EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual Report 2017

The European Medicines Agency's contribution to science, medicines and health in 2017

An agency of the European Union

Table of contents

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 (EC) as partners in a European medicines regulatory network, the European Medicines Agency (EMA):

- 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 EC;
- implements measures for continuously monitoring and supervising the quality, safety and efficacy of all medicines authorised in the European Union (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 EC;
- 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 EC to the harmonisation of regulatory standards at the international level.

Legal role

The EMA is the 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 very pleased to introduce the 2017 annual report which describes the many activities of EMA over the last year. 2017 was a particularly challenging year for the Agency and the network as a whole.

When the UK government formally notified the European Council at the end of March of its intention to leave the EU by 29 March 2019, the clock started ticking for all of us to get ready. The European medicines regulatory network stood together and committed to safeguard patients' well-being despite the changes forced on us by Brexit.

First of all, the UK's withdrawal means EMA has to relocate. In November, the EU27 Member States decided to move the Agency to Amsterdam. As Chair of the Management Board, I am committed to doing my utmost to support the Agency throughout the relocation process to ensure that we create the right environment in which EMA can continue its valuable work to protect public health and animal health in the EU.

This will be a challenge but I am reassured by the Agency's business continuity planning that there will be no significant interruption to the important activities of the Agency.

Brexit also means that the assessment work carried out so far by the UK will have to be redistributed among other Member States, in terms of workload and expertise. As a top priority, the Board supported the mapping exercise among the EU27 aimed at assessing whether the national competent authorities could manage the post-Brexit workload.

Over the last year, many of the national institutions have invested in their capacity and their capability. This, together with the work done by the two working groups on operational preparedness created by EMA – one on human medicines and the other on veterinary medicines – gives me great confidence that the network will be able to compensate for the UK's work and expertise and continue to protect the health of patients and animals in the EU.

Also, we are not starting from scratch. Over many years, the Management Board has supported initiatives to increase the participation of NCAs, especially those of smaller Member States and those who have joined since 2004. Particularly in the context of Brexit, we are seeing the significance of EMA's multinational assessment team initiative, which expanded in April to also cover the post-authorisation phase. The value of the EU network is reflected in the fact that we are able to work together in multinational teams – without borders – in order to make use of the best-available expertise from across the EU to assess medicines. Similarly, the EU network training centre continues to address the training needs of the EU medicines regulatory network with respect to both human and veterinary medicines. For the first time, the key activities of the training centre are reported in this annual report.

2017 was not all about Brexit, despite the huge time and resource commitments required to steer EMA and the network through these challenges. I am very pleased to highlight a number of achievements and projects that advanced significantly or were concluded last year.

The Board finalised its data-gathering initiative. We have established estimates of the time it takes to conduct certain assessments coordinated by EMA to inform any future discussions concerning a potential revision of the fee legislation and ensure the network is fit for purpose and continues to operate well.

The launch of the new and improved version of the EudraVigilance system was a key achievement in 2017. The upgraded system will strengthen the safety monitoring of medicines and make the reporting process more efficient for stakeholders across the network.

The Board also appreciates the hard work that went into the preparation of the Agency's first public hearing that took place in September. We fully support the goal of the Agency to increase engagement with the public as part of its work.

The development of the EU's clinical trial portal and database made some progress during the year, but there is still much work to be done. This is an extremely complex and ambitious project and the Board continues to keep a very close eye, not only on the timelines for delivery, but also on the quality of the portal and database, to ensure that a fully functional system is delivered to the EU regulatory network.

Finally, on behalf of the Board, I would like to express my sincere appreciation to the Agency's staff who, after an extended period of uncertainty, now being asked to make life-changing decisions for themselves and their families. It is my hope that the majority of them will relocate with the Agency to its new home in Amsterdam.

Introduction

by Guido Rasi
EMA Executive Director

In 2017, all in all, the Agency achieved a tremendous amount despite the unprecedented challenges that we faced as a result of the United Kingdom's decision to withdraw from the EU. In particular, we experienced a high degree of uncertainty around the future seat of the Agency. The decision of the EU27 in November, to relocate EMA from London to Amsterdam, a city that ticks many of our boxes, therefore came as a welcome relief. We are now embarking, with our Dutch counterparts, on the complex undertaking of moving EMA in time for it to be operational in its new host country by 30 March 2019, and preparing for a second move from our temporary to our final premises in Amsterdam in the same year.

A business continuity plan has been put in place which aims to ensure that the Agency's core activities are maintained whilst enabling sufficient resources to be released to prepare for both relocation and the operational changes that will result from Brexit. This has meant that we have had to re-prioritise some work, and cut down or delay some activities. For example, reducing the number of trainings and audits, meetings and conferences with key stakeholders and partners, and delaying some much-needed upgrades to our own IT infrastructure. Clearly, this is not something that we can sustain in the long term because it would eventually impact the quality and efficiency of our activities.

We have been working closely with the network to ensure that the resources and capacity required are available to guarantee an orderly redistribution of the work currently undertaken by the UK. It has been very reassuring to see the national competent authorities in the EU27 coming together and committing to increase their capacity to ensure a smooth continuation of EMA's activities and to help protect human and animal health in Europe.

In these challenging times, thanks to good planning and the extraordinary resilience of EMA staff, we were still able to deliver our core business to the quality our stakeholders expect from us. We were also able to carry out several other activities that underline our commitment for better public health in the EU. I would like to highlight just a few.

In September, we held the first public hearing at EMA. Patients, carers, doctors, pharmacists and academia shared their experience with valproate, a medicine that treats epilepsy, bipolar disorder and migraine. For the first time, EU citizens were invited to participate in the evaluation of a medicine by responding to questions to complement the available scientific evidence.

Another step forward in our engagement with the public was the launch of a new framework and action plan with academia last year, setting out a clear path to further develop interactions with this important stakeholder group.

We made major progress in terms of patient safety when the new and improved EudraVigilance system went live in November. This information system is the backbone for the reporting of suspected side effects to medicines in the EU. It holds vast amounts of data. In 2017 alone, 1.4 million new suspected adverse drug reaction reports were added to the database. In 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) assessed 82 signals of new or changing safety issues and about two thirds of these were detected in full or part from EudraVigilance. Adverse drug reactions can be life threatening and their rapid detection through EudraVigilance allowed direct action to protect patients. The new version will facilitate reporting and increase the transparency and access to data for patients and researchers. It also contributes to global pharmacovigilance by promptly making all EU adverse reaction reports available to the World Health Organization (WHO). The new EudraVigilance will further improve our ability to detect and assess emerging issues on medicines and to promote and protect public health.

In 2017, we also continued to look for ways to facilitate and promote drug development for patients in need of new treatments by further improving early engagement with developers. Our PRIority MEdicines (PRIME) scheme marked its first anniversary. By the end of 2017, a total of 34 medicines had been included in this scheme which provides early and enhanced support to products that can demonstrate a major therapeutic advantage in addressing patients' unmet medical needs. The first marketing authorisation applications for medicines receiving PRIME support were submitted during 2017 and we expect the first recommendations in 2018.

Scientific advice, one of the key instruments available for developers to clarify regulatory requirements, reached an

all-time high for human medicines in 2017. Almost 5% of scientific advice was given jointly with health technology assessment (HTA) bodies. This cooperation between regulators and HTAs can help medicine developers to improve the generation of the safety and efficacy data that both groups require as the basis for their decision-making.

Overall, 2017 was another strong year for new medicines. EMA recommended the authorisation of 92 medicines for human use, including 35 with a new active substance. Many of these medicines represented significant progress in their therapeutic areas. In the veterinary area, 18 medicines were recommended for authorisation, including seven new active substances and ten vaccines. Over 60% were for food-producing animals. Assessment times for both human and veterinary were shorter than at any other time during the last five years, without compromising the rigorous evaluation of the medicines. This is an indicator that our Brexit prioritisation is working well.

The achievements outlined in this annual report make me optimistic that our transition from London to Amsterdam can be managed without risking a public health crisis. We can accomplish this because we are part of a strong and flexible European network that has shown by its actions that it is committed to adapt to the changes ahead.

While Brexit is a challenge, it has also given the network new impetus for constructive joint responses to transformative trends in medical science – whether it is the use of big data, personalised medicines or a rethink of the system of clinical trials, to name but a few. Preserving EMA's ability to coordinate these efforts over the next few years will be key to securing our place in medical research and knowledge transfer.

EMA is what it is today because of all those who contribute to its work: the members of the scientific committees, the working parties and scientific advisory groups, the Management Board and 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.

EMA prepares for the United Kingdom's withdrawal from the European Union

On 29 March 2017, the United Kingdom invoked Article 50 of the Treaty on European Union. This step formally started a two-year countdown to the UK's departure from the EU (Brexit). As a result, the two EU agencies located in London have to relocate to one of the remaining EU Member States.

Following the EU referendum in the UK in June 2016, the Agency started to prepare for its eventual relocation, wherever that would be; most importantly, it began to develop plans to ensure that the assessment and safety monitoring of medicines would not be disrupted and that patients in Europe would continue to have access to high-quality, safe and effective medicines.

In the course of 2017, as well as continuing with its day-to-day work, EMA initiated the first phase of a business continuity plan aimed at preserving the Agency's ability to protect public and animal health. Towards the end of the year, the Agency finally received the long-awaited decision on its new home: on 20 November 2017, the General Affairs Council (Art. 50) decided on Amsterdam as EMA's new location. Amsterdam's was one of 19 offers to host EMA submitted by the Member States at the end of July 2017. The decision ended a long period of uncertainty and allowed the Agency to begin more concrete decision-making on how to ensure a successful move and retain a large majority of the existing staff.

The timeline below summarises the key Brexit-related dates and actions undertaken by the Agency in 2017.

Throughout the year, the Agency worked closely with the national competent authorities (NCAs) to help prepare the network for the impact of the UK's withdrawal. EMA and the Member States identified possible gaps in expertise so that appropriate measures can be taken at an early stage to address them. The EMA working groups developed a methodology to transfer the current UK portfolio of medicinesnto rapporteurs or co-rapporteurs from other Member States.

In parallel, EMA, together with the EC prepared guidance for pharmaceutical companies to enable them to take the necessary steps to mitigate any detrimental impact of the UK's withdrawal on manufacturing, control and supply of their medicines.

Key milestones in 2017

29 March

UK triggers Article 50, giving formal notification of its intention to leave the EU

27 April

First information meeting with Management Board and heads of NCAs to discuss future work sharing between Member States

1 May

Phase 1 of Brexit preparedness business continuity plan launched

30 September

European Commission publishes its examination of Member States' offers. EMA supports the technical assessment

4 October

First meeting with industry associations to discuss Brexit planning for human medicines

13 October

First meeting with veterinary industry associations

20 November

General Affairs Council (Art. 50) votes to relocate EMA to Amsterdam, the Netherlands

EMA immediately begins working with the Dutch authorities to prepare for the move and take up its operations in Amsterdam by 30 March 2019

27 November

Procedural guidance published to help pharmaceutical companies prepare for Brexit

1 December

Updated Q&As for companies to prepare for Brexit published

2 May

First notice to marketing authorisation holders published to help pharmaceutical companies prepare for the impact of Brexit

24 May

European Council and Commission publish draft procedure for the decision on the relocation of EMA

31 May

First questions and answers (Q&As) for companies to prepare for Brexit published by EMA and European Commission

22 June

Heads of states at the European Council adopt process and time frame for the decision-making on EMA's new location

31 July

Deadline for Member States to submit formal offers to host EMA. All 19 offers received are made public

4 September

Second staff survey to assess readiness of EMA staff to relocate

8 December

The Netherlands helpdesk opens at EMA to offer guidance to staff

13 December

Dutch delegation presents next steps concerning the relocation process to the Management Board

December

EMA and the Netherlands agree joint governance structure

Chapter 1
Key achievements in 2017

The Agency's activities to protect and promote the health of people and animals in the European Union and highlights of major achievements in 2017

Human and veterinary medicines highlights

This section provides an overview of some of EMA's major recommendations on medicines in 2017. 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

In 2017, EMA recommended 92 medicines for marketing authorisation. Of these, 35 had a new active substance, i.e. one which had never previously been authorised in EU.

Many of these medicines represent a significant improvement in their therapeutic areas; they include medicines for children, for rare diseases and advanced therapies.

Medicines for children:

Brineura for the treatment of a very rare, fatal neurodegenerative condition in children called neuronal ceroid lipofuscinosis type 2 (CLN2) disease. This is the first medicine approved in the EU for the treatment of CLN2.

Spinraza to treat spinal muscular atrophy (SMA), an inherited disease that affects the motor neurons and is usually diagnosed in the first year of life. This is the first medicine approved in the EU for the treatment of SMA.

Alkindi for the treatment of primary adrenal insufficiency, a rare hormonal disorder in infants, children and adolescents.

Crysvita for the treatment of X-linked hypophosphataemia (a genetic bone disorder leading to rickets and impaired growth) in children and adolescents with growing skeletons.

Advanced therapy medicinal products:

Spherox to treat adult patients who have symptomatic cartilage defects in the knee joint.

Alofisel for the treatment of complex perianal fistulas in patients with Crohn's disease. Perianal fistulas occur when an abnormal passageway develops between the rectum and the outside of the body.

Rare diseases:

Oxervate for the treatment of neurotrophic keratitis, a rare eye disease.

Qarziba (previously Dinutuximab beta Apeiron) for the treatment of high-risk neuroblastoma (a cancer of nerve cells).

Xermelo for the treatment of carcinoid syndrome (a rare cancer-related condition leading to diarrhoea and flushing).

23 January

Publication of the 10-year report on conditional marketing authorisation.

24 January

Publication of EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the EU, and the resulting impacts on food safety (RONAFA).

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

Three 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.

In addition, the Committee for Medicinal Products for Human Use (CHMP) issued negative opinions on six medicines in 2017. This means that the CHMP could not conclude that the benefits of the medicine outweighed the risks.

Some 90% of all opinions (positive and negative) were reached by consensus among the CHMP members, meaning that its experts were in agreement on all aspects of the marketing authorisations following in-depth discussions.

Around 62% of the applicants who received a positive opinion for their medicine had received scientific advice from EMA during the development phase of their product. This procedure allows EMA to provide early input on the kind of evidence that would be required for authorisation, and helps to reduce the risk of patients taking part in unnecessary or poorly designed clinical trials.

Keeping medicines safe

Once a medicine has been authorised, EMA and the EU Member States continuously monitor the quality and the benefit-risk balance of the medicine on the market. This allows new or changing safety issues to be detected and managed and ensures that any quality issues are rapidly dealt with.

When an issue is detected, regulatory responses may range from a change in the product information to the suspension or withdrawal of a medicine or recall of certain batches.

Important new safety advice issued in 2017 included:

- Update to product information about a potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the **SGLT2 inhibitors** canagliflozin, dapagliflozin and empagliflozin for type 2 diabetes.
- Recommendations to suspend the authorisations of some **linear gadolinium agents** used in MRI body scans and restrict the use of others. EMA's scientific review found that small amounts of gadolinium may remain in the brain after a scan with these agents, although there is currently no evidence that these small amounts cause any harm.
- Recommendation to restrict the use of the multiple sclerosis medicine **Zinbryta** in view of the risk of serious liver damage in some patients.
- Recommendation to suspend marketing of **paracetamol medicines** designed to release the active ingredient over a long period (modified-release medicines) because of the difficulty in managing overdoses.
- New contraindication for **Uptravi**, which must not be taken at the same time as medicines, such as gemfibrozil, that are strong blockers (inhibitors) of the liver enzyme CYP2C8.
- Updated and less onerous contraception recommendations for male patients following further evaluation of the risk of **mycophenolate medicines** (used to prevent rejection of transplanted organs) causing miscarriages or birth defects in their untreated female partners.

Product information for 397 medicines was updated on the basis of new safety data.

The revised information is expected to help patients and healthcare professionals to make informed decisions when using or prescribing a medicine.

30/31 January

Multi-stakeholder paediatric oncology strategy workshop (ACCELERATE platform).

10 February

The 1,000th study is uploaded in the EU electronic Register of Post-Authorisation Studies.

Ensuring integrity of clinical trial conduct and the manufacture and supply of medicines

Medicine development and manufacturing is global. It is important for EU regulators to ensure that the relevant standards are met, no matter where clinical trials or manufacturing takes place.

- In 2017, two centralised marketing authorisation applications were withdrawn as a result of non-compliance with EU good manufacturing practice (GMP) and one as a result of non-compliance with good clinical practice (GCP).
- The CHMP also adopted two negative opinions (refusing the granting of the marketing authorisation) for medicines for which GCP inspections reported non-compliance issues with the clinical studies submitted.
- Seven batches of zoledronic acid were recalled from hospitals, pharmacies and wholesalers in six EU Member States following sampling from the EU market and testing by an Official Medicines Control Laboratory as part of the Agency's routine market surveillance programme. A subsequent GMP inspection of the manufacturer verified that the cause of the problem was limited to the batches in question and that appropriate corrective actions were implemented.
- Findings following GCP inspections of two sites of a contract research organisation (Micro Therapeutic Research) led to a review by EMA. The outcome was that a number of nationally authorised medicines whose authorisations relied on studies carried out at these two sites were recommended for suspension.

Veterinary medicines

New medicines to benefit animal health in Europe

In 2017, EMA recommended 18 new veterinary medicines for marketing authorisation; seven of these contain a new active substance. Among the 18 medicines recommended for marketing authorisation, ten were vaccines – a twofold increase compared to 2016. Six of these vaccines were developed by means of biotechnological processes, such as recombinant DNA technology.

The Agency's Committee for Medicinal Products for Veterinary Use (CVMP) recommended the granting of a marketing authorisation for the first monoclonal antibody in a veterinary medicine in the European Union. **Cytopoint** is a solution for injection containing the new active substance lokivetmab. It is intended for the treatment of dogs with atopic dermatitis, a common allergic skin disease.

Two vaccines against diseases that can be transmitted from animals to people were recommended for approval. **Respiporc FLUpan H1N1** protects pigs against swine influenza caused by pandemic subtype H1N1. Swine influenza or swine flu is a disease of the lungs and airways in pigs. People with regular exposure to pigs may be at increased risk of swine flu infection. **Rabitec** is a bait vaccine that protects wild foxes and raccoon dogs against rabies. This life-threatening viral disease causes inflammation in the brain and it can be transmitted to people by bites or saliva from an infected animal.

Rabitec and **Oxybee** (a medicine for the treatment of honey bees in hives infested with Varroa destructor), were both recommended for marketing authorisation under 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.

EMA recommended one vaccine that has the potential to reduce the need for antimicrobial treatment in food-producing animals and therefore to limit the development of antimicrobial resistance. **Vepured** protects piglets against oedema disease and reduces the associated loss of daily weight gain until slaughter.

17 February

The Committee for Advanced Therapies elects Dr Martina Schüssler-Lenz as its new chair.

2 March

Regulators in the EU and the United States agree on mutual recognition of inspections of medicine manufacturers.

Optimising the safe and effective use of veterinary medicines

Important new safety advice issued in 2017 included:

- Veterinary medicines containing **methylprednisolone hydrogen succinate** should no longer be used for the treatment of inflammatory or allergic conditions and for treatment and prevention of shock conditions, to ensure consumers are not exposed to the medicine in the meat of treated cattle.
- **Zinc oxide**-containing veterinary medicines should no longer be used in medicated feeding stuff for piglets, as these products increase zinc concentrations in the soil to levels considered harmful for the environment, and potentially increase the prevalence of antibiotic resistant bacteria.
- New risk mitigation measures and warnings in the product information of **moxidectin**-containing antiparasitic veterinary medicines used in cattle, sheep and horses, as these medicines might have a negative long-term impact on the environment.
- Change withdrawal periods (the time required after administration of a medicine before an animal can be slaughtered and the meat used for human consumption) for cattle, sheep and goats for the anthelmintic **Zanil** and associated names and generics, to protect consumer safety.

Product information for 17 medicines was updated on the basis of new safety data. The revised information is expected to help animal owners and healthcare professionals to make informed decisions when using or prescribing a medicine. The CVMP adopted six positive opinions for extensions of existing authorisations.

Protecting consumers

If a medicine is supposed to be used in a food-producing animal, it needs to be safe for people to eat the food that comes from this animal. The maximum residue limits (MRLs) recommended by EMA reflect the level of residues of the veterinary medicine in food derived from a treated animal that can be considered safe for consumption. In 2017, MRLs were established for the following active substances:

Alarelin
in medicines for all food-producing species

Bromelain
in medicines for pigs

Porcine prolactin
in medicines for pigs

Solvent naphtha, light aromatic
in medicines for all food-producing species.

6 March

Kick-off meeting of the new task force on big data established by the Heads of Medicines Agencies (HMA) and EMA.

7 March

First anniversary of PRIME.

14 March

Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP) joint workshop on personalised medicines.

Advancing human health

Patients' needs are at the centre of everything EMA does. The Agency encourages and supports the development of new medicines and vaccines addressing real public health needs. At the same time, it monitors the safety of all medicines marketed in Europe across their lifespan to protect patient health and ensure that medicines continue to benefit patients after their authorisation.

Supporting the development of promising or much-needed medicines for patients

Many patients with serious diseases have no or only unsatisfactory therapeutic options and should be able to benefit from scientific advancement and cutting-edge medicines as early as possible. EMA supports the medicine development process from an early stage and provides regulatory mechanisms to help promising new medicines reach patients as early as possible. Early regulatory engagement with medicines developers helps provide patients with the timely access to new, safe and effective medicines that they rightly demand, while protecting them and maximising the value of their involvement by ensuring that the studies in the development plan are appropriately designed to produce robust and useful data. It also helps minimise the administrative burden of development by ensuring that the most appropriate regulatory pathway is chosen, and potentially allows other parties involved in the approval process, such as HTAs and payers*, to provide input about their needs at an earlier stage.

First anniversary of PRIME

In 2017, EMA celebrated the first anniversary of its PRIority MEdicines (PRIME) scheme, an initiative launched in March 2016 to provide early and enhanced support to medicines that can potentially address patients' unmet medical needs.

To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Between its launch in 2016 and December 2017, EMA received and reviewed a total of 154 applications for PRIME, 77 of which came from small and medium-sized enterprises (SMEs). A total of 34 medicines were accepted into the scheme. The most represented therapeutic area is cancer, with a total of 12 medicines accepted.

During 2017, the Agency provided support for PRIME products through 30 scientific advice procedures and 17 multidisciplinary kick-off meetings. In addition, three marketing authorisation applications for products accepted into the scheme were submitted.

PRIME is meant for the most promising medicines and EMA focuses its attention on medicines that can demonstrate a major therapeutic advantage. On average, only 20% of applications are accepted into the scheme. Within PRIME, Advanced Therapies Medicinal Products (ATMPs) are of special relevance, making up close to 40% of the medicines admitted to the scheme. This reflects the potential for this type of therapy to address unmet medical needs.

In May 2017, the Agency organised a meeting with users and potential users of this scheme to review the experience gained after the first year of its implementation. The meeting was an opportunity to discuss how the criteria for eligibility have been applied and what types of support applicants have received so far. It also allowed review of some practical examples that illustrate the benefits of PRIME and how the scheme makes optimal use of existing tools supporting regulatory and scientific advice.

Overall, stakeholders gave positive feedback on the scheme's performance after the first year of implementation.

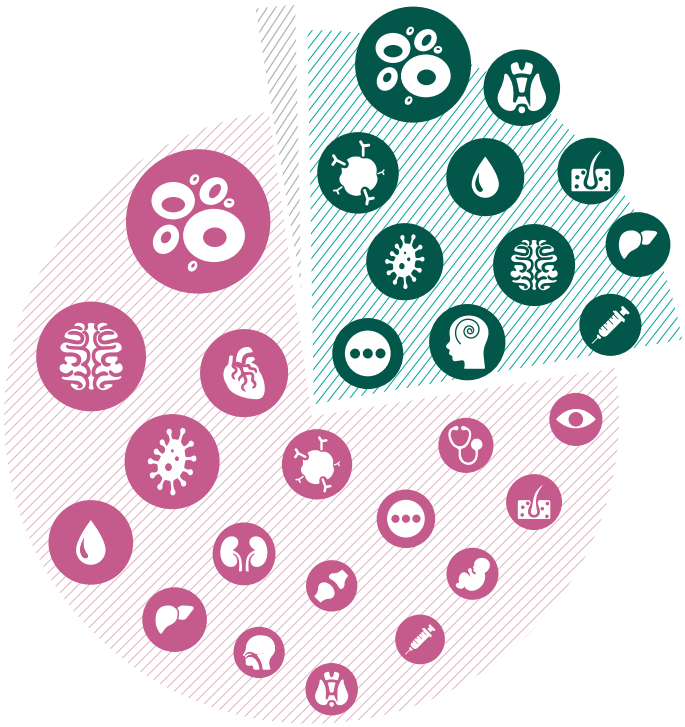
*Throughout this annual report, "payer" means an organisation involved in the pricing/reimbursement of a medicinal product under a public healthcare scheme. In some Member States there are also private healthcare schemes which may not be subject to all rules applicable to public bodies.

17 March

EMA's Management Board adopted a new policy (Policy 072) on EMA's handling of information disclosed by external sources on alleged improprieties concerning EMA activities in the area of the authorisation, supervision and maintenance of human and animal medicinal products.

PRIME key figures from March 2016 to December 2017

Applications and eligibility decisions



granted applications / 34

denied applications / 114

out-of-scope applications / 6

Therapeutic areas

- Cardiovascular diseases — *8 denied*
- Dermatology — *1 granted / 4 denied*
- Diagnostic — *1 denied*
- Neurology — *2 granted / 13 denied*
- Oncology — *12 granted / 40 denied*
- Ophthalmology — *4 denied*
- Endocrinology-gynaecology-fertility-metabolism — *2 granted / 3 denied*
- Gastroenterology-hepatology — *2 granted / 5 denied*
- Haematology-haemostaseology — *7 granted / 7 denied*
- Immunology-rheumatology-transplantation — *2 granted / 6 denied*
- Infectious diseases — *2 granted / 9 denied*
- Musculoskeletal system — *1 denied*
- Neonatology-paediatric intensive care — *1 denied*
- Other — *1 granted / 1 denied*
- Oto-rhino-laryngology — *1 denied*
- Pneumology-allergology — *5 denied*
- Psychiatry — *2 granted*
- Uro-ephrology — *1 denied*
- Vaccines — *1 granted / 4 denied*

Type of applicant

SME	15	62
Other	19	49
Academic	3	

On average:

20% of applications are accepted in the scheme

40% of medicines admitted in the scheme are Advanced Therapies Medicinal Products (ATMPs)

3 marketing authorisation applications for products accepted into the scheme were submitted in 2017

January to December 2017

The Agency provided support to PRIME products through:

30 scientific advice procedures

17 multidisciplinary kick-off meetings

Supporting development of medicines for children

2017 marked the tenth anniversary of the EU Paediatric Regulation. In its report to the European Parliament and the Council, published in October under the title 'State of Paediatric Medicines in the EU', the EC concluded that the progress made in the development of medicines for children, including the authorisation of over 260 new medicines, could not have been achieved without specific EU legislation and EMA's role in its implementation.

The Commission's analysis took into account a technical report prepared by EMA and its Paediatric Committee. The report showed that research into paediatric medicines has substantially increased since the legislation came into force, leading to more evidence-based information when medicines are used in children. The number of agreed paediatric investigation plans (PIPs) – an important step in shaping the development of medicines for children – passed the 1,000 mark in 2017.

Despite the overall positive impact on the health of children, the report also acknowledges that the results from the paediatric legislation are not evenly spread across all therapeutic areas. While it works very well in areas where the needs of adult and paediatric patients overlap, major therapeutic advances have yet to materialise in diseases that are rare and/or unique to children. The report identified concrete areas for action which EMA and the EC are now working to address, initially by reflecting on the best way forward with a broad range of stakeholders, including patients/carers, academia, healthcare professionals and industry.

Global research collaboration to benefit children

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) held its ninth annual workshop in May 2017. Enpr-EMA is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children. Its aim is to foster high-quality ethical research in children in order to provide knowledge and support regarding quality, safety and efficacy of paediatric medicines. This year's workshop emphasised the need for international, global collaboration and provided a dedicated session on interaction between the EU and the US for global paediatric research.

During the workshop, the Executive Director of EMA, Guido Rasi, and Mark Turner, Chair of Enpr-EMA, highlighted the successes of the Paediatric Regulation ten years after its implementation. They stated that, in order to improve the conduct of paediatric trials, it is crucial that they be run internationally, supported by global paediatric research networks and in collaboration with regional regulators.

Conditional marketing authorisation gives patients access to important new medicines earlier

In 2017, EMA reviewed its experience with conditional marketing authorisation (CMA) ten years after it was first introduced. A report published in January 2017 showed the positive impact of this important tool. Conditional marketing authorisation applies to medicines that target seriously debilitating or life-threatening conditions such as HIV infection, breast cancer, severe epilepsy in infants or multi-drug resistant tuberculosis. The report indicates that CMA has provided early access to such medicines for patients who previously lacked or only had unsatisfactory treatment options, and over a period of ten years, no medicine with a CMA has had to be revoked or suspended.

As part of the authorisation, the company is obliged to carry out further studies to obtain complete data. According to EMA's analysis, marketing authorisation holders comply with the specific obligations imposed by the Agency, on average, within four years after authorisation, at which time the CMA can be converted into a full authorisation. More than 90% of completed specific obligations did not result in major changes of scope and about 70% of specific obligations did not require an extension to the originally specified timelines.

Going forward, the report called for further improvements, including wider use of early dialogue between EMA and applicants and engaging further stakeholder groups, such as (HTAs).

3 April

EMA publishes a new framework of collaboration with academia.

21 April

EMA adopts a set of revised guidelines on data requirements for immunological veterinary medicinal products intended for minor use or minor species (MUMS)/limited market.

Collaborating with HTA bodies and healthcare payers

Some new medicines that receive marketing authorisation fail to get reimbursed or become accessible for patients. Close interaction between regulators, HTAs and other relevant decision-makers is critical to support medicine development programmes that generate data relevant for all these stakeholder groups, with the ultimate aim of ensuring patient access to important new medicines.

In November 2017, EMA and the European Network for Health Technology Assessment (EUnetHTA) finalised their new joint work plan outlining key areas of collaboration until 2020. It foresees continued focus on areas in which major progress has already been made, including early dialogue and scientific advice. A joint platform for parallel consultation was created in July 2017 to provide developers of medicines with simultaneous, coordinated regulatory and HTA advice on their development plans and to facilitate alignment of data requirements.

EMA and EUnetHTA will also continue their information exchanges on the outcome of the regulatory assessment when a new medicine is granted a marketing authorisation. In 2017, a new collaboration started to support the HTAs in their relative effectiveness assessment after CHMP opinion. EMA and EUnetHTA also committed to work to optimise tools for the generation of evidence post-authorisation, such as patient registries.

New areas in the collaboration include the plan to explore possible synergies in how HTA bodies and regulators apply the concepts of unmet medical need and therapeutic innovation, and to understand the conceptual similarities and differences between the significant benefit of orphan medicines versus their added therapeutic value.

> “Access to orphan medicines is a hot topic in Europe. In terms of scientific assessment, the regulatory considerations on significant benefit and the HTA considerations on relative effectiveness are very close. We are starting a joint review of these concepts to better understand the similarities and to facilitate better communication about them.”

Kristina Larsson
Head of Orphan Medicines, EMA

26/27 April

Second tripartite meeting between EMA, PMDA and FDA to discuss regulatory approaches for the evaluation of antibacterial agents.

5 May

Publication of a new guide on biosimilar medicines for healthcare professionals.

Breaking new ground with healthcare payers

As a complementary initiative to the collaboration with HTAs, EMA and EU healthcare payers held their first joint meeting in September 2017. EMA and representatives from the Association Internationale de la Mutualité (AIM), an association of mutuals and other non-profit healthcare payers, the European Social Insurance Platform (ESIP), the Medicine Evaluation Committee (MEDEV) and the multi-stakeholder platform Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA) discussed how their cooperation might contribute to boosting sustainable access to medicines for EU citizens.

EMA and EU payers will consider organising follow-up activities and discuss how to create a more effective partnership in order to improve the exchange of knowledge and information between regulators and payers.

> “Regulators, HTA bodies and payers – we all perform an important task in one way or the other as gatekeepers for medicines to the healthcare systems in the EU. But we also have an increasingly important role as enablers of medicine development. Our cooperation can help medicine developers to address some of the inefficiencies in the current system of clinical research so that they become better at generating the evidence each of us needs for good decision-making.”

Guido Rasi
EMA Executive Director

16 May

9th annual workshop of the European network of paediatric research at EMA (Enpr-EMA).

18/19 May

EMA meets with East African regulators.

Supporting development of new antimicrobial medicines and treatment approaches

EMA, the Japanese Pharmaceutical and Medical Devices Agency and the United States Food and Drug Administration reached an agreement in 2017 to align data requirements for certain aspects of the clinical development of new antibiotics. This is expected to stimulate the development of new treatments to fight antimicrobial resistance and protect global public health.

Representatives from the three regulatory agencies held two tripartite meetings in 2017. The aim of this collaboration is to facilitate a single development programme for new antibacterials that can satisfy the regulatory requirements of each of the three agencies.

The three regulators agreed a common approach for clinical trials designed to study the effects of new antibiotics in certain indications, such as uncomplicated gonorrhoea or uncomplicated urinary tract infections. Stressing the importance of gathering meaningful clinical data in children, they also committed to working together to streamline paediatric development of new antibacterial agents.

These talks took place under the terms of the respective confidentiality agreements of the three agencies.

Fostering a constructive dialogue with the pharmaceutical industry and supporting innovation in SMEs

In 2017, EMA set up a new platform to discuss research and development support for pharmaceutical industry stakeholders. The aim is to foster more integrated support activities through continuous improvement and mutual learning. EMA and industry associations will regularly meet to address all areas of product development support, including scientific advice, paediatric and orphan medicines and innovation support. This new platform provides an opportunity for both general updates and more focused discussions on specific processes or issues to foster a constructive dialogue with industry stakeholders.

Because SMEs are a motor of innovation in the pharmaceutical industry, EMA launched a new action plan to support SMEs in the development of new human and veterinary medicines. The plan covers the period up to 2020 and aims to aims to raise awareness of EMA's SME initiative, by increasing engagement with actors in the pharmaceutical innovation environment such as incubators, universities and investors. It also includes actions around training and education of SMEs and academia, actions to support the development of innovative medicines, and actions to support continued engagement with SMEs, EU partners and stakeholders.

For the first time the annual SME Info Day, held in November 2017, was organised together with the EU Innovation Network (EU-IN). Attendees were given information on EU initiatives supporting development of human medicines, future EU funding opportunities and on platforms for early regulatory dialogue with EMA and the EU network.

31 May

EMA publishes an action plan for small and medium-sized enterprises as drivers of pharmaceutical innovation.

Responding to regulatory challenges in innovative fields of medicine

EMA constantly reviews and improves its standards and guidance. This allows the Agency to respond to the particular challenges of developing innovative medicines in new fields, such as advanced therapies or personalised medicines, with the ultimate aim of providing patients with timely access to innovative treatments.

The EU Innovation Network (EU-IN)

The EU Innovation Offices Network (EU-IN) is a joint initiative launched by EMA and the Heads of Medicines Agencies in October 2016 to support innovation in medicines. Its focus is on SMEs and academic innovators.

During 2017, 23 innovation offices established in NCAs voluntarily joined the network. The EU-IN held discussions on emerging areas of innovation with expected impacts on regulatory evaluation standards and practices in the pharmaceutical sector, namely nanomedicines and novel manufacturing strategies (including continuous manufacturing, point-of-care manufacturing and 3D printing), and borderline products.

Another aspect of its work is horizon scanning. In 2017, the EU-IN prepared a survey of foresight activities across the network. The aim was to review how current practice nationally could be shared and consolidated at EU level and contribute to international initiatives as appropriate.

Advanced therapies action plan

In October, EMA and the EC's Directorate-General for Health and Food Safety (DG SANTE) launched a new joint action plan to foster the development of ATMPs.

The action plan contains 19 actions in different key areas. The main aim is to engage with a wide range of stakeholders and to facilitate the progression of ATMPs from early development to patients. This includes the streamlining of procedures to better address the specific requirements of ATMP developers.

One of the actions, a new guideline on good manufacturing practice for ATMPs, was completed in November 2017, when the document was published by the EC. The objective of the guideline is to ensure that these novel medicinal products are consistently produced and controlled according to high quality standards, for the benefit and safety of patients.

Other actions include:

- dialogue with NCAs to address the interplay between the legislation on genetically modified organisms (GMO) and on medicines, to reduce discrepancies across the EU regarding the application of GMO rules;
- new EMA scientific guidelines on ATMPs, including investigational ATMPs, to clarify regulatory expectations;
- continuous awareness and training sessions organised by EMA for the EU regulatory network on ATMP-related topics (e.g. expert meetings on adeno-associated viral vectors and genome editing);
- engagement with HTAs and other stakeholders with the aim of improving patient access.

1 June

PMDA joins the EMA/FDA GCP initiative as observers. The EMA/FDA GCP initiative started in 2009 and has enabled a more efficient use of limited resources, improved inspection coverage and better understanding of each agency's inspection procedures.

At its February meeting, the Agency's Committee for Advanced Therapies (CAT) elected Dr Martina Schüssler-Lenz as its new chair, for a three-year mandate. Dr Schüssler-Lenz is the deputy head of the Advanced Therapy Medicinal Products Section at the Paul-Ehrlich Institute (PEI) in Langen, Germany, and has been vice-chair of the CAT since March 2014.

Personalised medicines

Personalised medicine is often seen as the next frontier in patient-centred health care. There is no common definition of the term, but it is often referred to as a medical model for tailoring the right therapeutic strategy for the right person at the right time, on the basis of an individual's characteristics and genetic make-up.

To discuss evolving concepts and regulatory challenges, as well as opportunities in the development of personalised medicines, EMA organised a joint workshop on personalised medicine with EMA's PCWP and HCPWP in March 2017.

The participants discussed how the Agency and the European medicines regulatory network both approach and support the development and evaluation of personalised medicines. They also explored how patients and healthcare professionals can contribute to this process and what their priorities might be in this area. A report summarising the main conclusions of the workshop was published in May 2017.

12 June

EMA, FDA and Health Canada workshop on paediatric pulmonary arterial hypertension.

23 June

EMA approves the first-ever guidance at EU level for stem-cell-based medicines for veterinary use.

Ensuring patient safety throughout the life cycle of medicines

EMA constantly strives to improve its regulatory standards to ensure the protection of patients throughout the life cycle of medicines, from their development to their use across Europe.

Revision of the guideline on first-in-human clinical trials

In 2017, EMA finalised the revision of its guidance on first-in-human clinical trials. Developed in cooperation with the EC and the EU Member States, the revised guideline further helps clinical trial sponsors and regulators to identify and mitigate risks for trial participants. The revision took into account the comments received during a public consultation and a follow-up workshop.

The safety and well-being of trial participants should always be the utmost priority when designing early clinical trials. The guideline emphasises the sponsor's responsibility to define the uncertainty associated with the medicine tested at each step of the development and to describe how the potential risks that might arise from this uncertainty will be addressed by the design and conduct of the trial. The approach must be supported by a well-documented scientific rationale from the outset and be responsive to data emerging over the course of the trial.

Better labelling of excipients for safe use of medicines

EMA and the EC updated the annex to the European Commission guideline on excipients in the labelling and package leaflet on human medicines with new safety advice for 15 excipients. Excipients refer to everything in a medicine other than the active substance. While most excipients are considered inactive, some can have a known action or effect in certain circumstances. These must be declared in the labelling of the medicine. The updated annex contains all excipients that must be declared in a medicine's labelling and package leaflet as well as related safety warnings. The main aim of this update was to take into account safety concerns which were not addressed in the existing annex to the guideline. It also paid specific attention to, for example, the safety of these excipients when included in medicines used in children or pregnant women.

The updated annex, which took into account the comments received for each excipient during public consultations, is published in all EU languages along with the relevant scientific reports, applies to both centrally and nationally authorised products. The updated document includes five new excipients and new safety warnings for ten existing excipients. The new safety information will help patients and healthcare professionals make more informed decisions about the medicines they take and prescribe.

New and improved EudraVigilance to simplify reporting and data analysis

On 22 November 2017, EMA launched a new and improved version of EudraVigilance, the European database and analytical system that holds reports of suspected adverse reactions to human medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA). EudraVigilance is a key tool for patient safety in Europe and the new system makes it easier for marketing authorisation holders and sponsors of clinical trials to report suspected adverse reactions and facilitates the analysis of this information.

19 July

EMA agrees on principles for involving patients and consumers under the age of 18 in the Agency's activities.

27 July

ECDC, EFSA and EMA publish an updated version of their Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report.

The enhancements and expected benefits of the new EudraVigilance are:

- simplified reporting of individual case safety reports (ICSR) and reduced duplication of efforts. Marketing authorisation holders now report directly to EudraVigilance rather than individual NCAs, who instead access the ICSRs from EudraVigilance;
- better detection of new or changing safety issues, enabling rapid action by regulators to protect public health;
- better searchability and more efficient data analysis based on the use of the ISO/ICH agreed standard for ICSRs and new query functions;
- increased system capacity to support large volumes of users and reports;
- greater transparency in safety monitoring and much greater access to data and information for patients and healthcare professionals;
- more efficient collaboration with the WHO, with EMA making all ICSRs originating in the EEA directly available from EudraVigilance to the WHO Uppsala Monitoring Centre (UMC).

Stakeholders were supported through the process with a change management plan developed through the PRAC. Support included regular webinars, an online training module and the opportunity for system testing prior to go-live. EMA also ensured all relevant guidance was updated, including good pharmacovigilance practice on reporting suspected adverse drug reactions and the detection and management of safety signals.

18/19 September

EMA holds the first awareness session for international regulators and NGOs on the work of the Agency and European medicines regulatory system.

Contributing to animal and human health in relation to veterinary medicines

EMA and the EU NCAs safeguard animal health in the 28 EU Member States, as well as in the EEA countries, by ensuring that all medicines available on the market are safe, effective and of high quality.

In 2017, EMA's veterinary medicines activities mainly focused on the availability of new veterinary medicines, particularly for minor species, facilitating research and innovation for the benefit of animal welfare, and the continued fight against antimicrobial resistance (AMR).

The Agency provided support to the EC in the drafting of the new veterinary regulation. One of the aims of the new legislation is to simplify administrative processes, which will have a considerable impact on the Agency's operations. In preparation for this, EMA completed a review and streamlining of its major business processes, as a first step towards a leaner administration and to ensure efficiency to meet the increased demand that is expected to arise from the new legislation.

Facilitating availability of new veterinary medicines

New development guidelines for medicines for minor use/minor species or limited markets

In April 2017, EMA adopted a set of revised guidelines that clarify the data needed to support an application for a marketing authorisation for veterinary medicines intended for minor uses and minor species, the so-called MUMS and limited markets. The revision is part of the overall strategy of the Agency's CVMP to encourage development of veterinary medicines for diseases that occur infrequently or in limited geographical areas in major species and for minor species. These medicines may otherwise not be developed under the current market conditions.

Clarifying requirements for field trials for vaccines

At its November meeting, the CVMP accepted recommendations to help applicants understand in which situations a justification to omit field efficacy studies (i.e. studies in animals under real-life conditions in the field) would be acceptable, in the authorisation of veterinary vaccines. Improving clarity on this topic will facilitate the availability of veterinary vaccines in the EU.

These recommendations were made by the joint EMA and HMA Steering Group on veterinary vaccine availability on the basis of the outcome of a joint EMA/HMA stakeholder focus group meeting held in June 2017. They come in the context of a joint action plan to facilitate timely access to the EU market for new or improved veterinary vaccines, in the interest of animal and public health and animal welfare.

Supporting activities for development of medicines for fish

In July 2017, regulatory barriers and solutions for improving the availability of fish medicines were discussed in a meeting with the FishMedPlus Coalition. The topics covered ranged from the authorisation of new products, extension of use of already authorised products and stimulation of interest in marketing medicines for fish.

Encouraging research and innovation in veterinary medicines

Interest and research activities into novel therapies for animals, such as cell-based or gene-therapy techniques have gathered speed over the last few years. The term 'novel therapies' in this context refers to therapies that are either genuinely new, or new only to the veterinary domain, although often well known in the context of human medicines. Additional guidance from regulators is often needed in these areas to help stimulate development in these new fields.

19 September

EMA and EU healthcare payers meet for the first time to explore synergies and foster mutual cooperation.

26 September

Agency holds its first public hearing at PRAC in the context of a safety review for valproate medicines.

Stem-cell therapies – priority area for guidance

In June 2017, the Agency approved the first-ever guidance at EU level for stem-cell-based medicines for veterinary use. The guidance addresses the concerns raised by manufacturers and authorities with regard to the sterility (absence of bacteria, fungi and mycoplasma), tumorigenicity and management of extraneous agents of specific stem cell therapies in the veterinary sector. It was prepared by the CVMP's Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT).

First guidance for veterinary monoclonal antibodies

Another priority area for guidance is monoclonal antibodies for use in animals. The first guidance document in this area was published in December 2017.

Monoclonal antibodies are bioengineered molecules that recognise and bind to a specific target protein, and have not been used in veterinary medicines until recently. In human medicine, these therapies have been authorised for many years for use against cancer and diseases affecting the immune system, such as rheumatoid arthritis. Therapies that are new to veterinary medicine face particular challenges since regulatory guidance has yet to be developed once more experience has been gained.

Fighting antimicrobial resistance – a holistic one-health approach

AMR is an increasingly serious threat to global public health affecting both people and animals. No country or organisation can face the challenge of AMR alone, so it requires coordinated action across all government sectors and society.

EMA supports a 'one-health' approach, promoting close and integrated cooperation between the human and veterinary fields.

The Agency is collaborating with the EC, the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) to develop and implement the initiatives set out in the EC's new one-health action plan against AMR launched in 2017. In recognition for this joint work, EMA together with its EU partners were shortlisted in the category "Excellence in collaboration" for the first EU Ombudsman award.

An information session organised by EMA and ECDC was an opportunity to review the present challenges with AMR and the various ongoing initiatives at EU level to tackle the threat. The event brought together representatives of the WHO, the EC, Member States, patients organisations and healthcare professionals.

Promoting responsible use of antimicrobials in animals

In 2017, EMA launched a public consultation on a reflection paper on the use of aminoglycosides in animals, to critically review the current knowledge on the usage of these medicines and the potential impact on animal and human health.

A consultation was launched on the off-label use of antimicrobials in veterinary medicine. The purpose of this was to define off-label use and to better understand the underlying reasons for existing veterinary practices in relation to the use of antimicrobials.

In January 2017, EMA and EFSA published a joint opinion on the measures the EU must take to reduce the use of antimicrobials. The measures recommended by the two agencies include the setting of national targets to minimise the use of antimicrobials, implementing farming practices that help to prevent diseases, and considering alternative farming systems that could reduce the use of antimicrobials.

9 October

EMA and the EC update the annex to the European Commission guideline on excipients in the labelling and package leaflet of medicines for human use.

12/13 October

EMA hosts the 42nd meeting of the Data Protection Network.

> AMR can only be addressed if all sectors of society are involved. Our role as international organisations is to keep civil society informed and to engage with it during the decision-making.

Carmem Pessoa da Silva
WHO infection control specialist

Collecting data for evidence-based policy-making

ESVAC report 2017

The 2017 results of the annual European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report on the sales of veterinary antibiotics were encouraging. Between 2011 and 2015, the sales of antibiotics for animal use decreased overall by 13% in the 30 participating countries. The report also highlighted that the situation in the EU remains variable: despite an overall decrease in use, eight countries reported an increase of 5% or more. However, the report gives reason for optimism that the substantial reduction in the sales of antimicrobials for food-producing species observed in some countries could serve as a model for other Member States.

Assessing progress regarding reduction of antimicrobial resistance and antimicrobial consumption

In October 2017, ECDC, EFSA and EMA recommended a set of indicators to measure Member State progress in reducing the use of antimicrobials and combatting AMR. The indicators address both the human and animal sectors and reflect antimicrobial consumption and antimicrobial resistance in the community, in hospitals and in food-producing animals. The indicators are based on data already gathered through existing EU monitoring networks.

JIACRA report: more evidence of link between antibiotic use and antibiotic resistance

In July 2017, ECDC, EFSA and EMA published an updated version of their JIACRA report. The report confirmed the link between antibiotic consumption and antibiotic resistance in both humans and food-producing animals. It highlighted that there are still important differences across the EU in the use of antibiotics in animals and humans.

Overall, antibiotic use is higher in food-producing animals than in humans, but the situation varies across countries and according to the antibiotics.

In particular, a class of antibiotics called polymyxins – which includes colistin – is used widely in the veterinary sector. Recommendations were made to reduce animal use of such antibiotics, which are increasingly used in hospitals to treat multi-drug-resistant infections.

Other antibiotics are more often used in humans than in animals. These include third- and fourth-generation cephalosporins and quinolones, antibiotics that are also considered critically important for human health.

16 October

EMA publishes its Business Continuity Plan for Brexit.

16 October

EMA publishes its 7th ESVAC report on the sales of veterinary antibiotics.

Optimising the operation of the network

To ensure that the European Union's medicine system protects human and animal health, EMA works closely with more than 50 national competent authorities in the EEA, the EC and a broad range of stakeholders, including patients and consumers, healthcare professionals, academia and the industry.

It is essential that this network responds in a timely and effective way to technical and scientific developments as well as new public health challenges, such as shortages of medicines. Hence, the Agency is making consistent efforts to strengthen the network and to engage better with all categories of stakeholders. This is now more important than ever as the EU medicines network has to prepare for the United Kingdom's withdrawal from the EU and the redistribution of work currently performed by the UK.

A stronger European medicines network for European citizens

By working closely together in a network, EMA, the EC and Member States are reducing duplication, sharing the workload and ensuring the efficient and effective regulation of medicines across the EU. The Agency operates at the heart of this network, coordinating and supporting interactions between its members.

Joint task force to ensure availability of medicines in the EU

Shortages of medicines are an increasing problem in Europe and have been recognised by HMAs and EMA as an area of great concern affecting all stakeholder groups.

Such shortages have an impact not only on the supply chain but ultimately on healthcare systems, resulting in a significant impact on end-users. They can lead to medicines rationing, delay of critical treatments, and use of alternatives that may be less efficacious or increase the risk of medication errors and lead to adverse events. With respect to veterinary medicines, shortages may also cause concern for animal health and welfare in cases where alternative medicines do not exist or are not marketed.

The causes of a shortage vary and include economic factors (e.g. pricing differences leading to parallel distribution and depletion of medicine in one market, lack of reimbursement or company decision not to market medicine), and problems in manufacturing and quality issues (e.g. non-compliance with good manufacturing practice).

To tackle this issue, in December 2016 EMA and the HMA created a joint task force to develop and coordinate the necessary actions to help guarantee uninterrupted supply of human and veterinary medicines. The work of the Task Force covers both human and veterinary medicinal products regardless of their authorisation route (centralised, decentralised, mutual recognition or purely national procedure), in the following cases:

- when medicines are authorised but not marketed (or no longer marketed);
- when authorised medicines are affected by supply chain disruptions that directly prevent their availability. Such disruptions may occur due to GMP, GCP and/or GDP problems, quality defects, etc.

The task force is composed of three Thematic Working Groups (TWGs) tackling the problem from the three critical angles: marketing authorisation, supply chain disruptions and communication.

Its main purposes are:

- to assess why authorised medicines are not marketed in EU Member States;
- to establish definitions of shortage / supply chain disruption and metrics for better shortage management;
- to develop communication strategies within the network and with other actors in the healthcare system during shortages.

20 October

EMA and DG SANTE publish an action plan to foster the development of advanced therapies.

20 October

First anniversary of the clinical data publication website.

Regulatory Science Observatory

EMA set up its new Regulatory Science Observatory (RSO) to identify and meet emerging trends in science and technology and promote the strategic application of science in the regulation of pharmaceutical products.

As one of its first major actions, throughout 2017, the RSO surveyed key trends in science, technology and regulatory tools that can impact EMA operations. The aim was to better understand if and how these trends influence EMA operations, assess the current level of network engagement and make preliminary recommendations for future engagement. A report resulting from this exercise will be finalised early in 2018. It will serve as a reference source to support the development of a Regulatory Science Strategy.

Use of big data to improve human and animal health

In 2017, EMA and the NCAs established a new task force to explore how big data can be used to support research, innovation and robust medicines development for the benefit of human and animal health. The task force kick-off meeting took place on 6 March 2017.

The term big data refers to large sets of information which require specialised computational tools to enable their analysis and exploitation. These data might come from electronic health records from millions of patients, genomics, social media, clinical trials or spontaneous adverse reaction reports, to name just a few.

The task force, chaired by the Danish Medicines Agency and EMA, is composed of experienced staff from medicines regulatory agencies in the network. Their efforts are complemented on an ad hoc basis by external experts in big data collection analysis. A mandate for the group with a set of deliverables has also been agreed.

Strengthening safety monitoring through better use of real-world evidence

Analysis of data of medicines in the 'real world', i.e. in normal conditions of use, has the potential to support regulatory decision-making throughout the product life cycle. Until now, such use of real-world data has mainly focused on monitoring the safety of products on the market. In 2017, EMA continued to support benefit-risk evaluations of medicines made by the PRAC and other committees by analysing data on the drug utilisation and safety of medicinal products in real-world clinical use. Such support included:

- A collaborative study on the utilisation of codeine for the treatment of pain in children to assess the effectiveness of risk-minimisation measures introduced in October 2013; the collaboration included the Spanish Agency of Medicines and Medical Devices (AEMPS), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and EMA.

- Several studies conducted in-house by EMA with databases of electronic healthcare records (the THIN database) and claims data (the IMS database).

- Two EMA-funded studies assessing the effectiveness of the risk-minimisation measures for diclofenac and hydroxyzine were launched in 2017 through procurements to academic centres.

- Five other studies were ongoing.

A review of EU-funded initiatives linked to real-world evidence was performed to determine whether their outputs could be used as resources for the generation of real-world data able to support regulatory decision-making on medicines. Of 171 initially identified EU-funded initiatives, 65 were selected and characterised.

In parallel, a review of electronic healthcare databases available in Europe was performed to identify the data sources considered adequate to respond to regulatory questions on the benefit-risk of medicines. Out of 77 data sources, 34 were retained for further investigation and fully described.

EMA has continued to support the registration of post-authorisation studies in the EUPAS Register, which included more than 1,200 studies by the end of 2017 and represents one of the largest inventories of observational studies in the world.

24 October

Third tripartite meeting between EMA, PMDA and FDA to discuss regulatory approaches for the evaluation of antibacterial agents.

26 October

ECDC, EFSA and EMA publish a new set of indicators to assess progress on reduction of antimicrobial resistance and antimicrobial consumption.

Increasing the utility of patient registries in regulation

Post-authorisation studies based on patient registries are frequently requested by the EMA Committees to support the monitoring of the safety or efficacy of marketed drugs in the real world. However, regulators and pharmaceutical companies often face challenges in using existing registries or establishing new ones. For this reason, in 2015, EMA launched a patient registry initiative to support a more systematic approach to the contribution of existing disease registries to the benefit-risk evaluation of medicines. In 2017, EMA defined a vision, strategy and workplan for the patient registry initiative and organised two workshops with concerned stakeholders on cystic fibrosis registries and multiple sclerosis registries.

In order to increase transparency on disease registries which are used or may be used for regulatory purpose, EMA also initiated the registration of multinational disease registries in the ENCePP resource database. By the end of 2017, the inventory included a total of 66 disease registries.

EU Network Training Centre

Evolving science and technology requires the network to keep its knowledge and expertise continuously up to date in order to meet new regulatory challenges. The EU Network Training Centre (EU NTC) provides a central platform for the supply of scientific and regulatory training practices between EMA and NCAs in the EEA to ensure the spread of good practices and improve the work done in the EU regulatory network.

This involves:

- using and coordinating the expertise in the network to create training curricula;
- supporting the organisation of training sessions to fill existing knowledge gaps;
- centralising training offers from EMA and the national authorities in the regulatory network into one training catalogue;

The EU NTC catalogue increased from 48 courses in 2015 to 100 courses in 2017. The EU NTC Learning Management System (LMS), a digital training platform, is available to network staff in all 28 Member States. Following a successful pilot phase, the LMS was fully implemented in January 2017.

Multinational assessment teams – broader involvement of national authorities in the work of EMA's scientific committees

A multinational assessment team, in which experts from several national agencies work together rather than assigning all the responsibility to a single country, allows wider involvement of national competent authorities in the work of the EMA scientific committees and optimises the use of national resources, whilst maintaining the committees' high-quality scientific work.

This initiative is available to all Member States, and it applies to:

- rapporteurs and co-rapporteurs;
- rapporteurs for maximum residue limit applications.
- coordinators for scientific advice procedures for both human and veterinary medicines.

As of April 2017, EMA expanded the multinational assessment team initiative to post-authorisation assessments, which means that these teams can be used for the assessment of extensions of marketing authorisations for existing medicines. In the first phase, it applies only to the multinational teams that were used for the initial marketing authorisation evaluation.

26 October

Adoption of the 10-year Report on the Paediatric Regulation by the EC to the European Parliament (EP) and Council.

1 November

EU-US mutual recognition of inspections of medicines manufacturers comes into operation.

Data-gathering initiative

The data-gathering initiative was concluded in 2017. The Management Board started this initiative in 2014 to gather evidence needed by the EC to support a future redraft of the legislation governing the fees charged by the Agency. The Data-gathering Steering Group was set up with the primary objective of collecting information on the time spent by staff, both within the EMA secretariat and across the network of NCAs regulating medicines, on the range of procedures and activities relating to the regulation of human and veterinary medicines. In adopting the final report from the group, the Management Board considered that the data collected were a useful insight into the work of the network and could inform the ongoing debate as to how the medicines regulatory system in Europe is resourced sustainably.

Crisis simulation exercise coordinated by EMA in October 2017

The Agency coordinated a crisis simulation exercise together with the EC and NCAs in October 2017 to test processes and procedures in place to deal with major incidents which could have a serious impact on public health. The simulation focused on a fictitious human medicines safety issue and, based on the findings, EMA will consolidate relevant procedures and guidance. The lessons learned from the running of the crisis simulation exercise cover areas such as: process streamlining, communications and interactions, memberships and technical considerations.

Management of the network technical systems

EMA looks after the IT systems connecting all parties in the network. They facilitate important exchanges of information on aspects such as safety monitoring of medicines, authorisation and supervision of clinical trials, and compliance with good manufacturing and distribution practices.

Management board adopts new information management strategy to 2020

At its December 2017 meeting, the Agency's Management Board adopted a new information management strategy in the light of EMA's relocation. This prioritises actions necessary for relocation, in order to maintain and improve operational excellence and deliver effective information services throughout the process.

EMA's cloud strategy

In early 2017, EMA decided to adopt cloud computing as a core element of its information management strategy, after a period of extensive research and consultation with the network and with stakeholder groups. Cloud computing is the delivery of IT services – servers, storage, databases, networking, software, analytics and more – over the internet ("the cloud"), as opposed to being provided from an organisation's own servers.

EMA will only adopt cloud solutions where feasible and where there is value. The first cloud service to be implemented has been a document repository for individual case safety reports submitted via the new EudraVigilance system.

13 November

EMA and EUnetHTA publish a joint work plan outlining key areas of collaboration for the next three years.

15 November

EMA publishes an action plan to improve the product information for EU medicines.

Towards better digital identification of medicinal products – the SPOR project

EMA is currently implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP). The ISO IDMP standards provide data elements, formats and terminologies to unambiguously identify medicines and exchange information about them. Following a phased implementation process, pharmaceutical companies will be required to submit data to EMA in accordance with the new formats and terminologies.

To facilitate the implementation of these ISO IDMP standards, EMA is delivering a set of master data management services **for the four domains of master data in pharmaceutical regulatory processes:** substance, product, organisation and referential (attributes such as pharmaceutical form and route) data. These four domains or areas are known collectively as SPOR.

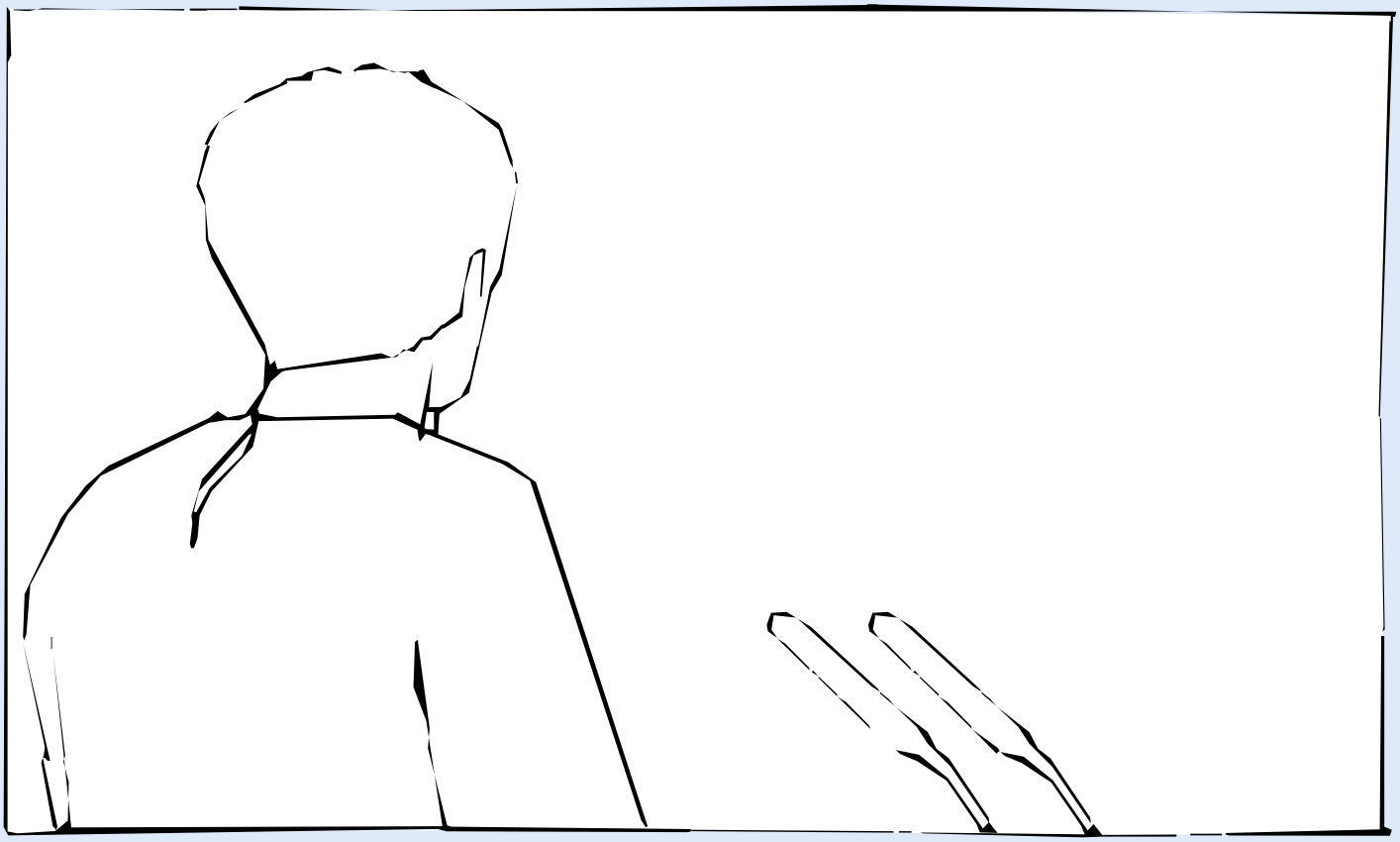
The first two services, the referentials management service (RMS) and organisations management service (OMS) were launched in June 2017 to cover two out of four SPOR domains. This did not immediately change any regulatory submission processes, apart from the use of OMS in electronic application forms for marketing authorisations holders. However, EMA is consulting stakeholders on the benefits of using the SPOR services to support different regulatory procedures (e.g. simplification of Type IA variations).

17 November

Info day for micro, small and medium-sized enterprises: supporting development of innovative medicines' and early access.

20 November

The EU Member States vote for Amsterdam to become the Agency's new host city.



Always in touch with stakeholders

First EMA public hearing

On 26 September 2017, EMA held its first-ever public hearing. This new tool for citizen engagement was introduced by the EU's pharmacovigilance legislation. It enables the PRAC to hold public hearings during certain safety reviews of medicines to support its decision-making by providing perspectives, knowledge and insights into the way medicines are used.

Public hearings are held on a case-by-case basis, where PRAC determines that collecting the views of the public would bring added value to its review, in addition to the other channels of stakeholder engagement, such as stakeholder submissions or through inclusion of patients and healthcare professionals in expert meetings.

EMA's first public hearing gave patients, carers, doctors, pharmacists and academia a chance to share their experience with valproate – a medicine that treats epilepsy, bipolar disorder and migraine. The public hearing was part of a review of the safety of valproate in women and girls who are pregnant or of childbearing age. Malformations and neurodevelopmental problems can occur in babies who are exposed to valproate in the womb and the review followed concerns that current EU-wide measures to reduce the risk were not sufficiently effective.

The hearing gave EU citizens an opportunity to make their voices heard to complement the available scientific evidence in the evaluation of this medicine. The total number of attendees was 65, including 28 patients and patient representatives, 19 healthcare professionals and academics, 11 from the pharmaceutical industry and 7 from the media. There were a total of 25 speaker contributions, grouped into 16 speaker slots.

The speakers came up with important ideas for new risk-minimisation measures, such as including visual reminders of the risks on the outer packaging of valproate medicines and promoting the need for regular treatment reviews for all women receiving valproate long term to ensure that in future no woman taking this medicine is unaware of the risks.

All input received during the hearing was taken into account by the PRAC in its assessment of valproate, which was not concluded before the end of 2017.

The European Parliament insisted on including public hearings in the EU law on medicines safety. The positive experience from EMA's first public hearing confirms that giving patients a platform to tell their story was the right thing to do.

Linda McAvan
Member of the European Parliament

The public hearing was a great opportunity to hear many different views in a relatively short time on a problem of high complexity.Discrepancies in the healthcare systems between EU countries and huge challenges that lie ahead when it comes to restrictions in the use of valproate make this topic a wise choice for a first hearing in Europe.

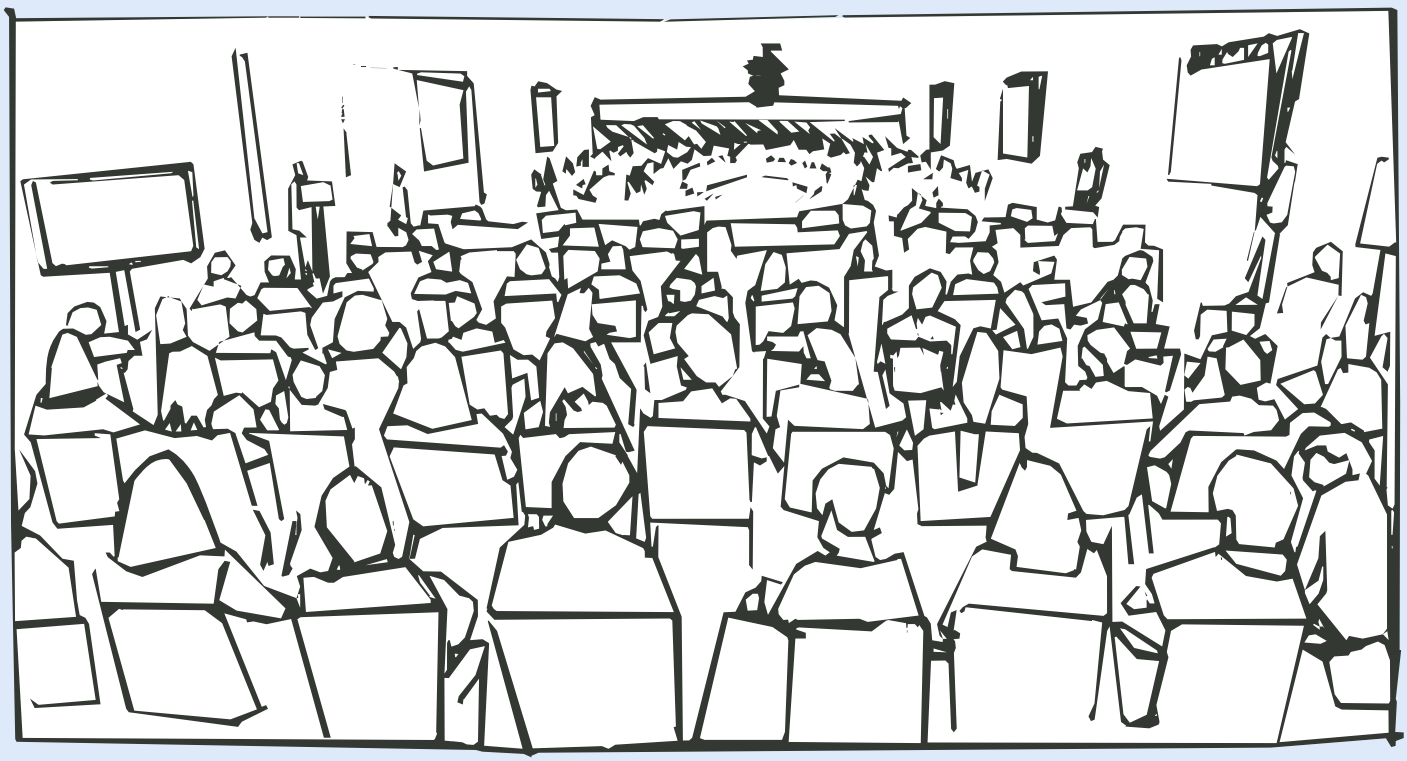
Martin Brodie
International Bureau for Epilepsy

The hearing today went absolutely well, beyond expectations. There was an open, non-judgemental atmosphere that allowed all participants to talk with equal credibility. The hearing was carried out in a special ambiance characterised by solemnity, seriousness and openness.

François Houÿez
EURORDIS

I very much welcome EMA's efforts to engage with the 'real world' when making regulatory decisions. It was a great opportunity to share experience and ideas with PRAC members on how community pharmacists could play an increased role in raising awareness about the risks of valproate in women of childbearing age.

Jūratė Švarcaitė
Pharmaceutical Group of the European Union (PGEU)



EMA steps up interaction with academia

In April 2017, EMA launched its new framework and action plan with academia, to formalise, structure and further develop interactions with this important stakeholder group.

The framework's overall objectives are to:

- raise awareness of the mandate and work of the European medicines regulatory network, so as to increase academia's trust in and engagement with the regulatory system;
- encourage the translation of academic research into novel methodologies and medicines which meet regulatory standards and address the needs of public and animal health;
- ensure that the best scientific expertise and academic research are available in time to support effective evidence generation, regulatory advice and guidance, as well as decision-making in regulatory processes;
- work with academia to develop regulatory science that embraces scientific progress in medicines development without compromising patient safety, such as, for example, the use of novel end points or novel methodologies.

Along with the framework, EMA has developed an action plan which includes, among other activities, initiatives for mutual education and training, staff exchange programmes to promote mutual learning, a strategic research agenda for regulatory science and the creation of an EMA entry point for academia to receive information on available support within the EU regulatory network.

> An effective framework that facilitates communication and knowledge exchange between the regulators and expert academic groups will stimulate innovation in the development of new therapeutic approaches leading ultimately to improved patient benefit.
>
> **Professor Bernard Charpentier**
> President of the Federation of European Academies of Medicine (FEAM)

> This is the platform needed to: 1) promote regulatory awareness, 2) support academic research, and 3) boost communication between the two parties. Now it is time to work!
>
> **Dr Rosa Giuliani**, EU Policy Committee, European Society for Medical Oncology (ESMO)

22 November

EMA launches a new and improved version of EudraVigilance.

22 November

The EC publishes the Guidelines on Good Manufacturing Practice specific to ATMPs, drafted with extensive input from CAT and GMP/GDP inspectors working group.

Involving young people in EMA activities

Young patients and consumers can make an important contribution to committee discussions on medicines by sharing their experience and perspectives of living with a disease or condition.

In 2017, EMA agreed on principles for involving patients and consumers under the age of 18 in the activities of its scientific committees and working parties. The principles define what input young people could provide and suggest options on how best to capture their opinions. They also establish a process for identifying, supporting and consulting with young people.

According to the new principles, involving young people in the Agency's activities will be considered on a case-by-case basis when it is expected that their views could enhance scientific discussions related to the development and assessment of medicines for children and adolescents.

The key forum in which young people could participate in the Agency's activities would be its Paediatric Committee (PDCO), but experience has demonstrated that the Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC) and the Scientific Advice Working Party (SAWP) can also benefit from young people's input when these groups review medicines for children.

New guide on biosimilar medicines for healthcare professionals

EMA and the EC published an information guide for healthcare professionals on biosimilar medicines. Biosimilars are biological medicines that are highly similar in all essential aspects to a biological medicine that has already been authorised. To date, the Agency's CHMP has recommended 28 biosimilars for use in the EU.

23 November

Joint Biologics Working Party and Quality Working Party workshop with stakeholders, in relation to prior knowledge and its use in regulatory applications.

The objective of the guide is to provide healthcare professionals with reference information on both the science and regulation underpinning the use of biosimilars.

The guide was developed in collaboration with EU scientific experts, in response to requests from healthcare professionals. Organisations from across the EU representing doctors, nurses, pharmacists and patients contributed to ensure that the guide adequately addresses questions relevant to healthcare professionals.

Access to clinical data – one year on

20 October 2017 marked the first anniversary of EMA's groundbreaking transparency initiative to publish clinical reports underpinning the market authorisation of new medicines for human use. This enables citizens, including researchers and academics, to directly access these reports via EMA's clinical data publication (CDP) website (https://clinicaldata.ema.europa.eu/home).

EMA is the first regulatory authority to provide such broad access to clinical reports.

As of the end of 2017, clinical reports on 55 medicines, including orphan, biosimilar and generic medicines, as well as medicines for use in children, are publicly available on the CDP website. This amounts to 3,583 clinical documents, totalling more than 1.3 million pages.

Published data have attracted a total of 2,361 new users (1,877 general and 484 non-commercial research users), resulting in 29,232 document views and 96,977 document downloads for non-commercial research purposes.

A 2017 survey of the website users, such as researchers, healthcare professionals, patients and industry, showed that three quarters of responders agreed that the publication of clinical data builds public trust and confidence in EMA's scientific and decision-making processes. Two out of three responders agreed that the data made available help researchers to reassess the clinical data.

62% of the users said that the data are useful and 87% confirmed that the data are presented in an understandable format, despite the redaction or anonymisation of certain information in line with European legislation on commercially confidential information and personal data protection.

Reporting irregularities that may affect medicines

At its March 2017 meeting, EMA's Management Board adopted a new policy to handle allegations of improprieties submitted by external parties, to complement the existing policy on whistle-blowing applying to the Agency's staff.

The goal of the new policy is to create an environment where individuals from outside the Agency feel confident to raise their concerns on improprieties. The policy helps EMA assess these reports and coordinate any further investigation in a structured way, while protecting the identity of the reporter.

Since 2013, when a dedicated email inbox was created, EMA has received a total of 43 reports that relate, for example, to the manufacturing of medicines or the conduct of clinical trials. Citizens can raise their concerns by sending a message or providing information to the address 'reporting@ema.europa.eu'. They can also send a letter to the Agency. Their identity is kept confidential.

1 December

1 December – EMA hosts an international workshop on how data anonymisation can enable clinical data sharing.

11 December

EMA publishes the first-ever guidance at EU level for monoclonal antibody therapies for veterinary use.

Regulatory collaboration to improve global health

A central pillar in EMA's strategy to protect public health is the strengthening of collaboration with other international regulators. In 2017, the Agency continued to work with its partners in Europe and beyond to contribute to the health of EU citizens and people around the world.

Bilateral interactions with non-EU regulators

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

A new milestone in EU-US relations

On 1 November 2017, the mutual recognition agreement between the EU and the US to recognise inspections of manufacturing sites for human medicines conducted in their respective territories became operational. This agreement, which updates an agreement from 1998, allows for recognition of each other's inspection outcomes and hence for better use of inspection expertise and resources.

In June, the European Commission confirmed that the US FDA has the capability, capacity and procedures in place to carry out GMP inspections at a level equivalent to the EU. The FDA confirmed the capability of eight EU Member States (Austria, Croatia, France, Italy, Malta, Spain, Sweden and United Kingdom). The remaining EU inspectorates will continue to be assessed until 15 July 2019.

The new agreement allows EMA and the FDA to make decisions based on findings in each other's inspections. It is a major milestone towards closer cooperation and improves the use of available resources to safeguard the quality and safety of medicines.

The agreement will avoid duplication, reduce costs and enable the regulators to focus on manufacturing sites in parts of the world where there is greater risk. Around 40% of finished medicines marketed in the EU come from overseas and 80% of the manufacturers of active pharmaceutical ingredients for medicines available in the EU are located outside the Union.

> "We need to think globally and work strategically with partners from around the world to make best use of our inspection capacity, so that patients can rely on the quality, safety and efficacy of all medicines, no matter where they have been manufactured. The new commitment with FDA is a testimony to the trust that exists between our regions and that has grown over many years of cooperation for the benefit of patients on both sides of the Atlantic."

Guido Rasi
Executive Director

11-12 December

EMA holds an international workshop on common data models for real-world use of medicines.

New EMA-Japan fellowship programme

In 2017, EMA, MHLW and PMDA agreed to establish a fellowship programme based on the model of EMA's fellowships with the FDA. The first EMA fellow visited Japan in October. She focused on procedural aspects of marketing authorisations, from the pre- to post-authorisation stages and aims, among other aspects, to improve understanding of the work and decisions taken by both agencies and deepen effective collaboration in strategic areas.

EMA also hosted a meeting with PMDA and FDA to discuss regulatory approaches for the evaluation of antibacterial agents. For more information, please see the section on 'contributing to animal and human health in relation to veterinary medicines'.

Multilateral work

In 2017, EMA continued to cooperate in a multilateral context with organisations such as:

- World Health Organization (WHO)
- The International Council for Harmonisation (ICH)
- International Coalition of Medicines Regulatory Authorities (ICMRA/ICDRA)
- International Pharmaceutical Regulators Forum (IPRF)
- International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)

European cooperation as a model for Africa

A delegation from the East African Community (EAC) visited the Agency in May 2017 as part of EMA's ongoing collaboration with African regulators. The goal of the meeting was to gather information and experience to support the potential creation of a networking medicines agency for the EAC.

The delegation included the heads of national agencies from the EAC partner states (Burundi, Kenya, Rwanda, South Sudan, Tanzania and Uganda), as well as representatives from the WHO and the World Bank Group. Participants discussed the structure and operations of EMA as a model for a regional networking agency that could coordinate the work of the national regulatory agencies in the assessment of human and veterinary medicines.

A workshop with the CHMP and African regulators in March 2017 looked at how to promote reliance on the scientific output of the CHMP, and in particular the Agency's 'Article 58 procedure' for global health products intended for use outside the EU. The workshop was organised with the support of the Bill and Melinda Gates Foundation.

"It is clear that there is political will and a strong commitment of regulators from the EAC to improve public health by ensuring citizens have access to affordable, safe, efficacious and quality medicines. We look forward to stronger mutual cooperation with regulators in Africa to help us improve global health."

Agnes Saint Raymond
Head of International Affairs, EMA

Promoting awareness of the EU regulatory system

In September 2017, the Agency organised for the first time a two-day awareness session for international regulators and non-governmental organisations (NGOs) on the European medicines regulatory network and EMA's role. Sixty regulators from non EU-European, African, Asian and American countries and several international NGOs attended the session. Based on the positive feedback received, EMA will organise further sessions.

Chapter 2
Fostering innovation and access to medicines

EMA staff and representatives from the Agency's partners and stakeholder groups discuss how to foster innovation and access to medicines from three different perspectives: (1) Personalised medicines – an ongoing revolution, (2) How pharmacovigilance enables innovation and (3) Collaboration between regulators, HTAs and payers

1 Personalised medicines – an ongoing revolution

Personalised medicine is often seen as the next frontier in patient-centred healthcare. It is often referred to as a medical model for tailoring the right therapeutic strategy for the right person at the right time, on the basis of an individual's characteristics and genetic make-up. Jan Müller-Berghaus, Ulrich Jäger and Corinne de Vries discuss how this concept is changing medicine development, what the promising trends are and what challenges need to be dealt with by regulators and doctors.

Q We hear a lot these days about 'personalised medicine' and 'patient-centred healthcare'. What exactly is meant by personalised medicine and is it the same as, or somehow related to, patient-centred healthcare?

Jan Müller-Berghaus: Patient-centred healthcare is something that is really related to the clinical care and clinical decision-making for an individual patient. It involves the interaction of the patient with the physician, care-taker and family, and is about the patient's values and views. Aspects of personalised medicines may still be part of that. But generally, in the regulatory world, patient-centred healthcare is not something that plays a major role.

Personalised medicines can be distinguished either as stratified medicines, such as biomarker-based medicines or individualised medicine, such as autologous medicines (treatments that are made from an individual and applied to the same individual, such as CAR-T cells).

Personalised medicines are part of patient-centred healthcare in a very broad sense. However, the overlap in practical terms is limited.

Ulrich Jäger: There is no such thing as a harmonised definition. I would agree that patient-centred healthcare includes personalised medicines. For me, as a doctor caring for patients, the most important part is the individualisation where we look at patients and their condition, sex, age, etc. At the same time, we try to deliver targeted treatments as opposed to untargeted chemotherapeutic treatments. I would make the distinction between individualised treatment and targeted therapy.

Corinne de Vries: We tailor therapies to individual patients based on a predictable response due to their underlying characteristics, such as the genetic build-up of a cancer or a certain risk of disease. Personalised medicines result in smaller, more focused trials, which is a different approach to medicine development. There is also an increase in the use of patient-reported outcomes, including quality of life, as important measures of beneficial, as well as adverse, treatment results.

Jan Müller-Berghaus
Clinical assessor,
Paul-Ehrlich-Institute

Q How has this new approach to medicine changed medicine development, and how has this actually delivered for patients?

Ulrich Jäger: The most notable changes are improved diagnosis, improved treatments and a better recognition that patients are different from each other. We have more possibilities to combine diagnostics and treatments. Having a better understanding of disease aetiology has resulted in a recognition that diseases in our prior thinking, which cover hundreds of thousands of patients in Europe, actually consist of many, much smaller, groups or subcategories of these diseases. This will influence the way we think about how we conduct clinical trials. We are accumulating more knowledge, for instance on CAR-T cells or genetically-modified treatments. In my field, this has already had an impact on how we view medicines. We moved from very broad diseases to almost every disease being a rare disease now.

Jan Müller-Berghaus: Even if we are looking now at sub-populations based on biomarkers, there is still a sizeable population for whom we don't have a specific marker and I am concerned that we don't leave these people behind, as they also need the development of new therapies. From a regulatory point of view, it is interesting to look into biomarkers and how we regulate them. Specifically, in Europe, we have had a separate system for medicines versus device regulations. We realise now that we need to have a more collaborative approach between the different systems because many of these markers and their diagnosis can be validated only in clinical trials in which the medicine development goes hand in hand with that of the accompanying companion diagnostics.

Corinne de Vries: Indeed, biomarkers are increasingly used also for non-clinical screening and for the stratification of patients into clinical trials. Whereas personalised medicines originally have been mostly developed in cancer, now there is a move into other therapeutic areas, such as immunology and the central nervous system.

The European regulatory system is delivering for patients: back in 2008, 17-20% of clinical trials had people recruited based on biomarkers, while now we have more than half of clinical trials for which we use biomarkers for patient selection. Six out of 26 new active substances approved in 2016 were related to medicines that were developed with biomarker stratification.

Ulrich Jäger

Head of the Hematology and Hemostaseology Division at the Medical University of Vienna

Q Can you tell us about what the latest exciting developments or promising trends are in this area from your perspective? Also, what are the challenges?

Ulrich Jäger: I think the novel cellular therapies and gene therapy approaches will require our full attention. We have experience with CAR-T cell therapies which are very promising. However, the way we need to handle these treatments as patients, doctors, or regulators is a bit different from what we are used to in pharmaceutical medicines. The other important field is better diagnostics knowledge, from radiology/nuclear medicine to molecular diagnostics. We can have the genome of an individual, which gives us information, for instance, on how a certain person metabolises a medicine. There are developments that will be game changing in the next few years. My problem, as a doctor, is how I can handle all this information.

Jan Müller-Berghaus: I would rather point out a major challenge: CAR-T cells in clinical practice. I am also worried that, if we don't get alignment between different stakeholders and the regulatory system, promising therapies will just get a negative pricing evaluation from an HTA body and will not get reimbursed.

Corinne de Vries: We move from treatment of symptoms towards treatments that cure diseases. With the exception of anti-infective treatments, this was largely unheard of 20 years ago. We need to think how we are going to handle this trend both from a clinical and a regulatory perspective. We need to collaborate globally, not only at the European level, to make sure that what has been developed is taken forward in the best way possible for patients worldwide. There are also novel methodologies based on personalised medicines which may result in completely individualised therapies. That means we have to deal with blurred boundaries. Is it a medicine, is it a transplant, is it a tissue? At present, this poses quite a challenge and we almost risk not being able to bring a novel treatment to Europe if we don't have the right legislation in place. There are also promising trends: we see more and more advanced therapy medicinal products (ATMPs) coming for scientific advice. Even if this has not yet resulted in a comparable increase in the number of marketing authorisation applications, it does suggest the number of ATMPs coming to the market over the next few years is likely to go up. We see more gene therapies. 3D printing will also contribute significantly to this area.

A challenge is related to how EMA is trying to support the development of personalised medicines very early. A significant part of this development takes place in academia, SMEs and spin-offs, but they are not so engaged when it comes to regulatory requirements to get a marketing authorisation. Regulators need to continue to make concerted efforts to help ensure constructive dialogue at the appropriate time early on in innovative medicine development.

Corinne de Vries
Head of the Science and Innovation Support, EMA

Q Are there any initiatives or measures that regulators are taking, or should be taking, specifically to support personalised medicine benefiting patients?

Corinne de Vries: EMA tries to enable dialogue early on, for example through our Innovation Task Force, which aims to ensure that innovative medicine development is done with sufficient awareness of regulatory aspects, if the medicine developed is indeed to benefit patients ultimately.

Jan Müller-Berghaus: First of all, patients want and need to be more involved in the decision-making process. Secondly, the level of expertise that is necessary on the regulatory side needs to be further developed. How should complex data be evaluated in a meaningful way? Are we prepared for such an approach? We need to have the right experts.

Another aspect is the harmonisation of clinical trials. It is extremely important to reach a level where clinical trials, once they are submitted, will get a common approach in Europe, and not be the subject of country-specific amendments. For innovative approaches we need to make available innovative trials.

Corinne de Vries: At EMA, we work together with the European Commission to raise awareness of the available regulatory resources and interaction opportunities for research and development and to meet the training needs of academics, SMEs, patients or regulators at EU level.

Ulrich Jäger: One aspect where we can all work together is the political aspect. There might be patients who are involved in issues concerning genomics, diagnostics, innovative medicines, but politicians are not aware that there is a scientific revolution going on. We need their support as well.

2 How pharmacovigilance enables innovation

During the last five years, pharmacovigilance for medicines for human use in Europe has been transformed. The pharmacovigilance legislation brought greater proactivity, better tools, a clear allocation of roles and responsibilities, and emphasis on collaboration and transparency. This led to faster regulatory actions which significantly strengthened the benefit risk management of medicines on the European market. June Raine, Olaf Klungel and Peter Arlett discuss how these tools and initiatives to ensure the safety of medicines in the EU contribute to EMA's efforts to support and enable timely access to innovative medicines.

Q What are the key tools in the EU pharmacovigilance system supporting access to innovative medicines?

Peter Arlett: Pharmacovigilance is critical to enabling innovation to reach the market. In the European Union, we have a robust system in place to constantly monitor the benefits and risks of medicines throughout their life cycle. If it weren't for that system, regulators might be reluctant to put on the market medicines with risks that still need to be managed or for which we have knowledge gaps, hence we might allow far less innovation to reach the market. The combination of various planning tools to collect data and information once a medicine is authorised, including risk management plans (RMPs), the authority to require safety and efficacy studies to be conducted and the ability to impose risk-minimisation measures to be put in place, is a very powerful package to support the market entry of innovative products.

June Raine: The fact that RMPs are now systematically required for all new medicines was a major change towards a proactive approach to pharmacovigilance. These plans give regulators the ability to manage benefits and risks of a medicine post-authorisation and handle more uncertainties, which is particularly helpful for innovation, where we want the public to access transformative medicines with no more delay than necessary. For example, the availability of innovative treatments such as ATMPs and new medicines for cystic fibrosis has been supported by patient registries that enable ongoing close monitoring of benefit-risk. Another important tool is transparency. Publishing more and better information about how risks are going to be proactively managed and investigated helps empower patients and healthcare professionals and to bring them with us: greater transparency enables stakeholders to accept their respective responsibilities for safe and effective use of medicines, and this in turn supports innovation.

June Raine

Chair of the Pharmacovigilance Risk Assessment Committee (PRAC), EMA

Olaf Klungel: Certain initiatives from EMA such as workshops contribute to this transparency. The open dialogue with stakeholders, for example as it happened with ATMPs, is helpful in identifying the issues that need further development, the barriers in introducing these products (at regulatory level, or more at production level), and seeing what can be improved to allow access to these products.

Q How do we measure the success of the pharmacovigilance system in providing access to innovation?

June Raine: Things have changed and we are no longer in the reactive 'fire-fighting' mode in which pharmacovigilance used to be. When we detect signals of new or changing safety issues in relation to an innovative medicine on the market, our experts' reaction is not only to ask "how are we going to manage this risk?", but also "what studies are ongoing, what data collection systems are already in place"? For example, in the light of emerging safety signals for certain new antidiabetic medicines, we were able to react quickly to review the evidence, provide advice for healthcare professionals and patients and mitigate the risks to allow continued safe use while awaiting the results of well-planned studies.

Olaf Klungel: Evaluation of the system is essential. We need to assess whether the uncertainties initially managed through RMPs are actually solved and the risks effectively minimised during the life cycle of a product and how effective this tool is. For this, it is key to develop methodologies, as there is no gold standard on how to measure the impact of pharmacovigilance measures. Regulators need to work with academics on this, and this is ongoing in the context of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). We need evidence-based regulation, and this is an area where Europe is ahead. Framework contracts allowing EMA to support academic research are also very helpful to address these questions.

Peter Arlett: The ultimate goal is to influence the healthcare system to optimise the safe and effective prescribing of medicines. The PRAC has developed a strategy for measuring the impact of pharmacovigilance activities, which looks at how to measure the efficiency and effectiveness of risk-minimisation measures for specific medicines, studies the different pharmacovigilance processes (signal detection, referrals, changes product information, etc.), and develops new and better methods. I believe that this structured and systematic approach to measuring impact will drive evidence-based improvements in the future.

Olaf Klungel
Professor of Pharmacoepidemiologic Methods, Utrecht University

Q What further improvements could be envisaged to strengthen the system and better support access to innovative medicines?

Peter Arlett: A key challenge will be to realise the potential of real-world data (RWD) to support decision-making in regulation and health technology assessment and in the clinic. Following the workshops held in recent years by EMA, including on big data and a common data model, we now have a much clearer idea of what the use cases are, i.e. which decisions could be better supported by RWD, and what the logistics and feasibility of responding to these questions are right now, in terms of access to data and speed of analysis. Now regulators will need to work with stakeholders, with academia but also industry, to improve access to and analysis of RWD to support healthcare decision-making.

Olaf Klungel: The use of RWD and specifically, integration of data from various sources using common protocols and common data models, and evaluation of different approaches are indeed areas for further research and development. Other regulators worldwide are developing data networks and rapid assessment of risks in these networks, and in Europe we have an opportunity to do the same. It may be more challenging because of the heterogeneity in terms of data, the different countries and languages, and differences in data privacy approaches, but this is something we will need to work on collaboratively because RWD is a tool for the future that we will really need. EMA is in a good position to play a key role in this field and should take up this challenge.

June Raine: In addition to having more data in the post-authorisation setting, we will also need to have it more quickly as in our experience it can sometimes take years to get further data. Once we have the infrastructure for the collection of data, we need to analyse it as we go along, enabling real-time benefit-risk monitoring. Pharmacovigilance aspects particularly for evidence to fill the gaps also need to be taken into account much earlier in the medicines development process. The earlier the industry starts talking to regulators, or to data owners, or to registry managers about how to collect data in the post authorisation phase, the better the chance of collecting good data as soon as the product goes on the market, and the higher the chance of regulators confirming a product's benefit-risk profile is positive because they will be assured that the risk-management planning is robust, well planned, and ready to start as soon as the product is on the market. Therefore, the sooner the planning of data collection starts, the better.

Peter Arlett
Head of Pharmacovigilance and Epidemiology, EMA

3 Collaboration between regulators, HTAs and payers

The regulation and assessment of medicines can no longer be carried out in isolation. Strong collaboration between regulators, HTA bodies and payers can boost medicine development and facilitate an early and affordable access for patients to innovative treatments. Chantal Bélorgey, Ad Schuurman and Michael Berntgen discuss the challenges and benefits of fostering mutual understanding among decision-makers.

Q

Which tools and initiatives specific to your respective area aim to facilitate patients' access to innovative medicines?

Michael Berntgen: The pharmaceutical legislation provides regulators with a number of tools to foster innovation. Mechanisms like accelerated assessment (applied seven times in 2017) and conditional market authorisation (three medicines last year) are aimed at medicines that address unmet medical needs. To stimulate optimisation of development plans, EMA has the mandate to provide scientific advice and protocol assistance to developers. In 2017, such advice has been given around 650 times. This service has become one of the Agency's key instruments to support the development of high-quality and innovative medicines, and also serves as a platform for collaboration with HTAs. And then, of course, there is the PRIME scheme, an initiative to facilitate optimised development input for now more than 30 medicines since its establishment in 2016. PRIME focuses on medicines that make a real difference to patients and encourages early dialogue among different stakeholders, including other decision-makers.

Chantal Bélorgey: In France, there are several tools to allow early access to medicines to patients, the main one being the Temporary Authorisation for Use (ATU) system. In terms of assessment of health technologies, three main areas provide early access to potential innovation to patients. Firstly, we help medicine developers to optimise the quality and robustness of data they submit to us. We offer them scientific advice and early dialogue not only nationally, but also now at EU level with other HTA bodies through EUnetHTA; this includes the EMA and HTA parallel consultation launched in 2017 that has proved to be very successful. Secondly, innovative products have an option for earlier HTA assessment, before marketing authorisation, which would be conducted in parallel with the CHMP. Thirdly, HAS is in the process of designing in very specific situations (i.e. unmet needs) a kind of "conditional HTA opinion" for innovative medicines for which we don't receive enough data. Short-term reassessment of new evidence is one of the conditions. Companies with innovative products can also consider the option of submitting the product for joint assessment via EUnetHTA. When HAS has participated in this process, the French national-level appraisal has been shown to be faster.

Chantal Bélorgey
Director of Medical, Economic and Public Health Assessment, Haute Autorité de Santé (HAS), France

Ad Schuurman: The payers' scenario in Europe is varied. Every Member State has its own systems to speed up access for patients to innovation which are linked to decisions about price and reimbursement. Some countries have a system in which medicines are reimbursed immediately, before evaluation. Other Member States prefer to focus on helping HTA and regulators to do a quick assessment. A good collaboration between regulators and HTAs is very important if we want to speed up the process, as medicine developers know early in the process all the requirements and information they will need to provide.

Q

Why is it important for regulators, HTAs and payers to foster mutual understanding and to strengthen their collaboration? What are the benefits and the challenges?

Ad Schuurman: In my opinion, the main benefit of collaboration among regulators, payers and HTAs, when we share each other's expertise, is the effective use of resources and information. When we work together, we also understand each other better, learn our respective responsibilities and limits, and foster improvement in a constructive atmosphere. The main challenges are related to logistics – lack of time and difficulties to bridge the different objectives. In 2017, we made a good preparatory work. The meeting we had with EMA and payers was very constructive and promising for the future, to make sure payers will join the discussion early with the other stakeholders and patients. Many payers are now better aligned with collaborative thinking.

Chantal Bélorgey: Science is very dynamic. We need to interact with each other and be prepared for new complex medicines that have a strong impact on patients and our national health organisations and budgets. Information-sharing among regulators, HTAs and payers will enable anticipation. We need to foster mutual understanding, learn from differences and anticipate potential discrepancies for the benefit of patients and health systems. Actions like the new EMA and EUnetHTA joint work plan launched in 2017 can help us to overcome the challenges and outline specific areas of collaboration.

Michael Berntgen: There are different types of collaboration, from dialogue to foster mutual understanding of processes and methodologies, to joint data analysis and exploring opportunities to align evidence needs. Through all of them we are building mutual trust and learning whilst respecting each other's remit. EMA has been cooperating with HTAs since 2010 and the development over the years has been impressive. We have been able to identify a number of key areas for exchange of information and put in place concrete actions, like optimising outputs and developing ways to jointly discuss with developers, to name a few. With the payers community we are in an earlier stage. The meeting we had in September 2017 was very important; we discussed key topics like principles for labelling, horizon scanning, the definition of unmet medical need and, overall, we set a foundation to work on different levels for collaboration and mutual understanding.

Ad Schuurman

Chair of the Medicine Evaluation Committee (MEDEV) and Head, International Department, National Health Care Institute (ZIN), The Netherlands

Q What are the future priority areas of collaboration for regulators, HTAs and payers?

Ad Schuurman: In 2018, we should work on implementing an early dialogue about orphan diseases among all stakeholders, involving also patients, doctors and companies. HTAs and payers would like to receive information from EMA's Committees as early and precise as possible in order not to duplicate work and use our experts in a more effective way. It would be good to have common patient registries too. A very important priority is to harmonise the concept of "unmet medical need" – it doesn't need to be the same definition for everyone, but it is important that we understand each other. Finally, we can make progress on horizon scanning by making EMA's information on future products available for other stakeholders in a feasible way.

Chantal Bélorgey: Our priorities should work around the concepts of anticipation and horizon scanning. We should develop better and simpler procedures to foster information-sharing during the assessment of medicines and work together on evidence generation, particularly the way we integrate information coming from databases and big data. We also need more collaboration regarding the development of complex products and medicines targeting a specific population, for instance children. We should also share our experience and work together to better involve patients and consumers in our work.

Michael Berntgen: The good work and experience so far serves as foundation for our collaboration in the future. The EMA-EUnetHTA action plan 2017-2020 and the 'Synergy paper' from the HTA network outline guiding principles and priority areas for years to come. From EMA's perspective, an important priority is to ensure evidence is generated that serves various decision-makers and covers the entire life cycle. Specific fields that can benefit from such input by regulators, HTAs and payers include orphan medicines and ATMPs. For us, it is also very important to get HTAs' and payers' feedback to optimise our regulatory outputs; exchange more information at the time of licensing; and collaborate on horizon-scanning activities. We should embrace new challenges like personalised medicines or concepts of evidence transfer while keeping in mind the interest of public health and the sustainability of healthcare systems.

Michael Berntgen
Head of Product Development
Scientific Support, EMA

Chapter 3
Key figures in 2017

Core statistics from 2017 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

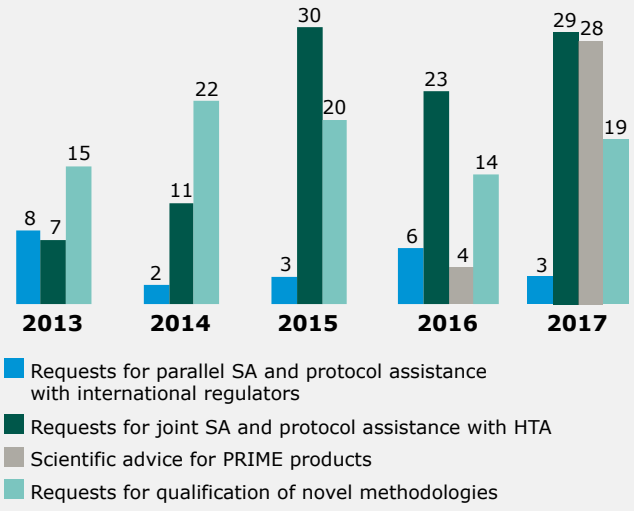
Promoting innovation and research in medicine development so that patients can benefit from much-needed safe, high-quality and effective medicines is a key priority for the Agency. EMA and its scientific committees and groups of experts from the EU NCAs are fostering early interaction and dialogue with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

Scientific advice

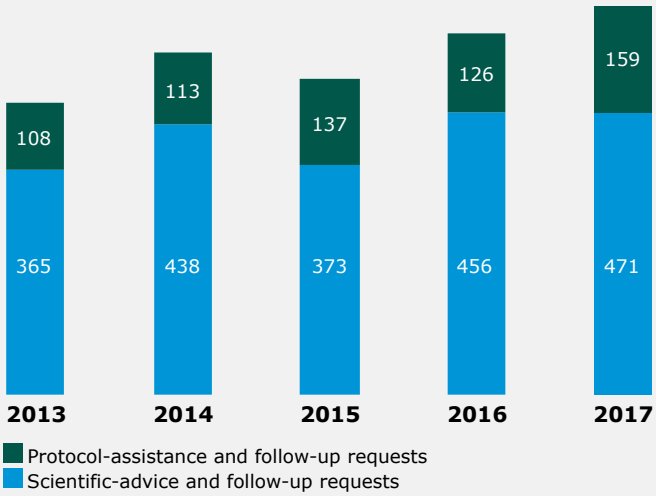
The Agency provides scientific advice (SA) and protocol assistance to medicine developers throughout the life cycle of their medicines. Scientific advice is one of the Agency's key instruments to support the development of high-quality, effective and safe medicines that meet patients' needs. Early dialogue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

In 2017, the requests for scientific advice and protocol assistance increased by 8%. This was mainly driven by a 26% growth in requests for protocol assistance, a form of scientific advice given to developers of orphan medicines.

Scientific advice and protocol assistance requests received - subset special programmes



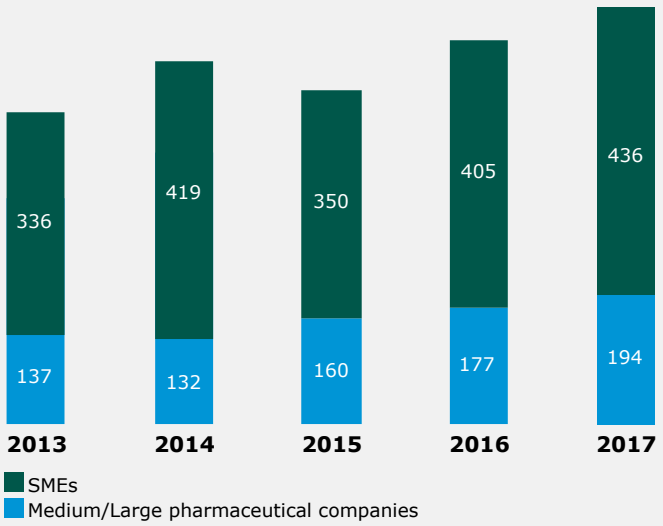
Scientific advice and protocol assistance requests received - total



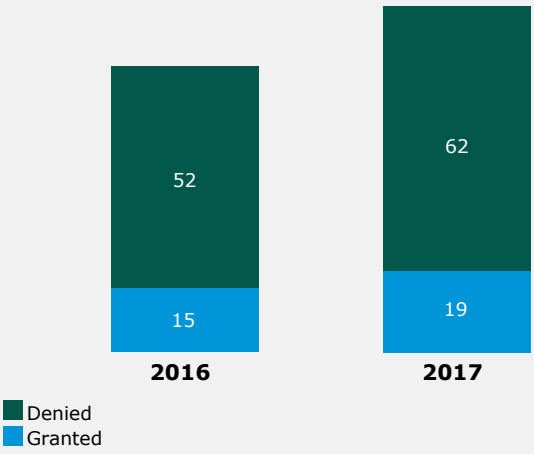
Scientific advice is the core of many of EMA's special programmes to encourage development and availability of new and innovative medicines. This includes the Agency's PRIME scheme, which saw a significant rise in requests in its second year, as well as parallel scientific advice with HTA bodies.

As in previous years, more than half of requests for scientific advice related to clinical issues, 27% to preclinical issues, and 21% to quality issues. 55% of requests related to medicines in phase III and 32% to medicines in phase II of their clinical development.

Scientific advice requests by affiliation of requester



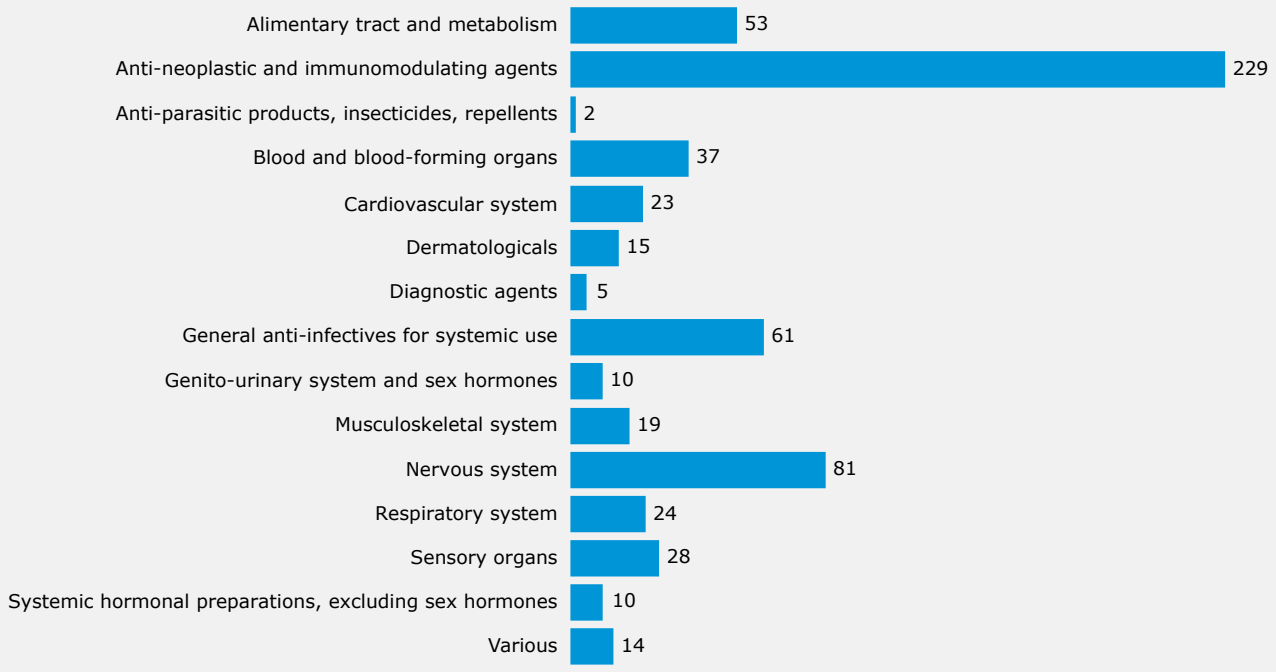
PRIME - eligibility recommendations



SMEs increasingly make use of scientific advice. In 2017, 194 of the 630 requests came from SMEs, 10% more than in 2016 and 41% more than in 2013.

In 2017, the PRIority MEdicines (PRIME) scheme, an initiative launched in March 2016 to provide early and enhanced support to medicines that can potentially address patients' unmet medical needs, came into its second year of application. EMA adopted a total of 81 eligibility recommendations in 2017, 20% more than in 2016. The success rate for acceptance into PRIME remained low, with only one out of five applications being successful, to ensure the Agency focuses on the most promising medicines.

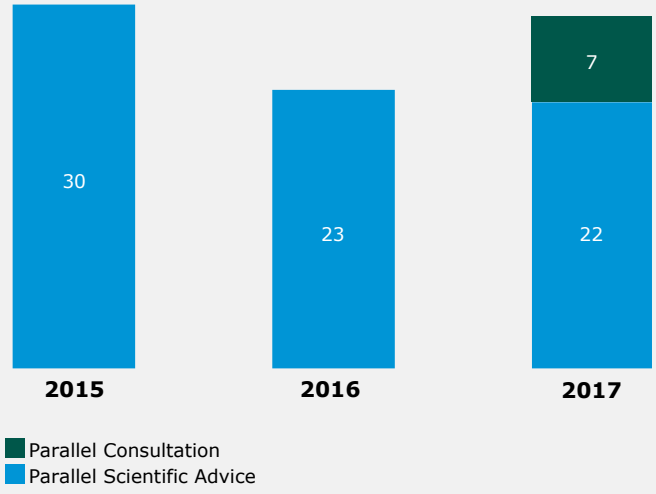
Scientific advice requests by therapeutic area (2017)



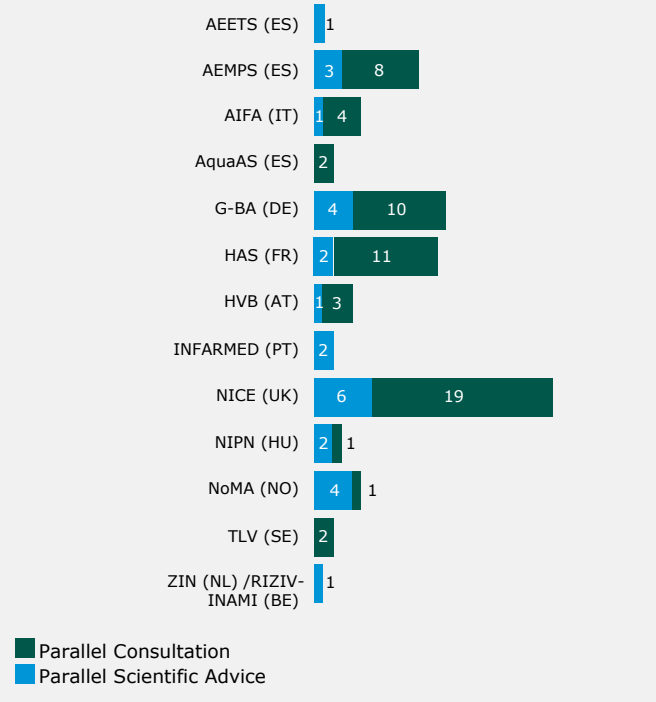
Collaboration with HTAs

EMA and HTA bodies work together to provide medicine developers with simultaneous feedback on development plans with the aim of ensuring that the data requirements for both parties are met. Requests for joint SA and protocol assistance with HTAs rose by 26% in 2017. A new platform for parallel consultation (PC) was launched in July 2017, replacing the previous Parallel EMA/HTA Scientific Advice (PSA) process. From the 29 requests for parallel advice on evidence generation in 2017, 7 were submitted via this new tool.

New requests for Parallel Scientific Advice and Consultation



HTA bodies contributions to Parallel Scientific Advice and Consultation (2017)



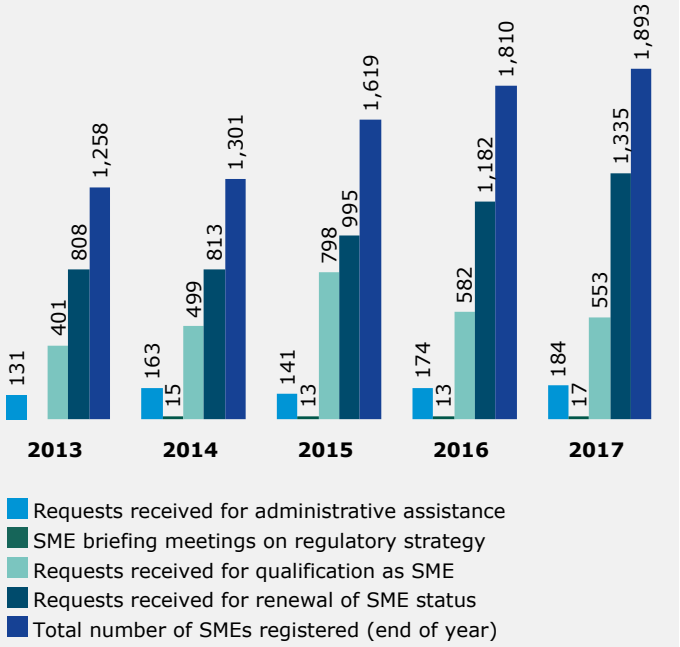
More than half of the requests were for anti-neoplastic and immunomodulating agents (15), followed by alimentary tract and metabolism (5), nervous system (4), and cardiovascular system (2). Two requests were for PRIME products, three for orphan medicines, and three from SME developers.

HTA bodies from across Europe contributed to such procedures in 2017.

Support for SMEs

SMEs are recognised as a driver of innovation in the EU. The Agency promotes innovation and the development of medicines by SMEs through 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 2017, EMA launched a new action plan to support SMEs in the development of new human and veterinary medicines until 2020.

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



In 2017, the SME office dealt with 184 requests for direct assistance on administrative or regulatory aspects and organised 17 briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. A total of 1,893 SMEs were registered at the end of 2017.

In 2017, 20 applications for marketing authorisation were submitted, seven of which were for orphan designated medicines. 12 applications received a positive opinion from the CHMP: this is the highest number in the past five years, and represents 13% of all positive opinions in 2017.

Initial evaluation applications and SMEs (human medicines)					
	2013	**2014**	**2015**	**2016**	**2017**
Initial MAAs submitted by SMEs	8	7	15	27	20
Positive opinions	11	5	9	4	12
Negative opinions	3	1	2	1	2
Withdrawals	4	3	1	5	7

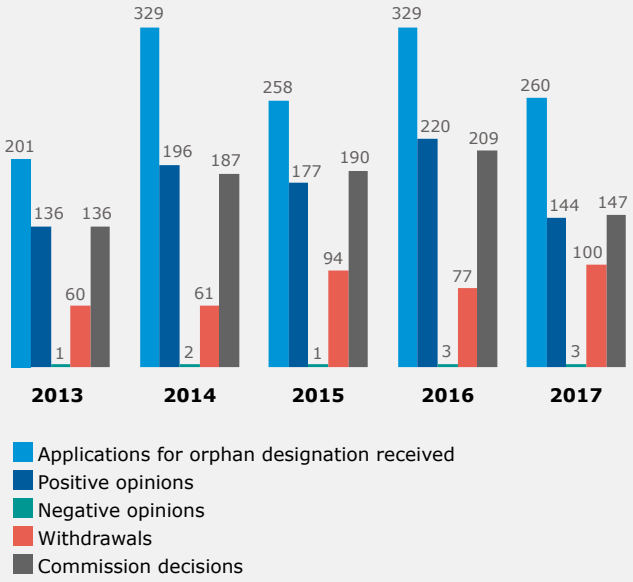
Orphan-medicine designation

The EU framework for orphan medicines aims to encourage the development and marketing of medicines for patients with rare diseases by providing incentives for developers. Medicines with an EU orphan designation benefit from ten years of market exclusivity if they are granted a marketing authorisation. 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.

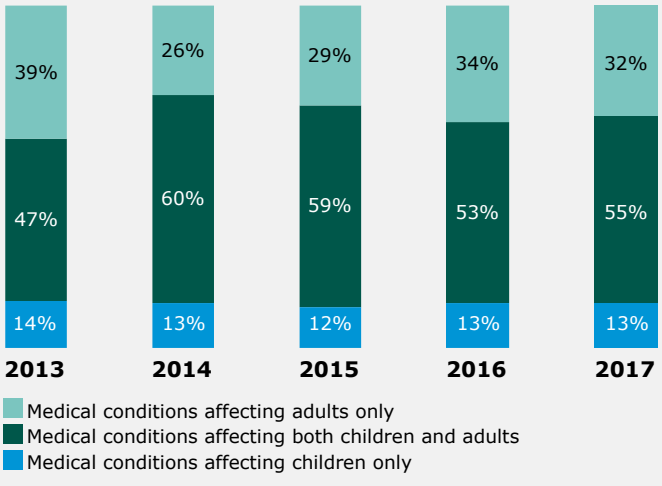
The number of applications for orphan designations in 2017 was 260, and 144 applications were granted a designation, thereby allowing them to benefit from the incentives under the orphan programme.

The EC supports the development of medicines for rare diseases financially, with more than €13 million provided in 2017. More than 60% of the Commission's special contribution was used to provide protocol assistance to medicine developers and 23% for the assessment of applications for marketing authorisation.

Orphan medicine designation procedures



Designated orphan medicines for the treatment of children and adults



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

Medicines for children

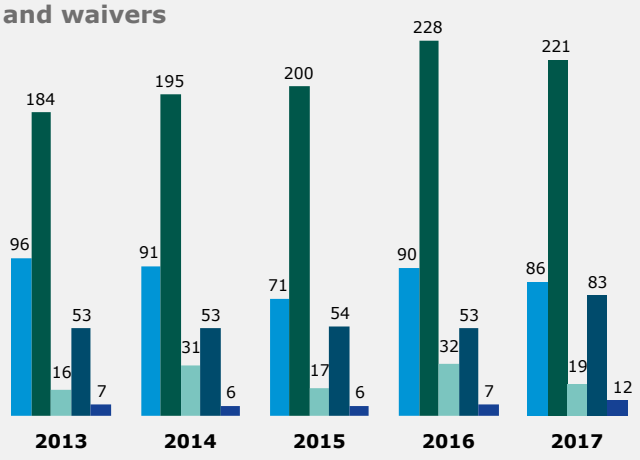
The Agency also promotes the development of medicines for children. EMA assesses and verifies compliance with PIPs and PIP waivers through the PDCO. In addition, it provides secretarial support to Enpr-EMA. 2017 marked the tenth anniversary of the EU Paediatric Regulation, which aims to stimulate the development of high-quality, safe and effective medicines for children.

A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. Where a study in children is inappropriate or unnecessary, a waiver may be granted. In 2017, the Agency's PDCO agreed 86 initial PIPs.

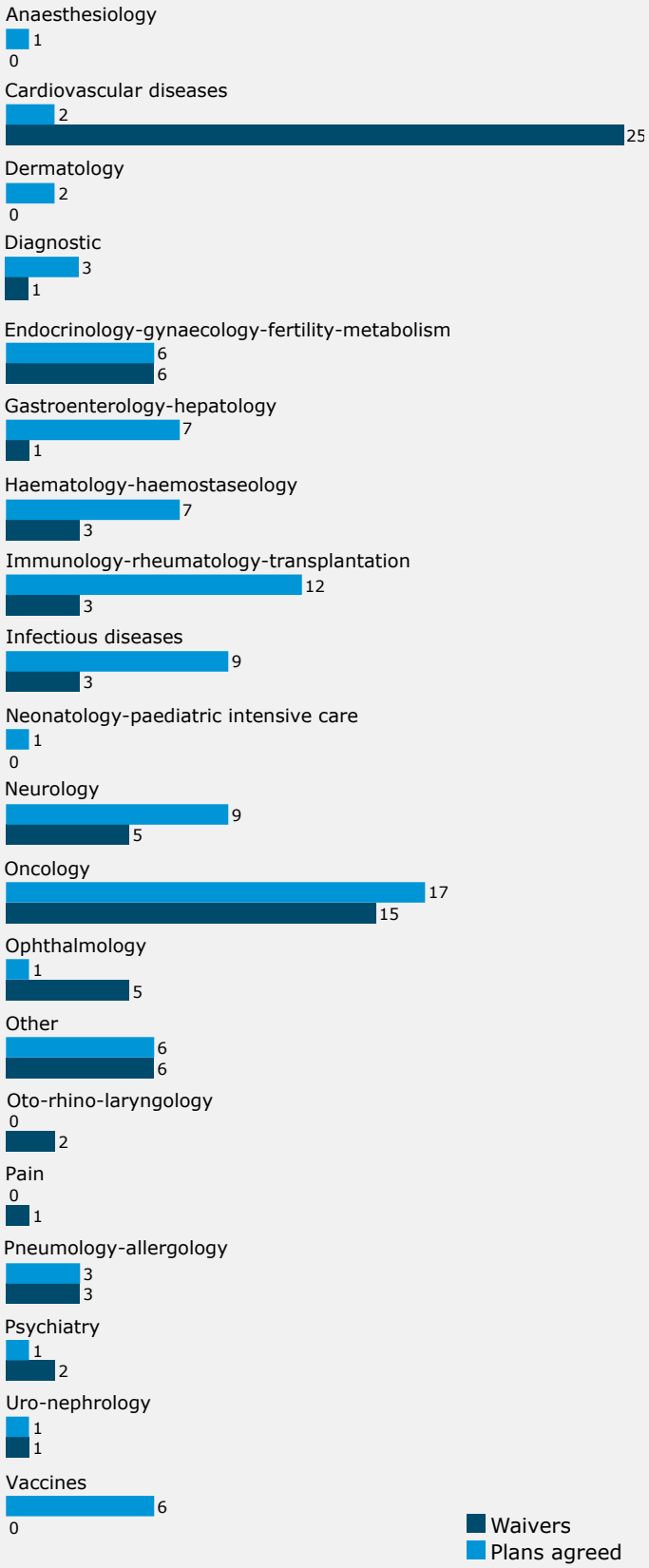
Medicine developers increasingly request scientific advice on paediatric issues. This trend was confirmed in 2017, with a total of 166 scientific advice requests received – a figure that is very similar to 2016 (165 requests) but 50% higher than in 2015.

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 2017, EMA assessed 88 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



Paediatric investigation plans agreed and waivers granted (2017)



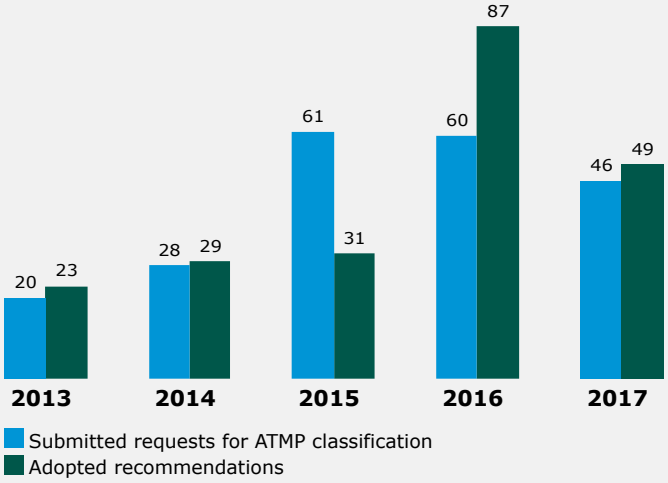
Note: All the PDCO decisions can be found in the annexes.

Advanced-therapy medicinal products

Advanced-therapy medicinal products (ATMPs) are medicines based on genes or cells that offer ground-breaking new opportunities for the treatment of disease. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate.

The 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.

Scientific recommendations on advanced therapy classifications



Note: In a given year, the number of adopted recommendations may be higher than the applications submitted because some procedures were started in previous years.

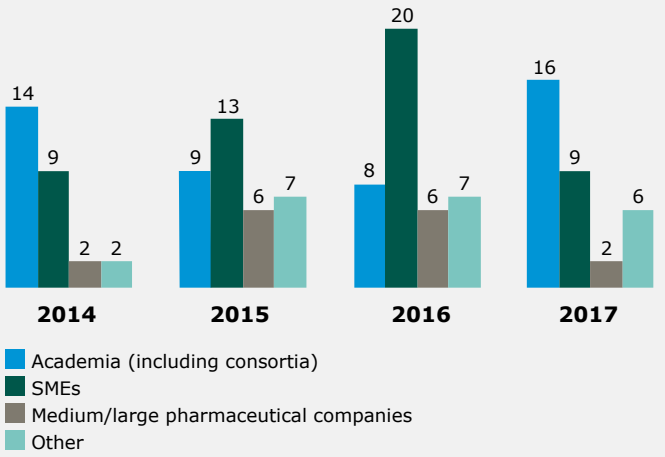
A total of 49 recommendations were adopted in 2017, 43% less than in 2016. The number of requests for ATMP classification was also lower in 2017 – 46 requests compared to 60 in 2016. The 2017 figures represent the return to trend, following an increase in 2015 and 2016. This increase was due to the decision of one Member State (Poland) to recommend to all academics developing cell-based products to apply for ATMP classification (prior to them starting any clinical trial).

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.

In 2017, there were 33 meetings compared to 41 in 2016; 16 of these meetings, almost half of the total and double that in 2016, were held with academic developers. This reflects a decision to proactively invite research consortia funded under the Horizon 2020 programme, including IMI projects, to ITF briefing meetings; this should be seen in the context of enhancing EMA engagement with academia. One in four ITF briefing meetings was held with SMEs.

Briefing meetings by affiliation



One out of three meetings concerned ATMPs, 18% related to innovative methods to support the development of medicines and 15% were on regulatory topics.

Four applications for marketing authorisation for an ATMP were received in 2017. Two ATMPs were recommended for marketing authorisation in 2017: Spherox, a medicine composed of spheroids, i.e. spherical aggregates of chondrocytes (cells that are found in healthy cartilage) to treat adult patients who have symptomatic articular cartilage defects in the knee; and Alofisel, a cell-based therapy for the treatment of complex perianal fistulas in patients with Crohn's disease. Alofisel is the tenth ATMP to receive a positive opinion from the Agency.

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 medicines development and ensure that the medicines available to patients are safe, effective and of high quality.

Guidelines are drafted by EMA working parties comprising 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 2017 is listed below:

Topic	Content
First-in-human clinical trials	Developed in cooperation with the EC and EU Member States, the revised guideline further helps clinical trial sponsors and regulators to identify and mitigate risks for trial participants
Guideline on good manufacturing practice for ATMPs	The new guidelines adapt the EU GMP requirements to the specific characteristics of ATMPs and address the novel and complex manufacturing scenarios utilised for these products. Developed by the EC with extensive input from the Agency
Annex to the European Commission guideline on excipients	EMA and EC updated the annex to the EC guideline on excipients in the labelling and package leaflet of human medicines with new safety advice for 15 excipients
Guidelines on the requirements for quality documentation concerning chemical and biological investigational medicinal products in clinical trials	These revised guidelines address the specific requirements for quality documentation for Investigational Medicinal Products (IMPs), concerning biological/biotechnology derived and chemically defined active substances, respectively
ICH Q11: Q&A Development and manufacture of drug substances (chemical entities and biotechnological/ biological entities)	The Q&A provides additional information to facilitate global convergence on development of the active substance, with regulatory expectations on starting materials and other aspects of Common Technical Document dossier content

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

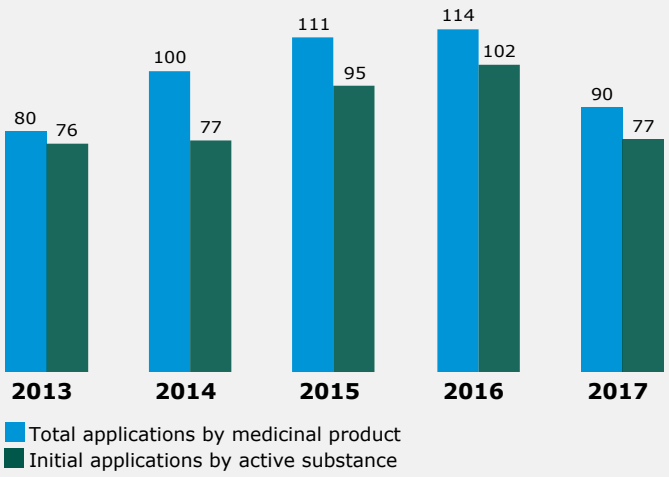
Recommendations for marketing authorisation

Applications for initial evaluation

EMA's scientific committees carry out robust scientific evaluations of medicines. This forms the basis of the EC'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 EC.

The overall number of applications for initial evaluation received in 2017 was lower than in 2016, breaking the upward trend observed over the past five years. The decline was driven mainly by a 30% decrease in the number of applications received for orphan-designated medicines and a drop of over 50% in the number of applications for generic medicines.

Initial-evaluation applications



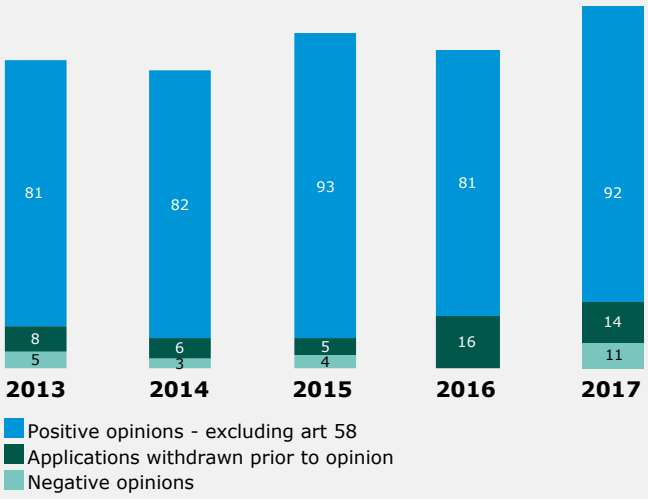
However, EMA received more applications for ATMPs (a total of 4 applications, the highest number in the last five years), paediatric-use marketing authorisations (PUMA), and biosimilar medicines. The number of applications for biosimilar medicines continues to increase year on year with 17 applications received in 2017, the highest number received in one year to date.

EMA received an application to review a medicine under the Article 58 procedure. This regulatory procedure allows the Agency to assess the quality, safety and efficacy of a medicine and give an opinion on its benefit-risk balance when used in low-income countries outside the EU. Article 58 products are assessed by EMA in collaboration with WHO and are required to meet the same standards as medicines intended for EU citizens.

Outcome of initial evaluation

In 2017, EMA recommended 92 medicines for marketing authorisation. Of these, 35 had a new active substance, i.e. one which had never previously been authorised in the EU.

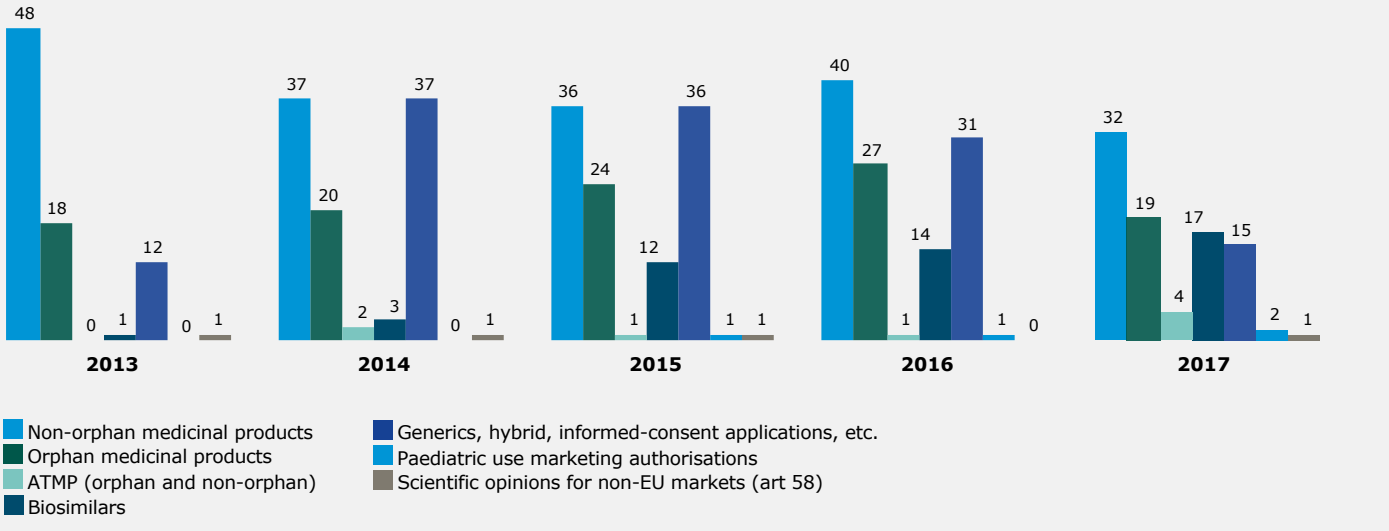
Outcome of initial-evaluation applications



The CHMP did not recommend to grant marketing authorisation for six medicines in 2017. The applicants for five of these medicines requested the Committee to re-examine its initial opinion. After considering the grounds for these requests, the CHMP re-examined the opinions and confirmed its previous recommendations. This makes a total of 11 negative opinions adopted by the Committee in 2017.

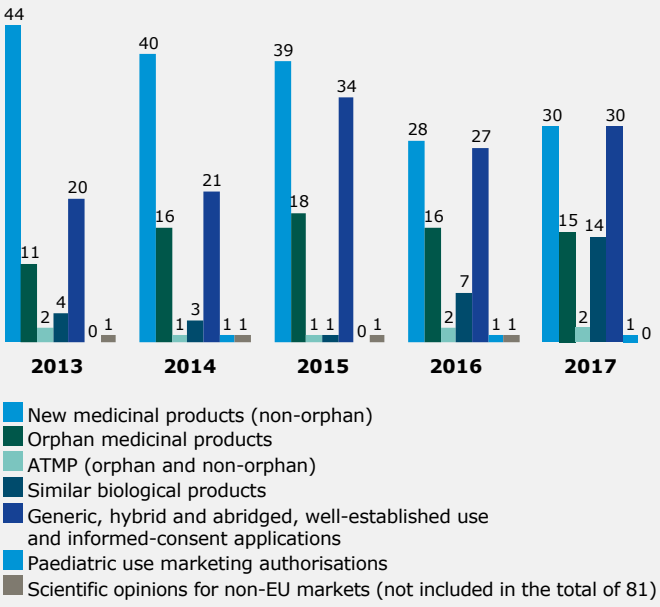
The applications for 14 medicines were withdrawn by the applicants prior to CHMP opinion, in most cases because the data included in the application were insufficient to support a marketing authorisation.

Initial-evaluation applications by type of application



62% of applicants granted a positive opinion from the CHMP in 2017 had received scientific advice during the development phase of their medicine.

Positive opinions by type of procedure



Conditional marketing authorisations

Of the 92 medicines granted a positive opinion in 2017, three were recommended for a conditional marketing authorisation (CMA). 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 while they are already being used.

In 2017, five medicines that had previously received a CMA were granted a recommendation for a full marketing authorisation by the CHMP after fulfilling their post-authorisation obligations.

Since the introduction of CMA in 2006, 18 medicines out of 36 have been granted a full marketing authorisation following a CMA. On average, it took four years for companies to fulfil their post-authorisation obligations and get their products fully authorised.

Conditional marketing authorisation and switch to standard marketing authorisation (excluding withdrawals)

	2013	2014	2015	2016	2017
Positive opinions for CMAs	5	5*	3	8	3
Opinions recommending switch of CMA to standard marketing authorisation	3	2	2	2	5

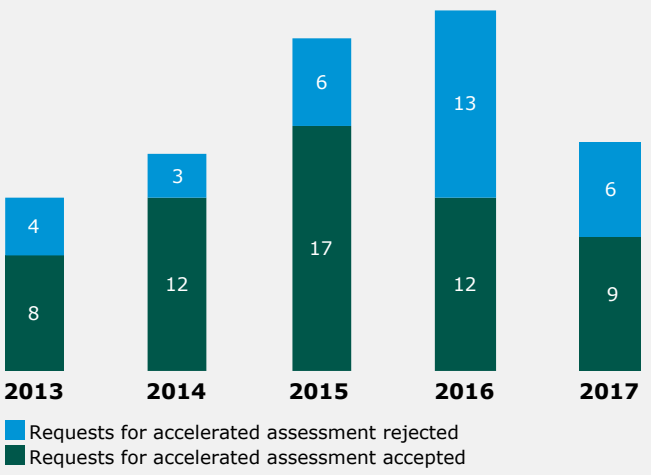
*Three of these marketing authorisation applications were withdrawn by the sponsor following the CHMP opinions and prior to final decisions by the EC

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.

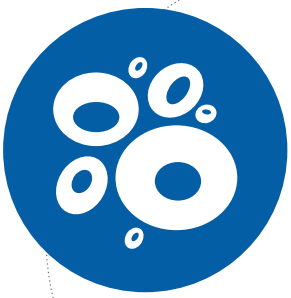
In 2017, 9 requests for accelerated assessment were accepted and 6 were rejected. The main reasons for rejection were that either the unmet medical need was not adequately justified or the data was not sufficient to justify a major public health interest.

Accelerated assessment requests



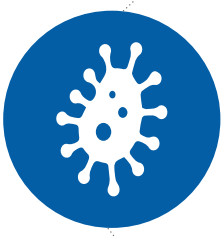
Medicines recommended for approval in 2017

Cancer



Axumin
Bavencio ● ●
Besponsa ●
Blitzima
Fotivda
Fulvestrant Mylan
Herzuma
Imatinib Teva B.V.
Kisqali
Lutathera ●
Mvasi
Ontruzant
Pemetrexed Hospira Limited
Qarziba (previously Dinutuximab beta Apeiron) ● ●
Ritemvia
Rixathon
Riximyo
Rydapt ●
Tecentriq
Tookad
Tuxella
Varuby
Zejula ●

Infections

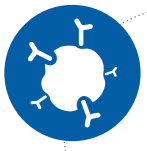


Daptomycin Hospira
Darunavir Krka
Darunavir Krka d.d.
Efavirenz/Emtricitabine/Tenofovir disoproxil Krka
Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan
Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva
Emtricitabine/Tenofovir disoproxil Krka d.d.
Entecavir Accord
Entecavir Mylan
Maviret ●
Prevymis ●
Ritonavir Mylan
Symtuza
Trumenba
Vosevi ●

Endocrinology

Alkindi
Crysvita ● ●
Insulin lispro Sanofi
Intrarosa
Ivabradine Accord
Miglustat Gen.Orph
Natpar ● ●
Nitisinone MendeliKABS
Ozempic
Ucedane
Xermelo ●
Yargesa

Immunology/ Rheumatology/ Transplantation



Amgevita
Cyltezo
Erelzi
Imraldi
Jylamvo 2mg/ml Oral Solution
Kevzara
Solymbic
Spherox ●
Tacforius
Tremyfa
Xeljanz

Neurology

Brineura ● ● ●
Lacosamide Accord
Mavenclad
Nyxoid
Ocrevus
Oxervate ● ●
Reagila
Spinraza ● ●
Verkazia ● ●
Zubsolv

Uro-nephrology

Elmiron ●
Lokelma
Tadalafil Lilly
Veltassa

Haematology/ Haemostaseology

Adynovi
Anagrelide Mylan
Refixia ●
VeraSeal

Pneumology/ Allergology

Elebrato Ellipta
Fasenra
Rolufta
Trelegy Ellipta
Trimbow

Dermatology

Dupixent
Kyntheum
Skilarence

Hepatology/ Gastroenterology

Jorveza ● ●
Alofisel ● ●

Metabolism

Cuprior ●
Febuxostat Mylan

Cardiovassular

Roteas

● ATMP ● Orphan medicine ● Accelerated assessment ● Conditional marketing authorisation ● Approval under exceptional circumstances

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

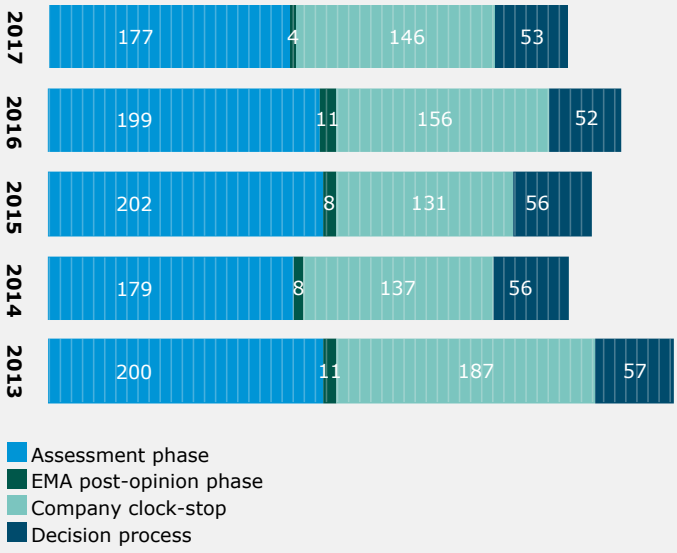
Average assessment time

EMA has a maximum of 210 active 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, any 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.

Once issued, the CHMP opinion is transmitted to the EC which has the ultimate authority to grant the marketing authorisation and will do so within 67 days of receipt of the CHMP opinion.

The overall time required for the centralised procedure was on average 380 days, 28 days less than in 2016. The average time needed for the assessment of initial marketing authorisation applications was 22 days less than in 2016.

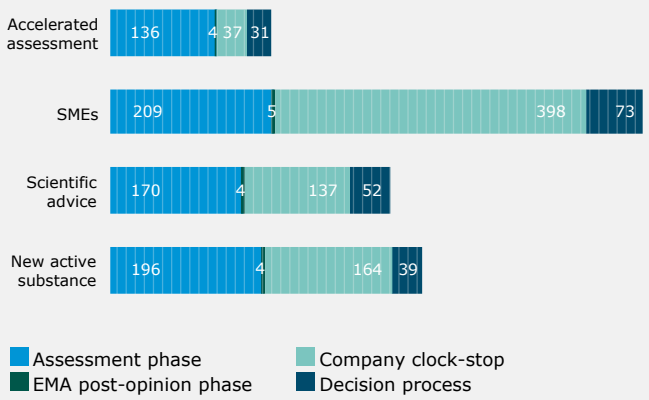
Average number of days for centralised procedures - positive opinions



For medicines evaluated under an accelerated procedure, the average assessment days per phase were: assessment, 136 days; post-opinion, 4 days; company clock-stop, 37 days; and decision process, 31 days. This means that, on average, the total time from start of assessment until granting of authorisation for a medicine under accelerated assessment to reach patients was reduced by a little less than 6 months, allowing faster patient access to medicines fulfilling unmet medical needs.

Company clock-stop for applications submitted by SMEs was longer than average (398 days compared to 146 on average).

Average number of days for centralised procedure - subset (2017)



Post-authorisation activities

In 2017, the CHMP adopted 51 positive recommendations for extension of the therapeutic indication of already authorised medicines.

In line with previous years, in 2017, EMA received applications for:

- 3,080 type-IA variations
- 2,054 type IB variations
- 1,133 type-II variations
- 21 extensions of marketing authorisations

In the context of type-II variations, the product information for 397 authorised medicines was updated as new safety data were made available and assessed by EMA.

Extensions of therapeutic indications – highlights of 2017

Name of medicine	What it is used for.
Darzalex	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.*
Gazyvaro	In combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.*
Orkambi	For the treatment of cystic fibrosis in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.*
Soliris	For the treatment of refractory generalised myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody positive.
Truvada	For the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first-line agents.

* The CHMP considered this represented a significant extension of the existing indication and recommended granting an additional year of market exclusivity for this medicine. A complete list of extensions of indications can be found in the annex.

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.

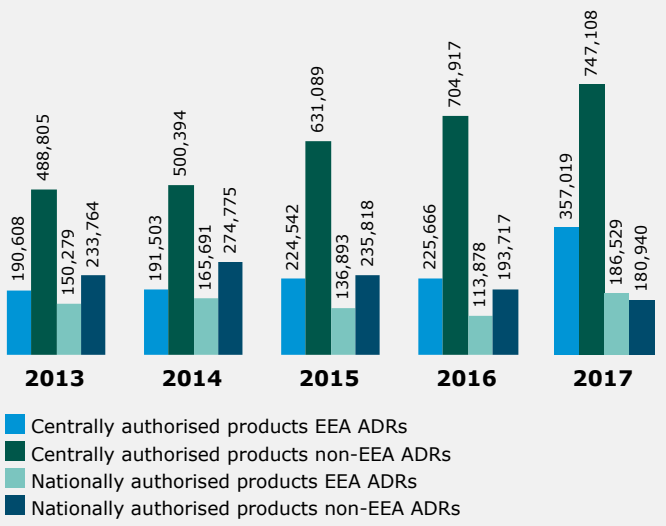
EudraVigilance – collecting suspected adverse drug reactions

The Agency's main responsibilities in relation to the safety monitoring of medicines include coordination of the European pharmacovigilance system, setting standards and guidelines for pharmacovigilance, provision of information on the safe and effective use of medicines, detecting new safety issues for centrally authorised products, 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 1.4 million ADRs were reported to EudraVigilance in 2017, which represents a 19% increase compared to the previous year. This was driven by a 60% increase in the number of reports originating from the EEA in 2017, including reports submitted directly by European patients and consumers, which nearly doubled compared to 2016, to a total of 90,385 reports.

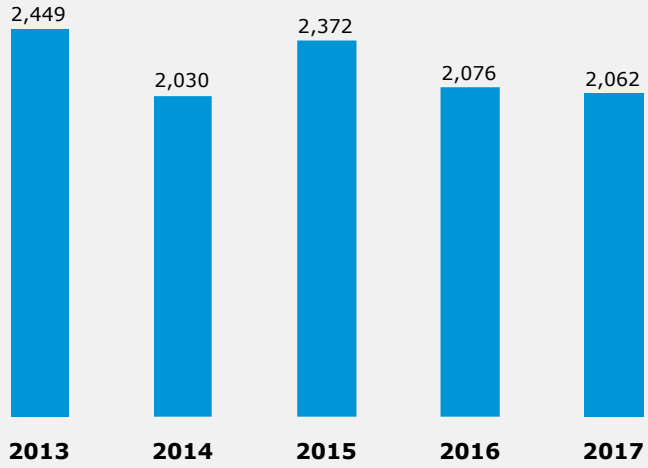
This is explained in part by the launch of the new EudraVigilance system on 22 November 2017 which was accompanied by the addition of mandatory reporting of non-serious cases to the existing serious case reporting. In addition, the positive trend shows patients' increased commitment to reporting the side effects they experience, following EU and national campaigns.

EEA and non-EEA ADR reports received

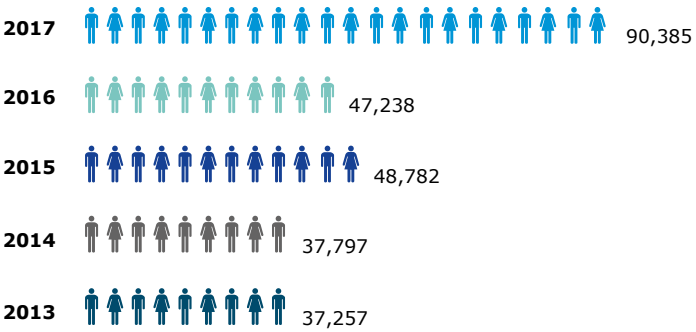


In 2017, 2,062 potential signals were reviewed by EMA, 82% of which originated from monitoring the EudraVigilance database.

Signal detection



Number of reports from patients



Outcome of signal assessment

82 confirmed signals were prioritised and assessed by the PRAC

43 signals detected and validated by EMA

39 signals detected and validated by EU

1 signal led to a referral procedure to further investigate the issue;

33 signals led to an update to the product information; 2 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers;

28 signals were still under review by the PRAC at the end of 2017 as further data were required;

20 signals led to recommendation for routine pharmacovigilance.

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).

Periodic safety update 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.

In 2017, 842 recommendations were issued by the PRAC based on the assessment of PSURs and PSUSAs, a 6% increase over 2016. Close to a third of the procedures consisted of single assessments of active substances only contained in nationally authorised medicines, an activity initiated by EMA in 2015.

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

PSURs and PSUSAs finalised

	2013	2014	2015	2016	2017
PSURs stand-alone (CAPs only)	430	426	470	511	540
PSURs single assessment (CAPs with NAPs)	6	45	27	16	39
PSURs single assessment (NAPs only)	0	0	136	264	263
Total outcomes	436	471	633	791	842

PRAC outcomes of PSURs and PSUSAs

	2013	2014	2015	2016	2017
Maintenance	360	383	500	637	680
NAPs only	–	–	–	–	207
CAPs/NAPs and CAPs only	–	–	–	–	473
Variation	76	88	133	154	162
NAPs only	–	–	–	–	56
CAPs/NAPs and CAPs only	–	–	–	–	106
Total outcomes	436	471	633	791	842

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. The PRAC also reviews large numbers of PASS in the context of risk management plan assessments.

In 2017, the PRAC assessed 5 imposed PASS protocols that were requested to obtain further information on a medicine's safety. It conducted 265 procedures to assess non-imposed PASS protocols.

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.

19 PAES 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. For centrally authorised medicines, companies also need to notify EMA of withdrawals for commercial reasons. The Agency 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.

In 2017, the number of notifications of withdrawn products increased by a factor of 2.5. This appears to be driven by commercial reasons as no significant increase in safety withdrawal was seen.

Notifications of withdrawn products received

2014	2015	2016	2017
132	160	118	302

Medicines under additional monitoring

Additional monitoring, introduced by the 2010 pharmacovigilance legislation, aims primarily to enhance ADR reporting for certain types of medicinal products. The list of medicines under additional monitoring is reviewed every month by the PRAC and is available on EMA's website and also published by the NCAs.

In 2017, 65 medicinal products were added to the list and 30 were removed from the list. In December 2017, the list contained 336 products and 13 annexes (1,555 NAPs in annexes, 1,891 products in total). Each of these annexes has been created to list all the products containing the same active substance subject to a PASS imposed during a referral procedure, which is one of the legislative triggers for identifying a product as being subject to additional monitoring.

The number of products in the additional monitoring list over time is presented below:

Products under additional monitoring

	2013	2014	2015	2016	2017
Number of products added	156	55	72	65	65
Number of products removed	4	6	12	27	30
Cumulative total	152	201	263	301	336
Cumulative total in Annexes	319	1269	1893	1798	1555
Cumulative total (List + Annexes)	471	1470	2156	2099	1891

Measurement of the impact of pharmacovigilance activities

The PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities was launched in January 2016 and was revised in December 2017. A three-year work plan for implementing the strategy's objectives is built around four pillars:

- effectiveness of risk-minimisation activities;
- effectiveness of specific pharmacovigilance processes;
- enablers of effective pharmacovigilance and stakeholder engagement;
- identification and development of analytical methods.

The PRAC Interest Group (IG) on Impact has the mandate to oversee the implementation of the strategy. During a 12-month pilot, further follow-up measurement of the impact was considered relevant by the PRAC IG for five regulatory actions related to one Article 31 referral, two signal evaluations and two evaluations of imposed PASS results.

A systematic review of methodologies measuring the impact of medicines regulatory interventions was performed in 2017, based on an analysis of 153 published articles, and made publicly available in November.

Several studies measuring the impact of pharmacovigilance were finalised or initiated in 2017 using real-world data.

Referral procedures

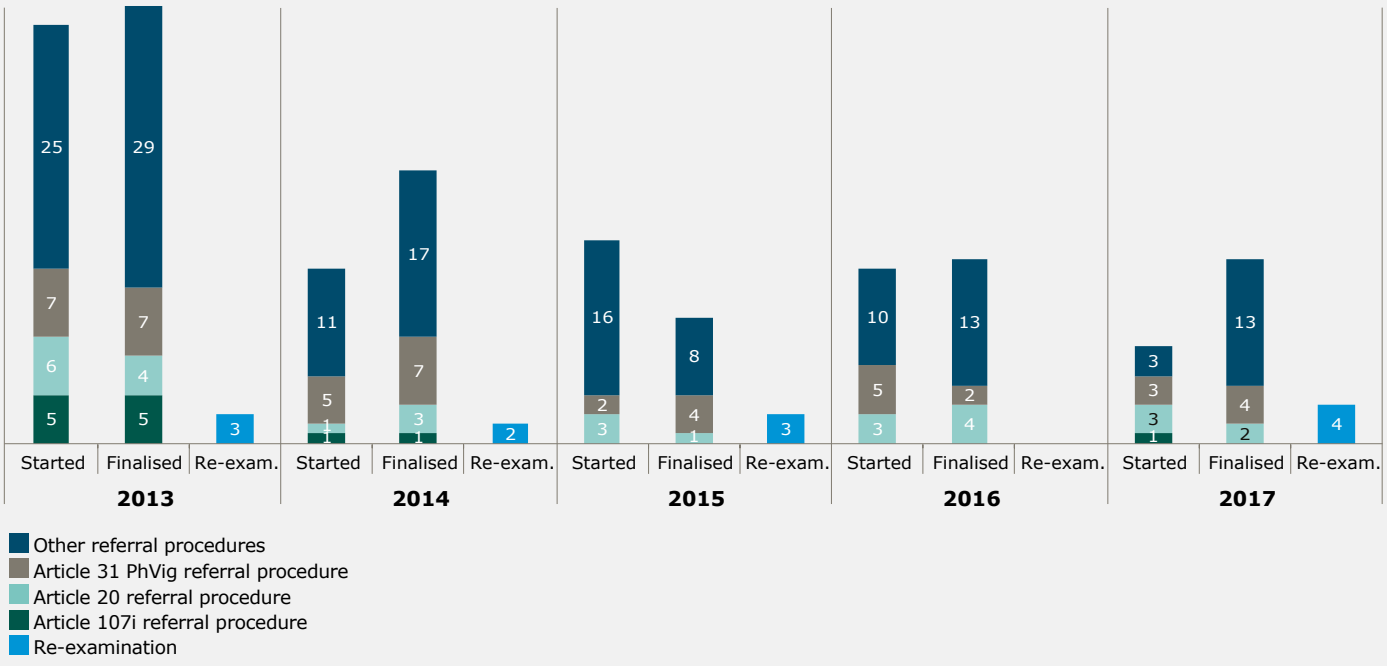
Referral procedures are used to address concerns over the safety or benefit-risk balance of a medicine, or disagreement among Member States on the use of a medicine. In a referral, the Agency is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine or class of medicines, and issues a cross-EU recommendation. The recommendation subsequently results in a legally binding decision throughout the Union issued by the EC 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, the same number as in 2016. Among these, six were pharmacovigilance-related (under Articles 31, 20 or 107i of the pharmacovigilance legislation): four of these led to changes to the product information, one led to the suspension of marketing authorisations, and one procedure led both to changes to the product information for some of the medicines concerned and the suspension of others. Two of these procedures covered a very high number of medicines authorised at national level (one concerned 367 medicines and the other 524).

The remaining 13 referral procedures were conducted 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



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

A total of 30 consultations took place in 2017 in the form of SAG meetings, compared to 19 in 2016. 25 of these consultations included patients or carers. Among these 30 consultations, 13 were ad-hoc expert groups and the other 17 were SAG meetings, in the areas of oncology (10), neurology (4), psychiatry (2) and cardiovascular diseases (1).

Procedures with scientific advisory group or ad-hoc expert group involvement (number of consultations)

	2013	2014	2015	2016	2017
Marketing authorisation (new MAA, new MAA re-examination, Art 58)	20	14	7	8	14
Extension of indication (including line extensions)	3	2	2	6	3
Referral (including re-examination)	2	5	3	5	11
Guideline	2	1	1	0	1
Other topics (renewal, PSUR, signal, class review)	0	1	3	0	1
Total	27	23	16	19	30

Patient involvement in EMA activities (interactions)

	2013	2014	2015	2016	2017
Scientific advice/protocol assistance	28	37	76	82	158
SAGs/ad-hoc expert meetings	33	35	23	28	46
Scientific committee/working party consultations	10	25	24	50	104
Workshops	87	104	115	141	138
Working groups and other ad hoc activities	219	192	313	271	269
Patient membership in MB, committees, working parties	39	55	55	58	59
Document reviews conducted by patients and consumers	174	185	137	120	176

Involvement of patients and healthcare professionals

Patients and healthcare professionals (HCPs) are involved in a wide range of EMA 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.

HCP involvement in EMA activities (interactions)

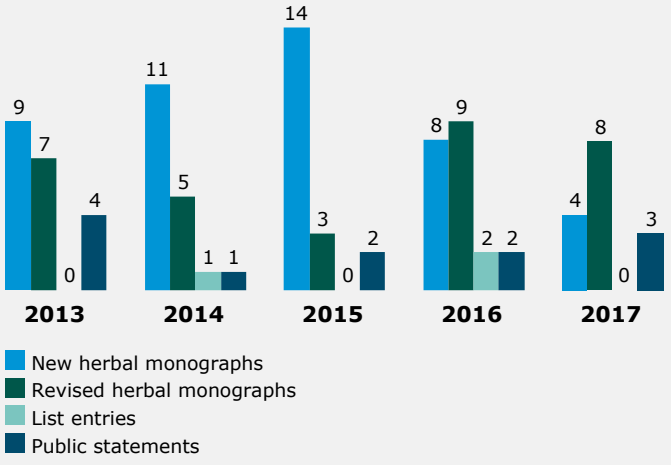
	2013	2014	2015	2016	2017
Scientific advice/protocol assistance	4	0	1	1	1
SAGs/ad-hoc expert meetings	49	32	21	26	40
Scientific committee/working party consultations	32	41	47	31	74
Workshops	n/a	64	59	106	83
Working groups and other ad hoc activities	n/a	67	184	129	160
HCP membership in MB, committees, working parties	33	49	47	51	54
Document reviews conducted by healthcare professionals	0	43	29	55	33

Herbal medicines

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

The assessment of seven new herbal substances was completed in 2016, leading to the publication of four final EU monographs and three final public statements, following public consultations. Eight monographs were updated following a systematic review of newly available data.

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



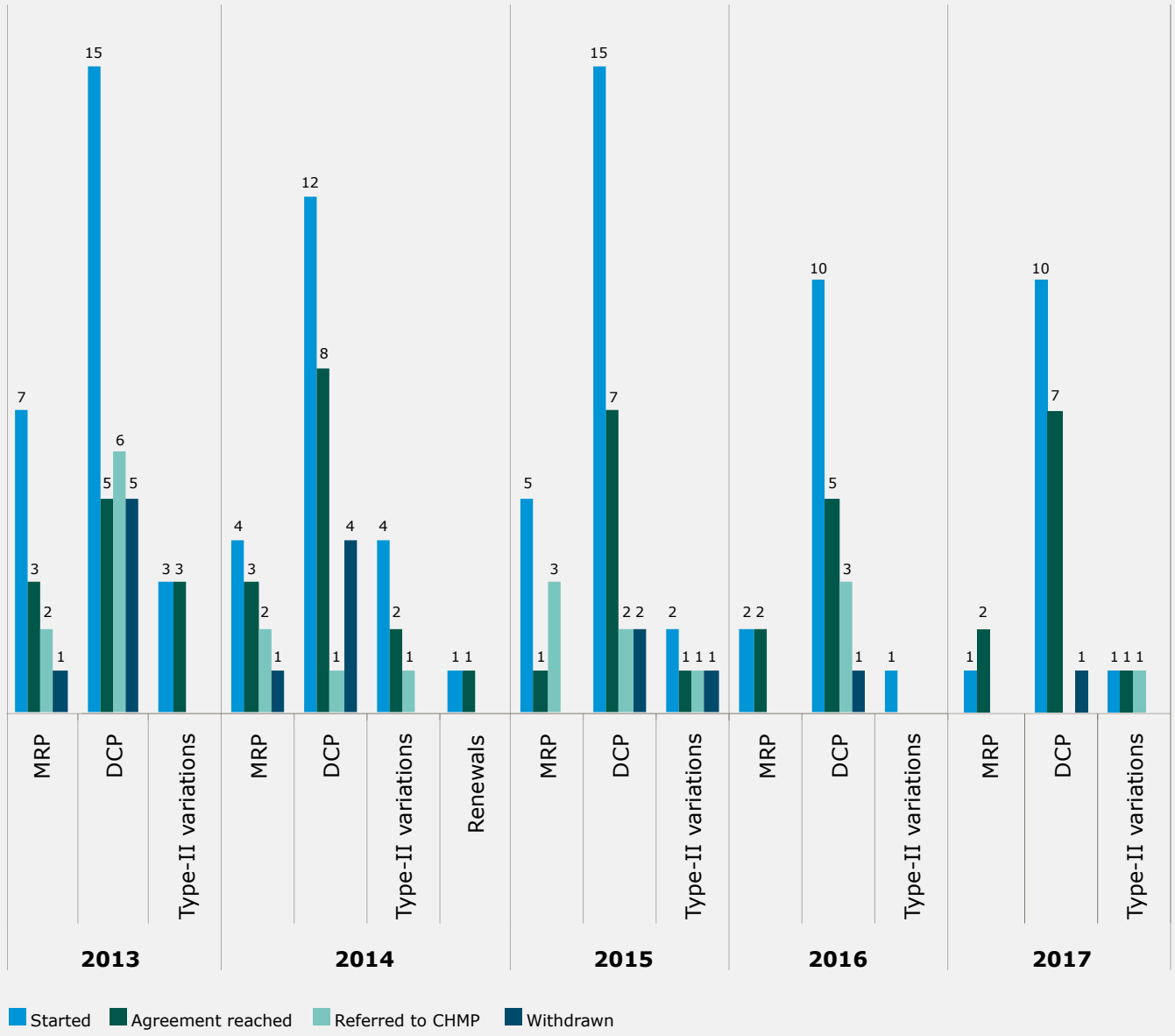
Note: A complete list of recommendations on herbal medicines can be found in the annexes.

Mutual-recognition and decentralised procedures

90% of the medicines entering the EU market are authorised nationally. 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, a separate body from EMA which represents the EU Member States plus Iceland, Liechtenstein and Norway, plays a key role, together with its working parties, in the authorisation and maintenance of these medicines. EMA provides secretarial support to the CMDh in accordance with the approved rules of procedure.

Detailed information about the work of the CMDh in 2017 in relation to pharmacovigilance and referrals can be found on the HMA website.

Applications referred to CMDh



Veterinary medicines

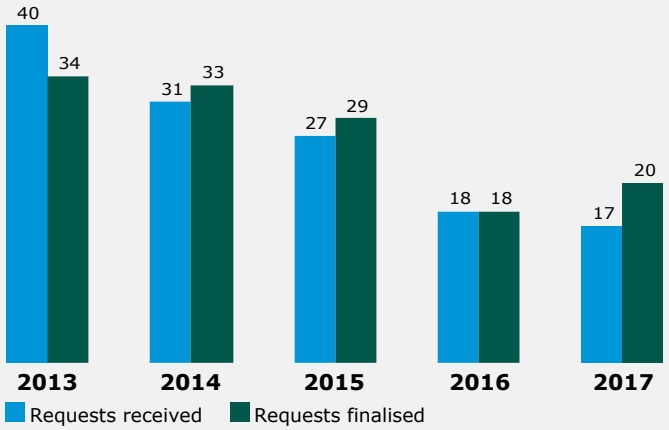
Activities supporting research and development

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

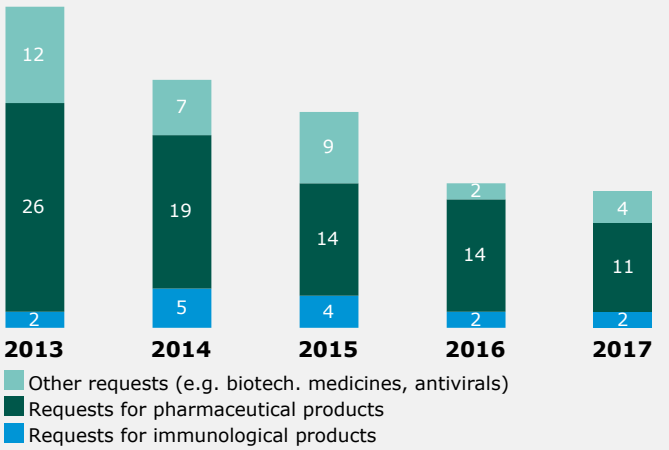
Scientific advice is provided on any aspects of research and development relating to the quality, safety or efficacy of medicines for veterinary use, and to the establishment of maximum residue limits. Scientific advice is a means of facilitating and improving the availability of new veterinary medicines.

Scientific-advice requests received and finalised



EMA received 17 requests for scientific advice in 2017 and finalised 20, including some pending from 2016. The number of requests seems to have declined since a peak in 2013. This may still be a prolonged tail of a fluctuation reflecting the industry's readiness to develop new veterinary medicines in the current environment and forthcoming changes in legislation.

Scientific-advice requests received by area



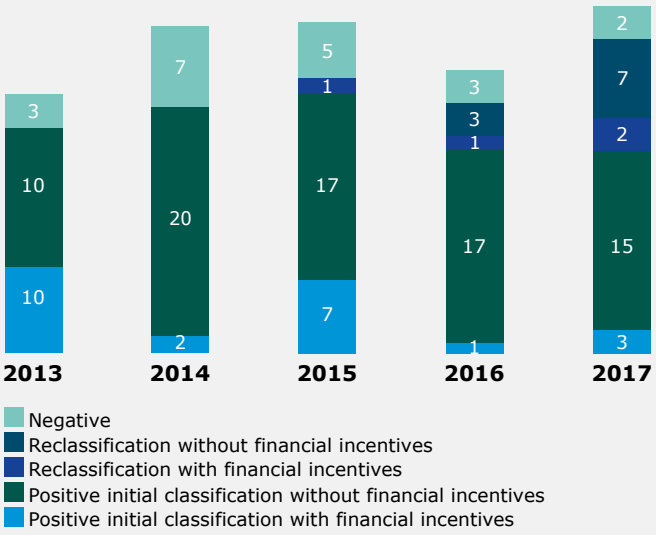
Minor Use Minor Species

The Agency's minor-use-minor-species (MUMS)/limited market policy adopted in 2009 aims to assist companies with the submission of applications for products for limited markets. The policy was revised in 2013/14 and a set of revised guidelines was adopted in April 2017. The objective is to encourage development of veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment.

In 2017, the Agency received a total of 25 new requests for the (re)classification of veterinary medicines intended for MUMS/limited market, showing a stable interest from medicine developers in developing products for minor uses or minor species.

In addition, 2017 saw the highest number of reclassification outcomes following the expiry of the initial five – year – classification, all the submitted requests were reclassified as MUMS/limited market for a further five-year period. A total of nine reclassifications were granted, two with financial incentives and seven without.

Initial requests for MUMS/Limited market classification finalised



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 incentives 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 dedicated newsletter.

Of the 1,893 SMEs registered with EMA at the end of 2017, 4% are developing veterinary products and 4%, both human and veterinary products.

SMEs submitted 6 of the 17 applications (35%) for marketing authorisation for veterinary medicines in 2017.

Two medicines that received a positive recommendation for a marketing authorisation for a veterinary medicine were developed by SMEs.

Of the 17 requests for scientific advice submitted in 2017, 7 came from SME applicants, representing 41% of the total.

Of the medicines classified previously as MUMS/limited market, two products were recommended by the CVMP for marketing authorisation in 2017:

Oxybee – a powder and solution intended for the treatment of honey bees in hives infested with Varroa destructor mites.

Rabitec – a bait vaccine for the immunisation of foxes and racoon dogs against rabies.

Initial marketing authorisation applications from SMEs (veterinary medicines)

	2013	2014	2015	2016	2017
Initial MAAs submitted by SMEs	2	2	4	9	6
Positive opinions	1	2	2	8	2
of which, new active substances	0	0	1	2	0
Negative opinions	0	0	1	0	0
Withdrawals	0	1	0	1	0

Innovation Task Force

The 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.

A record number of five ITF meetings were held in 2017 concerning the development of veterinary medicines, showing a growing interest in this activity.

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 medicines development and ensure that the medicines are safe, effective and of high quality.

Guidelines are drafted by EMA working parties comprising 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 and guidance issued or revised in 2017 is listed below:

Topics	Content
Minor-uses-minor-species (MUMS)	Revised guidelines that clarify the data needed to support an application for marketing authorisation for MUMS
Monoclonal antibodies	The first-ever guidance of its kind at EU level addresses the particularities of monoclonal antibodies for veterinary use, such as quality control for potential contaminants, stability testing, reproductive safety studies and data to address potential for indirect adverse effects.
Stem-cell therapies	The first-ever guidance at EU level for stem-cell therapy addresses the concerns raised by manufacturers and authorities with regard to the sterility, extraneous agents and tumorigenicity of allogenic stem-cell therapies in the veterinary sector.

Note: The full list of CVMP guidelines released in 2017 can be found in the annexes.

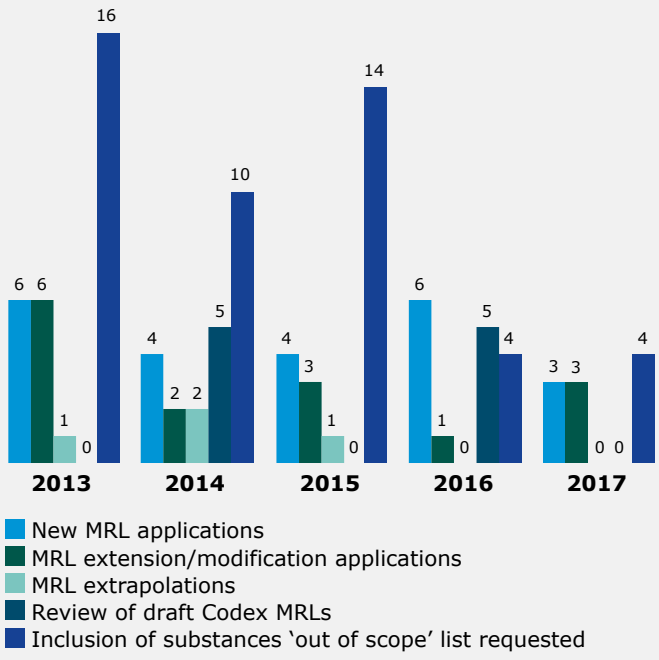
Maximum residue limits

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 food-producing animals. The objective is to ensure the safety of foodstuffs of animal origin, including meat, fish, milk, eggs and honey. EMA has a parallel responsibility for recommending MRLs for pharmacologically active substances in biocidal products used in animal husbandry. The EC formally establishes the MRL status.

Three applications for the establishment of MRLs for new substances were received in 2017. In addition, the CVMP received applications for the extension or modification of existing MRL classifications for three substances.

While the number of applications has declined slightly compared to previous years, the overall number of applications for MRLs indicates the continued interest the animal health industry has in developing new products for food-producing animals.

Evaluation of maximum residue limits



Authorisation activities

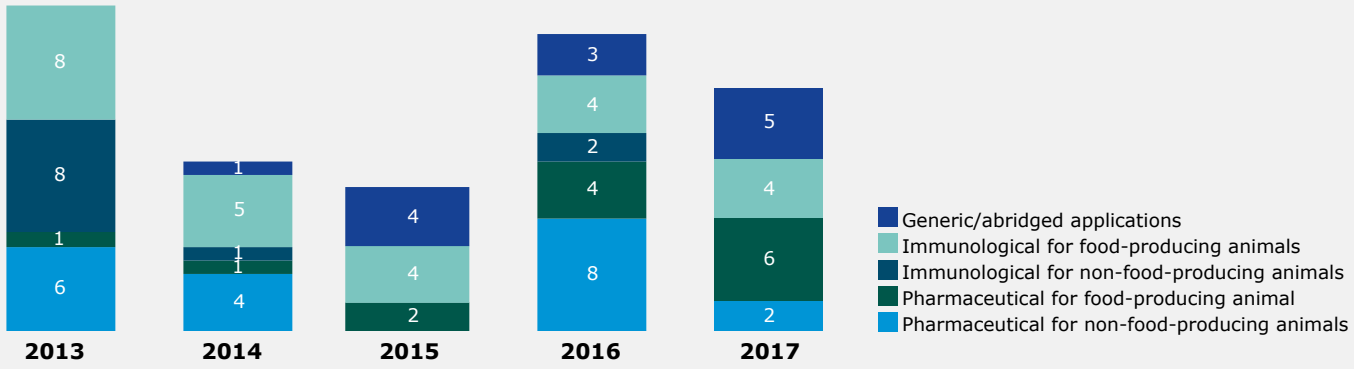
Applications for initial evaluation

The initial evaluation phase covers activities relating to the processing of marketing authorisation for veterinary medicines, ranging from pre-submission meetings with future applicants, through evaluation by the CVMP to the granting of marketing authorisation by the EC.

A total of 17 applications were received in 2017.

Six applications were for immunological products for food-producing animals. The growing number of applications demonstrates the animal health industry's continued strong interest in developing vaccines.

Applications for initial evaluations received



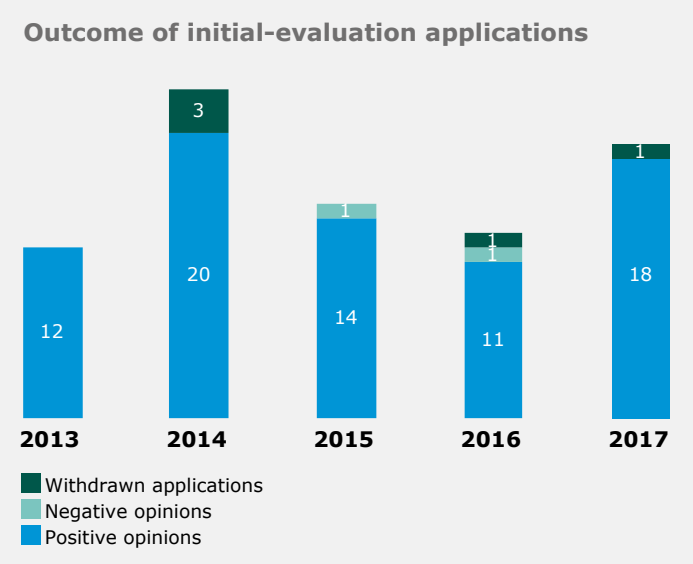
Medicines recommended for approval in 2017

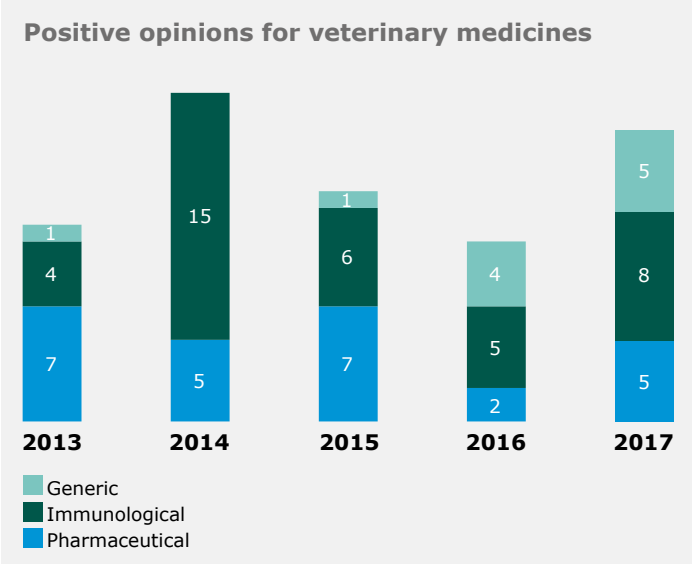
Medicines that contain a new active substance are highlighted in green

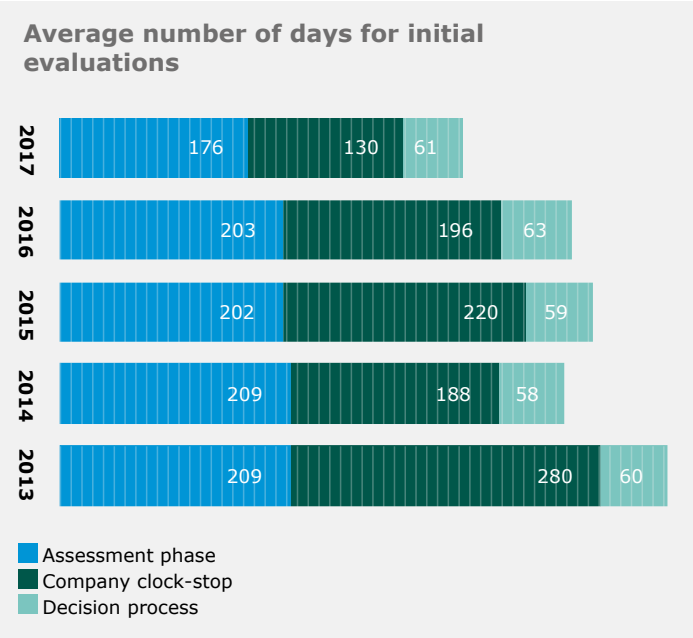
Recommendations for authorisation

18 new veterinary medicines were granted a positive opinion in 2017; seven of these contained new active substances.

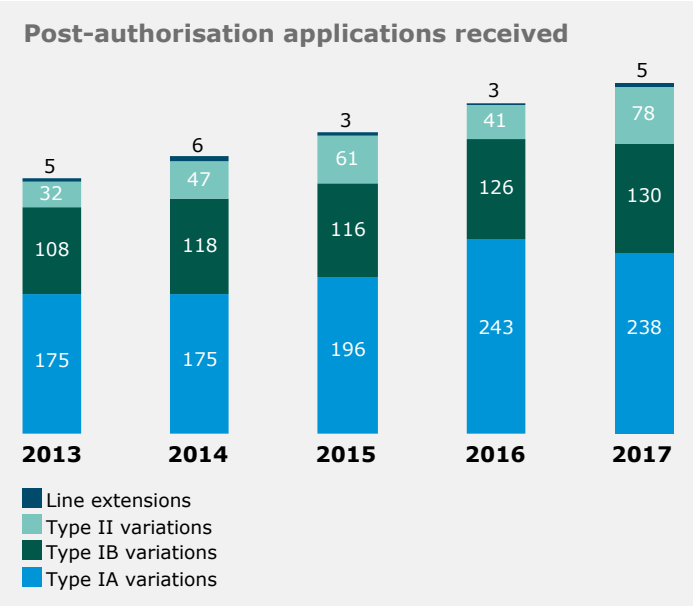
10 vaccines were recommended for marketing authorisation, a twofold increase compared to 2016 and 2015. This positive trend matches EMA's efforts to facilitate the availability of veterinary vaccines in the EU.







The overall time for the centralised procedure evaluation was reduced in 2017 due to some shorter procedures, such as informed consent applications. An informed consent application makes use of data from the dossier of a previously authorised medicine, with the marketing authorisation holder of that medicine giving consent for the use of their data in the application.



Post-authorisation activities

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

The total number of post-authorisation procedures continues to increase year-on-year, broadly in line with the number of products authorised through the centralised procedure.

The use of six known substances was expanded in 2017:

- Zactran also to be used in sheep and against a new pathogen causing swine respiratory disease;
- Nexgard Spectra, Activyl Tick Plus and Broadline also to be used for the treatment of and protection against further parasite species;
- Simparica also to be used in dogs for the treatment of ear mites and demodicosis, an inflammatory disease caused by various types of the Demodex mite;
- SevoFlo also to be used in cats as an anaesthetic.

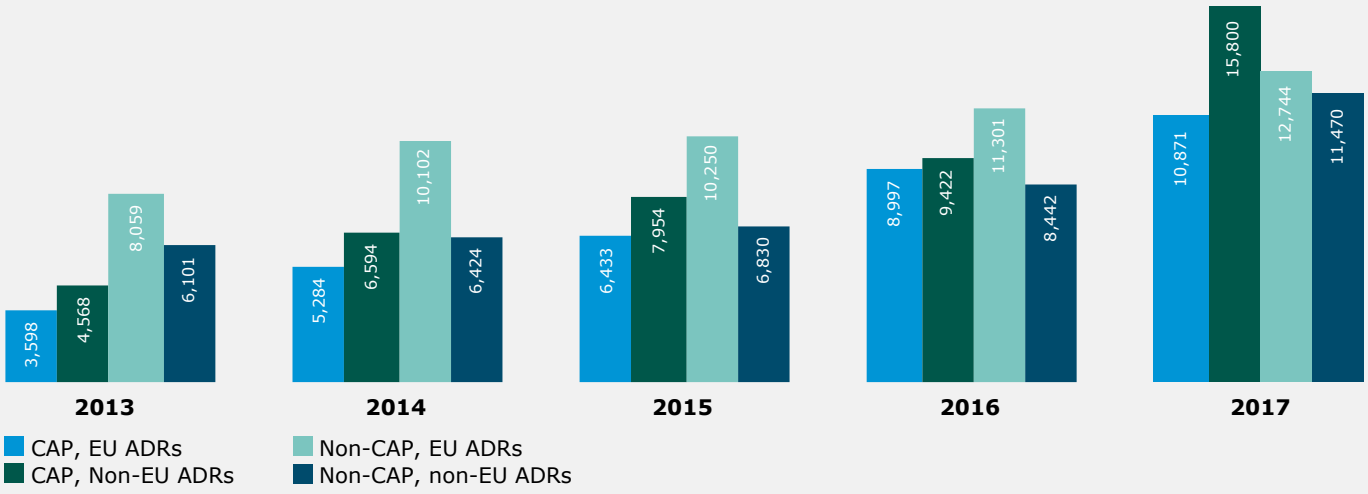
Safety monitoring of medicines

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 significant increase of 33% in the number of AE reports received in the EudraVigilance system in 2017 compared to 2016.

Adverse events reports in animals

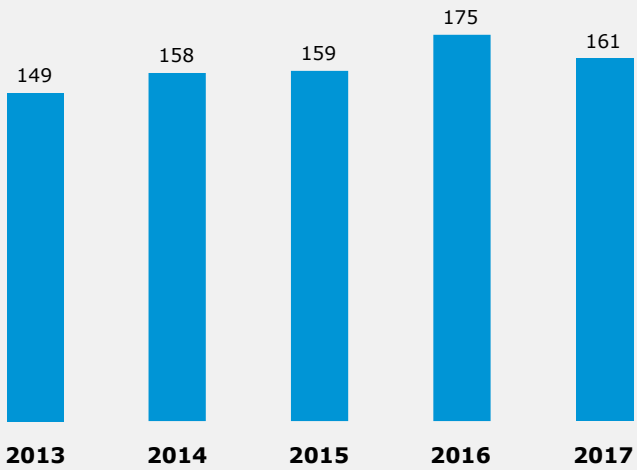


A long-term trend towards increased reporting is mainly attributed to the growing awareness among veterinarians of the value of pharmacovigilance reporting, as well as greater control by regulators of the implementation of pharmacovigilance legislative requirements by the veterinary pharmaceutical industry.

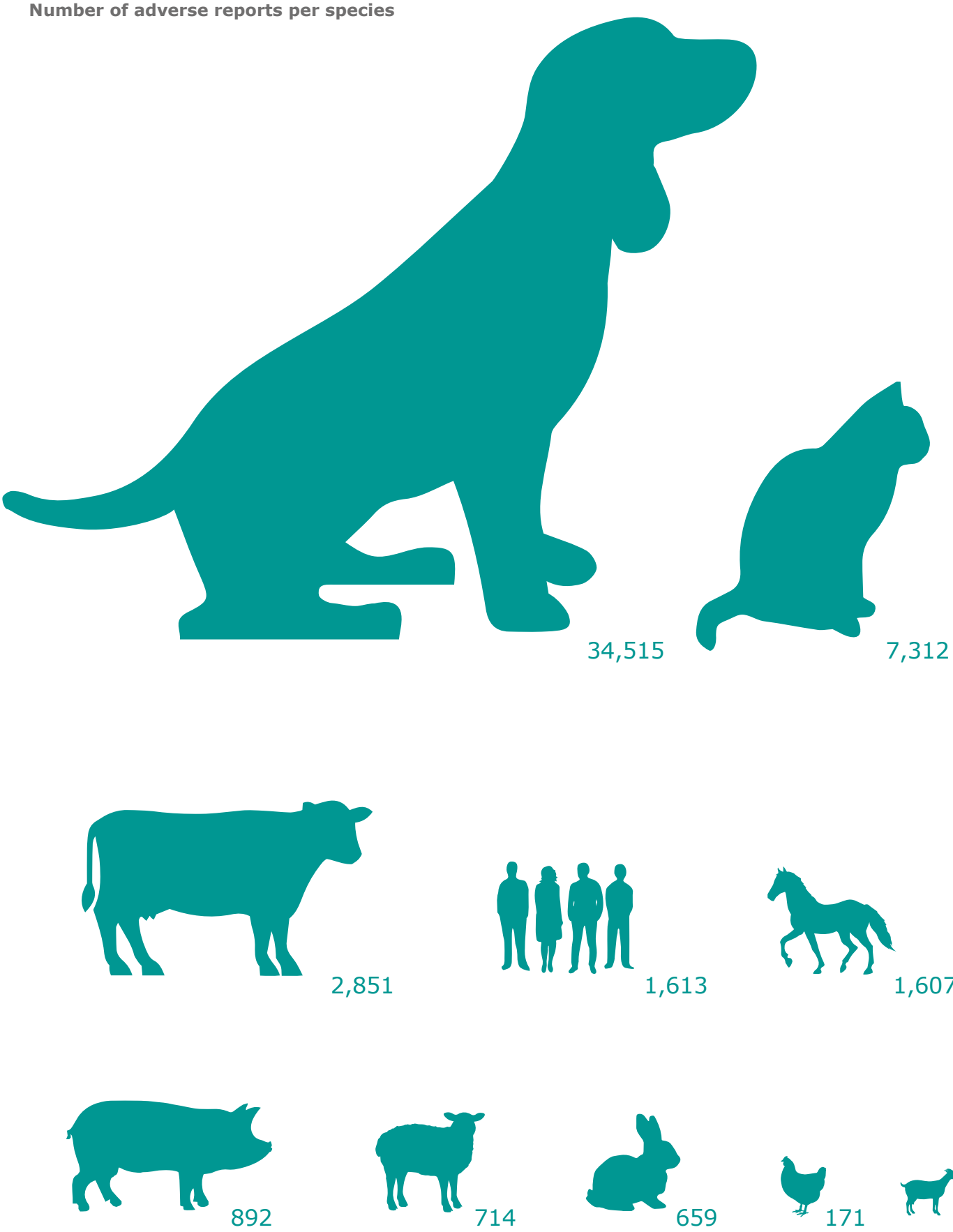
Periodic safety update reports (PSURs)

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



Number of adverse reports per species



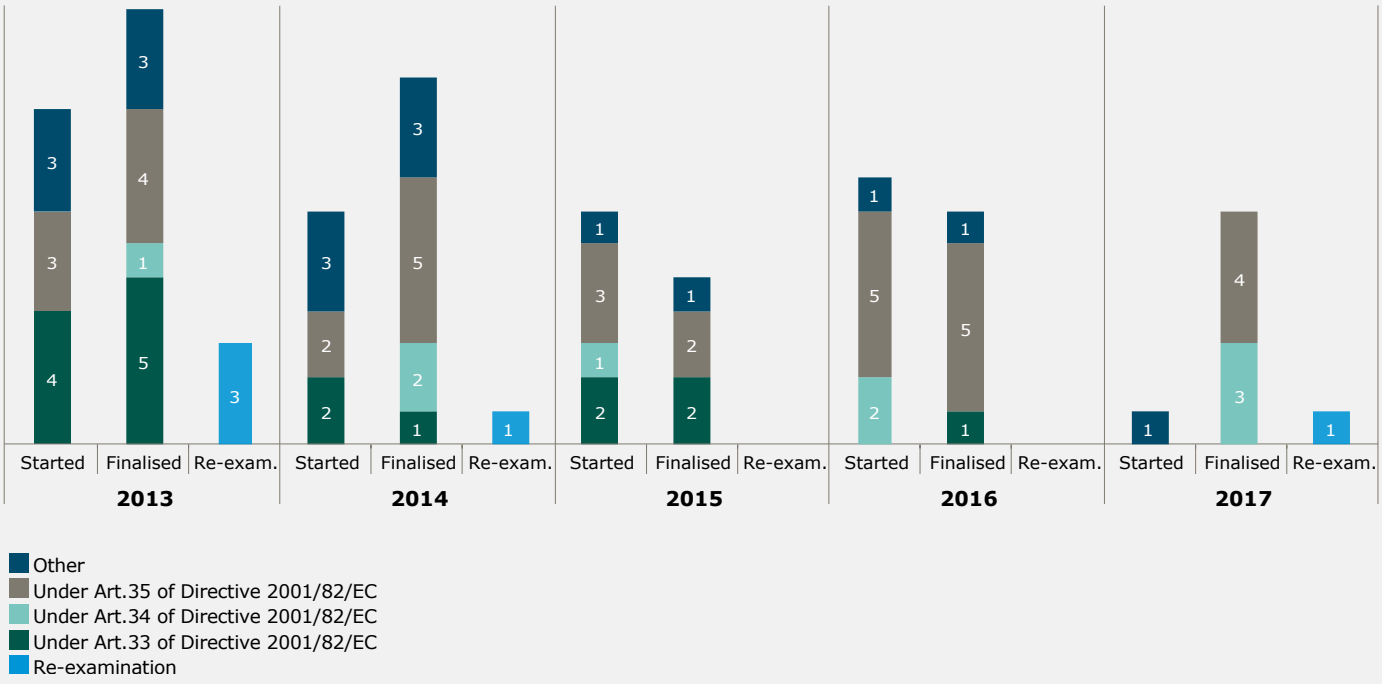
Referral procedures

Referral procedures are used to address concerns over the quality, safety, efficacy or benefit-risk balance of a veterinary medicine, or disagreement among Member States on the use of a veterinary medicine. In a referral, the Agency is requested, on behalf of the EU, to conduct a scientific assessment of a particular veterinary medicine or class of veterinary medicines, and issues a cross-EU recommendation. The recommendation subsequently results in a legally binding decision throughout the Union issued by the EC.

Seven referral procedures were finalised in 2017. Among these, four were safety- or efficacy-related (under Article 35 of Directive 2001/82/EC): one of these led to withdrawal of the marketing authorisation, one led to deletion of indication, one led to deletion of target species, one led to changes to the product information and conditions on the marketing authorisations, and one led to harmonised withdrawal periods. The remaining three procedures (under Article 34 of Directive 2001/82/EC) were related to divergent decisions taken by Member States resulting in differences in the product information and all three led to complete harmonisation of the product information.

Only one referral procedure was initiated in 2017 which is significantly lower than the high workload experienced for referrals in recent years. This might be due to lack of resources across the EU regulatory network (partially due to the work on complex referral procedures in 2017).

Arbitration and referrals for veterinary medicines

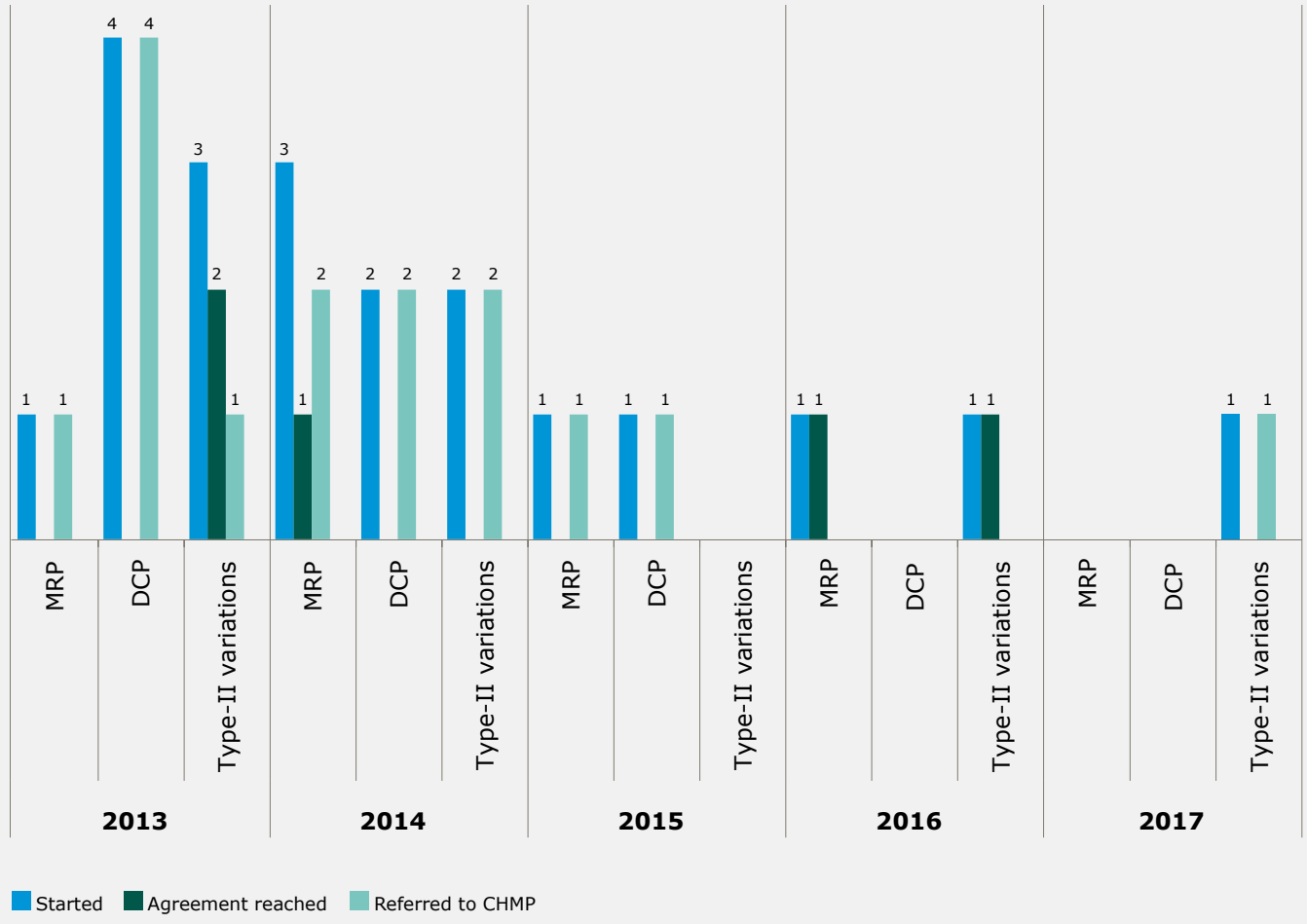


Note: Complete information on referral procedures can be found in the annexes.

Mutual-recognition and decentralised procedures

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

Applications referred to CMDv



European medicines regulatory network

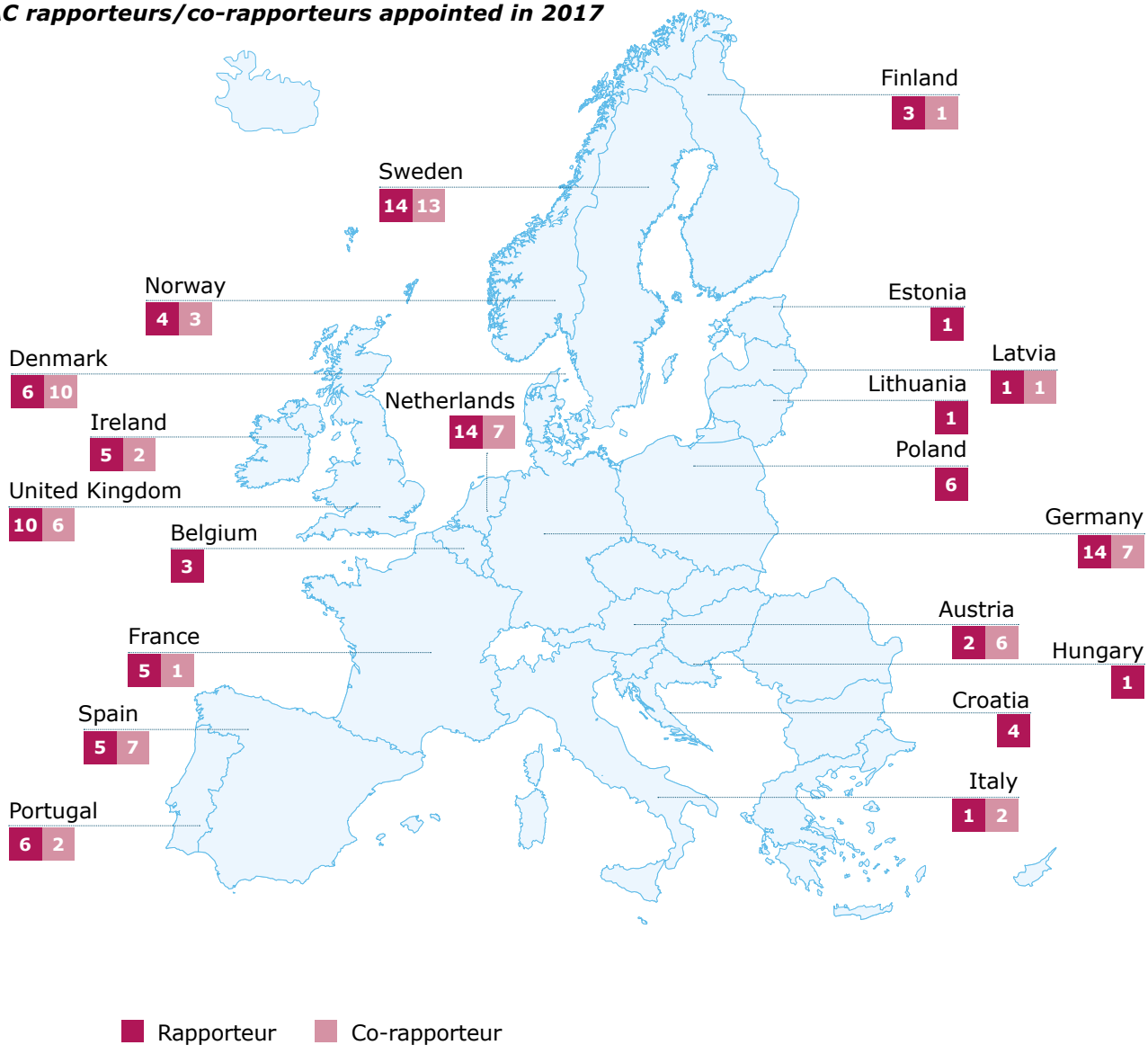
The European medicines regulatory network – a partnership between EMA, the EC and 50 medicine regulatory authorities in the EU and the EEA – is the basis of the Agency's success.

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 2017

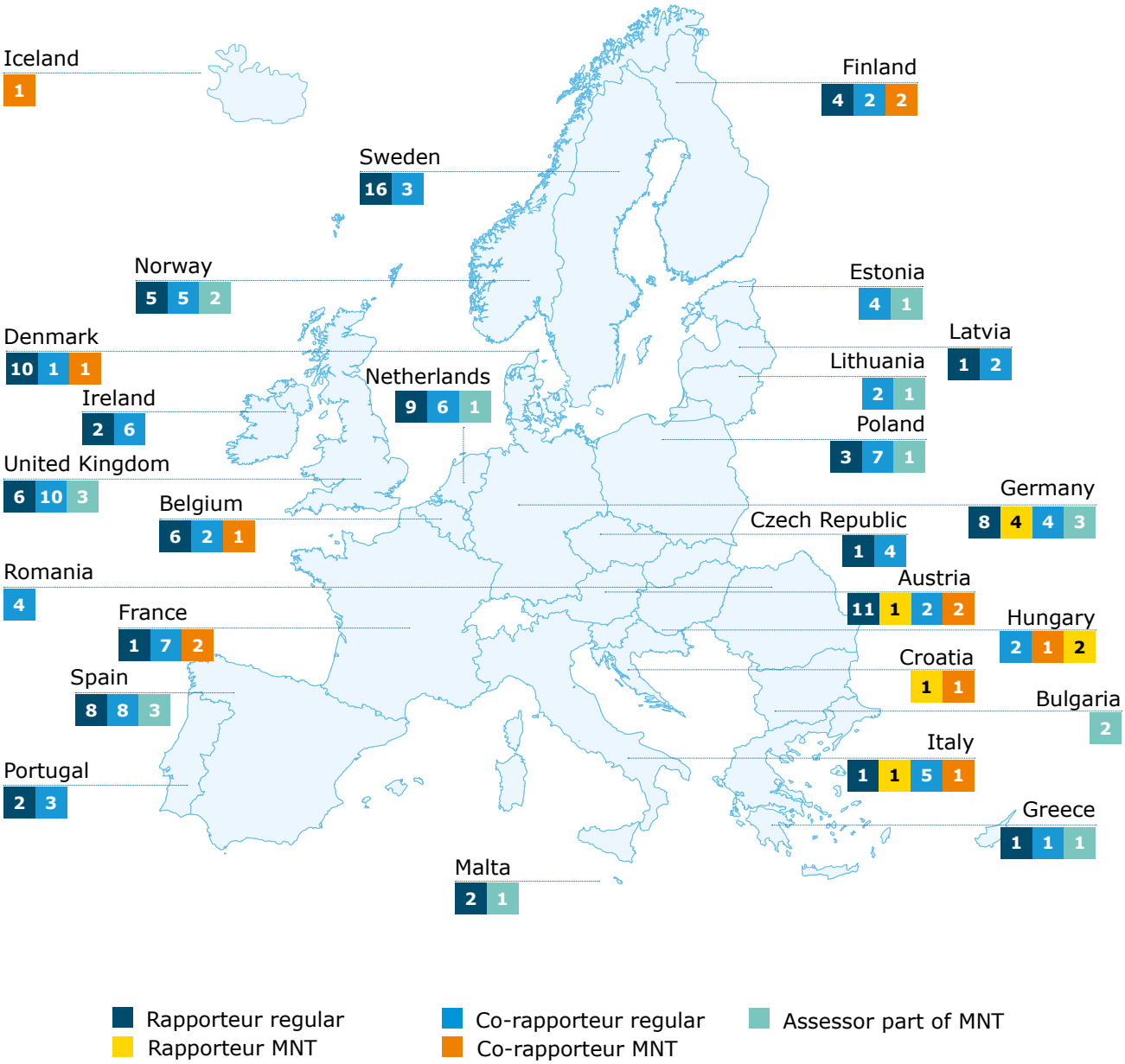


CHMP rapporteurships/co-rapporteurships

Since 2015, CHMP rapporteurs and co-rapporteurs have been able to create multinational teams (MNTs) for the initial assessment of marketing authorisation applications.

The map below presents the number of procedures in which each country was involved in 2017, 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.

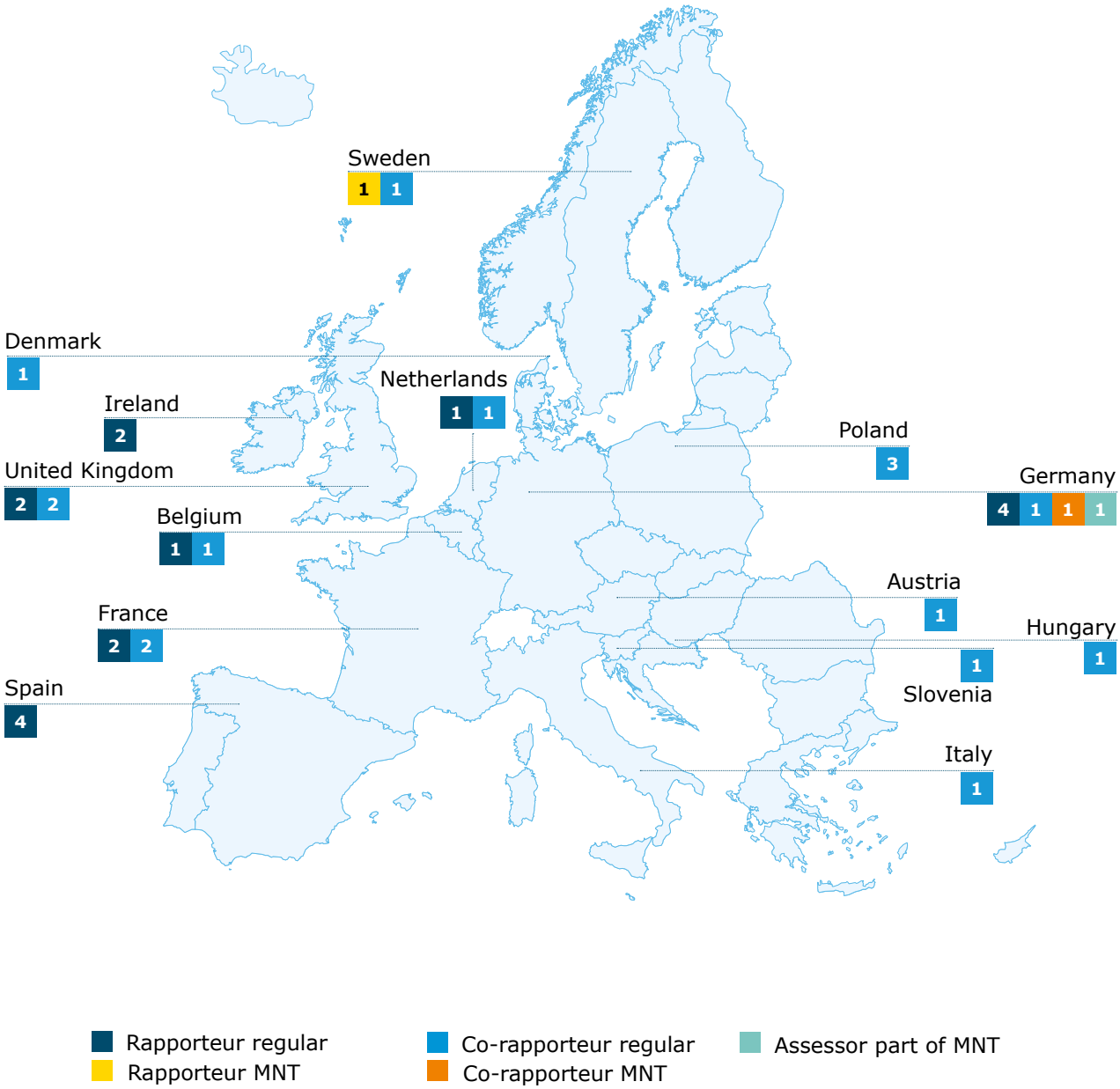
CHMP rapporteurs/co-rapporteurs appointed in 2017 (for initial MAs, including generics)



CVMP rapporteurships/co-rapporteurships

The concept of multinational teams continued in 2017.

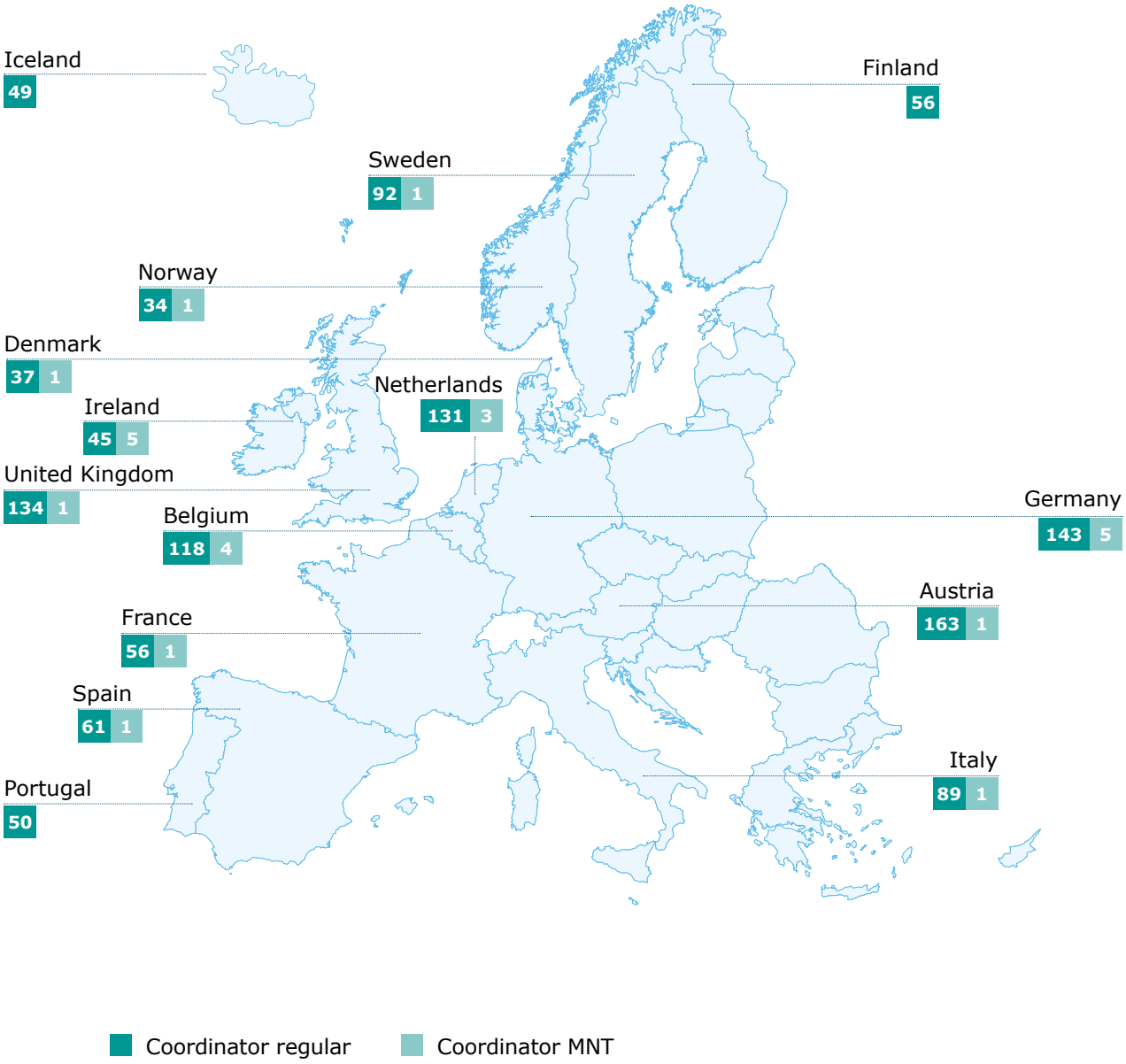
CVMP rapporteurs/co-rapporteurs appointed in 2017 (for initial MAs, including generics)



Scientific advice coordinators

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

SAWP coordinators appointed in 2017



EU network training centre

The EU Network Training Centre (EU NTC) is a joint initiative of EMA and the HMAs to address the training needs of the EU medicines regulatory network with respect to both human and veterinary medicines. The table below highlights the key activities of the EU NTC:

Activity	2015	2016	2017
New scientific, regulatory and telematics curricula developed	1	8	0
Number of training events advertised for the EU network	105	140	100
Number of reimbursed training events for the EU network	7	25	20
Number of NCAs that have opened their training to the EU NTC	6	14	8
Number of users registered in the EU NTC Learning Management System		2,117	3,583
Number of NCA experts registered in the EU NTC Learning Management System		1,225	2,668

Inspections and compliance

EMA 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 are inspections, which can either be carried out routinely or 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 responsibility for carrying out inspections rests with EU NCAs but EMA plays a coordinating role.

EMA also coordinates the preparation and maintenance of risk-based inspection programmes to verify compliance with the principles of GMP, GCP and pharmacovigilance at EU 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, EMA ensures the best use of resources by promoting mutual reliance and work sharing with other international authorities. For GMP inspections, there are a number of mutual-recognition agreements in place. In 2017, two major trade agreements covering GMP inspections entered into force provisionally: the MRA between the EU and the US (the EU-US MRA) and the Comprehensive Economic Trade Agreement with Canada (CETA).

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 its inspectors working groups, the Agency coordinates the development and setting of standards for GMP, GCP and GVP. This helps harmonise standards within the EU and internationally, and so strengthen global supply chains and improve 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 of suspected quality defects for centrally authorised medicinal products and coordinates their investigation, evaluation and follow-up. 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.

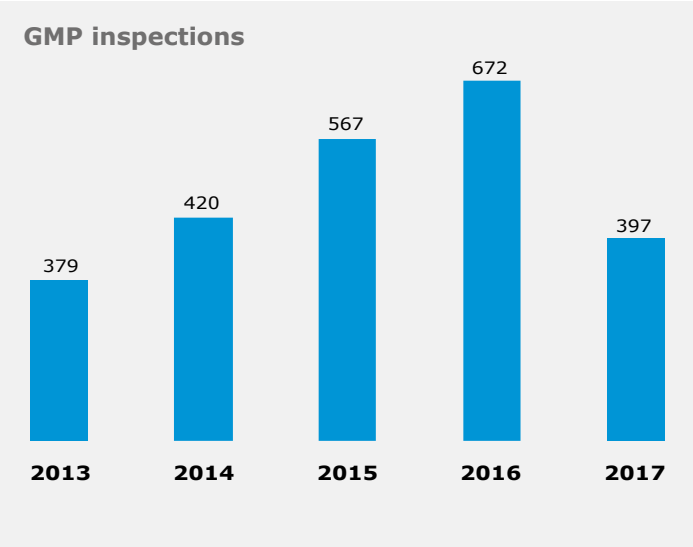
Inspections

GMP, GCP, GLP and pharmacovigilance inspections requested by the CHMP or CVMP take place worldwide. However, they represent just a small part of the total number of inspections performed by the EU/EEA inspectors, who also carry out inspections as part of their national programmes in the context of:

- the evaluation of marketing-authorisation applications submitted to regulatory authorities across the EU;
- overseeing manufacturers importing medicines into the EU;
- overseeing the conduct of clinical trials in Europe;
- overseeing compliance with pharmacovigilance obligations.

GMP inspections

The number of GMP inspections requests within the context of centralised marketing procedure declined in 2017; a number of these inspections will take place in 2018. This decrease reflects the implementation of the EU-US MRA which is based on recognition of equivalence of supervisory standards and which reduces duplication of inspections on each other's territories.



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 and CVMP.

In 2017, less than 1% of the GMP inspections conducted by EEA authorities led to the issue of a non-compliance statement (17 out of 2,493).

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

- One non-compliance statement led to the suspension of the manufacturing and importation authorisation until the implementation of adequate corrective actions.
- 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 for a centrally authorised product. The same non-compliance statement resulted in the withdrawal by the applicant of two further applications for marketing authorisation.
- One non-compliance statement resulted in prohibition of the supply of centrally authorised medicinal products from the manufacturing site concerned.

GMP certificates and non-compliance statements issued by EEA/EU and other authorities worldwide

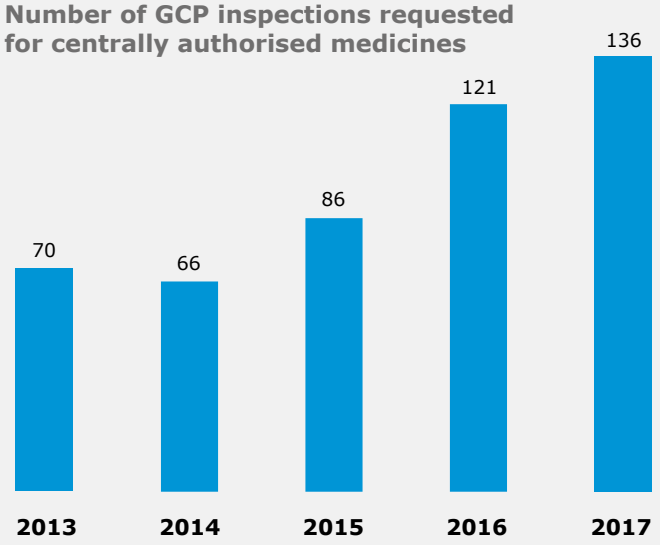
	2013		2014		2015		2016		2017	
	GMP certificate	GMP Non-compliance statement	GMP certificate	GMP Non-compliance statement	GMP certificate	GMP Non-compliance statement	GMP certificate	GMP Non-compliance statement	GMP certificate	GMP Non-compliance statement
EEA/EU	1,526	3	2,121	4	2,310	5	1,951	5	2,115	7
China	63	8	71	4	72	6	55	4	39	1
India	103	7	124	6	135	6	96	12	119	7
USA	81	0	125	0	110	1	86	3	106	0
Rest of the world	111	3	88	2	119	0	81	0	97	2
Total	1,884	21	2,529	16	2,746	18	2,269	24	2,476	17

Note: The chart shows the number of GMP certificates and non-compliance statements issued by EEA authorities as an outcome of GMP inspections conducted between 2013 and 2017. It includes GMP inspections requested by CHMP or CVMP.

GCP inspections

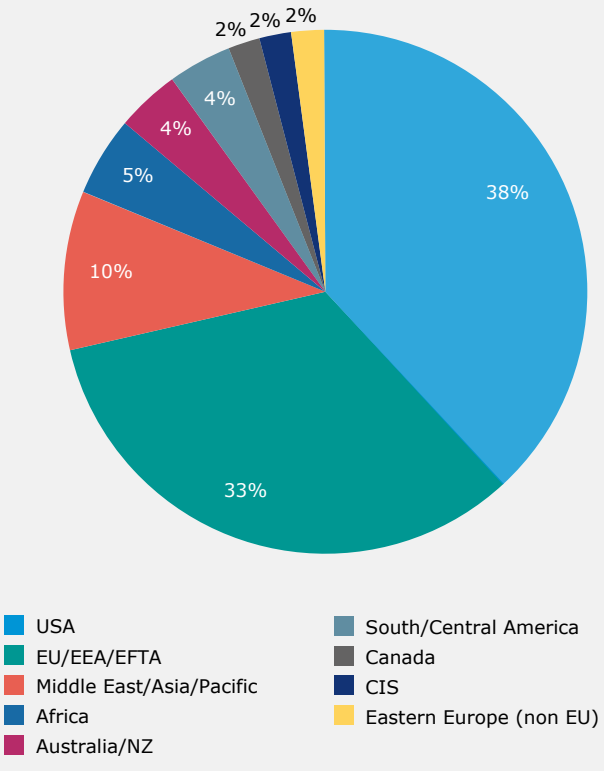
The number of GCP inspections increased by 12%, from 121 in 2016 to 136 in 2017.

Number of GCP inspections requested for centrally authorised medicines



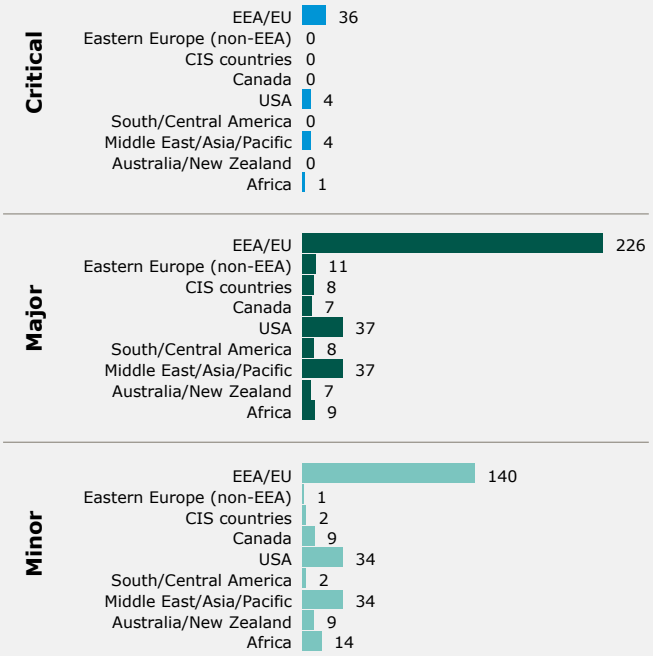
In 2017, the highest number of GCP inspections requested by the CHMP was conducted in the USA followed by EU/EEA/EFTA and the Middle East/Asia/Pacific regions which have the highest number of patients, investigator sites and pivotal clinical trials included in MAAs for centrally authorised products.

CHMP-requested GCP inspections finalised by EEA authorities (2017)



The classification of findings per region is presented in the table below and the most common grading was major.

Type of findings of CHMP-requested GCP inspections finalised by EEA authorities (2017)



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 2017, one centralised marketing authorisation application was withdrawn as a result of non-compliance with EU good clinical practice.

The CHMP adopted two negative opinions (refusing the granting of the marketing authorisation) for medicines for which GCP inspections reported non-compliance issues with the clinical studies submitted.

GCP inspections of two sites of a contract research organisation (CRO) led to an EU review of the impact of the findings. As an outcome of this review, the CHMP recommended the suspension of a number of nationally authorised medicines for which bioequivalence studies were conducted by the two CRO sites concerned.

Pharmacovigilance inspections

EMA, in cooperation with competent authorities in the Member States, 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 2017, 15 pharmacovigilance inspections were requested by the CHMP or CVMP, almost a twofold increase compared to 2016, when eight inspections were requested by the committees. The majority of EU/EEA pharmacovigilance inspections (over 90%) are conducted under the national pharmacovigilance inspection programmes which relate to marketing authorisation holders with product authorisations of all types (including centrally authorised products).

Market surveillance and quality defects

Manufacturers are required to inform authorities of quality defects in batches of manufactured products. 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 2017, the Agency received 161 suspected quality defect notifications. Of these, 140 cases were confirmed quality defects and led to batch recalls of 17 centrally authorised medicines.

Market surveillance testing

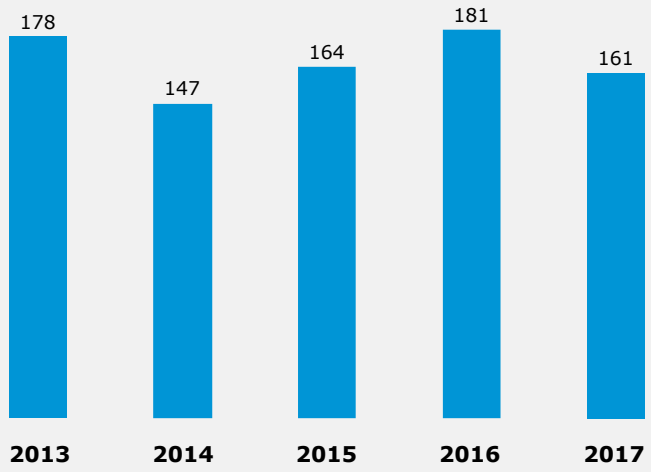
A total of four quality defects were identified following sampling from the EU market and testing by an Official Medicines Control Laboratory as part of the Agency's routine market surveillance programme.

Two cases were confirmed as out-of-specification test results and led to batch recalls from the market. Seven batches of a medicinal product for human use, zoledronic acid, were recalled from hospitals, pharmacies and wholesalers in six EU Member States. A subsequent GMP inspection of the manufacturer verified that the cause of the problem was limited to the batches in question and that appropriate corrective actions were implemented.

One batch of a medicinal product for veterinary use, meloxicam, was recalled from one member state.

Two cases were confirmed as labelling defects but the defect was not serious enough to warrant a batch recall.

Number of quality defects notifications received



Recalls	2014	2015	2016	2017
Recalls	14	15	16	17
Class 1	2	1	3	2
Class 2	8	3	9	8
Class 3	4	11	4	7

Parallel distribution

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

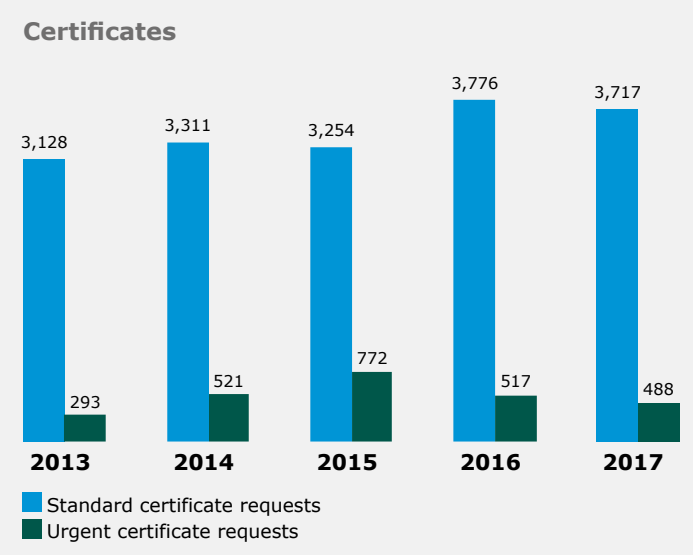
Parallel distribution notifications received

	2014	2015	2016	2017
Initial notifications	2,492	2,838	2,850	2,639
Notifications of change	1,295	2,096	1,847	1,975
Notifications of bulk change	9	13	8	6
Annual updates	2,339*	3,959**	3,815***	3,798****
Total	6,135	8,906	10,536	8,418

* Excludes 560 received in 2014 but processed in 2015
** Excludes 31 received in 2015 but processed in 2016
*** Excludes 1,323 received in 2016 but processed in 2017
**** Excludes approximately 1,900 in 2017 which will be processed in 2018

Certificates

EMA 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 and stakeholders

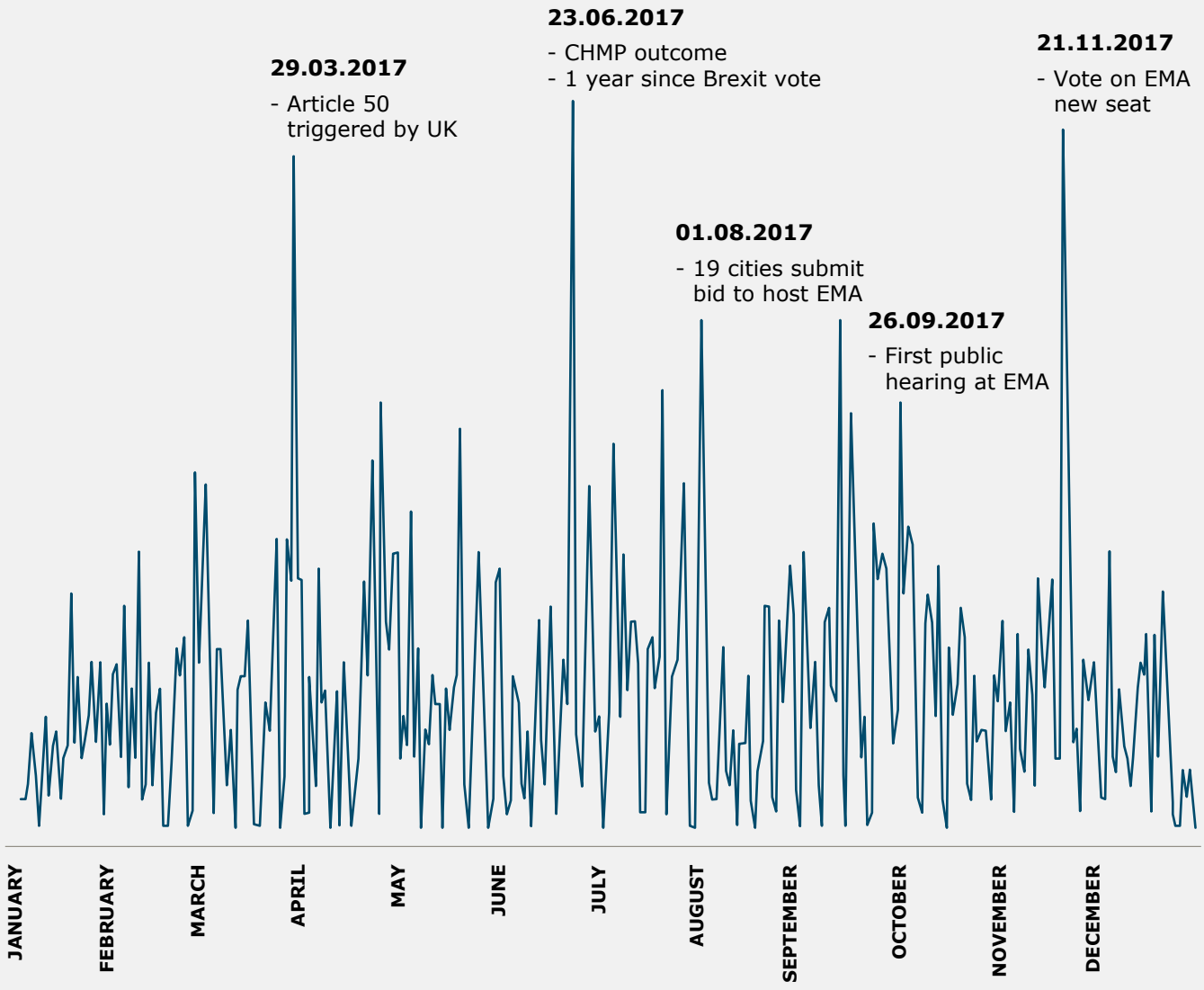
External communication

In 2017, EMA published 181 news releases.

The decision by the EU-27 to relocate the Agency to Amsterdam following the outcome of the UK's EU referendum was of great interest to the media. The Agency's first public hearing in September 2017 also generated coverage.

At the end of 2017, EMA had approximately 32,500 followers on Twitter, an increase of 30% compared to 2016. EMA's LinkedIn profile had over 29,900 followers at the end of 2017.

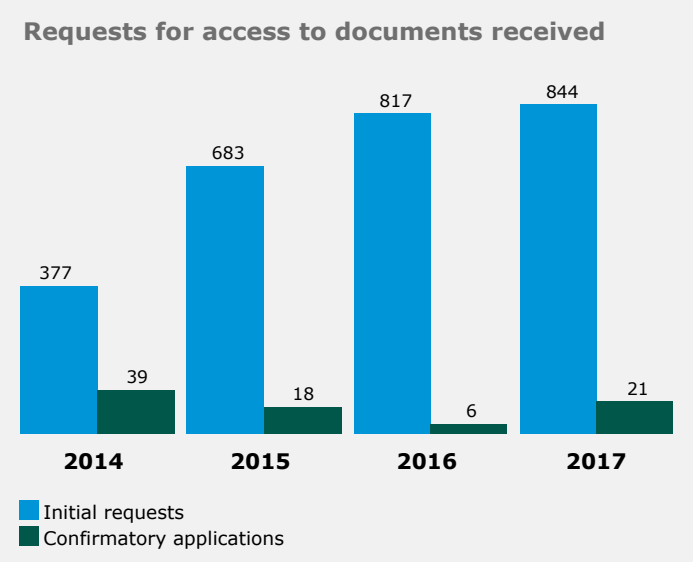
EMA mentions in main media outlets in 2017



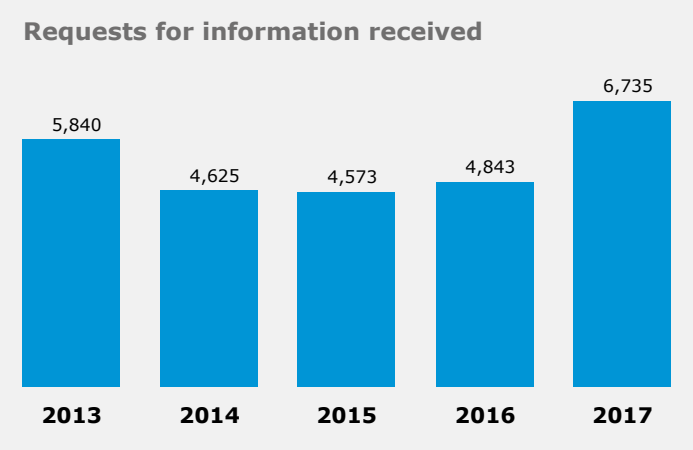
Requests for access to documents

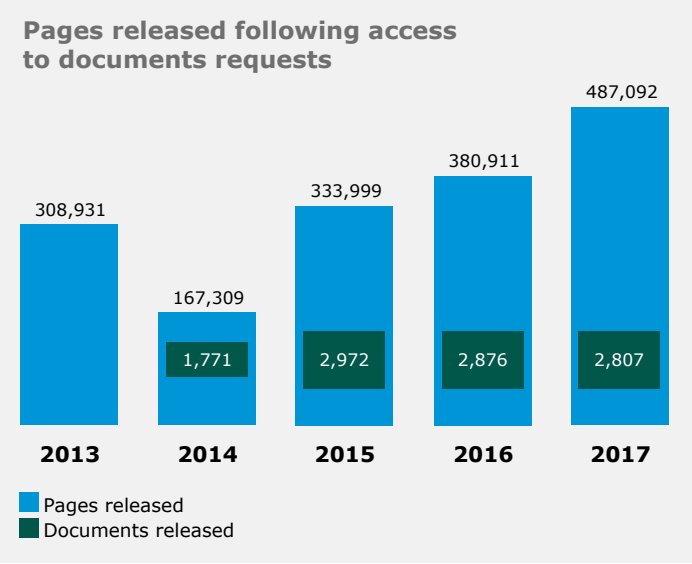
EU citizens have a right of access to documents held by EU institutions, bodies, offices and agencies. EMA grants this access according to the principles and further conditions as defined by the Regulation (EC) No 1049/2001 and its policy on access to documents.

The number of requests for access to documents continued to rise in 2017.



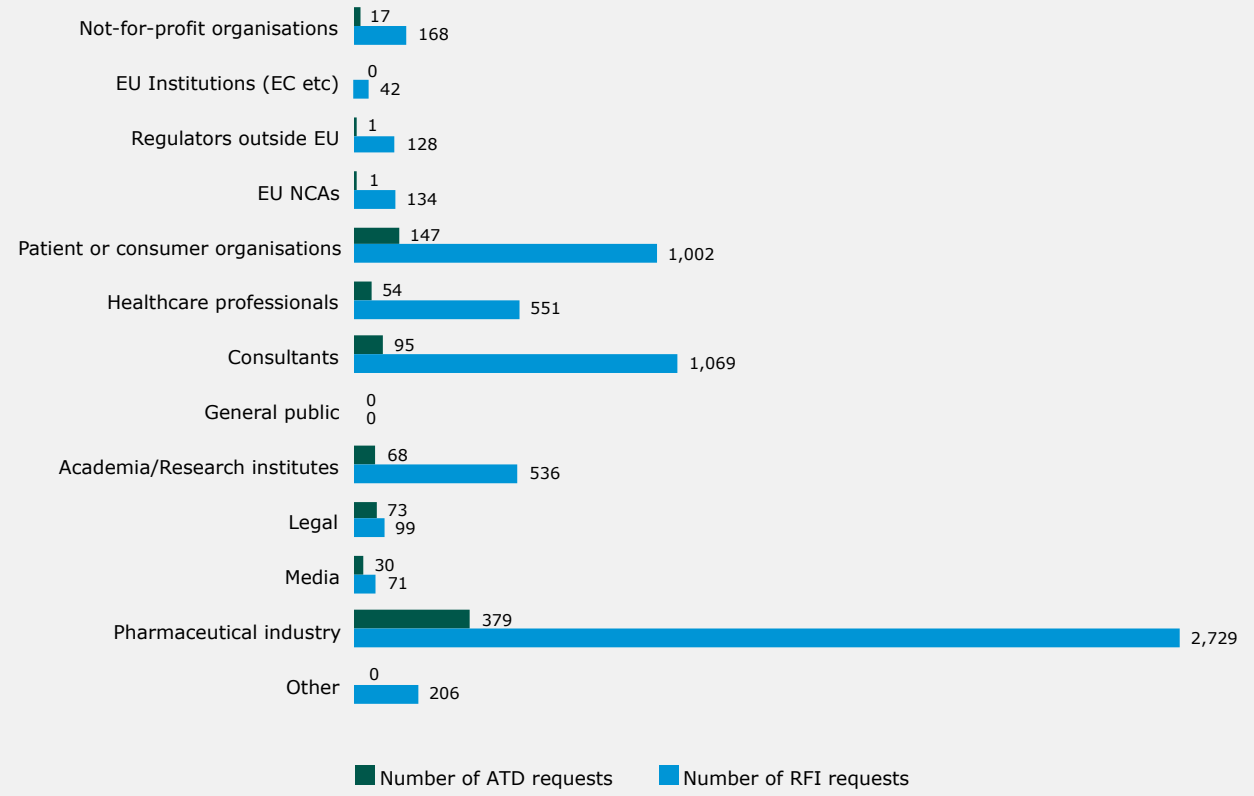
The number of requests for information increased by 40%, underlining the the Agency's enhanced visibility in recent years.





The number of pages has increased of 25% in 2017 due to a larger number of requests received and larger sizes of documents released.

Affiliation of access-to-documents and requests-for-information requesters (2017)



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

Requests for access to documents closed

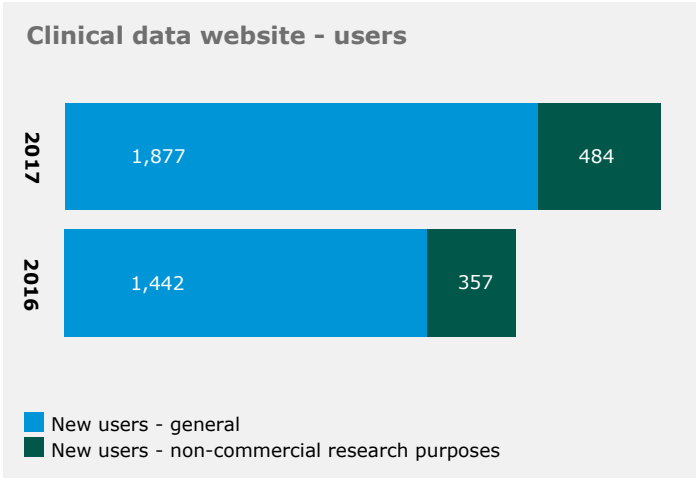
Requests for access to documents closed

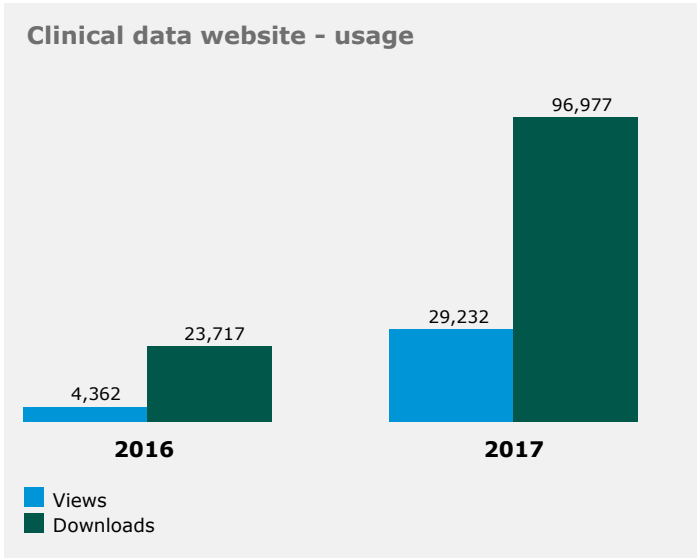
Decision	2014		2015		2016		2017	
	Initial	Confirmation application	Initial	Confirmation application	Initial	Confirmation application	Initial	Confirmation application
Fully granted	236	25	446	5	542	3	580	5
Partially granted	13	1	8	1	17	1	14	0
Refused	62	16	48	10	44	4	43	3
Total	311	42	502	16	603	8	637	8

Some of the initial requests were ongoing at the end of 2017. 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.

Publication of clinical data

In October 2016, EMA became the first regulatory authority to give open access to clinical data submitted by companies in support of their marketing authorisation applications. The chart below captures the use of the clinical data website from its launch in October 2016 to the end 2017.





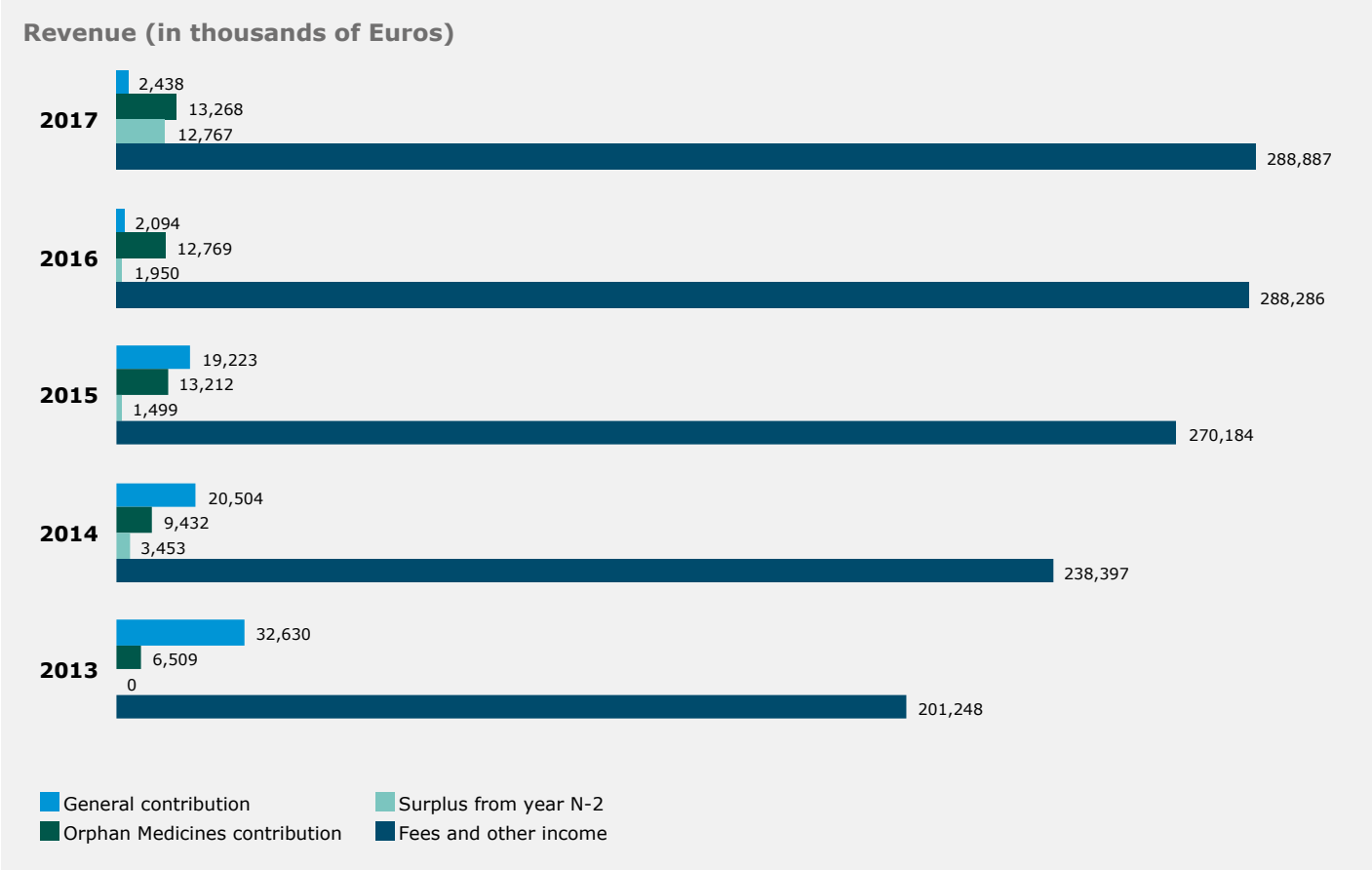
In addition, a total of 58 clinical dossiers for 55 products were published. This includes opinions and withdrawals for initial applications, line extensions and extensions of indication.

Administrative aspects

Budget

Total revenue

The Agency's total revenue in 2017 was €317,360,000 compared to €305,099,000 in 2016.

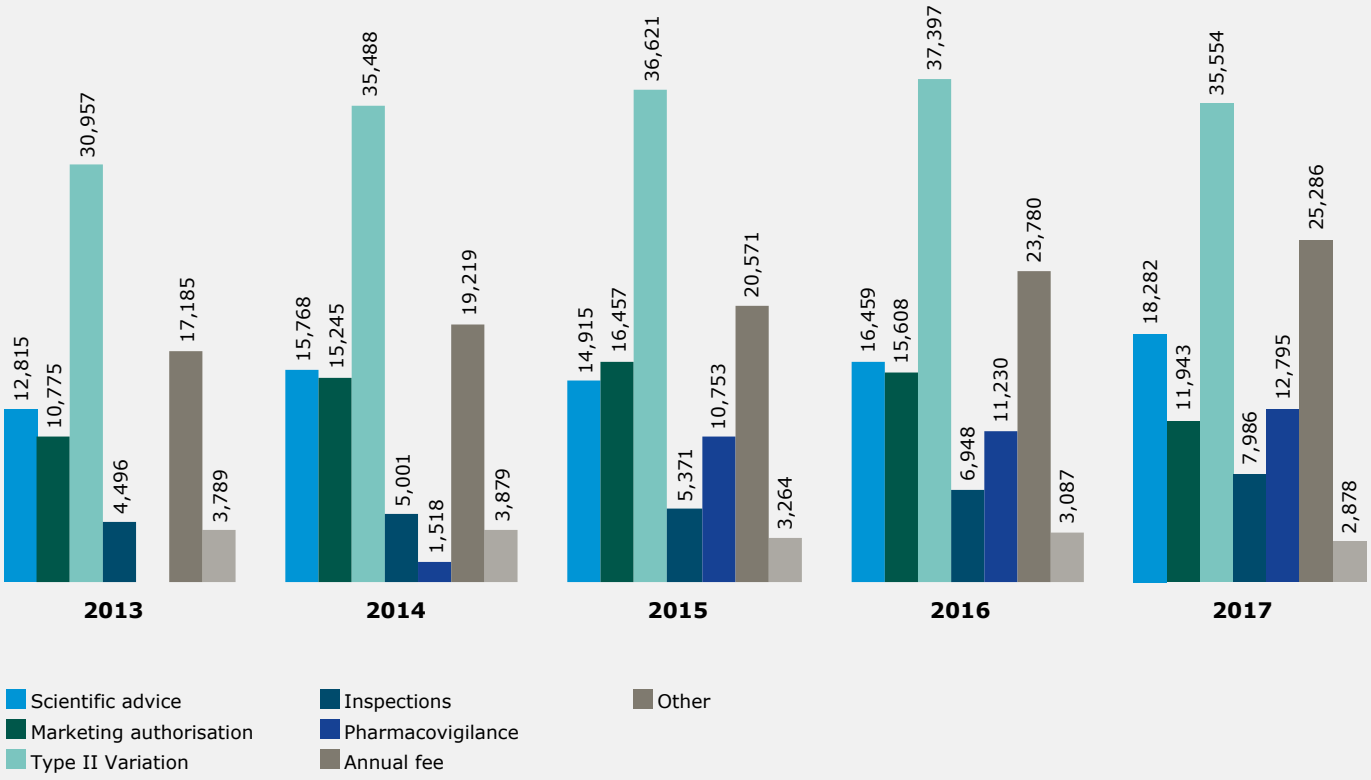


Expenditure (in thousands of euros)	2013	2014	2015	2016	2017
Staff expenditure	77,552	91,344	103,651	110,729	106,793
Infrastructure	62,056	55,251	49,422	40,407	49,364
Operational expenditure	103,811	119,825	142,082	145,777	151,668
Total	243,419	266,420	295,154	296,913	307,825

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.

Renumeration to national competent authorities per fiscal year (in thousands Euros)



In 2017, EMA paid a total of €114,724,000 to the national competent authorities, compared to €114,509,000 in 2016.

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.

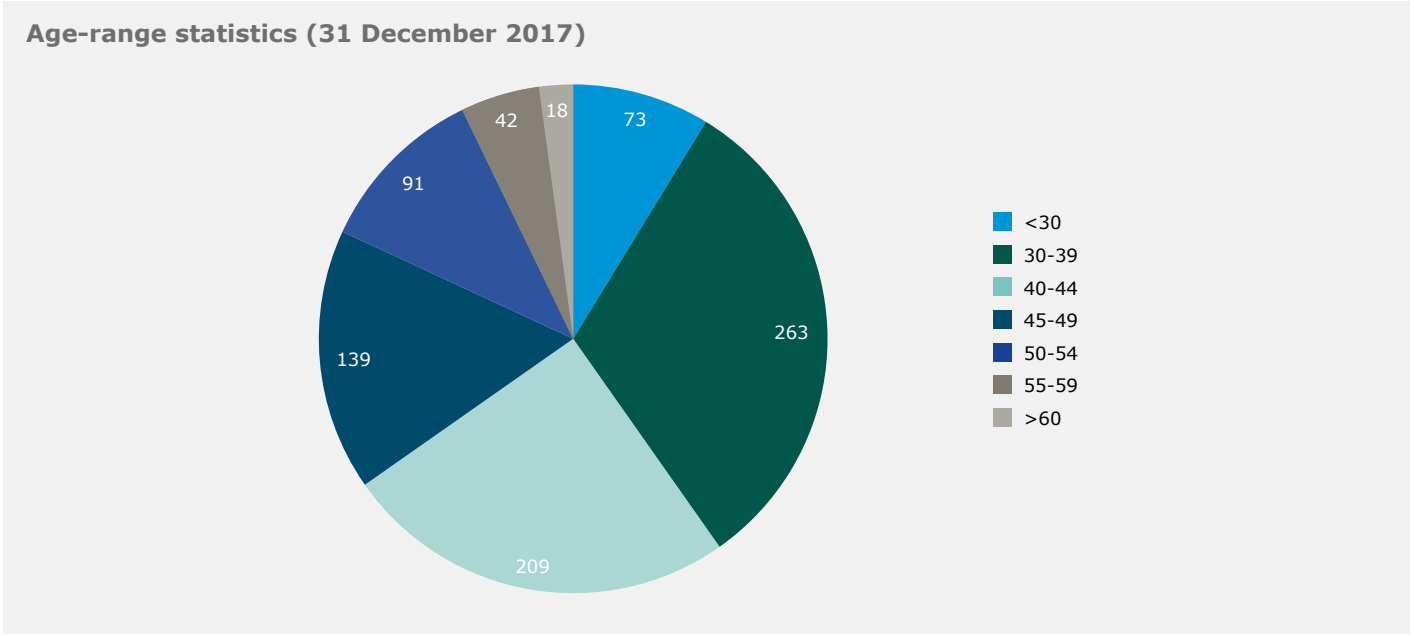
KPI	Description	Units	2013	2015	2016	2017
Energy efficiency	Electricity consumption	kWh	3,406,245	3,546,829	3,266,036	3,087,933
		kWh/m^2	163	145	133	126
Resource efficiency	Water consumption	m^3	5,130	2,607	1,345	1,525
	Paper consumption	metric tonnes	42	27	23	20
Waste management	Recycled waste	metric tonnes	67	73	46	51
	Non-recyclable waste	metric tonnes	87	54	32	36
Carbon footprint	Greenhouse gas emissions	CO_{2e}	2,679	2,843	2,854	2,903

Agency staff

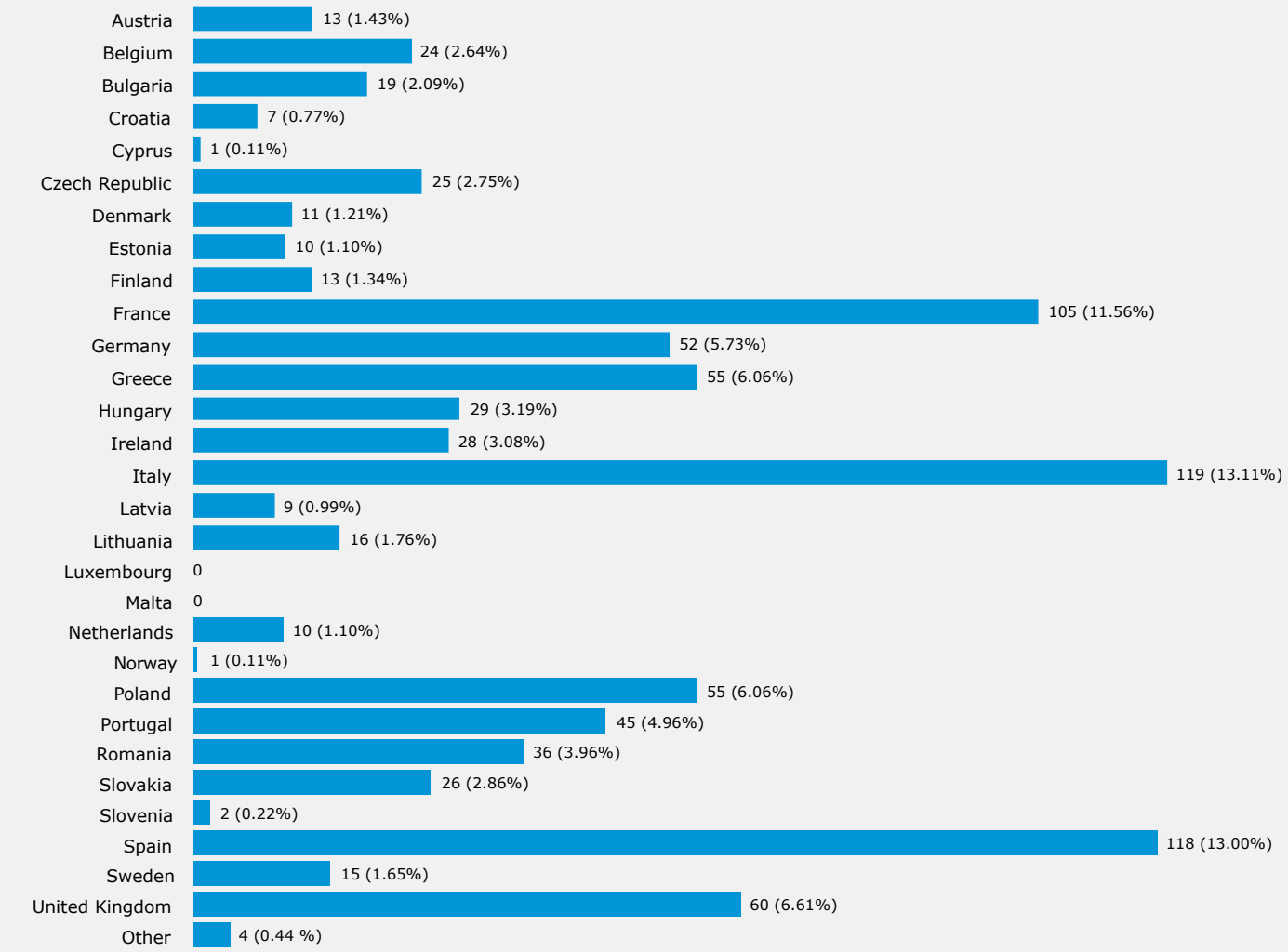
As of December 2017, Agency staff numbered 908: 645 women, 263 men.

Gender balance 2017

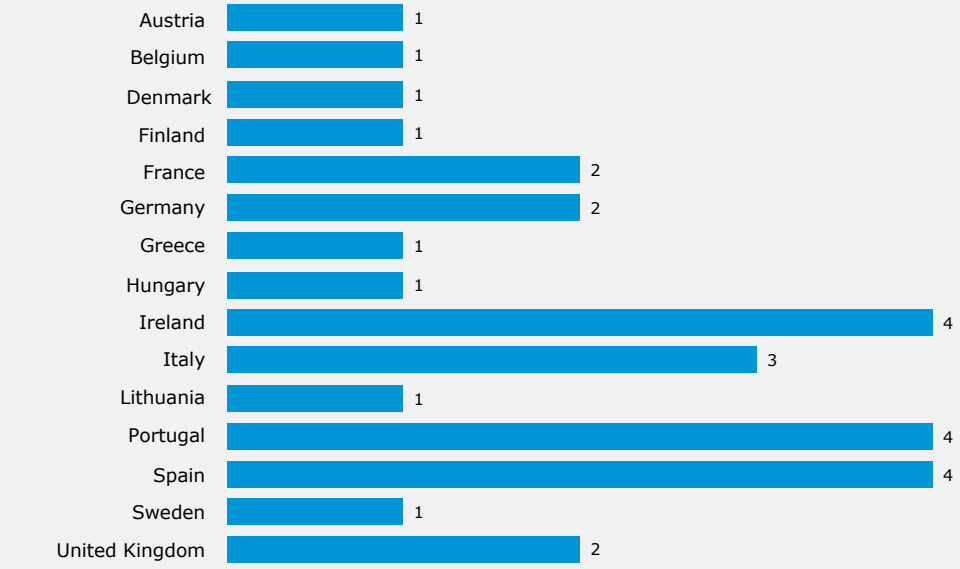
Status	Category AD (administrators)		Category AST (assistants)		All grades	
	Men	Women	Men	Women	Men	Women
Temporary agents	47%	53%	14%	86%	33%	67%
Contract agents	32%	68%	12%	88%	20%	80%
Total	45%	55%	13%	87%	30%	70%



National origins of Agency staff (2017)



National origins of Agency management (2017)



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.

Notes

Notes

Notes

Annexes

Annex 1 – Members of the Management Board

Annex 2 – Members of the Committee for Medicinal Products for Human Use

Annex 3 – Members of the Pharmacovigilance Risk Assessment Committee

Annex 4 – Members of the Committee for Medicinal Products for Veterinary Use

Annex 5 – Members of the Committee on Orphan Medicinal Products

Annex 6 – Members of the Committee on Herbal Medicinal Products

Annex 7 – Committee for Advanced Therapies

Annex 8 – Members of the Paediatric Committee

Annex 9 – Working parties and working groups

Annex 10 – CHMP opinions: initial evaluations and extensions of therapeutic indication

Annex 11 – Guidelines and concept papers adopted by CHMP

Annex 12 – CVMP opinions on medicinal products for veterinary use

Annex 13 – Guidelines and concept papers adopted by CVMP

Annex 14 – COMP opinions on designation of orphan medicinal products

Annex 15 – HMPC European Union herbal monographs

Annex 16 – PDCO opinions and EMEA decisions on paediatric investigation plans and waivers

Annex 17 – Referral procedures overview – human medicines

Annex 18 – Arbitrations and referrals – veterinary medicines

Annex 19 – Budget summaries 2016–2017

Annex 20 – European Medicines Agency Establishment Plan

Annex 21 – Access to documents requests

Annex 22 – Publications by Agency staff members and experts in 2017

The annexes can be found on the Agency's website

European Medicines Agency

30 Churchill Place
Canary Wharf
London E14 5EU
United Kingdon

Telephone +44 (0)20 3660 6000
Fax +44 (0)20 3660 5555
Send a question www.ema.europa.eu/contact

www.ema.europa.eu

Annual report 2017