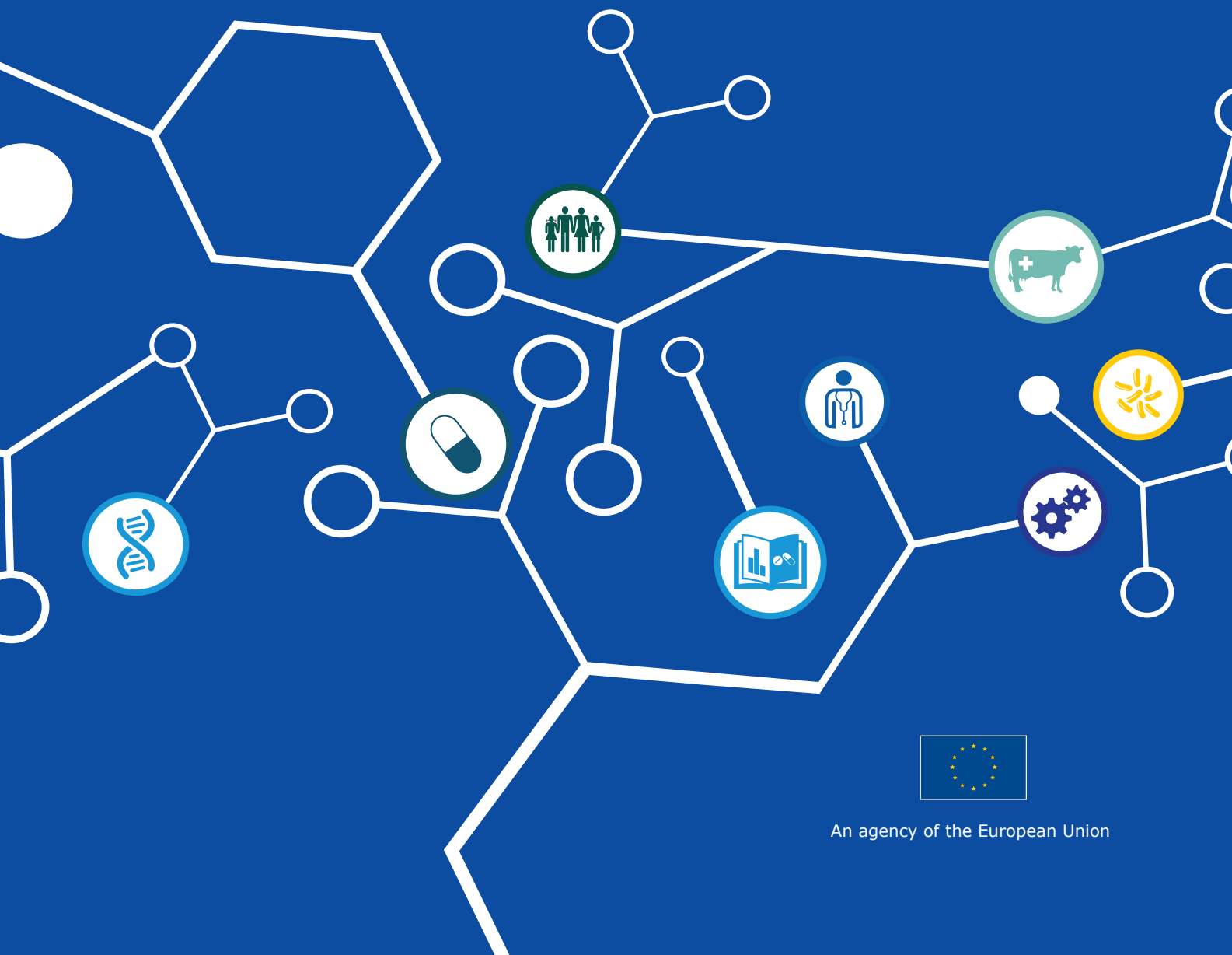




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual Report 2016



An agency of the European Union

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Mission statement

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

Guiding principles

- We are strongly committed to public and animal health.
- We make independent recommendations based on the best scientific evidence, using state-of-the-art knowledge and expertise in our field.
- We support research and innovation to stimulate the development of better medicines.
- We value the contribution made by 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 EU institutions with the best-possible advice on any questions 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 Christa Wirthumer-Hoche
Chair of EMA Management Board



I am pleased to introduce EMA's annual report for 2016 – my first year as Chair of EMA's Management Board.

This report provides an excellent overview of the work done by the Agency together with the national competent authorities of the European Union and the European Commission, which form the European medicines regulatory network. Working together, the network strives to apply the best scientific and regulatory standards to protect and promote the health of all citizens and animals in the EU.

The work of the network is guided by a joint strategy which is built around strategic priority areas where the network can make a concrete difference to human and animal health in the EU.

I would like to highlight a few key areas of activity that demonstrate the commitment to achieving these common goals.

Ensuring that the right scientific expertise is available within the network to respond effectively to new public health challenges is the cornerstone for the success of our activities. In this area, concrete actions took place in 2016 to further enhance the EU Network Training Centre (EU-NTC) and ensure the availability of highly trained experts across the network.

Another milestone is the expansion of the concept of a multinational assessment team for the evaluation of medicines. For a few years now, this approach has meant that assessment teams are formed not by country but based on expertise, thereby optimising the use of resources throughout the European regulatory system. This concept was extended to post-authorisation assessments in 2016.

A further priority area for the network is supporting the development of new medicines addressing public health needs. With the successful launch of PRIME (PRIority Medicines) we have introduced a scheme in Europe which brings together the expertise of all EMA's scientific committees to best support promising medicines that have the potential to address unmet medical needs.

In 2016, a lot of work was also done behind the scenes to prepare for the implementation of the new European Clinical Trial Regulation which opens up a new era for carrying out clinical trials in the EU. The Board has closely monitored the ongoing development of the EU's clinical trial portal and database, a system that will provide a single platform for the submission and maintenance of clinical trial applications and authorisations, and supports their coordinated assessment and supervision. It is of the utmost importance for the Board to ensure that the system is available for the network and to stakeholders within the agreed time frame.

Following the outcome of the UK referendum, which brings an unprecedented level of uncertainty regarding the Agency's future operations and location, EMA reacted promptly by setting up a task force to prepare for possible scenarios. As chair of the Management Board, I am committed together with the Board to supporting EMA to ensure we achieve the right circumstances in which the Agency can continue its valuable work to protect public and animal health and support innovation in Europe.

Finally, I wish to express my appreciation for the work done by EMA staff during 2016 under the leadership of Guido Rasi.

Introduction

by Guido Rasi
EMA Executive Director



2016 was a challenging year for EMA. It was a year in which we firmly demonstrated our commitment to put the needs of patients at the centre of everything we do in the European medicines regulatory system. But it was also a year in which we were confronted with a decision that will potentially result in the Agency and its staff leaving London and the UK and moving to another country and city in Europe. But first things first: let me highlight just a few of the initiatives on which, together with our partners in the national competent authorities and the European Commission, we have made progress on in 2016.

We looked at ways to facilitate and promote drug development for the benefit of patients who are in desperate need of new or better treatments. The key initiative in 2016 was the launch of PRIME (PRIority MEDicines), a new scheme through which we give early, proactive and enhanced support to those developing medicines that target an unmet medical need. In order to get breakthroughs in medicines to patients more quickly, PRIME aims to foster better planning of medicine development. This will help companies to generate the high-quality data we need to assess the quality, safety and efficacy of medicines. Patients and their families who have long been hoping for earlier access to safe treatments for diseases, such as rare cancers, Alzheimer's disease and other dementias, have welcomed our initiative.

We improved our ability to detect, assess and take appropriate actions on medicine safety issues. Throughout the year, with stakeholders and data experts we explored how to harness the power of big data. We investigated how these data can help us to better understand how a medicine performs when used in real life by doctors and patients and support regulatory decision-making throughout its lifespan.

We made recommendations on the safe and sustainable use of antibiotics in animals so as to protect their ability to fight infections in humans and animals. Antimicrobial resistance (AMR) is a global public health challenge and we are working with our partners in and beyond Europe to promote the responsible use of the medicines we have, encourage development of new antibiotics, and collect high-quality data to enable sound decision-making.

Last, but not least, we started publishing the clinical data that support marketing authorisations for new medicines. We are the first regulatory authority in the world to do so and our initiative has shaped the global debate in favour of the transparency of clinical data. Access to comprehensive data will lead to a dramatic increase in accessible knowledge about individual medicines. The new database will allow researchers and academics to use clinical study reports to ask new questions about a medicine, pursue new lines of enquiry and research, and also provide regulators with a more robust evidence base. Our initiative will ultimately benefit the practice of medicines as a whole and will help us to achieve our aim of making available the best-possible medicines to address the medical needs of EU patients.

But, as already mentioned above, 2016 was also a year with huge significance for EMA's future. On 23 June 2016, a majority of UK voters backed leaving the EU. The full consequences of this vote are still unknown and will be determined by negotiations between the EU and UK that will take place in the next few years. At EMA, we are faced with the likely prospect of relocation and loss of expertise.

EMA is a core building block of the common market for medicines in the EU. The Agency can be compared to well-oiled machinery that works like an assembly line bringing together the best experts from across the EU to do the right job at the right time with the right people in the right room. Our scientific recommendations are vital to protect the health of EU citizens, provide them with effective, safe and high-quality medicines, and enable an environment in which European pharmaceutical companies can thrive to develop new medicines and create high-quality jobs across the EU. We cannot afford for this machine to start stuttering.

Therefore, we set up a task force to assess the likely impact of Brexit on EMA operations, and to identify the parameters that are essential for us to continue our operations efficiently in a new location. The decision on the Agency's new host country and city will be taken by the Member States, and the task force is expected to contribute to the decision by identifying our requirements. We want to be ready for a smooth move once the decision has been taken.

The achievements detailed in this annual report give me great confidence that we will successfully overcome the challenges we are facing. The network of European medicines regulatory agencies is strong and flexible. It has demonstrated many times that it can adapt to changes without putting at risk the quality and effectiveness of its scientific work. I would like to thank all those involved in EMA's work for their expertise, passion and their commitment to advancing the health of 500 million EU citizens: the members of the scientific committees, the working parties and scientific advisory groups, the Management Board and all the national experts, the Agency's staff and all our stakeholders who share their views and concerns to help us protect public and animal health.



Chapter 1

Key achievements in 2016

Evaluation and monitoring of medicines

This section provides an overview of EMA's most important recommendations on medicines in 2016.

These include recommendations to grant new EU-wide marketing authorisations for medicines that are expected to bring significant benefits to patients and animals, as well as changes to the conditions of use of existing medicines to ensure they are used in the best possible way by patients, healthcare professionals and veterinarians in the EU.

Human medicines highlights

Bringing significant benefits to patients

In 2016, EMA recommended 81 medicines for marketing authorisation, including 27 new active substances, i.e. substances that have previously never been authorised in a medicine in the EU.

Innovation in healthcare brings new opportunities to treat certain diseases and is essential to advancing public health.

Many of the innovative substances recommended for approval in 2016 build on the advances made in biomedical science and have the potential to make a difference in people's lives. A number of them are complex therapies requiring specialised expertise for their evaluation.

94% of the opinions were reached by consensus among the members of the Committee for Medicinal Products for Human Use (CHMP), meaning that experts could reach an agreement on all aspects of the marketing authorisations through in-depth discussions.

More than half of the applicants who received a positive opinion for their medicine had received scientific advice from EMA during the development phase of their product.

Scientific advice is EMA's key tool for promoting the collection of high-quality data and helping to ensure that patients take part in clinical trials that are robust enough to support a marketing authorisation application.



A gene therapy (**Strimvelis**) for children born with an ultra-rare disorder (ADA-SCID) who have virtually no immunity was recommended for approval in 2016. The therapy helps patient cells develop into different types of immune cells that can fight off everyday infections.



A cell-based therapy containing genetically modified T-cells (**Zalmoxis**) aids immune reconstitution and reduces the risk of graft-versus-host disease in patients receiving a transplant to treat serious blood diseases.



A new treatment option (**Zavicefta**) helps fight multi-drug resistant bacteria: the combination of two antibiotics with different mechanisms of action is effective against many of the carbapenem-resistant Enterobacteriaceae. As patients currently have very few options available to them due to the increasing resistance to anti-infectives, there is an important need for new treatments.



EMA also adopted a positive opinion on a medicine to be used outside the EU (**Umbipro**) under its joint evaluation programme with the World Health Organization (WHO) (Article 58). The antiseptic gel helps prevent umbilical cord infections in newborn babies.

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

In 2016, more than one in three medicines containing a new active substance was recommended for approval using at least one of EMA's tools to facilitate early access to medicines that address unmet medical needs.

Seven new medicines were recommended for marketing authorisation following a review under accelerated assessment; this mechanism allows for a faster assessment of eligible medicines by the EMA's scientific committees (within 150 days rather than up to 210 days).

Eight medicines received a recommendation for a conditional marketing authorisation. This tool enables the early approval of a medicine that addresses an unmet clinical need 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.

Many of the innovative substances recommended for approval in 2016 build on the advances made in biomedical science and have the potential to make a difference in people's lives.

Protecting public health

Once a medicine has been put on the market, EMA and the EU Member States continuously monitor the benefits and risks that patients experience with this medicine in real life.

This is to ensure that the medicine is used in the best possible way for patients in the EU. Regulatory measures range from a change in the product information to the suspension or withdrawal of a medicine if evidence collected during the post-authorisation phase leads to the conclusion that the medicine's risks have come to outweigh its benefits.

Product information for over 300 medicines was updated on the basis of new safety data. The revised information is expected to enable patients and healthcare professionals to make informed decisions when using or prescribing a medicine.

In 2016, new contra-indications were included for Adempas, a medicine for patients with certain forms of pulmonary hypertension. Stronger warnings were introduced for Noxafil to avoid medication errors between two different dosages of the medicine.

New recommendations to minimise the risks of certain side effects were adopted for diabetes medicines containing SGLT2 inhibitors, the multiple sclerosis medicine Tysabri, and the anticancer medicine Zydrelig.

As medicine development and manufacturing becomes increasingly globalised, it is essential for regulators to ensure that EU standards are adhered to no matter where the clinical trials or manufacturing take place. In 2016, a number of marketing authorisations were either suspended or not granted as a result of serious non-compliance with good clinical practice. In addition, the supply of certain medicines to the EU was stopped and some marketing authorisation applications were withdrawn when serious non-compliance with good manufacturing practice (GMP) was identified during inspections.



Veterinary medicines highlights

New medicines to progress animal health in Europe

In 2016, EMA recommended 11 new veterinary medicines for marketing authorisation; six of these contain a new active substance.

Almost one in three medicines recommended for approval prevent viral or bacterial infections in food-producing animals. Among these is the first DNA vaccine (Clynav) to protect Atlantic salmon against salmon pancreas disease caused by salmon alphavirus subtype 3, a serious infectious disease which can kill salmon. A vaccine to protect rabbits against a new subtype of a viral infection for which all vaccinations were previously ineffective (Eravac) is also available now.

A new antiparasitic medicine (VarroMed) can treat the Varroa mite infestation in honey bee colonies, which is considered to be the most significant parasitic health concern affecting honey bees worldwide.

VarroMed, Eravac and Clynav, as well as Letifend – a biotechnological vaccine to protect dogs against leishmaniasis – were recommended for marketing authorisation under the EMA's minor-use-minor-species (MUMS)/limited market programme. This scheme aims to stimulate development of new veterinary medicines for minor species and for rare diseases in major species that would otherwise not be developed under current market conditions.

Two additional vaccines (Evalon and Coliprotec F4/F18) have the potential to reduce the need for antimicrobial treatment in food-producing animals and therefore to limit the development of antimicrobial resistance. Evalon protects chickens against coccidial infections which are currently widely treated with antimicrobial substances that can induce resistance. Coliprotec F4/F18 protects pigs against post-weaning diarrhoea caused by enterotoxigenic *E.coli*.



Clynav



Eravac



VarroMed



Evalon



Coliprotec



Letifend



Monitoring in real life – optimising the 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 both human and animal health and for the environment.

In 2016, Velactis, a medicine used in dairy cows as an aid to reducing milk production, was suspended after serious adverse events were reported in cattle.

Another important recommendation in 2016 was that all medicines containing colistin in combination with other antimicrobials to be administered orally were recommended to be withdrawn from the market. This is part of the overall strategy to promote the responsible use of the last-resort antibiotic colistin and limit the development of resistance.

To protect the environment, EMA recommended measures to make sure that altrenogest, a steroidal hormone for pigs, has no adverse effects on the reproduction of aquatic organisms. In addition, the Agency recommended the refusal of marketing authorisations and the withdrawal of currently authorised medicines containing zinc oxide used in medicated feeding stuff for piglets, as they increase zinc concentrations in soils to levels considered harmful for the environment.



EMA recommended **11 new veterinary medicines** for marketing authorisation; six of these medicines contain a new active substance.

1 in 3

medicines recommended for approval prevent viral or bacterial infections in food-producing animals.

Advancing human health

The Agency firmly places patients' needs at the centre of everything it does.

It encourages and supports the development of new medicines and vaccines to promote timely access to new beneficial and safe treatments. It also puts in place measures to ensure that EU citizens are protected against major public health threats, such as growing antimicrobial resistance or existing and new infectious diseases. At the same time, the Agency monitors the safety of all medicines marketed in Europe across their lifespan to protect patient health and ensure that the medicines continue to benefit patients.

Supporting development of promising or much-needed medicines for patients

EMA, together with its committees and working parties, plays a key role in ensuring that the right tests and studies are conducted to provide the robust data needed to support marketing authorisation applications. In 2016, the Agency launched a number of initiatives which aim to foster better planning and better design of medicine development so that promising new medicines can reach patients as early as possible without compromising patient safety.

Successful launch of PRIME

In March 2016, EMA launched PRIME (PRIority Medicines), a new scheme providing early and enhanced support to medicines that have the potential to address patients' unmet needs.

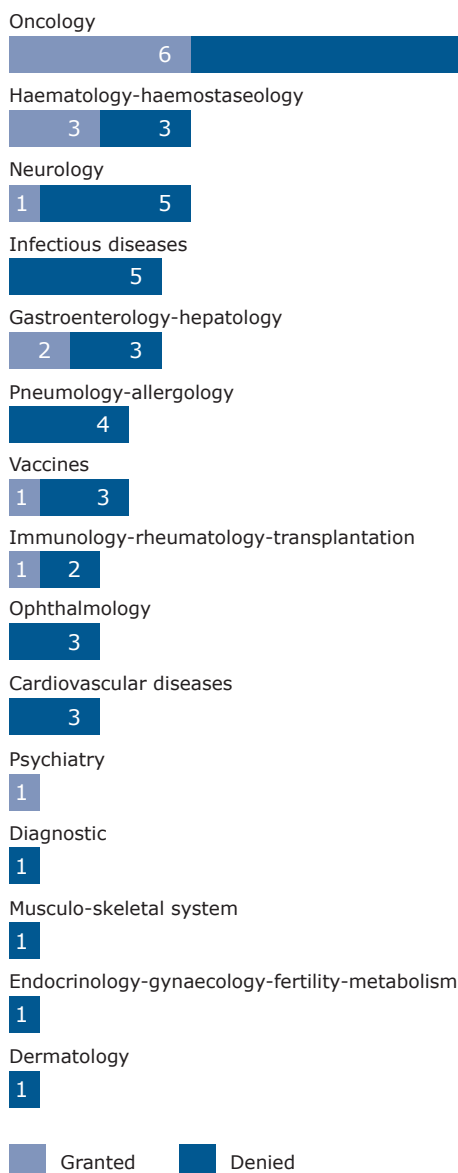
The scheme helps those developing promising medicines to optimise their development plans, collect robust data and submit high-quality marketing authorisation applications, so that these treatments can be authorised in a timely manner for the benefit of patients.

Companies wishing to receive PRIME support need to submit an application showing that their medicine addresses an unmet medical need and including data which demonstrate that it could bring a major therapeutic advantage to patients.

Most applications for PRIME received in 2016 were for cancer medicines; among them were promising innovative immunotherapy medicines based on genetically modified T-cells (called CAR T-cells).

PRIME has received a lot of interest, as evidenced by the high number of applications. As the programme is intended for the most promising medicines, only a relatively small number have been accepted in the scheme so far.

PRIME requests granted and denied



84

PRIME applications received in 2016 –
one in two from SMEs

15

medicines granted PRIME,
of which 10 are advanced therapies

Exploring adaptive pathways together with stakeholders

Throughout 2016, the Agency continued to explore adaptive pathways, a product development and data-gathering approach for medicines that aim to address patients' unmet needs. In August 2016, EMA completed a two-year pilot project that explored how the adaptive pathways concept can be applied in practice. The experience from the pilot was discussed with stakeholders during a workshop held in December 2016 and organised together with the European Commission.

Adaptive pathways can be defined as a structured approach aspiring to bring a medicine to patients in a progressive manner. Under this approach, the medicine will initially be authorised in a small patient population that is likely to benefit most from it. Then, additional evidence is gathered over time, potentially resulting in changes to the marketing authorisation reflecting the expanded knowledge acquired.

The adaptive pathways approach involves working with the full range of relevant stakeholders from very early in the development process to proactively plan the most appropriate ways of obtaining evidence. It also identifies the most appropriate tools to generate that evidence. This may mean making more use of observational (real-world) data to supplement randomised controlled trials, especially where the latter alone are inadequate.

The workshop tackled important questions arising from the adaptive pathways pilot, including how best to address patients' needs and expectations; how to generate appropriate data to aid medicine evaluation; and how to ensure that high standards for approval in the EU continue to be met.



“Adaptive pathways is a response to problems which have long existed in medicines regulation but have grown more acute in recent years. One such problem is the access-versus-evidence conundrum: on the one hand, there are patients today with serious illnesses for whom time is of the essence, while on the other there are patients in the future for whom complete knowledge of benefits and risks will be paramount.”

Hans-Georg Eichler
EMA Senior Medical Officer

EMA took stock of the different views expressed by its stakeholders. The Agency will integrate the learnings from the pilot and the feedback from stakeholders into its existing mechanism of scientific advice, which can bring together health technology assessment (HTA) bodies, patients and healthcare professionals.

Medicine developers interested in following the adaptive pathways approach can submit a proposal to EMA.

The Agency will provide regular updates on the experience gained and will continue dialogue with its stakeholders through various fora.

Collaborating with HTA bodies

In 2016, EMA started offering parallel scientific advice with HTA bodies on a routine basis as part of the Agency's scientific advice activities. This joint scientific advice is based on the experience gained from a five-year pilot project enabling developers of new medicines to receive simultaneous feedback on their development plans from both EMA and HTA bodies. Sixty-three parallel scientific advice procedures were included in the pilot and a report showed that such procedures achieved a high level of alignment between the data requirements of both the regulators and HTA bodies.

EMA published a consolidated best practice guide which sets out the different phases of the process for regulatory-HTA parallel scientific advice and highlights ideal timelines and actions for all parties involved. This guide, together with a document giving an overview of the HTA bodies that have participated in this EMA initiative to date, provides comprehensive information on the procedure.

Parallel scientific advice is one of the Agency's key initiatives to improve patient access to important new medicines because it ensures that medicine development programmes generate appropriate data for regulators and HTA bodies and allow for the assessment of both benefit-risk balance and added value. This can reduce delays between a medicine's marketing authorisation for the European market and decisions on reimbursement that are taken at the national level.

Towards a global approach to support the development of new antibiotics

The emergence of antimicrobial resistance is a major public health concern. It has been estimated that infections from multidrug-resistant bacteria cause 25,000 deaths in the EU every year.

New antibiotics are urgently needed to treat patients with serious infections caused by pathogenic bacterial strains. A central pillar in EMA's strategy to fight

antimicrobial resistance is the creation of an environment that stimulates and facilitates the development of new antibiotics.

In September 2016, EMA, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the United States' Food and Drug Administration (FDA) met at the EMA premises to discuss regulatory approaches for the evaluation of new antibacterial agents. The conclusions from this meeting were presented at the G7 Health Ministers' meeting organised by the government of Japan in Kobe on 11-12 September 2016.

The three agencies:

- agreed that some flexibility should be applied to the requirements for clinical development programmes for antibacterial agents, in particular where treatment options for patients are limited due to antimicrobial resistance;
- reiterated that it may be appropriate to accept abbreviated clinical development programmes for new antibiotics that can address an unmet need related to antimicrobial resistance;
- agreed that alignment of data requirements by regulators worldwide can contribute to stimulating the development of new antibiotics and protecting global public health.

At the end of 2016, EMA and FDA discussed the establishment of a joint working group to consider in more detail clinical development and data requirement aspects in the context of concrete applications for new antibiotics.

Supporting the development of medicines for dementia

Dementia is a key public health priority and follows a multi-stakeholder approach to facilitate research and development of more effective medicines. Alzheimer's disease is the most common cause of dementia in the elderly, affecting more than 5 million people in the EU.

Medicines available today for Alzheimer's disease only treat the symptoms of the disease. Despite active research and development in this field, no medicines targeting the underlying causes of the disease have been approved so far and a number of drug candidates failed in clinical trials.

Through a data-sharing initiative launched by EMA, open discussions took place with medicine developers to identify the reasons for these failures.

The initiative offered a platform to discuss key issues occurring during their development with companies from across the globe as well as regulators from Canada, Japan and the United States.

These insights will inform the revision of a guideline on medicines for the treatment of Alzheimer's disease and other types of dementia which is currently under way.

Advanced therapies workshop

In May 2016, EMA organised a multi-stakeholder expert meeting to explore possible ways to foster the development of advanced therapy medicinal products (ATMPs) in Europe and expand patients' access to these new treatments.

ATMPs comprise gene therapies, tissue-engineered products and somatic cell therapies. These medicines have the potential to reshape the treatment of a wide range of conditions, particularly in disease areas where conventional approaches have proven to be inadequate. However, since the EU legislation on ATMPs entered into force in 2008, only eight ATMPs have been authorised. At the same time, clinical trials investigating ATMPs represent a fast-growing field of interest, underlining the need to better support innovation through a coherent and appropriate regulatory environment.

The discussion focused on:

- facilitation of research and development;
- optimisation of regulatory processes for ATMPs;
- the move from hospital exemption to marketing authorisation;
- improvements in funding, investment and patient access.

Based on the ideas and solutions proposed, EMA and its scientific committees, together with the European Commission and the national competent authorities, are developing an action plan to be published in 2017.

“

We have organised this meeting with all relevant stakeholders to discuss concrete proposals on how we can nurture a regulatory environment that encourages development of ATMPs, safeguards public health and, ultimately, facilitates timely access for patients to much-needed treatments.”

Guido Rasi

EMA Executive Director

Smart regulation for safer medicines

To fulfil its mission to promote and protect public health and ensure the safety of medicines authorised in the EU, EMA strives to constantly reflect on and improve its processes and regulatory standards for the more efficient monitoring of medicines across their life cycle. For the Agency, this means engaging in new areas of emerging science, such as big data applied to healthcare, finding ways to measure the impact of the decisions it takes to ensure that they have been effective, and contributing to improving the safety monitoring standards for medicines through research in regulatory science.

Real-world data: filling knowledge gaps

In 2016, the Agency explored ways to improve the knowledge and use of real-world data. This can be defined as healthcare-related data which are collected outside the limitations of conventional randomised clinical trials. The range is wide and includes sources such as electronic health records, registries, hospital records and health insurance data. Increasingly, other data, including biobank, genomic and digital phenotyping information, are being integrated into real-world data sets.

Regulators need real-world data throughout the post-marketing decision-making process, for example to support pharmacovigilance activities, assess safety signals and measure the impact of regulatory measures, understand the benefit-risk balance and effectiveness of medicines, inform on resource utilisation, and support HTA decisions.

While such data are currently used predominantly in the post-marketing phase, there is a growing focus on their use throughout a medicine's entire lifespan. However, difficulties remain in accessing these data and methodological challenges associated with their integration and analysis.

One of the Agency's most advanced projects in this field concerns patient registries. Registries collect information over time on patients who are diagnosed with a particular disease or who receive particular treatment(s). They complement the data available on medicines from other sources to more effectively monitor the risks and benefits of authorised medicines. In this context, EMA organised a workshop in 2016 to discuss concrete solutions for the better use of existing patient registries that collect high-quality data from medicines in clinical practice, as well as to determine how new registries can be established when needed.

Workshop on big data

Real-world data is a subset of big data. Big data is a term that describes very large data sets of far greater volume and variety than traditional data sets and which may represent both the breadth of data from large numbers of individuals and/or multiple sources and the depth of data on each individual.

These data have the ability to significantly contribute to the way the benefit-risk balance of medicines is assessed over their entire life cycle.

In November 2016, the Agency organised a workshop to identify the opportunities and challenges associated with the use of big data in medicine development and regulation.

The workshop brought together a wide range of individuals from the healthcare environment and from technology companies, who spoke about the advances being made in the field of big data and the opportunities for its application in medicine regulation. From EMA's perspective, the tools and data discussed at the workshop will not replace randomised clinical trials, but can improve clinical trials and also complement trial data, supporting decision-making on medicines. The participants agreed that regulators need to develop the skills and regulatory tools to take full advantage of the value of this type of evidence, differentiate causal associations from those that are simply coincidental and make robust decisions.



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This is not a European challenge, it is a global challenge, and the more we work together and share experiences across borders, the better.”

Dr Thomas Senderovitz

Director General of the Danish Medicines Agency

Measuring the impact of pharmacovigilance activities

In Europe, various activities are carried out to ensure that medicines are used as safely as possible. These include the proactive planning of risk-minimisation measures before a medicine is authorised, the collection and analysis of reports on suspected adverse drug reactions (ADR), the detection and management of potential new safety signals for medicines, as well as the planning of post-authorisation studies to generate data on the use of medicines in the real world. It also includes measures taken for specific products after an EU safety review.

Measuring the impact of such activities is crucial in order to establish whether or not the actions taken to minimise the risks of a medicine have been effective. It also allows regulators and stakeholders to determine which activities are most successful and to identify enablers for, and barriers to, relevant measures.

In January 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted a 'Strategy on measuring the impact of pharmacovigilance activities'. This details how to gather data and knowledge on the concrete effect of the risk management measures and processes meant to ensure the safe use of medicines for patients in the EU.

This was further discussed at a workshop held in December 2016 which resulted in a number of recommendations and proposals to modify the strategy for a more systematic public health approach. This could help to determine how regulatory actions affect patient outcomes and enable regulators to change decision-making in the future.



“

Results of PROTECT are being implemented into routine pharmacovigilance and regulatory practice. They have already started to improve day-to-day medicine monitoring operations of regulators and pharmaceutical companies, for better safety of European patients.”

Peter Arlett

Head of EMA's Pharmacovigilance department

Regulatory science for safety monitoring: IMI PROTECT impact assessment

In 2016, several key findings of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project were published in medical journals.

PROTECT's goal was to develop innovative methods to improve and strengthen the monitoring of the benefits and risks of medicines marketed in the EU. An impact assessment was carried out to evaluate how these regulatory science research projects have been or will be implemented in regulatory practice. It showed that PROTECT reached its objectives and deliverables.

PROTECT sparked a significant amount of scientific research across the EU. The project is behind a total of 74 original articles in peer-reviewed scientific journals, of which 26 were co-authored by EMA staff. In addition, PROTECT projects were the subject of 14 doctoral theses and 3 master theses carried out in universities across the EU.

PROTECT was funded by the Innovative Medicines Initiative joint undertaking. The 34-strong multinational consortium of academics, regulators and pharmaceutical companies was coordinated by EMA and an industry project lead from September 2009 until June 2015.

Addressing public health challenges

The Agency is supporting global efforts to respond to existing and emerging public health threats, such as emergencies like the Zika virus outbreak, or the risk posed by falsified medicines. It has also reacted swiftly to new concerns over the conduct of first-in-human clinical trials and started to update its guidance.

Response to emergencies – Zika virus

In 2015, when the spread of Zika virus infections raised worldwide concerns, the Agency contributed its expertise to the global response to this threat and gave advice on scientific and regulatory matters regarding research and development of medicines or vaccines against the virus.

The Agency and competent authorities in the EU Member States also carried out an assessment of plasma-derived or urine-derived medicines and concluded that there is no increased risk of contamination with the Zika virus for patients who take these medicines. Plasma- and urine-derived medicines are produced from body fluids which might be sourced in parts of the world where the Zika virus is prevalent. EU regulators sought reassurance that even if plasma or urine came from donors who had contracted the Zika virus, there is no risk of the virus contaminating the final products and thus affecting the patients taking them.

Improve the safety of first-in-human clinical trials

In 2016, the Agency worked on an overhaul of the EU guideline on first-in-human clinical trials, to further improve the safety of trial participants. EMA's current guideline, released in 2007, provides advice in particular on the data needed for the appropriate design of these trials and the initiation of treatment in trial participants.

The revision of the guideline aimed to reflect the evolution of practice over the last 10 years, marked by the increasing complexity of the protocols of first-in-human clinical trials. While the 2007 guideline focused on the single-ascending-dose design used at that time, the practice for conducting first-in-human clinical trials has meanwhile evolved towards a more integrated approach, with sponsors conducting several steps in the clinical development within a single clinical trial protocol (e.g. to assess single and multiple ascending doses, food interactions, or different age groups). The review also took into account the lessons learnt from a tragic incident which took place during a phase-I first-in-human clinical trial in Rennes, France, in January 2016, which led to the death of one trial participant.

Between July and the end of September 2016, EMA released for public consultation a concept paper which outlined the major areas that needed to be revised in the guideline. This consultation served as the basis for revising the guideline, which was carried out by EMA with experts from national competent authorities, who authorise clinical trials in the EU. The draft revised guideline was released for public consultation in November 2016, and the final version will be published in the first half of 2017.

Protect citizens from falsified medicines

Falsified medicines are fake medicines that are passed off as real, authorised medicines. In July 2011, the EU strengthened the protection of patients and consumers by publishing a new Directive on falsified medicines for human use. This provided the basis for a number of legislative implementation measures, including the introduction of two safety features: a unique identifier (a 2-dimension bar code) and an anti-tampering device to be placed on the packaging of most medicines for human use. A delegated regulation, published in February 2016 in the Official Journal of the European Union, provided details on the way these two safety features should be implemented.

The Agency and the European Commission developed an implementation plan outlining the regulatory requirements for the placing of the unique identifier and/or the anti-tampering device on centrally authorised medicines.

Marketing-authorisation holders are required to place the safety features on the packaging of most prescription medicines and certain non-prescription medicines no later than 9 February 2019.

The safety features will help protect European citizens against the threat of falsified medicines and strengthen the security of the medicine supply chain – from manufacturers to distributors to pharmacies and hospitals.

Open access to clinical data

In October 2016, EMA took a major step towards greater transparency by giving open access to clinical reports for new medicines for human use authorised in the EU on a dedicated website. Citizens, including researchers and academics, can now directly access thousands of pages from clinical reports submitted by pharmaceutical companies to EMA within the context of marketing-authorisation applications for every new medicine. The Agency is the first regulatory authority worldwide to provide such broad access to clinical data.

“EMA is highly committed to transparency. With its policy on the publication of clinical data, the Agency set a new standard that will benefit academic research and the practice of medicine as a whole.”

Noël Wathion

EMA's Deputy Executive Director

The publication of the clinical reports follows EMA's adoption of its policy 0070 on the publication, in October 2014, of clinical data for human medicines.

The new clinical data website will include the clinical reports contained in all initial marketing-authorisation applications submitted to the Agency on or after the policy's entry into force on 1 January 2015. The policy also applies to applications submitted on or after 1 July 2015 to vary a marketing authorisation for an extension/modification of indication or a line extension. The documents are published once the European Commission has decided whether or not to grant a marketing authorisation. They are also published when applications are withdrawn before an EMA opinion has been given.

In October 2016, EMA launched its new website with the publication of data submitted for two medicines, representing approximately 260,000 pages of information in over 100 clinical reports. Data will be progressively added online for all applications concerned since the policy entered into force. By the end of 2016, data for a total of six medicines was available. According to current forecasts, EMA expects to provide access to approximately 4,500 clinical reports per year once the website is fully operational.

Clinical data website use in 2016:

1,820 users, including 350 academics

6,474 documents viewed

23,443 documents downloaded

330 downloads per day

While the policy gives unprecedented access to clinical data, it also demands the highest standard of protection of patients' personal data. During the development process, the Agency consulted extensively with all stakeholders, making sure to integrate their sometimes divergent views.

EMA's proactive provision of access to clinical data will benefit patients, healthcare professionals, and academia as well as the pharmaceutical industry.

The initiative prompted support from a very broad range of stakeholders, including editors of medical journals, academia, transparency campaigners, patient and consumer organisations, major health organisations as well as the pharmaceutical industry.

What our stakeholders say

“Patients and clinicians have been waiting a long time for clinical trial data. This new approach will at last provide transparent information on all results of clinical trials, positive or negative, as submitted to the EMA.”

Yann Le Cam
Chief Executive Officer of EURORDIS-Rare Diseases Europe and member of the EMA's Management Board

“Recent studies find journal articles to be an incomplete source of information on new medicines—particularly their adverse effects—compared with clinical study reports. EMA's policy will go a long way towards ensuring access to detailed information on medicines that enter clinical use. As editor of a medical journal, I look forward to the improvements in drug development and clinical care that will result from peer-reviewed analyses of this newly transparent data.”

Larry Peiperl
Chief Editor, PLOS Medicine

“The publication of clinical studies reports significantly benefits patients and public health, both in terms of progress in medical research and in terms of access to vital information. This move is much needed to considerably boost transparency in the pharmaceutical sector. It will also help increase consumers' trust in regulatory authorities and ultimately in the safety of medicines.”

Ilaria Passarini
Head of the Food and Health Department
BEUC – the European Consumer Association

“Prospective availability of clinical study reports will allow service users, physicians, researchers and all those interested in healthcare to access detailed documents reporting design, evolution and results of clinical trials and other studies on humans. Provided text redactions are kept to a bare minimum, this initiative will help to minimise the effects of reporting bias of trials which blights large swathes of contemporary "scientific" literature.”

Tom Jefferson
Honorary Research Fellow, Centre for Evidence Based Medicine,
Oxford, UK

“The launch of EMA's much discussed Policy 0070 marks the second of the European regulator's landmark — and still unparalleled — achievements in democratizing access to clinical trial data and other regulatory documents. Whereas other regulators have taken a "hands off" approach, EMA has proactively re-examined its approach to claims of commercial confidentiality - and generally moved in favor of public health. Policy 0070 promises a near barrier-free way for anybody with an internet connection to access clinical study reports of trials for new medicines. It confirms EMA's conviction that the transparency of clinical study reports and regulatory documents is fundamental to achieving its public health mission. Other regulators should take heed.”

Peter Doshi
Department of Pharmaceutical Health Services Research
University of Maryland School of Pharmacy, US

“This is a sound step for transparency in science. Opening up access to trial results has the potential to boost knowledge sharing, drive innovation and ultimately accelerate the development of lifesaving drugs and vaccines. This could benefit researchers, patients and global health as a whole.”

Seth Berkley
CEO, Gavi, The Vaccine Alliance

“Patients are waiting for more effective medicines - and sometimes even cures. The researchers in my member companies have learnt that we can be much more productive if we share all the information we collect. My companies are involved in many data-sharing programs, and more will come. EMA's new policy is a major step forward in the same direction.”

Richard Bergström
Director General, European Federation of Pharmaceutical Industries and Associations (EFPIA)

“It is very welcome news that EMA is starting to publish all clinical study reports it receives. The 700 organisations in the AllTrials campaign, who between them represent hundreds of millions of people worldwide, have been calling for this. We all now hope that other global medicines regulators will follow EMA's great lead.”

EMA's new policy means there will be a lot more information about our future medicines available for scrutiny. This is fantastic. However, the majority of medicines we use now, and will continue to use for years to come, were approved in the past. And it's the information on these medicines that remains hidden. Regulators like EMA need to do everything they can to ensure all information about all our medicines is available to doctors and researchers.”

Sile Lane
Director of Campaigns and Policy, Sense about Science

“EMA continues to strengthen their position as the patients' advocate in Europe with another important deliverable that helps define the landscape and educate on the critical opportunities from data sharing. CDISC supports and embraces all moves towards greater transparency and structure of patient data through the use of global, freely available consensus-based clinical data standards that will facilitate data sharing to advance research at an optimum rate and more readily unlock cures.”

Rebecca D. Kush
Founder, President and CEO, Clinical Data Interchange Standards Consortium (CDISC)

“The European Association of Clinical Pharmacology (EACPT) welcome EMA's policy aimed to make publicly available results from individual clinical studies. The EACPT believes that this is a critical step forward toward the transparency that society demands. The initiative of making available to the public scrutiny these data will mean a clear signal to industry and regulators to increase the quality in producing and assessing the data.”

Gonzalo Calvo
European Association for Clinical Pharmacology and Therapeutics (EACPT) and co-Chair of EMA's Healthcare Professionals Working Party (HCPWP)

“Scientifically robust, transparent, verifiable data are critical components of decision-making throughout the life cycle of medical products - from discovery to use by patients. While respecting personal privacy, complete data sets from all trials allow stakeholders globally to make better and truly informed decisions. Access to such data will give us better knowledge; how we apply that knowledge will define our wisdom.*”

Murray M. Lumpkin
Deputy Director, Integrated Development (Regulatory Affairs)
Lead for Global Regulatory Systems Initiatives
Bill & Melinda Gates Foundation

“We owe it to those who take part in clinical trials to make the most of their contribution. Ensuring responsible access to trial data enables innovative research and should accelerate the development of new treatments. EMA's policy is a significant step towards this goal, ensuring the important information contained in clinical reports is available for wider scrutiny and re-use.”

Nicola Perrin
Head of Policy, Wellcome

Contributing to animal health and human health in relation to veterinary medicines

EMA and EU national competent authorities safeguard animal health in 28 EU Member States, as well as in the European Economic Area countries, by ensuring that all medicines available on the market are safe, effective and of high quality.

The Agency's key responsibilities are scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in animals. In 2016, EMA's veterinary medicine activities mainly focused on the availability of veterinary vaccines, minimising the risks to human and animal health that can arise from the use of antibiotics in animals, and research and innovation for the benefit of animal welfare.

Increase the availability of vaccines

Vaccines contribute to animal health management strategies by helping to prevent and control serious contagious diseases, such as foot-and-mouth and bluetongue disease. They also have an impact on human health as they ensure the safety of food and prevent animal-to-human transmission of infectious diseases. In addition, veterinary vaccines reduce the need to use antibiotics in animals and thus are crucial in the fight against antimicrobial resistance, currently one of the greatest threats to global public health.

EMA and its partners in the European medicines regulatory network started the implementation of an action plan to help increase the availability of veterinary vaccines in the EU. This plan aims to implement the conclusions of a workshop on improving the availability of veterinary vaccines in the EU, organised jointly by EMA and the Heads of Medicines Agencies (HMA) in March 2015.

The outcome of the workshop was also included in the annual veterinary medicines information day that took place at EMA in March 2016.

Encourage research and innovation

The Agency initiated a public consultation for stakeholders on possible issues encountered when new veterinary medicines are developed which are based on stem cells or monoclonal antibodies. The outcome of the consultation is the starting point for developing future guidance for these types of innovative veterinary medicines, also building on the experience gained so far with these technologies in human medicines.

This initiative is led by EMA's Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) which was established in 2014 to give advice to the Committee for Medicinal Products for Veterinary Use (CVMP) on issues regarding innovative and advanced technologies.

Tackle antimicrobial resistance through responsible use of antibiotics in animals

Antimicrobial resistance (AMR) is a global public health challenge affecting both animal and human health.

Antibiotic use in animals may contribute to the rise in resistant bacteria that can be transferred to humans either through the food chain or by direct contact. This can reduce the effectiveness of antimicrobials in treating human disease. In relation to veterinary medicines, EMA contributes to the global fight against AMR by promoting the responsible use of antibiotics in animals and collecting robust data on animals' antimicrobial consumption to allow policy-makers in Europe to make evidence-based decisions.

In October 2016, the Agency's CVMP adopted a strategy on antimicrobials for 2016-2020. The aim of this is to secure the availability of effective antibiotics for the treatment of serious infectious diseases in animals, while minimising the risks to animals or humans emerging from their use.

To achieve this objective, the Agency will:

- make recommendations to foster the safe and sustainable use of antibiotics in animals;
- advise on the risks to public health that could arise from the use of antimicrobials in animals;
- monitor and analyse the sales and use of already authorised veterinary antibiotics to protect their continued effectiveness;
- encourage the development of new and existing veterinary antibiotics and alternatives;
- work together with the European Commission and other EU public health agencies, competent authorities in the Member States, international regulatory bodies, human and animal health organisations, and the pharmaceutical and livestock industries to address this global public health challenge.

Recommendations for responsible use

Following a request from the European Commission, EMA and the European Food Safety Authority (EFSA) were asked to deliver a joint scientific opinion on measures to reduce the overall need to use antimicrobials in food-producing animals (RONAFA). In this context, in 2016, the EMA reviewed and assessed the measures that have been or are being taken by Member States and recommended options to reduce antimicrobial use in animals.



“This EMA-EFSA joint opinion will influence future policy on measures to be taken in the veterinary sector to address the public health risk associated with antimicrobial resistance.”

David Murphy
Chair of EMA's CVMP

There are only a few new antibiotics in pharmaceutical companies' development pipelines, which means that those already available need to be used responsibly to maintain their effectiveness for the future. One of the so-called last-resort antibiotics is colistin which can still be used to treat infections that resist every other kind of antimicrobial. Thus, EMA has recommended that colistin-containing medicines should only be used as a second-line treatment in animals. Over the next three to four years, all Member States should reduce the use of colistin in animals at least to a target level of 5 mg colistin/population correction unit (PCU). If successfully applied, this could result in an overall reduction of approximately 65% in the current sales of colistin for veterinary use at EU level.

Collecting data

In 2016, EMA published the sixth European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report. This includes sales figures of antimicrobials in animals from 2014, collected through the ESVAC initiative in a total of 29 countries (28 countries in the EU and European Economic Area (EEA) and Switzerland). The report is published each year and the continuous efforts from the Agency and national competent authorities to collect and analyse this information are reflected in the improved overall quality of sales data observed year on year. The trends highlight a more responsible attitude towards the use of antibiotics in animals.

EMA also held a public consultation on a new ESVAC strategy for 2016-2020. The strategy details the Agency's approach over the next four years to collect and publish overall sales data from as many EU and EEA countries as possible. This will help policy-makers to better analyse European-level trends in antimicrobial consumption per animal species.

A strong network for regulatory excellence

EMA is part of a family of medicine regulators across the EU.

While the Agency has a coordinating role, the national competent authorities are best placed to liaise directly with patients, healthcare professionals, animal owners and animal health professionals, academia and industry that live and operate in their territories. Together, we provide EU citizens with the best possible information on medicines, listen to their needs, and explain and promote the benefits of the medicine regulation system in Europe.

Improving cooperation within the network

Optimising the operation of the network is one of the key priorities of the joint strategy adopted by EMA and the national competent authorities in December 2015.

In 2013, EMA initiated fundamental organisational changes that were pursued in 2016 to better support EMA's public- and animal-health mission, and its role as part of the European medicines regulatory system. These changes complement the ongoing review of its internal processes. As part of this initiative, the Agency has reviewed the way it supports the evaluation of medicines and has adopted a complexity-based approach whereby the network's expertise can be mobilised when complex applications are received. This helps focus the network's limited resources on what is really important for patients. In addition, the Agency has undertaken a number of actions that will make the lifecycle management of medicines simpler, more predictable and faster, for the benefit of all stakeholders as well as the national competent authorities in the EU.

Seeking operational excellence

In 2016, EMA pursued its reorganisation of the human medicines area, which was initiated in 2013, to further improve the efficiency and effectiveness of its operations and achieve a leaner, more streamlined architecture.

The new structure relates to the medicines life cycle more closely, with one operational division responsible for supporting medicine developers, one for the evaluation of medicines bringing scientific and procedure management under one umbrella, and one for the oversight of medicines, including pharmacovigilance and inspections. The changes also introduced the creation of a new function dedicated to strengthening the collaboration between EMA and the national competent authorities by overseeing the implementation of the joint network strategy to 2020.

On the operational side, the Agency has optimised its model for managing the evaluation procedures for human medicines, which builds on recent efforts to streamline and simplify internal processes to focus on activities that add value. With the new model, procedure managers and procedure assistants are now assigned to a product, rather than to a procedure whilst maintaining a consistent approach across a given regulatory procedure. This is expected to improve the coordination of regulatory activities regarding one product, particularly where multiple regulatory procedures are processed in parallel for the same product.

A similar review is currently ongoing for the veterinary medicines area within the organisation.

EMA also increased its interactions with industry stakeholders by organising regular platform meetings and webinars. The Agency also carried out a survey to obtain feedback on its various post-authorisation processes and procedures. This led to a number of improvements, simplifications and new regulatory guidance to support applicants with life-cycle management.

The improvements for medicines for human use include in particular:

- a simplified way to submit changes to risk management plans;
- a simplified approach for the handling of complex grouped quality-related changes when a new manufacturing site is introduced for the active and/or finished product (this was also implemented for veterinary medicines);
- more flexibility in the submission of type-II variations with the introduction of weekly (instead of monthly) timetables to help even out workload peaks for assessors and give more flexibility to companies to submit important changes in relation to their products' marketing authorisation;
- faster implementation of changes to product information as part of type-II variations plus the introduction of an additional linguistic review cycle – this review ensures the quality and consistency of the product information across all EU languages;
- an improved periodic safety update report (PSUR) single assessment process by developing additional guidance that reflects a common understanding about the submission requirements, evaluation and implementation considerations.

Strengthening capacity and expertise

EMA has been encouraging the formation of multinational assessment teams since 2013, initially for the assessment of new medicines. Multinational assessment teams enable the involvement of a wide range of Member States in the work of EMA's scientific committees. They contribute to optimising the use of resources throughout the European regulatory system for medicines and encourage cross-border fertilisation of scientific expertise for the committees' high-quality work.

In 2016, 25 Member States participated in the assessment of new medicines for human use, either as rapporteur or co-rapporteur, compared to 16 in 2010. For veterinary medicines, 17 Member States participated in the assessment of new medicine applications in 2016.

In December 2016, the extension of the concept of multinational assessment teams to post-authorisation assessments was endorsed by EMA's Management Board. This means that, as of April 2017, assessment teams comprising experts from several Member States will be able to evaluate applications for extensions of marketing authorisations of existing medicines.

To strengthen the network's expert capacity and ensure good scientific and regulatory practice across the assessment teams, the EU Network Training Centre (EU NTC) was established in 2014 by EMA and national competent authorities, and became fully developed in 2016.

The central online platform provides access to high-quality and relevant regulatory and scientific training materials that are made available either by EMA or by national competent authorities. The network-wide training catalogue included 110 courses and 55 training webinars at the end of 2016.

A new learning management system was also launched to make it easier for users to find, register for, give feedback on and recommend courses from the EU NTC catalogue.

Supporting innovation throughout the EU

In 2016, an EU innovation network was formally created, comprising EMA's innovation task force and those national agencies' innovation offices wishing to collaborate. In 2016, 17 countries participated.

The network aims to facilitate the development of innovative medicines by making available seamless early regulatory support at national and EU level.

It also provides a platform for regulators to share their experience with upcoming innovative therapies and discuss regulatory science challenges emerging at an early stage in medicine development.

The platform enables EU regulators to identify and address gaps in regulatory science and anticipate the expertise needed for the assessment of innovative medicines. The initiative is closely linked with the EU NTC which identifies areas where training may be required to ensure the appropriate capabilities within the network.

EMA's innovation task force provided a means for companies to enter into dialogue with regulators at an early stage in the development of veterinary medicines, too.

Strengthened engagement with stakeholders, including civil society

In 2016, the Management Board adopted an overarching framework for stakeholder relations management which defines the guiding principles for the management of interactions with key stakeholders. The framework builds on the Agency's experience of interacting with stakeholder associations representing patients and consumers, healthcare professionals, animal health professionals, the pharmaceutical industry and, more recently, academia. It aims to streamline activities across the various stakeholder groups and align working methodologies where possible.

Key developments which took place in 2016 to formalise EMA's engagement with some of these groups include:

Public hearings

Public hearings are a new tool allowing EMA to engage with EU citizens on the supervision of medicines for human use and to listen to their views and experiences. Contributions from the public during these hearings will be considered by the Pharmacovigilance Risk Assessment Committee (PRAC) and inform its decision-making.

In 2016, the PRAC adopted the rules of procedure for public hearings, following their endorsement by EMA's Management Board. The rules explain the process and practical arrangements for public hearings, including how the PRAC will decide when to hold a public hearing and how members of the public can participate – either as a speaker or an observer. EMA carried out an internal practice exercise, or dry run, to test the process and procedures for the hearings. Using a fictional safety review, the PRAC experienced how such a hearing might unfold. This enabled the Agency to ensure that all practical arrangements needed are in place and allowed PRAC members to test this new form of interaction. Following the successful simulation, the PRAC is now ready to incorporate public hearings into its core activities.



“Although we have many years of experience in involving patients and healthcare professionals in our work, public hearings are a new concept for EMA as they will open up the process of assessing medicines in the EU to the wider public for the first time”

Noël Wathion

EMA Deputy Executive Director

Integrating patients' views in clinical studies of cancer medicines

In April 2016, EMA published new guidance on the use of patient-reported outcome measures in oncology studies. The guidance document, issued by the CHMP and its Oncology Working Party, acknowledges the importance of including patients' perspectives in the assessment of the benefits and risks of cancer medicines.

Patients' and Consumers' Working Party: 2006-2016

The Agency celebrated 10 years of its Patients' and Consumers' Working Party (PCWP) in 2016.

The PCWP provides a platform to exchange information and discuss issues of common interest among EMA and patients and consumers. At their 10-year anniversary meeting in June, the working party reflected on the key achievements of their first decade, considered priorities for the coming years and how to address the challenges ahead. A collection of articles and video interviews to mark the 10th anniversary of the PCWP were also published.

Pilot study: benefit risk evaluation – capturing patient preferences

Following the experience gained in a small pilot project on patients' perspectives on the benefits and risks of treatments, EMA, together with Myeloma UK and the University of Groningen, conducted a larger study involving 560 multiple myeloma patients from the UK. Through an online survey based on multi-criteria decision analysis, these patients were asked to express their willingness to do a trade-off between a product's favourable and unfavourable effects. The study demonstrated that there is considerable diversity in how myeloma patients value the benefits and risk of treatments and this technique may complement other more direct methods used to gather patients' views (e.g. face-to-face). More studies in other therapeutic areas are foreseen.

Enhancing interaction with academia

In 2016, EMA further strengthened its long-standing collaboration with academics and researchers. In June, the Agency held a workshop with representatives from academia to explore new ways of engaging with this key stakeholder group. At that meeting, which was hosted by EMA's Healthcare Professionals' Working Party (HCPWP), it presented the pillars of a framework of collaboration with academia. Key objectives include enhancing academia's understanding of the EU medicines regulatory framework and increasing regulators' understanding of the needs and expectations of academia. The framework will be further considered by the Management Board in 2017.

Involving general practitioners in regulatory decisions

In April 2016, EMA hosted a workshop with representatives of general practitioners and family doctors to explore new ways of engaging with these providers of primary care and further involve them in EMA activities. The workshop led to the creation of an expert group of general practitioners who will act as facilitators and communicate to their broader communities. This group will be involved in a wide range of EMA activities whenever their specific feedback is needed. They can, for example, contribute to EMA's scientific advice to medicine developers, give input on the feasibility and impact on patients of risk-minimisation measures, review product information, and disseminate information to their networks and patients. EMA's existing framework of interaction with healthcare professionals was updated to reflect this new focus on involving general practitioners and family physicians.

“

Academia play an important role in helping the EU medicines regulatory network to keep abreast of the opportunities and challenges brought by science and providing access to the right expertise to evaluate these innovative medicines. Interaction with EU regulators and a better understanding of the regulatory environment can help academia translate their discoveries into patient-focused medicines.”

Guido Rasi

EMA Executive Director

Engaging with the veterinary community

As part of a public consultation on a reflection paper on anthelmintic resistance, a stakeholder meeting was organised in June 2016 with academia, veterinarians, industry and representatives of the regulatory network. The objective was to provide an overview of the situation concerning anthelmintic resistance in Europe and to exchange information on factors influencing the development of anthelmintic resistance and on best practices for prudent use.

In November 2016, EMA held a stakeholder focus group meeting on the promotion of pharmacovigilance for food-producing animals. The meeting was attended by representatives from various stakeholder groups and mainly targeted practising veterinarians specialising in cattle, pigs, poultry, fish and horses. The meeting discussed the reasons for under-reporting adverse events in food-producing animals and ways to encourage reporting and provide feedback to reporters.

Shaping the global regulatory environment

A central pillar in EMA's strategy to protect public health is the strengthening of collaboration with other regulatory authorities.

In 2016, the Agency continued to work with partners in Europe and beyond to contribute to global public health.

The Agency's international strategy aims to ensure 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 the convergence of global standards in global regulatory forums. It also offers its expertise to support countries with less regulatory experience and infrastructure, reinforcing its role as a global reference authority which provides the oversight expected by citizens in the EU and worldwide.

Bilateral interactions reinforced and extended

The Agency continued to collaborate closely with the Therapeutic Goods Administration (TGA) in Australia, Health Canada, 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, which are based on confidentiality arrangements, take place almost daily, partly structured around clusters of activities, and partly ad hoc.

EMA and the FDA set up two new working groups, or clusters, in 2016. The first cluster, on patient engagement, will provide a forum to share experiences and best practices on the way the two agencies involve patients in development, evaluation and post-authorisation activities related to medicines.

The second cluster, on rare diseases in humans, aims to exchange information on the development and scientific evaluation of medicines for rare diseases. Topics include conducting clinical trials in small populations, collecting preclinical evidence to support development programmes, risk management strategies for long-term safety issues, and the design of post-marketing studies, in particular in the context of early-access mechanisms such as EMA's conditional marketing authorisation and FDA's accelerated approval.

The creation of these two clusters is an important step in the wider approach being taken by both EMA and FDA to expand and reinforce international collaboration.

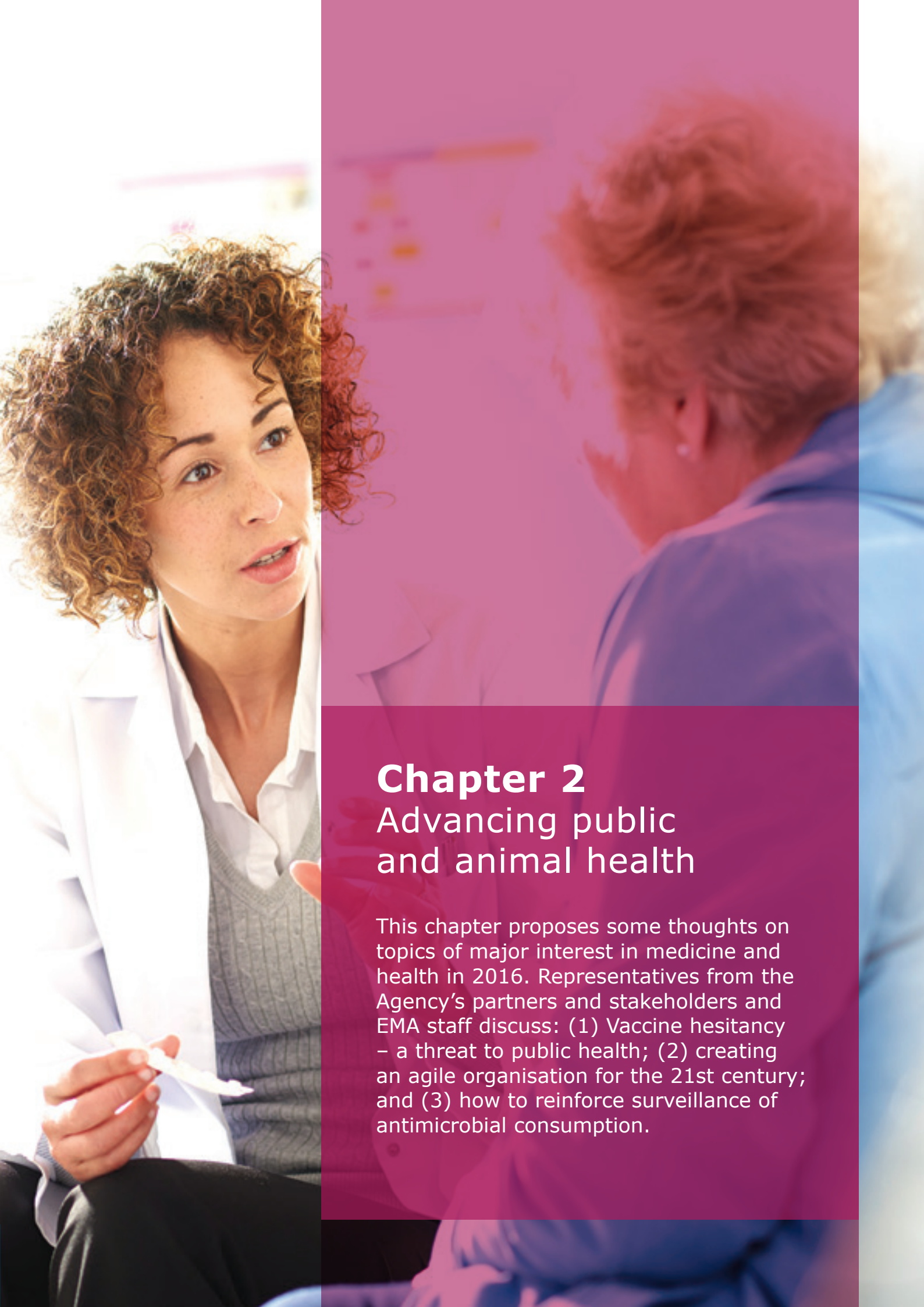
Addressing global challenges through multilateral interactions

In December 2016, the ongoing collaboration on good manufacturing practice inspections of active-pharmaceutical-ingredient (API) manufacturers between EMA and its international partners was expanded to include Japan's PMDA. This international collaboration will enable participants to share information on inspections, including planning, policy and reports, of API manufacturers located outside the participating countries. The overall aim is to increase cooperation and mutual reliance between regulators participating in the initiative, as well as to ensure the best use of inspection resources worldwide.

EMA also hosted a meeting with PMDA and FDA to discuss regulatory approaches for the evaluation of antibacterial agents.

Mapping international regulatory initiatives

In 2016, EMA published an overview of existing international regulatory initiatives for human medicines. The mapping was carried out by the Agency on behalf of the International Coalition of Medicines Regulatory Authorities (ICMRA). The report lists all international projects and provides regulatory agencies with comprehensive details on the number and scope of global initiatives that can support decision-making regarding future engagement, prioritisation and coordination. The aim of the mapping exercise was to raise awareness of ongoing activities, establish a basis for more strategic coordination to avoid duplication of effort, and identify possible gaps. The report was presented at the annual ICMRA meeting in Interlaken, Switzerland in October.



Chapter 2

Advancing public and animal health

This chapter proposes some thoughts on topics of major interest in medicine and health in 2016. Representatives from the Agency's partners and stakeholders and EMA staff discuss: (1) Vaccine hesitancy – a threat to public health; (2) creating an agile organisation for the 21st century; and (3) how to reinforce surveillance of antimicrobial consumption.

Vaccine hesitancy – a threat to public health



Dr Heidi Larson

Associate Professor at the London School of Hygiene & Tropical Medicine, Director of the Vaccine Confidence Project

There seems to be a growing trend of vaccine hesitancy in Europe, i.e. people hesitating to vaccinate themselves or their children. What is the situation today?

Heidi Larson: Our research shows that although around the globe the overall sentiment towards vaccination remains positive, Europe is the most sceptical of all regions when it comes to vaccine safety. In France, the least confident globally among the 67 countries we studied, 41% of those surveyed disagreed that vaccines are safe. There are various reasons for this. It can be linked to distrust towards a specific vaccine, in particular recently against human papillomavirus (HPV) and flu vaccines. Concerning the flu, there is a strong sense among people that the vaccine is not needed because the disease is generally manageable, and people forget it kills more than Ebola ever did. There are also strong beliefs in natural, homeopathic modes of building up immunity.

Nena Kopcavar Gucek: What concerns me most as a family physician is that we are now seeing a strong resistance against even the obligatory vaccines, such as the DTP vaccine against diphtheria, tetanus and pertussis (whooping cough). This did not happen at all just 20 years ago. Some parents invoke concerns, for example, about the aluminium in vaccines, even though there is evidence that these are safe. I feel that the information era we are in, where any one-sided blog can have as much audience as evidence-based and sound information, is precipitating this trend.

Enrica Alteri: Vaccine hesitancy is already having an impact in Europe. In 2015 there was a case of an unvaccinated child who died of diphtheria in Spain. WHO flagged the decrease of vaccine coverage in Europe, resulting in an increased incidence of vaccine-preventable diseases. We need to take action to act in favour of the confidence in vaccines, which are one of the most effective public health interventions of the past century and have led to a significant reduction in the burden of infectious diseases.

What are the specific challenges when it comes to restoring confidence in vaccines?

EA: Communication is crucial but can be challenging. In 2015, EMA carried out a review of the evidence surrounding reports of two rare syndromes in young women given HPV vaccines. The clear conclusion was that no causal link between the vaccines and development of these syndromes could be identified. While our objective was to give a strong and reassuring message, following a thorough scientific review, some considered this as a dismissal of the concerns that were raised. Although for vaccine safety the science is very clear, individuals will focus on specific cases, therefore it is essential that the institution is trusted. When communicating around vaccines, we always need to put the risks in the context of the benefits of immunisation overall.

HL: Indeed, parents do not reason in terms of the benefit vs. risk like the public health community does, but risk vs. risk, i.e. what is the risk of the vaccine and what is the risk of the disease. They want a response that is 100% certain and science does not allow for this. I wish that statistics and scientific evidence could change the mindset of people, but it is not enough. We need to be able to translate the safety statistics in a way people will understand. One thing we know that does not work is to say, for example, that there is a one in a million chance that an adverse event might happen. Most parents will think only about whether that one

could be their child. We might need to put vaccines in a wider context: a lot of parents do not really realise how the safety of vaccines compares with that of other medicines they may take routinely. Another challenge in Europe is the immunisation schedules: for one vaccine, you can find 35 different schedules across multiple countries, which makes it difficult to convince a parent that one particular schedule is evidence-based.

NKG: We are also confronted with issues in medical practice. For the flu, most patients rely on the opinions of their physicians, but a high proportion of those physicians will not get vaccinated. Therefore, efforts should not only focus on lay people, but also on healthcare professionals. We must practice what we preach.



Dr Nena Kopcavar Gucek

Family Physician in Ljubljana, Slovenia, Member of EMA's Scientific Advisory Group on Vaccines



Dr Enrica Alteri

Head of Human Medicines
Research and Development
Support, EMA

Dr Nena Kopcavar Gucek, Family Physician in Slovenia, Dr Heidi Larson, Associate Professor at the London School of Hygiene & Tropical Medicine, United Kingdom, and Dr Enrica Alteri, Head of EMA's Human Medicines Research and Development Support, discuss the growing issue of vaccine hesitancy.

How can regulators like EMA contribute to restoring confidence in vaccines?

EA: As regulators, we realise that our job cannot stop at understanding and defining the benefit-risk profile of vaccines. There is a need for a more concerted effort from all public health bodies and healthcare professionals. Each should know its respective role and play its part in defending such an important public health measure. EMA needs to know what type of support researchers, physicians and patients require. If we want to be relied on and believed in, we must engage with those we serve. It is our role to do everything we can do to have more people around the table, to bring back more facts.

NKG: Physicians sometimes lack easily available data on vaccine coverage and safety, but we need to counter patients' concerns with objective facts. It is good that EMA is opening up to lay people, to the non-medical community. Promoting the fact that patients can directly report side effects of medicines/vaccines is also helpful.

HL: We have been progressing in leaps and bounds with the development and introduction of new vaccines, but have just kept assuming the public would continue to take more and more vaccines because they accepted the first ones. We are now paying for the time we did not spend on preparing the public and involving them before any new vaccine reaches their doctor's surgery. People can feel alienated and consider that decisions around immunisation are being made without them and that they are just expected to accept them. It is crucial to engage with citizens and it is good that EMA is making such an effort in that direction. We will always have some people who are extreme in their anti-vaccination stance; what we must do is to vaccinate with positive sentiment those who are undecided and hesitating, in the middle. We need to build and sustain vaccine confidence among those who are still vaccinating, but are starting to question, hesitate and perhaps refuse some vaccines.



Creating an agile organisation for the 21st century



Christa Wirthumer-Hoche

Chair of EMA's Management Board and Head of the Austrian Medicines and Medical Devices Agency (AGES-MEA)

EMA, like many other regulators, faces a number of challenges stemming from the fast pace of scientific development, new legislation to be implemented, new technologies to integrate in its processes, and an ever-changing environment. Christa Wirthumer-Hoche and Evdokia Korakianiti share their vision of how they would like to see the Agency operate in the coming years to address these challenges.

What is your vision for the Agency over the next 10 years?

EK: EMA has evolved a lot over the years and should keep modernising to ensure that we keep pace with upcoming scientific advances in research and development, understand their potential to benefit public health, and focus our efforts on what will really benefit patients. We want to be able to help translate these advances into medicines for patients. My vision is an Agency that is well attuned to its stakeholders, outward facing and fostering scientific dialogue across the EU, and able to engage fast with the right experts to deliver high-quality assessments. In this way, we will smooth the regulatory path to innovation and help deliver better medicines for patients

CW: We need to pick up early on scientific developments, in particular those that could lead to developments for new medicines in areas where there is still an unmet medical need. EMA should work as a facilitator to help identify upcoming developments, to facilitate the pathway of new ideas and coordination of the required expertise across Europe to ultimately facilitate earlier access to needed medicines. I agree that we need to stay tuned to advances in research and development and new scientific approaches via a closer collaboration with academia. It has to be said that this transfer of knowledge also comes primarily via national experts who have very close links with universities and research institutes.

What has been done so far to achieve this vision?

CW: There is a need to filter this knowledge and translate it into training for assessors to make sure that we have the right expertise when needed. We have achieved a lot in this area since the establishment of the EU Network Training Centre and I think it is important to say that this is really a network activity that has been achieved jointly by EMA and the NCAs which is the key to its success. The next step would be to open up the EU NTC to academia so that we can include training provided by academics in the system and academics can be trained on regulatory issues. We are already opening it up to authorities outside the EU to participate in training – both face-to-face courses and webinars.

EK: In recent years, we have created new platforms to allow us to interact more closely with our stakeholders. We are now better attuned in understanding their needs so that we can support them with guidance, IT solutions and training. We have also done a lot to simplify and streamline our ways of working. We have a high volume of medicines and therefore a high volume of evaluation procedures that all need to be assessed to the highest standards at a time of resource constraints across the network. We have developed an approach that allows us to identify the most critical or complex aspects in an application and mobilise the right internal and network resources in a risk-proportionate way. This approach has made us more efficient as it helps focus on what is really important for patients. We have been able to implement new strategic activities, such as PRIME and the proactive publication of clinical data, and to deliver IT solutions, such as the PSUR repository, with the resources saved.

How can EMA become a more agile organisation?

EK: We are now working more closely with all our stakeholders, the network and global partners and are organised so that we can respond to their needs faster. This is the basis of a more agile organisation. We need to continue our efforts to remove any impediments to easier, more fruitful collaboration between experts and to facilitate multidisciplinary interactions. It is essential to help our experts to keep continuously up to date with relevant scientific developments. Modern IT solutions can dramatically facilitate interactions and support knowledge sharing across the EU. When faced with new scientific approaches, we need to be able to identify the relevant EU experts and to mobilise them fast. The framework with academia, which is currently under development, will facilitate our interactions in this respect. In addition, we need to continuously improve our ways of working to ensure that we focus on value-adding activities for patients.

CW: One of the big challenges we are facing is a move towards a digital world and the availability of the huge amount of data that need to be handled and processed in a fast and smart way. We have had many major IT developments recently to simplify processes and become better connected across the network. The different repositories that are now operational also enable the network to react much faster because the information is directly available. There will be further improvements in the near future to streamline the handling of information for the benefit of all assessors across the EU.



Evdokia Korakianiti

Head of EMA's Procedure
Management Department



Antimicrobial resistance – how to reinforce surveillance of antimicrobial consumption



Arno Muller

Access and Use; Essential Medicines and Health Products, WHO, Switzerland

Antimicrobial resistance is one of the most serious global threats to human and animal health. In the EU, as in other parts of the world, programmes for the surveillance of antimicrobial consumption have been put in place to support policies on the rational use of these medicines to preserve their effectiveness for the benefit of animal and public health.

Why is it important to monitor the consumption of antimicrobials in humans and animals?

AM: Many countries still do not monitor the consumption of antibiotics and are not fully aware of the level of use both in humans and animals. Monitoring the use of antibiotics and making this information public raises awareness among all stakeholders, including public health and veterinary professionals and policy-makers as well as consumers, about the importance of using these medicines in a rational way. In many countries, important public campaigns and the implementation of new policies to reduce the consumption of antibiotics started when the first data on human or veterinary consumption were made public.

JTE: The Agency's ESVAC activity has had a significant impact on raising awareness of the need for a responsible use of antimicrobials in animals. The availability of data across most EU countries is likely to have prompted some policy-makers to take action. Also, the availability of data on critically important antimicrobials for human medicine, such as fluoroquinolones and cephalosporins, has helped certain Member States and stakeholders to identify patterns of use and put in place targeted policies to reduce the use of the highest-priority critically important antimicrobials in animals. In certain Nordic countries, these measures have led to a significant decrease in the use of the highest-priority critically important antimicrobials in animals. These surveillance programmes, as well as data from farms, show that some antibiotics might still be used to prevent, rather than treat, infections in the food-producing animal sector. This can be tackled by measures such as improving vaccination or better husbandry conditions. Together with EFSA, EMA has recently released an opinion on measures needed to reduce the use of antimicrobial agents in animal husbandry in the EU. It suggests that we should be aiming to phase out preventive use of antimicrobials as much as possible.

What changes have you seen since the start of surveillance programmes?

JTE: For many years most policies focused on human consumption and resistance in humans and animals separately. In the past five to 10 years, there has been a shift towards the 'one health' approach. It is now generally acknowledged that the use of antibiotics in animals does have an impact on the development of resistance in humans; however, we need to have more data to be able to quantify this impact. This is one of the aims of our joint JIACRA¹ project, produced together with EFSA and ECDC, which analyses correlations between the uses of different antibiotics in humans and animals, and resistance to them.

Is there a particular focus on critically important antimicrobials?

JTE: EMA has issued a number of opinions to regulate and restrict, where necessary, the use of certain substances which are considered critically important to human health – these recommendations have been implemented either by EU Member States or by users. There is now a growing awareness that we need to reserve certain classes of antibiotics for use in humans only, for example carbapenems. This is a big change from policies from decades ago. However, as there is a lack of antibiotics to treat both humans and animals, we also see that certain antibiotics that were traditionally, or mostly, only used in animals, for example

pleuromutilins, are now being used in humans. This has obliged regulators to introduce restrictions on the use of veterinary antibiotics, for example colistin, to minimise the transmission of resistance genes to humans due to its use in animals.

AM: In addition to the critically important antimicrobials, WHO is discussing defining a list of essential antibiotics which would be classified in three new categories: a core list of antibiotics, for instance first-line antibiotics; antibiotics to be used as a second-line treatment in certain circumstances (e.g. allergy, resistant pathogen); and a list of 'preserved antibiotics', i.e. antibiotics that should only be used in very specific or niche situations or as a last resort. This aims to further support the idea that we need to better use antibiotics and preserve them.

What needs to be improved?

AM: Many countries have set national targets to achieve reductions in certain classes of antibiotics and this strategy has proved to be very efficient. However, these targets should be based on scientific evidence and should be achievable. We also need to carefully monitor the consequences of these approaches to avoid shifting problems to other classes of antibiotics. To gain a better understanding of the situation in the field, WHO is considering complementing surveillance programmes at the national level with ad-hoc surveys in hospitals and at the community level. Another important point is the fact that current surveillance programmes are based mostly on high-level data, e.g. import data or data from wholesalers. To have a better estimation of actual use, we should move towards the collection of data by population of patients, e.g. males, females, children, age groups, etc.



Jordi Torren Edo

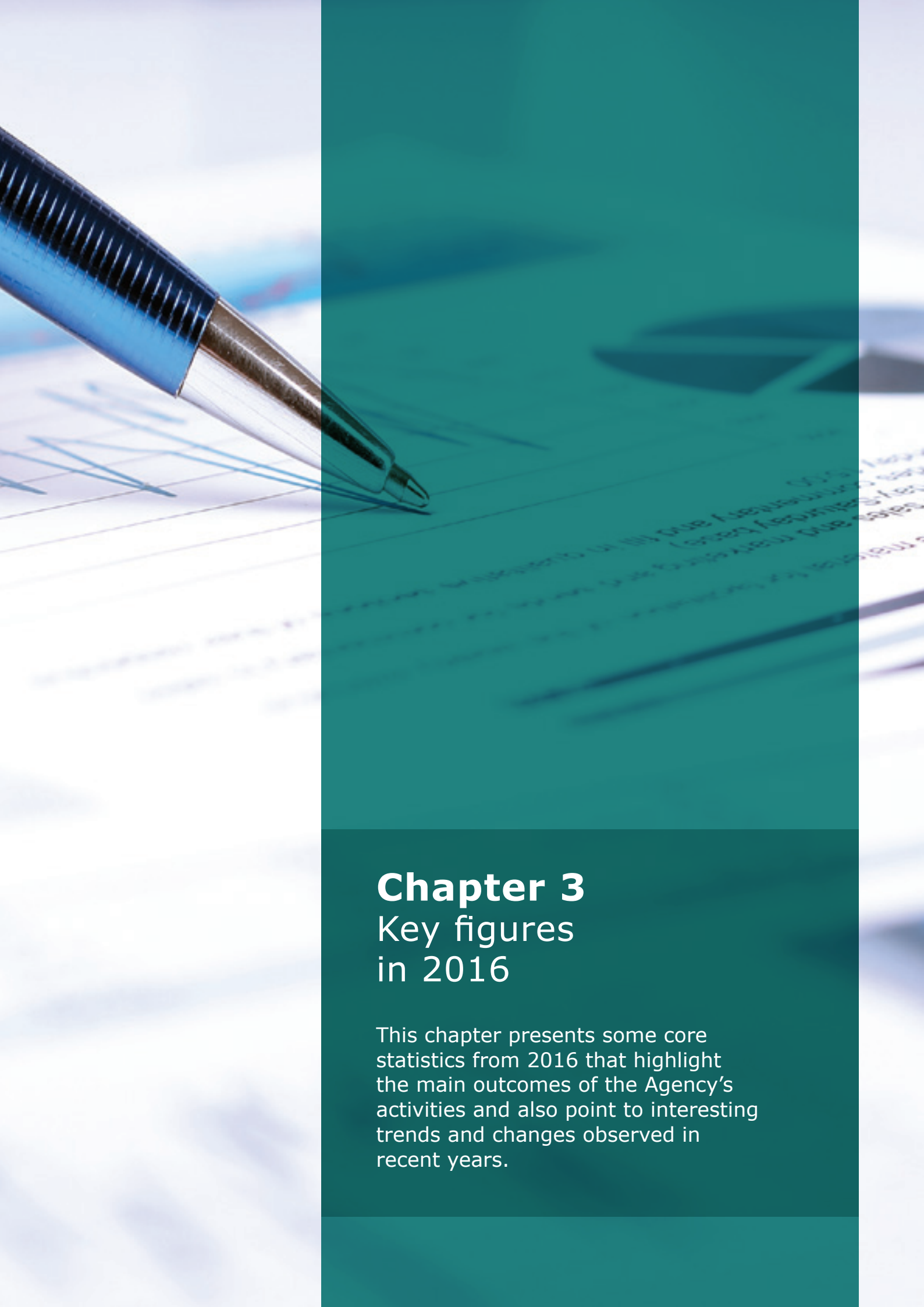
EMA's Animal and Public Health
Service, Veterinary Medicines
Division

JTE: Similarly, on the veterinary side, we are supporting Member States to provide data on the use of antimicrobials per species, with a specific focus on the three major food-producing species (pigs, poultry and cattle). We are also focusing on improving the quality of the sales data by further harmonising the methodologies used and publishing data for as many EU/EEA countries as possible.

What is the situation outside the EU?

AM: The EU has a long history in terms of antimicrobial surveillance programmes at country and regional level. At WHO, we are using the European experience to bring surveillance of antimicrobial consumption to other parts of the world, such as Africa and Asia. It is essential to encourage all countries to monitor and improve antimicrobial consumption.

¹ *Joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals.*



Chapter 3

Key figures in 2016

This chapter presents some core statistics from 2016 that highlight the main outcomes of the Agency's activities and also point to interesting trends and changes observed in recent years.

Human medicines

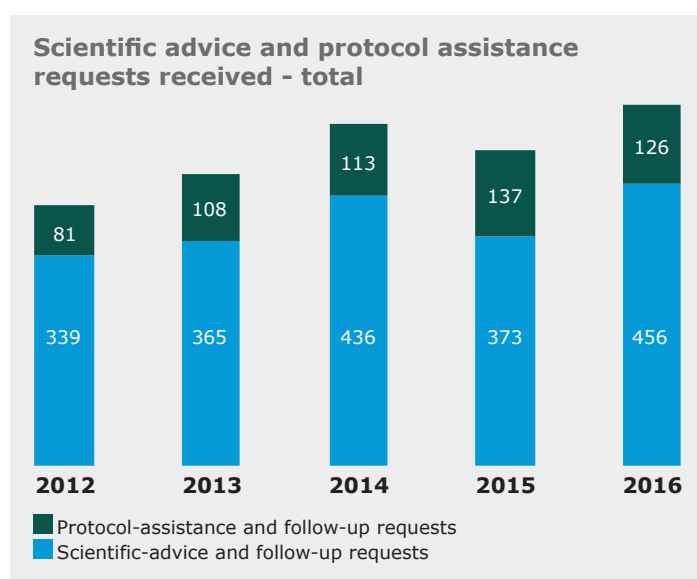
Supporting research and development

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 and its scientific committees and groups of experts from the EU national competent authorities are fostering early interaction and dialogue with developers to facilitate the development process, and help companies to collect adequate data and to comply with regulatory standards. These activities are increasingly being carried out in collaboration with HTA bodies and international partners.

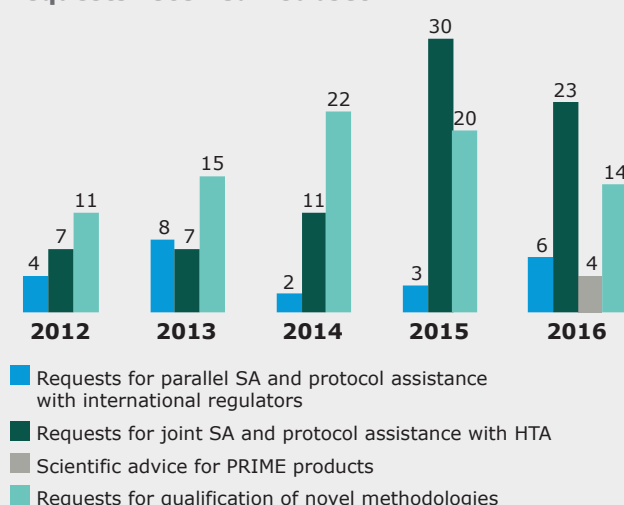
Scientific advice

The Agency provides scientific advice (SA) and protocol assistance to medicine developers throughout the life cycle of their medicines. Scientific advice is one of the Agency's key instruments to support the development of high-quality, effective and safe medicines that meet patients' needs. Early dialogue and scientific advice lead to better development plans, promote the collection of high-quality data, and most importantly help ensure that patients take part in clinical trials that are robust enough to support a marketing authorisation application or extensions of indications.

Requests for scientific advice rose by 20% compared to 2015. This is mainly due to an increased number of requests for scientific advice for medicines already authorised. EMA encourages companies to seek scientific advice throughout the life cycle of their medicines. Advice on study design can relate to: extensions of indication; the development of new doses and formulations; and the assessment of the medicine's safety and efficacy in real life.



Scientific advice and protocol assistance requests received - subset



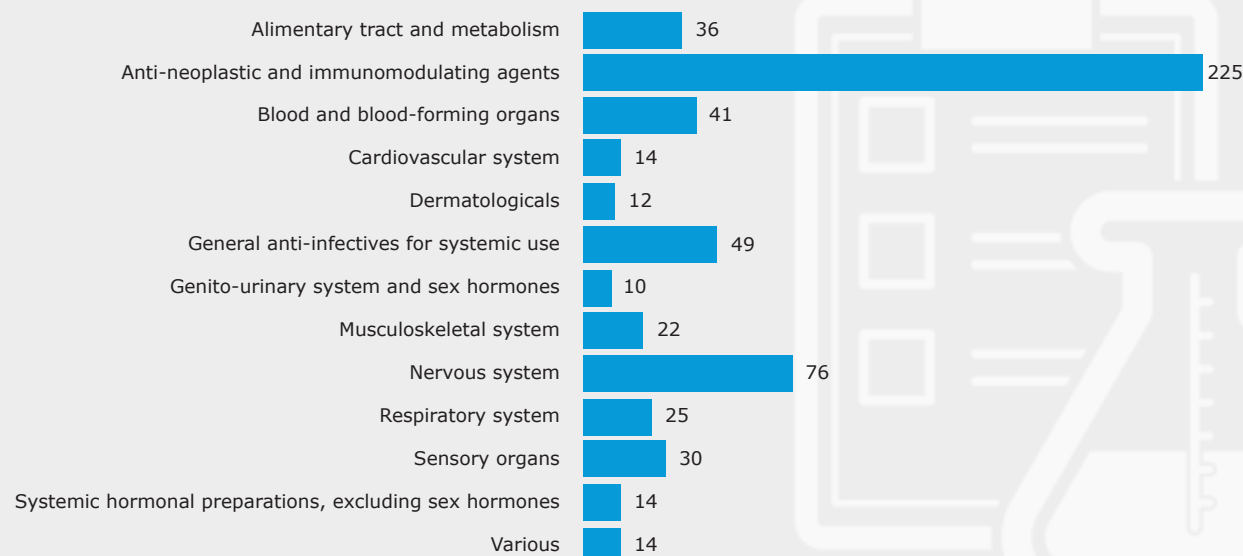
As in previous years, more than half of requests for scientific advice related to clinical issues, over one in four to preclinical issues, and the rest to quality issues: 56% of requests related to medicines in phase III and 27% to medicines in phase II of their clinical development.

Small and medium-sized enterprises (SMEs) increasingly make use of scientific advice. In 2016, 177 of the 582 requests came from SMEs, which is a 10% increase compared to 2015. SMEs accounted for a quarter of the requests received for parallel scientific advice with HTA bodies (6 out of 23). This tool allows regulators and HTA bodies to provide medicine developers with simultaneous feedback on development plans with the aim of aligning data requirements.

Scientific advice requests by affiliation of requester (2012-2016)



Scientific advice requests by therapeutic area (2016)



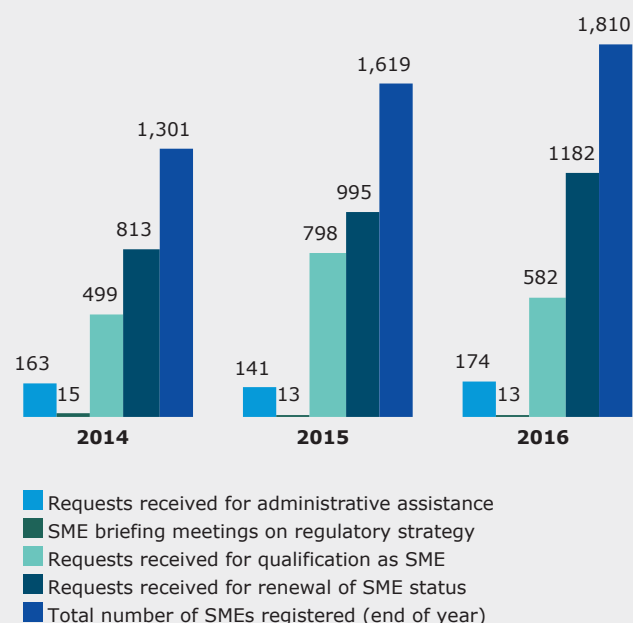
Support to small and medium-sized enterprises (SMEs)

SMEs are recognised as a driver of innovation in the EU. The Agency promotes innovation and the development of medicines by SMEs by giving active regulatory and administrative support to these companies. The Agency's SME office provides advice and guidance, organises topical workshops and produces a dedicated newsletter for SMEs registered with EMA. These companies also have access to a number of fee incentives to support their development process.

In 2016, EMA's user guide for SMEs underwent a major revision. The guide aims to support SMEs to better understand the EU legislative framework relating to medicines and the requirements for the development and authorisation of medicines for human or veterinary use.

The SME office dealt with 174 requests for direct assistance on administrative or regulatory aspects, the highest number since its creation in 2006, and organised 13 briefing meetings to assist SMEs that are unfamiliar with the EU regulatory system.

SME-related activities - requests received (2012-2016 human and veterinary medicines)



27 applications for marketing authorisation were submitted by SMEs in 2016. This is the highest number in the past six years and represents a quarter of all the marketing authorisation applications for human medicines received throughout the year; 11 of these are for orphan designated medicines.

Initial evaluation applications and SMEs (human medicines)					
	2012	2013	2014	2015	2016
Initial evaluation applications submitted by SMEs	20	8	7	15	27
Positive opinions	5	11	5	8	4
Negative opinions	0	3	1	1	1
Withdrawals	3	4	3	1	5

Orphan-medicine designation

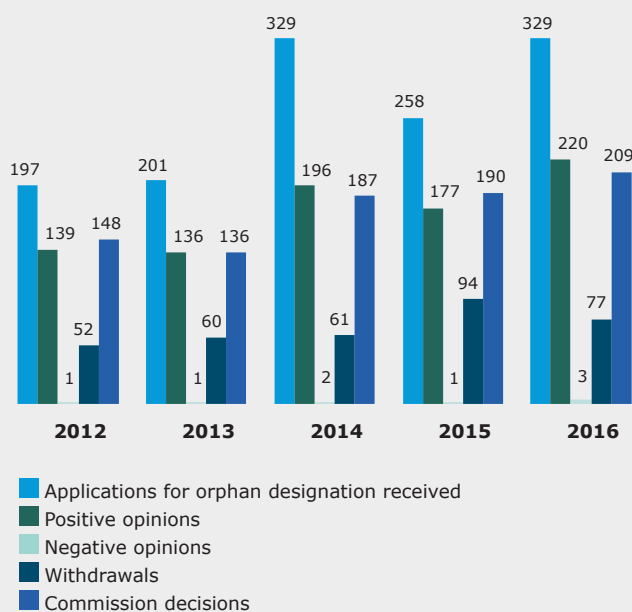
As it is often not profitable for companies to develop medicines for rare diseases under normal market conditions, the EU offers a range of incentives to encourage the development of so-called orphan medicines. Medicines with an EU orphan designation which have been granted a marketing authorisation benefit from 10 years of market exclusivity. During the development of an orphan medicine, other incentives such as fee reduction 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.

The number of applications for orphan designations reached a peak in 2016, with 329 compared to 258 in 2015. Almost half of applicants received advice from EMA on their request for orphan designation prior to submission, a service it has been offering since 2015.

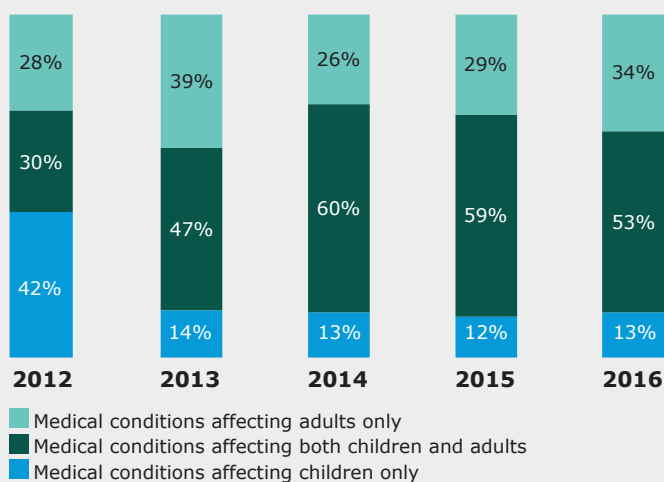
Almost one in three applications for orphan designation was submitted to EMA and to another regulatory authority in parallel in 2016. The Agency and its US and Japanese partners have put in place the parallel submission process to help rationalise and streamline the development of orphan medicines.

The European Commission supports the development of medicines for rare diseases financially, with over 12 million euros provided in 2016. More than 50% of the Commission's special contribution was used to provide protocol assistance to medicine developers and 28% for the assessment of applications for marketing authorisation.

Orphan medicine designation procedures (2012-2016)



Designated orphan medicines for the treatment of children and adults (2012-2016)



Note: All the COMP decisions on orphan designations can be found in the annex.

Medicines for children

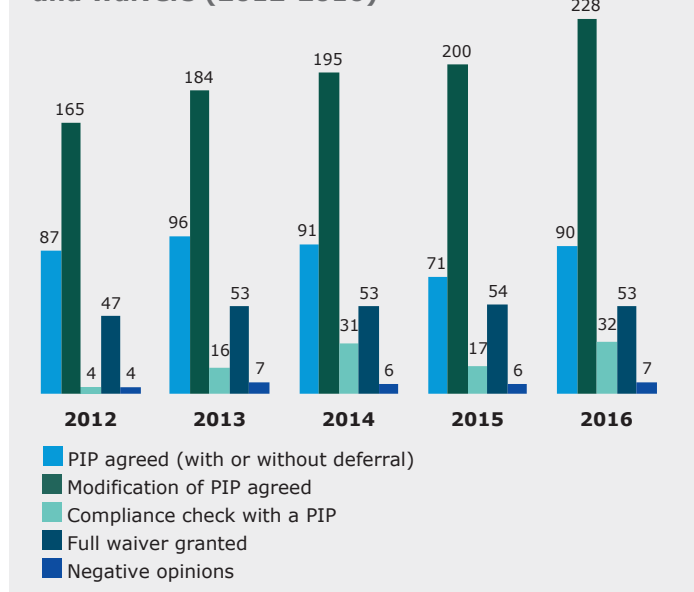
The Agency also promotes the development of medicines for children. The EMA assesses and verifies compliance with paediatric investigation plans (PIPs) and PIP waivers through the Paediatric Committee (PDCO). In addition, it provides secretarial support to the European Network of Paediatric Research at EMA (Enpr-EMA).

In 2016, the European Commission launched a public consultation to get views and feedback from stakeholders on the impact of the Paediatric Regulation after nearly 10 years of implementation. The consultation was based on a report prepared by EMA and its PDCO. The feedback received will form an integral part of the Commission's final report assessing the impact of the Paediatric Regulation on public health and the pharmaceutical industry, planned for publication in 2017.

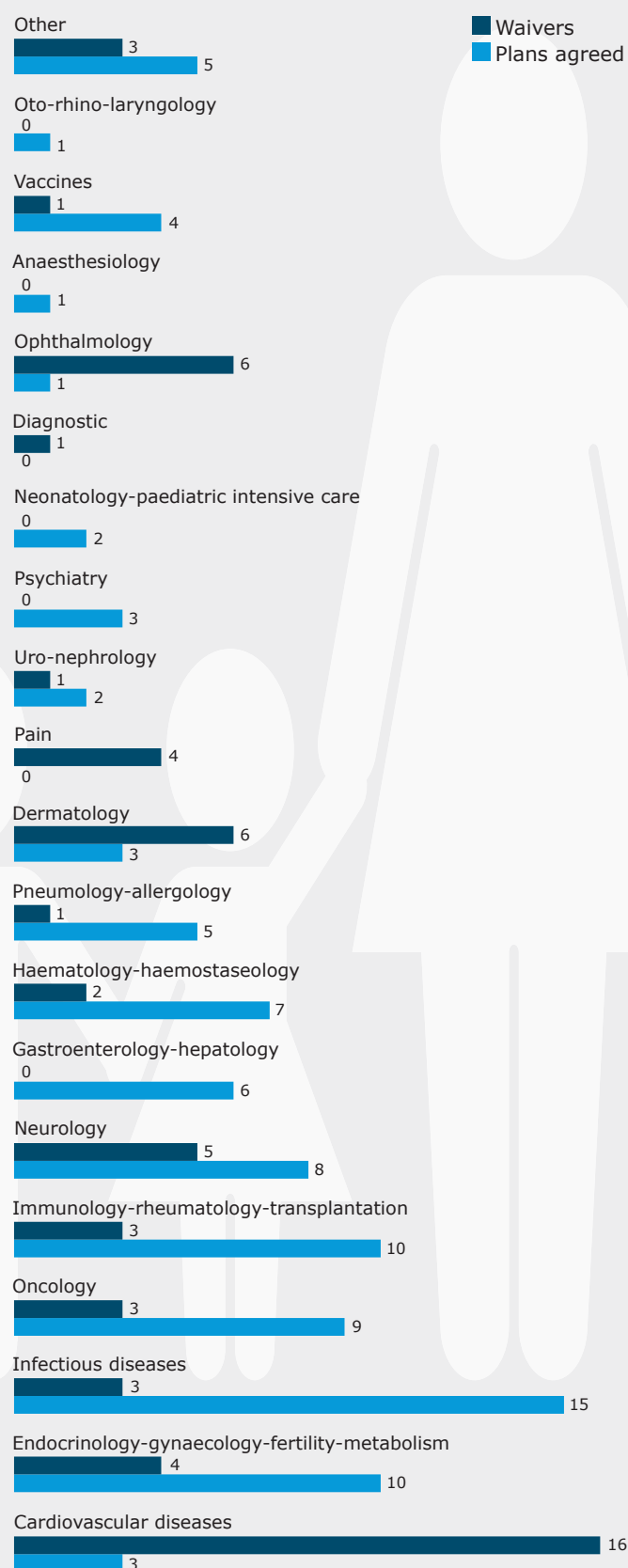
Medicine developers increasingly request advice on paediatric issues in the context of the Agency's scientific advice. In 2016, 165 scientific advice requests included questions on paediatric issues, compared to 109 in 2015.

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 2016, EMA assessed 121 paediatric studies in the context of article 46, all of which are available to the public through the EU Clinical Trials Register.

Opinions on paediatric investigation plans and waivers (2012-2016)



Paediatric investigation plans agreed and waivers granted (2016)

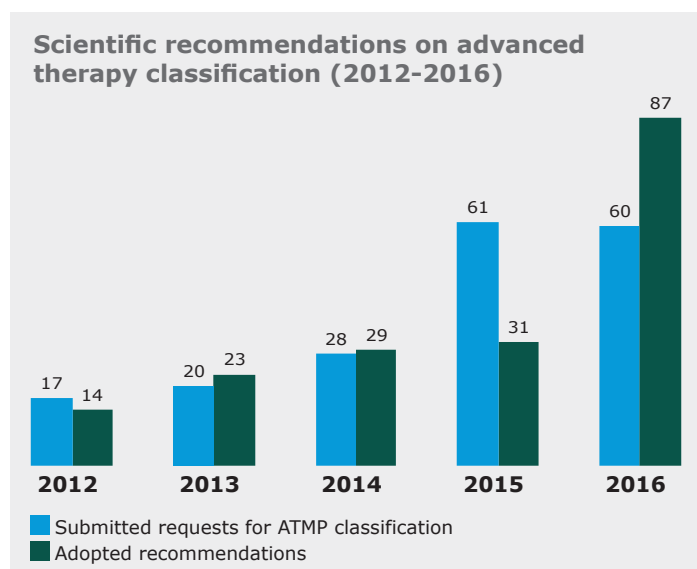


Note: All the PDCO decisions can be found in the annex.

Advanced-therapy medicinal products

Advanced-therapy medicinal products (ATMPs) comprise gene therapies, tissue-engineered products and somatic cell therapies. These medicines have the potential to reshape the treatment of a wide range of conditions, particularly in disease areas where conventional approaches are inadequate. 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.

Following a surge in the number of requests for ATMP classification in 2015, the number of recommendations adopted in 2016 reached a peak (87 compared to 31). The number of requests remained high in 2016.



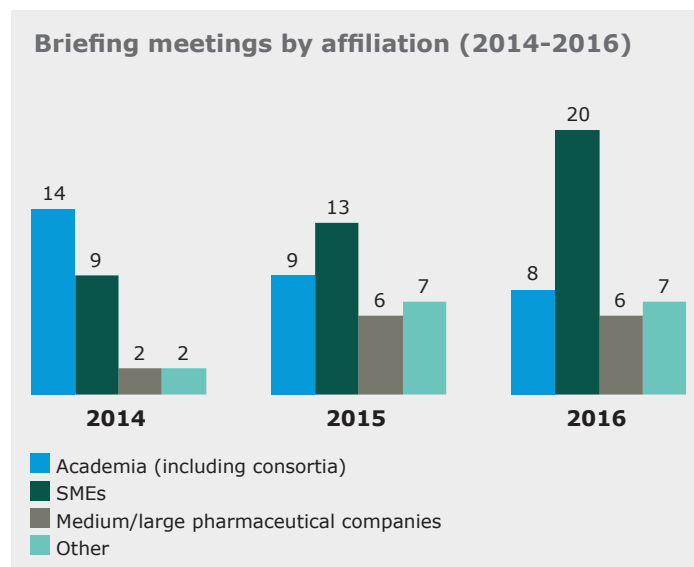
One application for marketing authorisation for an ATMP was received in 2016. This is for a therapy based on adult stem cells for the treatment of complex perianal fistulas.

Two ATMPs were recommended for marketing authorisation in 2016: Strimvelis, a gene therapy manufactured from a patient's own immature bone marrow cells that improves their ability to fight infection; and Zalmoxis, a cell-based therapy which contains T cells that have been genetically modified for patients receiving a haploidentical haematopoietic stem cell transplant (HSCT).

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.

41 meetings took place in 2016, compared to 35 in 2015; more than half of meetings were held with SMEs and one in five with academic developers.



40% of the meetings were on innovative ATMPs and 25% related to a broad spectrum of innovative methods to support the development of medicines and early exploration of novel (statistical) approaches in clinical trials, modelling and simulation.



Key scientific guidelines

The Agency develops scientific guidelines to provide advice to applicants or marketing-authorisation holders, competent authorities and other interested parties on the most appropriate way to test and monitor the safety, efficacy and quality of medicines. This is a key activity to support medicine development and ensure that the medicines available to patients are safe, effective and of high quality.

Guidelines are drafted by EMA working parties which comprise experts from across Europe.

EMA issues new guidelines and revises existing ones every year to reflect the latest scientific developments and experience gained through scientific advice and the evaluation and monitoring of medicines.

A selection of guidelines issued or revised in 2016 is listed below:

Topics	Content
First-in-human clinical trials	Draft revised guideline proposes changes to further improve the safety of trial participants.
Pharmacovigilance of biological medicines	New chapter in good pharmacovigilance practices (EU-GVP) introduces a set of measures to better monitor and manage the safety of biological medicines and optimise their safe and effective use in Europe.
Data integrity	New guidance defines set of questions and answers with advice for stakeholders on measures that ensure data integrity and minimise risks at all stages of the data life cycle in pharmaceutical quality systems.
Modelling and simulation	Draft guideline aims to support and guide the use of physiologically-based pharmacokinetic (PBPK) modelling currently being used during the development of medicines.
Patient-reported outcome measures in oncology studies	Guidance outlines scientific best practice for the use of patient-reported outcome and health-related quality-of-life measures in clinical studies in oncology.
Extrapolation of clinical trial data from adults to children	Draft reflection paper outlines a framework for the extrapolation of clinical trial data from adults to children to support the authorisation of new medicines for children.
Tuberculosis	Draft revision provides guidance on the evaluation of the efficacy of new medicines and new regimens and on the role of biomarkers to predict the effectiveness of the medicine(s) during clinical development.
Autism spectrum disorder (ASD)	First draft guidance for developers of medicines targeting autism is based on recent progress in the understanding of the pathological mechanisms behind ASD.
Alzheimer's disease and other types of dementias	Draft revised guideline on medicines for the treatment of Alzheimer's disease and other types of dementia takes into account recent progress in understanding the pathophysiology of Alzheimer's disease.

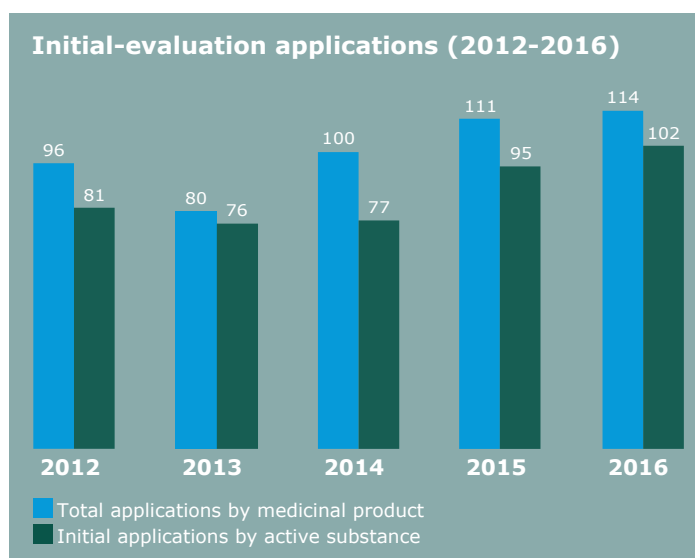
Note: a complete list of guidelines can be found in the annex.

Recommendations for marketing authorisation

Applications for initial evaluation

EMA's scientific committees carry out robust scientific evaluations of medicines. This forms the basis of the European Commission's decision on whether a medicine can be authorised for marketing throughout the EU. The initial evaluation covers all activities relating to the processing of marketing-authorisation applications for new medicines which 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.

The number of applications for initial evaluation received in 2016 was slightly higher than in 2015 and confirmed the upward trend observed over the past five years.

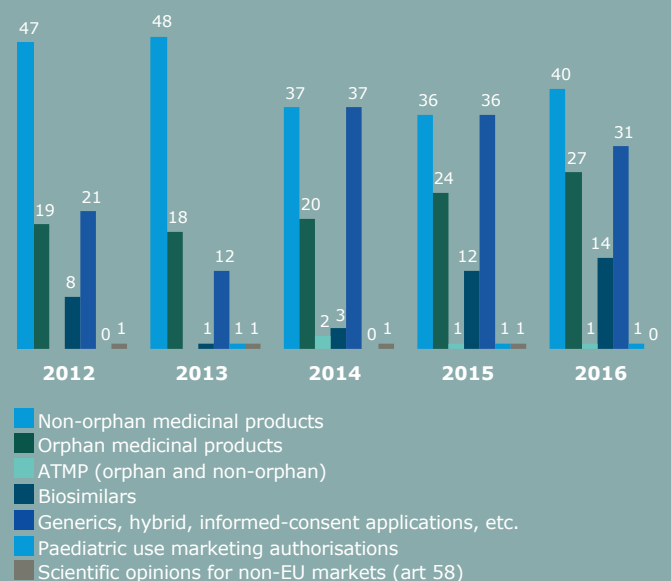


The number of applications for biosimilar medicines continues to increase year on year with 14 applications received in 2016 compared to eight five years ago. This is the highest number of applications for biosimilars received in one year so far.

As in previous years, about one in five applications concerned an orphan designated medicine.

EMA received one application for a paediatric-use marketing authorisation (PUMA). These are granted to medicines which are already authorised but are no longer under patent protection, and which are being explored for use in children.

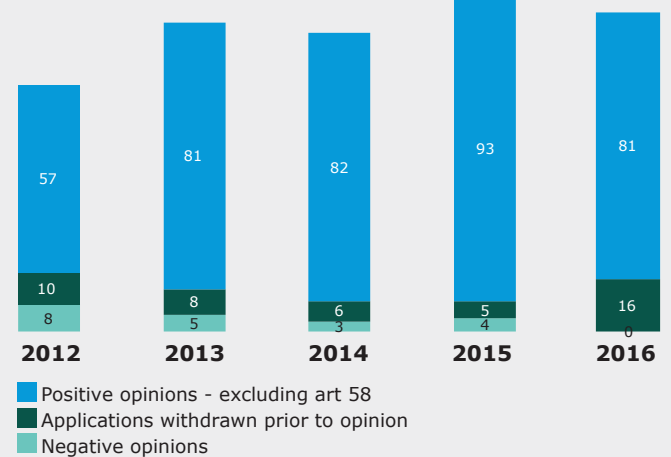
Initial-evaluation applications by type of application (2012-2016)



Outcome of initial evaluation

81 medicines for human use were recommended for approval in 2016, including 27 new active substances.

Outcome of initial-evaluation applications (2012-2016)

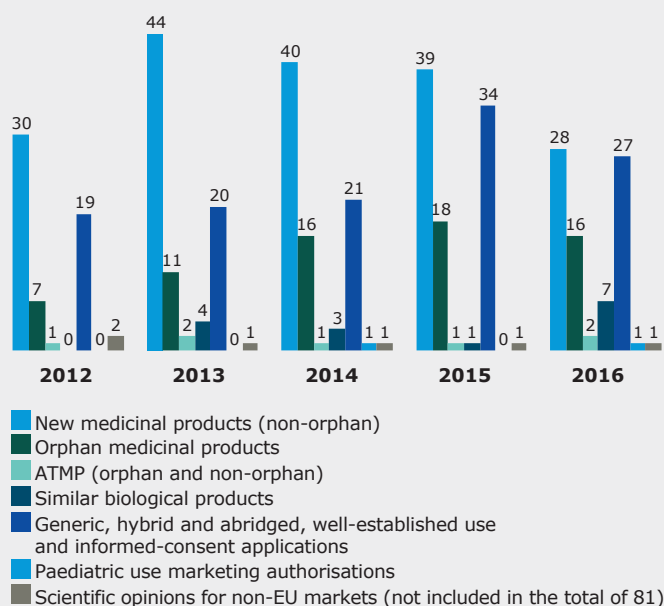


Two medicines initially received a negative opinion from the CHMP. Following re-examination, these medicines were also recommended for approval and are included in the 81 positive opinions for 2016.

The applications for 16 medicines were withdrawn by the applicants prior to CHMP opinion, the reason being that in most cases the data included in the application were insufficient to support a marketing authorisation.

57% of applicants granted a positive opinion from the CHMP in 2016 had received scientific advice during the development phase of their medicine. The applicants who initially received a negative opinion had not requested scientific advice.

Positive opinions by type of procedure (2012-2016)



Conditional marketing authorisations

Of the 81 medicines granted a positive opinion in 2016, eight were recommended for a conditional marketing authorisation. This tool allows for the early approval of a medicine based on 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 when they are already being used.

In 2016, two medicines that had previously received a conditional marketing authorisation (CMA) were granted a recommendation for a full marketing authorisation by the CHMP after fulfilling their post-authorisation obligations.

Since the introduction of the CMA tool in 2006, 13 medicines out of 33 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.

Note: A complete list of recommendations can be found in the annex.

CMA and switch to standard marketing authorisation

	2012	2013	2014	2015	2016
Positive opinions for CMAs	3	5	5*	3	8
Opinions recommending switch of CMA to standard marketing authorisation	0	3	2	2	2

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

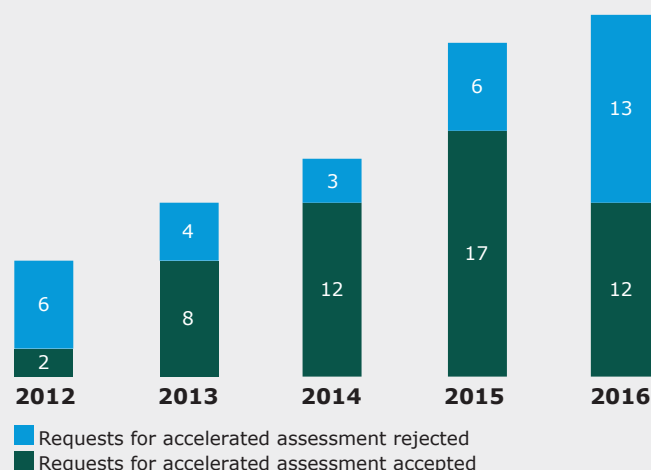
Accelerated assessment

Seven new medicines received a recommendation for marketing authorisation following an accelerated assessment. This mechanism is reserved for medicines that have the potential to address an unmet medical need in patients.

In addition, one medicine which received a positive opinion for use outside the EU also benefited from an accelerated assessment.

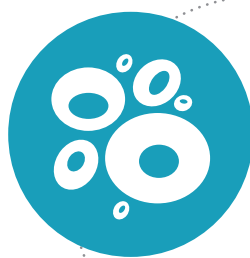
In 2016, 12 requests for accelerated assessment were accepted and 13 were rejected. The main reasons for rejection were that either the unmet medical need was not adequately justified or the data was not sufficient to justify a major public health interest.

Accelerated assessment requests (2012-2016)



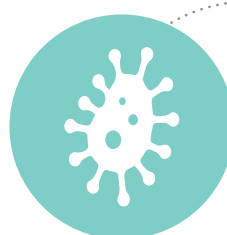
Medicines recommended for approval in 2016

Cancer



Aleccensa ●
Bortezomib Hospira
Bortezomib SUN
Cabometyx ●
Darzalex ●●●
Empliciti ●
Ibrance ●
Kispix ●
Lartruvo ●●●
Ledaga ●
Lonsurf ●
Ninlaro ●●
Onivyde ●
Pemetrexed Fresenius Kabi
SomaKit-TOC ●
Truxima (biosimilar)
Venclyxto ●●

Infections



Atazanavir Mylan
Darunavir Mylan
Descovy
Emtricitabine / Tenofovir disoproxil Mylan
Emtricitabine / Tenofovir disoproxil Krka
Emtricitabine - Tenofovir disoproxil Zentiva
Epclusa ●
Odefsey
Tenofovir disoproxil Mylan
Tenofovir disoproxil Zentiva
Vemlidy
Zavicefta
Zepatier
Zinplava

Cardiovascular



Amlodipine-Valsartan Mylan
Inhixa (biosimilar)
Ivabradine JensonR
Ivabradine Zentiva
Mysildecard
Neparvis
Uptрави
Tadalafil Generics
Thorinane (biosimilar)

Rheumatology



Flixabi (biosimilar)
Lifmior
Movymia (biosimilar)
Nordimet
Olumiant
Sialanar
Terrosa (biosimilar)
Truberzi

Metabolism



Chenodeoxycholic acid ●●
Cystadrops ●
Fiasp
Galafold ●
Glyxambi
Lusduna (biosimilar)
Qtern
Suliqua

Haematology/ Haemostaseology



Afstyla
Alprolix ●
Coagadex ●●
Idelvion ●
Vihuma
Zalmoxis ●●
(advanced therapy)

Hepatology/ Gastroenterology



Enzepti
Ocaliva ●●
Palonosetron Accord
Palonosetron Hospira

Pneumology/ Allergology



Aerivio Spiromax
Airexar Spiromax
Cinqaero
Granpidam

Neurology



Ongentys
Pregabalin Zentiva k.s.
Rasagiline Mylan
Zinbryta



Endocrinology

Parsabiv
Rekovelte



Immunology

Strimvelis ●
(advanced therapy)



Psychiatry

Zonisamide Mylan



Dermatology

Taltz



Radiolabelling agent

EndolucinBeta



Vaccine

Pandemic influenza vaccine (H5N1) MedImmune ●

- Orphan medicine
- Accelerated assessment
- Conditional marketing authorisation
- Approval under exceptional circumstances

The medicines that contain a new active substance are highlighted in blue

These figures reflect EMA's recommendations which are sent to the European Commission for the adoption of an EU-wide marketing authorisation.

*Two medicines initially received a negative opinion from the CHMP: Sialanar in 2016 and Ninlaro in May 2016. Following re-examination, Sialanar received a positive opinion from the Committee in July 2016 and Ninlaro received a positive opinion in September 2016. These two medicines are included in the 81 positive opinions for 2016.

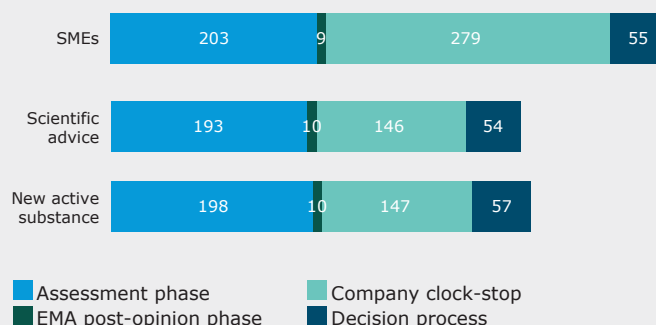
Average assessment time

EMA has a maximum of 210 days to carry out its assessment. Within this time frame, the CHMP must issue a scientific opinion on whether or not the medicine should be authorised. During the assessment, concerns with the application may be identified requiring further information or clarification from the company. In this case, the clock is stopped to give the company time to reply to the Agency, then restarted once the reply is received. The CHMP opinion is then transmitted to the European Commission which has the ultimate authority to grant the marketing authorisation and does so within 67 days after receipt of the CHMP opinion.

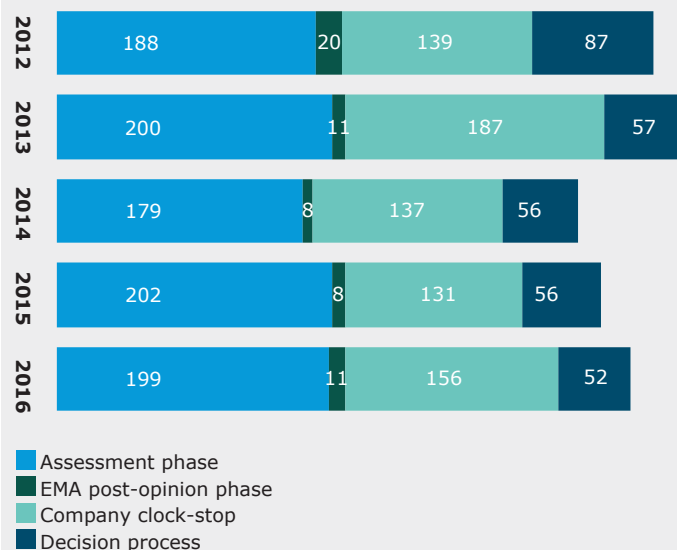
The overall time required for the assessment of initial marketing authorisation applications in 2016 remained stable.

Company clock-stop for applications submitted by SMEs was longer than average (279 days compared to 156 on average).

Average number of days for centralised procedure - subset (2016)



Average number of days for centralised procedures - positive opinions (2012-2016)



Post-authorisation activities

In 2016, the CHMP adopted 59 positive recommendations for extension of the therapeutic indication of already authorised medicines.

The CHMP found that five of these represented a significant extension of the existing indications and recommended granting an additional year of market exclusivity.

In line with previous years, in 2016 EMA received:

- 3,019 type-IA variations
- 2,000 type I-B variations
- 1,185 type-II variations
- 25 extensions of marketing authorisations

Extensions of therapeutic indications – highlights of 2016

Name of medicine	What is it used for?
Adcetris	For patients with Hodgkin's lymphoma at increased risk of relapse or progression
Caprelsa	For adults, children and adolescents aged 5 years and older with thyroid cancer
Gazyvaro	For patients with follicular lymphoma
Keytruda	For patients with non-small cell lung carcinoma
Opdivo	For patients with advanced renal cell carcinoma
Stelara	For patients with Crohn's disease
Truvada	For pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually-acquired human immunodeficiency virus type 1 (HIV-1) infection in adults at high risk
Zontivity	For patients with peripheral arterial disease

Note: A complete list of extensions of indications can be found in the annex.

Risk management plans

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

In 2016, 266 RMPs were submitted in relation to new marketing authorisation applications, which include changes made during the evaluation process; 739 requests to change existing RMPs were received.

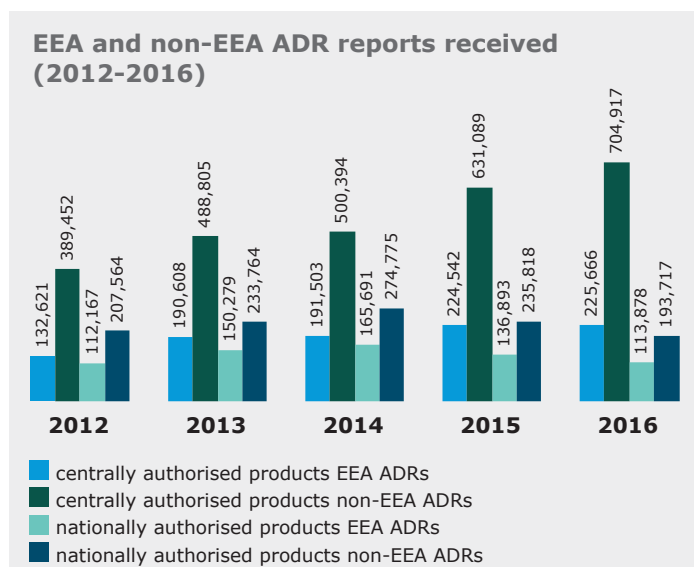
Safety monitoring of medicines

EMA and EU Member States are responsible for coordinating the EU's safety-monitoring or 'pharmacovigilance' system for medicines. They constantly monitor the safety of medicines 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 PRAC plays 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

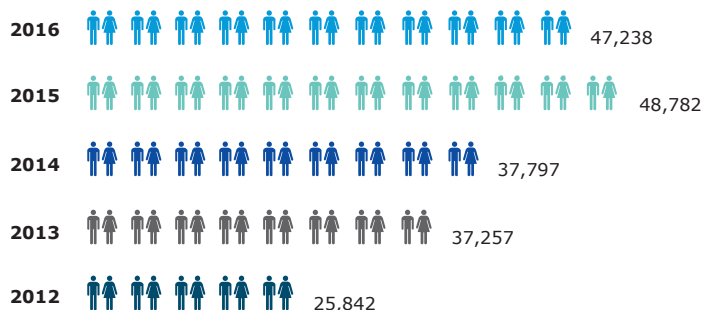
The Agency's main responsibilities in relation to the safety monitoring of medicines include coordination of the European pharmacovigilance system, provision of information on the safe and effective use of medicines, and the operation and maintenance of the EudraVigilance system. Both EMA and national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

More than 1.2 million ADRs were reported to EudraVigilance in 2016, a figure similar to the previous year.



The number of reports originating from patients in the European Economic Area (EEA) in 2016 was almost as high as in 2015 (approximately 47,000).

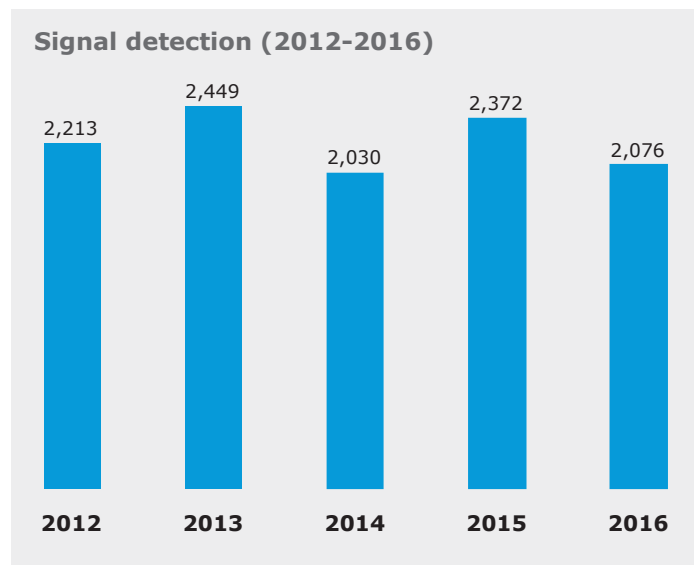
Number of reports from patients



Signal detection

A safety signal is information on a new or incompletely documented adverse event which is potentially caused by a medicine and 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 leads to changes in the information on medicines available for patients (in the package leaflet) and prescribers (in the summary of product characteristics).

In 2016, 2,076 potential signals were reviewed by EMA, 83% of which originated from monitoring the EudraVigilance database.



Outcome of signal assessment

**94 confirmed signals prioritised
and assessed by the PRAC**

48 signals detected
and validated by EMA

46 signals detected and validated
by EU Member States

4 signals led
to a referral
procedure to
further investigate
the issue

2 signals triggered
another regulatory
action such as a
recommendation
to update the
risk management
plan (RMP) or
assessment
through a study

28 signals led to
an update to the
product information

3 of these also
included a Direct
Healthcare
Professional
Communication
(DHPC) to highlight
important new
safety information
to prescribers

30 signals were
still under review
by the PRAC at
the end of 2016
as further data
were required

30 signals led to
recommendation
for routine
pharmacovigilance

Periodic update safety reviews

Marketing authorisation holders are required to submit a report on the evaluation of the benefit-risk balance of a medicine to the regulatory authorities at regular, predefined times 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 it (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. These reports are called Periodic Safety Update Reports (PSURs) and when the assessment procedure involves more than one medicinal product with the same active substance the procedures are referred to as Periodic Safety Update Single Assessment or PSUSA.

791 recommendations were issued by the PRAC based on the assessment of PSURs and PSUSAs in 2016, a 25% increase over 2015. This is due to the increasing number of single assessments of active substances only contained in nationally authorised medicines, an activity EMA initiated in 2015. These account for more than 33% of all the assessments finalised in 2016.

Almost one in five assessments led to changes in the product information to enable the safe and effective use of products by patients.

In addition to these, in the context of type-II variations, over 200 procedures led to changes to product information as new safety data were made available and assessed by EMA.

PSURs and PSUSAs finalised

	2013	2014	2015	2016
PSURs stand-alone (CAPs only)	430	426	470	511
PSUSAs - CAPs with NAPs	6	45	27	16
PSUSAs - NAPs only	0	0	136	264
Total outcomes	436	471	633	791

PRAC outcomes of PSURs and PSUSAs

	2013	2014	2015	2016
Maintenance	360	383	500	637
Changes to product information	76	88	133	154
Suspension	0	0	0	0
Revocation	0	0	0	0
Total outcomes	436	471	633	791

Post-authorisation safety studies and post-authorisation efficacy studies

A post-authorisation safety study (PASS) can be 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.

In 2016, the PRAC assessed 10 imposed PASS protocols that were requested to obtain further information on a medicine's safety.

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.

6 PAES, corresponding to five medicines, were imposed on companies by the CHMP in order to collect further data on the benefits of medicines while they are used by patients in real life.

Notification of withdrawals

Since 2014, companies have been required to report the cessation of the 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 coordinating these actions across the EU. These notifications are forwarded to all national competent authorities in the EEA. The list of withdrawn products is also published on the EMA website.

Notifications of withdrawn products for safety reasons

2014	2015	2016
132	160	118

Referral procedures

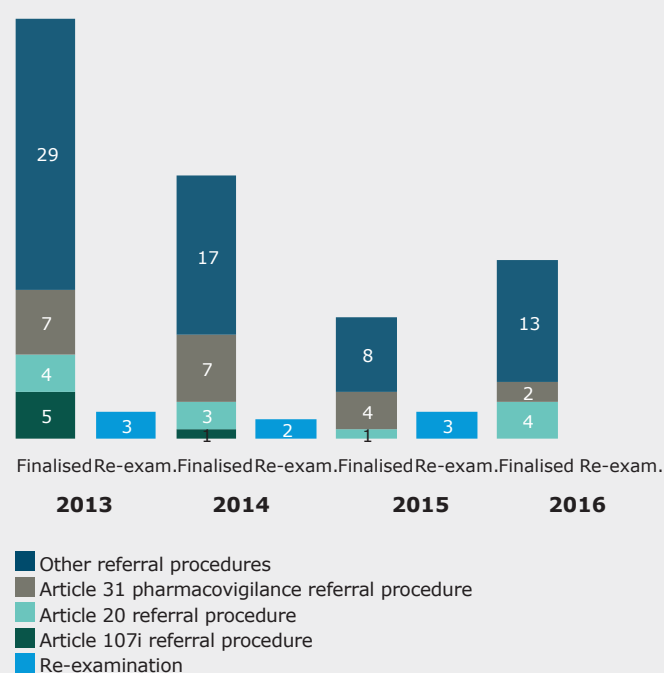
Referral procedures are used to address concerns over the safety or benefit-risk balance of a medicine, or disagreement among Member States on the use of a medicine. In a referral, the Agency is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine or class of medicines, and issues a cross-EU recommendation. The recommendation subsequently results in a legally binding decision throughout the Union issued by the European Commission or, less often, by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) in cases where only nationally authorised products are concerned.

19 referral procedures were finalised. Among these, six were pharmacovigilance-related (under articles 31, 20 or 107i of the pharmacovigilance legislation): five of these led to changes to the product information and one led to the revocation of marketing authorisations (Fusafungine nasal and oral solution).

The remaining 13 referral procedures were initiated to address either:

- efficacy or quality concerns with certain medicines;
- a need for EU-wide harmonisation of product information;
- differences between the Member States in the mutual-recognition and decentralised procedures.

Arbitration and referrals for human medicines finalised or re-examinations (2012-2016)



Note: Complete information on referral procedures can be found in the annexes.

Contribution of experts, patients and healthcare professionals to scientific assessments

EMA's scientific committees can consult additional experts, patients and healthcare professionals to enrich their scientific assessment of medicines. They are

involved in scientific advisory groups (SAG) or ad-hoc expert groups.

A total of 19 consultations took place in 2016 in the form of SAG meetings; 16 of these consultations included patients or carers.

Procedures with scientific advisory group or ad-hoc expert group involvement (number of consultations)					
	2012	2013	2014	2015	2016
Marketing authorisation (new MAA, new MAA re-examination, art. 58)	16	20	14	7	8
Extension of indication (including line extensions)	4	3	2	2	6
Referral (including re-examination)	5	2	5	3	5
Guideline	2	2	1	1	0
Other topics (renewal, PSUR, signal, class review)	1	0	1	3	0

Involvement of patients and healthcare professionals

Patients and healthcare professionals are involved in a wide range of EMAs activities. They bring a crucial 'real-life' perspective to scientific discussions on medicines, which is expected to lead to better outcomes in the regulatory process. Representatives of patients' and healthcare professionals' organisations participate by:

- contributing 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)				
	2013	2014	2015	2016
Scientific advice/protocol assistance	28	37	76	82
SAGs/ad-hoc expert meetings	33	35	23	28
Scientific committee/working party consultations	10	25	24	50
Workshops	87	104	115	141
Working groups and other ad-hoc activities	219	192	313	271
Document reviews conducted by patients and consumers	174	185	137	120

HCP involvement in EMA activities (interactions)				
	2013	2014	2015	2016
Scientific advice/protocol assistance	4	0	1	1
SAGs/ad-hoc expert meetings	49	32	21	26
Scientific committee/working party consultations	32	41	47	31
Workshops	n/a	64	59	106
Working groups and other ad-hoc activities	n/a	67	184	129
Document reviews conducted by healthcare professionals	0	43	29	55

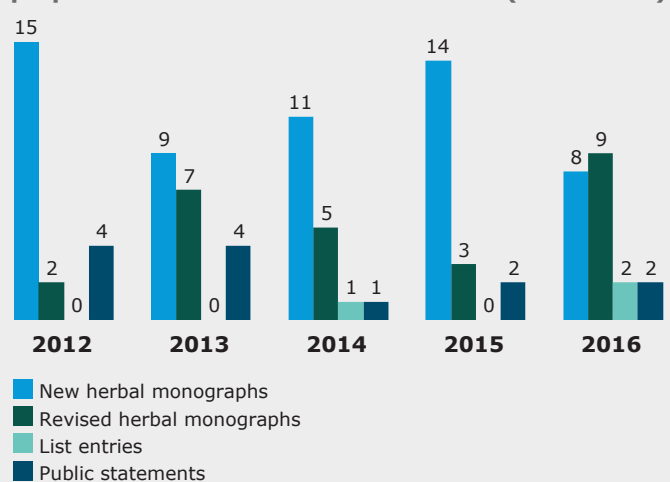
Herbal medicines

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

The assessment of 10 new herbal substances was completed in 2016, leading to the publication of eight final EU monographs and two final public statements, following public consultations.

Nine monographs were updated following a systematic review of newly available data.

Herbal monographs and list of herbal substances, preparations and combinations thereof (2012-2016)



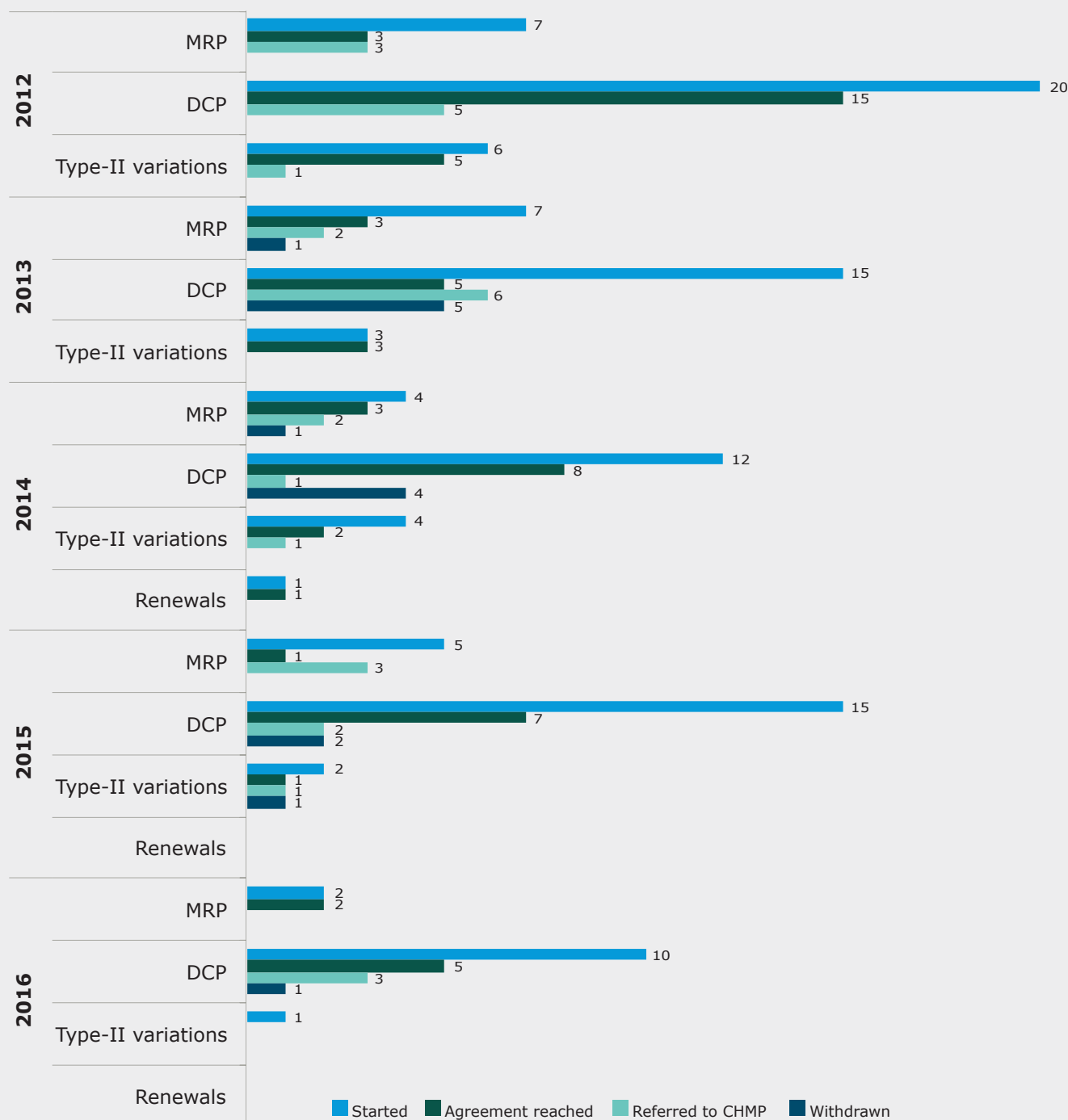
Note: A complete list of recommendations on herbal medicines can be found in the annex.

Mutual-recognition and decentralised procedures

90% of the medicines entering the EU market are nationally authorised. These are mainly generics which reach the market through the mutual recognition

procedure (MRP) and the decentralised procedure (DCP), the primary authorisation routes for generic applications within the EU. The CMDh and its working parties play a key role in the authorisation and maintenance of these medicines. EMA provides secretarial support to the CMDh in accordance with the approved rules of procedure.

Applications referred to CMDh (2012-2016)



Veterinary medicines

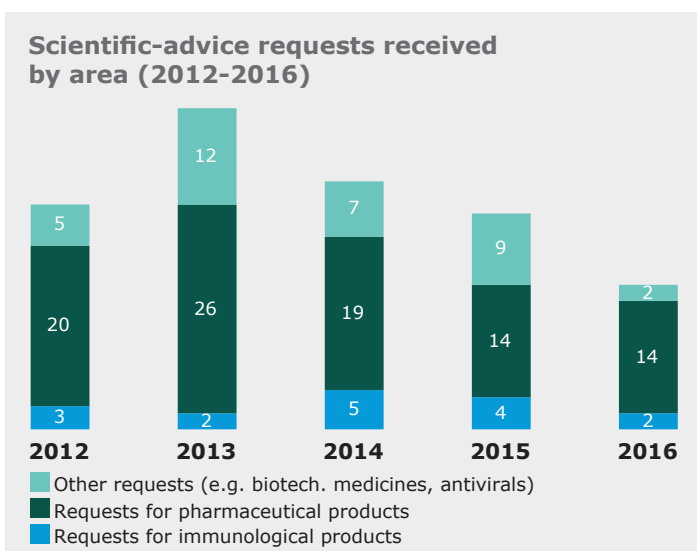
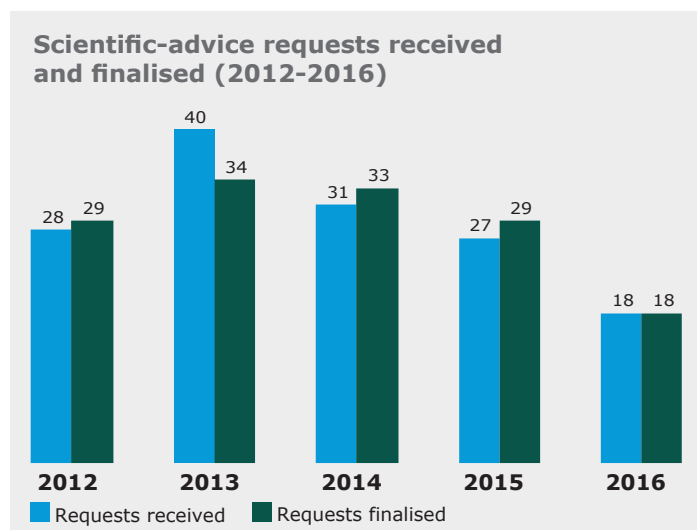
Activities supporting research and development

The Agency provides pre-authorisation support to medicine developers to boost innovation and research and enhance 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 facilitate 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 18 requests for scientific advice in 2016.

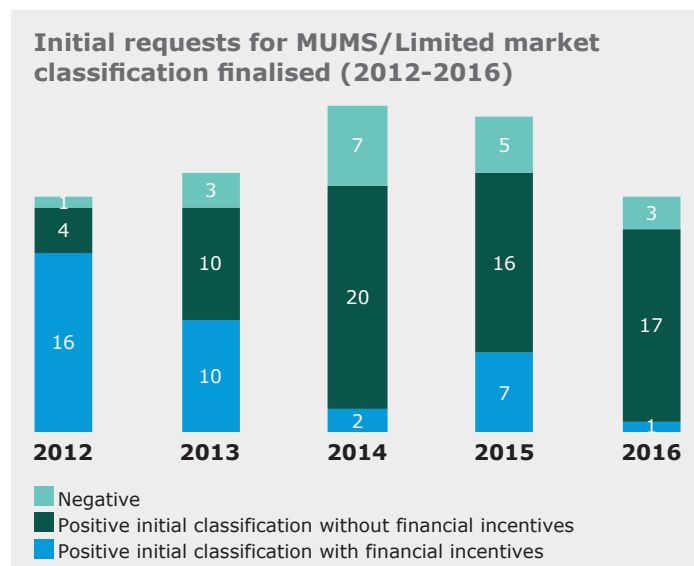


Minor Use Minor Species

The Agency's minor-use-minor-species (MUMS)/limited market policy was adopted in 2009 and 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.

In 2016, the Agency finalised 21 new requests for the classification of veterinary medicines intended for MUMS/limited market, showing a stable interest from medicine developers in developing products for MUMS/limited market.

In addition, four reclassification requests were submitted in 2016 following the expiry of the initial five-year classification, and all were reclassified as MUMS/limited market for a further five-year period (one with incentives and three without).



Of the medicines classified previously as MUMS/limited market, four products were recommended by the CVMP for marketing authorisation in 2016:

Clynav - a biotechnological vaccine that protects Atlantic salmon against pancreas disease

Eravac - a vaccine against the rabbit haemorrhagic disease virus

VarroMed - an antiparasitic medicine that treats the Varroa mite infestation in honey-bee colonies

Letifend - a biotechnological vaccine intended for leishmaniasis in dogs.

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 1,810 SMEs registered with EMA at the end of 2016, 4% are developing veterinary medicines and 5% are developing both human and veterinary medicines.

SMEs submitted nine of the 21 applications (43%) for marketing authorisation for veterinary medicines received in 2016.

In 2016, 18 requests for scientific advice were submitted, nine of which came from SME applicants, which represent 50% of all requests.

Five of the 11 medicines that received a positive opinion for a marketing authorisation were developed by SMEs; two of these contained new active substances.

Initial marketing authorisation applications from SMEs (veterinary medicines)					
	2012	2013	2014	2015	2016
Initial MAAs submitted by SMEs	2	2	2	4	9
Positive opinions	0	1	2	2	5
Negative opinions	0	0	0	1	0
Withdrawals	0	0	1	0	1

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 to emerging therapies and technologies.

In 2013, the scope of the Agency's ITF, which provides support to medicine innovation in the EU, was extended to cover support to veterinary medicines during the early stages of their development.

Four ITF meetings were requested and held in 2016 concerning the development of veterinary medicines.

Key scientific guidelines

A selection of guidelines issued or revised in 2016 is listed below:

Topics	Content
Antimicrobial resistance	Revised guideline on the demonstration of efficacy for veterinary medicines containing antimicrobial substances (antibiotics)
Toxic substances	Reflection paper on the authorisation of veterinary medicines containing potential persistent bioaccumulative and toxic substances
User safety	Draft guideline on the user safety of veterinary medicines administered locally
MUMS	Three revised guidelines on data requirements for pharmaceutical veterinary medicines intended for minor use or minor species (MUMS)/ limited market: quality; safety and residue; efficacy and target animal safety. One draft revised guideline on data requirements for immunological veterinary medicines for MUMS

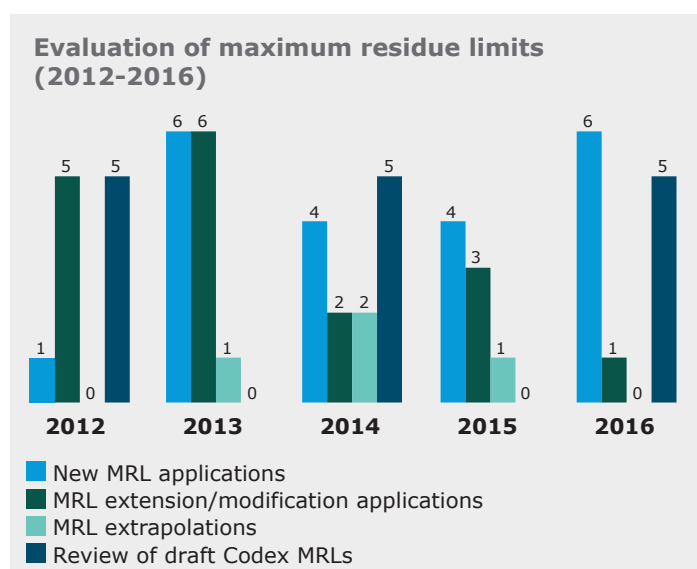
Note: The full list of CVMP guidelines released in 2016 can be found in the annex.

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. The goal is to ensure the safety of foodstuffs of animal origin, including meat, fish, milk, eggs and honey. EMA has the same responsibility for pharmacologically active substances in biocidal products used in animal husbandry. The European Commission formally establishes the MRL status.

Six applications for the establishment of new MRLs were received in 2016.

The continued submission in recent years of applications for MRLs indicates the continuing interest the animal health industry has in developing new products for food-producing animals.

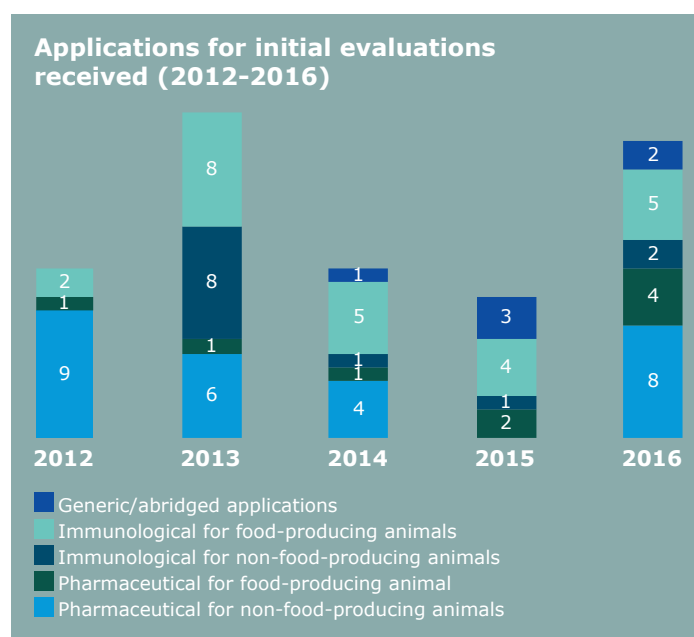


Authorisation activities

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.

21 applications for marketing authorisation were received in 2016, a twofold increase compared to 2015.

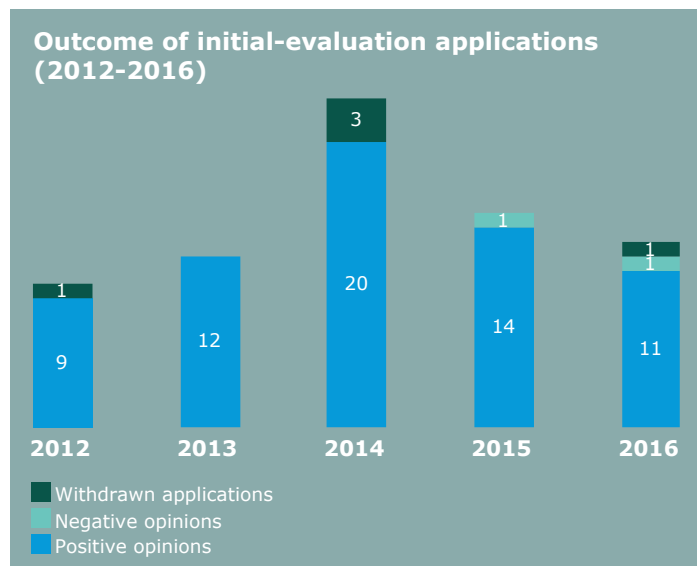


Five applications were for immunological products for food-producing animals. These applications demonstrate the continued interest of the animal health industry in developing vaccines. Vaccines are one type of alternative to antimicrobials to combat infectious diseases and to indirectly reduce the risk of AMR in food-producing animals.

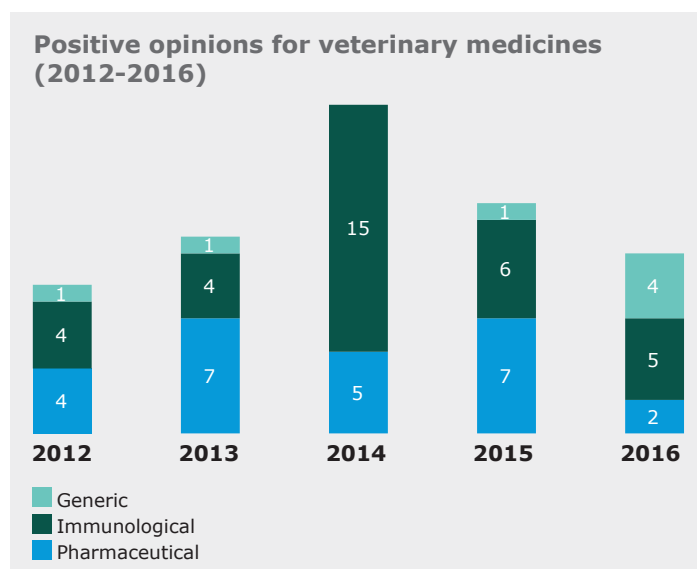


Recommendations for authorisation

11 new veterinary medicines were granted a positive opinion in 2016; five of these contained new active substances.



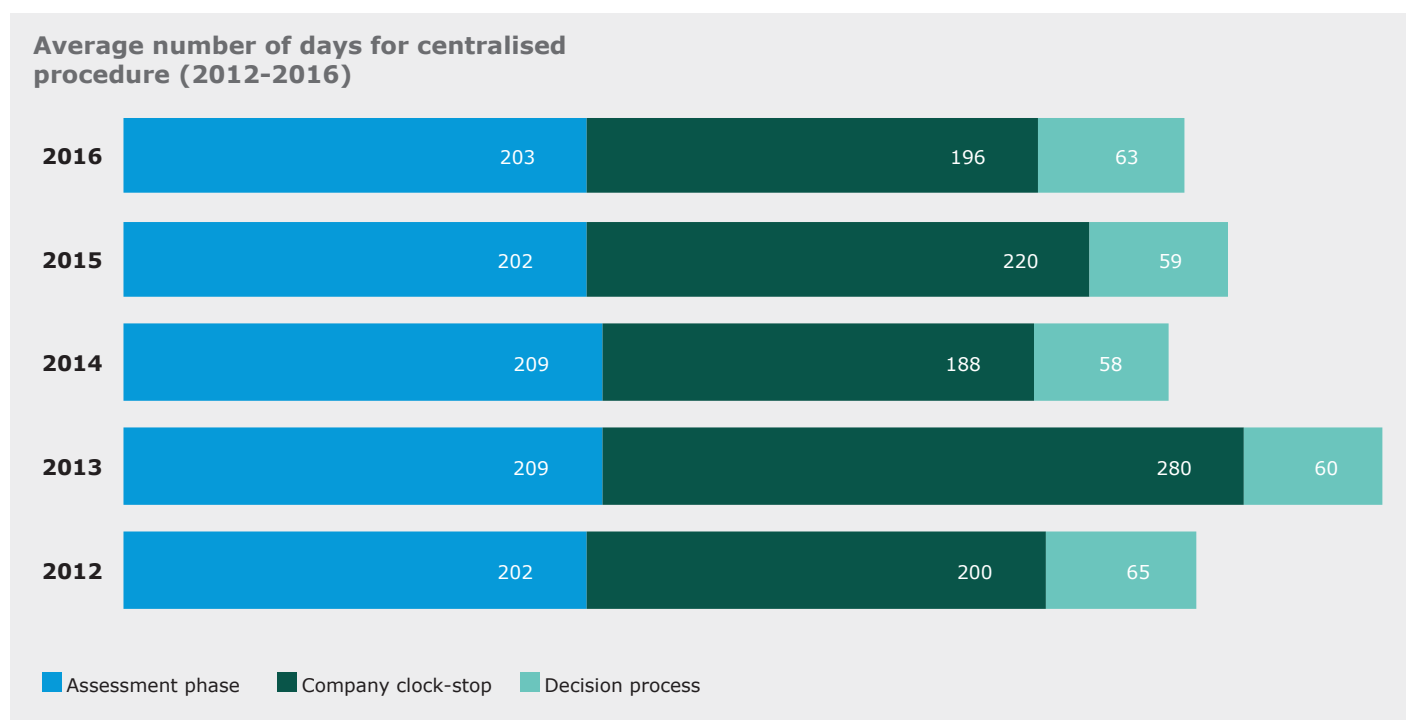
Five vaccines were recommended for marketing authorisation to prevent viral or bacterial infections in food-producing animals. Two of these vaccines were developed by means of a biotechnological process.



Veterinary medicine	What is it used for?	
Cepedex	A generic medicine used to sedate dogs and cats in case of moderately painful procedures and examinations	
Clynav - Atlantic salmon	A biotechnological vaccine based on a DNA plasmid that protects Atlantic salmon against pancreas disease caused by infection with salmonid alphavirus subtype 3	MUMS*
Coliprotec F4/F18 - pigs	A vaccine that protects against porcine post-weaning diarrhoea caused by <i>Escherichia coli</i> in pigs	
Eravac - rabbits	A vaccine that protects rabbits against a new variant of rabbit haemorrhagic disease virus called RHDV2	MUMS
Evalon - chickens	A vaccine that protects chicken against coccidiosis, a parasitic disease of the intestinal tract	
Halagon	A generic medicine used to treat newborn calves to prevent or reduce diarrhoea caused by an organism called <i>Cryptosporidium parvum</i>	
Letifend - dogs	A biotechnological vaccine based on a recombinant protein to protect dogs against leishmaniasis, a disease transmitted by sand flies	MUMS
Sedadex	A generic medicine used to sedate and relieve pain in dogs and cats	
Sevohale	A generic medicine that is used to produce and maintain general anaesthesia in dogs	
Stronghold plus	A medicine used to treat and prevent infestations with parasites that live on the skin or in the fur of cats and dogs, such as fleas and mites, as well as treating worm parasites that live inside the body	
VarroMed	An antiparasitic medicine that treats the varroa mite infestation in honey-bee colonies, considered to be the most significant parasitic health concern affecting honey bees worldwide	MUMS

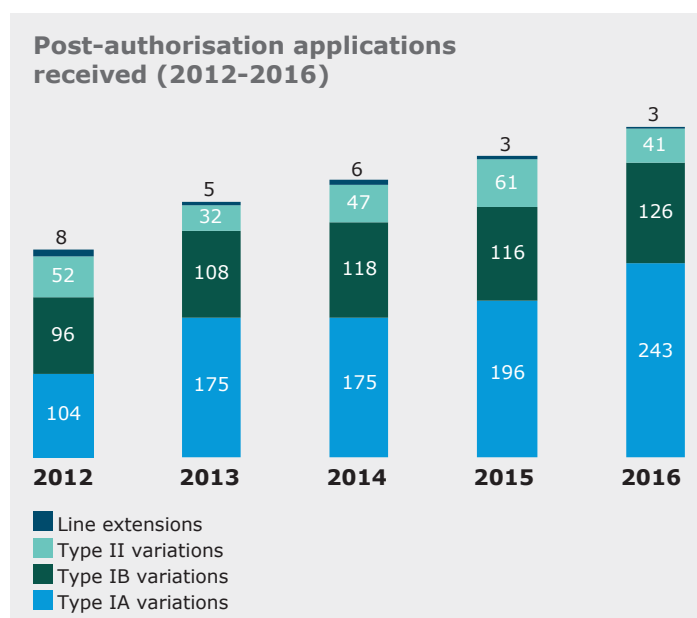
*MUMS = Minor-use-minor-species/Limited market

Average number of days for initial evaluations



Post-authorisation activities

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



The use of four known substances was expanded in 2016:

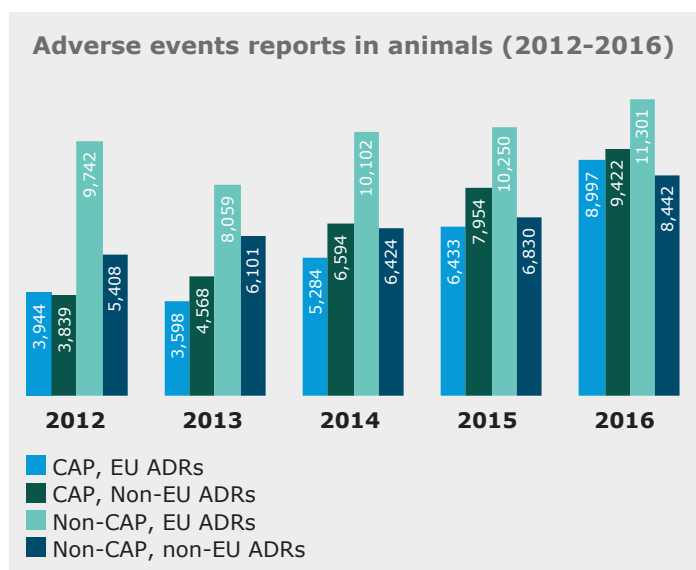
- Draxxin also to be used against swine respiratory disease (SRD)
- Profender also to be used as a spot-on solution for cats
- Poulvac E. coli also to be used in turkeys
- Trifexis also to be used to prevent and treat flea infestations in dogs.

Safety monitoring of medicines

Pharmacovigilance covers activities relating to the detection, reporting, assessment, understanding and prevention of adverse events (AEs) following the administration of veterinary medicines. It aims to ensure the monitoring of the safety of veterinary medicines and the effective management of risks throughout the EU.

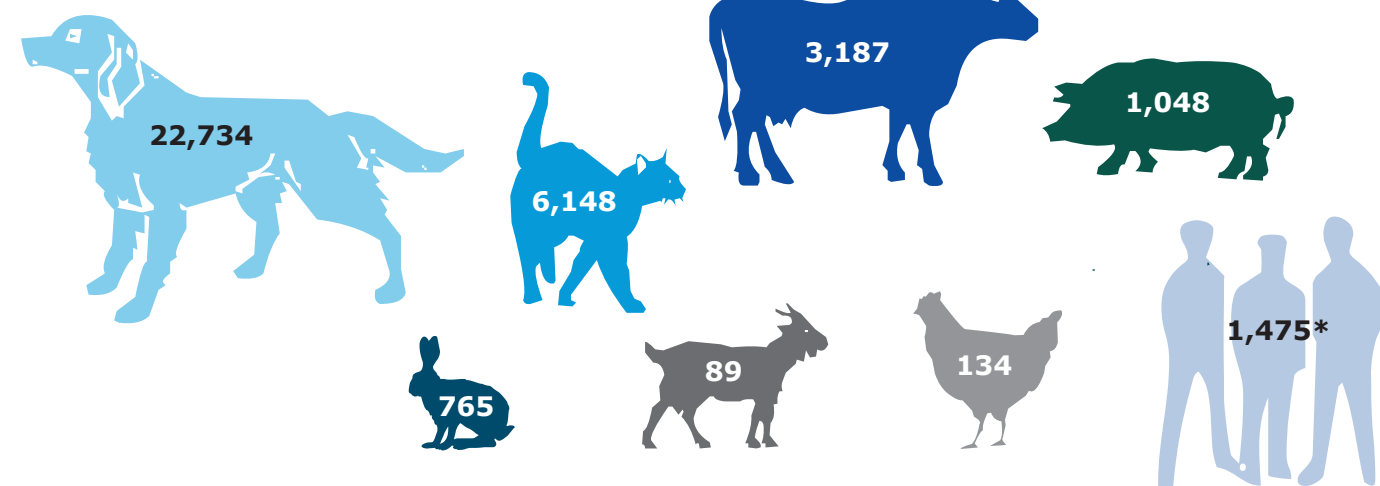
EudraVigilance

There was a general increase of 21% in the number of AE reports received in EudraVigilance in 2016 compared to 2015.



A long-term trend towards increased reporting is mainly attributed to the growing awareness among veterinarians of the value of pharmacovigilance reporting, as well as greater control by regulators of the implementation of pharmacovigilance legislative requirements by the veterinary pharmaceutical industry.

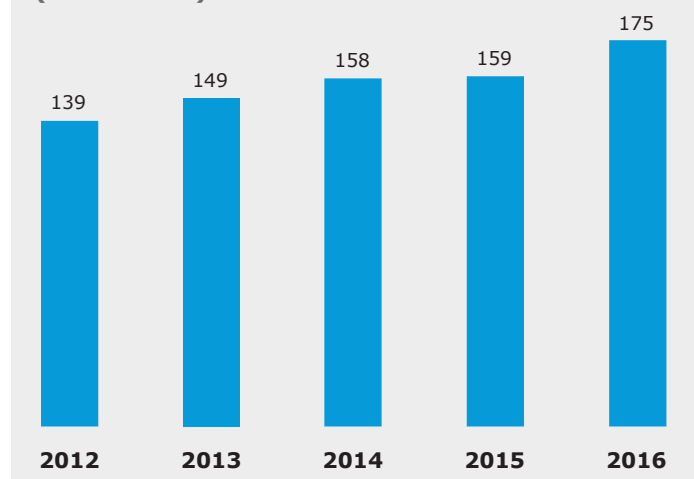
Number of adverse event reports per species



Periodic safety update reports (PSURs)

A PSUR provides 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).

Periodic safety update reports submitted (2012-2016)



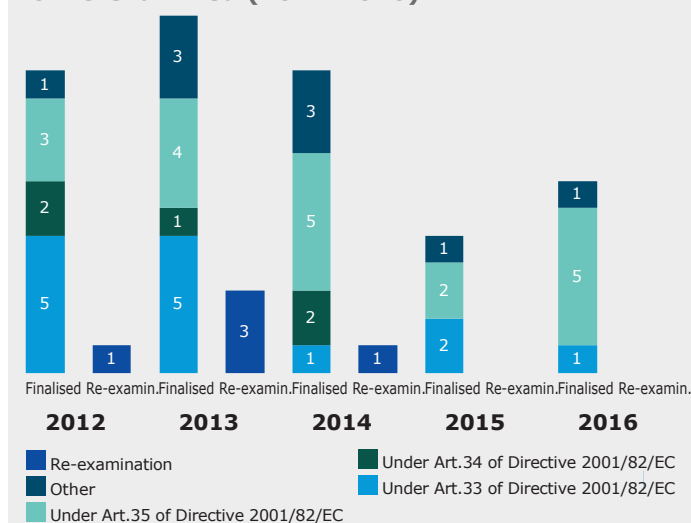
* Adverse events occurring in humans following exposure to a veterinary medicine, e.g. in case of accidental self-injection

Referral and arbitration procedures

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

Eight referral and arbitration procedures related to veterinary medicinal products began in 2016 and seven procedures were concluded.

Arbitrations and referrals finalised or re-examined (2012-2016)

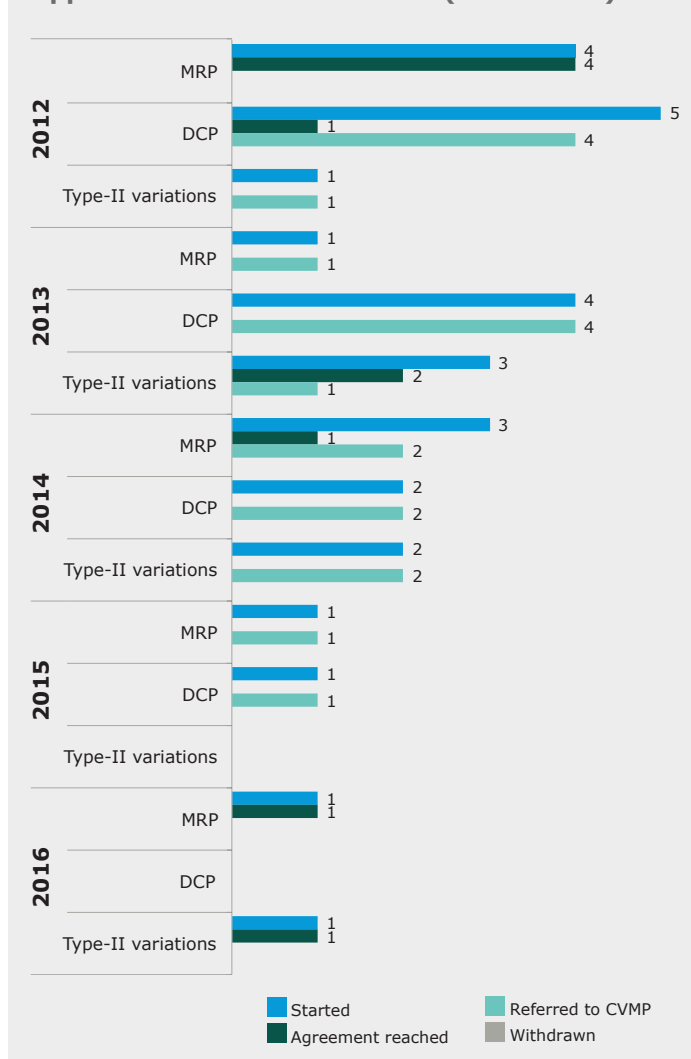


Note: Full information on referrals can be found in the annex.

Mutual-recognition and decentralised procedures

The Agency provides secretarial support to the Coordination 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 (2012-2016)



European medicines regulatory network

The European medicines regulatory network – a partnership between the European Medicines Agency, the European Commission and 50 medicine regulatory authorities in the EU and the EEA – is the basis of the Agency's success.

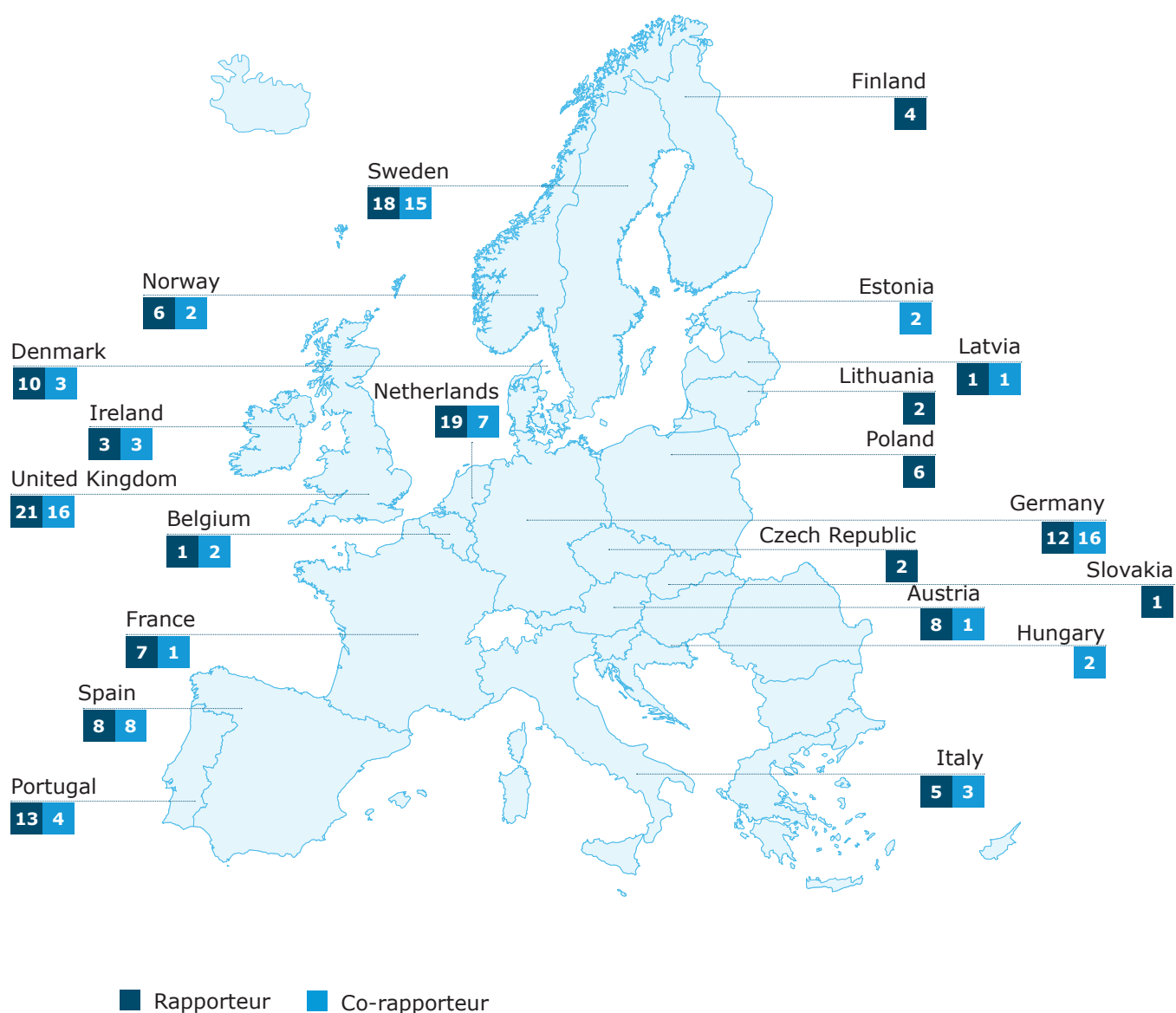
The network gives the Agency access to a pool of over 4,500 experts who provide the best-available scientific expertise for the regulation of medicines in the EU. Experts participate in the work of the Agency as members

of its seven scientific committees, 26 working parties, nine scientific advisory groups and a number of other ad-hoc advisory groups as well as members of the assessment teams carrying out the evaluation of medicines (see annex for further information on these groups).

Rapporteurships/co-rapporteurships

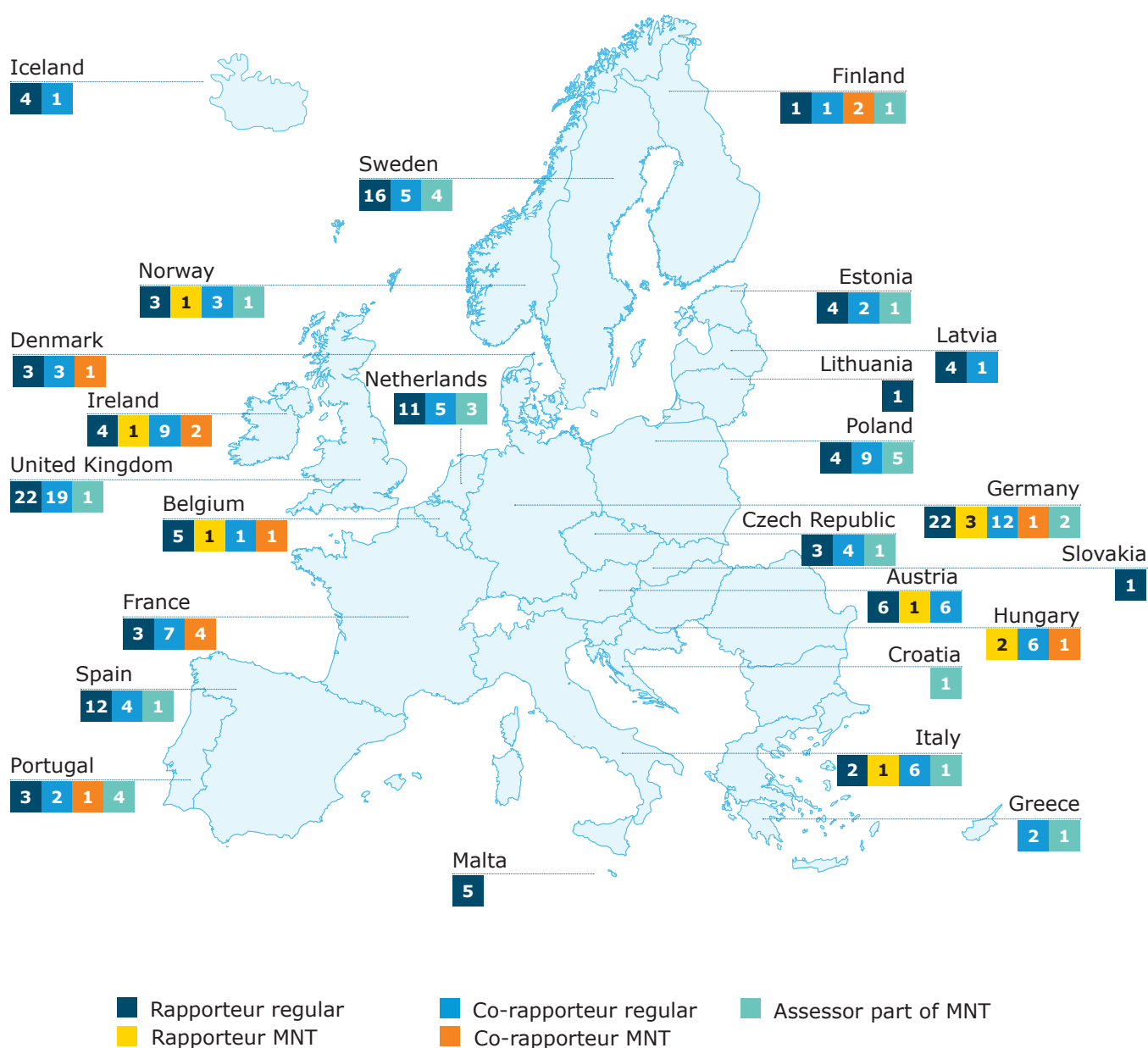
The assessment of a medicine by EMA's scientific committees is carried out by a rapporteur and a co-rapporteur who prepare the assessment reports and lead the discussions in the committees.

PRAC rapporteurs/co-rapporteurs appointed in 2016



CHMP rapporteurships/co-rapporteurships

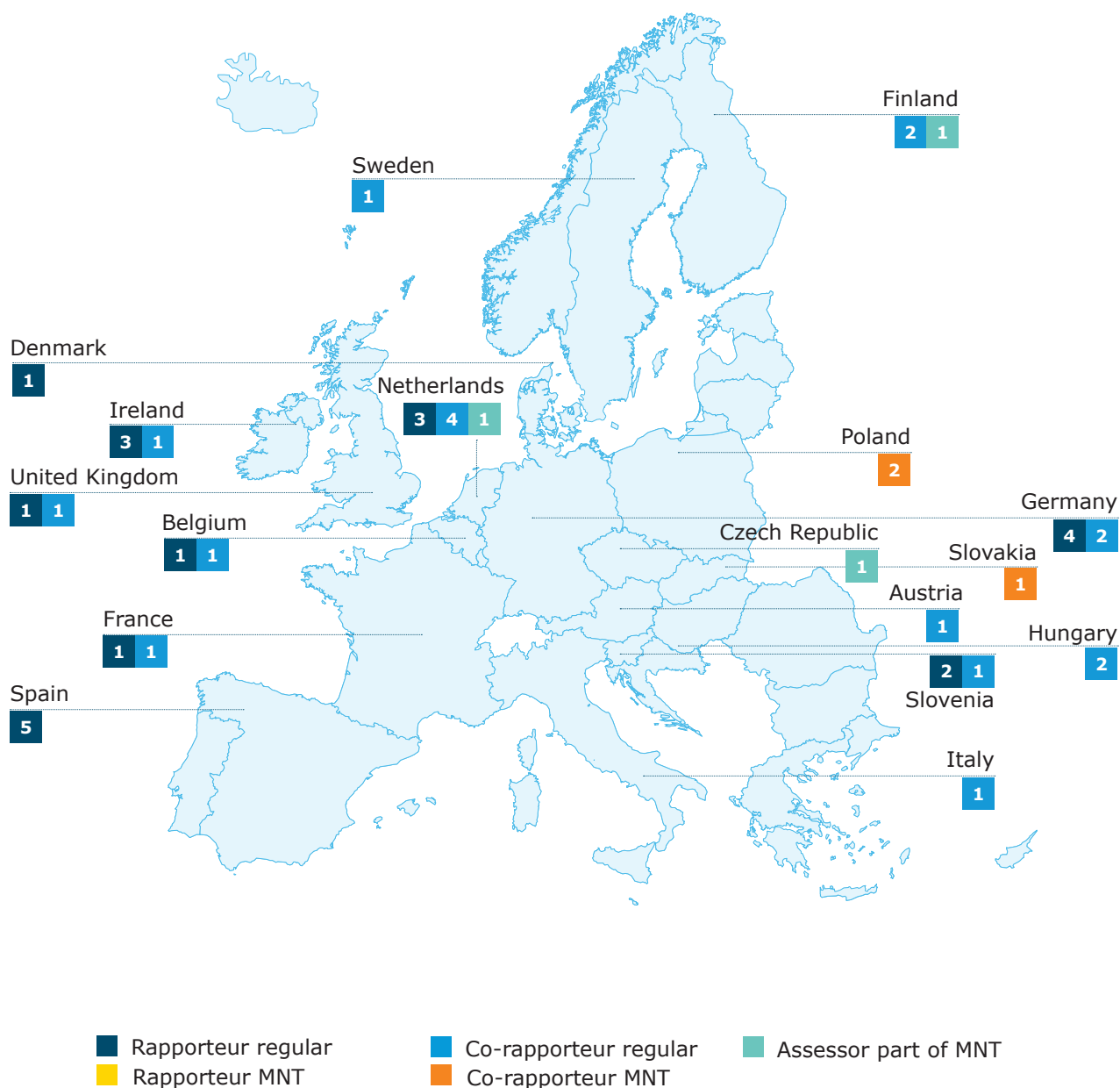
Since 2015, CHMP rapporteurs and co-rapporteurs have been able to create multinational teams (MNTs) for the initial assessment of marketing authorisation applications. Initially, in 2013, the scheme focused on co-rapporteurship. The table below presents the number of procedures in which each country was involved in 2016, 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 2016 (for initial MAs, including generics)

CVMP rapporteurships/co-rapporteurships

The concept of multinational teams was introduced in the CVMP in 2015 and continued in 2016.

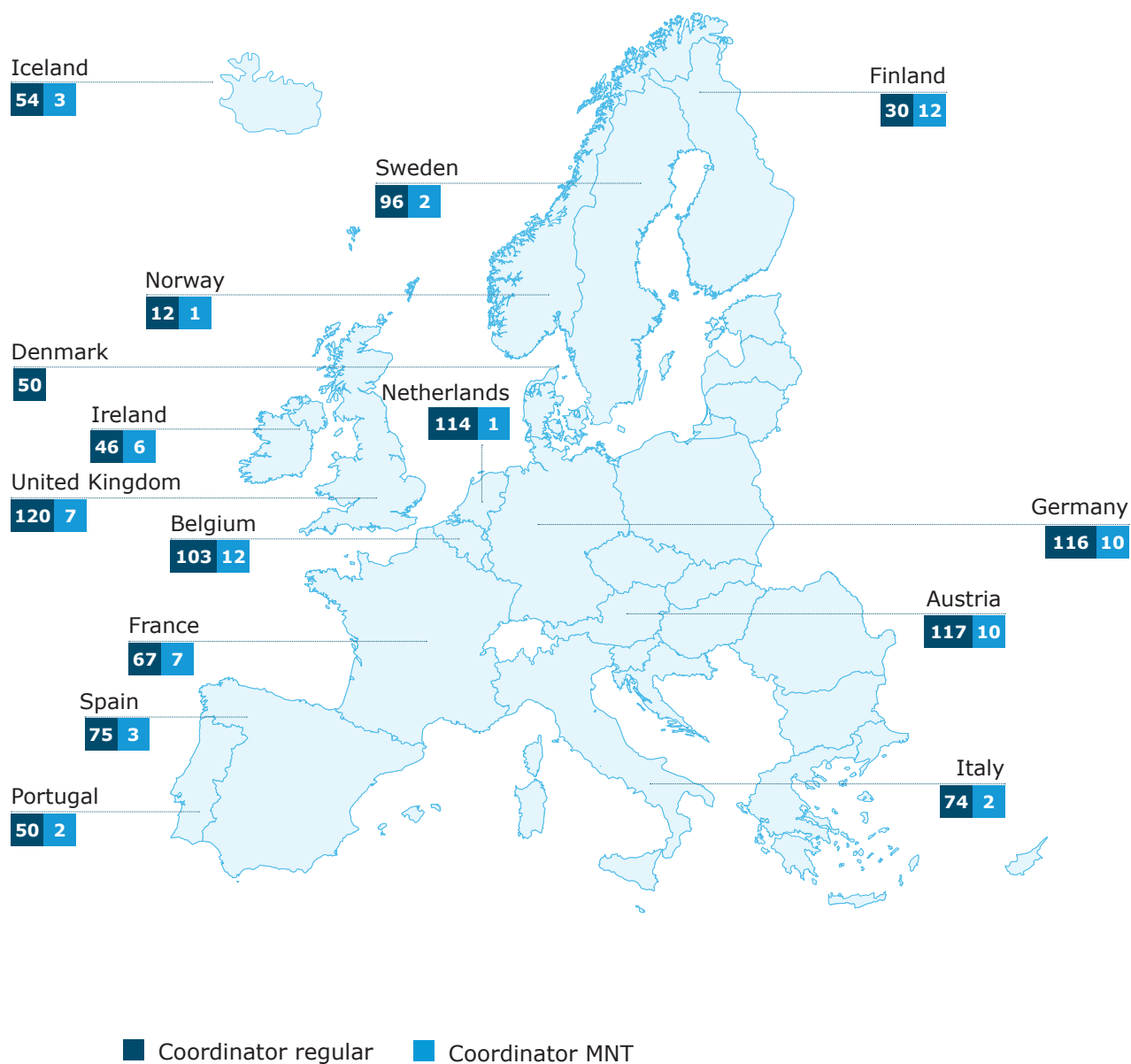
CVMP rapporteurs/co-rapporteurs appointed in 2016 (for initial MAs, including generics)



Scientific advice coordinators

The concept of multinational teams was also introduced in the CHMP Scientific Advice Working Party (SAWP).

CHMP SAWP coordinators appointed in 2016



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 an inspection requested by the CHMP or CVMP in the context of the assessment of marketing-authorisation applications and/or matters referred to these committees in accordance with EU legislation. The Agency plays a coordinating role while the responsibility for carrying out inspections rests with EU national competent authorities. EMA also coordinates the preparation and maintenance of risk-based inspection programmes for the verification of compliance with the principles of GMP, GCP and pharmacovigilance at Union level, as follows:

- risk-based programme for GMP inspections based on the results of inspections by trusted authorities;
- risk-based programme of routine GCP inspections of the clinical research organisations (CROs) most often used in the conduct of bioequivalence trials included in a marketing-authorisation application in the mutual-recognition and decentralised procedures (in collaboration with NCAs/CMDh);
- risk-based programme of routine pharmacovigilance inspections in relation to centrally authorised products (in collaboration with NCAs);
- a two-year programme of routine GCP inspections based on risk factors and a random element to ensure that a diverse range of applications, trials and sites and geographical locations are covered.

In the area of inspections, the Agency ensures the best use of resources through promoting mutual reliance and work sharing with other international authorities. For GMP inspections, there are a number of mutual-recognition agreements in place. GCP inspections include specific initiatives such as the EMA/FDA joint GCP inspections initiative, and the EMA/FDA/seven EU Member States regulatory authorities (Austria, France, Germany, Italy, Netherlands, Spain, United Kingdom) joint initiative to collaborate on the sharing of information and conduct of inspections of bioequivalence studies submitted in support of marketing-authorisation applications for generic medicines.

Through the work of the inspectors working groups, the Agency coordinates the development and setting of standards for GMP, GCP and GVP that facilitate harmonisation of standards within the EU and with standards set by international partners to facilitate global supply chains and access to authorised medicines.

The delivery of training and capacity building on inspection-related activities for inspectors and assessors, including non-EU regulators, is one area of focus for EMA.

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.

It 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.

Inspections

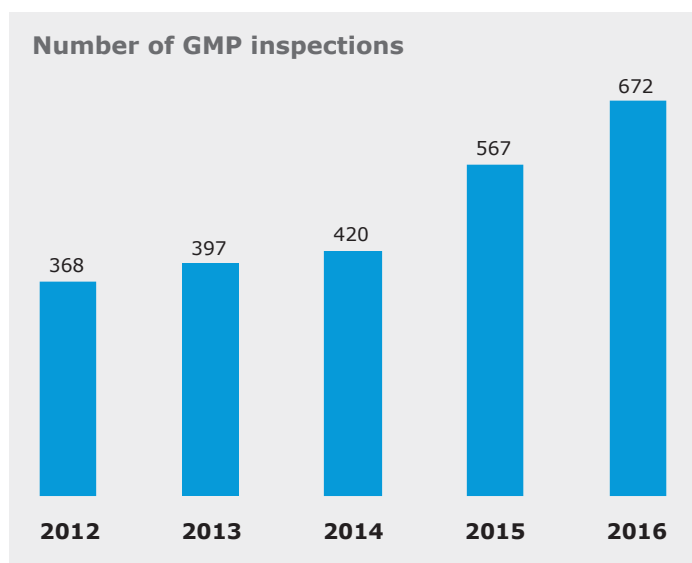
GMP, GCP and pharmacovigilance inspections requested by the CHMP or CVMP take place worldwide.

Such inspections requested by the CHMP represent just a small part of the total number of inspections performed by the EU/EEA inspectors as they also carry out inspections as part of their national programmes in the context of:

- the evaluation of marketing-authorisation applications (MRP, DCP or national procedures);
- the oversight of manufacturers importing medicines into the EU;
- the oversight of the conduct of clinical trials in Europe;
- the oversight of compliance with pharmacovigilance obligations.

GMP inspections

The number of GMP inspections requests increased by 18.5% in 2016, linked to the growing number of centrally authorised products.



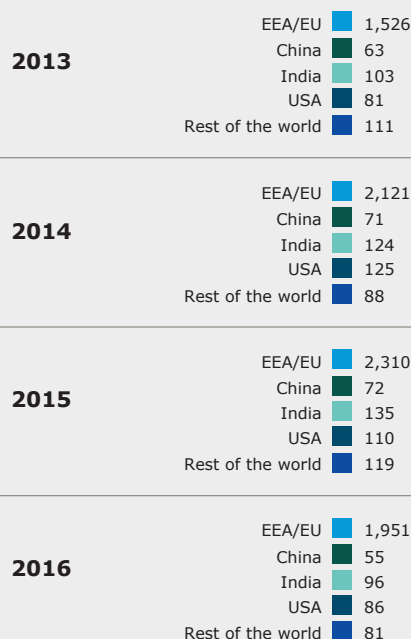
EudraGMDP is a database operated by EMA which supports the exchange of information on GMP compliance, as well as on manufacturing and importation authorisations. It holds all the data collected in inspections conducted by EU/EEA authorities, including those requested by the CHMP/CVMP.

In 2016, approximately 1% of the inspections conducted led to the issue of a non-compliance statement (24 out of 2,293).

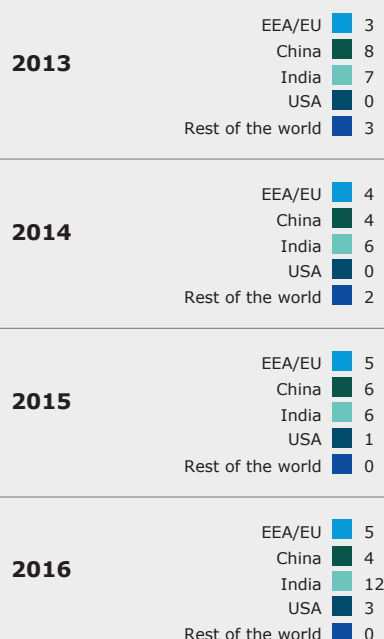
When inspections lead to findings, companies have to implement corrective action plans agreed with inspectors. Seven statements of non-compliance relating to centrally authorised products were issued either in relation to the active substance or to the finished product, which resulted in the following actions:

- one non-compliance statement prohibited the manufacturing site from supplying a centrally authorised medicine in the EU and the site was removed from the dossier.
- two non-compliance statements led to the prohibition of supply of active substance for non-critical medicines. In cases where import was allowed, additional testing of each batch of the imported active substance was required before it could be used.
- one non-compliance statement resulted in the removal and replacement of the manufacturing site during the assessment procedure prior to approval of the marketing-authorisation application.
- one non-compliance statement resulted in the withdrawal of an application for marketing authorisation by the applicant.
- one non-compliance statement resulted in the recall of marketed products and prohibited the supply of centrally authorised medicinal products from the manufacturing site concerned.
- one non-compliance statement resulted in no action as no centrally authorised products were manufactured during the period of non-compliance.

GMP certificates issued by EEA authorities



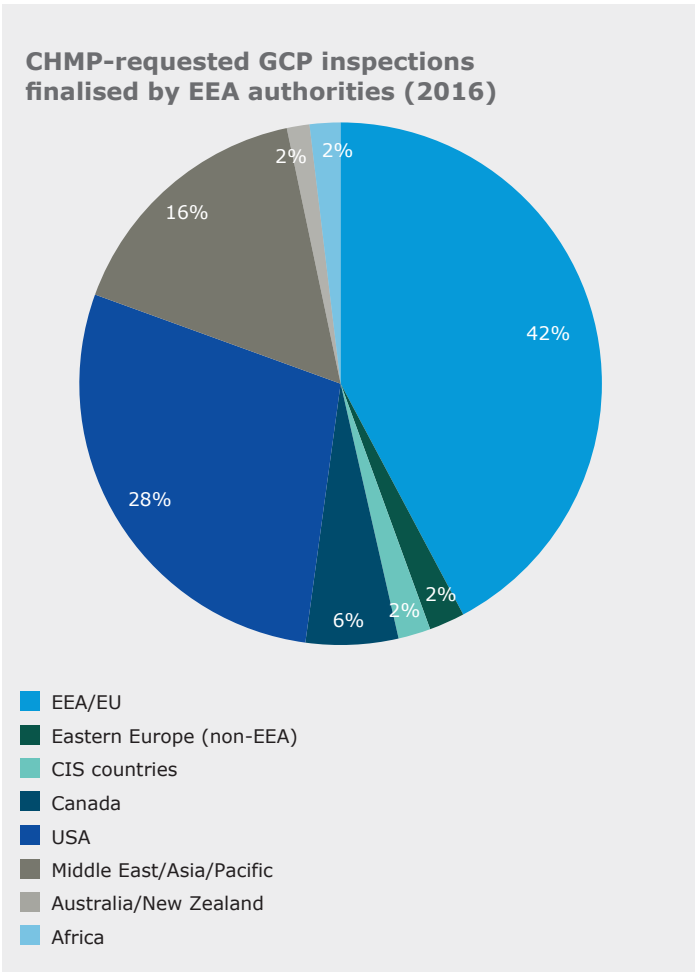
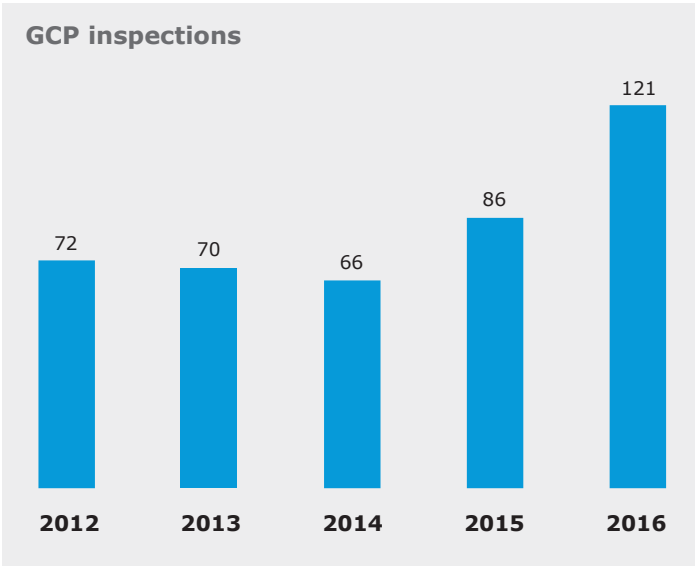
GMP non-compliance statements issued by EEA authorities



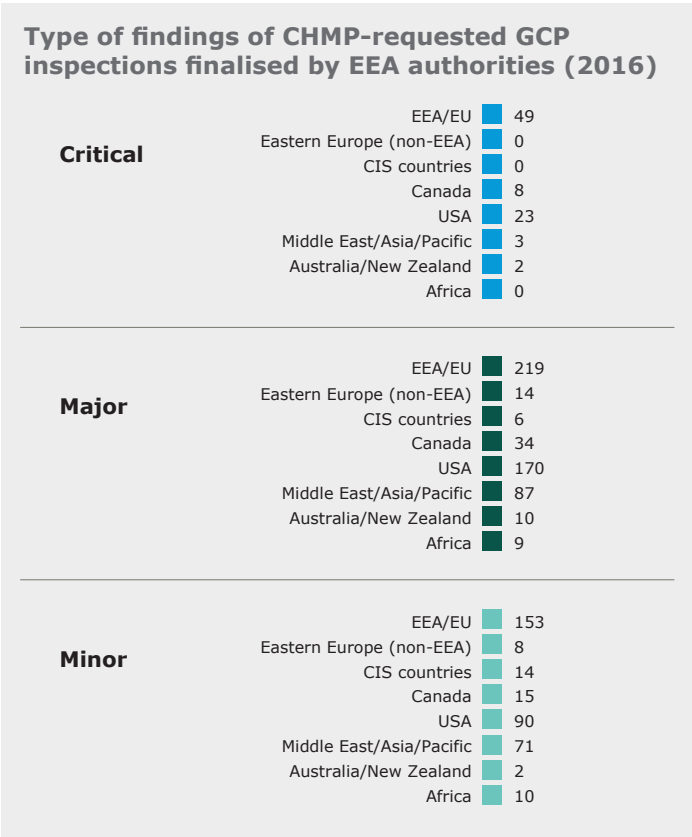
Note: These charts show the number of GMP certificates and non-compliance statements issued by EEA authorities as an outcome of GMP inspections conducted between 2013 and 2016. It includes GMP inspections requested by CHMP or CVMP.

GCP inspections

In 2016, the largest number of GCP inspections requested by the CHMP were conducted in the EU/EEA, followed by the USA and the Middle East/Asia/Pacific regions which have the highest number of patients, investigator sites and pivotal clinical trials included in MAAs for centrally authorised products.



In 2016, the majority of findings were reported in the EU/EEA region and the most common grading was major.



Where GCP inspections report critical and/or major findings in the conduct of studies forming the basis for an application for marketing authorisation or for the extension of indication of a medicine already authorised, the CHMP evaluates the impact of the inspection findings on the medicine’s benefit-risk balance.

Following this evaluation, the committee can request analyses of the data excluding affected patients and/or sites. When the findings affect the overall evaluation of the clinical development programme, the approval of the medicine is likely to be compromised.

In 2016, GCP inspections of two contract research organisations (CRO) led to European reviews of the impact of the findings. These reviews resulted in the suspension or non-granting of marketing authorisations of a number of pharmaceutical forms and strengths of medicines for which authorisation or marketing-authorisation application in the EU was based primarily on clinical studies conducted at those sites:

- recommendation to suspend a medicine (Riluzole Alkem) for which studies were conducted at the Alkem Laboratories Ltd site in Talaja, India, following a joint routine inspection by EU authorities in March 2015 which revealed the misrepresentation of data.

- recommendation to suspend medicines because of flawed studies at Semler Research Center Private Ltd, Bangalore, India, following EMA's review of an FDA inspection which identified several issues, including the substitution and manipulation of subjects' clinical samples.

Pharmacovigilance inspections

The Agency, in cooperation with Member State competent authorities, maintains the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders of centrally authorised products and ensures its implementation. It also plays a key role in the coordination of pharmacovigilance inspections specifically triggered by the CHMP or CVMP and in inspection follow-up.

In 2016, eight pharmacovigilance inspections were requested by the CHMP or CVMP. The majority of EU/EEA pharmacovigilance inspections (95%) are conducted under the national pharmacovigilance inspection programmes which relate to marketing authorisation holders with product authorisations of all types (including centrally authorised products).

Quality defects

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

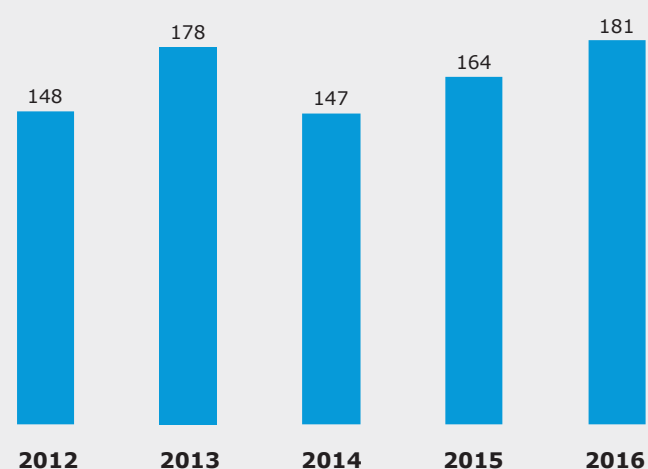
Where a defect is considered to be a risk to public or animal health, the marketing authorisation holder is requested to withdraw the affected batches of the centrally authorised product from the EU market and the supervisory authority issues a rapid alert. The alert is classified from 1 to 3 depending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

- Class 1 recall: the defect presents a life-threatening or serious risk to health;
- Class 2 recall: the defect may cause mistreatment or harm to the patient or animal, but is not life-threatening or serious;
- Class 3 recall: 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.

In 2016, the Agency received 181 suspected quality defects which led to a total of 16 recalls.

Of these, four were notifications of suspected defects identified as part of the sampling and testing market surveillance programme. Two of these cases were not confirmed by the marketing authorisation holder while two defects were confirmed (labelling not compliant) which did not require action.

Number of quality defects (2012-2016)



Quality defects reported

	2014	2015	2016
Recalls	14	15	16
Class 1	2	1	3
Class 2	8	3	9
Class 3	4	11	4

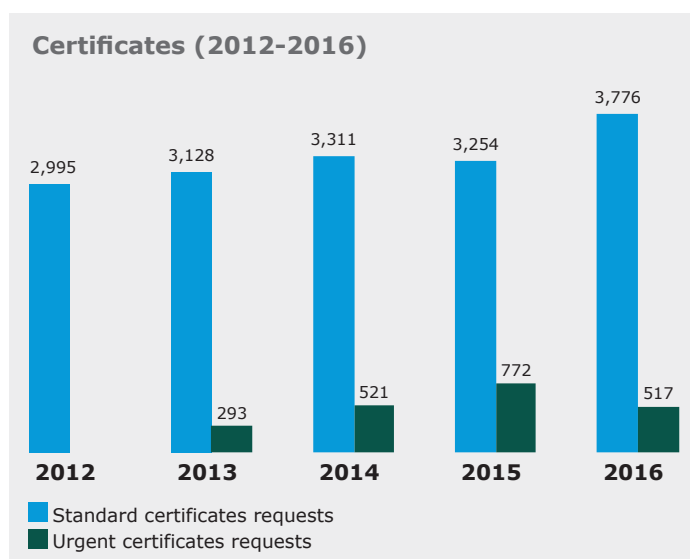
Parallel distribution

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.

Parallel distribution notifications received			
	2014	2015	2016
Initial notifications	2,492	2,838	2,850
Notifications of change	1,295	2,096	1,847
Notifications of bulk change	9	13	8
Annual updates	2,339	4,550	3,815
Total	6,135	9,497	8,520

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.

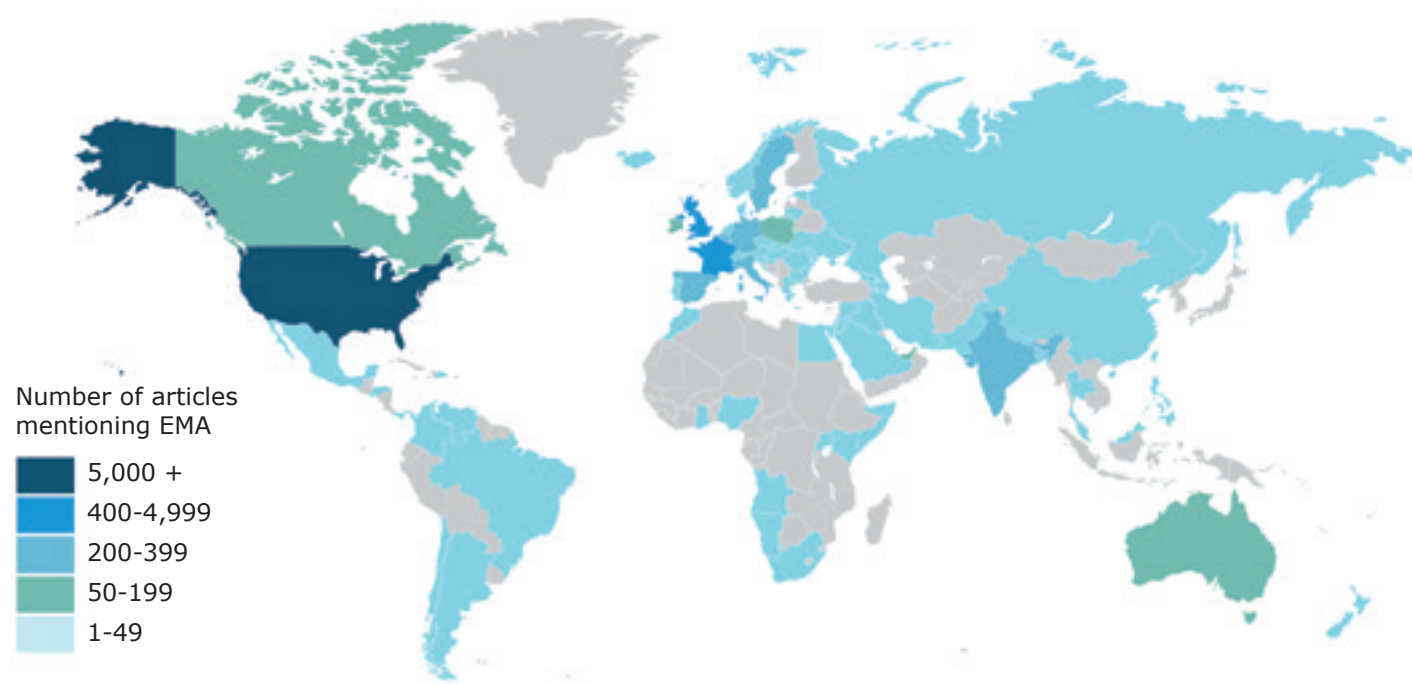


Communication

In 2016, EMA published 187 news releases.

The potential impact on the Agency following the outcome of the UK's EU referendum was of great interest to the media. EMA's 2015 review of HPV vaccines also generated significant media attention, as did the Agency's approach on adaptive pathways and its PRIME scheme.

EMA in the media around the world in 2016



Social media

At the end of 2016, EMA had approximately **25,000 followers** on Twitter, an increase of **25%** compared to 2015.

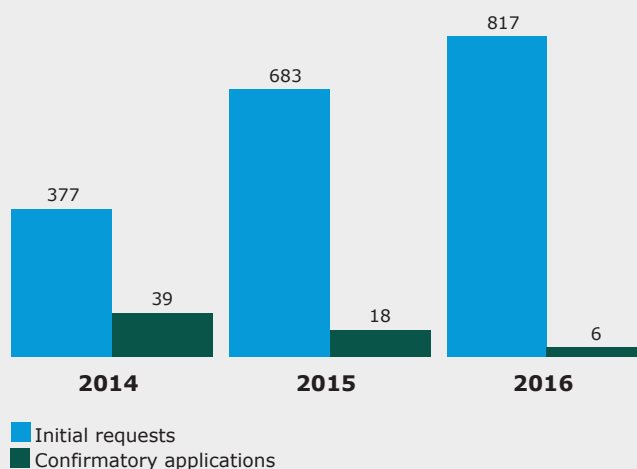
Administrative aspects

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.

The number of requests for access to documents continued to rise in 2016.

Requests for access to documents received (2014-2016)



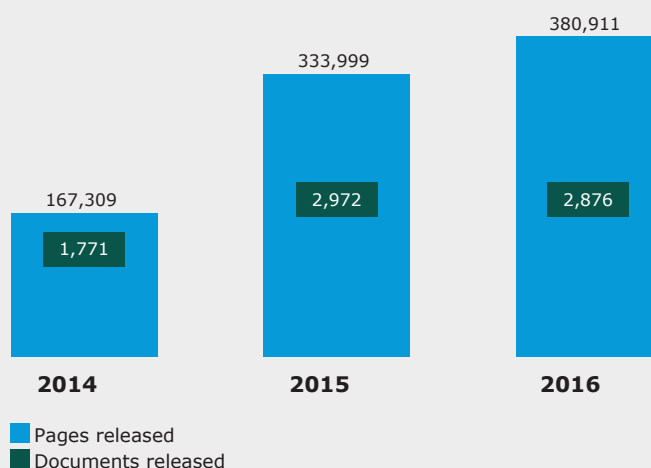
Requests for access to document closed

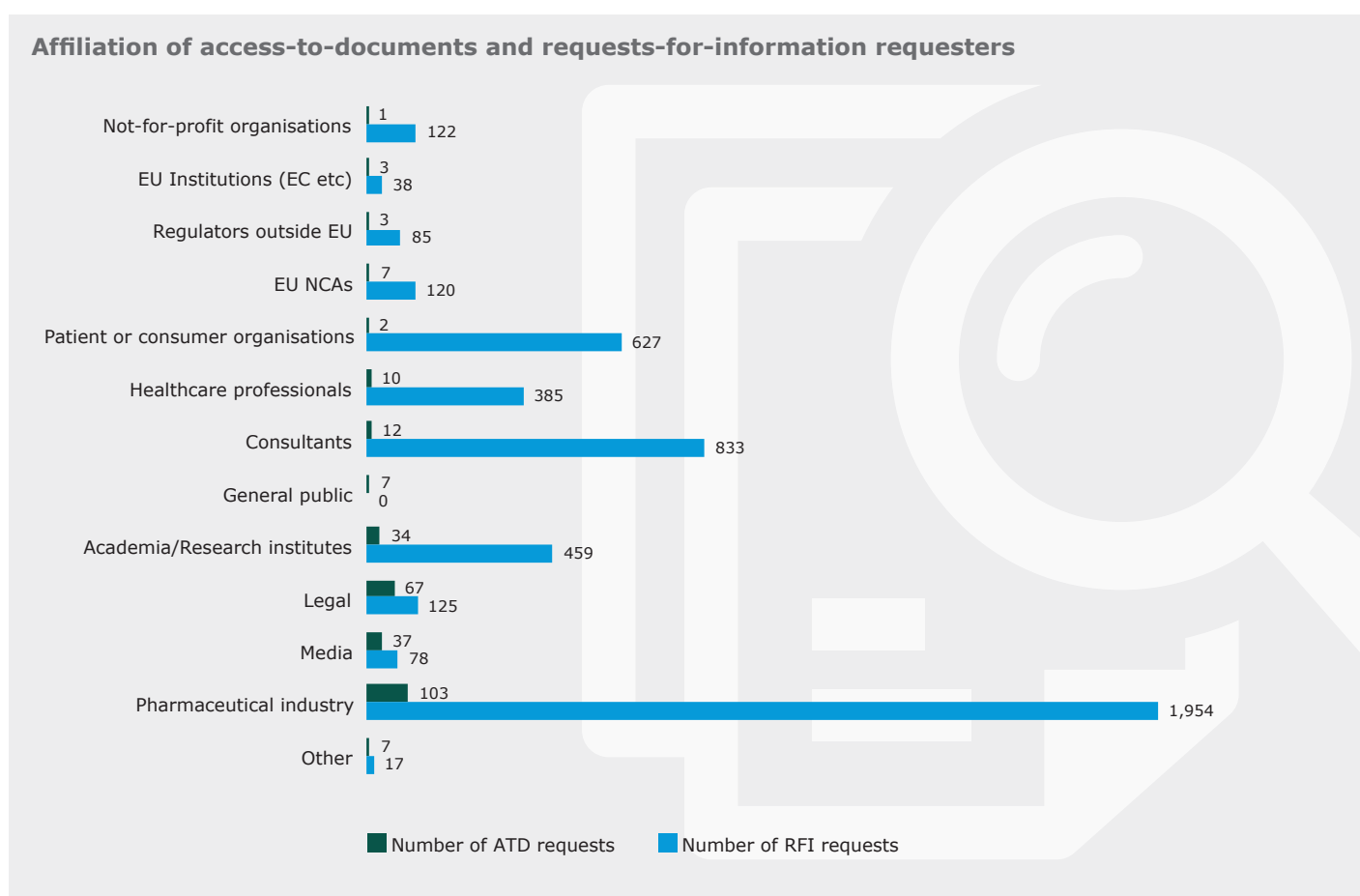
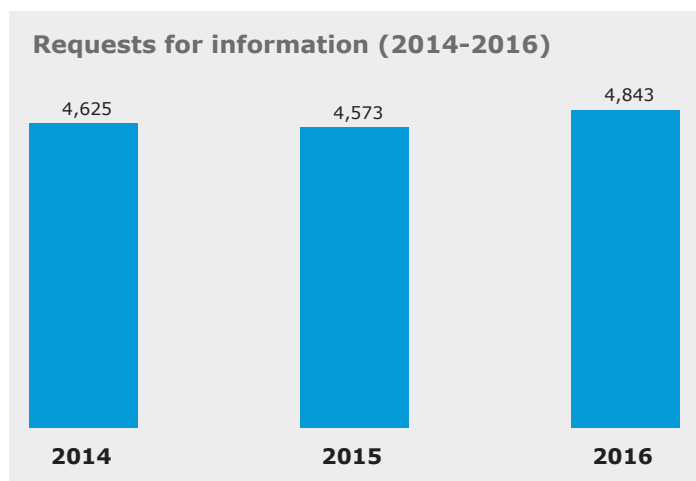
Decision	2014		2015		2016	
	Initial	Confirmatory	Initial	Confirmatory	Initial	Confirmatory
Fully granted	236	25	446	5	542	3
Partially granted (with redactions)	13	1	8	1	17	1
Refused	62	16	48	10	44	4
Total	311	42	502	16	603	8

Some of the initial requests were still ongoing at the end of 2016.

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

Pages released following access to documents requests (2014-2016)



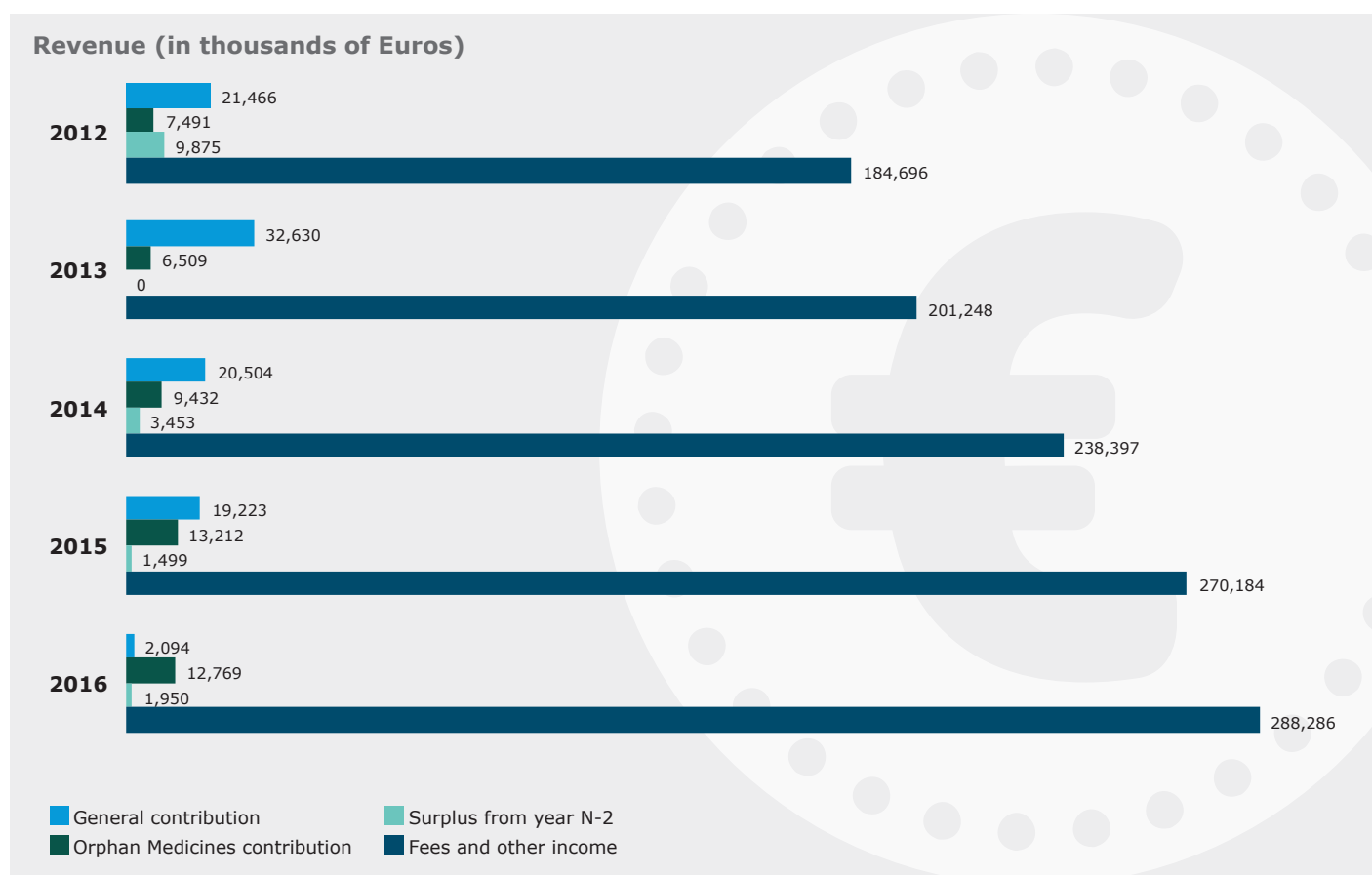


Note: More information on access to documents can be found in the annex.

Budget execution

Total revenue

The Agency's total revenue in 2016 was €305.099 million compared to €304.119 million in 2015.

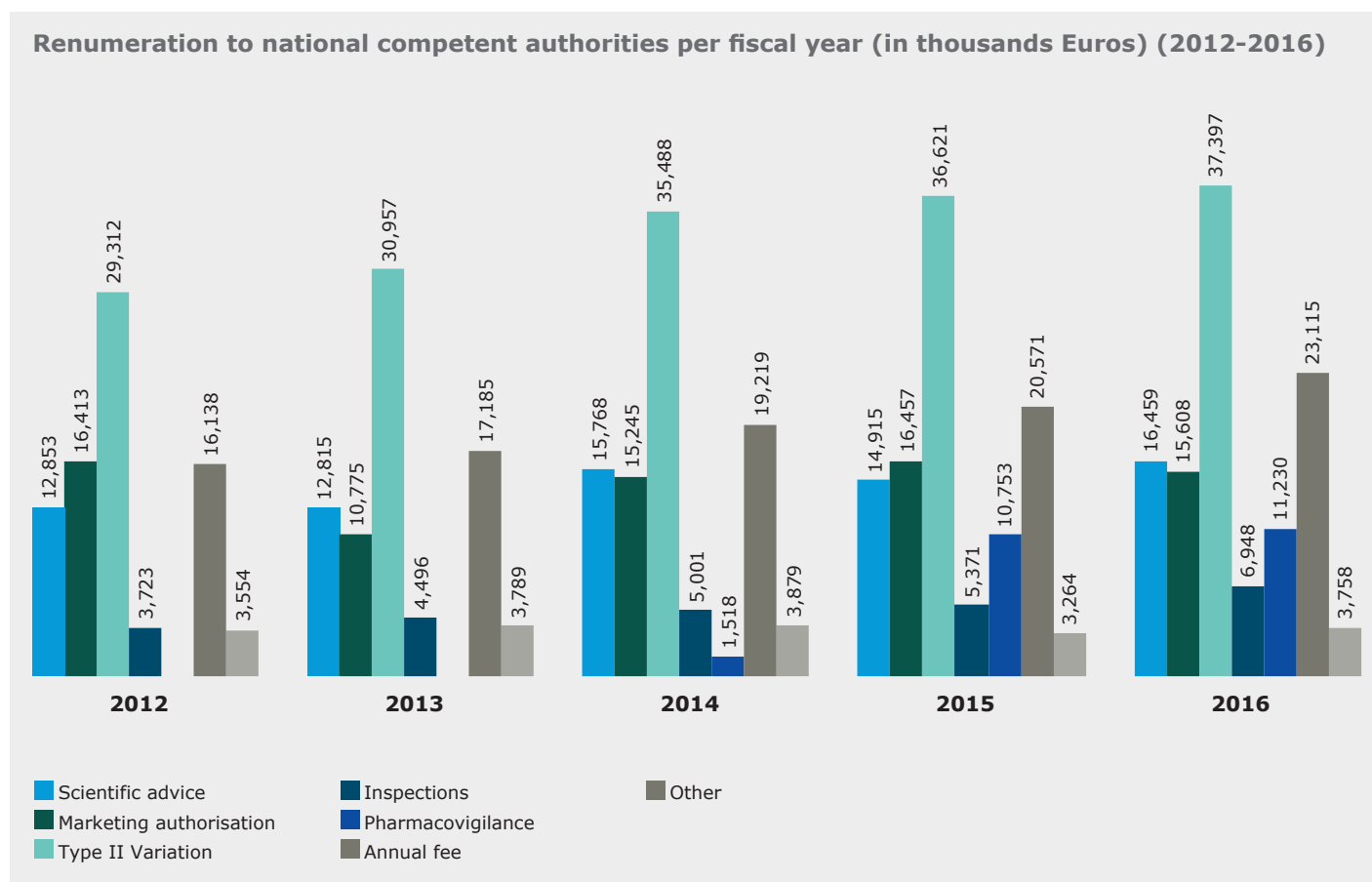


Expenditure (in thousands of euros)

Budget execution: expenditure EUR'000					
	2012	2013	2014	2015	2016
Staff expenditure	75,251	77,552	91,344	103,651	110,729
Infrastructure	30,817	62,056	55,251	49,422	40,407
Operational expenditure	112,790	103,811	119,825	142,082	150,294
Total	218,858	243,419	266,420	295,154	301,430

Remuneration to national competent authorities

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.



In 2016, EMA paid a total of €114.516 million to the national competent authorities (compared to €107.952 million in 2015).

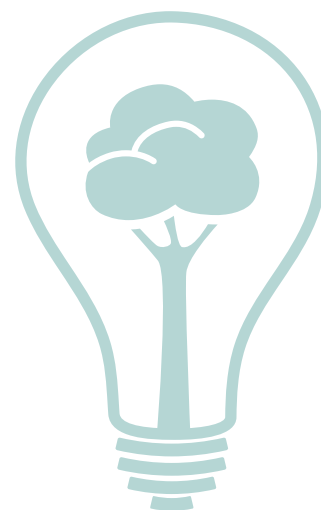
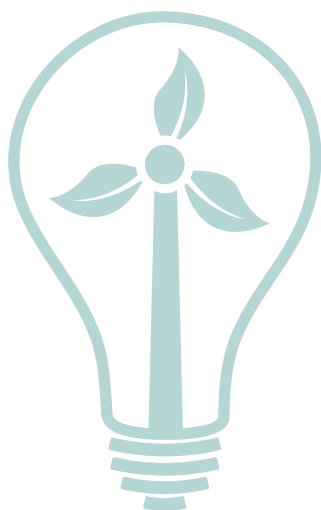
This sum includes remuneration for pharmacovigilance procedures, including the assessment of PSURs, PASS protocols and study results, and of pharmacovigilance-related referrals, for which the charging of fees began in August 2014. They are charged to companies whose medicines, whether authorised centrally or nationally, are included in these procedures.

Environmental reporting

EMA's office building at 30 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 has achieved 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	2016
Energy efficiency	Electricity consumption	kWh	3,414,782	3,406,245	3,069,676	3,546,829	3,266,036
		kWh/m ²	164	163	135	145	133
Resource efficiency	Water consumption	m ³	3,053	5,130	2,585	2,607	1,345
	Paper consumption	metric tonnes	41	42	41	27	23
Waste management	Recycled waste	metric tonnes	63	67	53	73	46
	Non-recyclable waste	metric tonnes	88	87	59	54	32
Carbon footprint	Greenhouse gas emissions	CO _{2e}	2,618	2,679	2,601	2,843	2,854

* The Agency moved to new premises in 2014, so the metrics and calculations changed during the year.

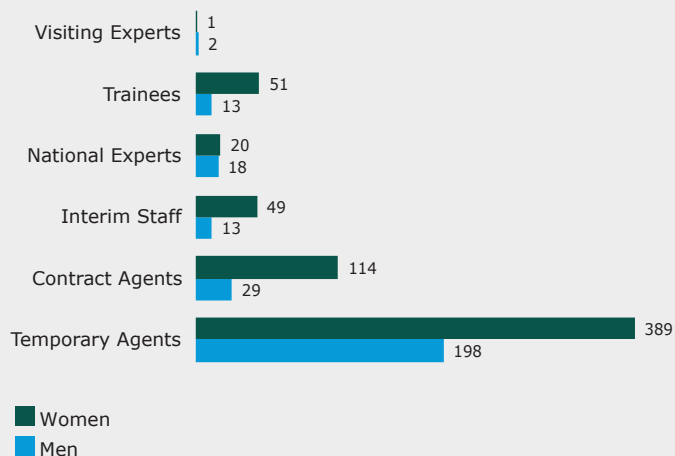


Agency staff

As of December 2016, Agency staff numbered 897: 624 women, 273 men.



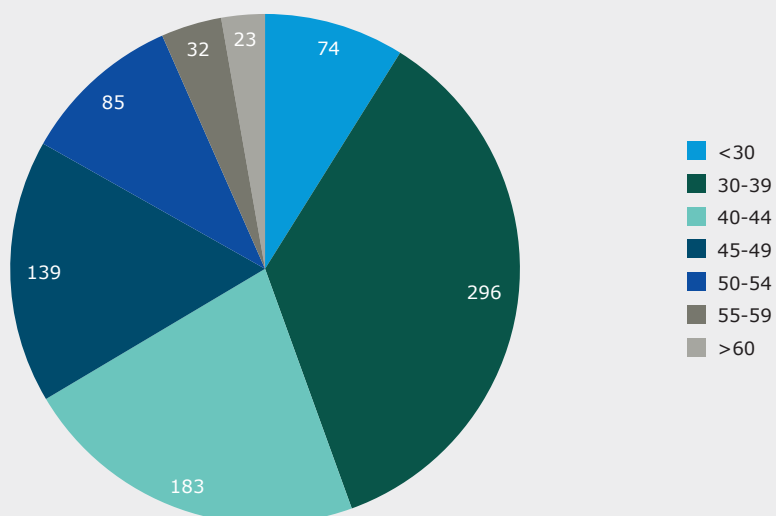
Agency staff (31 December 2016)



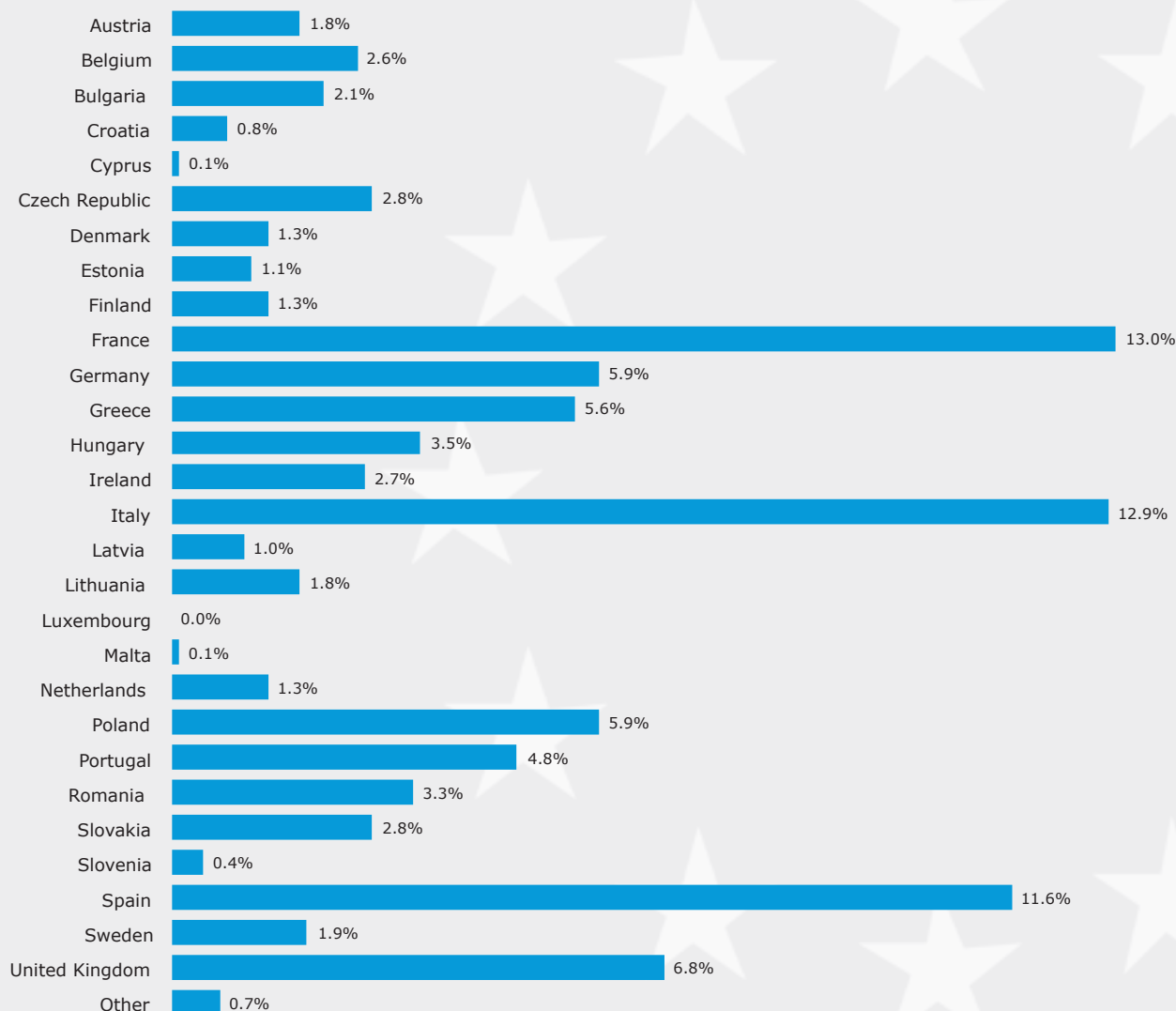
Gender balance 2016

Status	Category AD (administrators)		Category AST (assistants)		All grades	
	Men	Women	Men	Women	Men	Women
Temporary agents	49%	51%	14%	86%	34%	66%
Contract agents	31%	69%	13%	87%	20%	80%

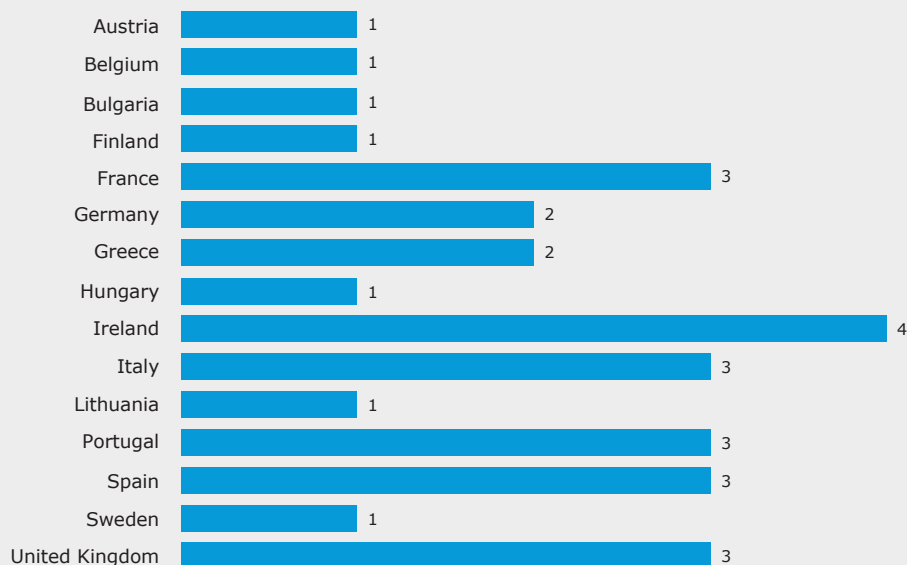
Age-range statistics (31 December 2016)



National origins of Agency staff (2016)



National origins of Agency management (2016)



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 for 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 10 a** – 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 the Committee for Medicinal Products for Veterinary Use
- Annex 12** – Opinions adopted by the Committee for Orphan Medicinal Products
- Annex 13** – European Union herbal monographs in 2014
- Annex 14** – Paediatric Committee opinions and EMA decisions on paediatric investigation plans and waivers in 2014
- Annex 15** – Referral procedures overview 2014 – human medicines
- Annex 16** – Arbitrations and referrals in 2014 – veterinary medicines
- Annex 17** – Budget summaries
- Annex 18** – European Medicines Agency Establishment Plan
- Annex 19** – Access to document requests
- Annex 20** – Media and public relations
- Annex 21** – Publications by Agency staff members and experts in 2014
- Annex 22** – Agency staff

The annexes can be found on the Agency's website

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Annual report 2016

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