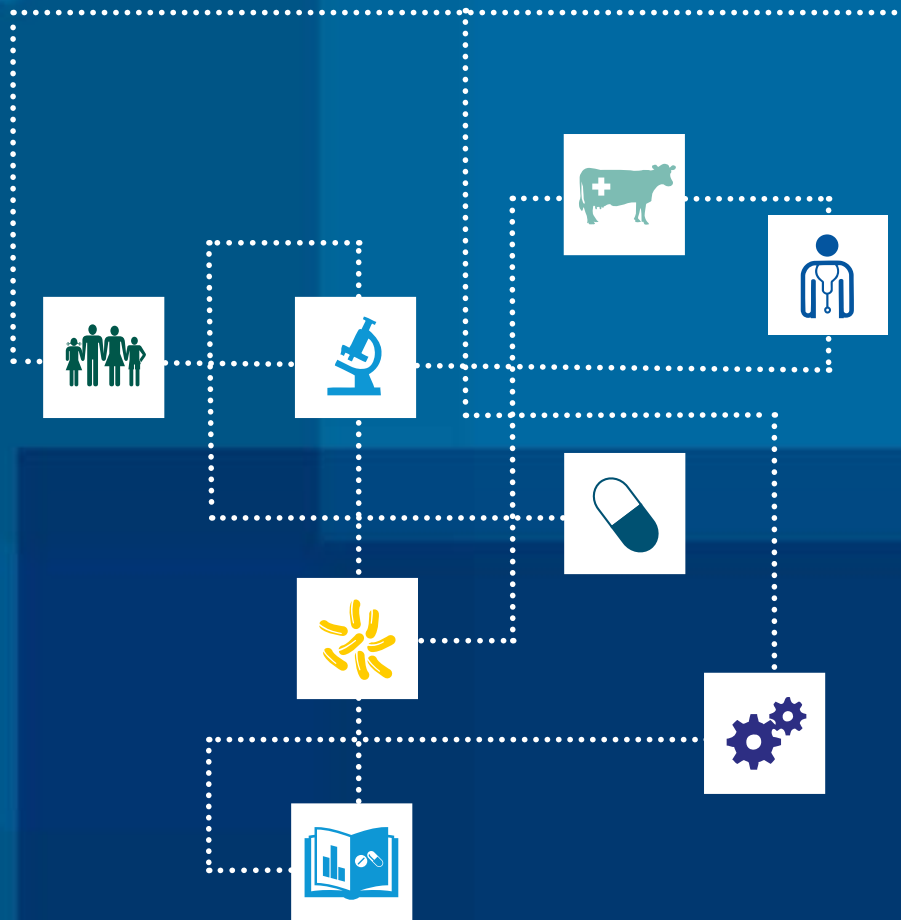




EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Annual Report 2015



An agency of the European Union

# Annual Report 2015



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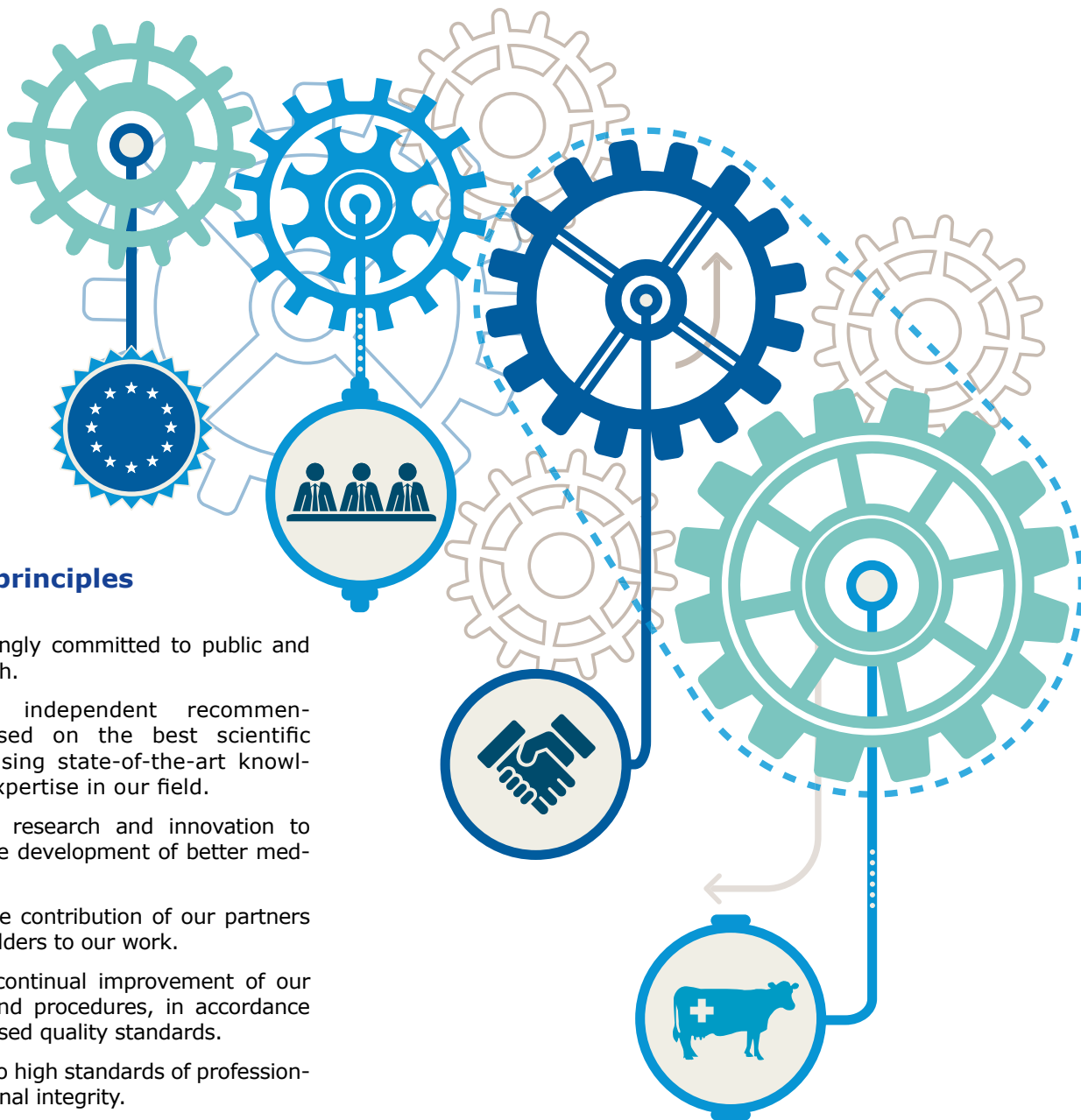
## Corrections:

19/05/2016 - The numbers on page 83 for Austria, Czech Republic and Slovenia were updated.

18/07/2016 - The key on page 44 was updated to correspond to correct data.

## 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

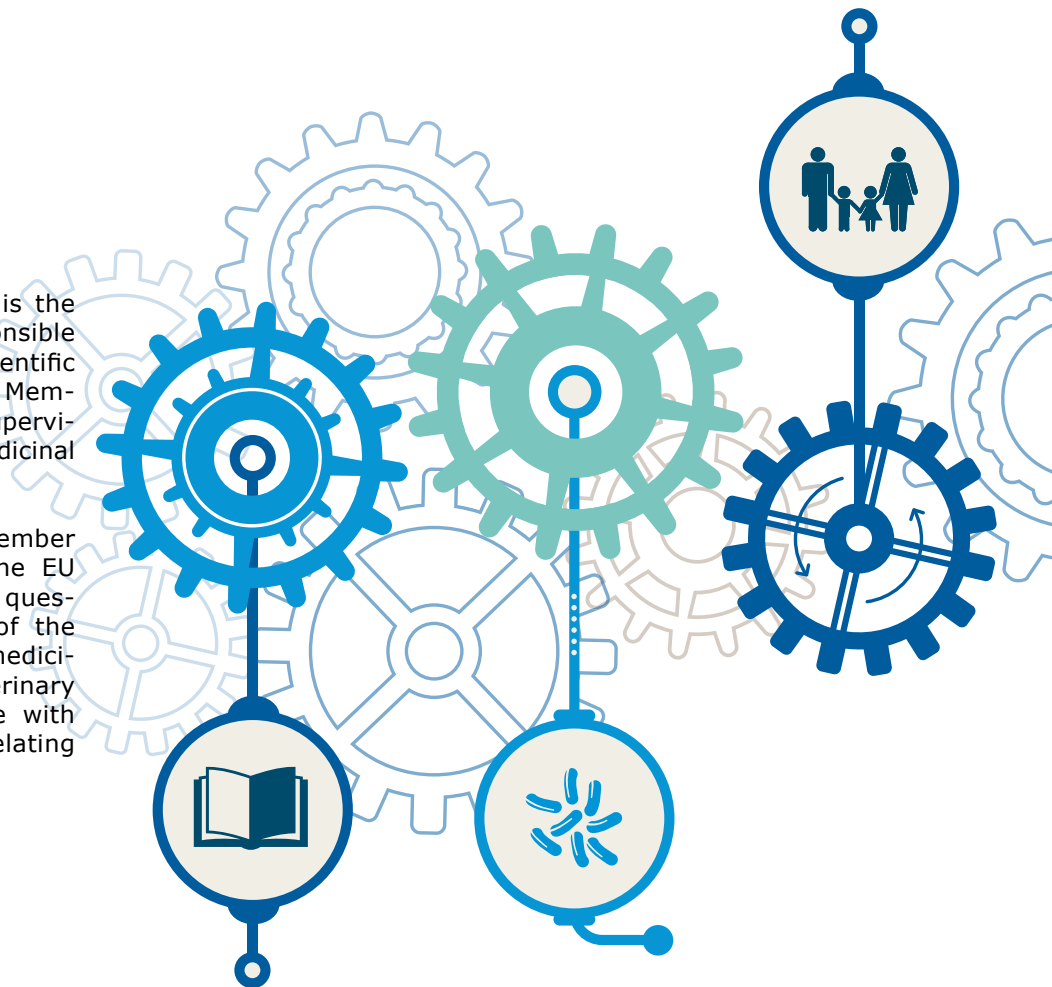
Working with the Member States and the European Commission as partners in a European medicines regulatory network, the European Medicines Agency:

- 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 Sir Kent Woods, Chair of EMA Management Board 2011-2015



**F**or the Management Board, one unprecedented event overshadowed the Agency's work in 2015. This was the ruling of the European Union (EU) Civil Service Tribunal (announced in November 2014) to annul the Commission's decision shortlisting the candidates and, consequently, the Board's appointment of the Executive Director three years earlier. The Executive Director post was immediately re-advertised. At the end of a fully competitive process, the Board appointed Professor Guido Rasi for a five-year mandate in November 2015.

During this unsettled period, leadership of the European Medicines Agency (EMA) passed to Andreas Pott, Deputy Executive Director, supported by Guido Rasi as Principal Adviser in charge of Strategy. It is a great credit to them both that the Agency was able to deliver the large programme of work described in the following pages.

I would like to draw attention to two areas of activity in particular. The first concerns support for innovation: a number of additional steps have been taken to both support and accelerate the progress of promising new

medicines through the regulatory process where there are major unmet clinical needs. New approaches, including adaptive pathways and PRIME (PRIority MEdicines), are described below. These work within the current EU legal framework and make full use of existing regulatory tools such as conditional authorisation and scientific advice (available from both the national agencies and EMA).

The second area to highlight is the work to enhance the transparency of EMA processes and to provide access to the clinical trials data on which regulatory decisions are made. This has raised some contentious issues, including freedom of information, commercial confidentiality and personal data protection. The results of wide consultation have been brought to the Management Board as the work progressed. There is still more to be done but EMA has established itself at the leading edge of regulatory transparency internationally.

EMA is well placed to deliver its full contribution to a newly adopted five-year strategy, for the first time developed jointly with the Heads of Medicines Agencies (HMA). Over the past twelve years, I have seen a steady strengthening of the EU network, comprising EMA, the national regulatory authorities and the Commission. This is a unique structure, bound together by a shared commitment to the application of best science for the benefit of public and animal health.

This is the fifth annual report which I have introduced and also my last, as I stepped down from the chairmanship at the end of the year. It has been a privilege to lead the Board. I also wish to thank the staff of EMA for the hard work and professionalism on which the Agency's success is securely based.

# INTRODUCTION

By Professor Guido Rasi, EMA Executive Director



This year, during which EMA has celebrated its 20<sup>th</sup> anniversary, has been a year of transition for the Agency. It has given us the opportunity to reflect and discuss with our EU partners how we can support and shape the transformation the medicine development and authorisation system is currently undergoing in order to improve the health of EU citizens. Scientific advancements made over the last 40 years in drug discovery have increased knowledge about the mechanisms behind the development of diseases, creating huge opportunities for the development of medicines. At the same time, the sustainability of healthcare systems across the EU is under threat, due to rising costs, an ageing population with more complex healthcare needs, and the continuous squeeze on public finances.

It is against this background that we adopted the first joint strategy for EMA and all national medicines agencies in the EU in December 2015. I am confident that this joint effort sets the European medicines regulatory network on the right course for the coming five years to keep pace with a rapidly changing environment.

Last year, we also took important steps to better support research and development of medicines that address patients' needs. Scientific advice remains the central pillar of the Agency's activities to stimulate innovation and the number of requests received every year is high. Scientific advice benefits patients as it promotes the generation of robust data and protects them from participating in badly designed or irrelevant clinical trials. Over the past few years, EMA has encouraged medicine developers to seek advice early in the development of a medicine when changes can be made more easily and at a lower cost compared to later stages. As in 2014, we have also seen a trend during 2015 of more developers requesting scientific advice for early phase 1 or 2 clinical trials.

Scientific advice is also a key platform for our collaboration with health technology assessment (HTA) bodies which aims to facilitate patients' access to new medicines. Interest in our pilot project for parallel scientific advice with HTA bodies rocketed in 2015. The Agency received three times as many requests as in the previous year, demonstrating that there is a need for an integrated approach to generating evidence for both benefit-risk and relative effectiveness assessments.

The pharmacovigilance legislation has been a key factor in our efforts to contribute to a more rapid translation of scientific progress into safe and effective authorised medicines that address patients' needs. Three years after it came into effect, the legislation has already significantly changed the way the safety of medicines is being monitored, allowing the Agency to be much more proactive and effective in its dual role as gatekeeper, protecting patients from unsafe treatments, and enabler, facilitating the development of new and innovative medicines. Implementation of the legislation continued in 2015 with improved and simplified monitoring of medicine safety in the EU.

Integrating new tasks stemming from legislative changes into our existing operations is a perennial priority. The Agency advanced the development of the clinical trial portal and database, EMA's key deliverable of the 2015 EU Clinical Trials Regulation. The Agency will provide the IT infrastructure required by this ambitious new piece of legislation, which is leading to the most significant overhaul of the processes for authorisation and oversight of clinical trials in the last two decades. The new portal and database will be used as a single entry point for submission and maintenance of clinical trial applications and authorisations, and allow for a coordinated assessment and supervision. EMA is working closely with national medicines agencies to ensure that the new IT systems will benefit researchers, patients and the public as a whole from day one, as foreseen by the Clinical Trial Regulation.

The threat of antimicrobial resistance (AMR) continued to be a high priority for EMA and the whole of the EU medicines regulatory network in 2015. In addition to speeding up development of new medicines and promoting the responsible use of existing antibiotics, EMA has an important role in the collection of data to guide policy and research. In January, together with its sister agencies, the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA), EMA published a joint integrated analysis of the consumption of antimicrobial agents and the occurrence of AMR in bacteria in humans and food-producing animals. This was the first time that data from humans, animals and food in Europe were analysed together, providing valuable insights for policy-makers across the EU.

Public health challenges do not stop at borders, as was demonstrated by the outbreak of the Ebola virus disease in West Africa which gripped the world at the beginning of 2015. EMA contributed to the global response by helping with the rapid identification and acceleration of the development of treatments

and vaccines. This has reinforced the Agency's commitment towards ever-closer cooperation between regulatory authorities worldwide in order to promote and protect public health around the globe.

Last but not least, 2015 was also the year when important progress was made in a number of therapeutic areas in the EU's public and animal health. Ninety-three new medicines for human use were recommended for marketing authorisation, relating to 39 new active substances. Many of these medicines represent therapeutic innovations that have the potential to make a difference to people's lives, building on the advances made in biomedical science that give us a better understanding of the causes of diseases and how to combat them.

In veterinary medicine, EMA recommended 14 new medicines for marketing authorisation, over a third of which were vaccines aimed at preventing viral or bacterial infections in food-producing animals.

None of the successes achieved in 2015 would have been possible without the network of European medicines regulatory agencies. This network gives EMA access to a pool of excellent scientists from across Europe, allowing the Agency to source the best-available experts for the regulation of medicines in the EU. I would like to thank all those involved in EMA's work for their contribution to advancing the health of 500 million European citizens: the members of its scientific committees, the working parties and scientific advisory groups, the Management Board, all the national experts, the Agency's staff, and last but not least our stakeholders who share their views and concerns to help us protect public and animal health. It gives me great pleasure to present our joint achievements in 2015.









## **1. KEY ACHIEVEMENTS IN 2015**

## 1.1 Evaluation and monitoring of medicines

### Human medicines

#### Bringing significant benefits to patients

In 2015, EMA recommended 93 medicines for marketing authorisation, which include 39 new active substances. These are substances that have previously never been authorised in a medicine in the European Union and that are not related to the chemical structure of any other authorised substances.

Many of these medicines represent therapeutic innovations that have the potential to make a difference to people's lives, building on advances in biomedical science which give us a better understanding of the causes of diseases and how to combat them.

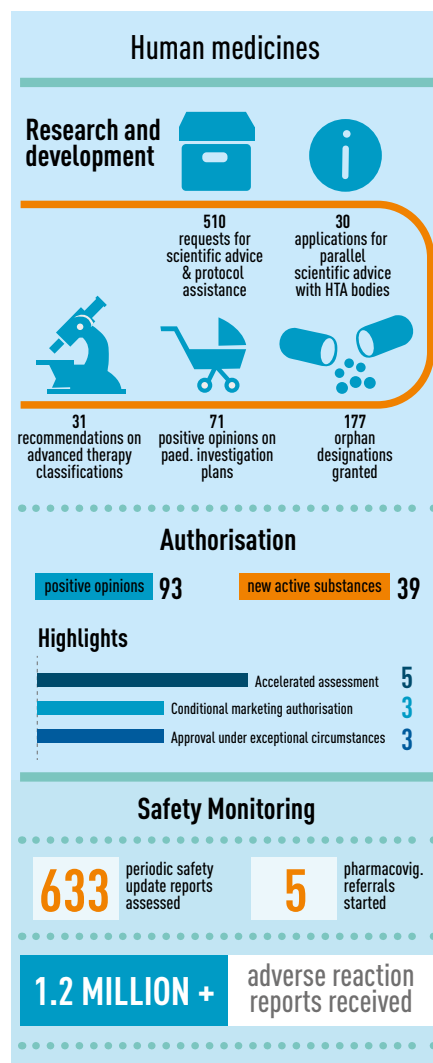
Most of the noteworthy therapeutic innovations in 2015 took place in the area of **cancer**. Newly approved cancer therapies deactivate 'suppressive signals' to kill cancer cells (Opdivo and Keytruda), use monoclonal antibodies to direct the immune

system towards cancer cells (Blinicyto), modulate the activity of genes to treat multiple myeloma (Farydak) or use a genetically engineered virus to kill cancer cells (Imlygic).

Innovative substances also found their way into the treatment of **cardiovascular disease**. They include, for example, monoclonal antibodies to treat hypercholesterolemia (Repatha and Praluent) and combination therapy with a dual action for heart failure (Entresto).

In **neurology**, a new medicine (Wakix) acts on histamine H3 receptors in the brain to treat narcolepsy, while in **haematology**, an antidote (Praxbind) neutralising the anticoagulant effect of Pradaxa was recommended for marketing authorisation.

Approximately half of all applicants who received a positive opinion for their medicine had received scientific advice from EMA during the development phase of their product; this figure rises to 85% when it comes to medicines containing a new active substance. Scientific advice is EMA's key tool to promote the collection of robust data on the benefits and risks of medicines.



### 19 January

Launch of initiative for sharing assessments of applications for generic medicines with collaborating regulatory agencies outside the EU in real time



### 26 January

20<sup>th</sup> anniversary of the establishment of EMA



### 26 January

Launch of an electronic repository for periodic safety update reports (PSURs)

**Facilitating market access for medicines that make a difference to patients’ lives**

In 2015, almost one in five medicines containing a new active substance made use of EMA’s tools to facilitate early access to medicines that address unmet medical needs.

Five new medicines received a recommendation for marketing authorisation following an **accelerated assessment**; this mechanism allows for a faster assessment of eligible medicines by EMA’s scientific committees (within up to 150 days rather than up to 210 days).

Three medicines received a recommendation for a **conditional marketing authorisation**, of which one also had an accelerated assessment. This tool enables the early approval of medicines on the basis of less-extensive clinical data than is normally required. It is intended for medicines that target seriously debilitating or life-threatening diseases, rare diseases or are intended for use in emergency situations in response to a public health threat. These medicines must show a positive benefit risk profile, but are subject to specific post-authorisation obligations that aim to collect more extensive data on the

CONTRIBUTING TO PUBLIC HEALTH BEYOND EUROPE

Mosquirix, the first vaccine against malaria, was assessed by the Committee for Medicinal Products for Human Use (CHMP) and recommended for use outside the EU in collaboration with the World Health Organization (WHO).

medicine, allowing ultimately for a full marketing authorisation to be granted when all the conditions have been met and the data obtained confirms the positive benefit-risk balance.

In addition, three medicines were recommended for **marketing authorisation under exceptional circumstances**; in these three cases, the medicines could not be approved under a standard authorisation as comprehensive data cannot be gathered due to the rarity of the disease they target. These medicines are subject to specific post-authorisation obligations and monitoring.

**Protecting public health**

Once a medicine is available to patients, EMA and the EU’s national competent authorities continuously monitor the benefits and risks that patients experience with the medicine in real life.

If problems arise, healthcare providers and patients can be informed immediately to protect them from harm.

**New safety advice for better risk management**

In 2015 the product information on many medicines was updated as new safety information became available. This includes information on bisphosphonates and denosumab, certain hepatitis C medicines (Harvoni, Sovaldi and Daklinza), adrenaline auto-injectors, mycophenolate, and two medicines for the treatment of multiple sclerosis (Tecfidera and Gilenya). The revised information should allow patients and healthcare professionals to make better informed decisions when using or prescribing the medicines.



**30 January**

Publication of ECDC/EFSA/EMA report with first integrated analysis of data from humans, animals and food on consumption of antimicrobials and occurrence of AMR



**19-20 February**

Finalisation of the PROTECT project on pharmacovigilance methods – workshop on results and recommendations



**5 March**

Working Parties with Patients’ and Consumers’ Organisations (PCWP) and Healthcare Professionals’ Organisations (HCPWP) joint workshop on biosimilars

### Adjusting product information for HIV medicines

EMA reviewed the product information of all centrally approved HIV medicines. In light of new data available, the Agency decided to remove warnings for most of them about the risk of body-fat changes and lactic acidosis.

### Review of human papillomavirus (HPV) vaccines

Following reports on two syndromes – complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) – in young women who received human papillomavirus vaccines, EMA carefully reviewed all available evidence. The vaccines are given to girls and young women to protect them from cervical cancer and other HPV-related cancers and precancerous conditions. EMA concluded that the available evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and these syndromes. Therefore, there is no reason to change the way the vaccines are used or amend the current product information.

More detailed information on the Agency’s assessment activities can be found in Chapter 3.

### Veterinary medicines

#### New medicines to improve animal health in Europe

In 2015, EMA recommended 14 new veterinary medicines for marketing authorisation; seven of these contain a new active substance. More than half of the new medicines were intended for food-producing animals.

#### Vaccines protecting food-producing animals from infectious diseases

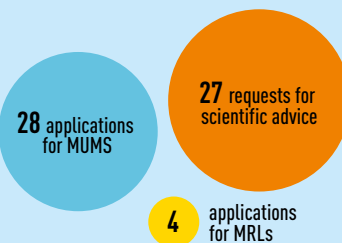
Five vaccines were recommended for marketing authorisation to prevent viral or bacterial infections in food-producing animals.

Four of these are biotechnology products (Porcilis PCV ID, Vectormune ND, Innovax-ILT and Suvaxyn Circo+MH RTU). This reflects the current shift in the manufacturing of veterinary vaccines from traditional methods towards biotechnology.

Two of the vaccines (Vectormune ND and Innovax-ILT) use a single vaccine organism to protect against two diseases, reducing the number of live organisms to which the treated animals (chickens) are exposed through vaccination.

### Veterinary medicines

#### Research & development



#### Authorisation

##### 10 new applications

##### 14 positive opinions

food producing species    companion animals



#### Safety monitoring

31 467

reports on suspected adverse reactions

159

periodic safety update reports submitted

7

referral procedures started



### 18 March

EMA 20<sup>th</sup> anniversary scientific conference

### 25 March

Joint EMA/HMA workshop on requirements for authorisation of veterinary vaccines in the EU

### 30 April

Joint EMA/European Society for Medical Oncology (ESMO) rare tumours initiative (Rare Cancers Europe) workshop

**Facilitating market access for medicines for minor use minor species**

EMA also recommended authorisation of a medicine (Zycortal) for the treatment of Addison’s disease in companion animals (dogs) under its minor use minor species (MUMS)/limited market programme. The Agency applies a more flexible approach in terms of data requirements for medicines that are classified as MUMS.

**New medicines to reduce risk of antimicrobial resistance**

EMA recommended marketing authorisation for two medicines (Velactis and Imrestor) that have the potential to reduce the need for antimicrobial treatment in food-producing animals (dairy cattle). Both are intended for the prevention of mastitis, a painful inflammation of the udder tissue. Mastitis is a significant animal health issue with important effects on both milk quality and the welfare of the affected animals.

**Monitoring in real life – optimising safe and effective use of medicines**

Once a veterinary medicine has been put on the market, EMA and the EU Member States continuously

monitor the benefits and risks for human and animal health and for the environment.

A review of Closamectin Pour-On Solution and associated names (closantel and ivermectin) began following suspension of its marketing authorisation in France. The suspension followed evaluation of pharmacovigilance data related to animal health concerns with this medicine. EMA recommended that the medicine should remain available, but that changes should be made to the product information to mitigate risks and improve surveillance.

EMA reviewed the risk to consumers from the use of the local anaesthetic lidocaine in food-producing species. The Agency issued recommendations to ensure that residues that may occur in milk after off-label use in cattle pose negligible risk to consumer safety. These recommendations advised communication with veterinarians to ensure there is an adequate time lapse between the administration of lidocaine and the taking of milk for human consumption.

EMA continued to contribute to reducing the need for testing in animals as part of the medicines authorisation process. A review of existing CVMP guidelines to ensure compliance with the

best 3Rs practice (Replacement, Reduction and Refinement of animal testing) was completed while a review of batch release tests being used for centrally authorised vaccines continued. At an international level, EMA led the development of draft VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guidelines on criteria to waive target animal batch safety testing of live vaccines for veterinary use.



**6 May**

Updated rules on declarations of interests for scientific committee members and experts



**28 May**

Annual workshop of the European network of paediatric research (Enpr-EMA)



**8 June**

Workshop on the therapeutic use of bacteriophages

## 1.2 Facilitating early phases of medicine development

The last decades have seen revolutionary advances in science, medicines and technology. Nevertheless, many patients with serious or life-threatening diseases still have no or only unsatisfactory therapeutic options. Encouraging the development of medicines that make a difference to patients' lives is one of EMA's key priorities.

### PRIME – extra support for priority medicines

From October to December 2015, EMA ran a public consultation on the key principles of its new PRIME scheme. PRIME aims to strengthen support for medicines that have the potential to offer a major therapeutic advantage to patients over existing treatments, or benefit patients with no or unsatisfactory treatment options for their disease. These are considered priority medicines by EMA, hence the name of the scheme.

Through this scheme, EMA will offer early and enhanced scientific and regulatory support

We want to focus our efforts on those medicines which have the potential to really improve patients' lives – so that innovation clearly translates into public health benefit.

*Guido Rasi, EMA Executive Director*

to medicine developers to optimise the generation of robust data and enable accelerated assessment by the CHMP, where appropriate. This allows patients to benefit from therapies that may significantly improve their quality of life as early as possible.

PRIME builds on existing regulatory tools, particularly scientific advice and accelerated assessment, which allow for an expedited review of medicines which are of major interest for public health because they address unmet medical needs or bring about a major therapeutic innovation for patients. Key features of the scheme include early appointment of a CHMP rapporteur and early scientific advice to improve development plans and the quality of data.

The scheme is expected to be launched in the first quarter of 2016<sup>1</sup>.

### Revision of guidelines for early access tools

EMA launched public consultations on its revised guidelines on accelerated assessment and conditional marketing authorisation, two key tools in the European legislation to speed up the regulatory path to medicines that address unmet medical needs.

The proposed changes were made based on the experience with these assessment tools. The updated guidelines will help medicine developers to better integrate these tools into their development programme. This is expected to contribute to patients' early access to medicines that address an unmet medical need. The fulfilment of unmet medical needs is clarified in the two guidelines with the focus on better addressing patients' needs. This includes more detailed guidance on how to justify major public

<sup>1</sup>) PRIME was launched on 7 March 2016.



### 16 June

Launch of early interaction meetings initiative to encourage paediatric needs to be considered in the early phases of medicine development



### 29 June

Workshop on the development of new medicines for the treatment of ulcerative colitis and Crohn's disease



### 1 July

Launch of EU-wide logo on the websites of online retailers that are registered in an EU Member State to protect patients from falsified medicines



health interest, how the benefit-risk balance should be assessed in absence of comprehensive data, and clarification that medicines providing major improvements in patient care over existing therapies can be eligible for conditional marketing authorisation in exceptional cases.

The revised guideline on conditional marketing authorisation also includes examples and further guidance on the degree of evidence required at the time of authorisation (e.g. use of intermediate end points that are likely to translate into clinical benefit) and the data that need to be provided after authorisation. The importance of data generation after authorisation is emphasised clearly reflecting that regulatory action may have to be taken in case of non-compliance.

**Adaptive pathways pilot project**

In 2015, EMA continued to accept applications for its adaptive pathways pilot project for the second year. Adaptive pathways is a scientific concept of medicine development and data generation which gives patients early and progressive access to a medicine.

Its key features are:

- staggered authorisation from very small, restricted patient populations to increasingly wider populations;

- iterative gathering of evidence through prospectively planned data generation, including real-life data;
- involvement of patients and health technology assessment (HTA) bodies.

The adaptive pathways pilot provides a framework for informal dialogue between stakeholders, including patients and health-technology-assessment bodies, to explore how the approach might work in the existing regulatory framework and discuss detailed technical and scientific questions based on concrete examples.

EMA encourages submission of applications to the pilot project in therapeutic areas where patients have high unmet medical needs and where collection of sufficiently large data sets via traditional routes is difficult.

In December 2015, EMA released more detailed guidance for medicine developers considering applying for the pilot.

A final report on the pilot should be published by the end of 2016, once six products have undergone parallel scientific advice from EMA and health-technology-assessment bodies.

**Early paediatric interaction meetings**

In June 2015, EMA also started offering early interaction meetings to foster efficient development of safe and effective medicines for children. The early paediatric interaction is intended to facilitate and encourage early dialogue between applicants and the EMA/PDCO regarding the strategy for the medicine’s paediatric development programme, in advance of a paediatric investigation plan (PIP) application. Applicants may request this meeting to discuss their paediatric strategy at the very early stages of development, when paediatric needs and the respective paediatric population are not yet clear from the available information. EMA received 10 requests for early paediatric interaction meetings between June and December 2015.

21 APPLICATIONS FOR  
MEDICINES IN DEVELOPMENT  
ACCEPTED BY END 2015

<p style="font-size: 2em; font-weight: bold;">4/21</p> <p>Advanced-therapy medicinal products</p>	<p style="font-size: 2em; font-weight: bold;">5/21</p> <p>Medicines targeting rare diseases</p>
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**15 July**

Launch of the public register of parallel distribution

**22 July**

Confidentiality arrangement between EU and Swiss regulators for sharing non-public information on the safety, quality and efficacy of medicines

### 1.3. Public health challenges

Over the past 50 years, the life expectancy of European citizens has risen. Europeans not only live longer but they also live healthier lives. Despite this positive development, people in Europe continue to face significant public health threats, such as AMR, emerging new diseases and the increasing epidemic of non-communicable conditions. These challenges require a holistic and global approach.

#### Antimicrobial resistance

AMR is a major global public health threat. In Europe alone, 25,000 people die each year from infections caused by resistant bacteria. AMR also places a tremendous burden on healthcare systems and society, with an annual cost due to healthcare expenditures and productivity losses estimated at approximately €1.5 billion in the EU.

The Agency continues to contribute to global initiatives to combat antibiotic resistance, such as the Trans-Atlantic Task Force for Antimicrobial Resistance (TATFAR). In October 2015, work started on a new work plan for the period up to 2020, including extending the membership to Canada and Norway.

#### Supporting the development of new antibiotics

The availability of medicines to treat infections caused by resistant organisms has become a major issue. A central pillar in EMA's strategy to fight AMR is to stimulate and facilitate the development of new antibiotics for use in humans.

In September 2015, the Agency released for public consultation a draft guideline on the use of pharmacokinetic and pharmacodynamic analyses in the development of antibiotics. The document provides guidance for medicine developers on how to conduct robust studies which could foster the development of new antibacterial agents including those that target multi-drug-resistant bacteria.

#### Exploring new approaches

In June 2015, EMA organised a workshop on the use of bacteriophages to treat bacterial infections. Bacteriophages are naturally occurring viruses that kill bacteria. Since their mechanism is completely different to that of antibiotics, bacteriophages could be effective against bacteria that have become resistant to antibiotics. Based on the current EU regulatory framework, the Agency provided a platform to discuss fixed phage

cocktails and is also taking steps to enable the development of such products.

#### Promoting responsible use of antibiotics

The responsible use of antibiotics, both in humans and in animals, is key to minimising the risk of AMR. Working with the European Commission and Member States in the framework of the Commission's action plan against AMR, EMA gives recommendations on the appropriate use of antibiotics in animals, especially for those substances that are critically important to protecting the lives of humans.

By following the 'One Health' approach, endorsed by the Commission and numerous organisations worldwide, EMA is addressing the use of antibiotics in humans and animals together. The new CVMP strategy on antimicrobials for 2016-2020, released by the Agency for public consultation in 2015, recognises the need to balance the continued requirement for antimicrobials to treat infectious disease in animals with the need to minimise the risks of AMR for animals and humans.

In addition, at the request of the European Commission, and together with the European Food Safety Authority (EFSA), EMA started working on a scientific opinion on



#### 23 July

Revision of class waiver list for medicines that are not required to submit a paediatric investigation plan (PIP)



#### 24 July

First malaria vaccine receives positive scientific opinion from EMA (Article 58)

how to reduce the need for antimicrobial agents in animal husbandry in the EU, and the possible impact on food safety. The scientific opinion is expected to be issued at the end of 2016.

**Collecting data to support EU decision makers**

In January 2015, together with the European Centre for Disease Prevention and Control (ECDC) and EFSA, the Agency published a joint integrated analysis of the consumption of antimicrobial agents and the occurrence of AMR in bacteria in humans and food-producing animals. This was the first integrated analysis of data from humans, animals and food in Europe.

Finally, as every year in October, the Agency published a report on sales of veterinary antimicrobials from the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. The latest ESVAC report published in 2015 shows that antibiotic sales for use in animals in Europe fell by approximately 8% between 2011 and 2013. According to Member States, factors that may have contributed to this decline include responsible-use campaigns, increased awareness of the threat of AMR, restrictions of use and targets, and changes in animal

demographics. At the same time as publishing the report, the Agency made available on its website an on-line tool to allow users to access, analyse and download the data contained in the ESVAC database, thereby promoting transparency on this important area for public and animal health.

Collecting accurate data on the sales of these medicines in food-producing animals is an essential first step in developing and monitoring policies on responsible use in the Member States.

**Responding to public health emergencies**

**Ebola outbreak**

The Ebola outbreak in West Africa that started in March 2014 was the largest and most complex Ebola outbreak to date. EMA, in cooperation with the European regulatory network and other international bodies, supported the World Health Organization (WHO) to promote rapid research, development and evaluation of vaccines and therapeutics to combat the disease. The Agency worked closely with the European Commission to ensure effective communication with Member States to safeguard public health in the EU. By the end of 2015, the Ebola crisis had been

contained, although new cases may still emerge, requiring constant vigilance and rapid response.

Currently, there are no approved medicines available that protect against Ebola, or treat the disease. In 2015, the Agency continued to support the development of Ebola medicines and vaccines through accelerated scientific advice and orphan designation. A key factor in these efforts is the ad-hoc task force with expertise in vaccines, infectious diseases and clinical trial design, which was established by EMA in August 2014. The group is involved in providing scientific advice for vaccines as well as in a review of the available scientific information on medicines under development for the treatment of Ebola. The review was finalised in early 2016.

**First vaccine against malaria**

In July 2015 the Agency gave a positive scientific opinion for the malaria vaccine Mosquirix, also known as RTS,S/AS01. The product had been submitted to EMA under Article 58 - a regulatory procedure that allows the Agency to assess quality, safety and efficacy of a medicine or vaccine and its benefit-risk balance, although it will not be marketed in the EU. Through Article 58, EMA issues scientific opinions to facilitate access



**27 July**

Start of public consultations on revised guidelines on accelerated assessment and conditional marketing authorisation

**28 July**

Launch of a pilot to encourage use of scientific advice for post-authorisation safety studies (PASS)

to new medicines for people outside the EU and shares its experience with regulatory authorities from relevant countries. The Agency worked closely with other partners, including the WHO and regulatory authorities from some of the countries where Mosquirix could be used. In its assessment of the vaccine, EMA applied the same rigorous standards as for medicines to be marketed within the EU.

After decades of research into malaria vaccinations, Mosquirix is the first vaccine for the disease that has been assessed by a regulatory agency. It is intended for use in areas where malaria is endemic. Mosquirix can protect children aged 6 weeks to 17 months against malaria caused by the Plasmodium falciparum parasite, and against hepatitis B.

Following EMA's positive opinion, the WHO Strategic Advisory Group of experts on immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) discussed the best way to deliver the vaccine. In October 2015, the two groups recommended launching 3 to 5 pilot projects to better understand how to make best use of this vaccine.

### Initiatives to prevent medicine shortages

Medicine shortages due to disruption of the supply chain represent a significant risk to public health. Such shortages have become a global problem during the past decade and also increasingly affect the EU with a potentially negative impact on patient care.

The Agency is taking proactive measures to prevent medicine shortages. In 2015, EMA convened a second stakeholder workshop, bringing together national competent authorities, industry, patient and healthcare professional representatives to discuss progress made since the publication of a reflection paper in 2012. The paper defined ways to support the EU regulatory network in preventing and managing shortages of important medicinal products, and reflected on the proactive management of shortages. The workshop

concluded that although the work done so far was encouraging, the challenge required further effort to avert shortages.

Collaboration between the various stakeholders and regulators, including international collaboration, combined with improved business continuity planning by the industry, and good communication between manufacturers and authorities can help prevent shortages. A follow-up workshop will take place in two years' time. In the interim, EMA will collaborate with the existing stakeholder participants to implement the recommendations made during the workshop.

Shortages of medicines impact the daily lives of many EU citizens and are therefore a top priority for EMA. The progression of our shortage strategy with regulatory, industry, patient and healthcare professionals has the potential to deliver tangible results that benefit patients.

*Anabela Luis de Lima Marcal, Head of Compliance and Inspections Department*



### 1 September

EMA's medical literature monitoring service becomes fully operational

### 16-17 September

Joint PCWP/HCPWP workshop on risk-minimisation tools

## 1.4. Implementation of new legislation

EU pharmaceutical legislation is constantly evolving and integrating new provisions into the Agency's existing operations in a zero-growth environment is a challenging task.

In 2015, the continued implementation and operation of the pharmacovigilance legislation, the most substantial change in the Agency's legal framework since its establishment in 1995, remained a priority. The Agency also continued to work on the implementation of the Falsified Medicines Directive and on the development of the EU portal and database for the implementation of the Clinical Trials Regulation.

In September 2014, the European Commission adopted its proposal for the revision of the legal framework governing the authorisation of veterinary medicines. This aims to promote the availability of veterinary medicines and address the challenge of AMR. During 2015, the Agency further analysed the new proposal for its impact on the EMA and the European medicines regulatory network and provided advice and assistance to the Commission as the proposal started the co-decision process in the European Council and the European Parliament.

### Pharmacovigilance legislation

Three years after it came into effect, the Pharmacovigilance legislation has already delivered a major change in

the way the safety of medicines is being monitored. It has also proven to contribute to the protection of patients. Implementation continued in 2015 and important progress was made in a number of areas.

### Preparation for enhancements to EudraVigilance

In October 2015, EMA published a change management plan to provide stakeholders with comprehensive information on upcoming improvements to the EudraVigilance system. The plan detailed the technical changes as well as changes in business processes in relation to reporting, managing and analysing individual case safety reports (ICSRs) from medicines in clinical use and from clinical trials.

EudraVigilance is a web-based information system of suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA) that was launched by EMA in December 2001. As a result of updates to the pharmacovigilance and clinical trials legislation, enhancements to EudraVigilance are expected to improve the safety monitoring of medicines and to turn EudraVigilance into a more efficient system for stakeholders. The development work is on track for an independent audit in the third quarter of 2016 and the introduction of centralised ICSR reporting in the third quarter of 2017.

### PSUR Repository

EMA launched an electronic repository for periodic safety update reports (PSURs) and their assessment reports in January 2015.

The central platform contains all the information related to PSURs in the EU. It aims to facilitate the assessment of PSURs by medicines regulatory authorities in the EU and to simplify reporting by companies.

The new central repository stores PSURs, PSUR assessment reports, comments, and final outcomes, and gives secure access to authorised users from national competent authorities in EU Member States, EMA, Agency committees, and the European Commission. It ensures that all people involved in benefit risk assessments of medicines have timely access to all relevant documents in one location. From June 2016 the repository will simplify industry reporting by being the unique route to submit PSURs.

### Publication of the outcomes of PSUR single assessments

In July 2015, the Agency started to publish the outcomes of single assessments of PSURs for active substances contained only in nationally authorised medicines. A single assessment of related PSURs is carried out for medicines that contain the same active substance or combination of active substances. The Agency already systematically publishes the outcomes of PSUR assessments for centrally authorised medicines as part of the European Public Assessment Report. This new initiative supports the harmonised implementation of new safety measures for medicines with the same active substance across EU Member States.



## 22 September

Confidentiality arrangement between EMA, EC and WHO for sharing non-public information on the safety, quality and efficacy of medicines



## 28 September

Start of public consultation on guidelines on the use of pharmacokinetics and pharmacodynamics analyses in the development of antibiotics

### Scientific Advice for PASS

In July 2015, EMA started a pilot to encourage companies to seek scientific advice for post-authorisation safety studies (PASS) for medicines. Through this voluntary and optional procedure the Agency gives advice to marketing authorisation holders on how to design studies in order to collect high-quality data. Further information on a medicine's safety will then be gathered during its use in real life. The pilot builds on the expertise of the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) which will agree the scientific advice for the PASS protocols.

The pilot fosters a more integrated approach to the planning of safety, efficacy and quality studies during the life cycle of a medicine.

### Medical literature monitoring

EMA started its full medical literature monitoring service on 1 September 2015. As part of this service, it is keeping track of publications on a total of 400 active substance groups: 300 chemical active substance groups and 100 herbal active substance groups.

This new service aims to improve the safety monitoring of medicines by enhancing the quality and consistency of the data reported through EudraVigilance. As regards the active substances and literature

covered by EMA activities, industry is no longer obliged to enter literature information on suspected adverse reactions into EudraVigilance. Individual cases of suspected adverse reactions found in the literature are made available to marketing authorisation holders to enable them to include the information in their safety databases and to meet their reporting obligations outside the European Economic Area (EEA). The service will benefit over 4,000 pharmaceutical companies and EMA is working closely with industry to deliver the maximum benefits over time.

### Article 57 database is functional for pharmacovigilance

At its December 2015 meeting, the Agency's Management Board confirmed that the Article 57 database of human medicines authorised in the EU is functional for pharmacovigilance. Notably, the database can now be relied upon to provide the name and contact details of the qualified person responsible for pharmacovigilance (QPPV) for each authorised medicine in the EU and

the location where the pharmacovigilance system master file (PSMF) of the marketing-authorisation holder of a given medicine is held.

As a result, companies are no longer required to submit type IA variations to notify regulators of changes in relation to the contact details of their QPPV or the location of their PSMF. This simplifies the notification of these changes for both companies and regulators and has been applied since 1 February 2016.

### Pharmacovigilance fees

In 2015, the Agency started collecting annual fees related to pharmacovigilance activities from marketing authorisation holders of medicines authorised nationally in addition to the existing annual fees for centrally authorised products. These fees will support information technology systems and literature-monitoring activities.

They complement the fees EMA has been charging since August 2014 for certain pharmacovigilance procedures, including the assessment of periodic safety update reports,

The EU pharmacovigilance system delivers robust health promotion and protection through planned product monitoring, and rapid detection and resolution of safety issues.

*Peter Arlett, Head of Pharmacovigilance Department*



## 2 October

Transparency rules endorsed for the EU portal and database



## 9 October

Workshop on product shortages due to manufacturing and quality problems: developing a proactive approach to prevention

and the assessment of PASS protocols and study results, and for pharmacovigilance-related referrals. Only those companies whose medicines, whether authorised centrally or nationally, are included in these procedures have to pay these fees.

### Medication errors guide and catalogue

In November 2015, EMA published a good practice guide on medication errors to support the reporting, evaluation and prevention of such errors by regulatory authorities and pharmaceutical companies throughout the EU.

The guide details how suspected adverse reactions that are caused by medication errors should be recorded, coded, reported and assessed. It also describes the main sources and types of medication errors and proposes options to minimise their risk.

In addition, EMA launched a web page highlighting measures recommended by the Agency to prevent medication errors for specific medicines. This page will be updated with clear and easy-to-understand information for patients and healthcare professionals to further promote the safe use of medicines, as necessary.

### Falsified medicines

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

### Logo for online retailers of medicines

The Directive that entered into force on 21 July 2011 introduced a logo that allows patients and consumers to identify authorised online retailers of medicines operating in the EU. As of 1 July 2015, the logo is to be displayed on the website of all recognised online pharmacies or retailers. By clicking on it, consumers are directed to the website of the appropriate national regulatory body where all legally operating online retailers of medicines in the respective Member State are listed. EMA has published a web page from which users can directly access national websites and registers.

### Clinical trial regulation

The Agency was given the responsibility to develop and maintain a portal and database for the submission, authorisation and supervision of clinical trials in the EU as part of the implementation of the new Clinical Trial Regulation (EU) No. 536/2014. The portal will provide access to a database which will serve as the source of public information on the full life cycle of all clinical trials conducted in the EU, from their initial review up to publication of their results.

In October 2015, the Agency's Management Board adopted the transparency provisions that will be applied to the EU portal and database. These were drawn up in collaboration with the Member States

and the European Commission and were subject to a broad public consultation. This document establishes the rules on what documents and information will be made publicly available and when.

The public will be able to access comprehensive details of each trial, including the major characteristics of the trial, the start and end of recruitment, the end date and substantial modifications to the trial. A summary of the results and a summary in lay language will normally be published 12 months after the end of the trial.

At its last meeting in 2015, the Agency's Management Board endorsed the delivery time frame for the implementation of the EU portal and database. According to this schedule, the portal and database will be audited independently by August 2017. If the system gets the green light from the auditors, the Clinical Trial Regulation will come into effect in October 2018 at the latest. This is a maximum time frame and all possible efforts will be made to shorten the process and bring the Regulation into operation as soon as possible.



## 12 October

Launch of EMA initiative on collecting high-quality information on medicines through patient registries

## 15 October

Publication of European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report on sales of veterinary antibiotics in Europe

## 1.5. Transparency and communication

Openness and effective communication are two of the Agency's key principles. Four developments in this area during 2015 are outlined below: the entry into force of EMA's policy on the publication of clinical data, the adoption of the framework for interaction with corporate stakeholders, the survey of partners and other stakeholders regarding their perception of EMA's external communication activities and materials, and greater engagement with patients and healthcare professionals.

### EMA policy on publication of clinical data

EMA's policy on the publication of clinical data entered into force on 1 January 2015 and applies to clinical reports included in marketing-authorisation applications submitted on or after this date. The first reports will be published as soon as the decision on an application has been taken. This is currently foreseen for September 2016.

From 1 July 2015, the policy will apply to extensions of indication/line extension applications for centrally authorised products submitted as of that date.

Throughout 2015, EMA worked on building new IT systems to publish clinical reports. The Agency also developed guidance on procedural aspects related to the submission of clinical reports for publication, the

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

*Guido Rasi, Executive Director*

identification and redaction of commercially confidential information in such clinical reports, and the anonymisation of personal data contained in these reports. The guidance documents are 'living documents' that will be updated in light of the experience gained during implementation of the policy. To prepare for the publication of the clinical reports and to help all stakeholders understand the requirements, the Agency organised a series of discussions and consultations with its stakeholders throughout the year. In October 2015, EMA met with the European Ombudsman and the European Data Protection Supervisor to consult on the new policy.

### Five years of access to documents

EMA's commitment to transparency is also being achieved through its release of data under the access to documents legislation. It has been five years since the Agency's policy on access to documents entered into force, establishing EMA as one of the most transparent regulatory authorities worldwide. In 2015 alone, 2,972 documents were released following often very complex access-to-documents requests, compared to 1,771 documents in

2014. For more details, please see the section on 'access-to documents requests' in Chapter 3.

### EudraVigilance access policy

A revised EudraVigilance access policy was agreed by the Management Board at its December 2015 meeting. The final policy was based on a broad public consultation generating close to 400 comments.

Through the revised policy, the public will have access to more information, including line listings of the side effect reports and summary presentations of individual adverse reaction reports received in EudraVigilance. Whilst ensuring that patients and those who have sent in reports of suspected side effects cannot be identified, the policy represents a significant increase in transparency for medicine users. Upon request, academia will be provided with extended access to data sets in support of their research activities.

These changes will come into effect in the third quarter of 2017 in parallel with the implementation of a series of technical improvements to the EudraVigilance system.



## 15 October

Workshop on good clinical practice (GCP) compliance for bioequivalence trials/generics



## 26 October

Start of public consultation on PRIME – a scheme to optimise development of priority medicines and facilitate patients' access



**PERCEPTION SURVEY: KEY RECOMMENDATIONS**

-  **CORPORATE WEBSITE OPTIMISATION** to improve findability, general usability and reduce complexity
-  **GREATER STAKEHOLDER ENGAGEMENT** across the different groups via targeted information and more active dialogue
-  **INCREASED USE OF SOCIAL MEDIA CHANNELS** to create a better awareness of EMA and its work
-  **SIMPLIFIED CONTENT** to make information more accessible

**Stakeholder perception survey**

In February 2015, EMA surveyed around 1,000 of its partners and stakeholders on their perception of the Agency’s communication activities. The purpose of the survey was to assess in both a qualitative and quantitative manner how EMA’s external communication is received and valued by its partners and stakeholders and whether they are satisfied with the service provided. The perception survey was conducted independently by an external consultancy group and in cooperation with the University of Sheffield, in the UK.

Overall, the survey showed that EMA’s communication activities are highly appreciated by its partners and stakeholders, with the corporate EMA website being used as the main information channel. However, there is a need to better target communication to the Agency’s various audiences as well as to engage more with specific audiences, particularly academia, media and

the general public. Key recommendations for improvement are outlined in the box above. They will be taken into account in EMA’s communication framework strategy 2016-2020 which is under preparation.

**Strengthening engagement with civil society**

Patients are at the heart of everything EMA does and the Agency is continuously improving its engagement with patients and civil society. Healthcare professionals, as prescribers and handlers of the medicines that EMA evaluates, are also key stakeholders for providing the Agency with specific knowledge in clinical

practice and the use of medicines. A few key developments that took place in 2015 are outlined below:

**The voice of patients and healthcare professionals in benefit-risk evaluation**

EMA’s pilot project to involve patients in the assessment of the benefits and risks of medicines in CHMP meetings continued in 2015. This pilot marks the next step to bring patients’ and carers’ views and values to the assessment of medicines. As part of the pilot project, when medicines that address an unmet medical need are under review, and the CHMP is undecided, patients are being invited to present their view to the Committee directly.

The pilot project has been extended into 2016 to allow for at least six medicines to be included in it. This will provide more data for analysis at the end of the pilot. A report on the experience gained will be presented to the CHMP at the end of the project.

**Workshop on risk minimisation measures**

In September 2015, EMA hosted a workshop on risk minimisation measures with representatives from patients’ and healthcare

All that we do must ultimately benefit patients. This is why we involve them more and more in our work, to ensure their views and needs are taken into account at every step of the process.

*Isabelle Moulon, Head of Patients and Healthcare Professionals Department*



**27 October**

Publication of change management plan to prepare stakeholders for improvements to the EudraVigilance system

**28-29 October**

Workshop on product quality lifecycle management

## PATIENT INVOLVEMENT IN BENEFIT RISK EVALUATION

In July 2015, during the CHMP's evaluation of Intuniv (guanfacine) to treat attention deficit hyperactivity disorder (ADHD), the Committee invited a young adult affected by ADHD and the mother of a patient with the condition to share their experiences with the Committee. Patients were also invited to the CHMP meeting in September 2015 during the evaluation of the type II variation for the multiple sclerosis medicine Tecfidera (dimethyl fumarate). The aim was to update the advice for doctors and patients to minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients being treated with this medicine.

order to facilitate an exchange of views and promote dialogue; improve delivery of efficient, targeted and timely communication; enhance understanding of the EU medicines regulatory framework by pharmaceutical companies; and increase the transparency of EMA's engagement with stakeholders from pharmaceutical industry. EMA will report on these interactions every year.

The framework covers a broad range of types of industry associations, including industry trade associations, organisations engaged early on in the innovation lifecycle, e.g. SME and biotechnology industry organisations, associations of service providers or professionals supporting the industry, and associations with multi-stakeholder membership including industry. The framework also includes an action plan for 2016.

professionals' organisations. Participants discussed the challenges and opportunities posed by the implementation and evaluation of risk minimisation measures in real-life clinical practice. A report of the workshop was made available.

by regulators, explored how to bridge the scientific evaluation with clinical reality and public acceptability of biosimilars, and provided an opportunity to discuss the role of communication in promoting a better understanding of biosimilars.

### Information session on biosimilars

An information session held in March was EMA's contribution to promote the further understanding of biosimilar medicines among patients, consumers and healthcare professionals. It provided an overview of the science behind biosimilars and how they are evaluated

### Framework for interaction with industry associations

A formal framework for interaction between EMA and industry associations was adopted by the Agency's Management Board in October 2015. The aim of the framework is to formalise and structure EMA's interaction with industry stakeholder groups in



## 6 November

Publication of guidance on methods to be used in the design and conduct of post authorisation efficacy studies



## 16 November

Guido Rasi takes office as Executive Director of EMA

## 1.6. Cooperation within the EU medicines regulatory network

The EU Member States make available around 4,500 experts who carry out the evaluation of medicines on behalf of EMA and are members of the Agency's scientific committees, working parties and Scientific Advisory Groups. This pool of experts allows EMA to source the best-available scientific expertise for the regulation of medicines, and ensures that the assessment activities as well as the scientific guidance produced by EMA are of high quality.

There has been a significant increase in workload in recent years as well as greater complexity as a result of the changing medicine development environment, an ever-evolving legislation framework, and growing economic pressures. Against this background, EMA has undertaken a number of initiatives to better support its scientific committees and EU national competent authorities in their work on behalf of the Agency. These initiatives include access to better training, a more reliable assessment of the upcoming workload and expertise needed, and the establishment of multinational teams.

### Multinational teams to assess medicines

In 2015, the evaluation of medicines through multinational teams was expanded. The scheme started in 2013 with a limited number of countries and was extended to all Member States in 2014. At that time, EMA invited all members of the CHMP and the Committee for Advanced Medicinal Products (CAT) to form multinational co-rapporteur teams for the assessment of initial marketing authorisations for medicines for human use. In 2015, this initiative was broadened to include the CHMP and CAT rapporteur teams as well. The scheme was also opened to the Committee for Veterinary Medicinal Products (CVMP) and the Scientific Advice Working Party (SAWP) (for more details see Chapter 3).

The aim of this initiative is to mobilise the best expertise for the assessment of a marketing authorisation application, regardless of where the experts are based in the EU. In 2015, 23 Member States participated in the assessment of new medicines for human use as either rapporteur or co-rapporteur, compared to 16 in 2010. EMA is now exploring how

the scheme can also be extended to certain post-authorisation assessment activities.

### EU Network Training Centre

The EU Network Training Centre (EU NTC) is a joint initiative from EMA and national competent authorities (NCAs) to address the training needs of the EU medicines regulatory network with respect to regulation of both human and veterinary medicines. The central online platform was established in 2014 to provide access to high-quality and relevant regulatory and scientific training materials that are made available either by EMA or by national competent authorities. The platform is designed to offer personalised and modular curricula adapted to the diversity of training needs.

In January 2015, the EU NTC published its first training catalogue for the whole European medicines regulatory network. The catalogue contains more than 100 training events open to both EMA and NCA staff.

The EU Network Training Centre aims to ensure that good scientific and regulatory practice as well as harmonised training standards are spread across the European medicines regulatory network.

*Zaide Frias, Head of Human Medicines Research and Development Support Division*



### 17 November

A new strategy on antimicrobials for 2016-2020 is adopted by the Committee for Medicinal Products for Veterinary Use (CVMP)



### 23 November

Workshop on the role of pharmacokinetic and pharmacodynamic (PK/PD) measurements in the clinical use of direct oral anticoagulants (DOACs)

### Supporting innovation and preparation for future medicines development

In 2015, EMA and the EU national competent authorities strengthened their collaboration to provide support to medicine innovation through the EU innovation network. The network was created in 2011 and comprises the EMA innovation task force and those national agencies' innovation offices wishing to collaborate. In 2015, four Member States joined the network bringing to 11 the number of countries participating.

The aim of the network is to make the regulatory support for medicines developers currently available at national and EU levels more visible and attractive to innovators.

Through this network, EMA and the national innovation offices also share experience, knowledge and best practice and discuss regulatory challenges and issues in relation to emerging innovative medicines.

The platform allows EU regulators to identify and address gaps in regulatory science, anticipate the expertise needed for the assessment of innovative medicines, and make the most effective use of available expertise and resources. The initiative is closely linked with the EU NTC, which identifies areas where training may be required to ensure the appropriate capability in the network.

### Improved planning

EMA started to provide quarterly updates on the number and type of applications for initial evaluations expected by the end of the year.

This complements the three-year forecast that is provided on an annual basis. EMA is also exploring tools to provide forecasts on post-authorisation marketing applications.

This addresses the need of scientific committees and national competent authorities in Member States to be provided with a clearer picture of the number and type of upcoming applications. Based on these updates, they can better plan their workload and ensure the availability of the expertise needed in the context of the assessment of innovative medicines in the coming years.



### 27 November

Publication of good practice guide on medication errors and launch of dedicated webpage

### 7 December

Workshop on demonstrating significant benefit of orphan medicines

## 1.7. International collaboration

The development and manufacturing of medicines are global activities. The increasing complexity of global supply chains and reliance on clinical data generated outside the EU create a strong public health interest in ensuring that these activities are properly monitored and controlled.

A central pillar in EMA's strategy to protect public health is the strengthening of collaboration with other regulatory authorities internationally. The Agency is working with partners in Europe and beyond to contribute to global public health for the benefit of people at home and globally.

Within the context of its international strategy, the Agency is ensuring the best use of resources by promoting mutual reliance and work sharing with other international authorities, supporting training and capacity building in countries with less-developed regulatory systems, and promoting convergence of global standards in global regulatory fora. EMA is also offering its expertise to support countries with less regulatory experience and infrastructure, reinforcing its role as a global reference authority providing the oversight that citizens in the EU and around the world expect.

### Bilateral interactions

The Agency has existing confidentiality arrangements with the Therapeutic Goods Administration (TGA)

in Australia, Health Canada (HC), the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the Food and Drug Administration (FDA) in the United States. Interactions with these authorities take place almost daily, partly structured around clusters of activities, and partly ad hoc.

In addition, in 2015, new arrangements were signed with the Swiss authorities and the WHO. In July, EMA and the European Commission agreed with the Swiss Agency for Therapeutic Products (Swissmedic) and the Swiss Federal Department of Home Affairs (FDHA) to share non-public information on the safety, quality and efficacy of medicines, already authorised or under review, in Switzerland and the EU in order to enhance public health protection. The arrangement supports efforts by European and Swiss regulators to improve the oversight of medicines for human and animal health.

In September 2015, the European Commission and EMA agreed with the WHO to share certain non-public information on the safety, quality and efficacy of medicines already authorised or under review in the EU, or pre-qualified or under review by the WHO. A framework allowing the direct transfer of data on suspected adverse reactions occurring in the EU to the WHO's Uppsala Monitoring Centre (UMC) was agreed in December.

In the framework of the Transatlantic Trade and Investment Partnership (TTIP), EMA continued

to support the European Commission and made progress on the mutual reliance of GMP inspections, biosimilars and paediatric medicines.

In 2015, the Agency intensified its collaboration with global regulators with whom no formal confidentiality agreements exist. EMA participated in two face-to-face meetings and one video conference with Indian regulatory authorities, supporting the European Commission. Indian regulators were invited as observers to the Herbal Medicinal Products Committee (HMPC) in November 2015.

In June, the annual bilateral meeting of the FDA, the European Commission and EMA led to further reinforcement of collaboration in the areas of patient engagement, safety of medicines, paediatrics, rare diseases, inspections and timely access to new medicines, to name but a few.

### Multilateral interactions

The International Council on Harmonisation (ICH), (formerly the International Conference on Harmonisation), is the longest-standing international forum in which the Agency participates. The ICH underwent major structural and organisational reforms in 2015 with its establishment as a legal entity, a non-profit international association under Swiss law of which the European Commission is a founding member. EMA contributed to this reorganisation and the Agency will continue to participate in the ICH by providing scientific



## 15 December

10-year anniversary of the SME regulation

## 18 December

Revised EudraVigilance access policy adopted by EMA Management Board

and technical support to the Commission, including coordinating the participation of experts from the network.

The Agency also took part in the International Pharmaceutical Regulators Forum (IPRF) which was established in 2013 as a protective space for discussion and promotion of harmonisation among regulatory authorities.

Corresponding international activities in the veterinary domain take place through the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products). In 2015, particular emphasis was placed on extension of regulatory convergence to non-VICH partners through the VICH Outreach Forum.

### Facilitating registration of medicines outside the EU

Throughout 2015, there were many examples of greater reliance on EU-network outcomes and on ensuring the best use of resources through mutual reliance and work sharing.

EMA collaborated with the WHO in a pilot project to facilitate the registration of centrally authorised products in developing countries. This allows marketing authorisation holders to share EMA assessment reports with regulatory authorities outside the EU, thereby enabling reliance on evaluation work already performed. In 2015, two applications to participate in this pilot

were received. Initial results from the first product, a medicine to treat HIV in children, showed that use of EMA assessments reduced registration timelines significantly in five African countries: Botswana, Côte d'Ivoire, Kenya, Namibia and Tanzania.

EMA continued its involvement in the Global Animal Health series of conferences by participating in a meeting in Tanzania in June aimed at capacity building in less-developed countries.

### Review of Article 58 procedure

Together with the European Commission and the Bill and Melinda Gates Foundation, EMA carried out a strategic review of the use, role and vision of the Article 58 procedure. This is a regulatory process that allows the Agency to assess the quality, safety and efficacy of a medicine or vaccine and its benefit-risk balance, even though it will not be marketed in the EU. This process means that the Agency can help facilitate access to new medicines for people living outside the EU. The review, which was

supported by external consultants, found for example that it is necessary to improve some operational and communication-related aspects of the Article 58 procedure.

### International Generic Drug Regulators Programme continues

The International Generic Drug Regulators Programme (IGDRP), which allows non-EU regulators to benefit from EU assessments of generic medicines in real time, continued in 2015. By December, 12 companies had submitted intentions to participate, which covered 26 products in the decentralised procedure (DCP, for medicines that are authorised nationally) and four products in the centralised procedure (CP, for medicines that have an EU-wide marketing authorisation). Under the scheme, assessment reports generated as part of the DCP or CP can be shared in real time with selected non-EU agencies in Australia, Canada, Switzerland and Taiwan.

The globalisation of the pharmaceutical industry means that greater collaboration with regulators beyond the EU is essential to ensure the supply of safe, effective and good-quality medicines for humans and animals. Greater use of work-sharing, mutual cooperation and efficiency saving will help us meet the challenges of globalisation, both within the EU and internationally.

*Emer Cooke, Head of International Affairs*

## 18 December

Article 57 database of medicines authorised in the EU endorsed by the EMA Management Board for routine use in pharmacovigilance

## 18 December

Network strategy to 2020 adopted by EMA Management Board and HMA







## **2. ADVANCING PUBLIC AND ANIMAL HEALTH**

### **What are the most significant developments in public health and how is the regulatory world changing in Europe and beyond?**

This chapter provides engaging thoughts on topics of major interest in medicines and health in 2015. Agency representatives and important stakeholder groups discuss: (1) how data requirements from regulators and HTA bodies can be better aligned; (2) whether the use of big data in healthcare is a challenge or an opportunity; and (3) how immunotherapies bring new hope to cancer patients.



*Niklas Hedberg,  
Chief Pharmacist, TLV  
(the Swedish Dental  
and Pharmaceuticals  
Benefits Agency)*

## 2.1 How aligned are regulators and HTA bodies in their data requirements?

Following regulatory approval, a growing number of Member States have systems in place that provide for HTA bodies to give recommendations on whether a medicine can be paid for by the healthcare system, taking into account the best possible use of available resources and national legislation. Better interaction between regulators and HTA bodies can therefore improve patient access to innovative medicines in Europe and ultimately public health in general.

### **Why have regulators and HTA bodies strengthened their collaboration over the past few years?**

**Niklas Hedberg:** While regulators assess the medicine's clinical value, excluding economic criteria, HTA bodies evaluate a medicine's relative effectiveness and economic value for the healthcare system within a framework of equal human value and solidarity with those with the most pressing medical needs. Although regulators and HTA bodies answer different questions and have different data requirements driven by different frameworks, they do have a lot of common ground in their medicine evaluation processes. Our common goal is to enable safe, efficient and affordable medicines with added value for the patient and the healthcare system, to reach patients in the EU in an equal and timely manner.

**Spiros Vamvakas:** Several new medicines authorised by the European Commission based on EMA's positive scientific opinions fail to be reimbursed and/or used as expected, because they do not meet the requirements of the HTA bodies. There is a clear need to improve patient access and reduce delays between a medicine's marketing authorisation and decisions on reimbursement. Since regulators and HTA bodies play an equally important role in patient access, we promote an early dialogue between medicine developers, regulatory and HTA bodies. The goal is to agree on development plans which will generate data that both parties can use to evaluate a medicine's benefit-risk balance and value.

### How does parallel scientific advice benefit patients and what role does it play in the collaboration between regulators and HTA bodies?

**Niklas Hedberg:** Parallel regulatory and HTA scientific advice is one of the key strategic developments which will bring vital medicines to patients more quickly. This voluntary process provides HTA bodies with a good platform to interact with the regulators and to expand mutual understanding and knowledge. By discussing our data requirements at an early stage, we are more able to address potential divergences and advise on a more efficient clinical trial development plan that will bring the medicine to the patient faster. Being able to sit at the same table with regulators and provide simultaneous feedback to companies on their development plans for new medicines has helped to evolve and consolidate our work.

**Spiros Vamvakas:** Obviously, the regulatory-only scientific advice system has been in place much longer than the parallel regulatory-HTA advice and it provides a well-established, pre-existing process on which we can base our collaboration. In the regulatory-only scientific advice system, we evaluated the impact of our advice on the success of the marketing authorisation. We found that receiving and following scientific advice doubled the likelihood of a positive opinion at marketing authorisation stage with success rates of more than 80% for those who followed the advice compared to only 41% for those who did not follow it. Another benefit for patients is that by providing guidance on the most useful study design we ensure that they will not have to participate in inappropriate clinical trials.

In our parallel regulatory-HTA advice, we concluded 63 procedures by the end of 2015, covering all major therapeutic areas including advanced therapies and orphan conditions. We also saw some participation of SMEs with whom we need to engage further. The procedure has resulted in significant advances in the development of common regulatory-HTA documents and guidance for companies as part of the parallel scientific advice process. And, of course, we aim to make further improvements and to involve more HTA bodies, in particular from smaller Member States.

*Spiros Vamvakas,  
Head of EMA's  
Scientific Advice Office*

### How can we better harmonise regulatory and HTA requirements in a single development plan?

**Niklas Hedberg:** We have already come a long way in our parallel scientific advice discussions as, for example, on clinical trial outcomes or end points. We have also shown that we can often overcome diverging issues by deepening our understanding of the regulatory decision-making process. Most importantly, we do identify early those issues where we probably cannot come to an agreement due to the fact that we pursue different duties. Divergence in relation to data requirements also exists across HTA bodies themselves. Identifying these differences in the context of an early dialogue in the framework of joint scientific advice can be equally useful for the medicine developers. It allows them to take action and shape their clinical trial design in order to receive a fully converged regulatory-HTA answer right from the start.

**Spiros Vamvakas:** We have seen that through intense dialogue we can successfully align and reach the same conclusion in the majority of cases. More specifically, an evaluation of a pilot parallel regulatory-HTA scientific advice indicated that in approximately 70% of the cases, regulators and HTA bodies were able to reconcile their data requirements into a single development plan. For the remaining cases, we should continue to work to find ways which facilitate more efficient data collection. If this is not possible we should try to integrate data requirements into a bigger trial to meet the requirements of all stakeholders and enable the medicine to reach a greater percentage of patients in Europe.





*Alessandro Spina, EMA's Data Protection Officer and Frank Pasquale, Professor of Law at the University of Maryland, USA*

## 2.2 Big data in healthcare: challenges and opportunities for medicine regulation and patient care

### Big data is the analysis and use of very large and diverse sets of information. What can it bring to patient care and medicine regulation?

**Frank Pasquale:** The common definition for big data revolves around the 3Vs: volume, velocity and variety. Concerning the 'velocity' aspect, advocates hope to very quickly discover any negative outcomes or side effects after a medicine is on the market. The faster they can access patient records, the better they can discover anomalies that may only emerge at the population level. The 'variety' facet is connected to new data sources – for example, "quantified selves" or self-monitoring, utilising biometric sensors in smart phones or wearables. Such micro-level surveillance may allow analysts to better understand how a patient responds to a variation in the dose of his medicine or to a different drug regime. And finally the 'volume' aspect: the collection of massive amounts of information about a patient could be useful to develop personalised comparisons of treatment effectiveness. The more a doctor has access to historical data on a treatment's efficacy with respect to "digital doppelgangers", patients just like the patient the doctor is treating, the better informed the doctor's decision may be.

### Do you see specific challenges in the use of big data for the regulation of medicines?

**Alessandro Spina:** There is a blurring of the distinction between non-health and health data. Non-health data, such as geolocation or lifestyle data, can be used to infer medically significant conclusions about someone's health. Similarly, information about the 'real-world' use of medicines can be as relevant as health data collected in a controlled environment (for example, during clinical trials). With this comes the issue of 'informed consent', too, as there can be uses of data for research purposes which are unforeseeable at the time of collection – for example, if people have agreed to the collection of data tracking their physical activity through a wearable device and then those data are reused to increase our understanding of cardiovascular diseases. Moreover, big data applications can result in bringing up unforeseen patterns in the use of a medicine and therefore raising pertinent scientific questions as to why that is and to generate hypotheses. However, other mechanisms, including randomised clinical trials, seem to be necessary in order to ascertain causality.

**Frank Pasquale:** What is also concerning is what we have seen recently: patients connecting through social networks and deciding to improvise a clinical study where they would take a lowered dose of their treatment to see if it is just as effective as a higher dose. There is also an issue around the quality of the data collected through big-data applications deployed at the population level. We cannot permit an 'n = all' mentality that would dispense with established statistical methods. Not everyone is included in even the 'biggest' data collection. There is always the possibility of bias, for example, when there is a need to use a smartphone to participate and those unable to afford such technology are under-represented.

### What can/should be the role of regulators when faced with the new field of big-data applications?

**Frank Pasquale:** We need to know where the data is coming from and what the rationale is behind the algorithms collecting and analysing it. Too often, critical code is not available to the authorities or the general public. That is very troubling: making claims without making accessible both the data and the code is something to watch out for. There is an asymmetry of power, if individuals consent to giving access to their data but we don't have transparency on how these data are being analysed or used. This raises very difficult issues for traditional models of informed consent in clinical practice, human subject research, and their slow integration into 'learning healthcare systems'. Regulators will need to stop some data transfers and secondary uses rather than assuming that consumers, by ticking a consent box, have any ability to forecast the potential misuse of their data. To do this, regulators will need to keep abreast of the latest industry practices.

**Alessandro Spina:** This means that if companies use big-data applications to substantiate claims of effectiveness or safety of medicines, regulators might need to review not only the results but also the code used to reach those results. This is a matter of accountability which is one of the key principles in both EU data-protection legislation and in the EU regulatory field. Looking forward, big-data applications could provide regulators with insights about the behavioural effect of interventions. These insights could be used to take more granular regulatory actions, effectively tailored for different groups of stakeholders.



*Professor Jan Schellens, Head of Clinical Pharmacology Department at the Netherlands Cancer Institute*



*Francesco Pignatti, Head of EMA's Office of Oncology, Haematology and Diagnostics*

## 2.3 A new type of immunotherapy to fight cancer – what does it mean for patients?

### A new type of immunotherapy to fight cancer cells was approved for the first time in the EU in 2015. What does this mean for patients?

**Jan Schellens:** There has been a paradigm shift in the area of cancer immunotherapy in the past few years. It has been known for decades that cancer patients treated with immunotherapies – i.e. therapies that activate the immune system to kill cancer cells – sometimes experience long-lasting responses and even, in rare cases, can be cured. But for a long time, we had no understanding of why the immune system worked in a particular patient and not in another. Gradually, the immune cells involved in these responses were identified and our understanding of the immune system as a whole has grown tremendously. The discovery of 'suppressive signals' (called 'checkpoints'), that prevent the development of an anti-cancer immune response, led to the development of a new type of therapy, which instead of activating the immune system deactivates 'suppressive signals'. These therapies offer completely new perspectives for the treatment of patients. Since their mechanism of action is different to existing cancer treatments, their efficacy and toxicity profiles are also very different. Therefore, they can be used in combination with other therapies with different mechanisms of action, resulting in very positive responses. In clinical trials, patients with advanced melanoma treated with such combinations show very long-lasting responses which indicate that some of these patients could be cured of their disease. Who would have predicted this ten years ago? Research is very active with this new immunotherapy approach and several types of cancer have shown good responses to treatments. We will learn much more in the next few years, building on what we know now. The identification of these checkpoints has boosted investment in immunotherapies across the globe, from companies, research institutes, non-profit organisations to charities. These activities will undoubtedly lead to new therapeutic strategies to fight cancer in the next few years.

### What are the challenges for these medicines to reach patients?

**Francesco Pignatti:** As for other cancer treatments, the challenge with this new type of immunotherapy is the ability to identify patients who are likely to respond to the treatment. To allow this, we need validated predictive biomarkers – a measurable characteristic that allows predicting response to a disease or treatment using a valid assay – and these are not yet available. As regulators, we pay extreme attention to this issue and strongly encourage companies to develop and implement strategies during the development of their medicine to identify and validate such biomarkers. This is essential if we want to maximise the chances for these medicines to reach patients. The identification of patients who will show a good response to a treatment is one of the key elements taken into account by healthcare systems in the context of reimbursement decisions. Elements that will facilitate the assessment of the relative efficacy by HTA bodies need to be in place to optimise and facilitate patients' access to these medicines across the EU.

### Are there challenges for the use of these medicines in clinical practice?

**Jan Schellens:** As this type of immunotherapy is very different to existing cancer treatments, also in terms of the toxicity profile, a lot of work needs to be done to ensure that it is used optimally in clinical practice. A broad clinical training programme needs to be implemented in hospitals. This starts with training medical specialists, nursing teams and the supporting clinical personnel who take care of patients. Hospital laboratories and radiologists also need to be trained to be able to interpret tests and monitor the progress of the disease. Such training programmes are starting to be implemented across the globe.

**Francesco Pignatti:** There is also a need for institutes and hospitals that treat patients to share their data, perhaps in a common repository, so that analyses can be done and assays can be cross-validated. Again, as this is a new type of therapy, we need a range of tests and tools to be validated to allow comparison across studies, medicines and indications. Perhaps a new model of data sharing needs to be envisaged if we want these therapies to realise their full potential for the benefit of patients.





### **3. KEY FIGURES IN 2015**

This chapter presents some core statistics from 2015 that highlight the main outcomes of the Agency's activities, and also point to interesting trends and changes observed in recent years.

## 3.1 Human medicines

### 3.1.1 Supporting research and development

Promoting innovation and research in medicine development so that patients can benefit from much-needed safe, high-quality and effective medicines is a key priority for the Agency. EMA fosters early interaction and dialogue with developers to facilitate the development process, help companies to collect adequate data and to comply with regulatory standards. These activities are increasingly carried out in collaboration with HTA bodies and international partners.

#### Scientific advice

The Agency provides scientific advice and protocol assistance to medicine developers during the research and development phase of medicines. Scientific advice is one of the Agency’s key tools to promote innovation and research and facilitate the availability of safe and effective medicines for patients and healthcare professionals. Early dialogue and scientific advice lead to better development plans, promote the collection of high-quality data and, most importantly, ensure that patients will not be exposed to sub-standard clinical trials or trials that are unlikely to be able to support a marketing authorisation application.

- The overall number of requests for scientific advice and protocol assistance was slightly lower in 2015 compared to 2014 (510 versus 551) but remained at a high level compared to previous years.



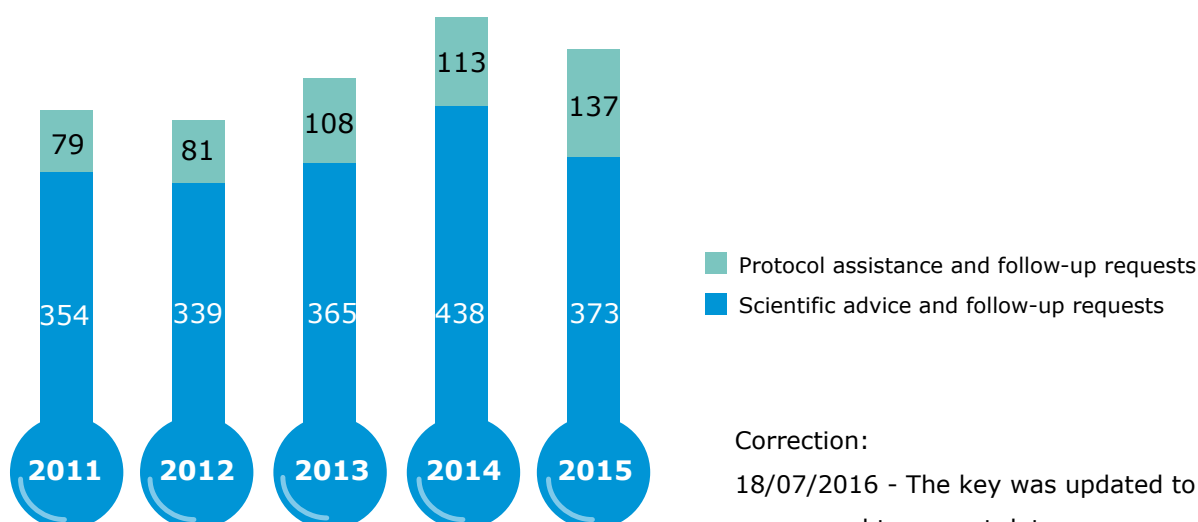
**The number of requests for parallel advice with HTA bodies almost tripled in 2015 compared to 2014 (30 in 2015; 11 in 2014).**

- Through this tool, regulators and HTA bodies provide medicine developers with simultaneous feedback on their development plans for new medicines with the aim of aligning data requirements.
- 46% of all scientific advice requests related to the early phases of medicines development (Phase I and Phase II trials). This trend had already been observed in 2014 and indicates that the Agency is successfully promoting early dialogue with medicine developers.
- As in previous years, more than one in two requests for scientific advice related to clinical issues, over one-quarter to preclinical issues and the rest to quality issues.

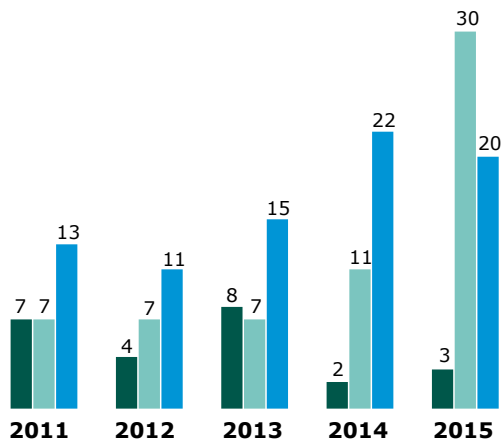


**SMEs are requesting more and more scientific advice: 160 of the 510 requests received in 2015 came from SMEs, a 20% increase compared to 2014. Five were for parallel advice with HTA bodies and seven for qualification of a new methodology to be used during the development of a medicine.**

#### SCIENTIFIC ADVICE AND PROTOCOL ASSISTANCE REQUESTS RECEIVED – TOTAL

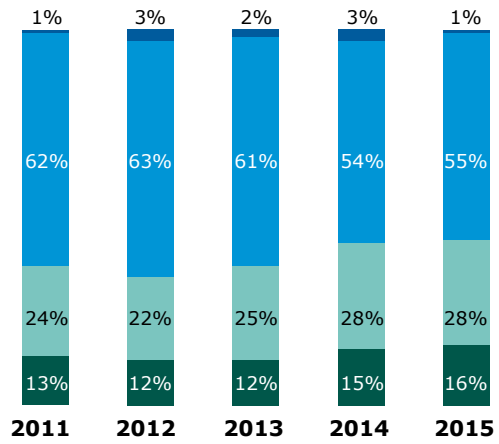


SCIENTIFIC ADVICE AND PROTOCOL ASSISTANCE REQUESTS RECEIVED – SUBSET



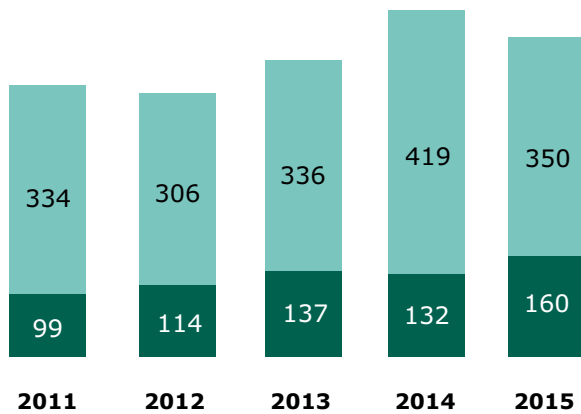
- Requests for parallel SA and protocol assistance with international regulators
- Requests for joint SA and protocol assistance with HTA
- Requests for qualification of novel methodologies

CLINICAL-TRIAL PHASES OF SCIENTIFIC ADVICE REQUESTS (2011-2015)



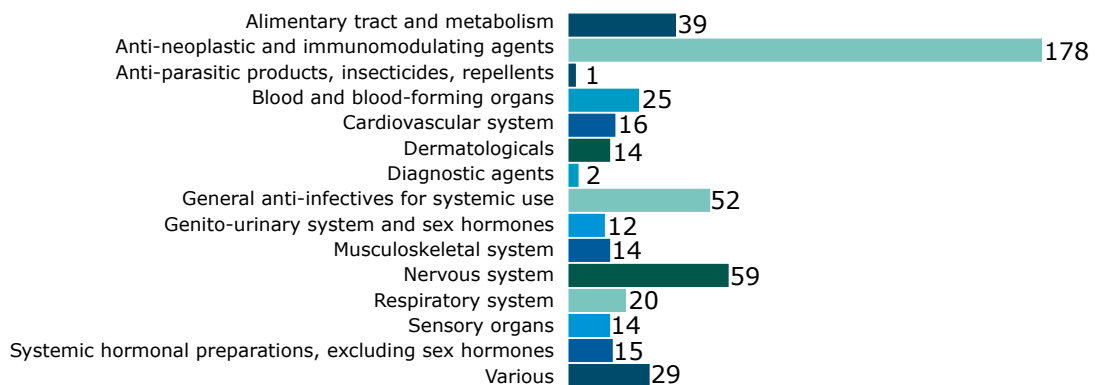
- Phase IV
- Phase III
- Phase II
- Phase I

SCIENTIFIC ADVICE REQUESTS BY AFFILIATION OF REQUESTER



- Large or intermediate sized companies
- SMEs

SCIENTIFIC ADVICE REQUESTS BY THERAPEUTIC AREA (2015)



### Support to small and medium-sized enterprises (SMEs)

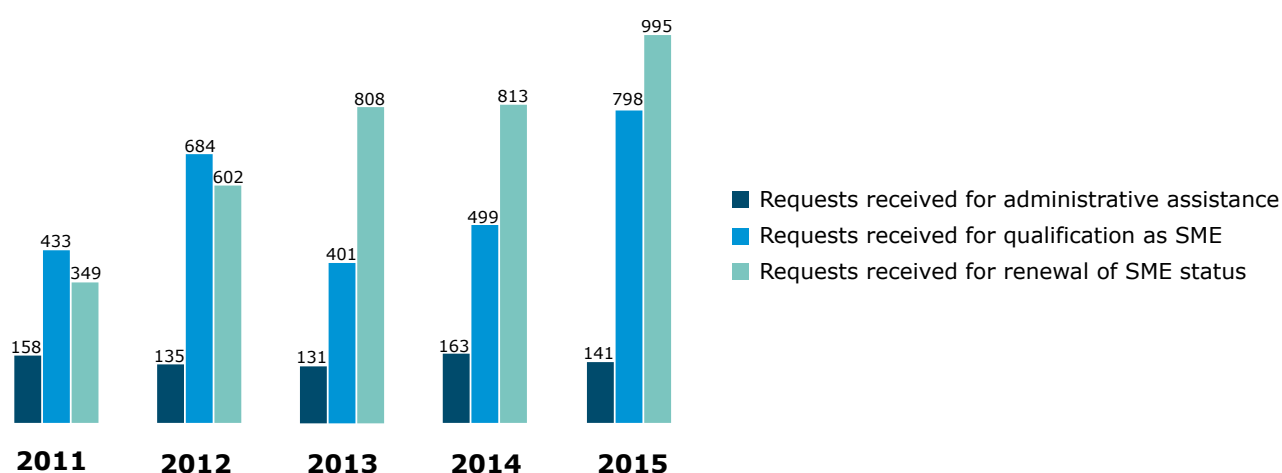
SMEs are recognised as a driver of innovation in the EU. The Agency promotes innovation and development of medicines by SMEs by giving them active regulatory, financial and administrative support. The Agency’s SME office<sup>2</sup> provides advice and guidance, organises topical workshops and disseminates a dedicated newsletter to SMEs registered with EMA. These companies also have access to a number of fee incentives to support their development process.

- At the end of 2015, 1,619 active SMEs had registered with EMA, compared to 1,301 in 2014. This increase may be explained by the incentives given to SMEs in relation to new annual pharmacovigilance fees for nationally authorised medicines implemented in 2015. These incentives may have encouraged SMEs with marketed medicines to register as SMEs. Of the companies registered at the end of 2015, the large majority are developing products for human use (76%).
- The SME office responded to 141 requests for direct assistance on administrative or regulatory aspects and organised 13 briefing meetings to assist SMEs that are unfamiliar with the EU regulatory system – most of these requests relate to medicines for human use.



**Approximately 13% of the marketing authorisation applications received in 2015 were submitted by SMEs. Of the 15 applications received, 8 were for orphan designated medicines.**

#### SME-RELATED ACTIVITIES – REQUESTS RECEIVED (2011-2015, HUMAN AND VETERINARY MEDICINES)



SMEs and initial marketing authorisation applications	
	2015
Marketing authorisation applications submitted by SMEs	15
Positive opinions	9
Negative opinions	2
Withdrawals	1

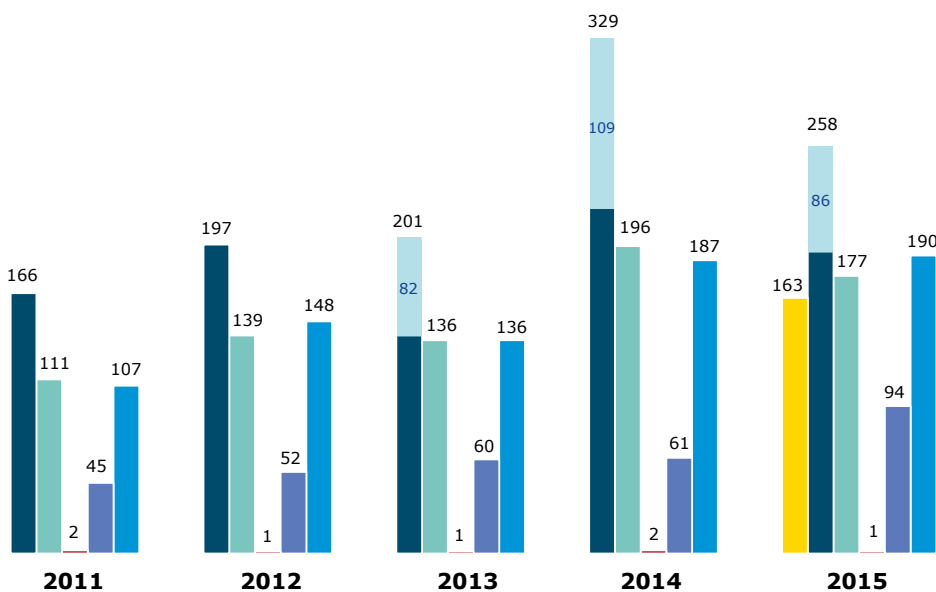
<sup>2)</sup> A report on the 10 years of the SME initiative can be found on the EMA website.

### Orphan medicine designation

As it is often not profitable for companies to develop medicines for rare diseases under normal market conditions, the EU offers a range of incentives to encourage the development of so-called orphan medicines. Medicines with an EU orphan designation that have been granted a marketing authorisation benefit from 10 years of market exclusivity. During the development of an orphan medicine, other incentives – such as fee reductions for scientific advice (protocol assistance) – are also available for medicine developers. EMA’s Committee for Orphan Medicinal Products (COMP) is responsible for assessing orphan designation applications.

- After a peak in 2014, the number of applications for orphan designations<sup>3</sup> fell from 329 to 258 in 2015 although this was still higher compared to the years before 2014.
- EMA fosters the global development of medicines for rare diseases through its collaboration with the US and Japanese regulatory authorities; the parallel submission process helps rationalise and streamline the development of orphan medicines. One in three applications for orphan designation was submitted to EMA and to another regulatory authority in parallel in 2015.
- In 2015, 163 pre-submission meetings were conducted with applicants to advise them on their request for orphan designation.
- The European Commission supports the development of medicines for rare diseases financially, with 6.5 million euros provided in 2015. More than 50% of the Commission’s special contribution was used to provide protocol assistance to medicine developers and 21% for the assessment of applications for marketing authorisation.

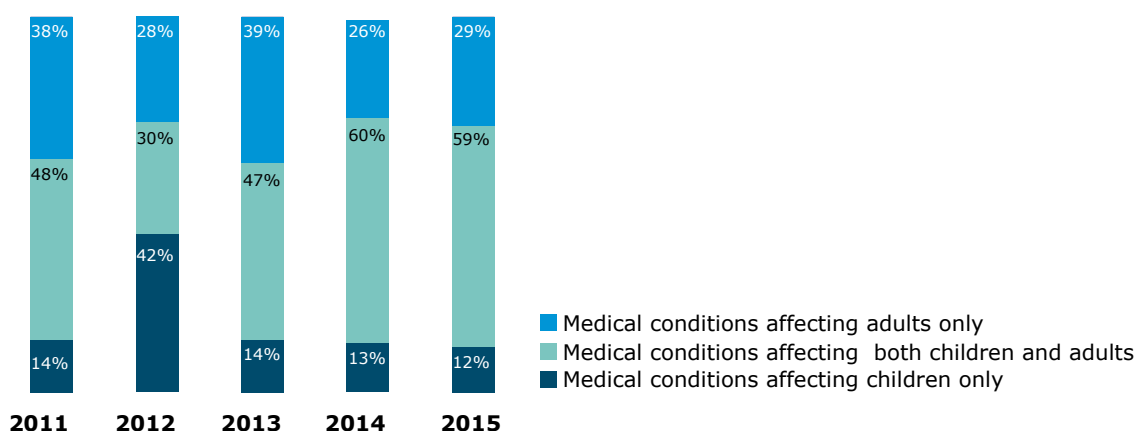
#### ORPHAN MEDICINE DESIGNATION PROCEDURES (2011-2015)



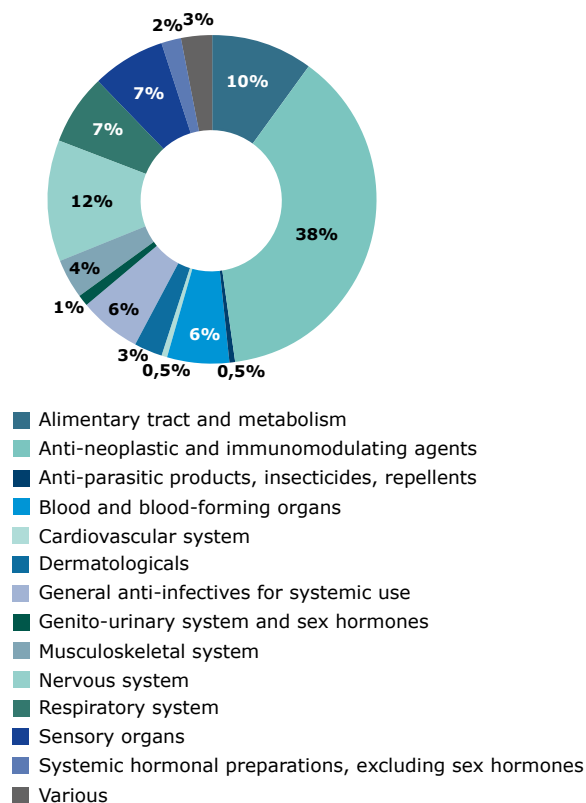
- Orphan medicines application pre-submission meetings
- Applications for orphan designation received
- Applications submitted in parallel with international regulators
- Positive opinions
- Negative opinions
- Withdrawals
- Commission decisions

<sup>3</sup>) Further information on recommendations for orphan designations can be found in annex 12.

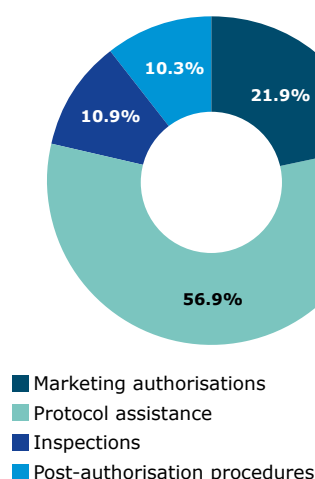
DESIGNATED ORPHAN MEDICINES FOR THE TREATMENT OF CHILDREN AND ADULTS (2011-2015)



POSITIVE OPINIONS BY THERAPEUTIC AREA (2015)



USE OF EU SPECIAL CONTRIBUTION FOR ORPHAN MEDICINES (2015)

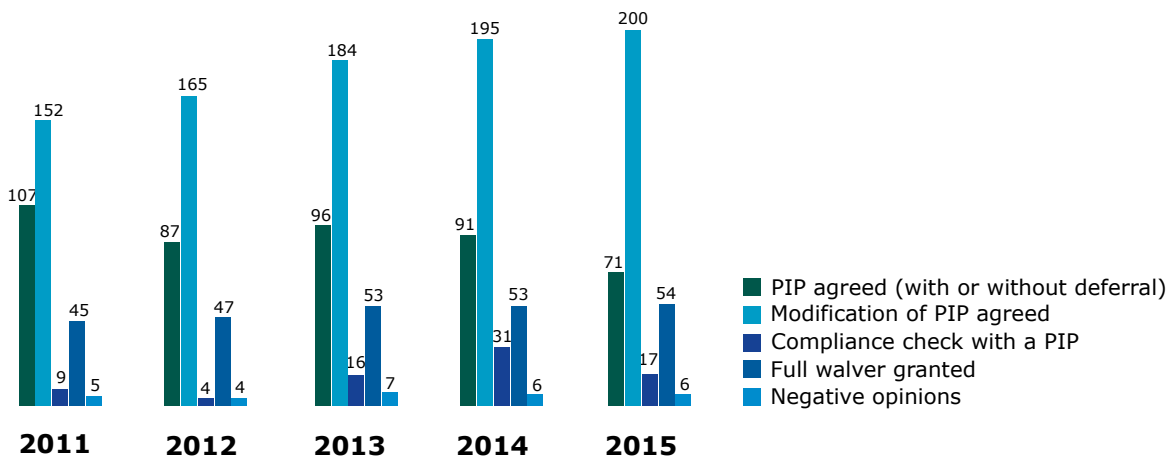


Medicines for children

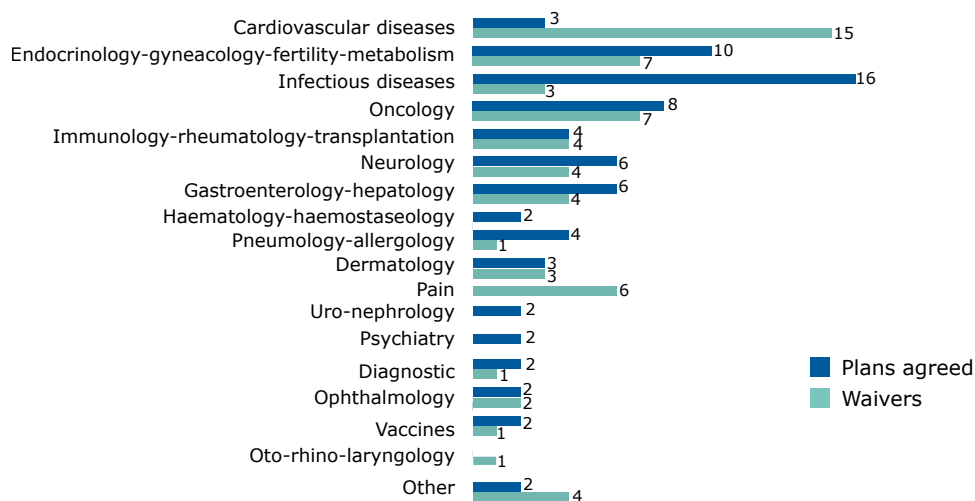
The Agency also promotes the development of medicines for children. EMA assesses and verifies compliance with paediatric investigation plans (PIPs) and PIP waivers through the Paediatric Committee (PDCO), and carries out other activities as mandated by the Paediatric Regulation, such as providing secretarial support to the European Network of Paediatric Research at EMA (Enpr-EMA).

- The number of applications received for new PIPs, including waivers (exemption of paediatric studies) and deferrals (paediatric studies can be conducted at a later stage), was slightly higher in 2015 compared to 2014 (210 in 2015; 172 in 2014). This is mirrored by almost twice the number of scientific advice requests received that included questions on paediatric issues (109 in 2015 compared with 57 in 2011).
- The number of modifications of agreed PIPs continued to grow at a steady rate, in line with the increasing number of initial PIPs already agreed but not yet completed<sup>4</sup>.
- Article 46 of the Paediatric Regulation requires marketing authorisation holders to submit studies on the use of already authorised medicines in children to regulatory authorities. This ensures that all paediatric studies are assessed by the relevant competent authorities. In 2015, EMA assessed 152 paediatric studies in the context of Article 46, which is a 25% increase compared to previous years. All of these studies are available to the public through the EU Clinical Trials Register.
- Enpr-EMA put together a comprehensive overview of the informed consent requirements of national ethics committees with regard to the recruitment of children and adolescents. The overview, which was published on the EMA website in December 2015, aims to facilitate the authorisation and conduct of clinical studies that include minors.

**OPINIONS ON PAEDIATRIC INVESTIGATION PLANS AND WAIVERS (2011-2015)**



**PAEDIATRIC INVESTIGATION PLANS AGREED AND WAIVERS GRANTED (2015)**



<sup>4</sup>) Further information on PIPs can be found in annex 14.

### Advanced-therapy medicinal products

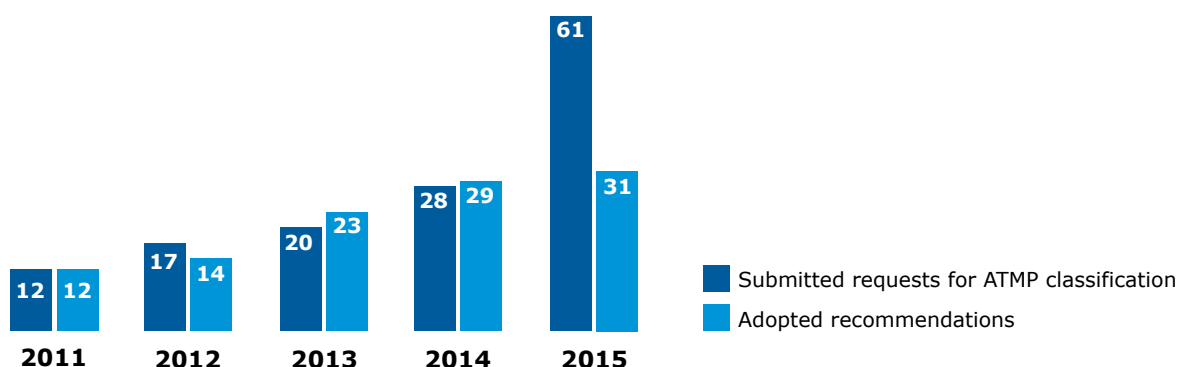
Advanced-therapy medicinal products (ATMPs) are made from genes and cells. They may offer ground-breaking new treatment opportunities for many diseases and injuries. The Committee for Advanced Therapies (CAT) is responsible for assessing the quality, safety and efficacy of ATMPs. It prepares a draft opinion on each ATMP application before the CHMP adopts a final opinion for the medicine concerned. The CAT also reviews requests for the certification of quality and non-clinical data for SMEs developing ATMPs, and provides scientific recommendations on the classification of ATMPs.



**There was a significant increase in the number of requests for ATMP classification in 2015 compared to 2014 (61 versus 28).**

- One application was received for marketing authorisation for an ATMP. This is for a cell-based therapy for the treatment of a severe immunodeficiency (SCID).
- The ATMP Imlygic, the first oncolytic immunotherapy, was recommended for marketing authorisation in 2015 for the treatment of melanoma.

### SCIENTIFIC RECOMMENDATIONS ON ADVANCED THERAPY CLASSIFICATION (2011-2015)



### Innovation Task Force

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

- 34 briefing meetings took place in 2015, almost two-thirds of which were on methods, for example to support the development of medicines (e.g. biomarkers), or to improve the manufacturing of medicines, particularly in the context of certain advanced therapies that need to be produced at the patient’s bedside.



**Almost 40% of requests originated from SMEs and 31% came from academic sponsors.**



## Key scientific guidelines

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

These guidelines are drafted by working parties comprising experts from across Europe who have the required expertise.

In 2015, the Agency developed new guidelines and revised existing guidance to reflect the latest scientific developments and experience gained in a wide range of areas.

A selection of guidelines is listed below. Further information on guidelines adopted in 2015 can be found in annex 10b.

Topics	Content
<b>Post-authorisation efficacy studies (PAES)</b>	A draft guideline which outlines how post-authorisation efficacy studies (PAES) should be designed by companies to support regulatory decision-making in the EU. The guideline applies to both imposed and voluntary PAES.
<b>Cardiovascular safety profile of medicines to treat cardiovascular and metabolic diseases</b>	A draft reflection paper providing recommendations for the evaluation of the cardiovascular safety profile of new, non-generic medicines that are intended for long-term treatment of certain cardiovascular and metabolic diseases. The paper clarifies requirements for these medicines at the time of assessment of the marketing authorisation application is assessed with respect to data needed for the evaluation of the cardiovascular safety profile.
<b>Evaluation of anticancer medicines in man</b>	Update to the appendix on the potential role of pathological complete response for approval for a medicine as an add-on to an established (neo) adjuvant regimen for the treatment of patients with high-risk early-stage breast cancer.
<b>Frailty</b>	Points to consider for public consultation outlining the general principles that may be applied for the categorisation of older patients enrolled in clinical studies on the basis of their frailty status.
<b>Pharmacokinetics and pharmacodynamics analyses in the development of antibiotics</b>	A draft guideline on the use of pharmacokinetic and pharmacodynamic analyses in the development of antibiotics. This provides guidance on conducting robust analyses to facilitate and speed up the development of new antibiotics, in particular those targeting multi-drug-resistant bacteria.
<b>Good clinical practice</b>	An addendum to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (R2) guideline on good clinical practice (GCP) for public consultation. The guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure the protection of clinical trial participants, and data integrity; and to update standards regarding electronic records and essential documents intended to increase the quality and efficacy of clinical trials.
<b>Bioequivalence studies</b>	Product-specific guidance on bioequivalence studies for four active substances: asenapine, prasugrel, sitagliptin and zonisamide, was released for public consultation. This follows the finalisation of bioequivalence guidance which covered 16 active substances in 2014 and 2015.
<b>Gene therapies</b>	A draft guideline on the quality, non-clinical and clinical aspects of gene therapies for public consultation. The guidance aims to support and facilitate the development of these innovative medicines by guiding developers on the types of evidence they should generate to support a marketing-authorisation application with a regulatory authority in the EU.

### 3.1.2 Recommendations for authorisation

#### Applications for initial evaluation

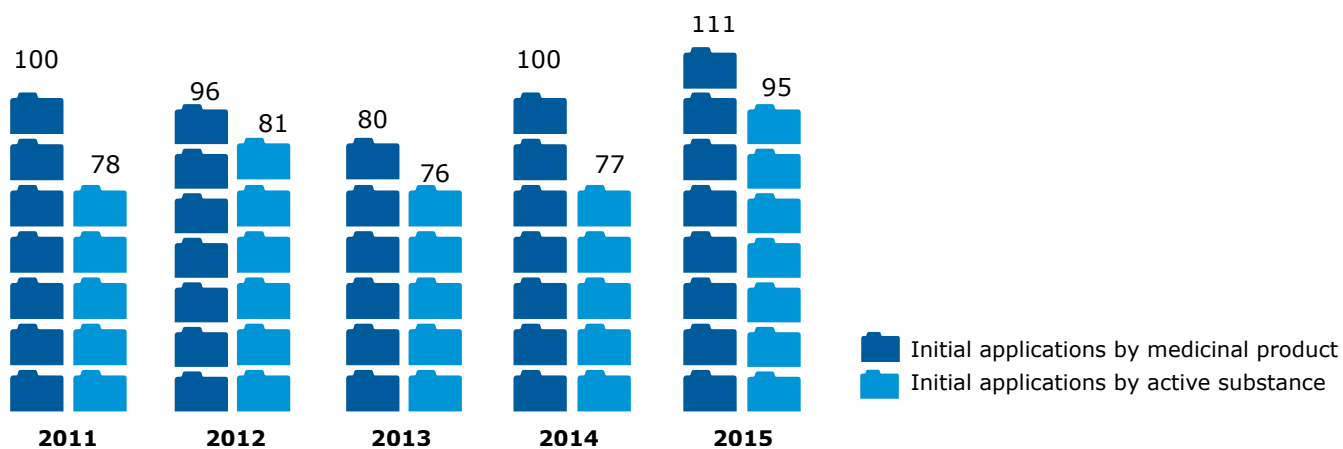
Initial evaluation covers all activities relating to the processing of marketing-authorisation applications for new medicines that have never been assessed before, from pre-submission discussion with future applicants, through evaluation by the CHMP, to the granting of a marketing authorisation by the European Commission.

- There was an 11% increase in the overall number of applications for initial evaluation received in 2015 compared to 2014.

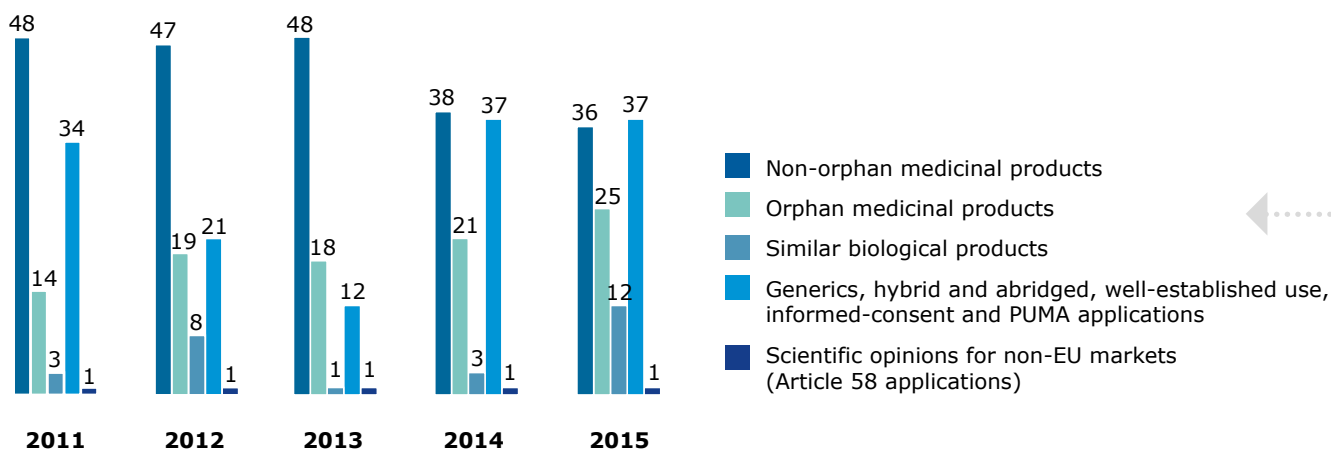
**➔ 12 applications for biosimilar medicines were received in 2015 compared to three in the previous year. This is the highest number of applications for biosimilars received in a year to date.**

- More than one in five applications received in 2015 were for orphan designated medicines – one was for an advanced therapy medicinal product (ATMP).
- EMA received one application for a paediatric-use marketing authorisation (PUMA). These are granted to medicines which are already authorised, but no longer under patent protection, and that have been developed specifically for children.
- The Agency also received one application for scientific opinion for a medicine for use exclusively outside the EU. This medicine was evaluated in collaboration with the World Health Organization (WHO).

#### INITIAL-EVALUATION APPLICATIONS (2011-2015)



#### INITIAL-EVALUATION APPLICATIONS BY TYPE OF APPLICATION (2011-2015)



**Outcome of initial evaluation**

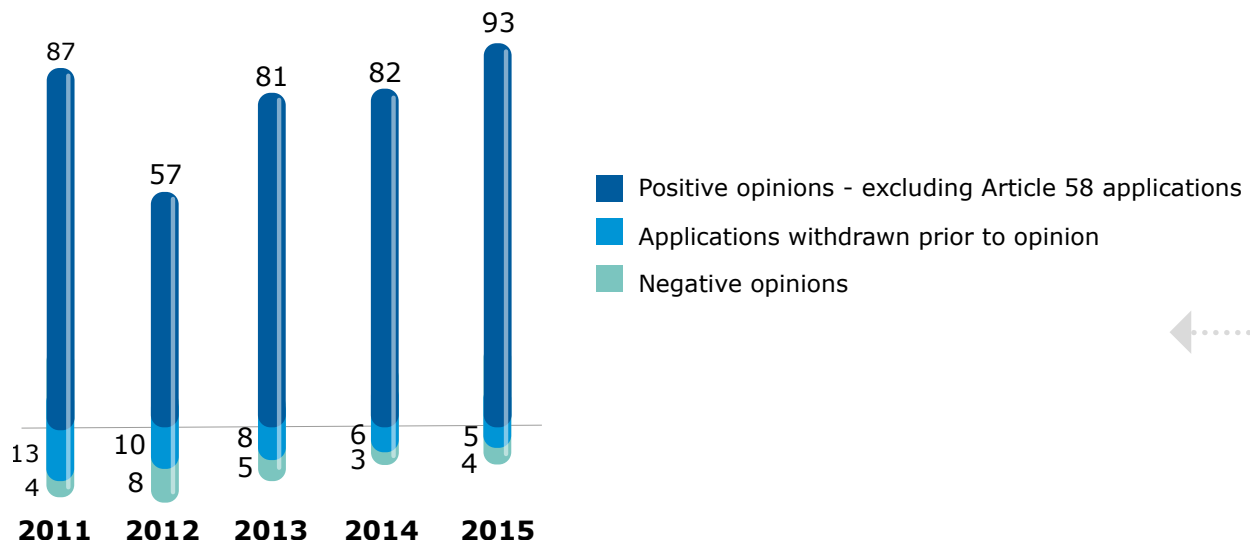


**93 medicines for human use were recommended for marketing authorisation in 2015, including 39 new active substances.**

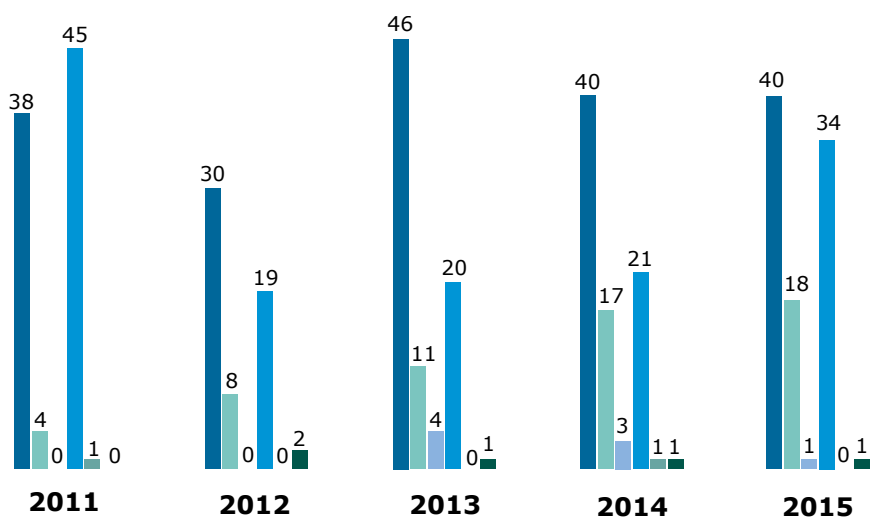
**1/3 of all medicines with a new active substance were for the treatment of cancer.**

- Four medicines received a negative opinion from the CHMP; five applications were withdrawn prior to the CHMP opinion.
- Approximately one in two applicants who received a positive opinion from the CHMP in 2015 had received scientific advice during the development phase of their medicine. This figure rises to 85% when it comes to medicines containing a new active substance. Two of the four medicines that had a negative opinion had received scientific advice.
- 92% of the positive opinions issued in 2015 were reached by consensus between CHMP members.

**OUTCOME OF INITIAL-EVALUATION APPLICATIONS (2011-2015)**

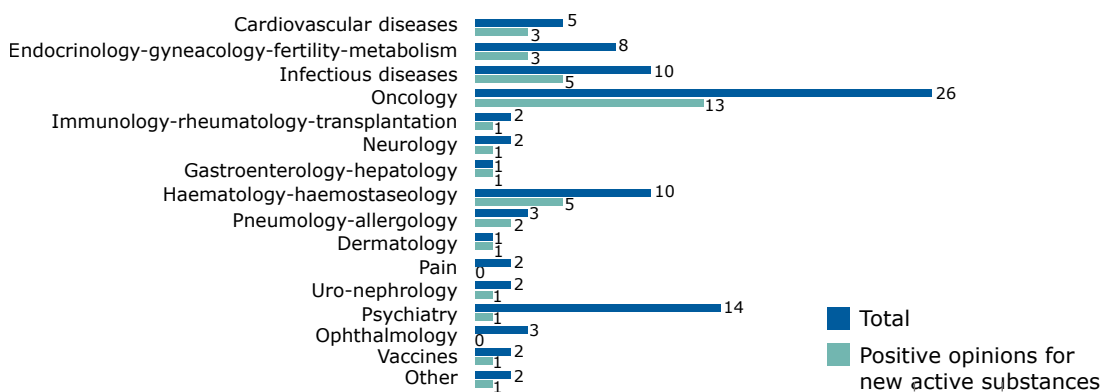


POSITIVE OPINIONS BY TYPE OF PROCEDURE (2011-2015)



- New medicinal products (non-orphan)
- Orphan medicinal products
- Similar biological products
- Generic, hybrid and abridged, well-established use and informed-consent applications
- Paediatric use marketing authorisations
- Scientific opinions for non-EU markets (Article 58 applications)

POSITIVE OPINIONS PER THERAPEUTIC AREA (2015)



Conditional marketing authorisations

- Three medicines received a recommendation for a conditional marketing authorisation, one of the EU’s early access routes to patients. This tool allows for the early approval of a medicine on the basis of less complete clinical data than is normally required. These medicines are subject to specific post-authorisation obligations that aim to obtain complete data on the medicine.
- In 2015, two medicines that had previously received a CMA were granted a recommendation for a full marketing authorisation by the CHMP after fulfilling their post-authorisation obligations. Since the introduction of the conditional marketing authorisation tool in 2006, 11 medicines out of 25 have been granted a full marketing authorisation following a CMA. On average, it took four years for companies to fulfil their post-authorisation obligations and get their products fully authorised.

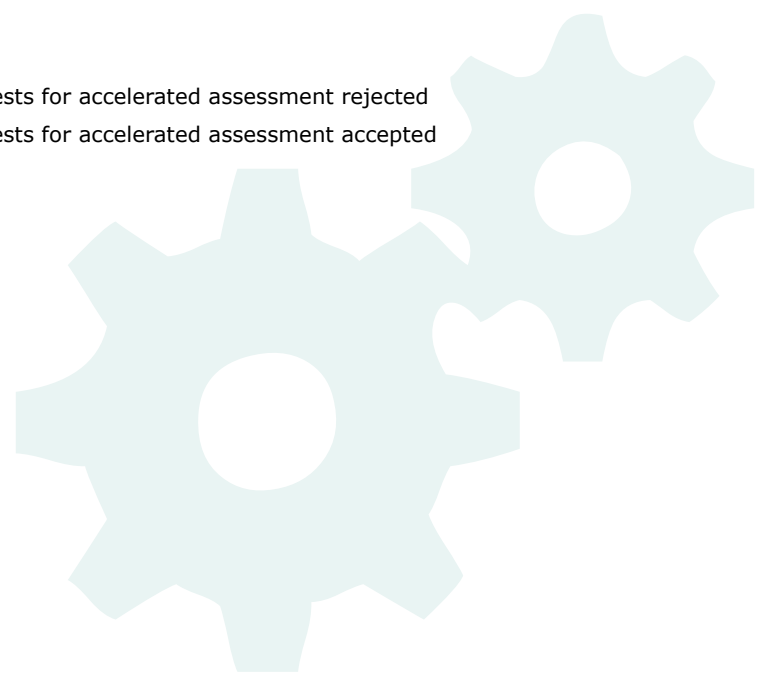
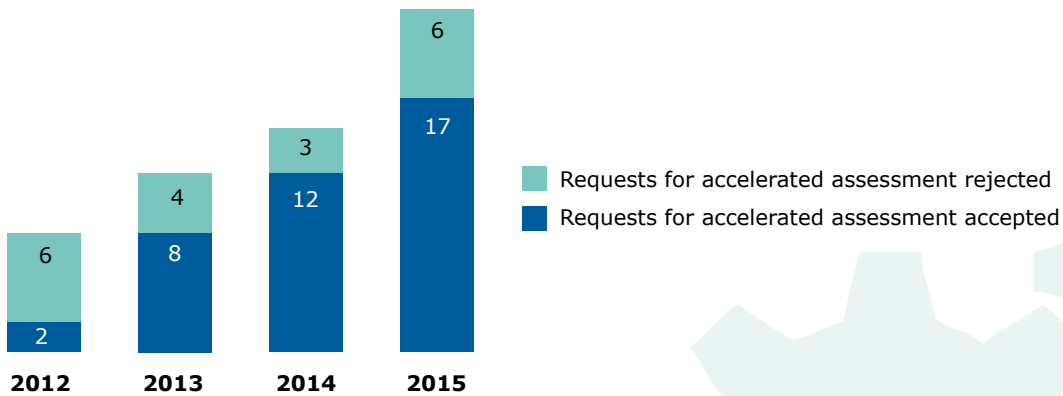
Conditional marketing authorisation and switch to standard marketing authorisation					
	2011	2012	2013	2014	2015
Positive opinions for CMAs	3	3	5	5*	3
Opinions recommending switch of CMA to standard marketing authorisation	1	0	3	2	2

\* Three of these marketing authorisation applications were withdrawn by the sponsor following the CHMP opinions and prior to a final decision by the European Commission

**Accelerated assessment**

- Five new medicines received a recommendation for marketing authorisation following an accelerated assessment, three of which were for the treatment of cancer. This mechanism is reserved for medicines that have the potential to address patients’ unmet medical needs.
- The assessment of four medicines that received a positive opinion for a marketing authorisation in 2015 began on accelerated timetables, but reverted to standard timetables during the evaluation. The reasons for reverting to standard timelines included the need to further discuss the clinical relevance of the data in certain patient populations, quality issues, as well as critical good clinical practice (GCP) issues identified during inspections.
- In 2015, 17 requests for accelerated assessment were accepted – seven of which were for the treatment of cancer and five for the treatment of infectious diseases. Six were rejected.

**ACCELERATED ASSESSMENT REQUESTS**



RECOMMENDATIONS OF NEW MEDICINES - HIGHLIGHTS OF 2015

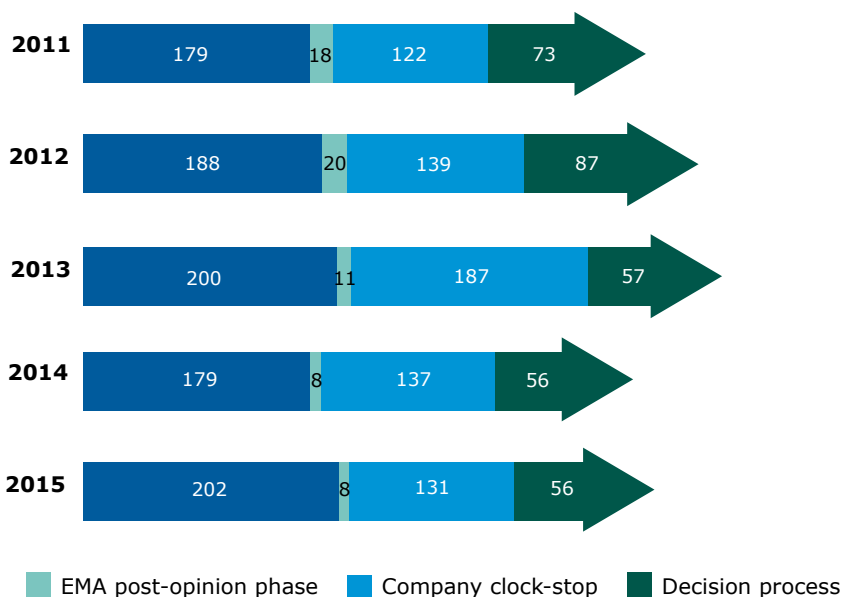
Name of medicine	What is it used for?	
<b>Blincyto</b> (blinatumomab)	Treatment of Philadelphia chromosome-negative acute lymphoblastic leukaemia	O, C
<b>Entresto</b> (sacubitril/valsartan)	Treatment of chronic heart failure	
<b>Farydak</b> (panobinostat)	Treatment of multiple myeloma	O
<b>Gardasil 9</b> (human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed))	A vaccine for the prevention of certain diseases caused by nine types of HPV (types 6, 11, 16, 18, 31, 33, 45, 52, 58)	
<b>Hetlioz</b> (tasimelteon)	Treatment of non-24-hour sleep-wake disorder in totally blind adults	O
<b>Imlygic</b> (talimogene laherparepvec)	Treatment of melanoma (a type of skin cancer): Imlygic is the first ATMP derived from a virus that has been genetically engineered to infect and kill cancer cells	
<b>Intuniv</b> (guanfacine)	Treatment of attention deficit hyperactivity disorder (ADHD)	
<b>Jinarc</b> (tolvaptan)	Treatment of autosomal dominant polycystic kidney disease (ADPKD)	O
<b>Kanuma</b> (sebelipase alfa)	Treatment of lysosomal acid lipase deficiency	O, A
<b>Keytruda</b> (pembrolizumab)	Treatment of melanoma	
<b>Kyprolis</b> (carfilzomib)	Treatment of multiple myeloma	O, A
<b>Lenvima</b> (lenvatinib)	Treatment of thyroid cancer	O, A
<b>Mosquirix</b> ( <i>plasmodium falciparum</i> and hepatitis B vaccine (recombinant, adjuvanted))	Indicated for active immunisation against malaria: Mosquirix is the first vaccine for malaria to be assessed by a regulatory agency for use outside the EU	Art. 58
<b>Nivolumab BMS</b> (nivolumab)	Cancer immunotherapy for the treatment of squamous non-small cell lung cancer (NSCLC)	
<b>Opdivo</b> (nivolumab)	Treatment of advanced (unresectable or metastatic) melanoma	
<b>Praluent</b> (alirocumab)	Treatment to lower high levels of cholesterol in the blood of people who are unable to control their cholesterol despite taking optimal doses of statins, or who cannot take statins	
<b>Praxbind</b> (idarucizumab)	Specific antidote to the anticoagulant medicine Pradaxa (dabigatran etexilate), when rapid reversal of its effect is required	A
<b>Repatha</b> (evolocumab)	Treatment to lower high levels of cholesterol in the blood of people who are unable to control their cholesterol despite taking optimal doses of statins or who cannot take statins, and for the treatment of homozygous familial hypercholesterolaemia	
<b>Saxenda</b> (liraglutide)	Weight management in overweight and obese adults.	
<b>Strensiq</b> (asfotase alfa)	Treatment of hypophosphatasia that started in childhood	O, E
<b>Tagrisso</b> (osimertinib)	Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with a specific mutation (T790M) of the epidermal growth factor receptor (EGFR)	A, C
<b>Unituxin</b> (dinutuximab)	Cancer immunotherapy for the treatment of high-risk neuroblastoma	O
<b>Wakix</b> (pitolisant)	Treatment of narcolepsy	O
<b>Zykadia</b> (ceritinib)	Treatment of anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC)	C

O = orphan designation; A = accelerated assessment; C = conditional approval; E = exceptional circumstances. The full list of medicines recommended for marketing authorisation in 2015, as well as the negative opinions and withdrawals can be found in annex 10.

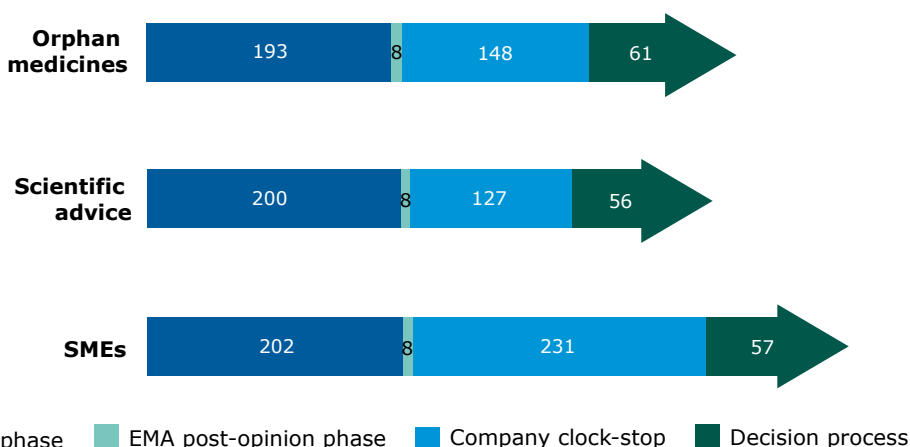
**Average assessment time**

- The overall time required for the assessment of initial marketing authorisation applications in 2015 is comparable to the previous year.
- Company clock-stop for applications submitted by SMEs however was longer than the average time. This highlights the importance of scientific and regulatory advice to this group of stakeholders.

**AVERAGE NUMBER OF DAYS FOR CENTRALISED PROCEDURES - POSITIVE OPINIONS (2011-2015)**



**AVERAGE NUMBER OF DAYS FOR CENTRALISED PROCEDURES - SUBSET (2015)**

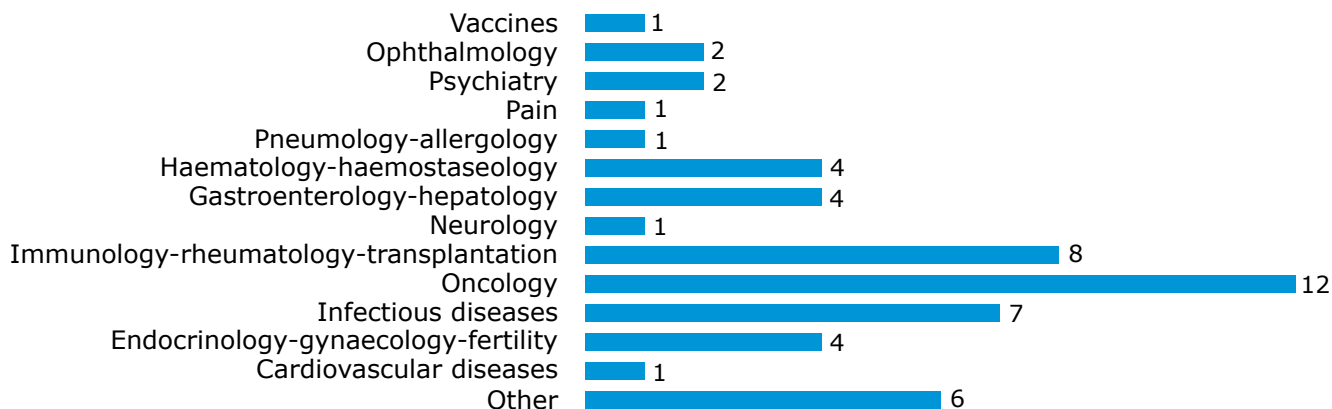


**Post-authorisation activities (or variations/changes to marketing authorisation)**

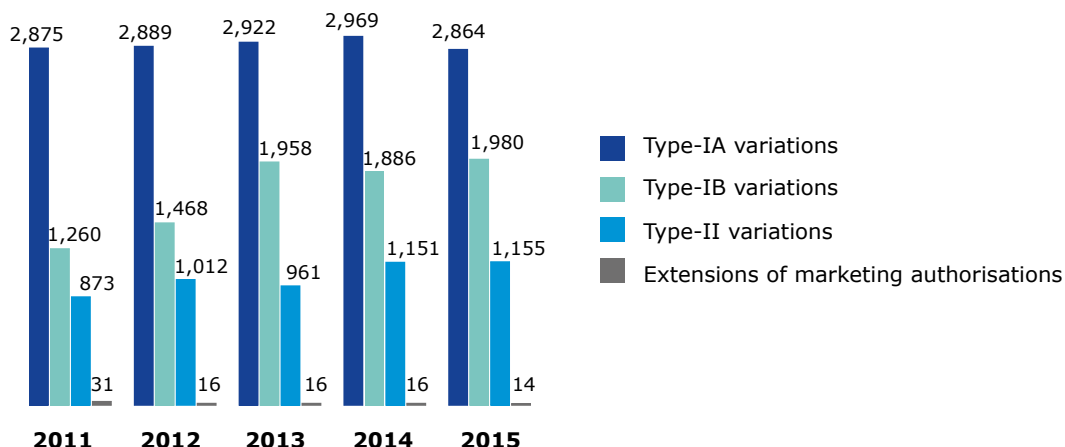
Post-authorisation activities include variations, extensions and transfers of marketing authorisations.

- CHMP adopted 54 positive recommendations for extension of the therapeutic indication of already authorised medicines in 2015, 12 of which were for medicines to treat cancer.

POSITIVE OPINIONS FOR EXTENSIONS OF INDICATIONS PER THERAPEUTIC AREA (2015)



POST-AUTHORISATION APPLICATIONS RECEIVED (2011-2015)



EXTENSIONS OF THERAPEUTIC INDICATIONS – HIGHLIGHTS OF 2015

Name of medicine	What is it used for?
<b>Humira</b> (adalimumab)	Treatment for patients with hidradenitis suppurativa (acne inversa)
<b>Imbruvica</b> (ibrutinib)	Treatment for patients with Waldenstrom’s macroglobulinemia
<b>Perjeta</b> (pertuzumab)	Treatment for patients with breast cancer undergoing surgery
<b>Tafinlar</b> (dabrafenib) and <b>Mekinist</b> (trametinib)	A combination treatment for patients with advanced melanoma
<b>Xalkori</b> (crizotinib)	Treatment for previously untreated patients with non-small cell lung cancer with ALK mutation

Further information on recommendations for extensions of indication can be found in annex 10a.

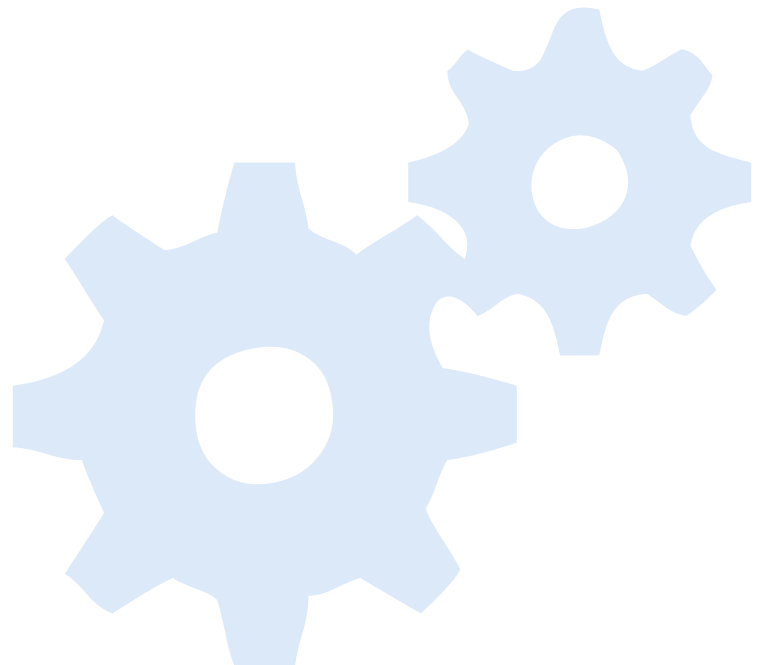
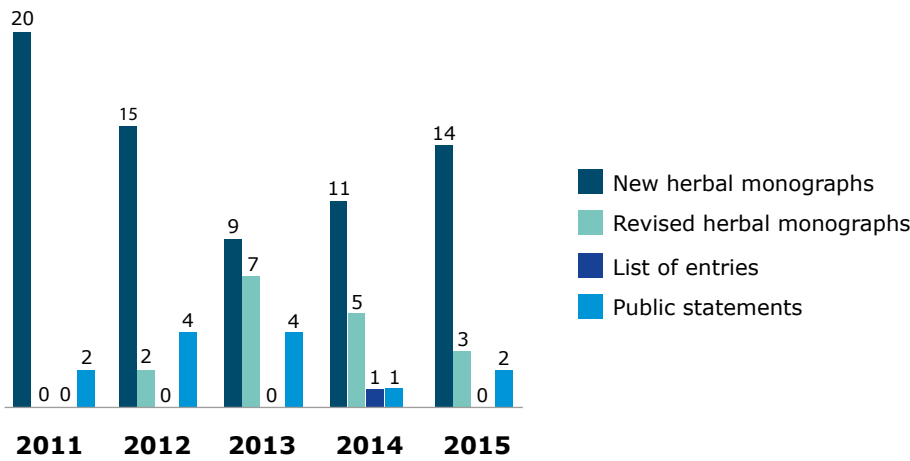


### 3.1.3 Herbal medicines

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

- The assessment of 16 new herbal substances was completed in 2015, leading to the publication of 14 final EU monographs and two final public statements, following public consultations<sup>5</sup>.
- Three monographs were updated and revised following systematic review of newly available data.

#### HERBAL MONOGRAPHS AND LIST OF HERBAL SUBSTANCES, PREPARATIONS AND COMBINATIONS THEREOF (2011-2015)



<sup>5</sup>) Further information on opinions on herbal monographs can be found in annex 13.

### 3.1.4 Safety monitoring

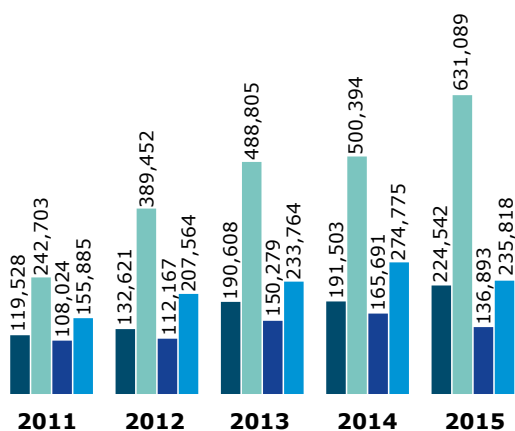
EMA and the EU Member States are responsible for coordinating the EU’s safety-monitoring or ‘pharmacovigilance’ system for medicines. They constantly monitor the safety of medicines through the EU network and can take action if information indicates that the safety profile or benefit-risk balance of a medicine has changed since it was authorised. EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has a key role in overseeing the safety of medicines in the EU. The committee’s activities cover all aspects of the safety monitoring and risk management of medicines.

#### EudraVigilance – adverse drug reactions

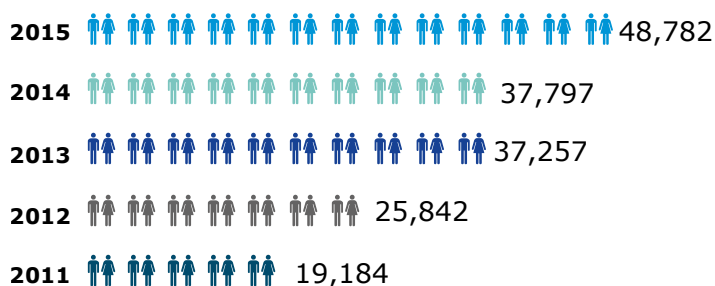
The Agency’s main responsibilities in relation to the safety monitoring of medicines include the coordination of the European pharmacovigilance system, the provision of information on the safe and effective use of medicines, and the operation and maintenance of the EudraVigilance system. Both EMA and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

- More than 1.2 million ADR reports were reported to EudraVigilance in 2015, an increase of 8.5%. This is mainly due to a progression in the number of reports in relation to centrally authorised products coming from non-EEA countries.
- Over 48,000 reports originated from patients in the EEA, a 30% increase compared to 2014. This is a positive trend showing patients’ increased commitment to report the side effects they experience.

EEA AND NON-EEA ADR REPORTS RECEIVED (2011-2015)



ADR REPORTS FROM PATIENTS (2011-2015)



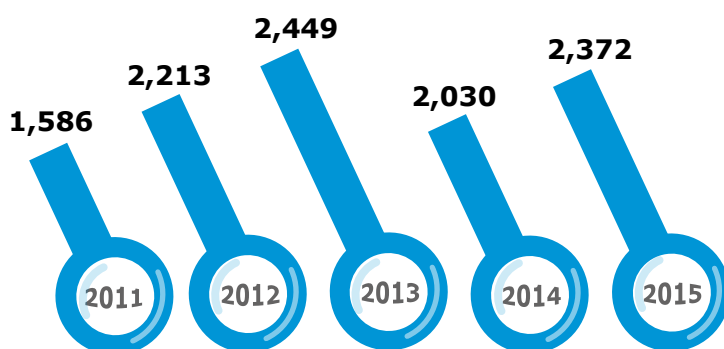
- CAP EEA ADRs
- CAP non-EEA ADRs
- NAP EEA ADRs
- NAP non-EEA ADRs

## Signal detection

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

- In 2015, 2,372 potential signals were reviewed by EMA, 88% of which originated from monitoring the EudraVigilance database.
- In total, 102 confirmed signals were prioritised and analysed by the PRAC in 2015.
- Among these signals, 61 were validated by EMA for further evaluation and 41 signals were detected and validated by Member States.
- One in three signals assessed by the PRAC resulted directly in a recommendation for an update of the product information, including distribution of a direct healthcare professional communication (DHPC) on four occasions to highlight important new safety information to prescribers.
- One signal required further evaluation in a referral procedure.
- Five signals triggered another regulatory action such as a recommendation to update the risk management plan (RMP) or to conduct a study.
- One-third of the validated signals were still under review by the PRAC at the end of 2015 as further data were required.
- Approximately one in four validated signals was closed and routine pharmacovigilance recommended as a follow-up.

### SIGNAL DETECTION (2011-2015)



## Periodic safety update reports

Marketing authorisation holders are required to submit to the regulatory authorities a report on the evaluation of the benefit-risk balance of a medicine at regular, predefined time points following a medicine’s authorisation. These reports summarise data on the benefits and risks of a medicine and take into consideration all studies carried out with this medicine (in authorised and unauthorised indications). The Agency is responsible for procedures supporting the analysis of these reports for centrally authorised products and for medicines authorised in more than one Member State. The reports are called periodic safety update reports (PSURs) but when the assessment involves more than one medicinal product with the same active substance the procedure is referred to as periodic safety update single assessment or PSUSA.

- 633 recommendations were issued by the PRAC based on the assessment of PSURs and PSUSAs in 2015, a 35% increase compared to 2014.



**In 2015, EMA started carrying out the single assessment of active substances contained only in nationally authorised medicines. These account for almost 30% of all the assessments finalised in 2015.**

- Just over one in five assessments lead to changes to product labelling, to enable safe and effective use of medicines by patients.

PSURs and PSUSAs finalised				
	2012	2013	2014	2015
<b>PSURs stand alone (CAPs only) finalised</b>	20	430	426	470
<b>PSURs single assessment finalised</b>	0	6	45	163
<b>PSURs single assessment (CAPs with NAPs) finalised</b>	0	6	45	27
<b>PSURs single assessment (NAPs only) finalised</b>	0	0	0	136
<b>Total outcomes</b>	20	436	471	633

PRAC outcomes of PSURs and PSUSAs				
	2012	2013	2014	2015
<b>Maintenance</b>	17	360	383	500
<b>CHMP/CMDh variation</b>	3	76	88	133
<b>Suspension</b>	0	0	0	0
<b>Revocation</b>	0	0	0	0
<b>Total outcomes</b>	20	436	471	633

*NAPs: nationally authorised medicines; CAPs: centrally authorised medicines*

### Post-authorisation safety studies and post-authorisation efficacy studies

A post-authorisation safety study (PASS) is a study that is carried out after a medicine has been authorised to obtain further information on its safety, or to gauge the effectiveness of risk-management measures. PASS can be imposed on marketing authorisation holders as part of their post-authorisation obligations. The Agency's PRAC is responsible for assessing the protocols of imposed PASSs and their results.

- The PRAC assessed 20 imposed PASS protocols that were requested to obtain further information on a medicine's safety in 2015.

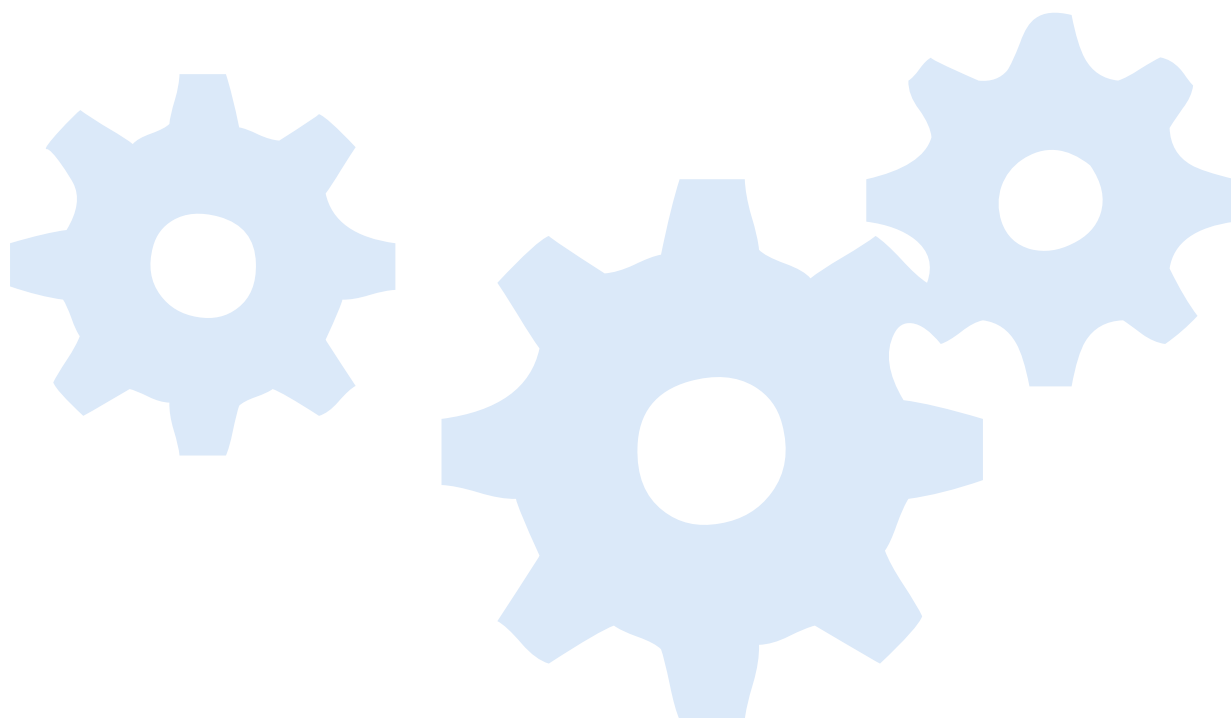
Post-authorisation efficacy studies (PAES) are conducted after a medicine has been granted a marketing authorisation, to collect data on aspects of the benefits in its approved indication that can only be explored once the medicine is marketed.

- 23 PAES were imposed on companies by the CHMP in order to collect further data on the benefits of medicines while they are being used by patients in real life.

### Notification of withdrawals

Since 2014, companies have been required to report the cessation of marketing of a medicine in any Member State for reasons affecting patient safety so that the authorities can ensure that the same action is taken across all Member States. EMA is responsible for the coordination of these actions across the EU.

- In 2015, EMA received 160 notifications of withdrawn products, compared to 132 in 2014.



### 3.1.5 Referral procedures

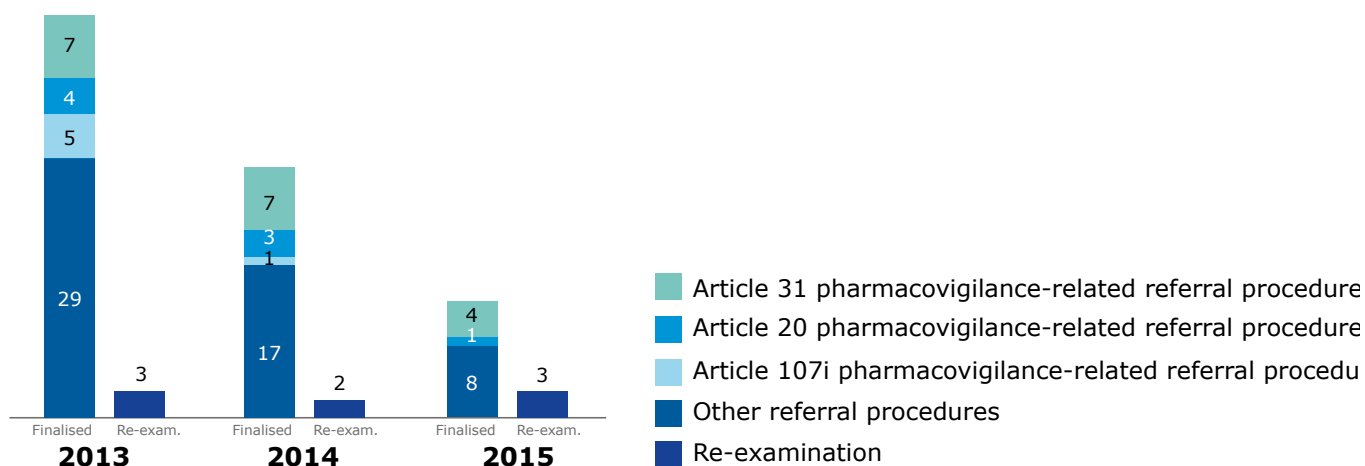
Referral procedures are used to address concerns over the safety or benefit-risk balance of a medicine, or disagreement among Member States on the use of a medicine. In a referral, the Agency is requested to conduct, on behalf of the EU, a scientific assessment of a particular medicine or class of medicines to agree on a recommendation for the harmonised position across the EU. The recommendation subsequently results in a legally binding decision throughout the EU issued by the European Commission or, less often and if only nationally authorised products are involved, by the CMDh (Co-ordination Group for Mutual-recognition and Decentralised Procedures – Human).

- 21 referral procedures were started in 2015.
- Among these, five were pharmacovigilance-related (under Articles 31, 20 or 107i of the pharmacovigilance legislation).
- The remaining 16 referral procedures were initiated to address either efficacy or quality concerns with certain medicines, or a need for EU-wide harmonisation of product information, or were triggered by differences between the Member States in the mutual recognition and decentralised procedures.

#### ARBITRATIONS AND REFERRALS FOR HUMAN MEDICINES STARTED (2013-2015)



#### ARBITRATIONS AND REFERRALS FOR HUMAN MEDICINES FINALISED OR RE-EXAMINATION (2013-2015)



Key recommendations issued as a result of a safety referral, a PSUR or a safety signal assessment are presented in the table below:

Medicine/review	Recommendation
<b>Ambroxol- and bromhexine-containing medicines</b>	Update to product information to include information about the small risk of severe allergic reactions and severe cutaneous adverse reactions (SCARs).
<b>Bisphosphonate medicines</b>	New measures to minimise the risk of osteonecrosis (death of bone tissue) in the jaw, including an update to the product information and the introduction of a patient reminder card.
<b>Codeine-containing medicines</b>	New measures to minimise the risk of serious side effects, including breathing problems when used for coughs and colds in children. Codeine is not to be used in children under 12 years for coughs and colds, and the use of codeine for coughs and colds is not recommended in children and adolescents between 12 and 18 years who have breathing problems.
<b>Gilenya (fingolimod)</b>	New advice for doctors and patients in order to minimise the risk of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma in patients treated with this medicine.
<b>Hepatitis C medicines and amiodarone</b>	Restrictions on the use of Harvoni (sofosbuvir with ledipasvir) or a combination of Sovaldi (sofosbuvir) and Daklinza (daclatasvir) when taken together with amiodarone (a medicine used to treat irregular heartbeat). Amiodarone should only be used in patients taking these medicines if other antiarrhythmics cannot be given.
<b>High-dose ibuprofen</b>	Updated advice on use of high-dose ibuprofen: high doses of ibuprofen should be avoided in patients with serious underlying heart or circulatory conditions, such as heart failure, heart disease and circulatory problems, or in those who have previously had a heart attack or stroke. Doctors should also assess a patient's risk factors for heart or circulatory conditions before initiating long-term treatment with ibuprofen, particularly if high doses are required.
<b>HIV medicines</b>	In 2015, EMA reviewed the product information of all HIV medicines and for most of them decided to remove certain warnings in relation to the impact on body fat changes and lactic acidosis, in light of new data available. These changes allow patients and healthcare professionals to use and prescribe these medicines in the best possible way.
<b>HPV vaccines</b>	An EMA review concluded that available evidence does not support that HPV vaccines cause complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women who have received human papillomavirus (HPV) vaccines. Therefore, there is no reason to change the way the vaccines are used or amend the current product information.
<b>Hydroxyzine-containing medicines</b>	New restrictions to minimise the risks of effects on heart rhythm with these medicines, including restricting the use of hydroxyzine in patients at high risk of heart rhythm problems and using the medicine at the lowest effective dose for as short a time as possible.
<b>Inductos (dibotermin alfa)</b>	Suspension of Inductos in the EU: Inductos is an implant used to help new bone develop in patients with spinal disc problems and leg fractures. The medicine will remain suspended until manufacturing issues are resolved.
<b>Mycophenolate</b>	Because of seriously harmful effects on the foetus, additional measures to prevent the use of mycophenolate in pregnancy. Pregnant women must not be exposed to the medicine unless there is no suitable alternative to prevent transplant rejection.
<b>Tecfidera (dimethyl fumarate)</b>	Updated recommendations for doctors and patients to minimise the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with this medicine.

Further information on referral procedures can be found in annex 15.

### 3.1.6 Experts, patients and healthcare professionals involved in scientific assessments

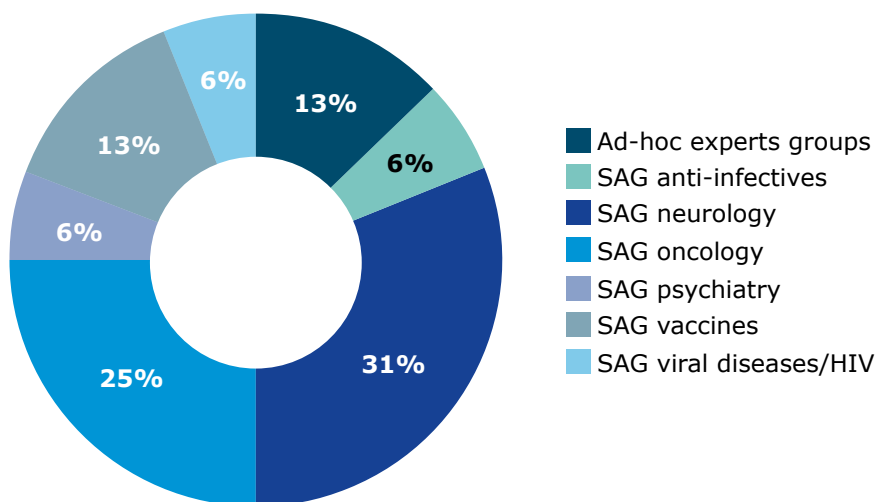
#### Consultation of scientific advisory groups

EMA scientific committees can consult additional experts, clinicians as well as patients and healthcare professionals, through scientific advisory groups (SAG) or ad-hoc expert groups, to enrich their scientific assessment in relation to the evaluation or safety monitoring of medicines.

A total of 15 consultations took place in 2015 in the form of SAG meetings; 13 of these included patients or carers.

Procedures with scientific advisory group or ad-hoc expert group involvement (number of consultations)					
	2011	2012	2013	2014	2015
Marketing authorisations (new MAA, new MAA re-examination, Art 58)	15	16	20	14	7
Extensions of indications (including line extensions)	5	4	3	2	2
Referrals (including re-examinations)	5	5	2	5	3
Other topics (renewals, PSURs, signals, class reviews)	2	1	0	1	3

#### CONSULTATIONS WITH SCIENTIFIC ADVISORY GROUPS AND AD-HOC EXPERTS GROUPS





### Involvement of patients and healthcare professionals

Representatives of patients and healthcare professionals are involved in a wide range of EMA activities. They bring a crucial 'real-life' perspective to scientific discussion on medicines, which is expected to lead to better outcomes in the regulatory process. They participate in a wide range of activities at the Agency, including:

- as members of scientific committees and the Management Board;
- being consulted on disease-specific requests by the scientific committees and working parties;
- taking part in discussions on the development and authorisation of medicines;
- reviewing written information on medicines prepared by the Agency;
- being involved in the preparation of guidelines;
- taking part in the Agency's conferences and workshops.

Patient involvement in EMA activities (interactions)	2015
Scientific advice/protocol assistance	76
SAGs/ad-hoc experts meetings	23
Scientific committee/working party consultations	24
Workshops	115
Working groups and other ad-hoc activities	312

Documents reviewed by patients and consumers	2015
European public assessment reports summaries	47
Package leaflets	71
Safety communications	19

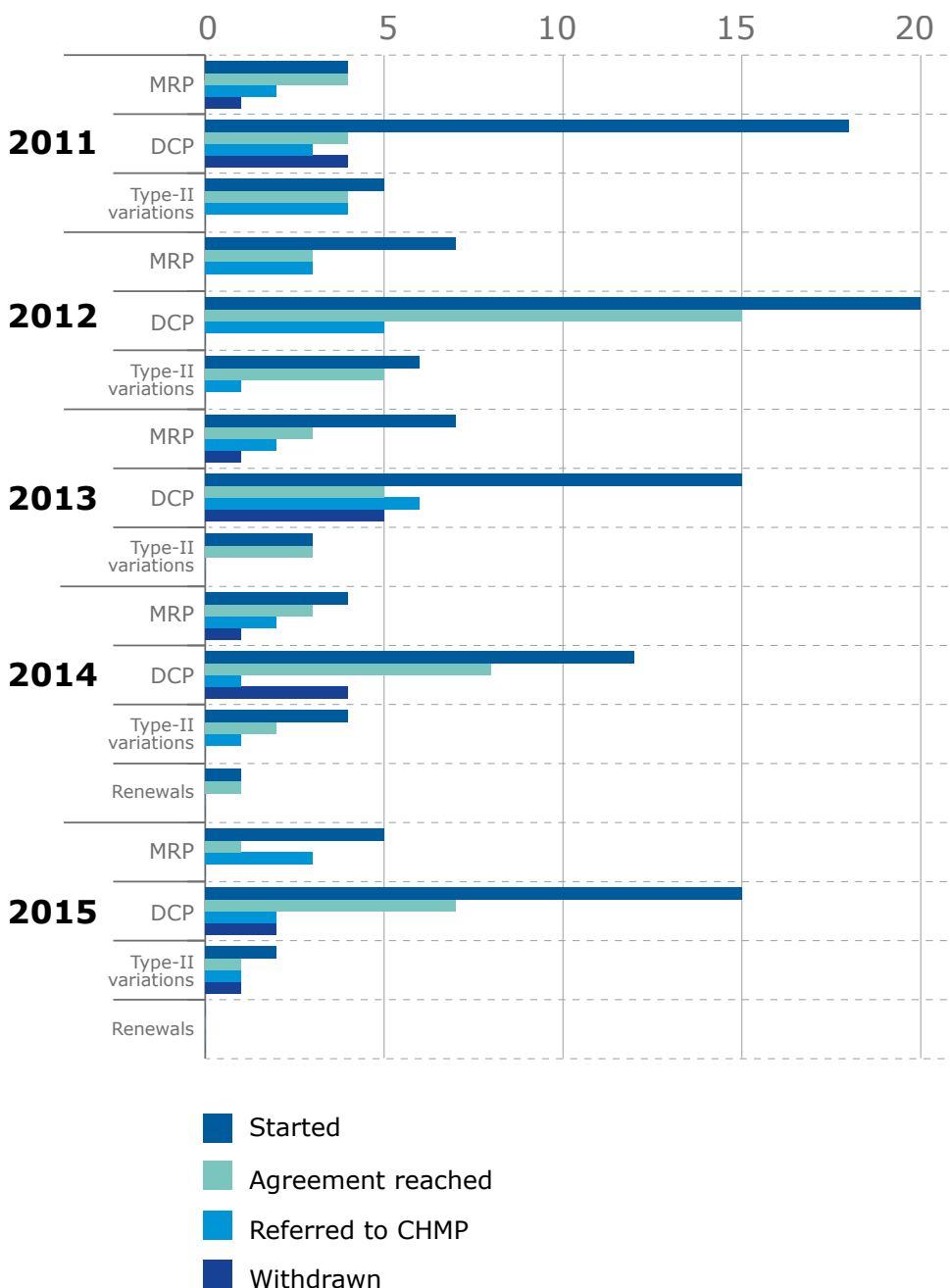
Healthcare professional involvement in EMA activities (interactions)	2015
Scientific advice/protocol assistance	1
SAGs/ad-hoc experts meetings	21
Scientific committee/working party consultations	47
Workshops	59
Working groups and other ad-hoc activities	198

Documents reviewed by healthcare professionals	2015
Safety communications	24
Direct healthcare professional communications (DHPC)	6

### 3.1.7 Mutual-recognition and decentralised procedures

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

APPLICATIONS REFERRED TO CMDh (2011-2015)



## 3.2. Veterinary medicines

### 3.2.1 Activities supporting research and development

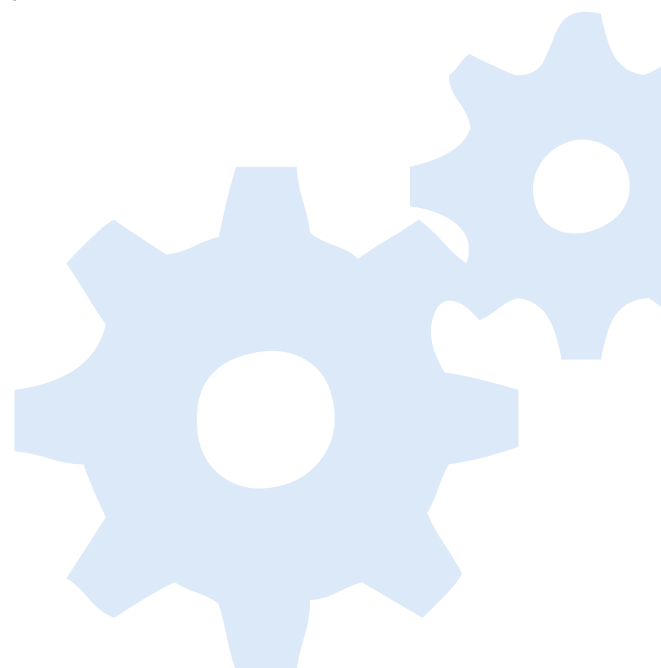
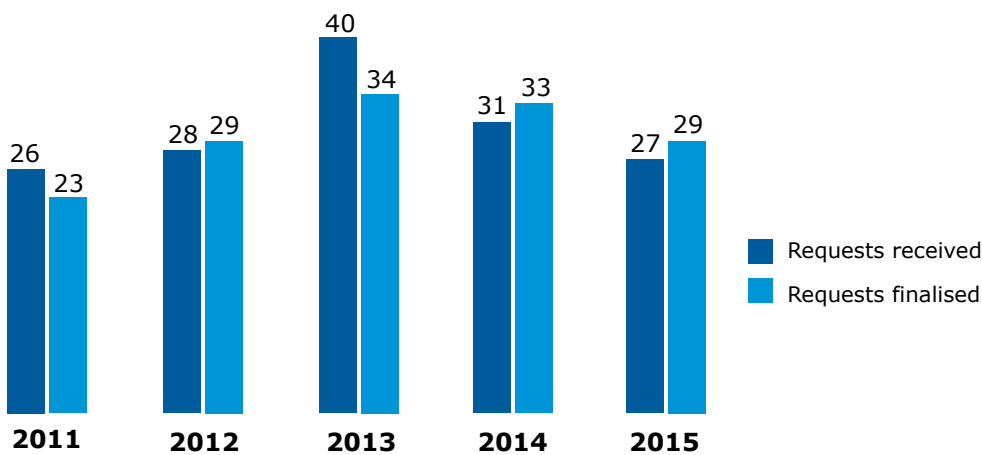
The Agency provides pre-authorisation support to medicine developers to promote innovation and research in order to facilitate the availability of safe and effective veterinary medicines. This is achieved through a number of activities and incentives offered to companies prior to submitting an application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

#### Scientific advice

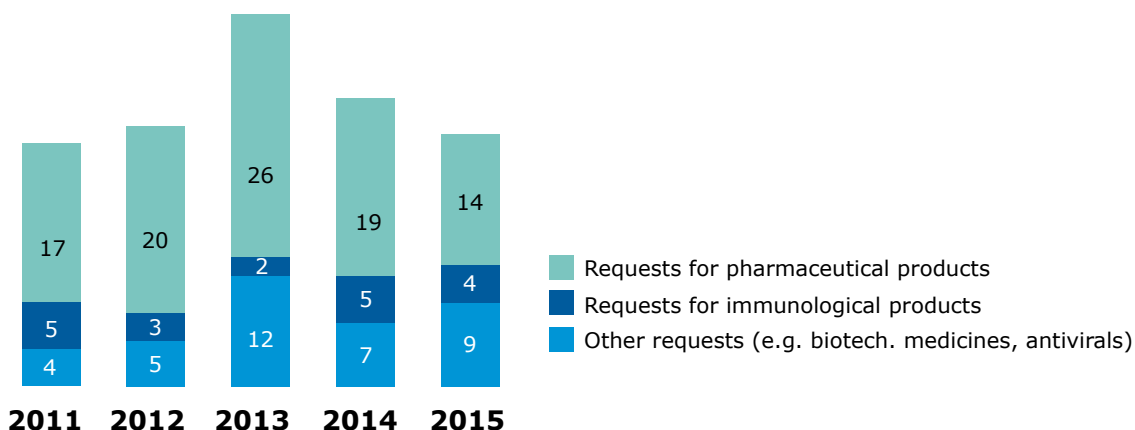
Scientific advice is provided on any aspect of research and development relating to the quality, safety or efficacy of medicines for veterinary use, and to the establishment of maximum residue limits. Scientific advice is a means of facilitating and improving the availability of new veterinary medicines.

- EMA received 27 requests for scientific advice in 2015. Whilst there have been some fluctuations in numbers from year to year, the current level of requests reflects a constant interest from developers in receiving scientific advice during the research and development phase of their veterinary medicinal products.

#### SCIENTIFIC-ADVICE REQUESTS RECEIVED AND FINALISED (2011-2015)



SCIENTIFIC-ADVICE REQUESTS RECEIVED BY AREA (2011-2015)



Minor Use Minor Species

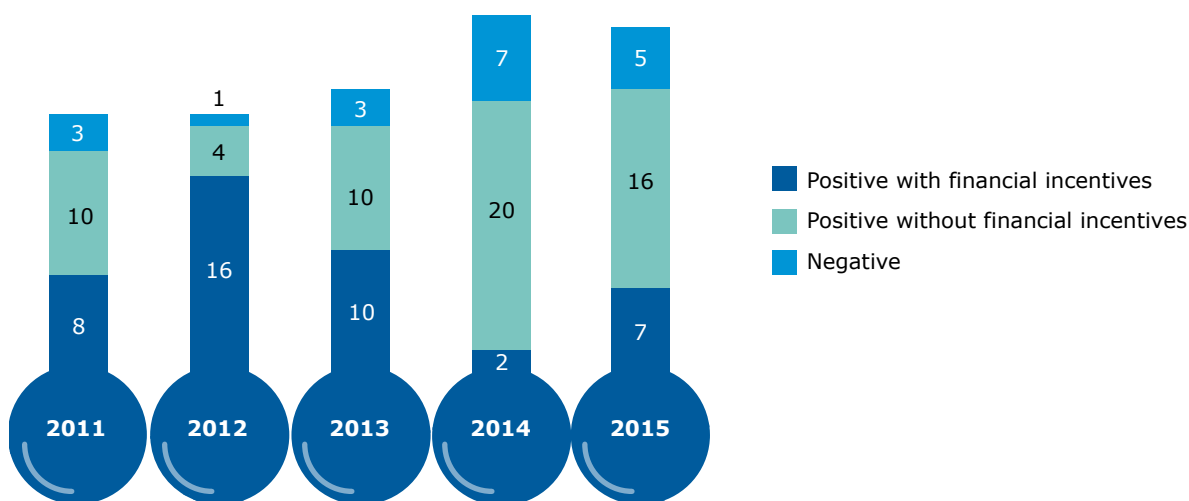
The Agency’s Minor Use Minor Species (MUMS)/limited market policy adopted in 2009 aims to assist companies with the submission of applications for products for limited markets. The policy was revised in 2013/2014. The goal is to stimulate development of new veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment.



**2015 saw the highest number of requests classified by CVMP as MUMS (23) in a year; seven of these 23 were also granted financial incentives such as access to free scientific advice and reduced application fees.**

- The Agency received a total of 28 requests for the classification of veterinary medicines intended for MUMS/limited market, showing a stable interest from medicine developers to develop products for MUMS/limited market.
- Of the medicines classified as MUMS, one product indicated for mineralocorticoid deficiency or Addison’s disease in dogs was recommended by CVMP for marketing authorisation.

OUTCOME OF MUMS/LIMITED MARKET APPLICATIONS FINALISED (2011-2015)



## Support to SMEs

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 SMEs 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.

- Of the 1,619 SMEs registered with EMA at the end of 2015, 4% are developing veterinary products and 5% are developing both human and veterinary products.



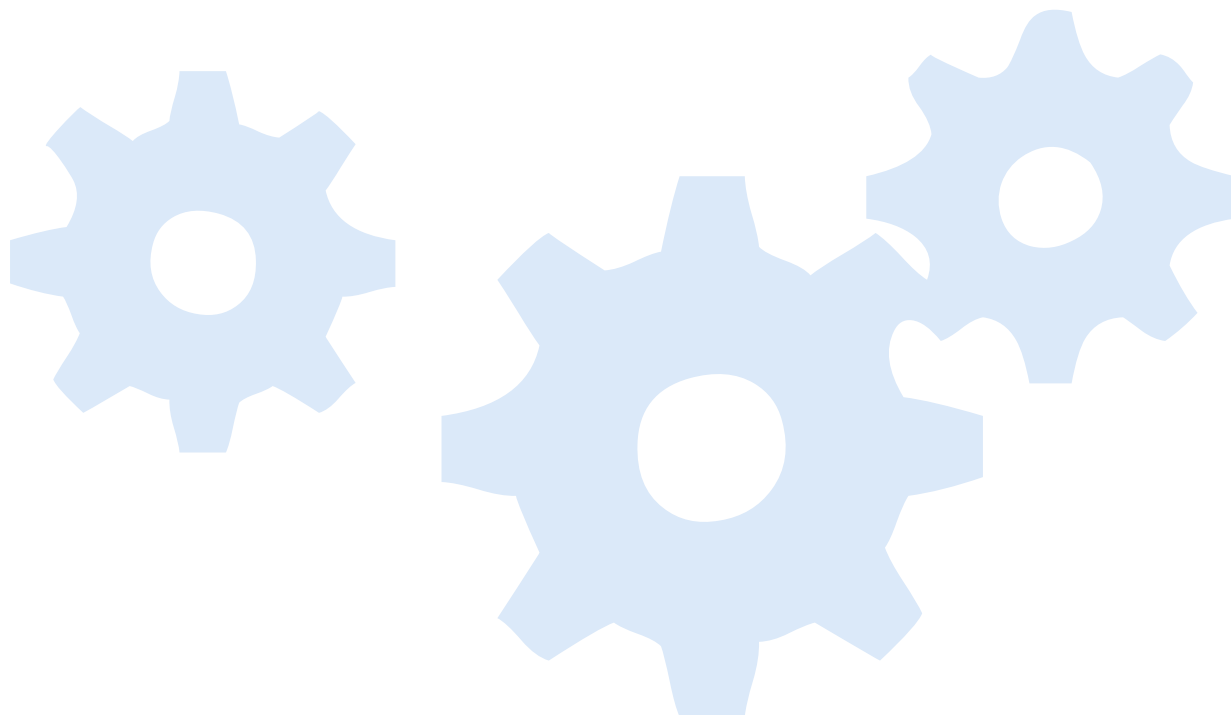
**SMEs submitted four of the 10 applications for marketing authorisation for veterinary medicines received in 2015.**

- In 2015, 27 requests for scientific advice were submitted, 12 of which came from SME applicants, which represent 44% of all requests.
- Two medicines that received a positive recommendation for a marketing authorisation for a veterinary medicine were developed by SMEs, one of which was a new active substance.

### SMEs and initial-evaluation applications (2015)

<b>Marketing authorisation applications submitted</b>	4
<b>Positive opinions</b>	2
<b>Negative opinions</b>	1

*A report on the 10 years of the SME initiative can be found on the EMA website.*



## Innovation Task Force

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

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

Two ITF briefing meetings were requested and held in 2015 in relation to the development of veterinary medicines.

## Key scientific guidelines

A number of guidelines and guidance documents were either adopted for consultation or published during 2015. They relate to the quality, safety, environmental risk assessment and efficacy of medicines for veterinary use. They also include guidance documents for antimicrobial medicines, including the CVMP Strategy on Antimicrobials for 2016-2020. This strategy sets out the priority areas the CVMP will address over the next five years in order to strike an appropriate balance between ensuring the continued availability of antimicrobials to treat infectious disease in animals and the need to minimise the risks from AMR arising from such use. The 'One Health' approach underlies the whole strategy whereby issues are addressed by bringing together experts from the animal, human and environmental domains to develop solutions to the common threat of AMR. Other key guidance documents developed in 2015 include:

Guidelines and working documents	Description
<p><b>Concept paper on the need for revision of the veterinary note of guidance on manufacture of the finished dosage form</b></p>	<p>This concept paper addresses the need to update and revise the veterinary Note for Guidance on Manufacture of the Finished Dosage Form (EMA/CVMP/126/95) (Ref 1). This guideline was originally adopted in December 1995 and came into operation in June 1996. Since then, the references to directives applicable to veterinary medicinal products have changed, revised Annex I to the Directive 2001/82/EC (i.e. Directive 2009/9/EC) was introduced, and several aspects described in the current guideline were further elaborated within other regulatory documents. In addition, the manufacture of finished dosage forms has spread worldwide and terms like 'holding time' and 'bulk product' are now important parts of the description of the manufacturing process. The guideline therefore needs to be revised to be in line with all these changes.</p>
<p><b>Concept paper on the need for a single veterinary note for guidance on the chemistry of active substances</b></p>	<p>This concept paper addresses the need to update and revise the guidance available on the chemistry of the active substance (new and existing active substances). There are currently two approved guidelines on the subject: EMA/CVMP/541/03/Final guideline on the chemistry of new active substances and 3AQ5A guideline on chemistry of the active substance. It is considered appropriate to combine the two documents into a single guideline to provide better clarity for applicants.</p>
<p><b>Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products</b></p>	<p>The aim of this document is to provide an initial framework that will allow further development of signal detection in veterinary pharmacovigilance, its practical modalities, interpretation and location in the signal management process. Surveillance has already been implemented for centrally authorised products in line with the document circulated in 2010: Recommendation for the basic surveillance of EudraVigilance veterinary data.</p>

Guidelines and working documents	Description
<b>Reflection paper on the risk of AMR transfer from companion animals</b>	Current knowledge relating to use of antimicrobials in companion animals and the risk of transfer of AMR is limited and currently there is no guidance when approving antimicrobials for companion animals. This reflection paper recommends developing such guidance.
<b>Draft guideline on the assessment of the risk to public health from AMR due to the use of an antimicrobial veterinary medicinal product in food-producing animals</b>	This guideline provides advice with regard to applications for marketing authorisations for antimicrobial veterinary medicinal products on the data required and the methodology to be used for performing an assessment of the risk to public health from AMR due to use of the product.
<b>CVMP Strategy on Antimicrobials 2016-2020</b>	The draft Committee for Medicinal Products for Veterinary Use (CVMP) strategy on antimicrobials for 2016-2020 sets clear objectives and a course of action for the next five years, based on a 'One Health' approach. The CVMP's vision is the availability of effective antimicrobial medicines for the treatment of important infectious diseases in animals with, at the same time, minimum risks to animals or humans arising from their use.
<b>Draft revised guideline on requirements for the production and control of immunological veterinary medicinal products</b>	The guideline was revised to include a new annex (annex 2) concerning the approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products for mammalian species and finfish, and to replace the table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines (7BIm10a).
<b>Concept paper on requirements for the production and control of allergen products for use in animals</b>	Recent developments require the revision of the existing CVMP/IWP Guideline on allergen products. Since the revision of this guideline in 1994, the scientific knowledge on structures, cross-reactivity, and stability of allergens has increased drastically, and many allergens have been produced as recombinant proteins. This scientific progress has several implications for the regulation and standardisation of allergen products. Special emphasis has to be granted to recombinant allergen products. Therefore, the revised guideline should redefine the statements on batch-to-batch consistency, characterisation and use of in-house reference preparations (IHR), control tests as well as on safety and efficacy testing. Moreover, it should be aimed at covering aspects specific for recombinant allergens that are not covered or specifically addressed by other guidelines on biotechnology-derived proteins.

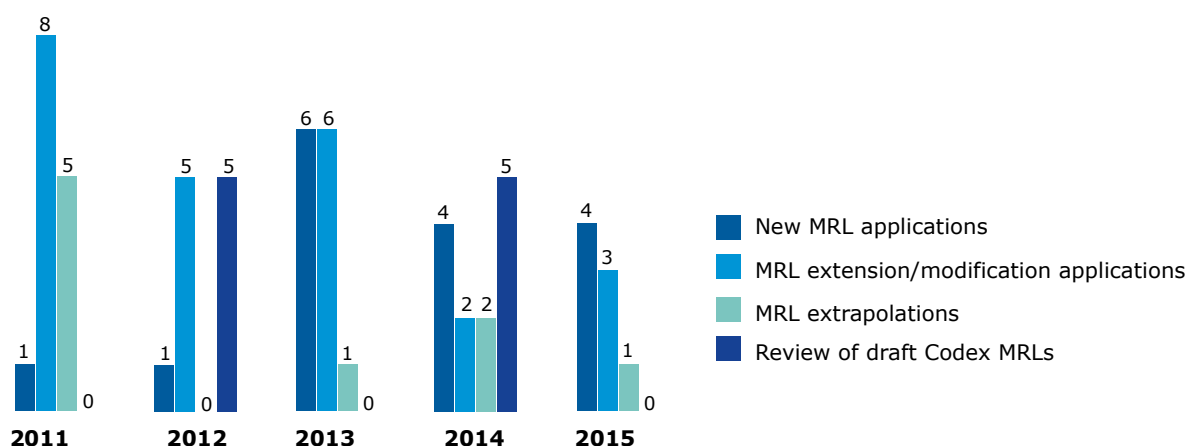
Further information on guidelines adopted in 2015 can be found in annex 11b.

### 3.2.2 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 assesses and recommends maximum residue limits (MRLs) for pharmacologically active substances in veterinary medicinal products used to treat animals, to provide for the safe use of foodstuffs of animal origin, including meat, fish, milk, eggs and honey. The Agency also has this responsibility for pharmacologically active substances in biocidal products used in animal husbandry. The European Commission formally establishes the MRL status.

- Four applications for the establishment of new MRLs were received in 2015.
- The continued submission over the past years in applications for MRLs indicates the ongoing interest of the animal health industry in developing new products for food-producing animals.

#### EVALUATION OF MAXIMUM RESIDUE LIMITS (2011-2015)



### 3.2.3 Authorisation activities

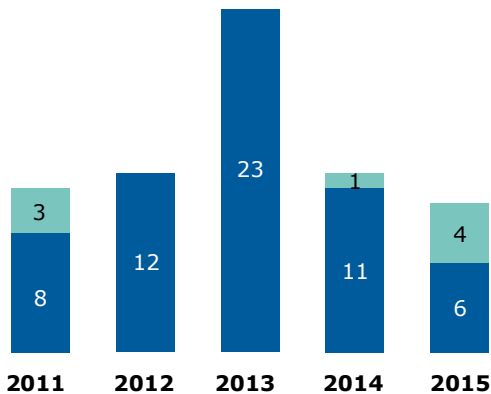
#### Applications for initial evaluation

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 CVMP to the granting of marketing authorisation by the European Commission.

- 10 applications for marketing authorisation were received in 2015, four of which were for immunological products for food-producing animals. This high level of immunological approaches to disease control demonstrates the interest of the animal health industry in developing alternatives to antimicrobials to combat infectious diseases and to reduce the risk of AMR in food-producing animals.

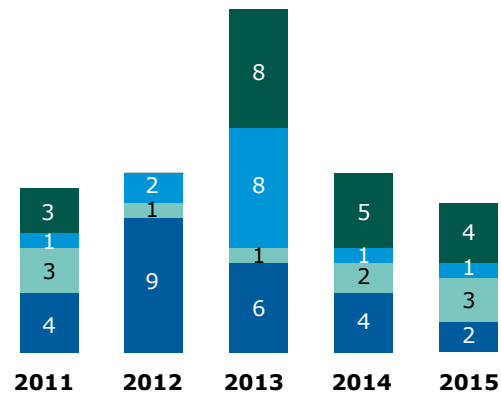


APPLICATIONS FOR INITIAL EVALUATIONS RECEIVED (2011-2015)



■ Generic/abridged applications  
 ■ Applications for new medicinal products

APPLICATIONS FOR INITIAL EVALUATIONS RECEIVED - BREAKDOWN (2011-2015)



■ Immunological for food-producing animals  
 ■ Immunological for companion animals  
 ■ Pharmaceutical for food-producing animals  
 ■ Pharmaceutical for companion animals

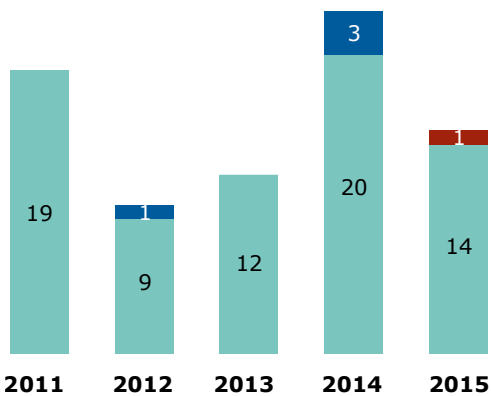
Recommendations for authorisation



**14 new veterinary medicines were recommended for marketing authorisation in 2015; seven of these contained new active substances.**

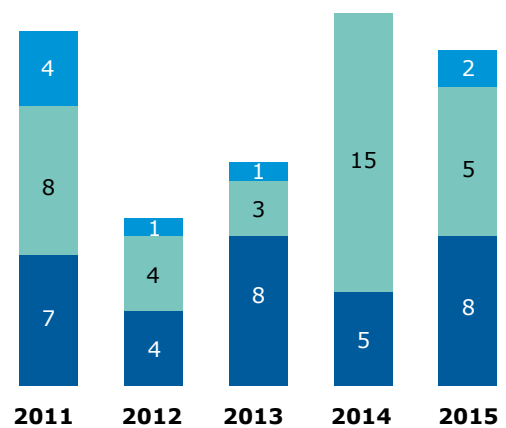
- Five vaccines were recommended for marketing authorisation to prevent viral or bacterial infections in food-producing animals, four of which were biotechnology products. This reflects the current shift in manufacturing of veterinary vaccines from traditional methods towards biotechnology.

OUTCOME OF INITIAL-EVALUATION APPLICATIONS (2011-2015)



■ Positive opinions  
 ■ Negative opinions  
 ■ Withdrawn applications

OPINIONS FOR VETERINARY MEDICINES ADOPTED (2011-2015)



■ Generic  
 ■ Immunological  
 ■ Pharmaceutical

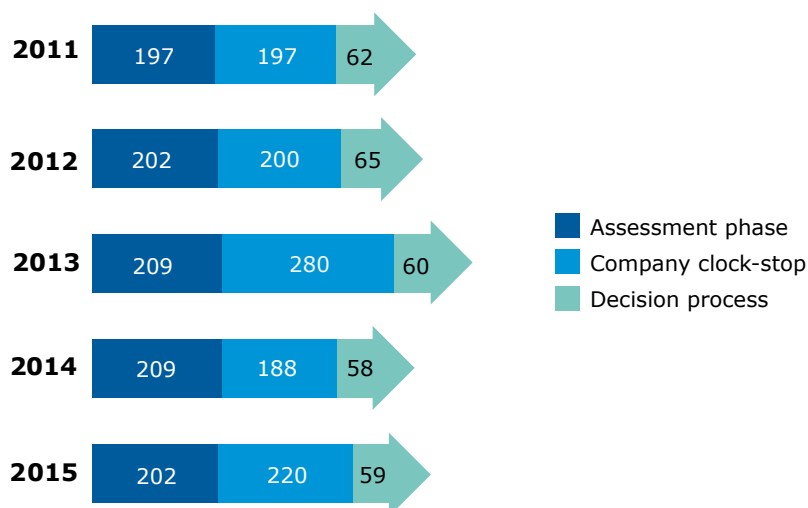
RECOMMENDATIONS FOR NEW MEDICINES – HIGHLIGHTS OF 2015

Veterinary medicine	What is it used for?	
<b>Coliprotec F4</b>	A live vaccine to protect against porcine post-weaning diarrhoea caused by enterotoxigenic Escherichia coli in pigs.	
<b>Imrestor</b>	A treatment to reduce the risk of clinical mastitis in dairy cows during the 30 days following calving.	
<b>Innovax-ILT</b>	A live vaccine to protect against both infectious laryngotracheitis and Marek’s disease in chicken.	
<b>Porcilis PCV ID</b>	An inactivated vaccine to protect against porcine circovirus in pigs.	
<b>Sileo</b>	A treatment to alleviate acute anxiety and fear associated with noise in dogs.	
<b>Suvaxyn Circo+MH RTU</b>	A combination vaccine against both porcine circovirus and Mycoplasma hyopneumoniae, infections commonly occurring together in pigs.	
<b>Vectormune ND</b>	A live vaccine to protect against Newcastle disease and Marek’s disease in chicken.	
<b>Velactis</b>	A treatment to reduce milk production during the dry-off period in dairy cows, reducing the risk of udder infections.	
<b>Zycortal</b>	Treatment for mineralocorticoid deficiency (Addison’s disease) in dogs. If untreated the deficiency may cause cardiovascular emergency in dogs.	MUMS

(MUMS) = Minor Use Minor Species. The full list of medicines recommended for marketing authorisation in 2015 can be found in annex 11.

Average number of days for initial evaluations

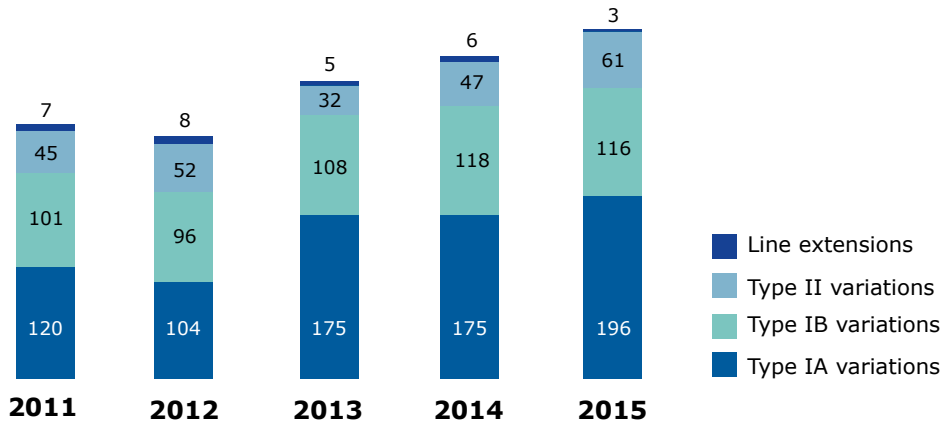
AVERAGE NUMBER OF DAYS FOR CENTRALISED PROCEDURES (2011-2015)



### 3.2.4 Post-authorisation activities

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

#### POST-AUTHORISATION APPLICATIONS RECEIVED (2011-2015)



- The number of post-authorisation procedures continues to increase year-on-year broadly in line with the number of products authorised through the centralised procedure.
- The CVMP adopted six positive opinions for extensions of the existing authorisation. Of particular interest, the CVMP recommended that the indication for the macrolide antibiotic Zactran (gamithromycin) be extended to include use in pigs to treat swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Haemophilus parasuis*.

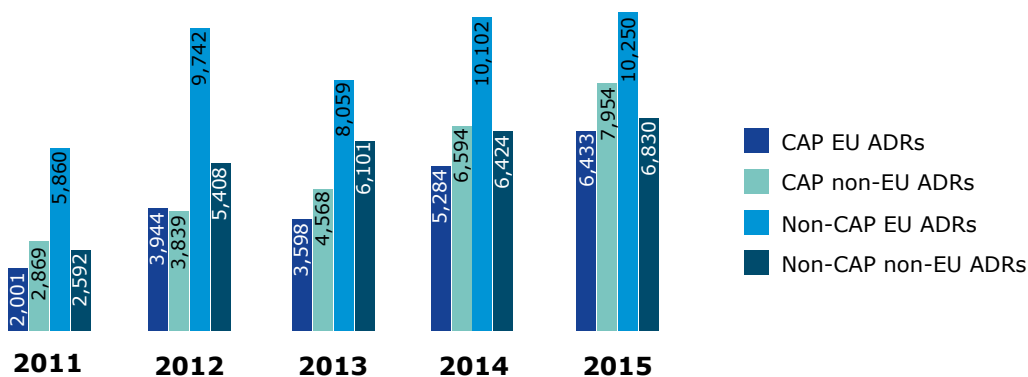
### 3.2.5. Safety monitoring of medicines

Pharmacovigilance covers activities relating to the detection, reporting, assessment, understanding and prevention of adverse events (AEs) following administration of veterinary medicines. It aims to ensure that post-authorisation monitoring and effective risk management are continuously applied to veterinary medicines throughout the EU.

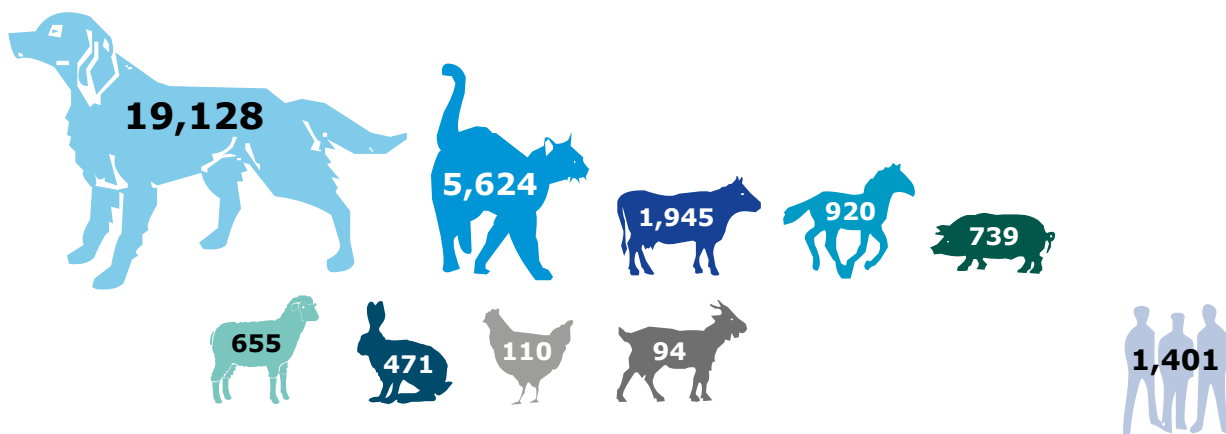
#### EudraVigilance

- A general increase in the number of AE reports received in EudraVigilance was observed in 2015 with a 10.8% rise compared to 2014.
- A long-term trend towards increased reporting is mainly attributed to the increased awareness of the value of pharmacovigilance reporting by veterinarians as well as greater control by the regulators of the implementation of the pharmacovigilance legislative requirements by the veterinary pharmaceutical industry.

ADVERSE EVENTS REPORTS IN ANIMALS AND HUMAN REACTIONS (2011-2015)



NUMBER OF ADVERSE EVENTS REPORTS IN 2015



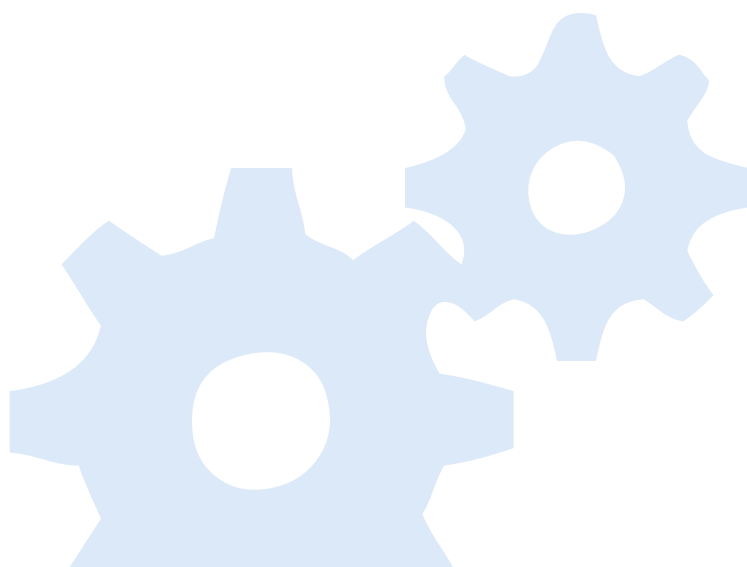
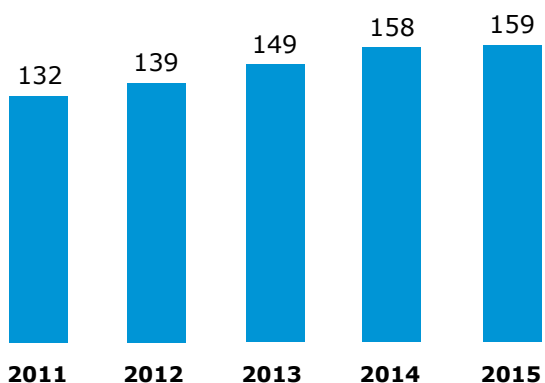
Adverse events occurring in a human being following exposure to a veterinary medicine, e.g. in case of accidental self-injection

Periodic safety update reports (PSURs)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at pre-defined times 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 on this medicine (in authorised and unauthorised indications).

- The CVMP started the assessment of 159 PSURs in 2015, almost the same number as in 2014.

PERIODIC SAFETY UPDATE REPORTS SUBMITTED (2011-2015)

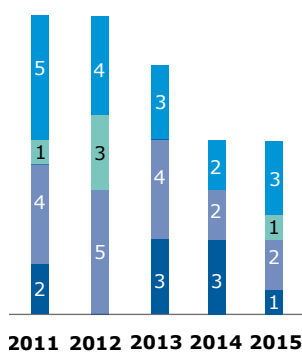


### 3.2.6 Referral and arbitration procedures

Arbitration procedures are used to overcome 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, and issue a recommendation for the whole of the EU.

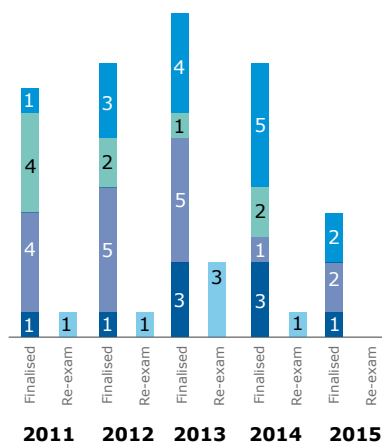
- Five referral and two arbitration procedures related to veterinary medicinal products started in 2015 and five procedures were concluded.
- Of those started in 2015, four procedures concerned individual antimicrobials or classes of antimicrobials which reflect continued European efforts to ensure that these medicines are used appropriately, in order to reduce the risk of AMR as much as possible.

**ARBITRATIONS AND REFERRALS STARTED (2011-2015)**



- Under Art.35 of directive 2001/82/EC
- Under Art.34 of directive 2001/82/EC
- Under Art.33 of directive 2001/82/EC
- Other

**ARBITRATIONS AND REFERRALS FINALISED OR RE-EXAMINATION (2011-2015)**



- Under Art.35 of directive 2001/82/EC
- Under Art.34 of directive 2001/82/EC
- Under Art.33 of directive 2001/82/EC
- Other
- Re-examination

Notable referral or arbitration procedures started or concluded in 2015 are shown in the table below.

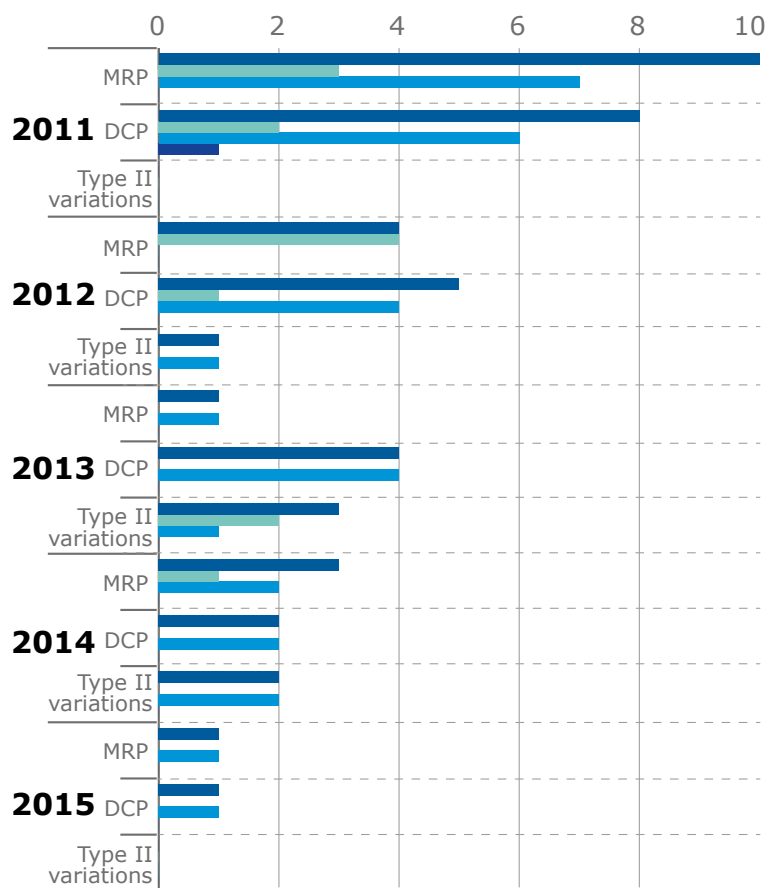
Veterinary medicine	What is it used for?
<b>Closamectin Pour-On Solution and associated names (closantel and ivermectin)</b>	A review was started following the suspension of marketing authorisation in France. The Agency recommended that the medicine should remain available but that changes should be made to the product information and conditions concerning risk-mitigation and surveillance measures.
<b>Lidocaine</b>	A review of the risk to consumers from the use of lidocaine in food-producing species. The Agency issued regulatory recommendations to ensure a negligible risk to consumer safety from residues that may occur in milk following off-label use in cattle. The Agency recommended communication with veterinarians in order to ensure that an adequate interval of time is allowed to elapse between the administration of lidocaine and the taking of milk for human consumption.

More information on referral procedures can be found in annex 16.

### 3.2.7 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).

#### APPLICATIONS REFERRED TO CMDv (2011-2015)



- Started
- Agreement reached
- Referred to CVMP
- Withdrawn

### 3.3 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 EU and the EEA – is the basis of the Agency’s success.

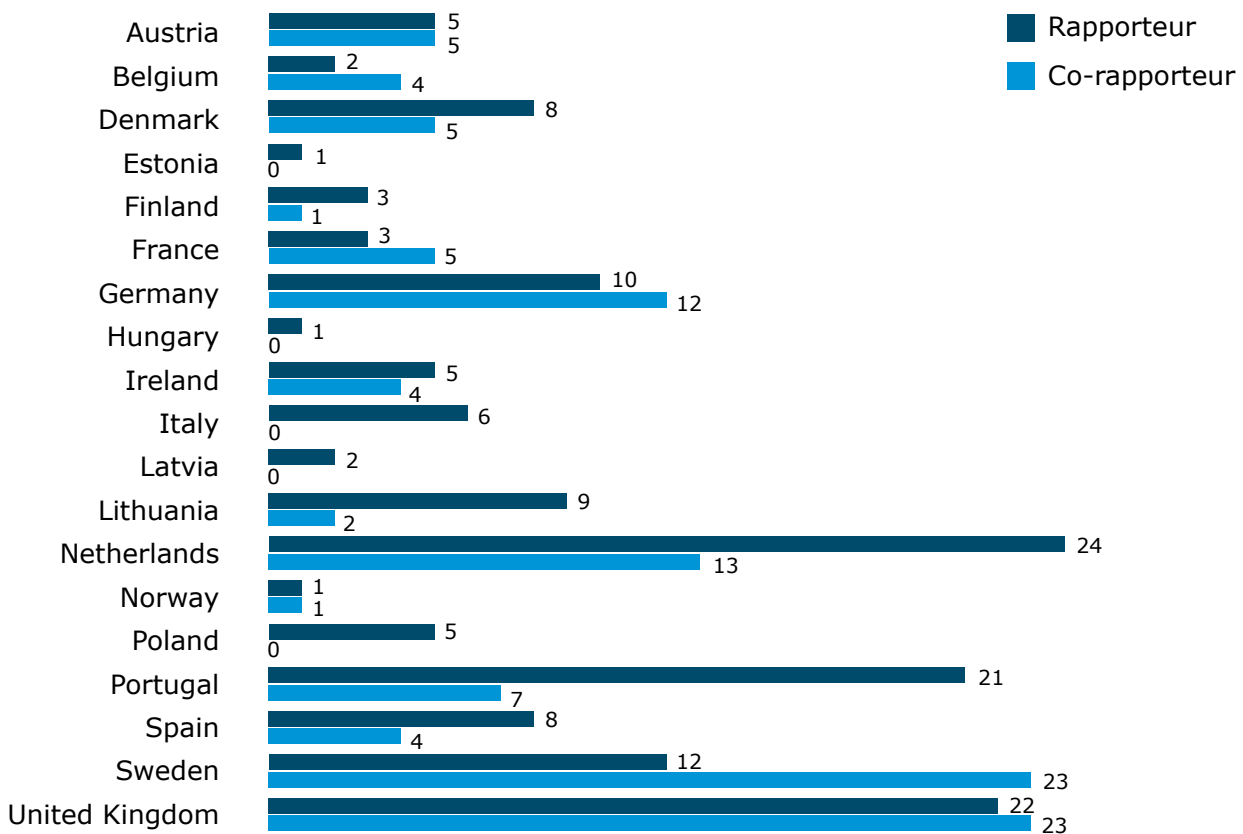
The network gives the Agency access to a pool of over 4,500 experts, allowing it to source the best-available scientific expertise for the regulation of medicines in the EU. Experts participate in the work of the Agency as members of its seven scientific committees, 26 working parties, nine scientific advisory groups and a number of other ad-hoc advisory groups as well as part of the assessment teams carrying out the evaluation of medicines (see annexes for further information on these groups).

#### 3.3.1 Rapporteurships/co-rapporteurships

The assessment of a medicine by EMA’s scientific committees is carried out by a rapporteur and a co-rapporteur who prepare the assessment reports and lead the discussions in the committees.

#### PRAC rapporteurships/co-rapporteurships

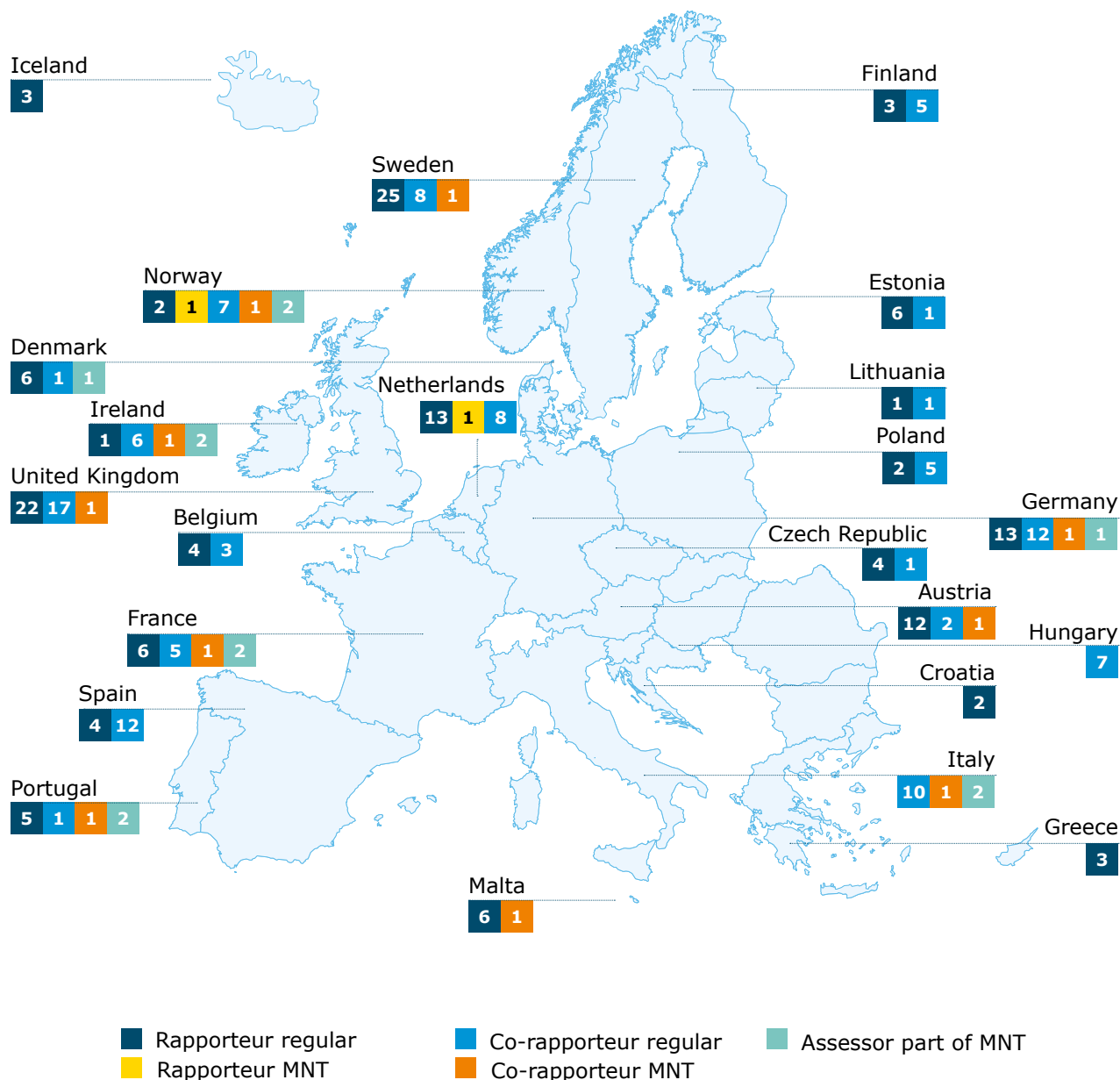
PRAC RAPPORTEURS/CO-RAPPORTEURS APPOINTED IN 2015



### CHMP rapporteurships/co-rapporteurships

Since 2015, CHMP rapporteurs and co-rapporteurs have had the possibility of forming multinational teams (MNT) for the initial assessment of marketing authorisation applications. This is an extension of a scheme focusing on co-rapporteurship that started in 2013. The table below presents the number of procedures in which each country was involved, either as a regular rapporteur or co-rapporteur, as a rapporteur or co-rapporteur leading a multinational team, or as an assessor as part of a multinational team.

#### CHMP RAPPORTEURS/CO-RAPPORTEURS APPOINTED IN 2015 (INCL. MULTINATIONAL TEAMS)

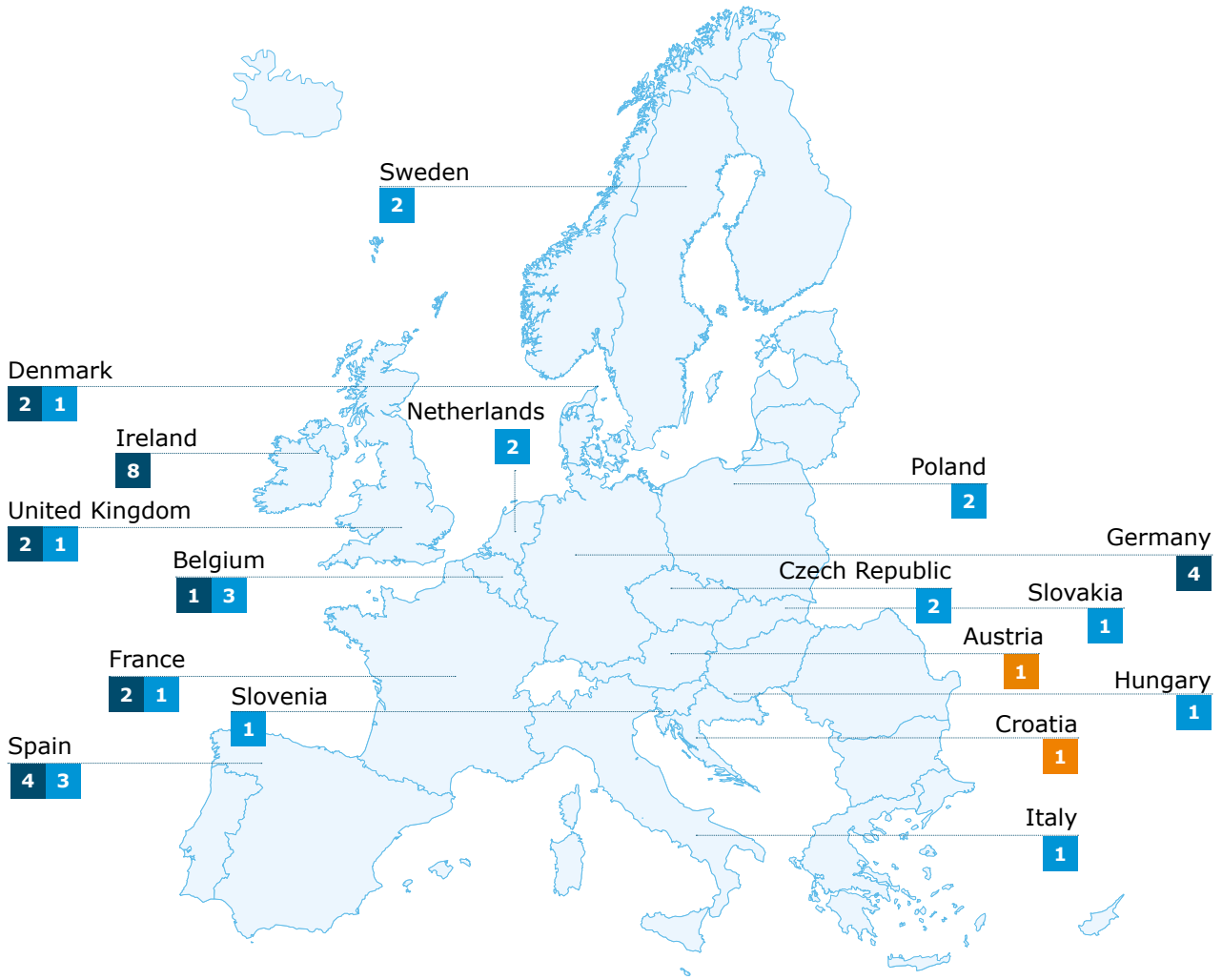




**CVMP rapporteurships/co-rapporteurships**

The concept of multinational teams was also introduced at the CVMP in 2015.

**CVMP RAPPORTEURS/CO-RAPPORTEURS APPOINTED IN 2015 (INCL. MULTINATIONAL TEAMS)**



Rapporteur regular  
 Co-rapporteur regular  
 Assessor part of MNT  
 Rapporteur MNT  
 Co-rapporteur MNT

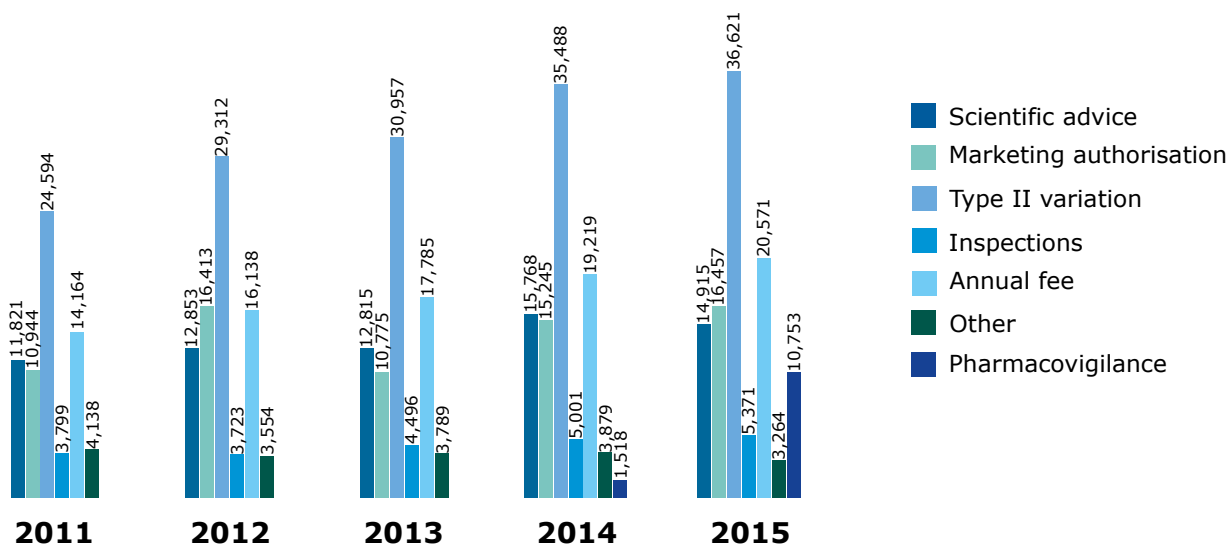
Correction:

19/05/2016 - The numbers for Austria, Czech Republic and Slovenia were updated.

### 3.3.2 Remuneration to national competent authorities (NCAs) for evaluation activities

The national competent authorities in the EU Member States receive a share of EMA’s revenue from fees for the assessments they carry out on behalf of the Agency.

REMUNERATION TO NATIONAL COMPETENT AUTHORITIES PER FISCAL YEAR (IN THOUSANDS OF EUROS) (2011-2015)



In 2015, a total of €108 million were committed by EMA for payments to the national competent authorities (compared to €96 million in 2014).

This sum includes remuneration for pharmacovigilance procedures, including the assessment of periodic safety update reports, of post-authorisation safety study (PASS) protocols and study results, and of pharmacovigilance-related referrals, for which fees were first charged in August 2014. They are charged to companies whose medicines, whether centrally or nationally authorised, are included in these procedures.

### 3.4 Inspections and compliance

The Agency coordinates the verification of compliance with the principles of good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), good pharmacovigilance practice (GVP), and certain aspects of the supervision of authorised medicinal products in the EU. The main verification tool is 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.

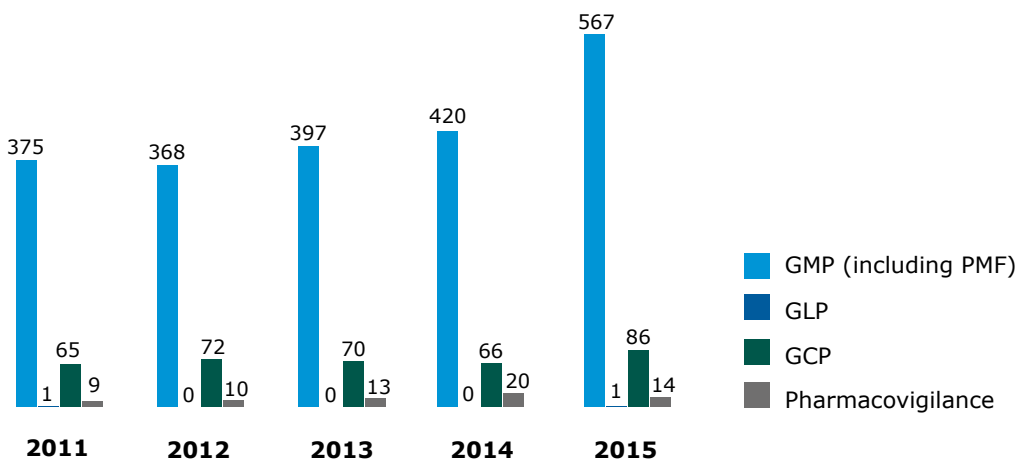
The Agency is the primary contact point for notification and coordination of the investigation, evaluation and follow-up of suspected quality defects for centrally authorised medicinal products.

EMA also operates a sampling and testing programme to supervise the quality of centrally authorised medicinal products placed on the market and to check compliance of these products with their authorised specifications.

#### 3.4.1 Inspections

In 2015, GMP, GCP and pharmacovigilance inspections requested by the CHMP or CVMP were carried out worldwide. The number of GMP inspections increased by 35% in 2015, linked to the growing number of centrally authorised products, and due to peak activity in the first quarter related to inspections requested in 2014.

NUMBER OF INSPECTIONS (2011-2015)



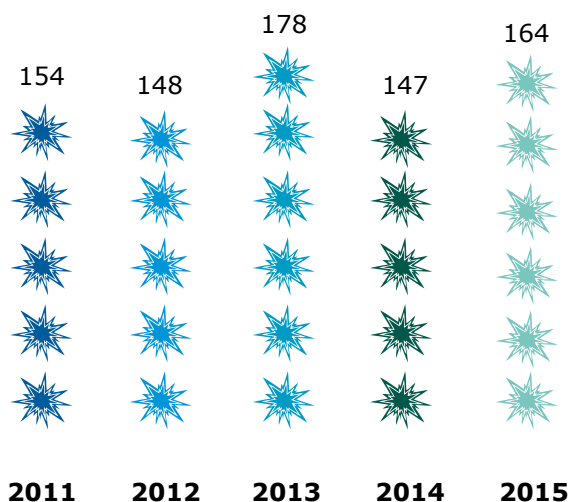
Where inspections produce findings, companies have to implement corrective action plans agreed with inspectors.

- One GMP inspection led to a GMP non-compliance statement preventing the manufacturing site from supplying a centrally authorised medicine in the EU (Inductos).
- GCP inspections led to the withdrawal of three marketing-authorisation applications prior to an opinion by the CHMP (Aripiprazole Mylan, Duloxetine Sandoz and Veraseal).
- GCP inspection of a contract research organisation (CRO) led to the suspension of a number of pharmaceutical forms and strengths of medicines for which authorisation in the EU was primarily based on clinical studies conducted at that site.

### Quality defects

Manufacturers are required to inform authorities of quality defects in batches of a manufactured product which can lead to a recall of batches from the market or prevention of their release by the manufacturer.

#### NUMBER OF QUALITY DEFECTS (2011-2015)



Where a defect is considered to be a risk to public or animal health, the marketing authorisation holder is requested to withdraw the affected batches of the centrally authorised product from the EU market and the supervisory authority issues a rapid alert. The alert is classified from 1 to 3 depending on the expected risk presented to the public or animal health by the defective product:

- Class 1 recalls: the defect presents a life-threatening or serious risk to health;
- Class 2 recalls: the defect may cause mistreatment or harm to the patient or animal, but it is not life threatening or serious;
- Class 3 recalls: the defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the MA or specification.

	2014	2015
<b>Class 1 recalls</b>	2	1
<b>Class 2 recalls</b>	8	3
<b>Class 3 recalls</b>	4	11

**Parallel distribution**

EMA checks that the parallel distribution of centrally authorised medicines from one Member State to another by a pharmaceutical company independent of the marketing authorisation holder is compliant with the rules.

In 2015, annual updates continued to rise since their introduction in 2013. This enables companies to combine all scopes of changes occurring within one year to one pharmaceutical form of medicinal products with one Member State of destination in one procedure.

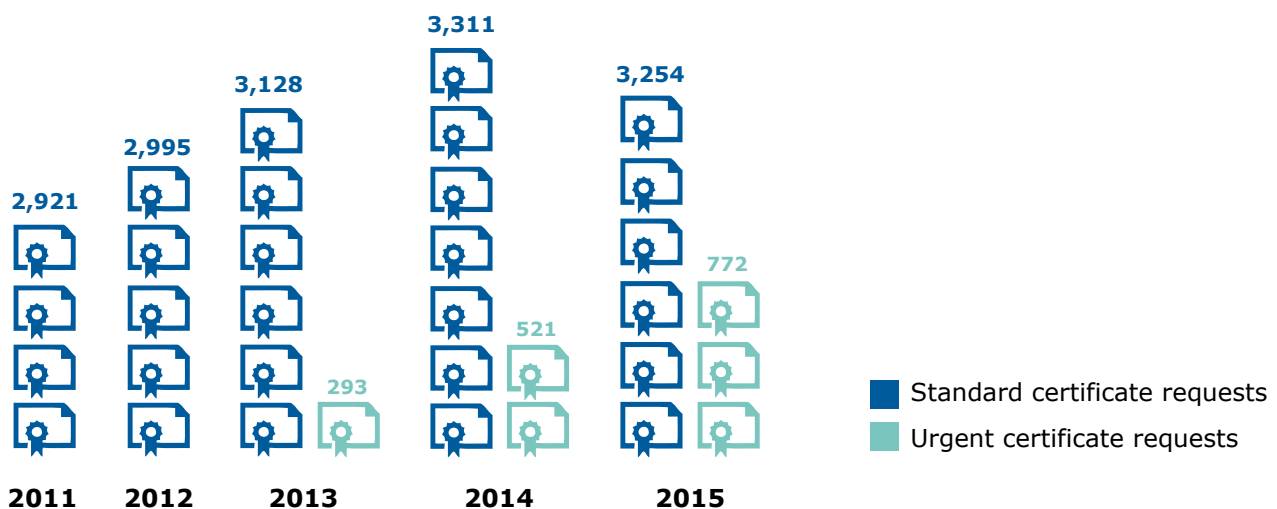
Parallel distribution notifications received					
	2011	2012	2013	2014	2015
<b>Initial notifications</b>	2,551	2,388	2,532	2,492	2,838
<b>Notifications of change</b>	2,150	3,264	2,563	1,295	2,096
<b>Notifications of bulk change</b>	0	0	1	9	13
<b>Annual updates</b>	0	0	1,279	2,339	4,550*
<b>Total</b>	4,701	5,652	6,375	6,135	9,497

\* 560 parallel distribution annual update notifications received in 2014 but processed in 2015 are included in the 2015 figure

**Certificates**

The Agency also 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.

**CERTIFICATES (2011-2015)**

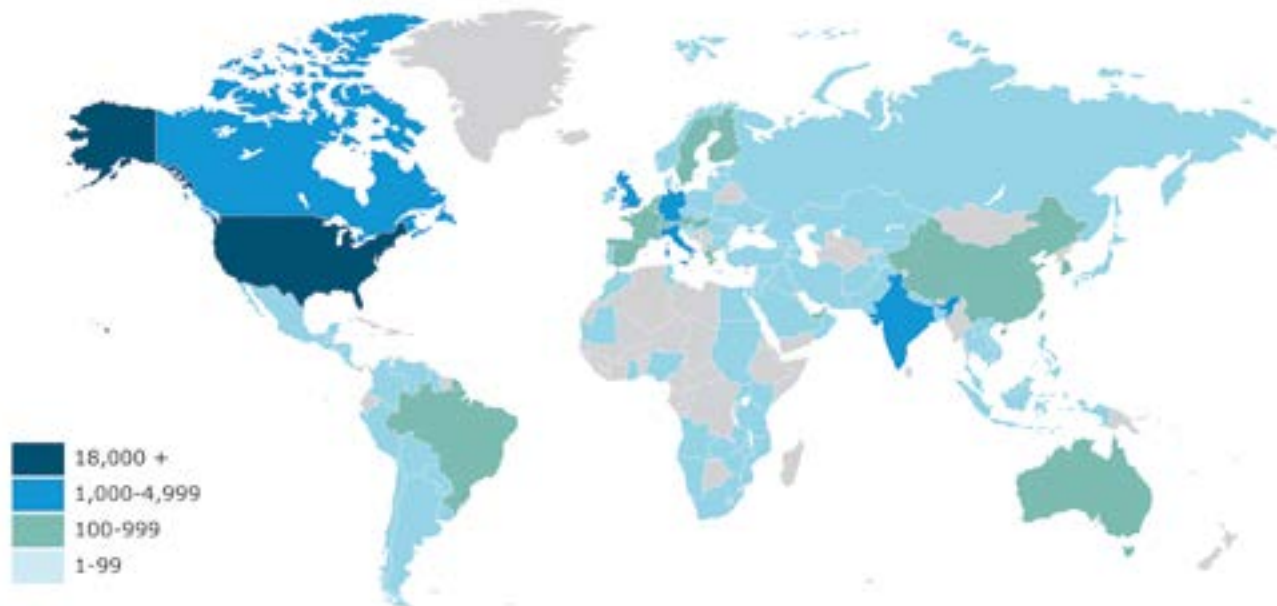


### 3.5 Communication

In 2015, EMA published 190 news releases. EMA’s scientific opinion on the first malaria vaccine Mosquirix, and the suspension of medicines following an inspection of a GVK biosciences’ site generated a lot of media attention. In addition, the Agency’s recommendation on HPV vaccines triggered much coverage, mainly in northern Europe. In total, EMA was mentioned over 32,000 times around the world last year.

The below map shows the number of articles mentioning EMA worldwide.

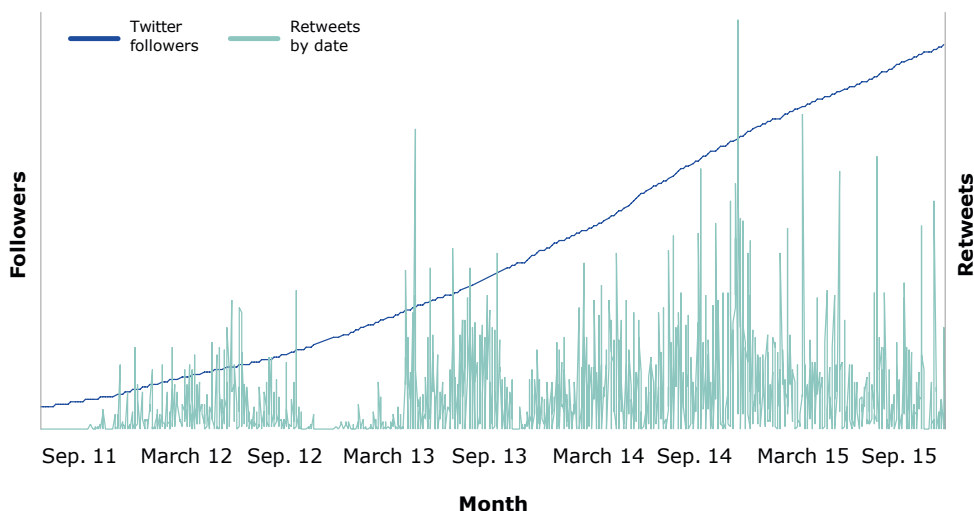
#### EMA IN THE MEDIA AROUND THE WORLD



#### Social media

At the end of 2015, EMA had approximately 19,500 followers on Twitter, an increase of 30% compared to 2014. The chart below shows the number of followers of @EMA\_news and retweets in 2015.

#### EMA TWITTER FOLLOWERS AND NUMBER OF RETWEETS



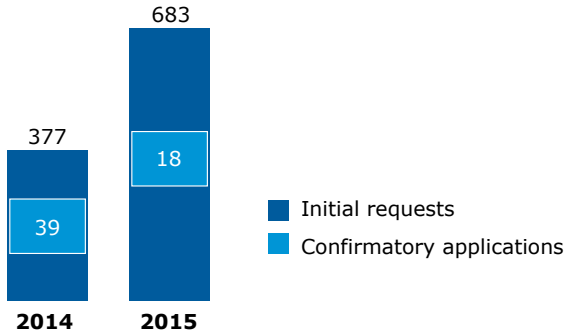
### 3.6 Administrative aspects

#### 3.6.1 Requests for access to documents

EU citizens have a right of access to documents held by EU institutions, bodies, offices and agencies. EMA grants this access according to the principles and further conditions as defined by the Regulation (EC) No 1049/2001 and its policy on access to documents.

There was a sharp rise in the number of requests for access to documents received by EMA in 2015<sup>6</sup>.

#### REQUESTS FOR ACCESS TO DOCUMENTS RECEIVED (2014-2015)

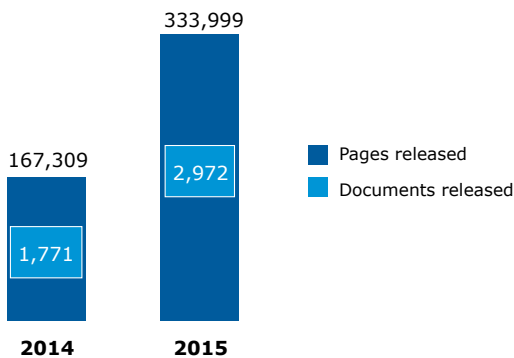


Requests for access to documents closed				
Decision	2014		2015	
	Initial requests	Confirmatory applications	Initial requests	Confirmatory applications
Fully granted	236	25	446	5
Partially granted (with redactions)	13	1	8	1
Refused	62	16	48	10
<b>Total</b>	<b>311</b>	<b>42</b>	<b>502</b>	<b>16</b>

Some of the initial requests were ongoing at the end of 2015.

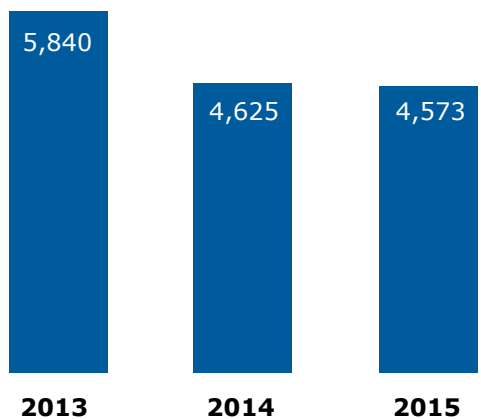
Confirmatory applications can be submitted by requesters whose initial request for access to documents was refused. Such applications are submitted directly to the EMA Executive Director for reconsideration.

#### PAGES RELEASED FOLLOWING ACCESS TO DOCUMENTS REQUESTS (2014-2015)

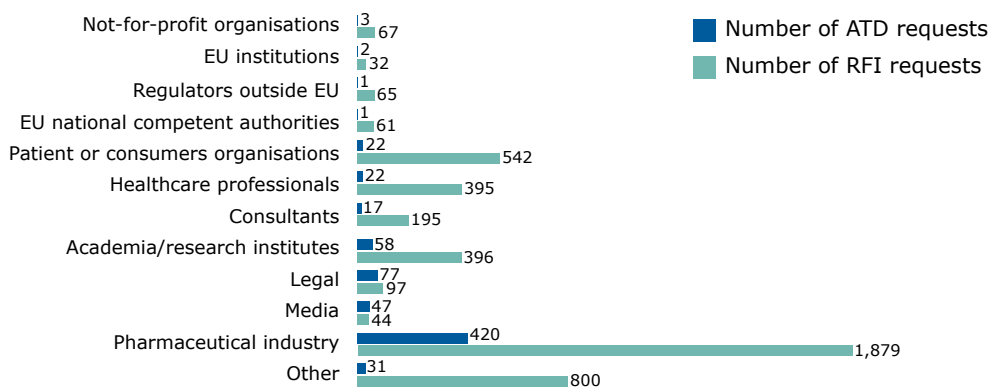


<sup>6</sup>) More information on access to documents can be found in annex 20.

REQUESTS FOR INFORMATION (2013-2015)



AFFILIATION OF ACCESS-TO-DOCUMENTS AND REQUESTS-FOR-INFORMATION REQUESTERS

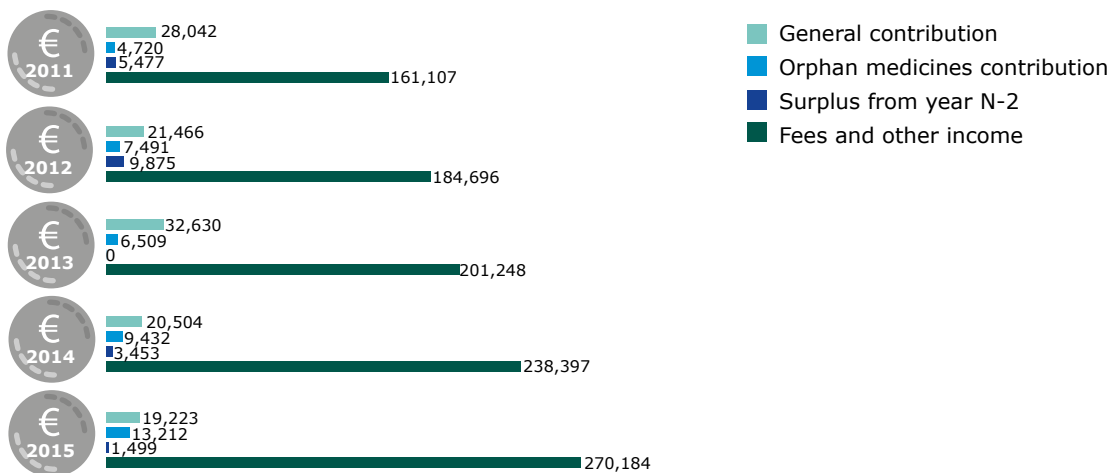


More information on access to documents can be found in annex 20.

3.6.2 Budget execution

The total revenue of the Agency in 2015 was €304.119 million, representing a 12% increase compared to 2014 (€271.786 million). This increase is mainly due to the implementation of the pharmacovigilance fee regulation<sup>7</sup> in August 2014.

REVENUE (IN THOUSANDS OF EUROS)



<sup>7</sup>) Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ L 189 p. 112 27.06.2014.



EXPENDITURE (IN THOUSANDS OF EUROS)

Expenditure	2011	2012	2013	2014	2015
Staff expenditure	72,539	75,251	77,552	91,344	103,651
Infrastructure	31,613	30,817	62,056	55,251	49,422
Operational expenditure	97,912	112,790	103,811	119,825	142,082

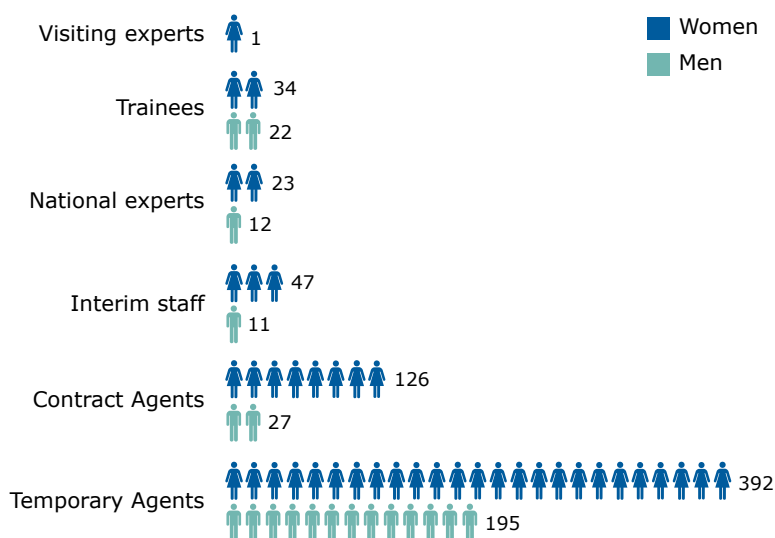
Environmental reporting

The EMA office building in Churchill Place in Canary Wharf, London includes many environmentally friendly features, such as photovoltaic (or solar) cells and a 'green' roof to enhance biodiversity. It achieves a new standard for environmental performance and energy efficiency in London and the design was awarded a Building Research Establishment Environmental Assessment Methodology (BREEAM) 'excellent' rating. The environmental rating is also confirmed by the Energy Performance Asset Rating B.

KPI	Description	Units	2012	2013	2014*	2015
Energy efficiency	Electricity consumption	kWh	3,414,782	3,406,245	3,069,676	3,546,829
		kWh/m <sup>2</sup>	164	163	135	145
Resource efficiency	Water consumption	m <sup>3</sup>	3,053	5,130	2,585	2,607
	Paper consumption	metric tonnes	41	42	41	27
Waste management	Recycled waste	metric tonnes	63	67	53	73
	Non-recyclable waste	metric tonnes	88	87	59	54
Carbon footprint	Greenhouse gas emissions	tonnes CO <sub>2</sub> e	2,618	2,679	2,601	2,843

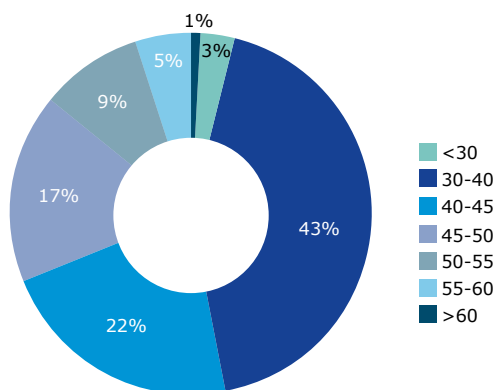
\* Please note that the Agency moved to new premises in 2014, therefore the metrics and calculations changed during the year.

AGENCY STAFF (31 DECEMBER 2015)

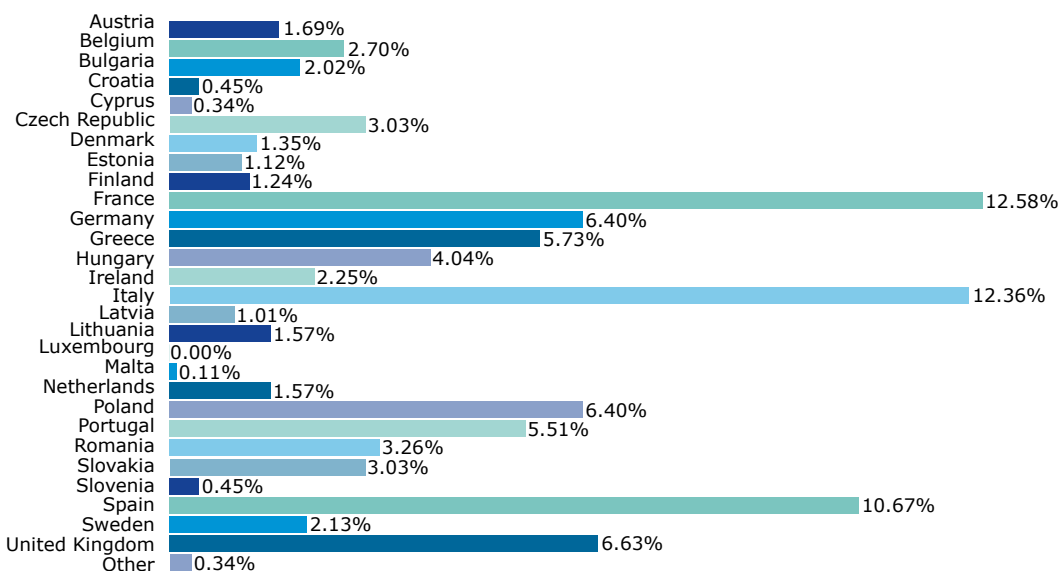


The total number of Agency staff as of December 2015 was 890 (623 women, 267 men).

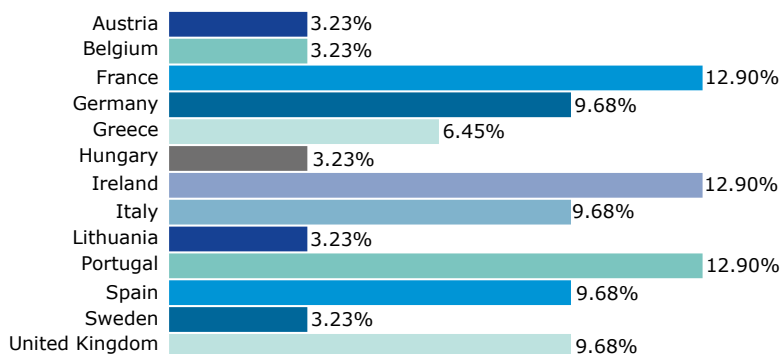
AGE RANGE STATISTICS (31 DECEMBER 2015)



NATIONAL ORIGINS OF AGENCY STAFF (2015)



NATIONAL ORIGINS OF AGENCY MANAGEMENT (2015)



Agency management includes the Agency’s Executive Director, the Deputy Executive Director, Heads of Division, Heads of Department, EMA’s Senior Medical Officer and Heads of Advisory Functions.

## Annexes

Annex 1	Members of the Management Board
Annex 2	Members of the Committee for Medicinal Products for Human Use
Annex 3	Members of the Pharmacovigilance Risk Assessment Committee
Annex 4	Members of the Committee for Medicinal Products for Veterinary Use
Annex 5	Members of the Committee on Orphan Medicinal Products
Annex 6	Members of the Committee on Herbal Medicinal Products
Annex 7	Members of the Committee for Advanced Therapies
Annex 8	Members of the Paediatric Committee
Annex 9	Working parties and working groups
Annex 10	Opinions adopted by the Committee for Medicinal Products for Human Use – initial evaluation
Annex 10a	Opinions adopted by the Committee for Medicinal Products for Human Use – extensions of indication
Annex 10b	Guidelines adopted by the Committee for Medicinal Products for Human Use
Annex 11	Opinions adopted by the Committee for Medicinal Products for Veterinary Use – initial evaluation
Annex 11a	Opinions adopted by the Committee for Medicinal Products for veterinary Use – extensions of indication
Annex 11b	Guidelines adopted by Committee for Medicinal Products for Veterinary Use
Annex 12	Opinions adopted by the Committee on Orphan Medicinal Products
Annex 13	European Union herbal monographs in 2015
Annex 14	Paediatric Committee opinions and EMA decisions on paediatric investigation plans and waivers in 2015
Annex 15	Referral procedures overview 2015 – human medicines
Annex 16	Arbitrations and referrals in 2015 – veterinary medicines
Annex 17	Budget summaries
Annex 18	European Medicines Agency Establishment Plan
Annex 19	Requests for access to documents
Annex 20	Publications by Agency staff members and experts in 2015

These **annexes** can be found on the agency website: ([www.ema.europa.eu](http://www.ema.europa.eu)) *via: About us > How we work > Governance and reporting > Annual reports and work programmes*







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**Annual report 2015**

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