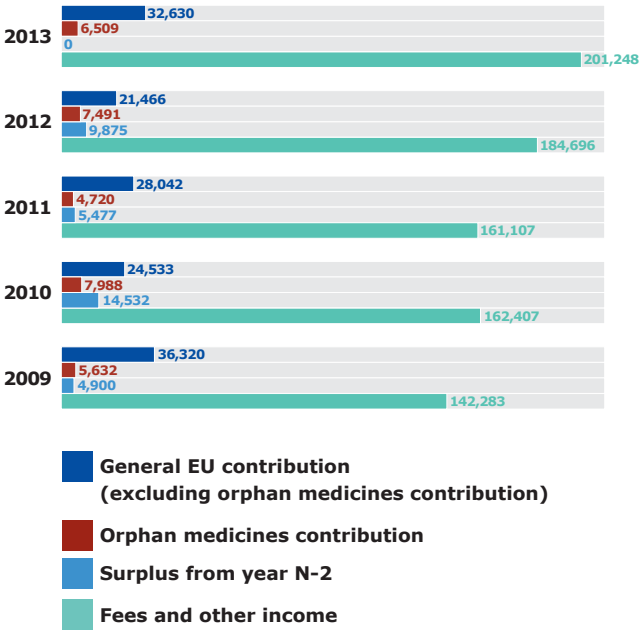
Affiliation of requesters (2013)

Affiliation	Number of requests received
Pharmaceutical industry	103
Legal	67
Media	37
Academia/research institute	34
Consultant	12
Healthcare professional	10
EU NCA	7
General public	7
EU institution (Commission etc)	3
Regulator outside EU	3
Patient's organisation	2
Not-for-profit organisation	1
Other	7
Total	293

Budget composition: revenue

The outturn of the Agency in 2013 was €240,387,000, representing a 7.5% increase compared with 2012. The EU general contribution represented 13.6% of the budget in 2013, compared with 9.6% in 2012.

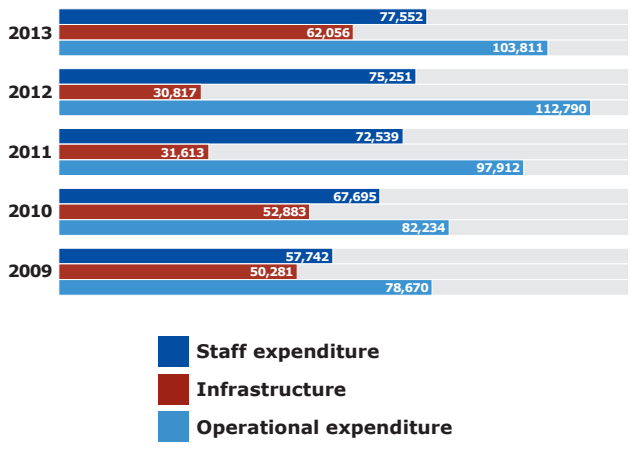
Revenue EUR '000



Budget composition: expenditure

The considerable increase in the cost for infrastructure in 2013 is due to investment costs for the fitting-out of the new premises in anticipation of the relocation of the Agency in 2014. These investment costs are split between financial years 2013 and 2014.

Expenditure EUR '000



Agency staff

	Men	Women	Total
Temporary agents	194	389	583
Contract agents	16	76	92
Interim staff	6	30	36
National experts	7	9	16
Trainees	15	43	58
Grand total	238	547	785

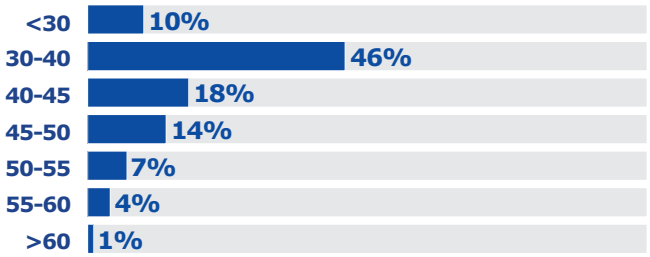
Gender balance

	Category AD (administrators)		Category AST (assistants)	
	Men	Women	Men	Women
Ratio men/women for temporary agents	156 (49%)	161 (51%)	38 (14%)	228 (86%)
Ratio men/women for contract agents	15 (33%)	31 (67%)	1 (2%)	45 (98%)
Total	171 (47%)	192 (53%)	39 (12%)	273 (88%)

National origins of Agency staff

Austria	1.48%
Belgium	3.56%
Bulgaria	1.33%
Czech Republic	3.26%
Denmark	1.93%
Estonia	1.33%
Finland	1.33%
France	14.52%
Germany	7.7%
Greece	5.33%
Hungary	3.11%
Ireland	2.07%
Italy	10.67%
Latvia	1.19%
Lithuania	1.48%
Malta	0.15%
Netherlands	0.74%
Poland	6.37%
Portugal	4.74%
Romania	1.93%
Slovakia	3.11%
Slovenia	0.3%
Spain	11.26%
Sweden	2.52%
United Kingdom	8.3%

Age-range statistics



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

Notes

Notes

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European Medicines Agency

7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Telephone +44 (0)20 7418 8400
Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu

www.ema.europa.eu

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EMA/95980/2013