EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual Report 2018

The European Medicines Agency's contribution to science, medicines and health in 2018

An agency of the European Union

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Mission statement

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

Guiding principles

- We are strongly committed to public and animal health.
- We make independent recommendations based on the best scientific evidence, using state-of-the-art knowledge and expertise in our field.
- We support research and innovation to stimulate the development of better medicines.
- We value the contribution made by our partners and stakeholders to our work.
- We assure continual improvement of our processes and procedures, in accordance with recognised quality standards.
- We adhere to high standards of professional and personal integrity.
- We communicate in an open, transparent manner with all of our partners, stakeholders and colleagues.
- We promote the well-being, motivation and ongoing professional development of every member of the Agency.

Principal activities

Working with the Member States and the European Commission (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 to 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 delighted to introduce EMA's annual report for 2018 – the year in which we celebrated the 100th meeting of the Agency's Management Board.

The year 2018 was another challenging year for the Agency, with Brexit featuring on the agenda of every meeting of the Board. Our discussions focused mostly on EMA's business continuity planning and staff retention measures, the second because it is important that a high percentage of EMA staff move with the Agency to the Netherlands. The physical relocation of the Agency to the Netherlands in 2019 was also an important topic.

In November, with a delegation of the Board, I visited EMA's future premises in Amsterdam and we were reassured about the progress made in terms of delivering new premises on time and to a high standard. Another memorable moment was when Guido Rasi and I signed EMA's new Seat Agreement on behalf of the Board in June. This was an important step in the relocation of EMA from London to Amsterdam, ensuring that the Agency can function properly and independently in the Netherlands.

To prepare for the withdrawal of the United Kingdom from the European Union, all Member States made significant efforts in 2018 to step up their capacity so that the work that is currently done by 28 Member States can be carried out by 27 countries in the future. The UK's workload relating to human and veterinary medicines was reallocated across the network. As of April, over 370 centrally authorised products (CAPs) had been transferred from the UK to new rapporteurs and co-rapporteurs from the EU27 Member States, plus Iceland and Norway.

There is no doubt that the UK's expertise in the network will be missed, but we are working hard to fill the gap. The EU Network Training Centre (EU NTC) has been indispensable in this regard. We have been looking at what kind of expertise will now be missing within the EU27 and have developed several new curricula in different fields of medicine regulation. Experts are now delivering the training.

In the interest of patients, we also have to do our utmost to avoid shortages of medicines as a result of Brexit or for any other reason. This is a topic that is really close to my heart – it is vital that the medicines that we authorise are available to patients. EMA and the Heads of Medicine Agencies held a joint workshop in November to gather perspectives from different stakeholders on how to better address potential problems with the supply of medicines. This workshop offered an excellent platform for us to start discussing solutions.

It is not just Brexit that kept us busy in 2018, as you will see in the report. There are a number of important ongoing projects that will have a significant impact on medicines regulation and clinical research. I would like to mention in particular the development of the EU's clinical trial information system, which will completely change the oversight of clinical trials in the EU. We had intensive discussions on this project in every board meeting in 2018. Although much work remains to be done, we continue to progress towards our shared goal of creating a new system that will offer a single EU entry point for clinical trial applications and will facilitate supervision of clinical trials across the EU.

On the legislative side, two major new pieces of legislation adopted by the European Parliament and Council will keep the Agency and the Board very busy in the coming years.

First, new veterinary legislation will provide a modern, innovative and fit-for-purpose legal framework, giving incentives to stimulate innovation and to increase the availability of veterinary medicines in the EU. We will need close collaboration across the entire network to implement the different elements of the legislation at the right time.

Second, the new Regulations on medical devices and in vitro diagnostic medical devices, which aim to catalyse the integration of science and technology in medicine development, will introduce new roles and responsibilities for EMA and national competent authorities (NCAs).

The period 2019 will be a year of transition for the Agency. I will do everything I can to support EMA in its valuable work to protect public and animal health in the EU.

On behalf of the Board, I would like to thank EMA and our colleagues across the network and in the Commission for all the work done in 2018 and wish the Agency all the very best for its relocation.

I hope that you enjoy reading this report.

Introduction

by Guido Rasi
EMA Executive Director

I look back at 2018 with mixed feelings. On one hand, I am very pleased about how far we have come with our preparations for Brexit and our relocation to Amsterdam. On the other hand, I am acutely aware of the sacrifices we had to make to achieve this and I am concerned that the impact of these sacrifices will be felt in the years to come.

We worked hard, together with the Dutch authorities, to ensure that the relocation of EMA before the end of March 2019 would be managed successfully. The progress made with our temporary and new permanent buildings in Amsterdam in 2018 and our joint measures aimed at supporting staff relocation give me confidence that we will be able to move to our new home smoothly without jeopardising our core duties to the citizens of the EU.

We also worked closely with the European Commission (EC) and the network to ensure an orderly redistribution of the work so far carried out by the UK. We gave detailed advice to pharmaceutical companies very early on, to help them take the necessary steps to be able to operate in the EU27 and continue to make their medicines available to patients.

All of this was possible because we implemented a phased business continuity plan during the year, which helped us to make available 82 staff members to work full-time on Brexit and relocation preparation. With the plan, we were able to protect all activities directly related to the evaluation and supervision of medicines as well as our core public health activities. However, we had to make cuts elsewhere. And while these cuts have focused mainly on suspending or postponing activities that will not have an immediate impact on public health, we cannot rule out a longer-term impact on this Agency unless the commitment is made to invest the necessary resources again in future.

Take, for instance, the development and revision of guidelines, which we had to severely reduce by the end of the year. Guidelines are one of EMA's key instruments for increasing the efficiency of medicines development in Europe. If their development or update starts to stutter, the whole system may suffer. A concrete example that underlines this point is the delay to the update of our guidelines on the development of new medicines to treat haemophilia A and B. There are exciting new developments based on novel therapies underway. However, we had to temporarily stop the revision of the current guideline to be able to concentrate on Brexit and relocation.

Another example that drives home the long-term consequences of the diversion of EMA's efforts to Brexit and relocation is the suspension of the proactive publication of clinical data. We had to take this decision just as our landmark policy started to yield the benefits we were expecting from it: enabling reassessment of data, facilitating research collaboration and increasing stakeholders' trust in the medicine evaluation process.

The final example I would like to highlight is the impact on our information systems. Our IT resources have already been stretched over many years due to the implementation of large telematics projects benefitting the whole European medicines network. Among such projects are the clinical trials information system, EudraVigilance and others. Brexit and preparation for our relocation now further delay much needed upgrades to our existing IT infrastructure, which is the backbone of our cooperation at the European level.

There is no escaping that these cutbacks have hampered, at least in the short term, the ability of this Agency to keep abreast of scientific and regulatory developments and to support research and development of medicines in Europe.

When it comes to our Brexit preparedness, however, I am very happy to report that we have not yet missed a beat. This is thanks to a tremendous planning exercise in 2018, on which Noël Wathion, EMA's Deputy Executive Director, will elaborate later in this annual report.

Despite these reservations, 2018 saw many advances regarding new medicines. Our PRIority MEdicines (PRIME) scheme started to deliver for patients, as the first two medicines supported through the programme received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for approval in the EU. These two medicines belong to a new generation of personalised immunotherapies called CAR T-cells.

Altogether, EMA recommended the authorisation of 84 new medicines for human use, including 42 with a new active substance. Many represented significant progress in their therapeutic areas.

EMA continued to work hard to ensure the safety and efficacy of medicines on the market. The discovery of impurities classified as probable human carcinogens (substances that could cause cancer) in certain sartan

blood pressure medicines led to an extensive review. This review explored the root cause of the presence of these impurities, their possible impact on patients and possible measures to reduce or eliminate these impurities from future batches. The response to this major incident showed the strength of EMA and the EU network, which acted promptly, transparently and in coordination with international partners to ensure patients' safety.

In 2018, we organised our second public hearing, reinforcing our commitment to always focus on the benefit for patients. We listened to the views and experiences of patients and the general public on the possible side effects reported with quinolones and fluoroquinolones, a class of antibiotics widely prescribed in the EU. These views greatly enriched the review carried out by the Pharmacovigilance Risk Assessment Committee (PRAC).

In the veterinary area, EMA recommended 10 medicines for marketing authorisation. Of these, four had a new active substance and three were vaccines. The fight against antimicrobial resistance (AMR) continued to be a priority. The eighth edition of our annual report on the sales of veterinary antibiotics showed that sales of antibiotics for use in animals in Europe fell by 20% between 2011 and 2016. While this is good news, we also see that the situation across the EU is patchy and a lot of work remains to be done to slow down the development of resistance. The new veterinary legislation, with its focus on AMR, will support these efforts.

We saw that 2018 was a year in which we initiated a reflection on the future of medicines' regulation. We had to start this reflection at this time, despite the challenge of Brexit, because of the dramatic acceleration of the pace of innovation in the last few years. Regulators need to be ready to assess increasingly complex medicines that often deliver healthcare solutions by converging different technologies, including, for example, diagnostics, devices or apps. To continue to do our job, we must make sure that we have the right skills and expertise to keep up with these scientific and technological developments. This is why we published our strategic reflections for a regulatory science strategy to 2025 for a six-months public consultation in December.

All in all, 2018 was challenging for all of us. We had to prepare our departure from the UK, a country that was a gracious host to EMA for twenty-four years and whose experts have made a significant contribution to the regulation of medicines. But 2018 was also the year which has proven the robustness and flexibility of an EU network that concentrated on its 'raison d'etre' which is to protect and advance public health at any time. I would like to thank all those who contribute to EMA's work: the members of its scientific committees, the working parties and scientific advisory groups (SAGs), the Management board and the national experts, the EC and of course EMA's staff. This last group stayed focused on their tasks, despite the fact that they all had manage their own personal relocation and deal with numerous individual challenges.

Chapter 1
Key achievements in 2018

The Agency’s activities to protect and promote the health of people and animals in the European Union and highlights of major achievements in 2018

Evaluation and monitoring of medicines—highlights

EMA is responsible for the scientific evaluation, supervision and safety monitoring of centrally authorised medicines in the EU. Since its foundation in 1995, EMA has recommended authorisation of over 1,200 medicines for use in humans and over 200 for use in animals. The Agency also coordinates the EU pharmacovigilance system, which monitors the safety of around 500,000 medicines on the EU market.

This section provides an overview of some of EMA's major recommendations on medicines in 2018. These include recommendations to grant new EU-wide marketing authorisations for medicines that are expected to bring significant benefits to patients and animals. They also include 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

AUTHORISATION OF NEW MEDICINES IN 2018

In 2018, EMA recommended 84 medicines for marketing authorisation. Of these, 42 had a new active substance, i.e. one that had not previously been authorised in the EU.

Some of the medicines approved in 2018 represent a significant advance in their respective therapeutic areas:

Advanced therapy medicinal products:

Kymriah and **Yescarta**, the first two chimeric antigen receptors (CAR) T-cell therapies in the EU intended for the treatment of certain blood cancers. Kymriah and Yescarta are also the first medicines supported through EMA's PRIME scheme that received a positive opinion from the CHMP.

Luxturna, for the treatment of adults and children with inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness.

Medicines for children:

Kigabeq, a new paediatric-use marketing authorisation (PUMA) for the treatment of infantile spasms (West's syndrome) and resistant partial epilepsy.

Slenyto, a new PUMA for the treatment of insomnia in children and adolescents with autism spectrum disorder or Smith-Magenis syndrome.

Amglidia, for the treatment of diabetes mellitus in newborns, infants and children.

Rare diseases:

Lamzede, long-term enzyme replacement therapy in adults, adolescents and children with mild to moderate forms of alpha-mannosidosis.

Mepsevii, for the treatment of mucopolysaccharidosis type VII.

Namuscla, for the treatment of myotonia in adult patients with non-dystrophic myotonic disorders. This is the first treatment for this disease to be authorised EU-wide.

17 January

EMA starts publishing an orphan maintenance assessment report (OMAR) for every orphan-designated medicine that has been recommended for marketing authorisation by the Agency.

1 February

EMA releases a draft revised guideline on the safety and efficacy follow-up and risk management of advanced therapy medicinal products (ATMPs) for a three-month public consultation.

Four medicines (Hemlibra, Onpattro, Tegsedi and Takhzyro) received a recommendation for marketing authorisation following an accelerated assessment. This mechanism is reserved for medicines that address unmet medical needs. It allows a faster assessment of eligible medicines by EMA's scientific committees by cutting the maximum number of days needed for the evaluation by 60, from 210 days to 150 days.

One cancer medicine, Rubraca, received a recommendation for a conditional marketing authorisation (CMA), one of the mechanisms in the EU to give patients early access to new medicines. As this medicine addresses an unmet medical need, conditional authorisation allows early approval on the basis of less complete clinical data than is normally required. This authorisation is subject to specific postauthorisation obligations to ensure that the pharmaceutical company generates complete data on the medicine.

In addition, the CHMP issued negative opinions on five medicines in 2018. In these cases, the CHMP could not conclude that the benefits of the medicine outweighed the risks.

Some 93% of all opinions (positive and negative) were reached by consensus among the 28 CHMP members, meaning that following in-depth discussions, the experts agreed on all aspects of the marketing authorisations. Around 69% of applicants who received a positive opinion for their medicine had received scientific advice from EMA during the development phase of their product. This early engagement with developers allows EMA to clarify what kind of evidence is required to evaluate a medicine for authorisation, and so protects patients from taking part in unnecessary or poorly designed clinical trials.

Monitoring the safety of medicines

Once a medicine has been put on the market, EMA and the EU Member States continuously monitor the quality and the benefit-risk balance of the medicine. The aim is to optimise the safe and effective use of the medicine, to achieve its full benefit and to protect patients from avoidable adverse effects. If the benefit-risk balance of a medicine changes, EMA can recommend regulatory measures that range from an amendment of the product information to the suspension or withdrawal of a medicine. The Agency can also recommend recalling batches of the medicine concerned.
Important new safety advice issued in 2018 included:

- Removal from the market of multiple sclerosis treatments containing **daclizumab** (Zinbryta and Zenapax) due to serious and sometimes fatal cases of autoimmune encephalitis.
- Recommendation to suspend some **quinolone and fluoroquinolone antibiotics** and introduce changes including restrictions on the use of all other antibiotics of this type following a review of disabling and potentially permanent side effects reported with these medicines.
- Warnings for **fluoroquinolone antibiotics** about the rare risk of aortic aneurysm and dissection.
- Recommendation of measures to avoid exposure of babies in the womb to **valproate medicines**, because exposed babies are at high risk of malformations and developmental problems.
- Recommendation to restrict the use of **retinoid medicines** during pregnancy. The review confirmed that all oral retinoids can harm the unborn child.
- Recommendation of measures to minimise the risk of rare but serious liver injury with **Esmya** (ulipristal acetate), a medicine for the treatment of moderate to severe symptoms of uterine fibroids.

6 February

The General Court delivers three landmark rulings for EMA, upholding EMA's decisions to release documents requested in accordance with Regulation (EC) No 1049/2001, the Transparency Regulation.

9 February

CAR-T Cell Therapy Registries Workshop

Monitoring the safety of medicines continued

- Recommendation to restrict the use of **Keytruda** (pembrolizumab) and **Tecentriq** (atezolizumab) as first line-treatments for urothelial cancer (cancer of the bladder and urinary tract) to patients with high levels of the protein PD-L1.
- Recommendation to restrict the use of **Xofigo** (radium-223 dichloride) to patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments, in view of the risk of early death and fractures in some patients.
- Warnings for the HIV treatment **dolutegravir** (Tivicay) regarding the possible risk of neural tube defects following exposure in very early pregnancy.
- Warning to healthcare professionals that **sildenafil** (Revatio, Viagra) was associated with an increased risk of pulmonary hypertension and death in infants exposed in utero in a clinical trial on growth retardation (off label).
- Warning to healthcare professionals that **rivaroxaban** (Xarelto) was associated with increased mortality, bleeding and clots in patients treated in a clinical trial for trans-catheter aortic valve replacement (off label).
- Recommendation of risk minimisation measures for use of **hydroxyethyl starch** (HES) solutions in patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill because of an increased risk of kidney injury and mortality. Measures include training, controlled access and a warning on the packaging.
- Recommendation to harmonise the maximum daily dose of the painkiller **metamizole** and the contraindications to its use in pregnancy or women who are breastfeeding. Marketed in many EU Member States, this medicine may occasionally cause severe side effects, such as effects on the blood.

Product information for 414 centrally authorised medicines was updated on the basis of new safety data in 2018. Furthermore, every year, PRAC recommendations on safety warnings are included in the product information of many thousands of nationally authorised products (NAPs). The revised information is expected to help patients and healthcare professionals to make informed decisions when using or prescribing a specific medicine.

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

Medicines development and manufacturing are global activities. It is important for regulators to ensure that EU standards are adhered to no matter where clinical trials or manufacturing take place.

In 2018, EMA started a review of the blood pressure medicines candesartan, irbesartan, losartan, olmesartan and valsartan in relation to impurities found in some batches of these medicines. Based on animal studies, the impurities detected, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), are classified as probable human carcinogens.

The review evaluated the root causes of the presence of these impurities, their possible impact on patients and what measures can be taken to reduce or eliminate these impurities from future batches. The CHMP also requested inspections of impacted manufacturing sites and sampling and testing of products available on the EU market. Some medicines covered by this review were recalled and are no longer marketed in the EU.

The CHMP adopted a negative opinion (refusing to recommend marketing authorisation) for a medicine for which a GCP (good clinical practice) inspection reported non-compliance issues with the clinical study submitted.

26 February

Publication of the report on EMA's actions to support the implementation of the 3Rs principles for the more ethical use of animals in medicine testing across the EU.

28 February

EMA adopts a revised guideline on clinical studies for medicines that target Alzheimer's disease.

Veterinary medicines

AUTHORISATION OF NEW MEDICINES IN 2018

In 2018, EMA recommended 10 veterinary medicines for marketing authorisation. Of these, four had a new active substance, i.e. one that had not previously been authorised in the EU, and three were vaccines.

The recommendations include:

Two vaccines that have the potential to reduce the need for antimicrobial treatment in food-producing animals and could therefore limit the development of AMR. **Ubac** intends to treat clinical mastitis (udder infections with visible signs in milk or the udder) caused by a bacteria called Streptococcus uberis in cows and heifers, which can reduce milk production. **Evant** is used to immunise chicks from the age of one day against coccidiosis, a disease of the gut caused by parasites, which results in reduced growth, severe diarrhoea, reduced egg production and a high death rate.

Arti-Cell Forte, Dany's BienenWohl and **Clevor**, recommended for marketing authorisation under EMA's minor-use-minor-species (MUMS)/limited market policy. 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.

Arti-Cell Forte is the first stem cell-based veterinary medicine intended to reduce mild-to-moderate and recurrent lameness associated with non-septic joint inflammation in horses. Dany's BienenWohl is a powder and solution intended for the treatment of honey bees in hives infested by a parasite called the varroa mite. Clevor is a veterinary medicine used to induce vomiting in dogs and applied as an eye drop.

Isemid, a new cardiovascular product intended for the treatment of clinical signs related to congestive heart failure in dogs, including pulmonary oedema.

Monitoring the safety of veterinary medicines

Once a veterinary medicine has been put on the market, EMA and EU Member States continuously monitor the quality and benefit-risk balance of the medicine. The aim is to optimise the safe and effective use of the veterinary medicine, to achieve its full benefit and to protect animals and users from avoidable adverse effects. If the benefit-risk balance of a veterinary medicine changes, EMA can take regulatory measures that range from an amendment of the product information to the suspensionor withdrawal of a medicine. The Agency can also recommend recalling batches of the medicine concerned.

Important new safety advice issued in 2018 included:

- Veterinary medicines containing **enrofloxacin** for chickens and/or turkeys should no longer be used for treatment of infections caused by E. coli.
- If **diethanolamine** is to be further used in veterinary medicinal products for any food-producing species, a maximum residue limit (MRL) evaluation will be required as a safety review could not rule out a risk for consumers.
- Histamine levels in **gentamicin-containing veterinary medicines** for horses need to be carefully controlled, with inclusion, where relevant, of a histamine limit in the active substance to minimise the possibility of adverse events (AEs).
- Inclusion of systemic and hypersensitivity reactions in the information on potential side effects of **Versican Plus L4, Versican Plus PiL4** and **Versican PiL4R** vaccines for dogs.
- Addition of special precautions and warnings in the product information for **Bravecto** to ensure the safety of the person handling and administering the treatment to dogs or cats.
- Inclusion of information on potential side effects, such as anxiety or behavioural disorders, in the

1 March

The mutual recognition agreement (MRA) between the EU and the United States (US) recognises inspections in Czechia, Greece, Hungary and Romania of sites manufacturing human medicines.

1 March

Ivo Claassen is nominated Head of the Veterinary Medicines Division.

7 March

Second anniversary of PRIME. On 7 May 2018, a two-year report summarising the main results of the scheme is published.

product information on the treatment of epilepsy in dogs for **Pexion**.

- Warnings and advice for **Osurnia**, regarding accidental eye exposure in the treated animal or accidental ingestion and skin contact in people handling the treatment.
- Addition of further advice in the product information for **Suvaxyn Circo+MH RTU** in case of accidental self-injection by the person administering the product.
- Addition of further advice in the product information for **Eryseng** and **Eryseng Parvo** on potential side effects following administration in pigs, such as anaphylactic-type reactions.
- Amendment of the product information on potential side effects following administration of **Cytopoint** regarding gastrointestinal reactions in treated dogs.
- Addition of instructions to the product information for **Nobilis IB4-91** to ensure the safety of the person handling and administering the treatment.
- Addition of further advice in the product information for **Rhiniseng** on potential side effects following administration in pigs, such as anaphylactic-type reactions.
- Inclusion of further advice in the product information for **Easotic** on possible hearing deterioration following administration in dogs.
- Addition of further advice in the product information for **MiPet Easecto** and **Simparica** on potential side effects following administration in dogs, such as systemic reactions.
- Addition of further advice in the product information for **Zycortal** on potential side effects following administration in dogs, such as pancreas disorders.
- Amending the product information on potential side effects of **Credelio** in relation to gastrointestinal reactions in dogs.
- Addition of further advice in the product information for **Apoquel**, such as observations in changes to clinical pathology in dogs.

Product information for 14 veterinary CAPs 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 Committee for Medicinal Products for Veterinary Use (CVMP) adopted six positive opinions for extensions of existing authorisations.

Protecting consumers

If a medicine is intended to be used in a food-producing animal, it must be safe for people to eat the food that comes from this animal. The MRL recommended by EMA reflects how much residue of a veterinary medicine in food derived from a treated animal is safe for consumption. The MRL is established before the medicine for food-producing animals is authorised in the EU.

In 2018, an MRL was established for the following active substance:

- **Ovotransferrin** – in chicken tissues and eggs, and tissues of other poultry species.

MRLs were extended to further species for the following active substances:

- **Paromomycin** – extended to chicken eggs and eggs of other poultry species.
- **Isoflurane** – extended to porcine species.

16 March

EMA, in collaboration with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), publishes Revision 4 of the ENCePP Code of Conduct providing a set of recommendations to promote the scientific independence and transparency of observational research.

20 March

EMA and EC joint workshop on the Paediatric Regulation.

Preparing for Brexit and the Agency's relocation: interview with Noël Wathion

Deputy Executive Director Noël Wathion has led EMA's operational and relocation preparedness activities for Brexit since the outcome of the UK referendum in June 2016. In this interview, he looks back on the Agency's preparations for Brexit and reflects on what the project has meant for him personally.

Tell us about 24 June 2016, when you found out that the UK had voted to leave the EU.
As soon as we heard the outcome of the referendum, we knew immediately that we needed to make a plan because people were in shock. We needed to get going straightaway, so we set up EMA's Brexit Operational and Relocation Preparedness Task Force. We had to make sure that the Agency was as prepared as possible for what was to come. The task force helped us to deal with the long period of uncertainty between the outcome of the referendum and when we found out on 20 November 2017 that we were relocating to Amsterdam. Once we knew we would go to Amsterdam, the task force could simply shift gear to start preparing for the physical move.

What does the task force do?
The underlying principle is public health first. This means that the centrally authorised medicines we look after must continue to be evaluated, supervised and available in the EU no matter what happens and that patients in the EU have access to these medicines. First, we had to make sure that pharmaceutical companies had all the information they need to remain operational in the EU post-Brexit. We developed guidance with the EC to make sure it was clear what industry needed to do.

We also conducted a survey to identify the medicines that are potentially at risk of a disruption in supply. We sent the survey to the marketing authorisation holders of all 694 centrally-authorised medicines with an important step in their regulatory processes in the UK.

In addition, we had to take the necessary measures to ensure that the loss of UK expertise could be compensated for by the remaining EU27. Therefore, we needed not only to re-allocate the UK lead roles for legacy medicines but also to allocate lead roles for new applications across the EU27. I would like to emphasise that all EU27 NCAs made significant efforts to increase the availability of the necessary expertise within the European medicines regulatory network.

The task force has also been working to ensure that our relocation to Amsterdam goes smoothly and that, as an organisation, we remain operational at all times – even if we encounter considerable staff losses. Our business continuity plan, which will enter its fourth phase in January 2019, ensures that we can safeguard core activities related to the evaluation and supervision of medicines. It's never nice to tell people that they have to stop certain activities, even if only on a temporary basis, but we had to do this to preserve as far as possible our core business of protecting human and animal health and to make sure that freed-up staff could be redeployed to allow us to ensure the continuity of our operations.

How concerned are you about staff losses?
Staff retention has always been one of the greatest concerns in relation to our relocation. So far, this is quite manageable. Overall staff annual turnover is still comparable to what we have seen in previous years but the number of resignations in that figure is now greater than before. However, the biggest staff losses will be seen in the first half of 2019. We remain optimistic, though, that we will be able to fill any vacancies quickly as recent recruitment efforts have shown that a lot of qualified people are interested in coming to Amsterdam and working
for EMA.

Have there been any unexpected challenges?
If I look back, we probably underestimated the complexity of the project to a certain extent. A lot of aspects were highly interlinked and we had to work with a lot of uncertainty. We started from the worst-case scenario of the UK becoming a third country as of the end of March 2019. We also saw in staff retention surveys that we could lose a substantial amount of our workforce and we had to plan for that. We have been progressing, though – through robust planning and monitoring and taking immediate action whenever needed. We had to build in quite a lot of flexibility to be equipped to deal with sudden changes with emerging events.

What about your relationship with the Dutch authorities?
The Dutch authorities were quite well prepared. It became apparent after they won the bid to host the Agency in November 2017 that they had done a lot of preparatory work and that helped a lot. Because of the commitment and responsibility on both sides, everything is now on track for our relocation and we will complete our move into the temporary building in Amsterdam by the end of March 2019. Trust had to be built as well, and that trust has grown as the project developed.

Colleagues who have moved to the Netherlands already seem to be happy with the quality of life that they can enjoy. It's a different culture of course, but it seems to be working for people. The Dutch authorities and the City of Amsterdam have made a significant contribution to our efforts to retain staff, not least through the practical support to the people who move to Amsterdam. For instance, they have helped staff to find accommodation or a school for their children.

And the network? How has it been preparing for Brexit?
We have seen that the EU network of medicines regulatory agencies, the largest network of experts in medicines regulation in the world, is a very strong and flexible system that can adapt to changes as necessary without putting at risk the quality of its work. All Member States have already taken steps to increase their capacity so that the work that is done by 28 Member States today can be carried out by 27 countries in the future. The UK's workload related to human and veterinary medicines has been reallocated. By last April, over 370 CAPs had been transferred to new rapporteurs and co-rapporteurs from the EU27 Member States, plus Iceland and Norway.

What is the impact of the MHRA leaving the network?
Our relationship with the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and also the Veterinary Medicines Directorate (VMD) has always been excellent and personally, I am sad to see them leave the network. The UK has been one of the major contributors to the activities of the network and to the activities of the Agency and the gap they leave will have to be filled. This has never been undertaken before so we needed to find ways to ensure that the loss of expertise can be replaced - both in qualitative and quantitative terms.

We have taken a number of initiatives, always emphasising the importance of stepping up the involvement of all EU Member States, taking their capacities into account. We wanted to avoid a scenario where one or two Member States take on the full burden. Prioritising training is a pivotal factor and our programme with the EU NTC supports this. That's why it's important that Member States invest in those resources. We have started well and now we have to see whether this can be sustained over a longer period of time.

What has this project meant for you personally?
I have been at the Agency for 22 years and I care a lot that this project is a success. It would be a great shame if the future of the Agency, and on a wider scale the protection of human and animal health in the EU, was somehow jeopardised because of Brexit. I feel some kind of moral duty to give this project all I have, to put all the knowledge and experience that I have gathered over the past 22 years into this project. We need to do a lot of horizontal thinking and I have often been out of my comfort zone, obliged to deal with several issues and situations not directly linked to my previous experience and expertise.

What I appreciate a lot is that I am surrounded by very capable and committed people who have been prepared to go the extra mile to make this project a success. We have worked as a team to make sure that we are all going in the same direction. The level of dedication in defending the interests of public and animal health – and of the Agency – has impressed me. I feel proud of what we have achieved, and somewhat relieved.

Looking ahead to 2019, are you optimistic?
Yes, I am optimistic. Brexit is a major obstacle that we did not foresee and it has had a significant impact on the Agency, its staff and the network – and of course on the fact that the Agency has had to relocate to a new country. However, we cannot afford to fail and we will not. Ultimately, we have a responsibility towards patients and users of medicines.

We must also never lose sight of our longer-term objectives. There is life beyond Brexit and we see the Agency – together with the network – playing an increasingly important role in public and animal health. EMA's role will evolve over the coming years and the current changes also provide an opportunity for us to refocus, become stronger and better prepared for the scientific, technological and regulatory challenges ahead.

And what about you, will you be moving to Amsterdam?
Yes, I will be moving to Amsterdam. This will bring me closer to my roots – my family are just a train ride away in Hasselt, Belgium.

Brexit Preparedness Business Continuity Plan

In 2018, EMA implemented a Brexit Preparedness Business Continuity Plan (BCP) to ensure sufficient resources remained available for the evaluation and supervision of medicines activities to continue. This had a significant impact on many of the areas that support the regulatory processes, such as guideline development, interaction with stakeholders, communication and transparency initiatives. Concrete examples of initiatives that had to be suspended or scaled down during the course of the year can be found in this chapter in the boxes on the 'Impact of BCP'.

Key milestones in 2018

1 January

EMA enters BCP phase 2.

23 January

EMA launches a survey to gather information from pharmaceutical companies on their Brexit preparedness plans and to identify any particular concerns with regard to medicines supply that might impact public or animal health.

8 March

EMA participates in a Brexit expert seminar on pharmaceuticals with the EU 27 organised by the EC.

23 March

EMA holds an industry stakeholder meeting on Brexit preparedness for human medicines.

28 May

The main construction work on EMA's new permanent building in Amsterdam-Zuidas starts after laying of the foundations is completed.

1 June

Christa Wirthumer-Hoche (Chair of EMA's Management Board), Guido Rasi and Ambassador Johan van der Werff (on behalf of the Dutch Government) sign EMA's seat agreement with the Netherlands. It enters into force on 30 March 2019.

1 October

EMA enters BCP phase 3.

23 October

EMA participates in a Brexit expert seminar on pharmaceuticals with the EU 27 organised by the EC.

7 November

A delegation of the EMA Management Board visits the future Agency premises in Amsterdam.

28 February

EMA's Management Board accepts the offer regarding the Agency's new permanent premises in Amsterdam-Zuidas and endorses the notification to the EU's Budgetary Authority of EMA's intention to move to the new building.

5 March

EMA launches a public relocation tracking tool, giving a transparent overview of the main milestones and workstream deliverables for the Agency's move to Amsterdam.

11 April

The EU27 Member States and EMA complete the reallocation of the medicines for which the MHRA and the VMD were rapporteur or co-rapporteur.

20 April

EMA holds an industry stakeholder meeting on Brexit preparedness for veterinary medicines.

1 July

EMA publishes preliminary results of its industry survey and identifies gaps in industry preparedness for Brexit.

24 September

EMA holds an industry stakeholder meeting on Brexit and publishes updated results of the industry survey, showing that companies have stepped up their efforts to ensure medicine supply post-Brexit.

14 November

An amendment to EMA's founding Regulation (726/2004) is signed, confirming that the Agency's seat will be in Amsterdam as of 30 March 2019.

25 November

EU leaders endorse the Withdrawal Agreement and adopt the Political Declaration setting out the Framework for the Future Relationship.

Contributing to human health

EMA puts patients' needs at the centre of everything it does. Its scientific recommendations are vital to provide EU citizens with effective, safe and high-quality medicines and to provide an environment in which pharmaceutical companies can develop new medicines.

The Agency's activities and initiatives focus on improving the availability of medicines and facilitating patients' access to medicines, strengthening EMA's ability to respond to public health emergencies, and implementing measures to safeguard the supply chain and thus reduce the risk of shortages. EMA also supports innovation for a vibrant EU life-science sector that translates progress in medical science into new medicines with real health benefits for EU citizens.

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

Many patients with serious diseases have no or only unsatisfactory therapeutic options and so 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 to reach patients in the shortest time possible.

Early regulatory engagement with medicines developers helps to provide patients with timely access to new, safe and effective medicines. It protects patients and maximises the value of their involvement by ensuring that the studies in companies' development plans are appropriately designed to produce robust and useful data. Early engagement helps to minimise the administrative burden of development by ensuring that the most appropriate regulatory pathway is chosen, and by potentially allowing other decision-makers, such as health-technology-assessment (HTA) bodies and payers[1], to also provide input at an earlier stage about the type of evidence needed.

PRIME: first results for the benefit of patients

EMA's PRIME scheme was launched in March 2016 to support and optimise medicine development so that patients whose diseases cannot be treated or who need better treatment options have earlier access to new medicines that enable them to live healthier lives.

In June 2018, the first two medicines supported through PRIME received a positive opinion from the CHMP for approval in the EU. Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) belong to a new generation of personalised immunotherapies called CAR T-cell medicines. These medicines are based on the collection and modification of a patient's own immune cells and are for the treatment of blood cancer.

Innovative treatments have the potential to change the outlook for patients with cancer. However, they also come with new scientific and regulatory challenges. PRIME has an important role to play in better planning the monitoring of benefits and risks of medicines along their whole lifecycle, especially for innovative treatments. PRIME contributed to the design of a more comprehensive risk-management plan for Kymriah and Yescarta by helping the developer to identify the data needed.

[1] 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 the rules applicable to public bodies.

22 March

EMA publishes its annual bulletin on the veterinary pharmacovigilance activities carried out to monitor medicines in practice and to ensure their safe and effective use.

12 April

EMA and its European and international partners publish a report on the international active pharmaceutical ingredient (API) inspection programme.

19 April

EMA Veterinary Medicines Innovation Day.

In November 2018, EMA hosted a joint workshop with the US Food and Drug Administration (FDA) to gather stakeholders' perspectives on quality development in early access approaches requiring accelerated development, such as PRIME and Breakthrough Therapies (the corresponding FDA scheme).

From the launch of PRIME to December 2018, EMA had received and assessed a total of 215 requests for eligibility. Of these, 48 (22%) have been accepted. The requests cover a wide range of therapeutic areas. Oncology and haematology medicines make up the largest share of PRIME products, but there have also been notable submissions for medicines that cover indications in infectious diseases, neurology and psychiatric disorders.

By December 2018, the Agency had organised 40 kick-off meetings with successful applicants. The PRIME kick-off meeting is a multidisciplinary meeting to initiate interaction between the applicant, experts from the EU regulatory network and the Agency and to familiarise the expert team with the product, its development programme, timelines and planned regulatory strategy.

Developers of medicines accepted into the PRIME scheme have increasingly made use of scientific advice and protocol assistance offered by EMA, with 36 developers making use of the support, some several times. Requests for scientific advice and protocol assistance increased from 28 in 2017 to 36 in 2018.

Scientific advice is one of the Agency's key instruments for clarifying regulatory requirements to support the development of high-quality, effective and safe medicines that meet patients' needs.

Of the medicines admitted into PRIME, 42% are ATMPs, which have the potential to reshape the treatment of a wide range of conditions. A large proportion of these medicines are being developed by small and medium-sized enterprises (SMEs). These often lack experience in the regulatory approval process and can receive valuable guidance through the scheme.

A detailed analysis of how the criteria for eligibility to the scheme have been applied and what type of support applicants have received so far has been published in a report that summarised the first two years of PRIME.

> “With PRIME we have established a platform that promotes the development of promising medicines for unmet medical needs and at the same time addresses the complexity of medicine development. Through PRIME, we offer early and enhanced dialogue to enable the generation of better data and more robust evidence on a medicine's benefits and risks.”

Guido Rasi
EMA's Executive Director

26 April

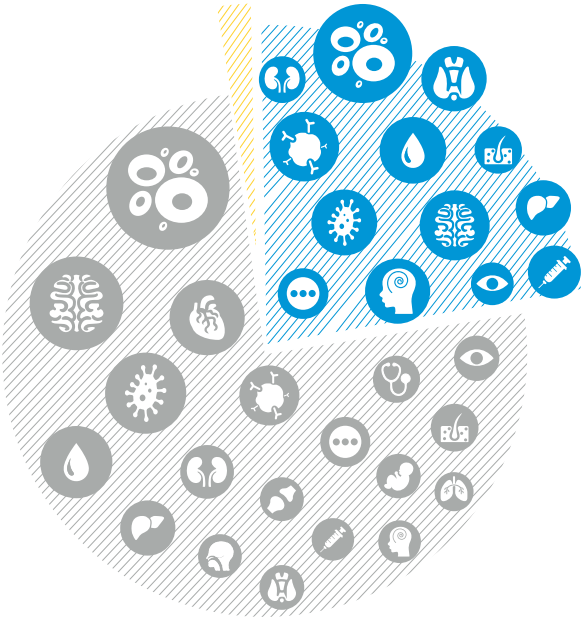
EMA releases a revised guideline on the clinical evaluation of vaccines for a six-month public consultation.

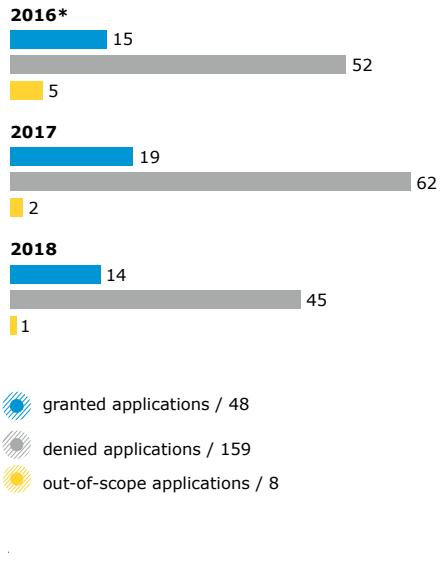
29-30 May

EMA, together with RD-ACTION (the European Joint Action for Rare Diseases) and DG SANTE of the EC, organise a workshop to explore how to work with the European Reference Networks (ERNs) in the field of complex and rare diseases.

PRIME key figures from March 2016 to December 2018

Applications and eligibility decisions





Therapeutic areas 2018

- Cardiovascular diseases — *3 denied*
- Dermatology — *3 denied*
- Neurology — *3 granted / 1 denied*
- Oncology — *1 granted / 15 denied*
- Ophthalmology — *1 granted / 1 denied*
- Endocrinology-gynaecology-fertility-metabolism — *2 granted / 3 denied*
- Gastroenterology-hepatology — *1 denied*
- Haematology-haemostaseology — *1 granted / 2 denied*
- Immunology-rheumatology-transplantation — *1 granted / 3 denied*
- Infectious diseases — *1 granted / 3 denied*
- Neonatology-paediatric intensive care — *1 denied*
- Other — *1 granted / 2 denied*
- Pneumology-allergology — *2 denied*
- Psychiatry — *2 denied*
- Uro-nephrology — *1 granted / 3 denied*
- Vaccines — *2 granted*

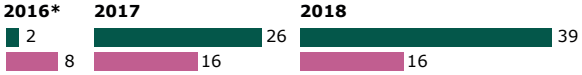
Type of applicant

Scientific advice and kick-off meetings

The Agency provided support to PRIME products through:

39 scientific advice procedures in 2018

16 multidisciplinary kick-off meetings in 2018



- Scientific advice procedures
- Kick-off meetings

*Data collected between May – December 2016

Other figures

22% of applications are accepted in the scheme

42% of medicines admitted in the scheme are Advanced Therapy Medicinal Products (ATMPs)

3 marketing authorisation applications for PRIME-designated products were submitted in 2018

2 CHMP positive opinions for PRIME products in 2018

Supporting innovative medicines

New and exciting medicines are getting close to marketing authorisation application. It is no surprise that ATMPs, frequently addressing unmet medical needs, are heavily represented in PRIME. While just three such products were authorised in 2018, the year saw a high number of activities to prepare the way forward. These are collected in an action plan, jointly launched by EMA and the EC's Directorate-General for Health and Food Safety (DG SANTE) in 2017. The aim of the plan is to improve the regulatory environment for ATMPs, thereby facilitating the development and authorisation of these products in the EU for the benefit of patients.

The plan contains 19 wide-ranging actions in key areas targeting challenges, identified by various stakeholders, at all stages of development, including manufacturing, early and later phases of development, marketing authorisation processes and the post-marketing setting. Actions include the streamlining of procedures to better address the specific requirements of ATMP developers, reduction of the administrative burden by adapting recommendations on manufacturing requirements, supporting exchanges of information with relevant stakeholders including inspectors, and several training and communication initiatives. Progress was made in all areas, and the plan was updated in April and November.

Prospectively optimising evidence generation

Evidence is the basis for decision-making on medicines. Ensuring that medicines development leads to robust and scientifically sound evidence for assessment by regulators is vital for the protection of public health. Beyond plans for individual medicines, there are opportunities to qualify innovative methodologies for use across development programmes for a range of medicines. This includes the identification of novel endpoints, the use of digital technologies and data collection using platforms such as patient registries.

The introduction of digital technologies in clinical development of medicines opens up new ways of capturing patient experiences of medical intervention. Wearable technologies are increasingly used for this purpose. It is important to ensure that the data collected is adequate to document a meaningful clinical benefit. With various regulatory, scientific and operational challenges surrounding such technologies, their qualification is an important milestone.

One example in 2018 was the qualification of stride velocity 95th centile measured by a wearable device at the ankle as an acceptable way to measure the ability to walk in patients with Duchenne muscular dystrophy. The qualification opinion supports this outcome measure as a secondary endpoint for regulatory decision-making. In terms of data capture, the acceptability of direct data capture from an electronic source (eSource Direct Data Capture) is expected to facilitate the conduct of clinical studies. Both methodologies can be applied across different product developments and have been published for a wider public consultation.

Prospective design of evidence generation is equally important to capture of information on the medicine once it is licensed. Patient registries represent one of several possible approaches to generate post-licensing evidence. In 2018, two specific patient registries were qualified for generating data that can be used in the context of regulatory decision-making. The qualification of patient registries from the European Cystic Fibrosis Society (ECFSPR) and the European Society for Blood and Marrow Transplantation (EBMT), allow data collection for pharmacoepidemiological studies for regulatory purposes. The quality of the registries facilitates data capture along the medicines' lifespan and better use of real-world data (RWD). It also provides opportunities to collaborate with other decision-makers, such as HTA bodies.

Boosting the development of medicines for children

Ensuring that the needs of children are addressed in the development and supervision of medicines remains an important public health priority for EMA. The EU Paediatric Regulation, which has been in place for over 10 years, has changed the mind-set regarding the need to study medicines in children as well as adults. The Paediatric Regulation has had a positive impact on the treatment of children with conditions such as infectious diseases or rheumatological conditions.

1 June

Two more EU Member States benefit from EU-US mutual recognition agreements for inspections: Lithuania and Ireland.

6 June

The CVMP adopts the first revision of its recommendation for the basic surveillance of medicines for animals in EudraVigilance Veterinary (EVVet).

Although research in children is no longer an afterthought but standard practice in the development of medicines, there are still some therapeutic areas, such as oncology or neonatology, where the changes brought about by the Regulation have not been as effective. To address these and other challenges identified by the EC's report 'State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation', EMA and the EC's DG SANTE adopted a joint action plan in October 2018, taking into account ideas and feedback collected at the 'EMA-EC multi-stakeholder workshop to further improve the implementation of the Paediatric Regulation' held at EMA on 20 March 2018.

The actions are clustered around five key areas:

- identifying paediatric medical needs;
- strengthening cooperation between decision-makers;
- ensuring timely completion of paediatric investigation plans (PIPs);
- improving the handling of PIP applications;
- increasing transparency around paediatric medicines.

It is expected that the implementation of the plan will increase the efficiency of paediatric regulatory processes in the current legal framework and boost the availability of medicines for children.

10th annual Enpr-EMA workshop

Research into medicines for children is supported by the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), which held its annual workshop on 7 and 8 June 2018. Enpr-EMA is a network of investigators, research networks and centres with recognised expertise in performing clinical studies in children, aiming to foster high-quality, ethical research in children.

This year's workshop marked the 10th anniversary of the network, which now includes 46 members. The opening addresses by Enrica Alteri, Head of the Human Medicines Research & Development Support Division of EMA, and by Mark Turner, Co-Chair of Enpr-EMA, highlighted the success of the network, which has grown substantially and expanded beyond Europe with the inclusion of networks from the US, Canada and Japan. In 2018, among other activities, Enpr-EMA provided input to the paediatric action plan, which now includes several initiatives supported by Enpr-EMA expertise. Among such initiatives are the increase in global interactions between regulators and networks, preparedness considerations for paediatric trials, information on assent/consent forms, and training of research nurses.

Towards a global approach for new antibiotic development

The lack of treatment options for infections caused by drug-resistant bacteria is cause for growing alarm for public health authorities worldwide. There is an urgent need for new medicines and treatment approaches. EMA has been working with its international partners, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the FDA for several years to explore and agree how to align data requirements as much as possible. This will allow medicine developers to design clinical trials that meet the evidence needs of multiple regulatory agencies.

A particular focus of the tripartite work is the development of new antibiotics for children. On 21 and 22 June 2018, the three regulatory agencies co-organised a workshop in London to discuss the topic.

The workshop provided an opportunity for international regulators, medicine developers, clinicians and clinical trial investigators to explore clinical development plans that would allow the timely development of antibiotics for children and to discuss a regulatory pathway for their approval.

Increased transparency on orphan medicinal products

In 2018 the Agency started to publish an OMAR for every orphan-designated medicine that had been recommended for marketing authorisation by the Agency. The new report summarises the reasoning of the Agency's Committee for Orphan Medicinal Products (COMP) on whether or not a medicine designated as an orphan medicine during its development still fulfils the designation criteria at the time of its authorisation. This is the precondition

7 June

EMA implements measures to strengthen the assessment of MRLs of veterinary medicines in food-producing animals.

7 June

100th Management Board meeting

8 June

Haemophilia registry workshop

7-8 June

Workshop of the European Network of Paediatric Research.

for granting a marketing authorisation for an orphan medicinal product by the EC and to benefit from ten-year market exclusivity, one of the incentives of the EU orphan-medicine framework. The report is published as part of a medicine's European Public Assessment Report (EPAR) once the EC has adopted its marketing authorisation decision.

A total of 28 OMARs were published (25 initial marketing authorisations and 3 variations) as well as 8 withdrawal assessment reports (4 initial marketing authorisations and 4 variations).

Impact of the BCP on activities to support medicines development

By November 2018, EMA had to restrict the development of new and revision of existing guidelines to those that address an urgent public health need or are necessary to support and facilitate preparations for Brexit. This step became necessary to ensure that EMA's core activities in relation to the authorisation and supervision of medicines could continue.

Work on a total of 119 guidelines and other guidance documents had to be put on hold. Examples include:

- Development of the good pharmacovigilance practice (GVP) module specific to elderly patients, which will be an important tool to monitor the benefit-risk profile of medicines in the elderly population. This population represents a large number of patients, yet is under-represented in clinical trials, and exhibits a variability that is best addressed by RWD collection.
- Guideline on the comparability for ATMPs, which will address a recurrent issue for almost all ATMP developments where manufacturing changes take place during the product development.
- Update of guidelines on the development of novel therapies (i.e. gene therapies) to treat haemophilia A and B.

EMA's work on guidelines plays a major role in the development of new medicines in the EU. Guidelines clarify how to apply legal and regulatory requirements in drug development programmes, taking into account the latest scientific and technological advances. Non-product-related working parties were also reduced as a consequence of the scaling back of guideline development.

Work on guidelines is important for the EU to remain at the cutting edge of scientific research and will resume as soon as BCP arrangements are no longer necessary.

13 June

EMA holds its second public hearing at the PRAC as part of a safety review for quinolone and fluoroquinolone antibiotics.

19 June

EMA launches IRIS, a new portal for orphan designation applications.

18-19 June

Bilateral regulatory dialogue between the EC, EMA and the FDA.

Working with HTA bodies and payers to facilitate access to medicines

Close interaction between regulators, HTA bodies and other relevant decision-makers is critical to supporting medicine development programmes that generate data relevant for all of these stakeholders, with the ultimate aim of ensuring patient access to important new medicines.

Some new medicines that receive marketing authorisation then fail to be reimbursed by health systems. Improving access to medicines therefore requires interaction between all actors involved in the development and use of a medicine along its lifespan. This includes activities to facilitate the flow of product-specific information between decision-makers to increase mutual understanding of principles and concepts for decision-making.

EMA interacts with numerous HTA bodies through the European Network for Health Technology Assessment (EUnetHTA), which is the central point for EU-level cooperation on HTA. The aim of this interaction is to facilitate patients' access to innovative medicines by optimising evidence generation, developing guidance and ensuring information flow and efficient use of resources.

One important pillar of this interaction is the so-called parallel consultation procedure. Here, EMA and HTA bodies give parallel scientific advice to medicine developers so that they can design a single development programme that fulfils the needs of both regulatory and relative effectiveness assessment.

A new platform for parallel consultation was launched in July 2017, replacing the previous Parallel EMA–HTA scientific advice (PSA) procedure. The year 2018 saw the first full calendar year of the new platform, with 27 procedures requested. This shows a consistent level of demand for parallel procedures over the last four years and a seamless transition to the new system.

A survey carried out among applicants who used this platform during the first year showed positive feedback overall, while highlighting areas for further development. Of the respondents, 46% stated that the parallel consultation facilitated a single approach for development trials or plans for their product to meet the evidentiary needs of the involved stakeholders. Furthermore, 67% said that the advice met their expectations and all applicants who responded said that they would repeat the procedure for other products or indications.

Pre-planning of evidence generation is also relevant for the post-licensing phase. In 2018, EMA saw its first qualification in parallel with HTA bodies from the ECFSPR. Furthermore, HTA bodies engaged in the qualification of the EBMT registry, which can support CAR T-cell medicines.

Building on the experience of the first three collaborations at market entry, EMA and EUnetHTA jointly reviewed their product-specific exchanges after CHMP opinion on a new medicine. The most frequent questions of interest by HTA bodies were on the interpretation of study results and the methodology for assessment. It is anticipated that these exchanges can guide optimisation of the regulatory output for subsequent decision-making by HTA bodies, foster mutual understanding of assessment practices and contribute to shared perspectives on available evidence. These activities are part of the EMA-EUnetHTA joint work plan for 2017–2020, which also includes activities to foster mutual understanding with decision-makers on key concepts and methodologies. In this regard, highlights in 2018 included a joint analysis of the concepts of significant benefit and relative effectiveness, clarification of the concept of unmet medical need and sharing experiences on the identification of the therapeutic indication.

These topics were reviewed by EMA and EUnetHTA at their 16th bilateral meeting in December. The meeting, held at the Agency's premises in London, saw for the first time representatives from the payer community attending as observers.

21-22 June

Workshop organised by the EU, Japan and the US discusses the development of antibiotics for children.

22 June

EMA recommended a marketing authorisation for the first veterinary stem-cell-based medicine in the EU.

EMA also welcomed the steps taken towards Europe-wide legislation for enhanced cooperation on health technology assessment as this is expected to provide a more stable framework for such exchange in the future. The current collaboration between EMA and EUnetHTA is expected to support these developments.

HTA bodies and payers participated in more than 15 meetings and workshops held at EMA in 2018. EMA also participated in a number of events organised by HTA bodies to facilitate the alignment of views and progress the development of topics of mutual interest.

Improving the availability of medicines in the EU

The availability and continuous supply of human and veterinary medicines authorised in the EU is a key priority of the EU network. Medicine shortages can occur for many reasons, including manufacturing difficulties or problems affecting the quality of medicines, which can both impact on patient care.

EMA and the Heads of Medicines Agencies (HMA) created an HMA-EMA Task Force on the Availability of Authorised Medicines for Human and Veterinary Use to tackle disruptions in supply of human and veterinary medicines and ensure their continued availability.

In 2018, the task force adopted a two-year work programme, which lists actions for regulators and pharmaceutical companies on how to try to prevent supply issues and minimise their impact on patients.

Its key priorities include:

- looking at ways to minimise supply disruptions and avoid shortages by facilitating approval and marketing of medicines using the existing regulatory framework (for example by work-sharing and reduced timetables when possible);
- developing strategies to improve prevention and management of shortages caused by disruptions in the supply chain (for example developing guidance for companies on reporting of shortages);
- encouraging best practices within the pharmaceutical industry to minimise the risk of shortages;
- improving sharing of information and best practices among EU regulatory authorities to better coordinate actions across the EU;
- fostering collaboration with stakeholders and enhancing communication on supply problems to EU citizens.

Following the publication of the work programme in September 2018, the task force organised a multi-stakeholder workshop on 8 and 9 November 2018 to gather stakeholders' perspectives on how to address availability issues and to include their input into the task force's deliverables.

29 June

EMA recommends the first two marketing authorisations for CAR T-cell medicines in the EU. Kymriah and Yescarta are also the first medicines supported through EMA's PRIME scheme to receive positive opinions from the CHMP.

2 July

EMA publishes a summary report on the crisis simulation exercise conducted in 2017.

EU Clinical Trial Regulation and the development of the Clinical Trials Information System

The way clinical trials are conducted in the EU will go through a major change when the Clinical Trial Regulation comes into application. The goal of this new legislation is to create an environment that is favourable to conducting clinical trials in the EU, with the highest standards of safety for participants and increased transparency of trial information.

The regulation harmonises the assessment and supervision processes for clinical trials throughout the Union via an EU portal and database, called the Clinical Trials Information System. EMA will set up and maintain this system in collaboration with the Member States and the EC. It will be the single entry point for submitting clinical trial information in the EU, which will be stored in the database. EMA will make information in the database publicly available, according to its transparency rules.

In 2018, the development of the auditable release of the system, the so-called release 0.7, progressed. The system is in a phase of pre-testing the auditable release by the Agency together with stakeholders before the seventh stage of user acceptance testing (UAT) can start. The Agency continues its work to fix the remaining bugs with the contractor and will implement improvements in the system prior to user acceptance testing. UAT is the last phase of the software testing process, when users test the software to make sure it can handle required tasks in real-world scenarios, according to specifications.

At the same time the work to develop the safety reporting part of the system also progressed. The project plan was revised to improve delivery and to ensure that stakeholders can give feedback more regularly during the process so that their expectations can be taken into account as early as possible.

Ensuring patient safety throughout the life cycle of medicines

Once a medicine has been put on the market, EMA and the EU Member States continuously monitor the quality and the benefit-risk balance of the medicine. This allows them to optimise the safe and effective use of the medicine to achieve its full benefit and to protect patients from any preventable adverse effects.

Safety monitoring of medicines used in children

In November 2018, EMA published the new GVP chapter IV on specific considerations for the paediatric population.

It offers a holistic view of paediatric pharmacovigilance and provides guidance on how to make best use of existing tools and processes to address the specific needs and challenges of safety monitoring of medicines used in children. In addition, it advises on how to adapt regulatory requirements to the paediatric population in the EU.

The new GVP chapter covers approved medicines with a paediatric indication or with ongoing paediatric development. It also covers medicines only approved for adults but used 'off-label' to treat children, that is, for a medical purpose not in accordance with the terms of the marketing authorisation.

A dedicated approach to pharmacovigilance in children is especially important given that paediatric clinical trials are often limited in size and duration, and adverse reactions in children may substantially differ in terms of frequency, nature, severity and presentation from those occurring in adults.

Patient voices in safety reviews – public hearings at EMA

EMA held its second public hearing on 13 June 2018. The hearing was part of a review carried out by the PRAC on quinolones and fluoroquinolones, a class of antibiotics widely prescribed in the EU.

The objective of the hearing was to listen to the views and experiences of patients and the general public on the possible side effects reported with this group of medicines. These reports included long-term disabilities and pain.

The EU's pharmacovigilance legislation enables the PRAC to hold public hearings during certain safety

5 July

EMA starts reviewing medicines containing the active substance valsartan, supplied by Zhejiang Huahai Pharmaceuticals.

5 July

Reflection paper on use of aminoglycosides in animals in the European Union in terms of the development of resistance and impact on human and animal health.

11 July

The PRAC elects Sabine Straus as its new chair.

reviews of medicines. These public hearings support the committee's decision-making by providing additional perspectives, knowledge and insights into the way medicines are used.

In total, 69 participants attended the hearing at the Agency's premises in London (or joined it by telephone), including 40 patients and patient representatives, 14 healthcare professionals and academics, 13 representatives from the pharmaceutical industry and two members of the media. Many other members of the public who could not attend sent submissions in writing to the PRAC.

Following the hearing, the Agency finished its review in November 2018 and recommended suspension of the marketing authorisations of quinolone medicines (cinoxacin, nalidixic acid and pipemidic acid) and of flumequine, and the introduction of changes, including restrictions on the use of the remaining fluoroquinolone antibiotics.

In addition, the information for healthcare professionals and the product information for patients will describe the disabling and potentially permanent side effects and advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving pain in the muscles, tendons or joints, or the nervous system.

Outcome of public hearing on valproate

2018 also saw the conclusion of the review of valproate-containing medicines, which had led to the Agency's first-ever public hearing on 26 September 2017. Valproate is used to treat epilepsy, bipolar disorder and migraine. Its safety in women and girls who are pregnant or of childbearing age was reviewed because of concerns that current EU-wide measures to reduce the risk of malformations and neurodevelopmental problems occurring in babies who are exposed to valproate in the womb were not fully effective.

In February 2018, after evaluating the available evidence, the PRAC recommended strengthening restrictions on the use of valproate and introducing new measures to avoid exposure of babies in the womb. Babies exposed are at risk of malformations and developmental problems. These measures were endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a body representing EU Member States, in March 2018.

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 was 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.

In 2018, the implementation of the revised strategy continued according to the work plan. A new chapter and annex on methods for pharmacovigilance impact research has been included in the annual revision of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Four impact studies were launched through EMA's framework contract to evaluate the post-referral utilisation, prescribing trends, patients' and healthcare professionals' awareness of EU label changes and pregnancy prevention programmes for medicines containing valproate and retinoids.

13 July

EMA publishes the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (7th Revision), which includes 34 authors and 593 references. It continues to be a worldwide reference document, with around 1,000 downloads and 4,500 views on average per month. The 7th Revision includes a new chapter on methods for pharmacovigilance impact research.

Big data and real world evidence

The increasing volume and complexity of data now being captured across multiple settings and devices offers opportunities for medicines regulation in terms of a better understanding of diseases, medicines and the performance of products in the healthcare system. In 2018, an HMA–EMA Joint Big Data Task Force, composed of experienced medicines regulators from 14 NCAs and EMA, described the big data landscape from a regulatory perspective. It did so to ensure that the EU regulatory system has the capability and capacity to guide, analyse and interpret these data for better decisions on the regulation of medicines. A draft report, including recommendations on six subgroups of data sources relevant to regulatory decision-making, was delivered by the Task Force in 2018 and will be published in 2019.

The term 'big data' encompasses routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials. As these data are collected outside the context of a specific study intervention, they are called RWD and their analysis is the source of real world evidence (RWE) that may be used to support regulatory decision-making. In 2018, EMA used two in-house databases of electronic healthcare records to perform 14 studies providing RWE to Committees. EMA also launched new framework contracts with 9 academic institutions or contract research organisations for EMA-funded efficacy or safety studies; 4 studies have been contracted through this framework to assess the effectiveness of risk minimisation measures taken for valproate and isotretinoin.

Patient registries are another important source of RWD. The EMA Patient Registry Initiative was initiated in 2015 to facilitate use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines. In 2018, the initiative made important progress by organising and publishing the reports of two workshops, on CAR-T cell therapies and on haemophilia registries, and by publishing for consultation a discussion paper on methodological and operational considerations for the use of patient registries for regulatory purposes. This document will be used to develop guidance on patient registries in 2019.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP is a network coordinated by EMA. The network's success is based on the expertise and commitment of a large number of participants, which by end of 2018 included 176 centres and 24 research networks from 19 different European countries, as well as 134 registered data sources. In 2018, ENCePP published a revision of the ENCePP Guide of Methodological Standards in Pharmacoepidemiology, an update of the ENCePP Code of Conduct and a revision of the ENCePP Checklist for Study Protocols.

EU PAS Register

The European Union electronic Register of Post-Authorisation Studies (PAS) Register, hosted on the ENCePP website, allows registration of studies and publication of study protocols and results. Registration of PAS is mandatory for studies imposed on marketing authorisation holders by regulators as a legal obligation and is recommended for other PAS. While initially developed for the registration of studies conducted in the EU, this unique tool promoting transparency is increasingly used worldwide. In 2018, 204 new studies were registered, with a total of 1,419 studies registered by end of December 2018. A process to check marketing authorisation holders' compliance with their registration obligation was formalised.

16 July

EMA publishes the first report on the implementation of its policy on the publication of clinical data (Policy 0070).

18 July

EU and Japan reinforce their collaboration on inspections of medicine manufacturers.

5–6 Sep

Third Strategic Accelerate Forum on Paediatric Medicines.

Contributing to animal health

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

The Agency's key responsibilities are scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in animals. In 2018, EMA's activities in the veterinary field mainly focused on increasing the availability of innovative veterinary medicines, encouraging a more ethical use of animals in medicine testing and supporting the fight against AMR. EMA also started to prepare for the implementation of the new EU veterinary medicines legislation.

Encouraging a more ethical use of animals in medicine testing

In February, EMA published its first report summarising the Agency's actions to support the implementation of the so-called 3Rs principles. '3Rs' is an acronym for replacement (switch from animal studies to non-animal methods), reduction (perform as few animal studies as required and necessary) and refinement (minimise animal stress). The actions described in this report are driven by a dedicated, long-term working group, the Joint CVMP/CHMP 3Rs Working Group (J3RsWG), which provides advice to the CVMP and the CHMP on all matters concerning the use of animals in the regulatory testing of medicines. The ultimate goal is to abolish the use of live animals in medicine testing. However, until scientific progress provides adequate alternatives, the use of animals will still be necessary in some areas of medical research to protect human and animal health as well as the environment. The Agency plans to maintain its engagement with stakeholders on 3Rs initiatives and to continue to provide expert input on regulatory issues to facilitate a smooth implementation of the principles.

New guidance on maximum residue limits

The EU requires by law that foodstuffs such as meat, milk or eggs must be free from residues of veterinary medicines or biocidal products that might pose a threat to the health of consumers. A set of three implementing measures envisaged in Regulation (EC) No 470/2009, and in relation to which the CVMP provided detailed scientific recommendations, were adopted by the EC in May 2018. These replace the previous guidance on the establishment of MRLs in the EU. The measures detail the CVMP approach to the assessment of MRLs for veterinary medicines and provide up-to-date guidance to companies who apply for the establishment of MRLs for their respective medicines.

Decrease in the sales of veterinary antimicrobials

Reducing the use of antimicrobials in food-producing animals and replacing antimicrobials where possible is essential for the sustainability of the future livestock production system. AMR is one of the world's most pressing public health issues and the use of antimicrobials in animals contributes to this problem. Therefore, it is crucial to eliminate unnecessary use of antimicrobials and promote its responsible use in animals.

In 2018, EMA published the 8th European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report. The report is published annually and, over the years, the overall quality of sales data collected and analysed has continuously improved. The trends highlight a more responsible attitude towards the use of antibiotics in animals. According to the report, the overall sales of veterinary antimicrobials across Europe has decreased by more than 20% between 2011 and 2016. However, the report still presents a mixed picture across the EU as sales vary greatly between Member States.

13 September

EMA and the EC publish information material (including a video) on biosimilar medicines, as part of their ongoing collaboration to improve understanding of biosimilars across the EU.

13 September

The COMP elects Violeta Stoyanova-Beninska as its new chair.

Impact of the BCP on activities to support animal health

By November 2018, EMA had to scale back the development of new and revision of existing guidelines to those that address an urgent animal health need or are necessary to support and facilitate preparations for Brexit. This step became necessary to ensure that EMA's core activities in relation to the authorisation and supervision of medicines could continue.

Work on a total of 24 guidelines and other guidance documents had to be put on hold. Examples include guidelines related to AMR, such as the risk assessment guideline for antimicrobials and the reflection paper on aminopenicillins. Work on guidance documents related to anti-parasitics was also delayed. This includes the guideline on veterinary medicinal products for control of *Varroa destructor* parasitosis in bees. Another important area for which work had to be scaled down was the reflection paper on measures to promote availability of veterinary vaccines in emergency situations.

EMA's work on guidelines plays a major role in the development of new medicines in the EU. Guidelines clarify how to apply legal and regulatory requirements in drug development programmes, taking into account the latest scientific and technological advances. Non-product-related working parties were also reduced as a consequence of the scaling back of guideline development.

Work on guidelines is important for the EU to remain at the cutting edge of scientific research and will resume as soon as BCP arrangements are no longer necessary.

14 September

The MRA between the EU and the US recognises inspections conducted in Portugal of sites manufacturing human medicines.

18 September

The CHMP elects Harald Enzmann as its new chair.

27 September

EMA launches its new corporate website.

Strengthening the operation of the network

To safeguard human and animal health in all 28 EU Member States, EMA works closely with more than 50 NCAs, the EC, international regulators and a broad range of stakeholders such as patients and consumers, healthcare professionals, academia, HTA bodies, payers and the pharmaceutical industry.

As the EU medicines network has had to prepare for the UK's withdrawal from the EU, redistribute the work performed by the UK and mitigate the impact of Brexit, this close collaboration has become even more important.

It is essential that this network responds in a timely and effective way to technical and scientific developments, as well as public health challenges such as shortages of medicines or AMR. Hence, the Agency is making consistent efforts to strengthen the network and to engage better with all stakeholders.

Preparing for the future - Regulatory Science to 2025

In December 2018, the Agency published its strategic reflections on 'EMA regulatory science to 2025' for a six-month public consultation. Regulatory science includes all scientific disciplines that are necessary to assess the quality, safety and efficacy of medicines and to inform regulatory decision-making throughout the lifespan of a medicine.

The strategy provides a plan for advancing regulatory science over the next five to ten years, covering both human and veterinary medicines. It seeks to offer informed guidance on modern medicines development and facilitate the optimisation of regulatory activities and the assessment of the benefits and risks of innovative therapies and diagnostics. The strategy is a response to the dramatic acceleration of the pace of innovation in recent years and the need for regulators to be ready to support the development of increasingly complex medicines, which often deliver healthcare solutions by converging different technologies.

Prior to the launch of the public consultation, EMA hosted two workshops. The feedback and insights from stakeholders and EU citizens on the key areas covered will be incorporated in the final strategy.
The outcome of this exercise will be a key element of the next European Regulatory Network Strategy to 2025, which will be developed together with the Member States and the EC. It will enable EMA to keep up with the accelerated technological change and innovation in medicine development. It will also allow the Agency to identify gaps between science and healthcare systems and bring together the various stakeholders needed to bridge those gaps.

EU Network Training Centre

Evolving science and technology requires the network to keep its knowledge and expertise continuously up to date to meet the new regulatory challenges. The EU NTC provides a central platform for scientific and regulatory training supporting the spread of good practices and improving the work performed by EMA and NCAs in the EU regulatory network.

In 2018, the number of training courses made available to the EU regulatory network continued to increase, with new training courses being offered across all curricula. By the end of the year, a total of 108 online courses were made available on the platform, with 60 new events advertised to the EU network in 2018. Two new training curricula, one for the assessment of non-clinical data and the other for the development of product information, were developed, bringing the total number of training curricula to eleven.

In addition, a joint HMA–EMA survey was carried out among NCAs to better understand the training needs in the EU network and Member States' capacity to provide training. The results of the survey will serve to further improve the EU NTC training offer.

2 October

EMA and DG SANTE publish an action plan to support the development of medicines for children in Europe.

8 October

EMA publishes the report of a workshop A Common Data Model for Europe? – Why? Which? How?

12 October

Focus group meeting on dose optimisation of established veterinary antibiotics for the summary of product characteristics harmonisation.

Impact of the BCP on strategic planning and training activities

The exercise to prioritise EMA's activities during the BCP acted as a key driver to prepare and release the regulatory science strategy for public consultation by the end of 2018. As it concerns the future planning of network resource distribution across the key regulatory challenges to be addressed through to 2025, the pressure on network resources represented yet another element of uncertainty to be factored into this reflection. In this regard, there was a particular emphasis on the turnover of existing expertise, consequent replacement opportunities and highlighting new expertise to address challenges identified.

The regulatory science strategy underlines the need for EMA experts and staff to keep up with technological and scientific developments to be able to assess innovative and increasingly complex medicines that are at the crossroads of many different technologies. Training will be the key to making the Agency and the network fit for the future.

Brexit has meant that the Agency needed to focus its efforts on providing training that will ensure transfer of knowledge to deal with staff losses. However, other courses had to be suspended, limiting the Agency's ability to keep its staff at the cutting edge of science.

Stakeholders, communication and transparency

A new corporate website

EMA relaunched its corporate website (www.ema.europa.eu) on a new platform in 2018. Working in close collaboration with the Directorate-General for Informatics (DG DIGIT) enabled EMA to deliver a new corporate website despite resource constraints due to the BCP. A number of new features to enhance user experience were incorporated, such as:

- an advanced search, allowing users to find content easily and to filter search results;
- a 'responsive' design for cleaner display on mobile devices;
- simpler URLs based on the location and title of webpages or documents;
- an updated visual design offering users a clearer reading experience and simpler navigation.

With this new version of the website, EMA aims to further improve its communication with partners and stakeholders, as well as to support the Agency in reaching out to EU citizens by providing them with evidence-based and easily accessible information on medicines.

Towards electronic product information for EU medicines

In November, EMA, the HMA and the EC organised a workshop to agree with stakeholders on common EU key principles for implementing electronic product information (ePI) for medicines across the EU.

The workshop followed up on a 2017 EC report which highlighted that, despite efforts to make the product information on medicines easy to read and useful, there is still a need to improve how this information is conveyed to patients and healthcare professionals. The use of electronic means for better dissemination of product information is one of the key priorities listed in an EMA action plan, also published in 2017, that aims to address the shortcomings identified in the EC report.
The workshop was the culmination of a year of mapping and consultation on the topic, and it offered a platform for healthcare professionals, patients and consumers, academics, non-profit organisations, regulators and the pharmaceutical industry to discuss their needs and concerns and the opportunities and challenges of ePI. It also looked at ongoing initiatives in the EU, and discussed how ePI fits into other EU and global initiatives.

The outcome of the workshop will serve as a basis for draft key principles for the use of ePI in the EU.

15 Oct

EMA publishes a report that shows the overall sales of veterinary antimicrobials across Europe dropped by more than 20% between 2011 and 2016.

18 October

EMA publishes the ENCePP Checklist for Study Protocols (Revision 4) aimed at stimulating researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol.

Impact of the BCP on stakeholders, communication and transparency

In 2018, the Agency reduced the levels at which it implemented its frameworks for interaction with stakeholders. Throughout the year, the number of stakeholder meetings was reduced, annual bilateral meetings with industry stakeholders were temporarily suspended and a planned industry stakeholder survey was put on hold.

In the fourth quarter of 2018, there was a further reduction in stakeholder interactions:

- Face-to-face meetings in the working parties for patients and consumers and for healthcare professionals and implementation of their 2018–2019 work plans were placed on hold.
- Annual training session for patients and healthcare professionals for involvement in EMA did not take place.
- EMA participation in external stakeholder events was reduced.

Resources were redirected to focus on Brexit-related activities. EMA and the EC continued to engage closely with stakeholders to prepare for the UK leaving the EU and becoming a third country. Dedicated webinars were set up to update stakeholders on Brexit-related activities.

To free up resources to focus on medicine evaluation and supervision, progress in implementing EMA's landmark policy on clinical data publication was halted in August 2018. Pending applications were completed and the publication of clinical data from new applications was suspended thereafter.

In 2018, due to BCP resource constraints, it was possible to commence work on only one of the six actions contained in the action plan to improve medicines product information: the ePI for medicines across the EU. Work on the other areas (aimed at improving content and user-testing) will commence once resources are made available.

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.

Orphan designation goes digital

EMA launched a secure online portal for orphan designation applications on 19 June 2018. The portal, named 'IRIS', allows applicants to submit and manage the information and documents related to their applications for orphan designation. This is expected to significantly reduce the time needed to submit applications, and to increase the security of confidential documents in new sharing systems. During the review process, applicants can check the status of their applications from any device and receive automatic notifications when the status changes.

IRIS is part of a longer-term programme that aims to make the handling of product-related applications easier and to integrate master data of pharmaceutical regulatory processes for substances, products, organisations and referentials (SPOR).

19 October

EMA recommends granting marketing authorisation to the first vaccine against dengue disease.

24 October

EMA hosts a workshop to gather insight from stakeholders on the key areas in human medicines to be covered in its regulatory science strategy to 2025.

8-9 November

EMA and the HMA organise a workshop on the availability of authorised human and veterinary medicines.

Data centre relocation project

EMA's data centre centralises the organisation's IT operations and equipment as well as storing, managing and disseminating its data. It houses EMA's most critical IT systems and business applications, which are vital for the continuity of operations of the European medicines regulatory network.

The data centre relocation project (DCRP) was launched in August 2017 to relocate the EMA data centre from London to Hamburg, Germany by 30 March 2019.

The project aimed to move the existing centre with minimal architectural changes and minimal downtime of production and non-production systems.

During 2018, the preparation for removal and transit was organised and physical removal began from September 2018, with the final transit phase taking place over the weekend of 19–20 January. The project delivered on time and within forecast budgets. It succeeded in minimising production system downtime during the relocation period and ensuring that there was no significant change in overall network latency following the centre's installation in Hamburg.

Impact of the BCP on management of the network technical systems

EMA's ability during 2018 to execute IT initiatives in line with its information management strategy were significantly impacted by the Agency's preparation for Brexit and relocation. Resources normally used for innovative IT projects and change were channelled towards a number of critical projects, including relocation of the EMA data centre to outside the UK and the introduction of a new offshore IT application maintenance model.

The reduction in the number of changes that could be introduced into EMA's existing operational IT applications during 2018 created a significant backlog of requests, subsequently impacting user efficiency and satisfaction across the network. The response and resolution times for unplanned outages and other issues impacting IT systems and business applications fell to 11% below the target, due to activities related to the onboarding of a new supplier such as knowledge transfer. Many IT upgrades were also postponed due to resource re-allocation into Brexit-related projects.

Initiatives focusing on building EMA's IT capability were also impacted during 2018 in areas such as risk management, project management and data governance. Implementation of certain IT processes, including those related to information security, was slowed. In addition, the activities to identify and establish a new project portfolio management tool and a project management methodology were put on hold during the year.

9 November

EMA publishes for consultation a discussion paper on the use of patient disease registries for regulatory purposes, looking at methodological and operational considerations.

13 November

EMA publishes a new GVP chapter IV on specific considerations for the paediatric population.

New chairs elected for three EMA committees

2018 saw changes at the helm of three of the Agency's scientific committees as the PRAC, COMP and CHMP all elected new chairs.

PRAC

In July 2018, the PRAC elected Dr Sabine Straus from the Netherlands as its new Chair. She took over from Dr June Raine, Director of Vigilance and Risk Management of Medicines at the United Kingdom's MHRA, who retired in September 2018, having chaired the Committee since its inception for two consecutive three-year mandates.

Dr Sabine Straus is a member of the Dutch NCA, the Medicines Evaluation Board (MEB), with strong expertise in pharmacovigilance. She has been a member of the PRAC since 2012, when the committee was established.

"I hope to provide leadership to the PRAC and I look forward to working collaboratively with all the PRAC members, EMA's other committees and its staff in the best interests of European Union citizens," said Dr Sabine Straus. "At the heart of all the activities of the PRAC are patient safety and the protection of public health. My aim is to maintain good, robust science as one of the most important drivers of the work of the committee."

Interview with Dr June Raine, former PRAC chair

Looking back at your years as PRAC chair, what achievements are you most proud of?

It was a unique and special privilege to serve as the first Chair of the PRAC. I am most proud of how we seized the opportunity of the new legal and regulatory tools provided by the pharmacovigilance legislation, to optimise public health protection. What did this mean in practice? Proactively filling evidence gaps for important new medicines, assessing changing evidence of risk in the context of the medicine's therapeutic role, managing risk and following up the impact of our actions. Particularly, enabling innovation to reach patients as soon as may be – we can't keep patients waiting any longer than they have to! Furthermore, the PRAC's work is being done in a new era of transparency and openness, with greater engagement with all our stakeholders, in particular patients and the public. Their concerns are our concerns, for theirs is the ultimate decision on benefit-risk, and without their trust in our systems we can't achieve our public health goal.

Can you remember one specific moment or event that was particularly meaningful to you or illustrates well the life of the committee?

I'll always remember the discussion around whether or not to have a public hearing in the context of the referral on valproate. The arguments had been fully aired by PRAC members and it seemed clear that clinical expert input and stakeholder views would be entirely adequate. Then our patient representatives, having listened carefully, took the floor. They explained the unique view that the patients and families would provide on the nature of the risk and the impact on their lives. They predicted that the families would offer clear and valuable insights into the necessary risk management approach. They completely turned the argument around and were instrumental in moving the PRAC forward to hold its first public hearing on the medicine, which proved beyond any doubt the added value of public involvement in PRAC decision-making.

Looking forward, what in your view, are the biggest challenges the PRAC will face?

There are two major challenges for the PRAC: realising the potential of RWE to support safe and effective use of medicines, and impacting how medicines are prescribed, dispensed and used, i.e. converting a label change into behaviour change. I believe that with the expertise at the PRAC's disposal in terms of cutting-edge science and pharmacoepidemiology, and the capability of EMA to commission timely studies, the PRAC is admirably well-placed to tackle these challenges and to continue to deliver in the best interests of EU citizens.

COMP

In September 2018, EMA's COMP elected Dr Violeta Stoyanova-Beninska as its new chair. She followed Professor Bruno Sepodes, who served as COMP chair for two three-year terms, the maximum number allowed.

Dr Stoyanova-Beninska has been working since 2007 at the Dutch NCA, the Medicines Evaluation Board (MEB), as a senior clinical assessor. She has strong expertise in neurology and psychiatry, as well as in ophthalmology, dermatology and pain management.

"I cherish the unique responsibility the COMP has in the interests of patients suffering from rare diseases. Building on what has been achieved over the past 18 years since the COMP was established, I will work closely with all committee members and experts, building on the high professionalism and the collaborative spirit in the committee," said Dr Violeta Stoyanova-Beninska. "Orphan medicines have their specific challenges, which we shall tackle involving all stakeholders. As chair, I would like to contribute to reinforcing the COMP's interaction and communication with other scientific committees at EMA and also with international partners."

Interview with Professor Bruno Sepodes, former COMP chair

Looking back at your years as COMP chair, what achievements are you most proud of?

I am very pleased with how we structured the approach to the assessment of the significant benefit of an orphan medicine. When companies submit a marketing authorisation application for an orphan medicine, they now have to include conclusive clinical data supporting the original assumption of benefit. This helps the COMP in its evaluation and leads to a better interaction between the COMP and the Scientific Advice Working Party (SAWP) when they give advice on the planning of clinical development. We also established the Orphan Maintenance Assessment Report (OMAR), which complements the EPAR for orphan medicines and facilitates a better understanding of the rationale behind the decision to grant the orphan status to a medicine.

Can you remember something that was particularly meaningful to you and illustrates well the life of the committee?

The most meaningful and rewarding part of our work was the continuous engagement with the patient community. Having patients and patient representatives involved at all levels of the committee's work has enriched our scientific understanding of rare diseases and taught us how to best adapt the regulatory framework and assessment work to patients' needs. Their inspiring voices and knowledge were constant reminders for us to always ask ourselves: 'Are we improving patients' lives with our work?'

Looking forward, what, in your view, are the biggest challenges the COMP will face?

Regulators must keep pace with innovation and, when possible, anticipate the future challenges that a scientific breakthrough will pose. The COMP, in particular, will have to adapt rapidly to the continuous evolution of ATMPs and navigate through the complexity of defining precisely each orphan disease. Lastly, the ongoing discussion around the incentives provided in the EU legislation to stimulate innovation as well as the development, availability and accessibility of orphan medicines will definitely shape the work of the committee in the years to come.

CHMP

At its September 2018 meeting, EMA's CHMP elected Dr Harald Enzmann from Germany as its new chair, with a three-year mandate. Dr Enzmann follows Dr Tomas Salmonson, senior scientific adviser at the Swedish Medical Products Agency (MPA), who retired as chair after the September 2018 meeting, having served the maximum of two three-year mandates at the helm of the committee.

Dr Enzmann, a medical doctor, works for the Federal Institute for Drugs and Medical Devices (BfArM) in Germany, where he is Head of European and International Affairs. Dr Enzmann has been a member of the CHMP since 2005 and served as its vice-chair from 2016 to 2018.

"The CHMP is at the cutting edge of medical progress. With science evolving at such a fast pace, our challenge will be to achieve a balance between being agile to find solutions to emerging scientific or regulatory issues and being consistent with previous decisions," said Dr Harald Enzmann. "As chair, I will try, in a constructive way, to elicit the committee members' views, encourage their involvement and structure our scientific discussions to foster consensual decision-making."

Interview with Dr Tomas Salmonson, former CHMP chair

Looking back at your years as CHMP chair, what achievements are you most proud of? Can you remember one specific moment/event that was particularly meaningful to you/illustrates well the life of the committee?

The main task of the chair is to ensure that the committee delivers robust scientific opinions. To achieve this, the discussions should focus on the right issues, all views should be put on the table and the voting should take place at the right time. Not too early, not too late. The NCAs have different capacities, and the support to each CHMP member differs. Hence, it is essential that the chair helps to focus discussions on issues that are key to decision-making, so that the key scientific arguments, and the regulatory framework, are understood by all members when the decisions are taken.

People attending the CHMP for the first time may have been surprised by its casual style, but no one should take this as a sign of lack of seriousness or dedication. On the contrary, I have created an informal atmosphere to allow everyone to speak their mind in a concise way. A robust, well-justified outcome sometimes requires a frank conversation. Having said that, as the agenda is often very busy, it is important to stop the discussion and take a vote when relevant issues have been covered.

I am proud of how the CHMP has performed during my years as chair. To lead a high-level, clear, frank and a bit heated discussion and later find committee members in friendly conversations during the coffee break is very rewarding.

Looking forward, what in your view are the biggest challenges the CHMP will face?

I am sure the CHMP will retain its high level of competency and will continue to be excellently supported by the NCAs and EMA. The biggest challenge is rather the changed role of the regulator. When I started as a regulator the decision and the SmPC was the most important outcome of the regulatory process. Today, and perhaps even more so tomorrow, the regulator is becoming more the competent assessor of available data, supporting other decision-makers. These include, of course, not only HTA bodies and payers but also the wider healthcare system. A specific focus should be on providing relevant information to patients and clearly demonstrating the direct relevance of the regulatory decisions for patients.

Another aspect is the life-cycle approach. Academia and industry today develop life-changing drugs that modify or even cure diseases. But we will often not understand the full clinical value of these drugs at the time of approval. Ensuring that we obtain answers to relevant questions from all stakeholders in the post-approval space is an increasing responsibility of the regulator.

New EU legislation applicable to EMA

At the end of 2018, Regulation (EU) 2019/6 on veterinary medicinal products was formally adopted by the European Parliament and the Council of the EU. This new piece of legislation was proposed by the EC in 2014 to increase the availability of veterinary medicines, reduce administrative burden for veterinary medicine developers, stimulate competitiveness and innovation in the veterinary sector, improve the functioning of the internal market and address, in particular, the public health risk of AMR. The new regulation covers all aspects of veterinary medicines regulation at national and EU levels and will start to apply from 28 January 2022.

In parallel with the new veterinary regulation, Regulation (EU) 2019/5 amending Regulation (EC) No 726/2004 was adopted in December 2018 to delete references to veterinary medicines and align EMA's Founding Regulation (726/2004) to Articles 290 and 291 of the Lisbon Treaty. This revision also included some changes unrelated to veterinary medicines, for instance with regard to penalties and alignment of certain provisions of EMA's basic act with the new EU financial regulation as well as the framework for conditional marketing authorisation and variations. These changes became applicable on 28 January 2019.

In 2018, the Agency continued to support the EC and Member States in the implementation of the new Regulation on medical devices (MDR), Regulation (EU) 2017/745, and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR), which introduce new responsibilities for EMA and for NCAs for medicinal products. EMA will have a role in the review of companion diagnostics and can be consulted for complex products that are considered borderline between medical product and other regulatory frameworks. These two new regulations, which came into force on 25 May 2017, replace the three existing medical device Directives (93/42/EEC, 98/79/EC and 90/385/EEC). They will become fully applicable in May 2020 for medical devices and May 2022 for in vitro diagnostic medical devices, following a transition period to allow manufacturers, notified bodies and authorities to comply with the changes.

On 11 December 2018, new data protection rules for EU institutions, including the EMA, entered into force. Regulation (EU) 2018/1725 (EU DPR) on data protection ensures that the standards of data protection within EU institutions are in line with those provided for in the General Data Protection Regulation (GDPR). The EU DPR introduces some changes in the way agencies must deal with personal data, such as the need to build data protection principles into operations from the outset (data protection 'by design' and 'by default'), the obligation to properly document all data processing operations and store such records in a publicly accessible central register and the obligation to promptly inform the European Data Protection Supervisor of data breaches.

16 November

EMA adopted a positive opinion for Fexinidazole Winthrop (fexinidazole), the first oral-only medicine for the treatment of human African trypanosomiasis (HAT), commonly known as sleeping sickness.

21 November

Publication of 'Antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products.'

Regulatory cooperation to improve global health

Medicines research, development and production is a global endeavour. Strengthening collaboration with other international regulators therefore remains a central pillar of EMA's strategy to protect public health.

In the field of international cooperation on pharmaceuticals, the Agency works closely with the EC (notably with DG SANTE) by providing scientific and technical support.

In 2018, 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, but had to significantly decrease its contribution. To protect public health, priority was given to activities related to ensuring supply chain integrity and as well as encouraging development of medicines for low- and middle-income countries. The main initiatives focused on improving global oversight of medicines production through international collaboration on inspections.

Through its participation in the activities of the International Council for Harmonisation, the Agency made a key contribution to the finalisation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E17 guideline on 'General principles for planning and design of multi-regional clinical trials', which is now implemented in the EU.

Interactions with non-EU regulators

The Agency collaborates with the Therapeutic Goods Administration (TGA) in Australia, Health Canada (HC), the Ministry of Health, Labour and Welfare (MHLW) and the PMDA in Japan and the FDA in the US based on confidentiality agreements. Interactions with these authorities take place almost daily, partly structured around clusters of activities and partly ad hoc.

Reinforced EU-US collaboration on medicines

In June 2018, senior officials from the EC, EMA and the FDA held a two-day bilateral meeting in Brussels, Belgium, to review joint initiatives, discuss strategic priorities for the coming years, taking into consideration the BCP, and further strengthen their close collaboration, with specific focus on the field of pharmaceuticals.

The parties discussed the EU-US MRA on pharmaceutical inspections of good manufacturing practices (GMP), which came into operation in November 2017 and was further progressed during the year. They committed to continue to work closely together at a technical level to further streamline the process, measure progress made and monitor closely the implementation of the MRA. The participants also discussed ongoing initiatives and strategic priorities, such as support for the development of ATMPs, where similar regulatory challenges are faced on both sides of the Atlantic. The parties agreed to encourage early parallel scientific advice and to further strengthen the existing collaboration on ATMPs with a view to developing common scientific approaches on the regulation of these medicines. Other topics discussed included identification of possible ways of streamlining the scientific requirements for approvals of generic medicines through technical guideline harmonisation (i.e. ICH), as well as RWE, where transatlantic collaboration can leverage expertise, experience and available data to help to address methodological and practical challenges related to its analysis.

26 November

EMA and the FDA organise a workshop to discuss how regulators can better guide and support medicine developers in generating quality data packages and manufacturing data packages in the context of development support programmes.

28 November

EMA, the HMA and the EC organise a workshop to agree with stakeholders on common EU key principles to pave the way for implementing ePI.

Improving oversight of global supply chains

Continued success of the international API inspection programme

EMA and its European and international partners have successfully strengthened their interactions to improve the oversight of API manufacturers worldwide.

This international collaboration allows EMA, several NCAs (France, Denmark, Ireland, Italy, and the United Kingdom), the European Directorate for the Quality of Medicines (EDQM), the FDA, Australia's TGA, Health Canada, the Japanese MHLW and PMDA, and the World Health Organization (WHO) to share information on GMP inspections of API manufacturers that are located outside the participating countries.

The overall objective of the initiative is to ensure more API production sites are monitored all over the world by making best use of inspection resources through increased cooperation and mutual reliance between participating regulatory bodies. This will reduce duplication of inspections as well as increase inspection coverage.

In 2018, the international API inspection programme report for 2011 to 2016 was published, concluding that there was an increase in the number of API sites inspected by participating authorities included in the programme and that this increase has supported the exchange of information on inspections, which in turn supported better GMP oversight for the participating authorities.

EU-US MRA for inspections makes further progress

Throughout 2018, the MRA between the EU and the US, which came into operation in November 2017, was further progressed. The agreement allows for recognition of each other's inspection outcomes and hence for better use of inspection expertise and resources. The FDA confirmed the capability of 12 additional EU Member States to carry out GMP inspections at a level equivalent to the FDA (Czechia, Greece, Hungary, Romania, Lithuania, Ireland, Portugal, Belgium, Denmark, Finland, Latvia and Estonia – Austria, Croatia, France, Italy, Malta, Spain, Sweden and the UK were already confirmed in 2017). This means that at the end of the year, the FDA relied on a total of 20 Member States, whose inspection results can replace their own inspections.

On the part of the EU, the EC had confirmed in June 2017 that the FDA has the capability, capacity and procedures in place to carry out GMP inspections at a level equivalent to the EU. The implementation of the MRA is progressing well and all EU Member States should be assessed by the FDA in 2019.

EU and Japan reinforce their collaboration on inspections

The EU and Japan agreed to broaden the range of medicines included in their MRA. This agreement, which has been operational since May 2004, allows regulators to rely on GMP inspections in each other's territories, to waive batch testing of medicines that enter Japan from EU countries and vice versa and to share information on inspections and quality defects.

The scope of the agreement was extended to include sterile medicines, certain biological medicines, including vaccines and immunologicals, and APIs of any medicine covered in the agreement. The full scope of the MRA now covers chemical pharmaceuticals; homeopathic medicinal products (as long as if treated as medicinal products and subject to GMP requirements in Japan); vitamins, minerals and herbal medicines (if considered as medicinal products in the EU and Japan); certain biological pharmaceuticals, including immunologicals and vaccines; and APIs and sterile products of the above categories.

As part of the expansion of the scope of medicines covered by the MRA, Japan also evaluated and recognised as equivalent all EU competent authorities for human medicines inspection.

29 November

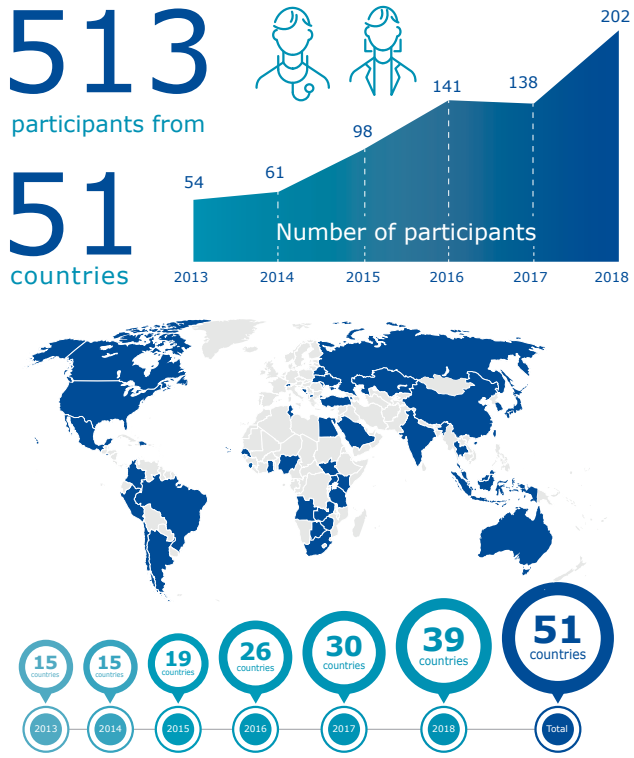
Belgium, Denmark, Finland, Latvia and Estonia benefit from EU-US MRA for inspections.

30 November

EMA publishes revised guidelines on the tests and studies needed to support marketing authorisation applications for certain haemophilia medicines.

The EU regulatory network as a global model

Rise in non-EU country participation in EMA courses



The participation of representatives of non-EU country regulators in training organised by EMA has grown steadily in the past few years. This peaked in 2018, when 202 people attended EMA courses, a growth of 47% compared to 2017. This training covered topics such as good clinical practice, good manufacturing practice, inspections and quality assessment of medicines. EMA courses help to build capacity for the oversight of the development and production of medicines in other parts of the world, and improve non-EU regulators' capabilities to better protect patients in their home countries and elsewhere.

Sharing EU expertise with African regulators

EMA's collaboration with African regulators continued in 2018. The Agency participated in workshops organised with Zazibona/the Southern African Development Community (SADC) in Lusaka (Zambia), and with the Economic Community of West African States (ECOWAS) in Dakar (Senegal). These meetings fostered trust in the scientific output of the CHMP, in particular the Agency's 'Article 58 procedure' for medicines intended for use outside the EU.

CHMP members, European experts and EMA staff participated in the events. This was an opportunity for African regulators to share and discuss their practice of the assessment of biosimilars/biologics, generic medicines, and medicines approved through article 58.

ISO award – increase global convergence of regulatory standards

Five EMA staff members – Paolo Alcini, Sabine Brosch, Tim Buxton, Ilaria Del Seppia and Panagiotis Telonis – won an International Organization for Standardization (ISO) Excellence Award for their achievements in the development of international standards for the identification of medicinal products (IDMP).

These standards facilitate the global exchange of information about medicines between regulators, data sources and pharmaceutical companies. They provide common formats, data structures, quality criteria and terminologies to identify medicines and enable information-sharing between regulators and healthcare communities worldwide. ISO IDMP cover the entire product lifecycle: medicines in development, medicines under evaluation and authorised products.

EMA's team was supported by other EMA staff and experts from across the EU. They were part of a global collaborative effort led by ISO, involving medical experts from 32 participating and 27 observing countries, who developed a set of five international IDMP standards.

"I congratulate my colleagues for their invaluable work and major contribution to global standardisation," said Guido Rasi, EMA's Executive Director. "Internationally accepted IDMP standards enable the efficient exchange of information on medicines and will improve the pharmacovigilance and safety monitoring that we carry out to ensure patient safety."

30 November

EMA publishes a revised guideline to assess the risk of human medicines for the environment.

6 December

EMA holds a workshop in advancing regulatory science to 2025 for veterinary medicines.

Impact of the BCP on activities to improve global health

Collaboration at international level was scaled back in 2018, with activities cancelled or postponed in 2018 to focus primarily on product-related requests, supply-chain integrity and procedures under Article 58. In other areas, such as the international harmonisation of technical requirements and collaboration between regulatory authorities, EMA had to switch from an active or leadership role to a more reactive position.

EMA's engagement in other global public health issues such as AMR or vaccines was maintained when possible, and its involvement in international initiatives reviewed on a case-by-case basis.

Training for international regulators was also affected. This includes the cancellation of the EU-funded training project in Southeast Asia and a planned awareness session at EMA.

It will be important to reinstate these collaborative activities at the earliest opportunity to maintain Europe's voice in international cooperation on medicinal products and its contribution to raising global standards.

17 December

EMA publishes a plan outlining how it would respond to an emerging cross-border threat to health, such as an influenza pandemic.

Chapter 2
Key figures in 2018

Core statistics from 2018 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.

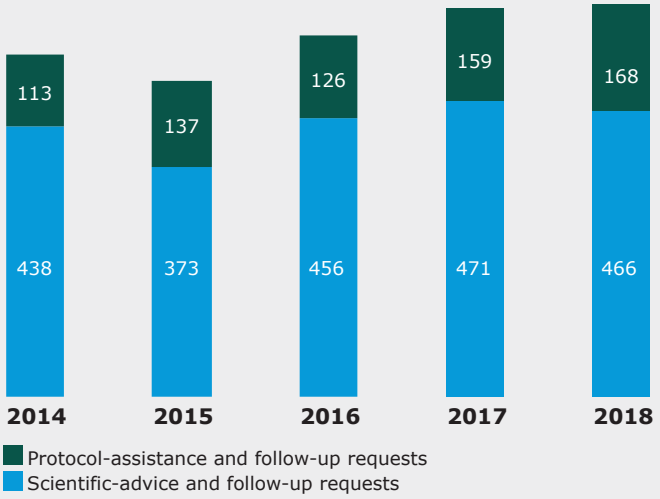
Scientific advice

The Agency provides scientific advice and protocol assistance to medicine developers throughout the life cycle of their medicines. Scientific advice is one of the Agency's key instruments for supporting 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 to ensure that patients only take part in those clinical trials that are likely to be robust enough to support a marketing authorisation application or extension of indication. Protocol assistance is the special form of scientific advice for developers of designated orphan medicines for rare diseases.

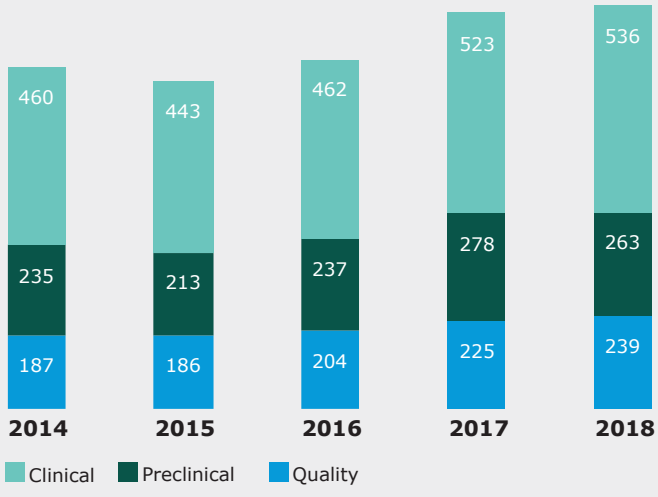
The number of requests for scientific advice and protocol assistance received remained at a stable high level in 2018, following increases of 14% in 2016 and 8% in 2017. 162 of the total of 634 requests received were for medicines in the post-authorisation phase. This represents an increase of 12.5% in the number of post-authorisation requests compared to 2017.

Scientific advice is the core of many of EMA's special programmes to encourage development and availability of new and innovative medicines. The requests for scientific advice for PRIME products has consistently grown since the launch of the scheme in 2016.

Scientific advice and protocol assistance requests received - total



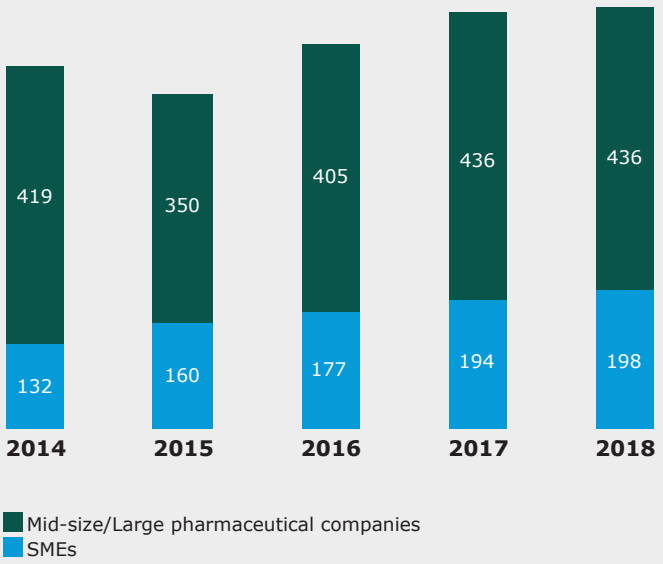
Scientific advice requests by topic



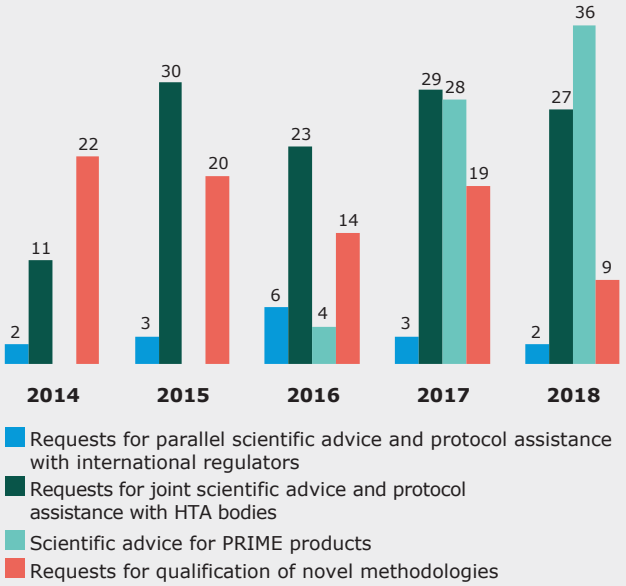
As in previous years, more than half of the requests for scientific advice related to clinical issues, 25% to preclinical issues and 23% to quality issues. In terms of development stage, 58% of requests related to medicines in phase III, 28% to medicines in phase II, 12% to medicines in phase I and 3% to medicines in phase IV of their clinical development.

The number of requests for scientific advice coming from SMEs has steadily grown since 2014. In 2018, 31% of the total of 634 requests came from SMEs.

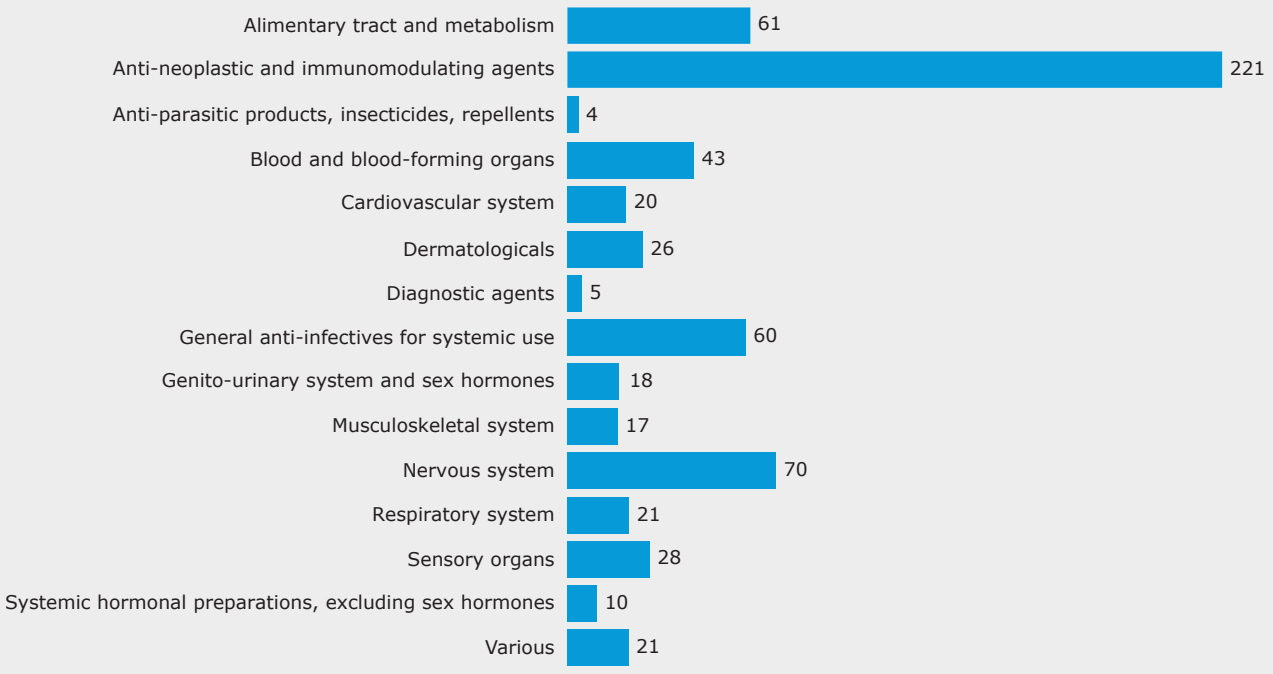
Scientific advice requests by affiliation of requester



Scientific advice and protocol assistance requests received - special programmes



Scientific advice requests by therapeutic area (2018)



Parallel consultation with HTA bodies

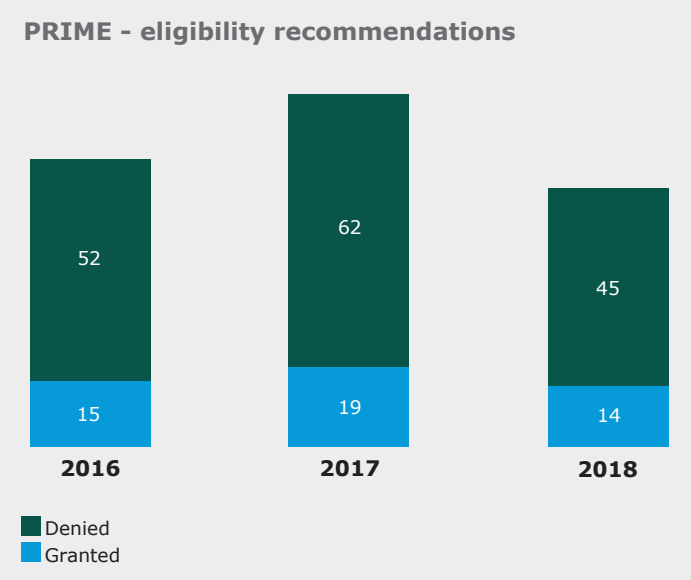
EMA and HTA bodies work together to provide medicine developers with simultaneous feedback on development plans with the aim of ensuring that the data requirements of both parties are met. A new platform for parallel consultation was launched in July 2017, replacing the previous Parallel EMA/HTA Scientific Advice procedure. In 2018, 27 requests for parallel advice on evidence generation were submitted via this tool. The requests were from the following therapeutic areas:

- Anti-neoplastic and immunomodulating agents (11)
- Nervous system (5)
- General anti-infectives for systemic use (4)
- Blood and blood-forming organs (2)
- Genito-urinary system and sex hormones (1)
- Respiratory system (1)
- Sensory organs (1)
- Various (2)

Six requests were for PRIME products, five for orphan medicines and three for ATMPs. Eight requests came from SME developers.

In terms of development stage, 67% of requests related to medicines in phase III, 29% to medicines in phase II and 4% to medicines in phase I of their clinical development.

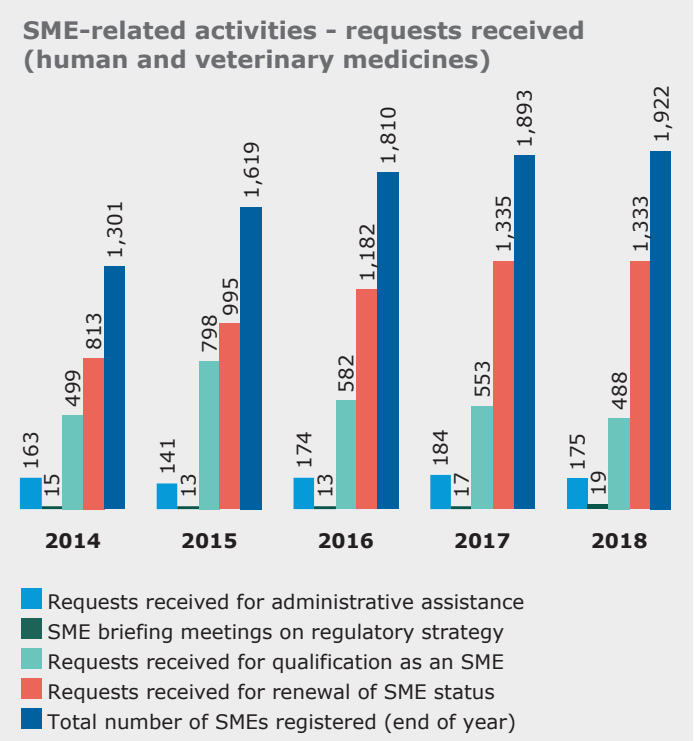
PRIME



Launched in March 2016, PRIME aims to support and optimise medicine development so that patients who have no or only unsatisfactory treatments for their disease have access to new medicines that enable them to live healthier lives. In 2018, EMA adopted a total of 59 recommendations on eligibility requests. The number of eligibility requests has been variable since 2016, when the scheme was launched. The success rate for acceptance into PRIME has remained stable at around 23%, with eligibility granted in 2018 to 14 new promising medicines, to which the Agency will provide enhanced support as part of the scheme.

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 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 various fee incentives to support their medicine-development programmes.



In 2018, the SME office dealt with 175 requests for direct assistance on administrative or regulatory aspects and organised 15 briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. A total of 1,922 SMEs were registered by the end of 2018.

Initial evaluation applications and SMEs (human medicines)					
	2014	**2015**	**2016**	**2017**	**2018**
Initial marketing authorisation applications submitted by SMEs	7	15	27	20	15
Positive opinions	5	9	4	12	13
Negative opinions	1	2	1	2	5
Withdrawals	3	1	5	7	5

In 2018, SMEs submitted 15 marketing authorisation applications, 4 of which were for orphan designated medicines. The CHMP gave a positive opinion for 13 applications. This is the highest number in the past five years, and represents 15% of all positive opinions in 2018. The CHMP gave a negative opinion for 5 applications, which is also the highest number in the past five years.

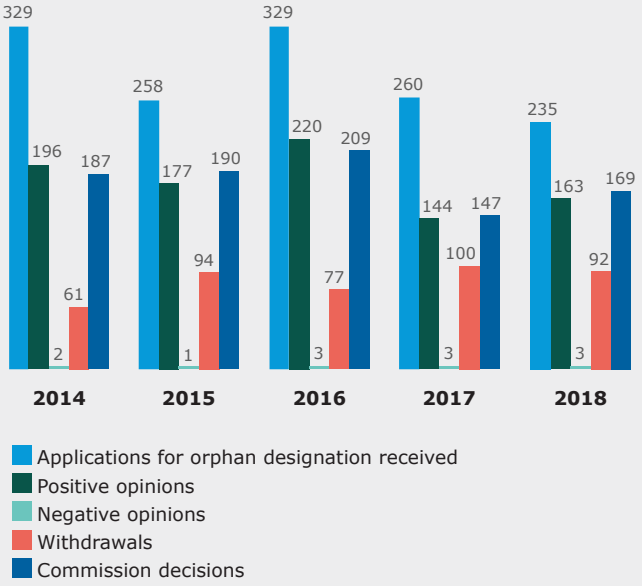
Orphan medicine designation

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 a fee reduction for scientific advice (protocol assistance) are also available for medicine developers. EMA's COMP is responsible for assessing orphan designation applications.

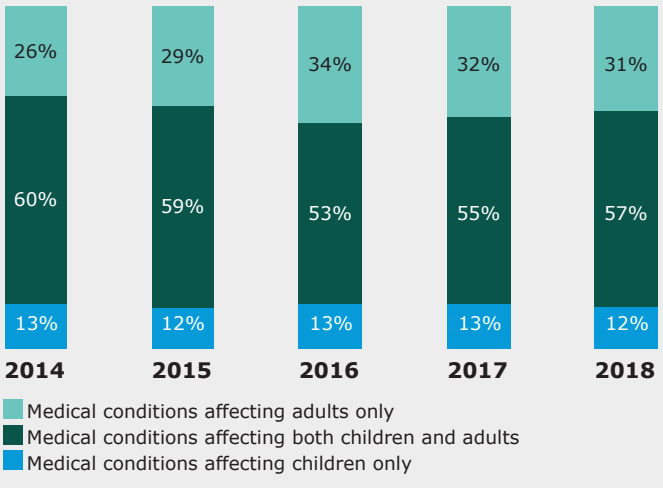
The number of applications for orphan designations was 235 in 2018, reflecting a steady identification of new targets to treat orphan diseases. Of these, 163 were granted a designation, allowing them to benefit from the incentives under the EU Orphan Framework, which is an increase compared to 2017.

The EC supports the development of medicines for rare diseases financially, with more than €11.8 million provided in 2018. More than 75% of the Commission's special contribution was used to provide protocol assistance to medicine developers and 14% for the assessment of applications for marketing authorisation.

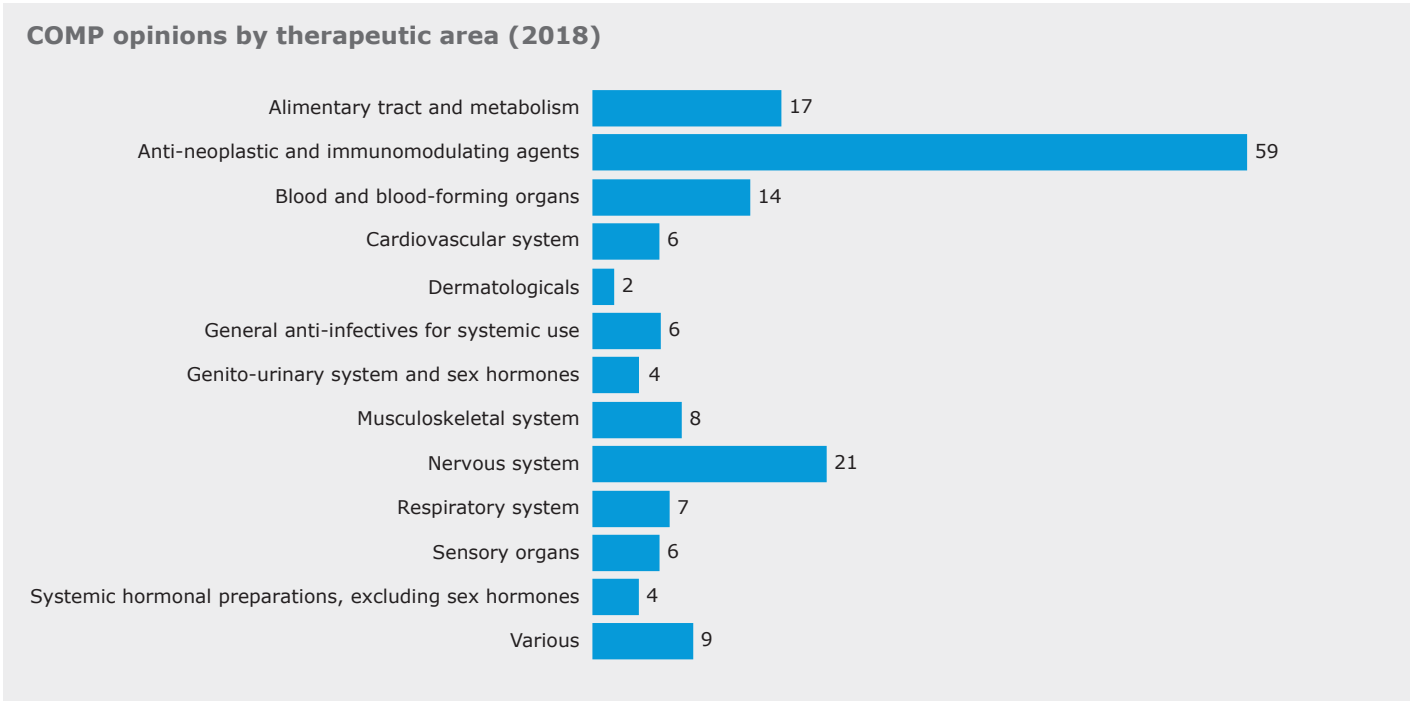
Orphan medicine designation procedures



Designated orphan medicines for the treatment of children and adults



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



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

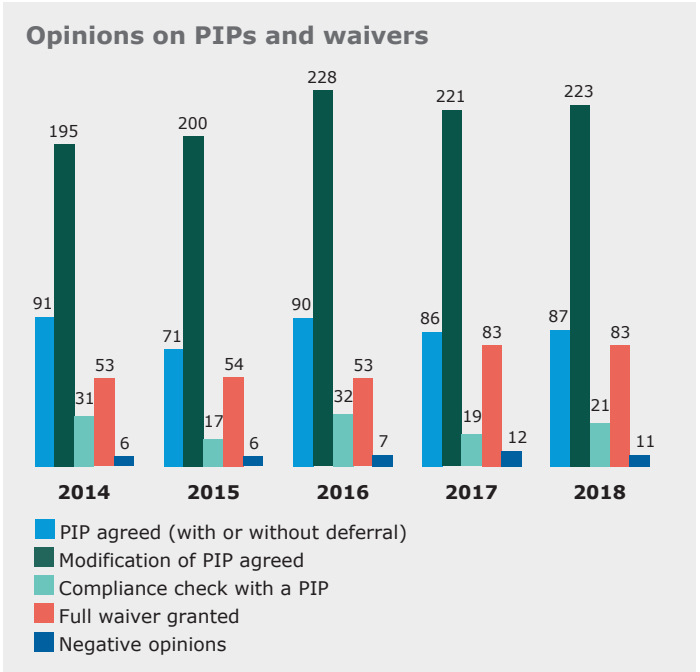
Medicines for children

The Agency also promotes the development of medicines for children. EMA's Paediatric Committee (PDCO) assesses and agrees PIPs as well as PIP waivers for medicines that are unlikely to benefit children. The committee also checks compliance with a PIP at the time of the submission of a marketing authorisation. To support research and development of medicines in children, EMA provides the secretariat for Enpr-EMA.

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 studies in children are inappropriate or unnecessary, a waiver may be granted. In 2018, the PDCO agreed 87 initial PIPs, a similar number to that in the previous year.

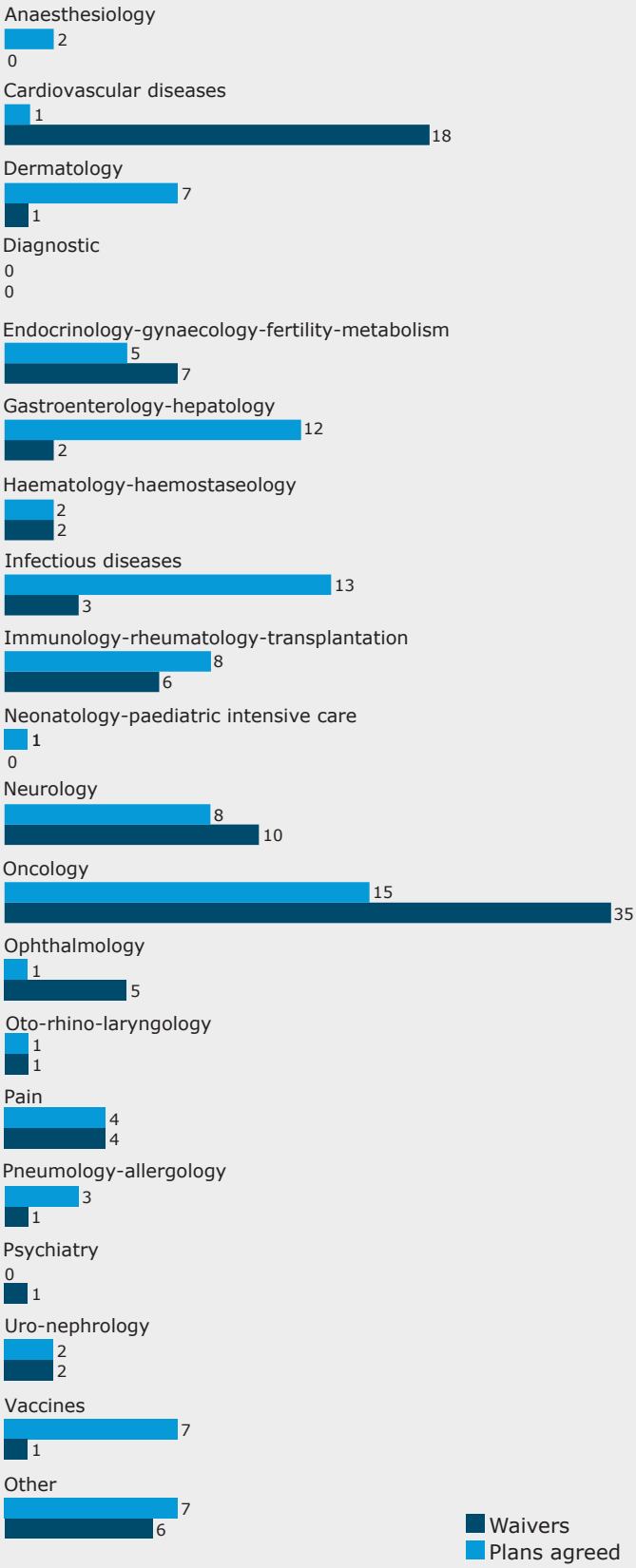
Requests for scientific advice on paediatric issues decreased slightly by 6% (from 166 to 156) compared to 2017.

A higher number of waivers were granted than in previous years. This is mainly due to the previous revocation of class waivers.



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 2018, EMA assessed 147 paediatric studies in the context of article 46, 67% more than in 2017. These studies are available to the public through the EU Clinical Trials Register.

Paediatric investigation plans agreed and waivers granted (2018)



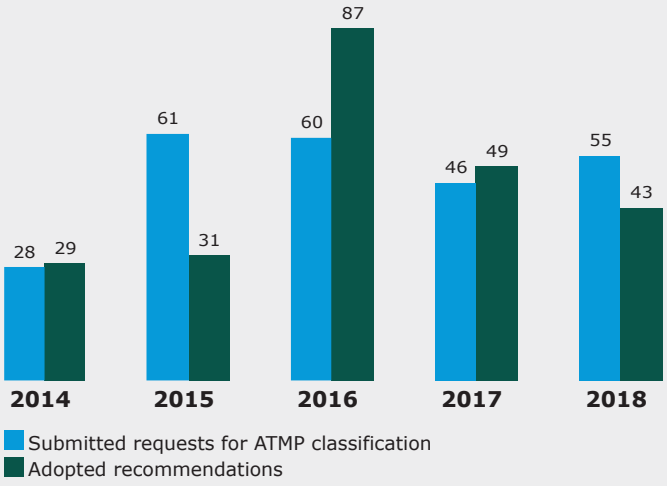
Note: All PDCO decisions can be found in the annexes.

Advanced-therapy medicinal products

ATMPs are medicines based on genes or cells that have the potential for groundbreaking new treatments. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate.

The Committee for Advanced Therapies (CAT) is responsible for assessing the quality, safety and efficacy of ATMPs. It prepares a draft opinion on each ATMP application before the CHMP adopts a final opinion for the medicine concerned. The CAT also reviews requests for the certification of quality and non-clinical data for SMEs developing ATMPs, and provides scientific recommendations on the classification of a medicine as an ATMP.

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.

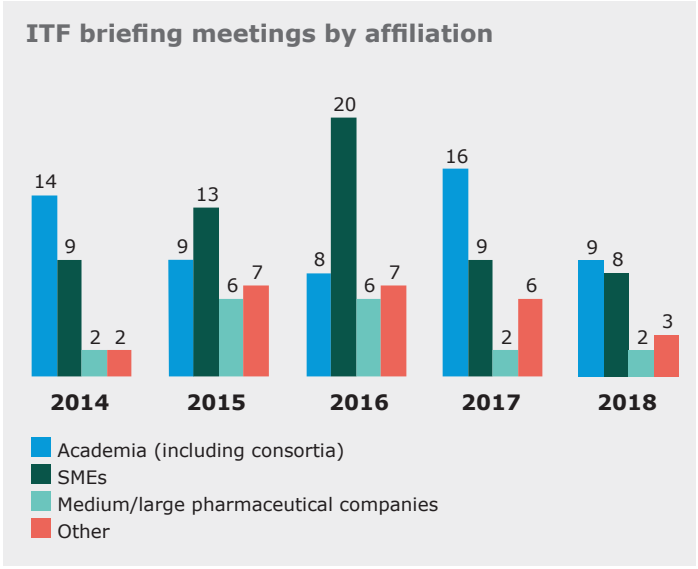
Three ATMPs were recommended for marketing authorisation by the CHMP in 2018: Luxturna, for the treatment of adults and children with inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness; and Kymriah and Yescarta the first two CAR T-cell therapies in the EU intended for the treatment of certain blood cancers.

Kymriah and Yescarta are also the first medicines supported through EMA's PRIME scheme that received a positive opinion from the CHMP (see chapter 1).

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.

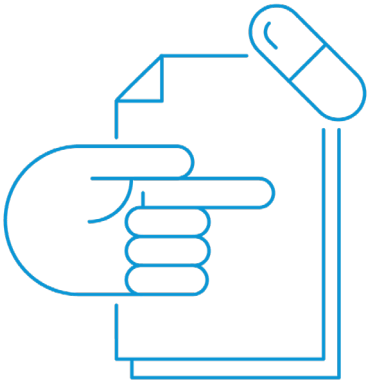
Out of 58 requests, 22 meetings took place in 2018, compared to 33 in 2017. Academic developers and SMEs took part in 77% of these meetings. Of the meetings that took place, 32% were related to innovative methods to support the development of medicines and 13% concerned ATMPs.



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.

Guidelines are drafted by EMA working parties comprised of experts from across Europe. The objective is to reflect the latest scientific developments and experience gained through scientific advice and the evaluation and monitoring of medicines. In 2018, due to EMA's Brexit preparedness plans, guideline development and revision was scaled back.



Guidelines revised in 2018 are listed below:

Topic	Content
Revised guidelines on the studies needed to support marketing authorisation applications for certain haemophilia medicines	The updated guidelines aim to optimise and facilitate the use of patient registries (rather than small clinical trials) for the investigation of recombinant and human plasma-derived factor VIII and factor IX haemophilia medicines.
Revised guideline on clinical studies for Alzheimer's disease medicines	The revised guidance is expected to facilitate the investigation and development of medicines for early and even asymptomatic stages of the disease.
Guideline on the environmental risk assessment of medicinal products for human use	The revision aims builds on the experience gained since the original guideline was introduced in 2006. New testing methods are introduced, together with an optimisation of the tiered testing strategy. Specific requirements for endocrine active substances are specifically addressed.

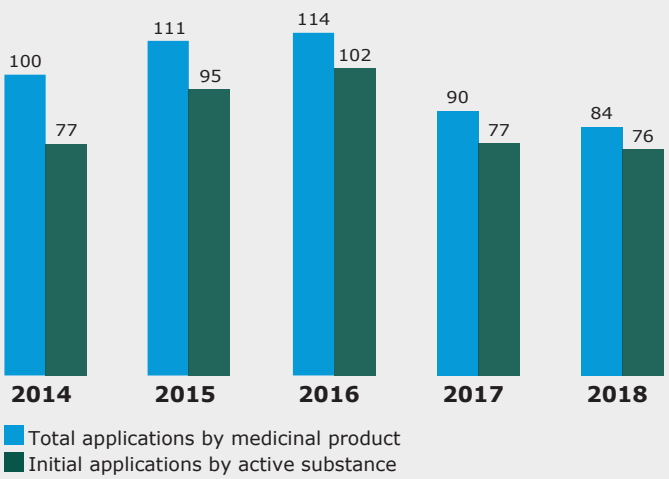
Recommendations for marketing authorisation

Applications for initial evaluation

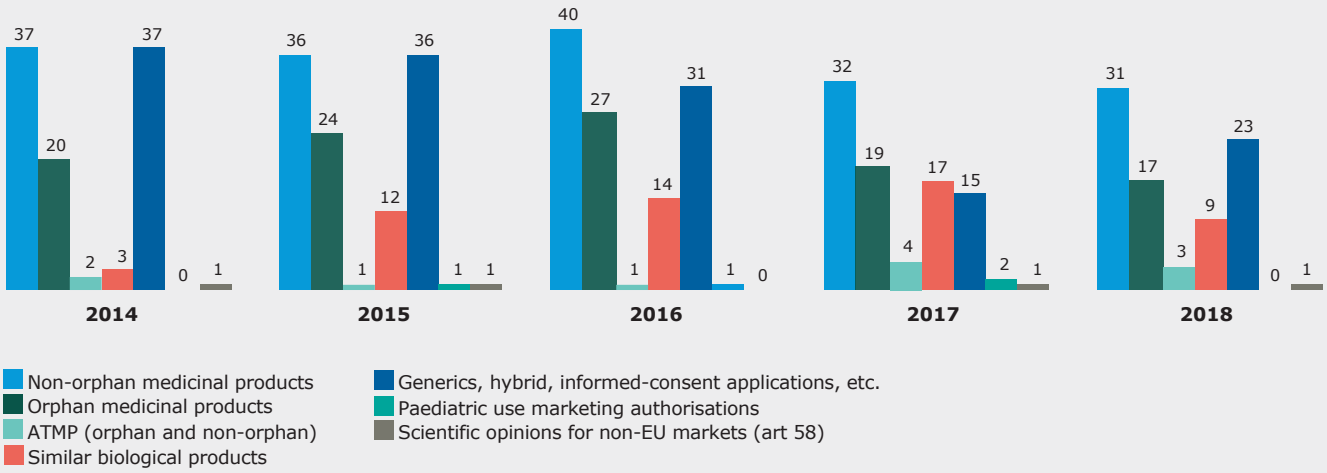
EMA's scientific committees carry out robust scientific evaluations of medicines and issue recommendations for the EC, which ultimately decides whether or not to authorise a medicine for marketing throughout the EU. The initial evaluation covers all activities relating to the processing of marketing authorisation applications for new medicines which have never been assessed before, from the pre-submission discussion with future applicants, through to the evaluation by the CHMP and the granting of the marketing authorisation by the EC.

EMA received a total of 84 applications for initial evaluation in 2018, 6% less than in 2017. Applications decreased for the second consecutive year, after the continuous growth observed between 2014 and 2016.

Initial-evaluation applications



Initial-evaluation applications by type of application



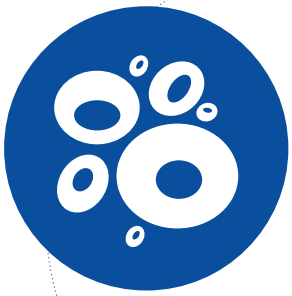
Applications for biosimilars dropped by almost half compared to 2017, breaking the upward trend observed in previous years. However, the number of applications for generic medicines rose by 80%.

EMA received one application to review a medicine under its Medicines for All programme. It is based on Article 58 of Regulation 726/2004, which allows the CHMP to assess a medicine for use in countries outside the EU in collaboration with the WHO.

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 non-EU countries. Article 58 products are required to meet the same standards as medicines intended for EU citizens.

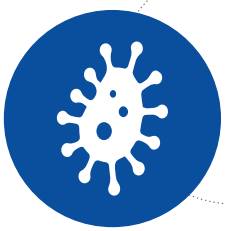
Medicines recommended for approval in 2018

Cancer



Alunbrig
Apealea
Braftovi
Carmustine Obvius
Erleada
Gefitinib Mylan
Imfinzi
Kanjinti
Kymriah
Lenalidomide Accord
Mektovi
Nerlynx
Ogivri
Pelgraz
Pemetrexed Krka
Poteligeo
Rubraca
Trazimera
Udenyca
Verzenios
Vyxeos
Yescarta
Zirabev

Infections



Alpivab
Biktarvy
Delstrigo
Fulphila
Juluca
Pelmeg
Pifeltro
Tobramycin PARI
Vabomere
Xerava
Ziextenzo

Neurology

Aimovig
Buvidal
Dzuveo
Emgality
Kigabeq
Namuscla
Onpattro
Rxulti
Slenyto
Tegsedi

Haematology/ haemostaseology

Besremi
Cablivi
Deferiprone Lipomed
Hemlibra
Jivi
Lusutrombopag Shionogi
Mylotarg
Trecondi
Veyvondi

Immunology/ rheumatology/ transplantation

Duzallo
Halimatoz
Hefiya
Hulio
Hyrimoz
Ilumetri
Zessly

Endocrinology

Lamzede
Macimorelin Aeterna Zentaris
Mepsevii
Myalepta
Nityr
Semglee

Metabolism

Amglidia
Miglustat Dipharma
Segluromet
Steglatro
Steglujan

Pneumology/ allergology

Bevespi Aerosphere
Riarify
Symkevi
Takhzyro
Trydonis

Vaccines

Dengvaxia
Flucelvax Tetra
Shingrix

Cardiovascular

Prasugrel Mylan

Hepatology/ gastroenterology

Rizmoic

Ophthalmology

Luxturna

Reproductive medicine

Ulipristal Acetate Richter

Uro-nephrology

Silodosin Recordati

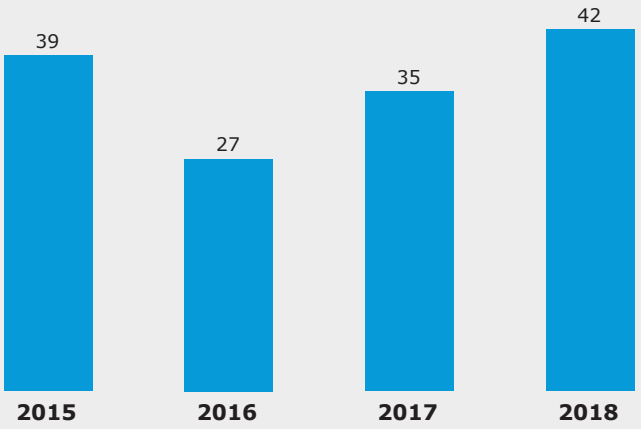
● Accelerated assessment ● Approval under exceptional circumstances ● ATMP ● Conditional marketing authorisation ● Orphan medicine ● PRIME

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

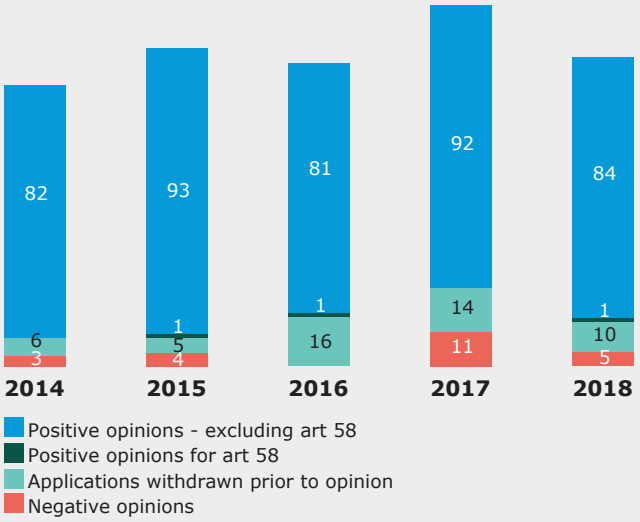
Outcome of initial evaluation

In 2018, EMA recommended 84 medicines for marketing authorisation. Of these, 42 had a new active substance which had never previously been authorised in the EU.

Positive opinions - new active substance



Outcome of initial-evaluation applications

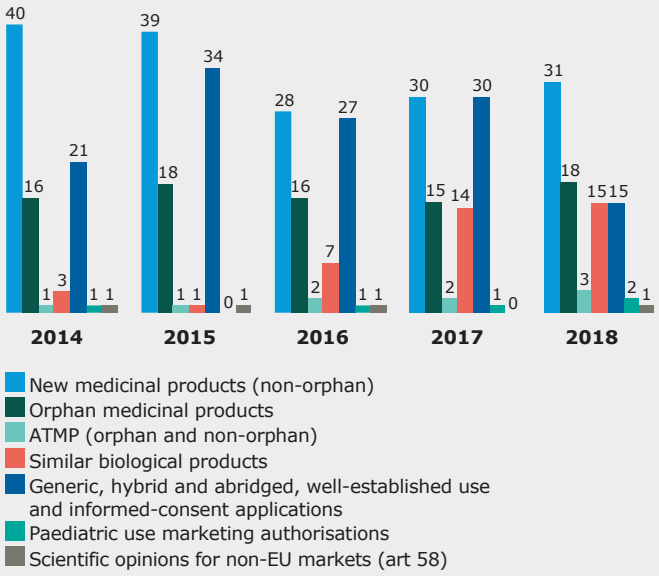


The CHMP refused to recommend marketing authorisation for 5 medicines in 2018. This figure does not include the initial negative opinion adopted on Nerlynx (neratinib) in February 2018. The applicant for this medicine requested re-examination of the committee's negative opinion and, after considering the grounds for this request, the CHMP recommended granting a marketing authorisation for Nerlynx in June 2018.

The applications for 10 medicines were withdrawn by the applicants prior to the CHMP adopting an opinion, in most cases because the data included in the application were insufficient to support a marketing authorisation.

Applicants for 69% of the medicines granted a positive opinion by the CHMP in 2018 had received scientific advice during the development phase of their medicine.

Positive opinions by type of procedure



Tenth medicine recommended for use outside the EU

In 2018, EMA adopted a positive opinion for Fexinidazole Winthrop (fexinidazole), the first oral-only medicine for the treatment of human African trypanosomiasis, commonly known as sleeping sickness, caused by Trypanosoma brucei gambiense. African trypanosomiasis is a life-threatening, neglected tropical disease that is endemic in sub-Saharan Africa. This medicine could potentially allow quicker and wider access to treatment in remote areas. It is the tenth medicine recommended by EMA under its Medicines for All programme.

Conditional marketing authorisations

One cancer medicine, Rubraca, received a recommendation for a CMA in 2018, one of the possibilities in the EU to give patients early access to new medicines. As this medicine addresses an unmet medical need, the conditional authorisation allows early approval on the basis of less complete clinical data than normally required. The authorisation is subject to specific postauthorisation obligations to generate complete data on the medicine.

In 2018, one medicine (Blincyto) that had previously received a CMA was granted a recommendation for a full marketing authorisation by the CHMP after fulfilling its post-authorisation obligations.

Since the introduction of CMA in 2006, 19 medicines out of 38 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.

CMA and switch to standard marketing authorisation (excluding withdrawals)

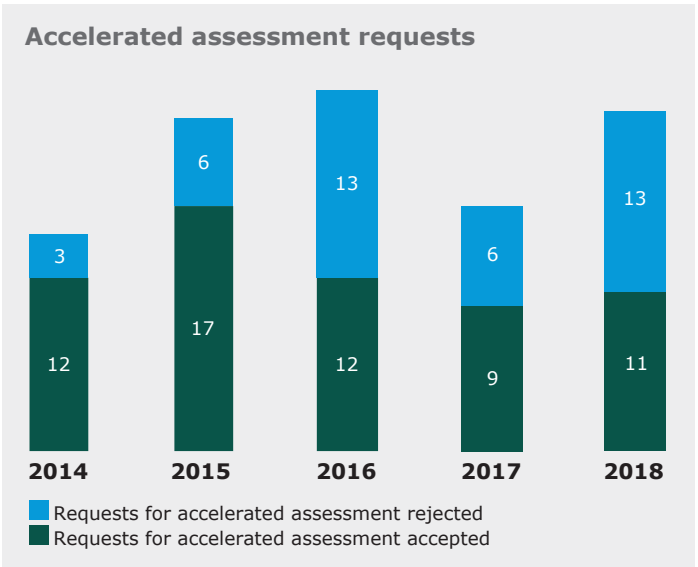
	2014	2015	2016	2017	2018
Positive opinions for CMAs	5*	3	8	3	1
Opinions recommending switch of CMA to standard marketing authorisation	2	2	2	5	1

*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

Four new medicines (Hemlibra, Onpattro, Tegsedi and Takhzyro) 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 2018, 11 requests from applicants for accelerated assessment of their medicine were accepted and 13 were rejected. The main reasons for rejection were either that the unmet medical need the medicine was expected to address was not adequately justified or that the data provided did not justify a major public health interest.



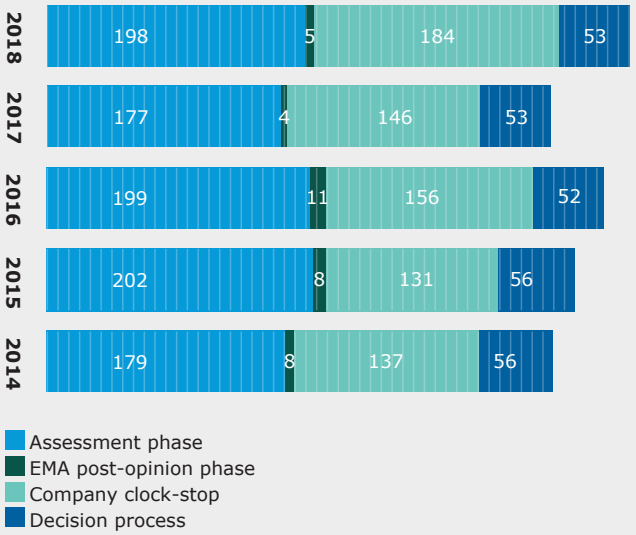
Average assessment time

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 under evaluation should be authorised. During the assessment, concerns with the application may be identified requiring further information or clarification from the company. In this case, the clock is stopped to give the company time to reply to the Agency. Once the reply is received, the counting of the days continues.

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

The overall time required for the centralised procedure in 2018 was an average of 440 days, 60 days more than in 2017. This overall increase was mainly due the companies' clock-stop time.

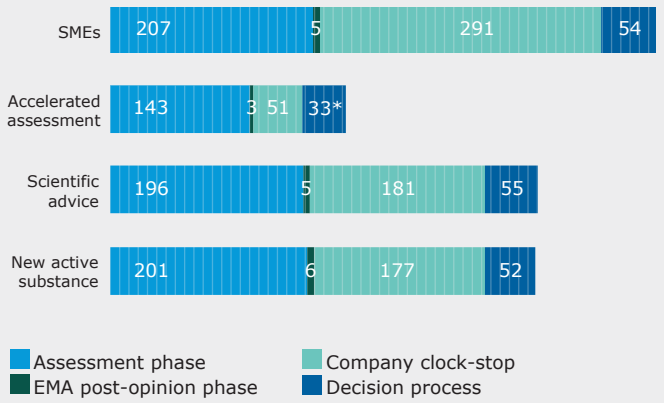
Average number of days for centralised procedures - positive opinions



For medicines evaluated under the **accelerated procedure**, the total time from start of assessment until granting of authorisation was reduced by around 4.5 months, allowing faster patient access to medicines fulfilling unmet medical needs.

The average company clock-stop for applications submitted by SMEs was longer than the overall average 184 days, but at 291 days, it was 107 days shorter than in 2017.

Average number of days for centralised procedures - subset (2018)



* This figure excludes the time until the granting of the marketing authorisation for the orphan medicinal product Verkazia.

Note: The average time for the decision process includes, in the case of orphan medicinal products, the time for the finalisation of the review of orphan designations carried out by EMA's COMP.

Post-authorisation activities

In 2018, the CHMP gave 65 positive recommendations for extension of the therapeutic indication of already authorised medicines. Almost half of these extensions of indication related to cancer medicines.

The most notable extension of a therapeutic indication was for Kineret (anakinra), for the treatment of children and adults with Still's disease, a rare disease causing inflammation of the joints as well as rash and fever.

In line with previous years, in 2018 EMA received applications for:

- 3,433 type-IA variations
- 2,164 type I-B variations
- 1,119 type-II variations
- 20 extensions of marketing authorisations

In the context of type-II variations, the product information for 414 authorised medicines was updated as new safety data were made available and assessed by EMA.

Safety monitoring of medicines

EMA and EU Member States are responsible for coordinating the EU's safety monitoring of medicines, also known as 'pharmacovigilance'. The regulatory authorities constantly monitor the safety of medicines and can take action if the safety profile or benefit-risk balance of a medicine has changed since it was authorised. EMA's safety committee, the PRAC, plays a key role in overseeing the safety of medicines in the EU as it supervises all aspects of the safety monitoring and risk management of medicines.

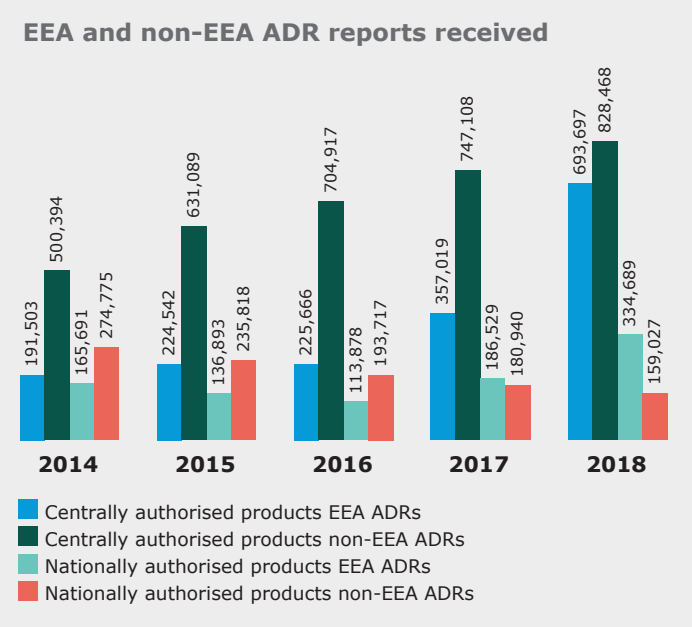
The Agency's main responsibilities in relation to the safety monitoring of medicines include coordination of the European pharmacovigilance system, operation of data and information systems in pharmacovigilance (including EudraVigilance), setting standards and guidelines for pharmacovigilance, provision of information on the safe and effective use of medicines, detecting new safety issues for CAPs, and operation and maintenance of the EudraVigilance system, including managing processes for pharmacovigilance assessments, including periodic safety update report (PSURs) and post-authorisation safety studies (PASS).

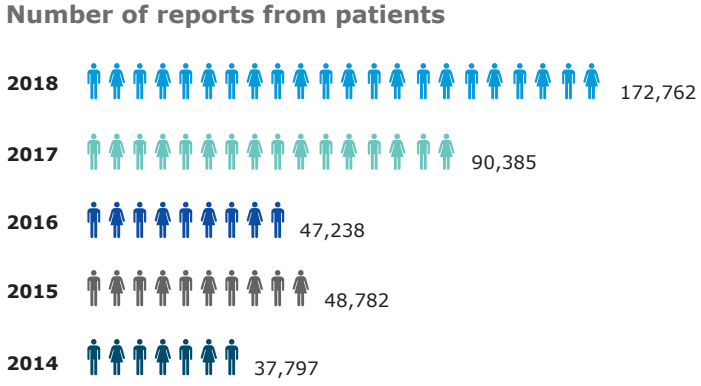
EudraVigilance

Both EMA and NCAs 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. EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or are being studied in clinical trials in the EEA.

More than 2 million ADR reports were submitted to EudraVigilance in 2018, an increase of 37% compared to 2017. This is explained in part by the launch of the new EudraVigilance system on 22 November 2017 which now also includes mandatory reporting of non-serious cases in addition to the existing serious case reporting from the EEA. Half of all reports received in EudraVigilance in 2018 originated in the EEA. Their volume increased by 89% between 2017 and 2018. The number of reports submitted by European patients and consumers almost doubled in the same period. This is a significant expansion, which reflects the reporting of non-serious reports to EudraVigilance and patients' commitment to reporting side effects as a result of EU and national information campaigns.

In 2018, 17 external requests for EudraVigilance analyses were sent to EMA by EU citizens, such as healthcare professionals, patients, academics, companies or journalists. This is almost half the number of requests received in 2017 (32). The reduction is likely due to more data being made available to the public in an improved and more accessible format, including redacted EU Individual Case Safety Reports (ICSRs). This increased access became available on www.adrreports.eu in late 2017.





Note: Following the launch of the new EudraVigilance system in November 2017, figures in 2017 and 2018 include reports of non-serious cases.

			2016	2017	2018
Number of external requests for EudraVigilance analyses			34	32	17

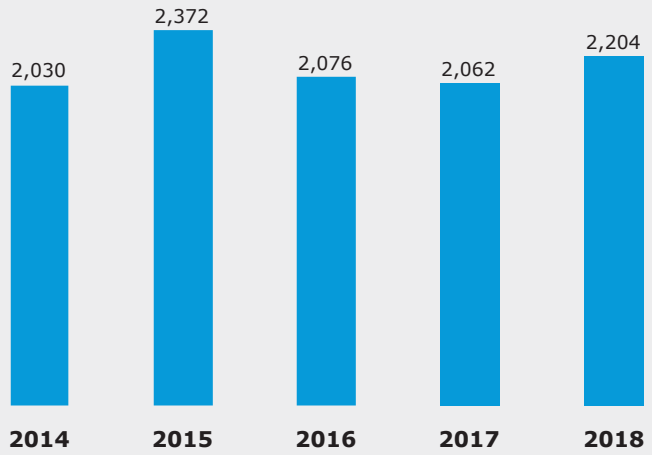
Signal detection

A safety signal is information on a new or known adverse event that 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 signal is a routine pharmacovigilance activity to establish whether or not there is a causal relationship between a medicine and a reported adverse event.

In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary. This mostly consists of changes in the information on medicines available for patients (in the package leaflet) and prescribers (in the summary of product characteristics).

In 2018, 2,204 potential signals were reviewed by EMA, almost 80% of which originated from monitoring the EudraVigilance database. This led to a significant increase in the number of EMA signals assessed by the PRAC. Furthermore, when the signals detected by the NCAs are included, there was a 39% increase in signals assessed by the PRAC. In addition to signal detection activities and assessments at PRAC level, experts from NCAs, in collaboration with EMA provided a major contribution to the signal detection methods development and to continuous process improvement.

Signal detection



Outcome of signal assessment

2,204 potential signals were reviewed by EMA.

114 confirmed signals were prioritised and assessed by the PRAC, an increase of almost 40% compared to 2017.

Out of these, 74 signals were detected and validated by EMA, representing a 72% increase compared to last year.

40 signals were detected and validated by EU Member States.

Out of 114 confirmed signals

- 50 signals led to an update of the product information
  6 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers
- 24 signals led to a recommendation for routine pharmacovigilance
- 39 signals were still under review by the PRAC at the end of 2018 as further data were required
- 1 signal led to the update of the Risk Management Plan (RMP) for better characterisation of the risk

Signal detection

	2014	2015	2016	2017	2018
Signals reviewed by EMA	2,030	2,372	2,076	2,062	2,204
Signals validated by EMA and assessed by the PRAC	34	61	48	43	74
Signals validated by Member States and assessed by the PRAC	56	41	46	39	40
Total signals validated and assessed by the PRAC	90	102	94	82	114

Signal assessment					
	2014	**2015**	**2016**	**2017**	**2018**
Total number of signals analysed by the PRAC	90	102	94	82	114
Signal assessment leading to update of product information	37	34	28	33	50
Signal assessment leading to update of product information + DHPC	7	4	3	2	6
Signal assessment leading to referral procedure	2	1	4	1	-
Signal assessment leading to other regulatory actions, e.g. change to RMP or conduct of study	2	5	2	-	1
Signal assessment closed and recommendation for routine pharmacovigilance	18	27	30	20	24
Signal assessment ongoing	31	35	30	28	39

Periodic safety update reports

At regular predefined intervals following the authorisation of a medicine, marketing authorisation holders are required to submit a report to the regulatory authorities on the evaluation of the benefit-risk balance of the medicine. These reports summarise data on the benefits and risks of a medicine and take into consideration all studies carried out with it, both in authorised and unauthorised indications.

The Agency is responsible for procedures supporting the analysis of these reports for CAPs and for NAPs that are authorised in more than one Member State. These reports are called Periodic Safety Update Reports (PSURs). 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 (PSUSA).

In 2018, the PRAC started the assessment of 881 PSURs and PSUSAs, of which one third represent single assessments of active substances only contained in NAPs, an activity initiated by EMA in 2015. Based on this assessments, 901 recommendations were issued by the PRAC, a 7% increase compared to 2017. Of the total assessments, 36% consisted of single assessments of active substances only contained in NAPs.

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

PSURs and PSUSAs finalised					
	2014	**2015**	**2016**	**2017**	**2018**
Stand-alone PSURs (CAPs only) finalised	426	470	511	540	537
Single-assessment PSURs (CAPs with NAPs) finalised	45	27	16	39	43
Single-assessment PSURs (NAPs only) finalised	0	136	264	263	321
Total outcomes	471	633	791	842	901

PRAC outcomes of PSURs and PSUSAs					
	2014	**2015**	**2016**	**2017**	**2018**
Maintenance	383	500	637	680	735
NAPs only				207	245
CAPs/NAPs and CAPs only				473	490
Variation	88	133	154	162	166
NAPs only				56	76
CAPs/NAPs and CAPs only				106	90
Total outcomes	471	633	791	842	901

Post-authorisation safety studies and post-authorisation efficacy studies

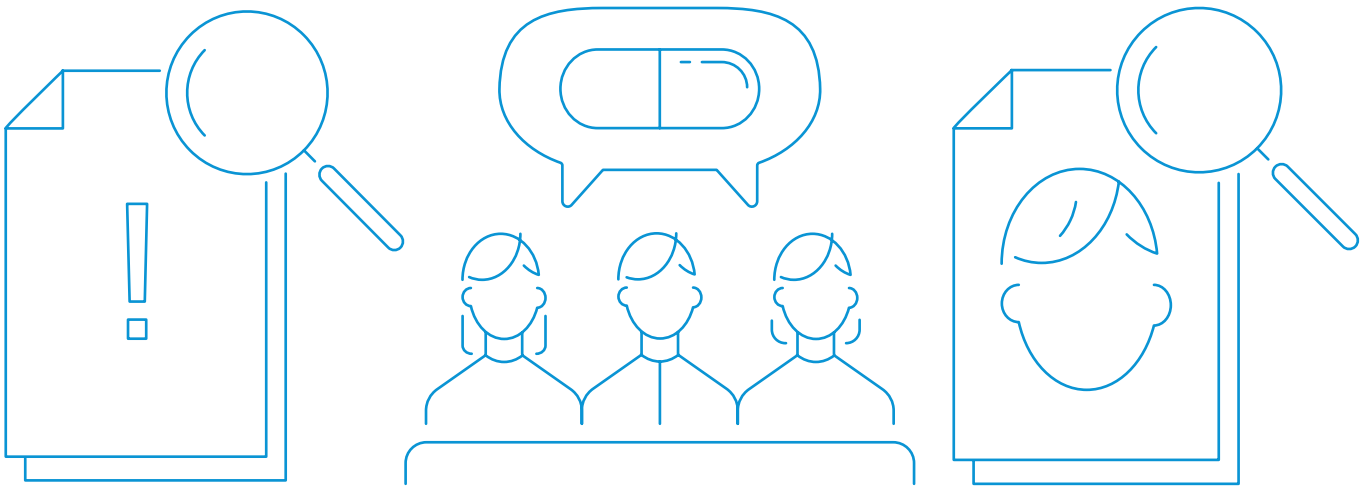
A post-authorisation safety study (PASS) can be carried out after a medicine has been authorised to obtain further information on its safety, or to determine the effectiveness of risk-management measures. A PASS can be imposed on marketing authorisation holders as part of their post-authorisation obligations. The PRAC is responsible for assessing the protocols of imposed PASSs and their results. The PRAC also reviews protocols of large numbers of voluntarily submitted PASSs in the context of RMP assessments.

In 2018, the PRAC assessed nine imposed PASS protocols that were requested to obtain further information on a medicine's safety, almost twice as many as in 2017. The committee conducted 196 procedures to assess non-imposed PASS protocols.

In addition, the PRAC started the assessment of the results of 8 imposed PASSs. The same number of PASS results was finalised in 2018.

Post-authorisation efficacy studies (PAES) are also 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.

The CHMP imposed four PAES on companies to collect further data on the benefits of medicines while they are used by patients in real life.



Post-authorisation safety studies					
	2014	**2015**	**2016**	**2017**	**2018**
Imposed PASS protocol procedures started	32	20	12	6	17
Imposed PASS protocol procedures finalised		20	10	5	9
Non-imposed PASS protocol procedures started	3			333	195
Non-imposed PASS protocol procedures finalised				265	196
PASS amendment	0	1	12 (started), 7 (finalised)	11 (started), 10 (finalised)	11 (started), 11 (finalised)
Imposed PASS result procedures started		2	3	6	8
Imposed PASS result procedures finalised	5	0	3	3	8
PASS scientific advice through SAWP		0	3	0	3

Post-authorisation efficacy studies					
	2014	**2015**	**2016**	**2017**	**2018**
PAES (imposed)	0	23		19	4
PAES (non-imposed)	0			1	2

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 regulatory 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 NCAs in the EEA. The list of withdrawn products is also published on the EMA website.

The number of notifications of withdrawn products rose by more than a third (37%) between 2017 and 2018. This increase was driven by commercial reasons, as no significant increase in safety withdrawals was seen. Of the 413 notifications in 2018, 39 (10%) were due to quality, safety or efficacy reasons.

Notifications of withdrawn products received					
	2014	**2015**	**2016**	**2017**	**2018**
Notifications related to quality, safety or efficacy	43	39	40	38	39
Notifications related to commercial/ industrial reasons	89	121	78	264	374
Total number of notifications	132	160	118	302	413

Other pharmacovigilance activities

Additional monitoring aims primarily to enhance ADR reporting for certain types of medicines. 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 2018, 351 medicines were subject to additional monitoring, an increase of 4% compared to 2017.

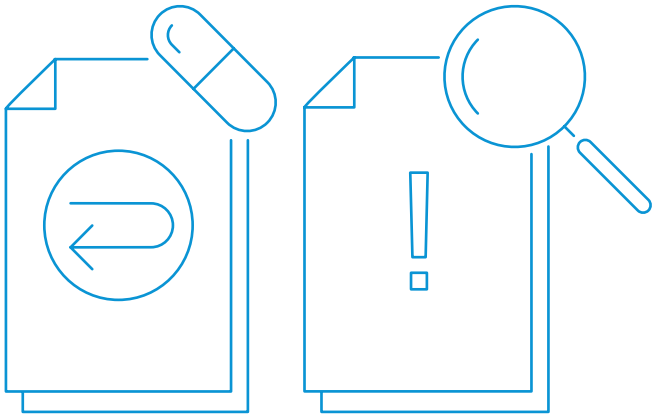
The EU **incident management plan** is coordinated by EMA and aims to ensure that concerned bodies in the EU take appropriate action whenever new events or information (known in this context as incidents) arise concerning human medicines. It covers medicines authorised centrally, nationally and through the decentralised procedure (DCP) and mutual-recognition procedures (MRP). The plan's execution involves representatives from EMA, the EC and regulatory authorities in the Member States. Since its inception, the plan has been reviewed and amended, in particular to reflect the provisions in the 2010 pharmacovigilance legislation. In 2018, 11 incidents triggered the plan, almost three times more than in the previous year. In addition, a crisis simulation exercise was completed and a summary report published on the EMA website.

The **European pharmacovigilance issues tracking tool (EPITT)** is a database developed by EMA to promote the discussion of pharmacovigilance and risk-management issues between the Agency and Member States. It provides access to documents related to the safety of medicinal products/substances authorised in the EEA. While EPITT is not exclusively part of the EudraVigilance system, it helps medicines regulatory authorities in the EEA and EMA to track signals at EU level. In 2018, 44 non-urgent information or rapid alert notifications were submitted through EPITT.

Scientific and medical literature is an important source of information to identify suspected adverse reactions to medicines authorised in the EU. EMA is responsible for monitoring a number of substances and selected medical literature to identify suspected adverse reactions to medicines authorised in the EU, and for entering the relevant information into the EudraVigilance database. In 2018, 13,275 ICSRs resulted from EMA's medical literature monitoring (MLM) service.

Other pharmacovigilance activities			
	2016	**2017**	**2018**
Cumulative number of products on the list of products to be subject to additional monitoring	301	336	351
Number of incidents triggering incident management plan	7	4	11
Number of non-urgent information or rapid alert notifications submitted through EPITT	49	61	44
Number of MLM ICSRs created	8,495	14,193	13,275

Referral procedures



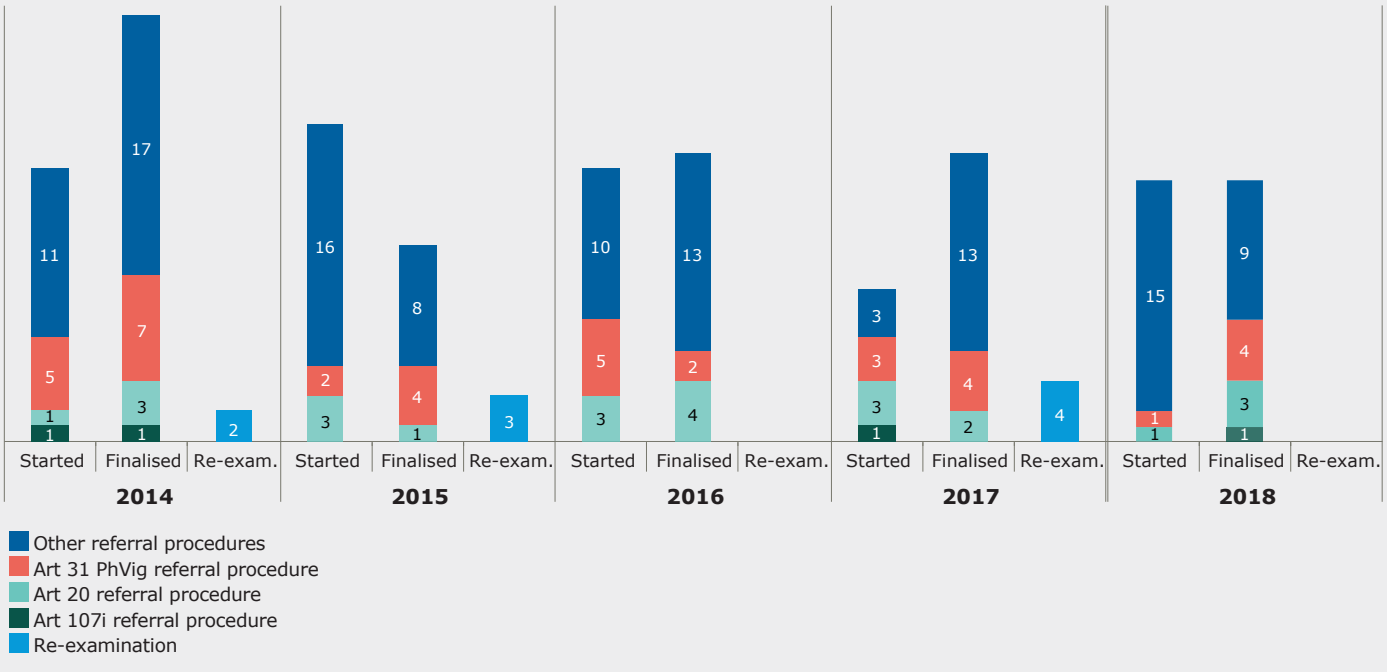
Referral procedures are initiated to address concerns over the safety or benefit-risk balance of a medicine, as well as to deal with disagreement among Member States on the use of a medicine. In a referral, EMA is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine or class of medicines, and issue a recommendation. Following the recommendation, the EC will issue a legally binding decision for the EU. Less often, in cases where only NAPs are concerned, the decision is taken by the CMDh. If the CMDh position is agreed by majority (not by consensus), the EC will issue a final decision that is applicable throughout the EU.

In 2018, 17 referral procedures were finalised. Of these, 8 were related to the safety of medicines, initiated under Articles 31, 20 or 107i of the pharmacovigilance legislation. Around one third of these procedures (5) led to changes to the product information, 2 led to the suspension of marketing authorisation and one resulted in revocation of marketing authorisation.

The remaining 9 referral procedures were initiated to address:

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

Referrals for human medicines finalised or re-examinations

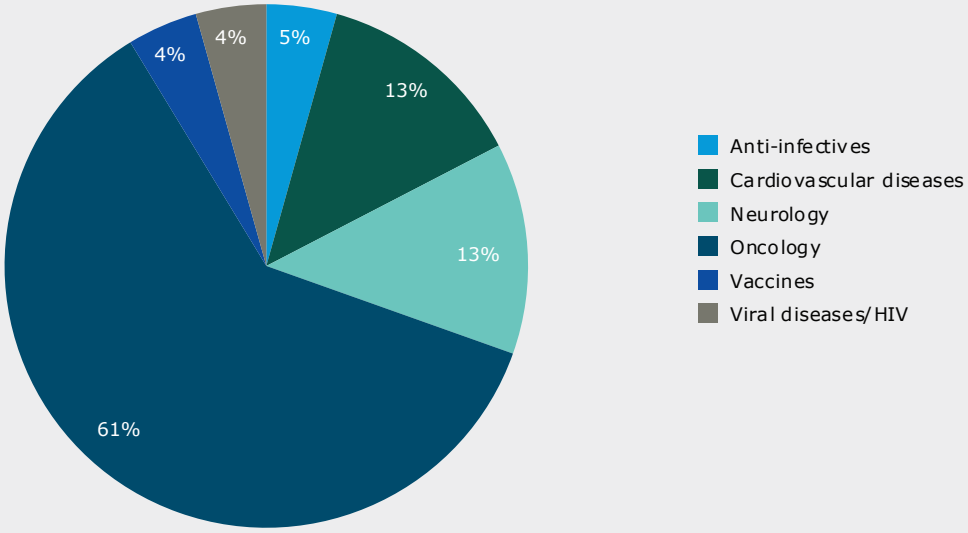


Contribution of experts, patients and healthcare professionals to scientific assessments

EMA's scientific committees can consult additional experts, patients and healthcare professionals to enrich their scientific assessment of medicines. These external parties may be involved in SAGs or ad-hoc expert groups.

A total of 32 consultations took place in 2018 in the form of SAG meetings, compared to 30 in 2017 and 19 in 2016. Of these, 25 consultations included patients or carers.

Areas of discussions - SAGs and ad-hoc expert groups meetings (2018)



Procedures with SAGs or ad hoc expert group involvement (number of consultations)

	2014	2015	2016	2017	2018
Marketing authorisation (new marketing authorisation applications, re-examinations of new marketing authorisation applications, Art 58)	14	7	8	14	19
Extension of indication (including line extensions)	2	2	6	3	10
Referral (including re-examination)	5	3	5	11	3
Guideline	1	1	0	1	0
Other topics (renewal, PSUR, signal, class review)	1	3	0	1	0
Total	23	16	19	30	32

Involvement of patients and healthcare professionals

Patients and healthcare professionals 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. Patients and healthcare professionals participate by:

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

Patient involvement in EMA activities (interactions)

	2014	2015	2016	2017	2018
Scientific advice/protocol assistance	37	76	82	158	107
SAGs/ad-hoc expert meetings	35	23	28	46	37
Scientific committee/working party consultations	25	24	50	104	112
Workshops	104	115	141	138	N/A*
Working groups and other ad hoc activities	192	313	290	269	N/A*
Patient membership in the Management Board, committees, working parties	55	55	58	59	59
Document reviews conducted by patients and consumers	185	137	120	176	178

* Triggered by EMA's BCP implementation in 2018, quantification of these activities has been discontinued.

Healthcare professional (HCP) involvement in EMA activities (interactions)

	2014	2015	2016	2017	2018
Scientific advice/protocol assistance	0	1	1	1	0
SAGs/ad-hoc expert meetings	32	21	26	40	31
Scientific committee/working party consultations	41	47	31	74	47
Workshops	64	59	106	83	N/A*
Working groups and other ad hoc activities	67	184	129	160	N/A*
HCP membership in Management Board, committees, working parties	49	47	51	54	54
Document reviews conducted by healthcare professionals	43	29	55	33	80

* Triggered by EMA's BCP implementation in 2018, quantification of these activities has been discontinued.

Herbal medicines

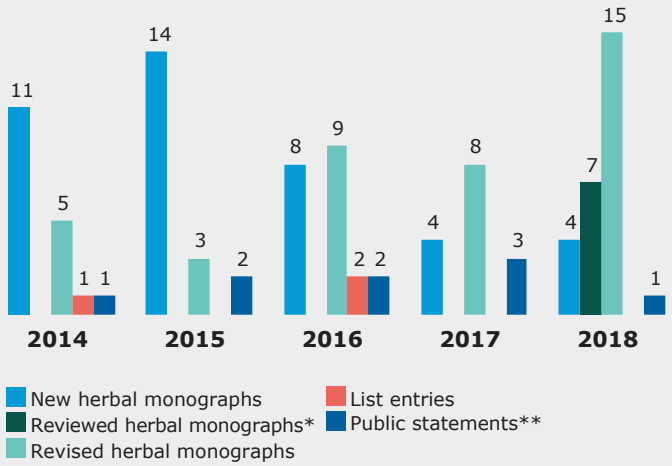
The Agency's Committee on Herbal Medicinal Products (HMPC) is responsible for preparing opinions on herbal medicines with the aim of promoting an increasingly harmonised process for licensing and information on herbal substances across the EU. The HMPC establishes EU monographs for traditional and well-established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

The assessment of 5 new herbal substances was completed in 2018, leading to the publication of 4 final EU monographs and 1 final public statement, following public consultations. Following a systematic review of newly-available data, 15 monographs were updated.

* When no change in monograph is required after review of new data, an addendum to the previous assessment report is prepared (otherwise start of revision procedure leads to a revised monograph.)

** When the assessment does not lead to a monograph, a public statement is prepared.

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



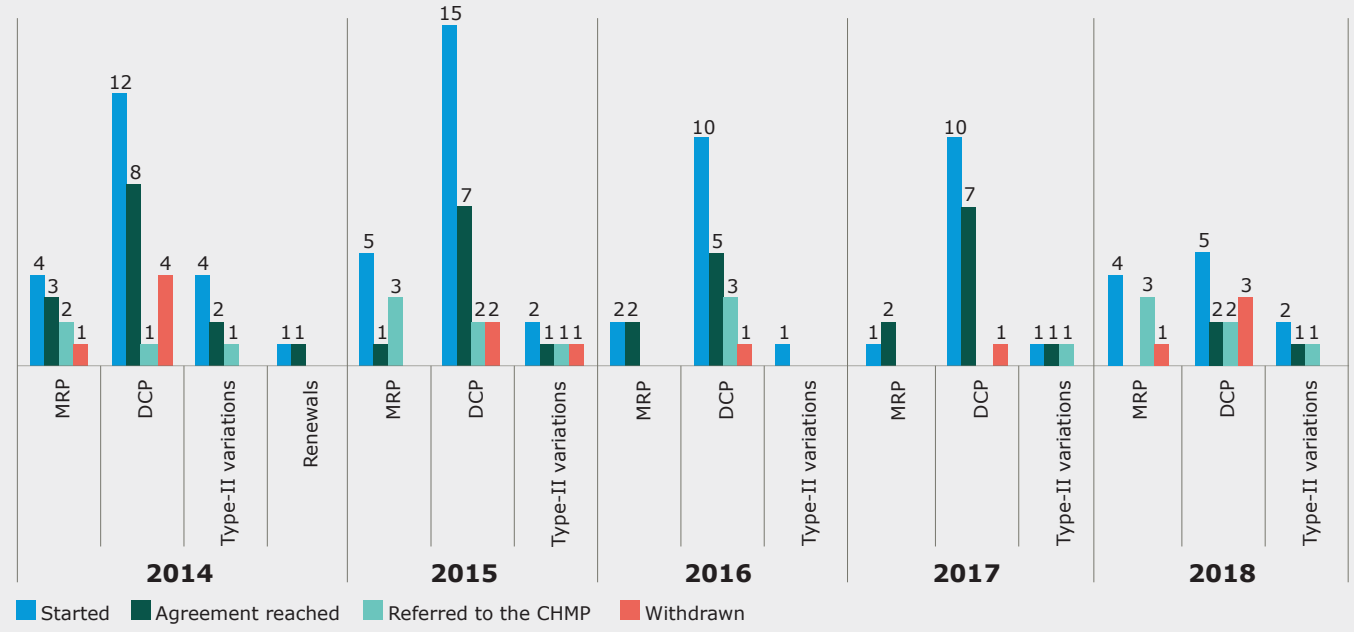
Note: A complete list of recommendations on herbal medicines can be found in the annexes.

Mutual-recognition and decentralised procedures

Of the medicines entering the EU market, 90% are nationally authorised. These are mainly generics which reach the market through the mutual recognition procedure and the decentralised procedure, 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. In addition to this, EMA has promoted consistency of scientific requirements applied by EU Member states through the publication of 14 product-specific bioequivalence guidelines, at the request of CMDh.

Detailed information about the work of the CMDh in 2018 in relation to pharmacovigilance and referrals can be found on the HMA website.

Applications referred to the CMDh



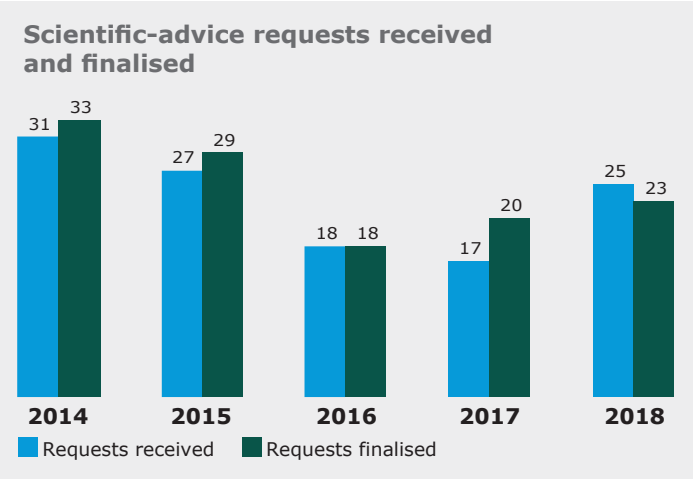
Veterinary medicines

Supporting research and development

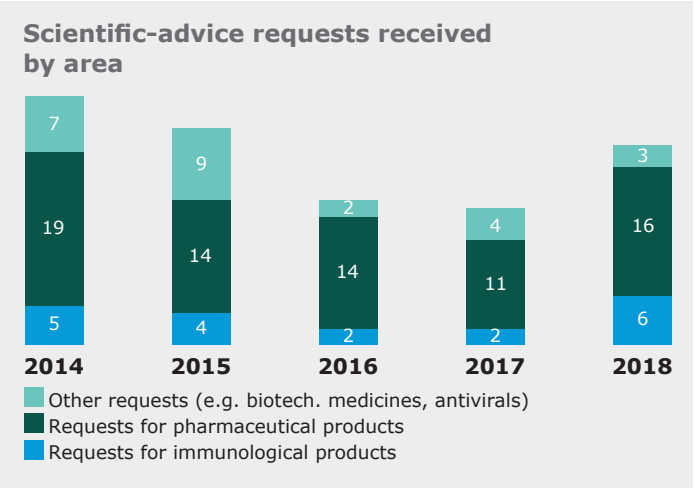
The Agency provides pre-authorisation support to medicine developers to boost innovation and research and enhance the availability of safe and effective veterinary medicines. This is achieved through a number of activities and incentives offered to companies prior to submitting an application for marketing 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 all 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.



EMA received 25 requests for scientific advice in 2018 and finalised 23, including some that had been pending from 2017. The number of requests has grown after a decline in the last two years, indicating an increased interest from medicine developers in engaging early with the Agency. Almost a quarter of all scientific advice requests received were for immunologicals, including vaccines. These types of medicine play a major role in protecting animal health by preventing and controlling serious epizootic diseases. They also have an impact on human health by ensuring safe food supplies and preventing animal-to-human transmission of infectious diseases. In addition, veterinary vaccines can be an efficient tool in reducing the need to use antibiotics in animals, thereby contributing to the fight against AMR.

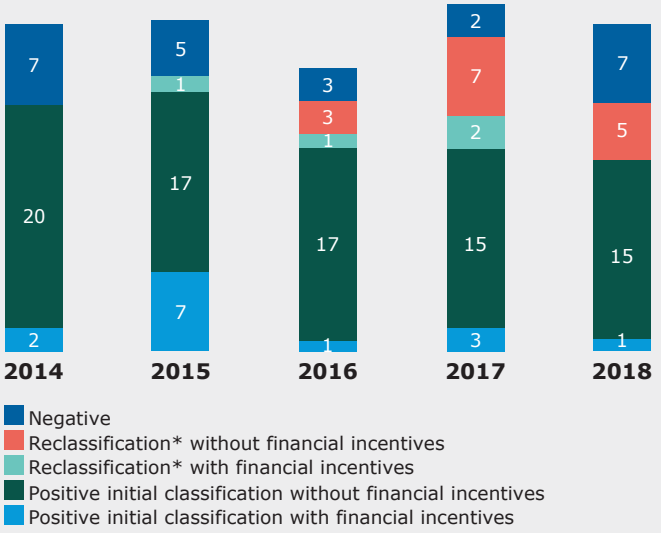


Minor Use Minor Species

The Agency's MUMS/limited market policy was adopted in 2009 and revised in 2013/2014. The goal is to stimulate development of new veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment.

In 2018, the Agency received a total of 32 new requests for the (re)classification of veterinary medicines intended for MUMS/limited markets, showing a stable interest from medicine developers in developing products for minor uses or minor species.

MUMS/limited market (re)classification requests outcome



* Reclassification only started in 2014, as the first MUMS designations were issued in 2009 and have a 5-year term.

Support to SMEs

The Agency began its SME initiative in December 2005 to promote innovation and development of medicines by SMEs. This initiative provides 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 a dedicated newsletter.

Of the 1,922 SMEs registered with EMA at the end of 2018, 70 are developing veterinary products and 81 both human and veterinary products.

Innovation Task Force

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

Five ITF meetings concerning the development of veterinary medicines were requested and held in 2018.

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.

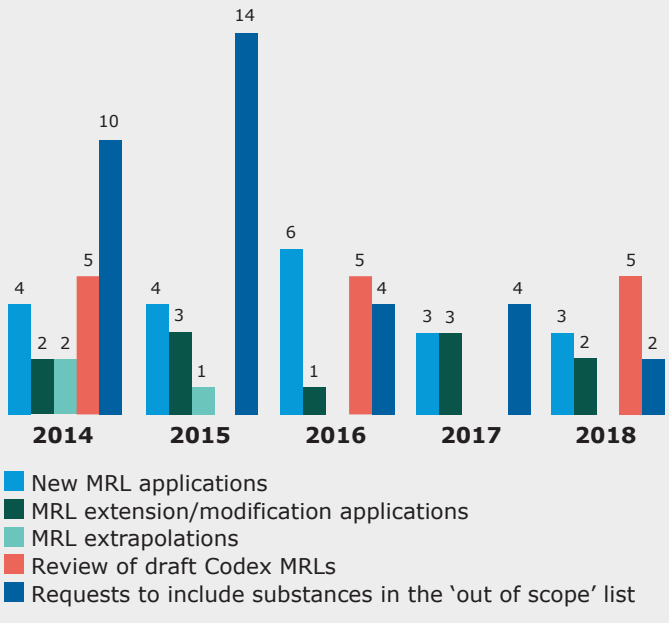
In spite of scaling back guideline development and revision in 2018, due to EMA's BCP, 21 guidelines and 7 reflection papers were published (either final or for public consultation) regarding veterinary medicines, mainly completing work initiated in previous years.

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 MRLs that establish how much residue of a pharmacologically active substance used in veterinary medicinal products for food-producing animals is safe for human consumption. The objective is to ensure the safety of foodstuffs of animal origin, including meat, fish, milk, eggs and honey. The MRL has to be established before a marketing authorisation application for a new medicine can be submitted. EMA is also responsible 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 2018. In addition, the CVMP received applications for the extension, modification or review of existing MRL classifications for two substances.

Evaluation of maximum residue limits



Recommendations for marketing authorisations

Applications for initial evaluation

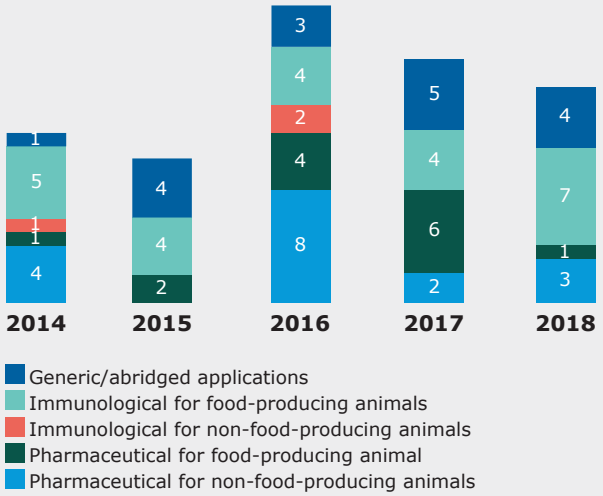
The initial evaluation phase covers activities relating to the processing of marketing authorisations for veterinary medicines, ranging from pre-submission meetings with future applicants, through evaluation by the CVMP to the granting of a marketing authorisation by the EC.

A total of 15 applications were received in 2018.

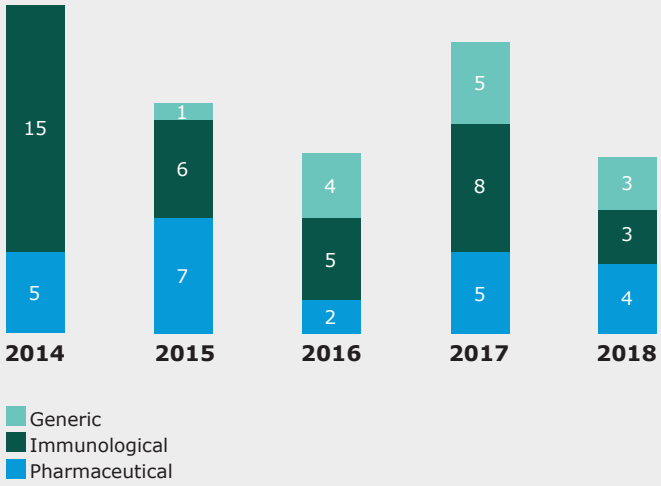
Recommendations for authorisation

Ten new veterinary medicines were granted a positive opinion in 2018. With three withdrawn applications and three negative opinions, the proportion of negative outcomes for applications was unusually high, at 37.5%.

Applications for initial evaluations received

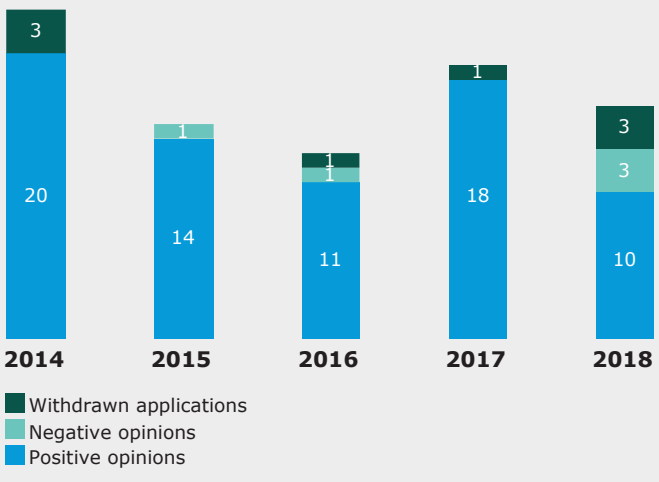


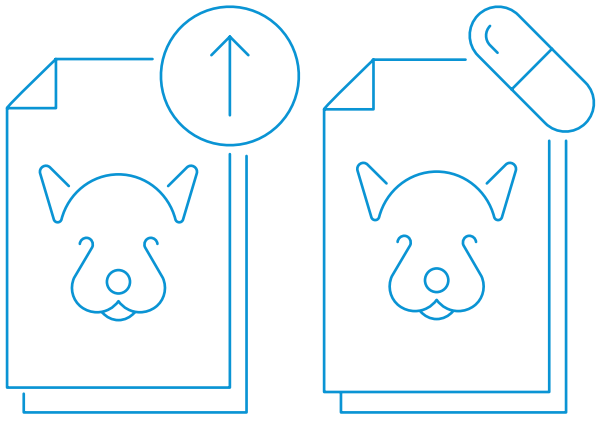
Positive opinions for veterinary medicines



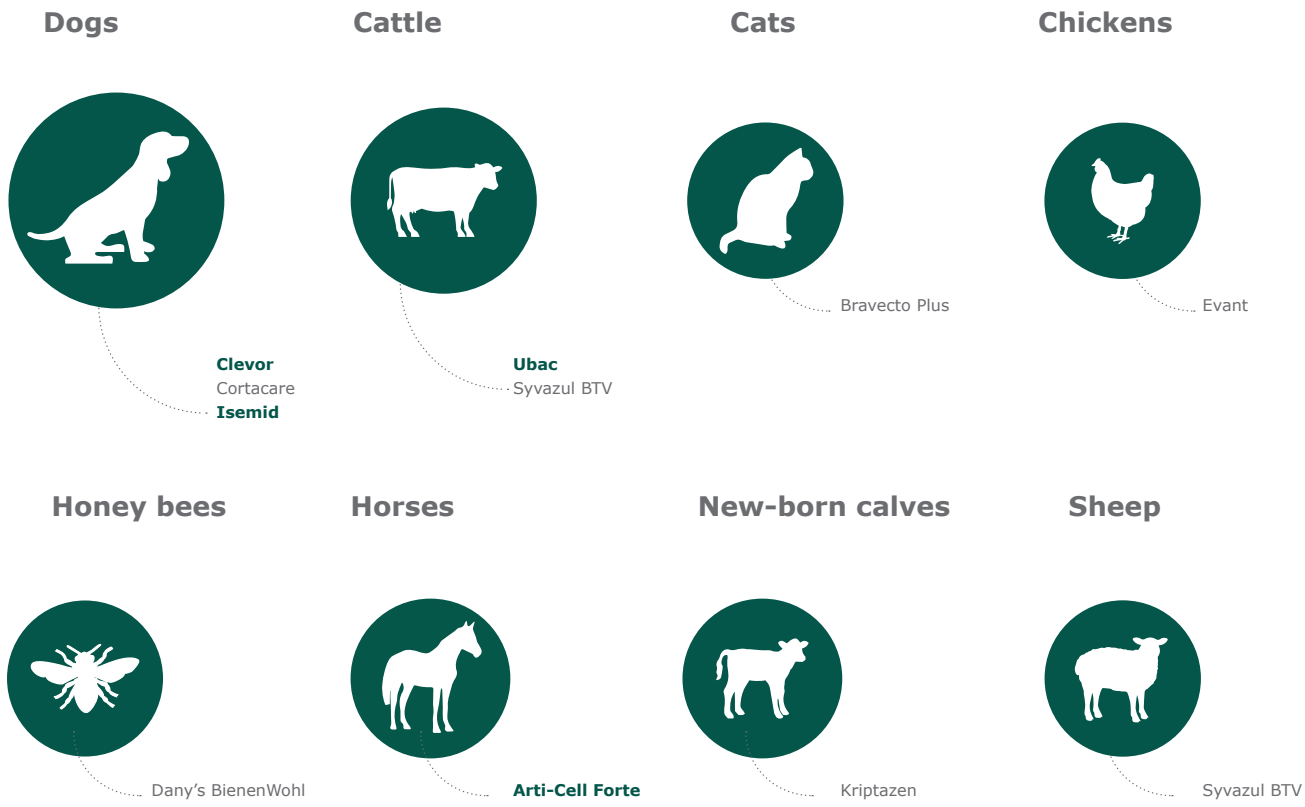
In 2018, 7 applications were for immunological products for food-producing animals. The steadily increasing number of applications demonstrates the animal health industry's continued strong interest in developing vaccines. Vaccines are an alternative option to combat infectious diseases and by reducing the need for antimicrobials they also indirectly reduce the risk of AMR in food-producing animals.

Outcome of initial-evaluation applications



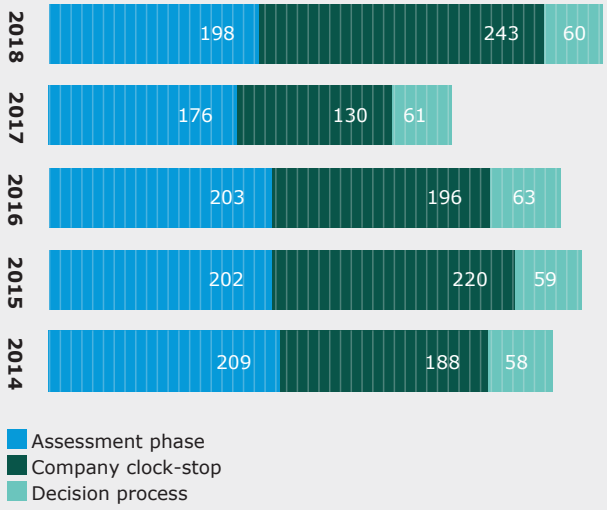


New veterinary medicines in 2018



Medicines that contain a new active substance are highlighted in green.

Average number of days for initial evaluations

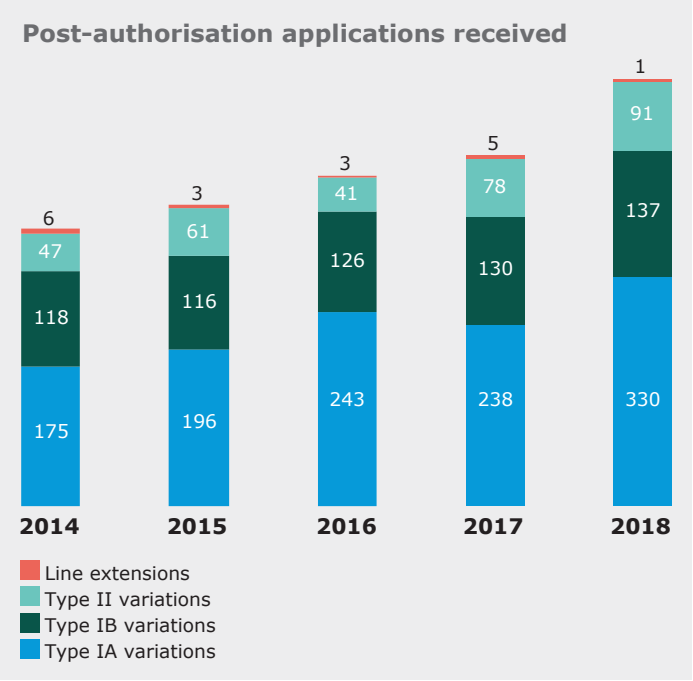


The average number of days taken for centralised procedures slightly increased compared to the past years, mostly due to longer clock-stops. It is not yet possible to determine if this increase in the time taken by companies to respond to issues arising during assessment is a trend or if it is due to the particular medicines assessed in 2018.

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, in line with the number of products authorised through the centralised procedure. In 2018, the overall number of post-authorisation applications increased by around 20%. This is a combination of an unusually high number of pharmacovigilance Type IA variations received in correlation to UK's withdrawal from the EU and the natural annual increase due to more products being on the market.

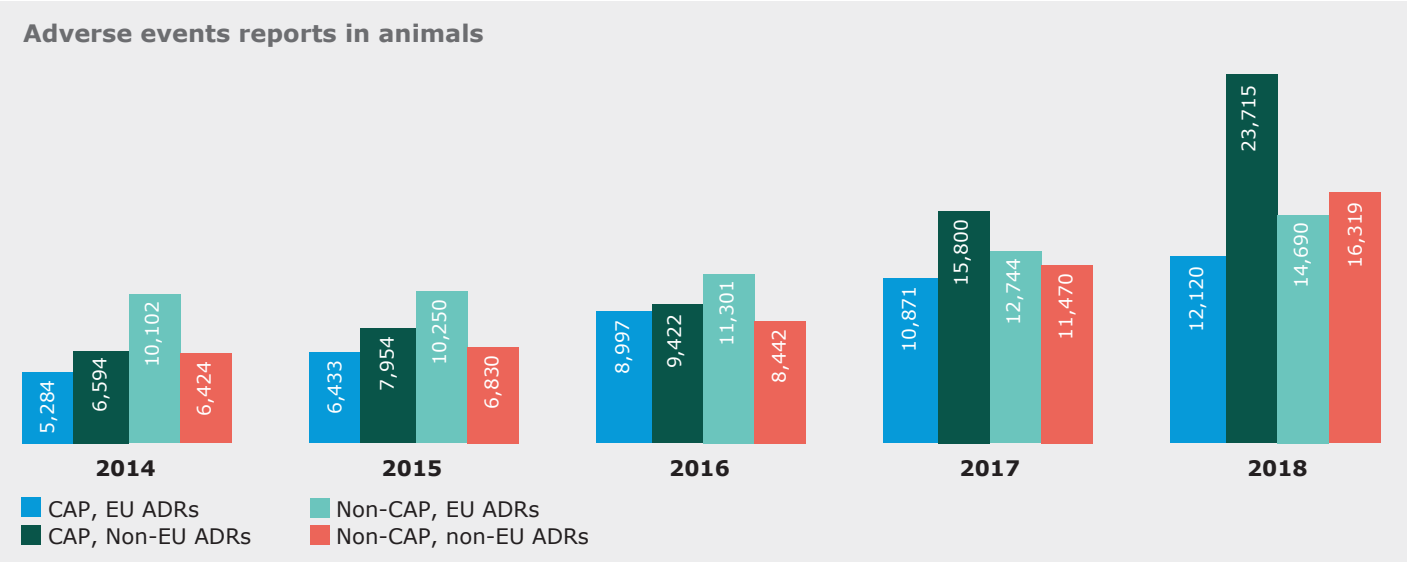


Safety monitoring of medicines

Pharmacovigilance covers activities relating to the detection, reporting, assessment, understanding and prevention of adverse events 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.

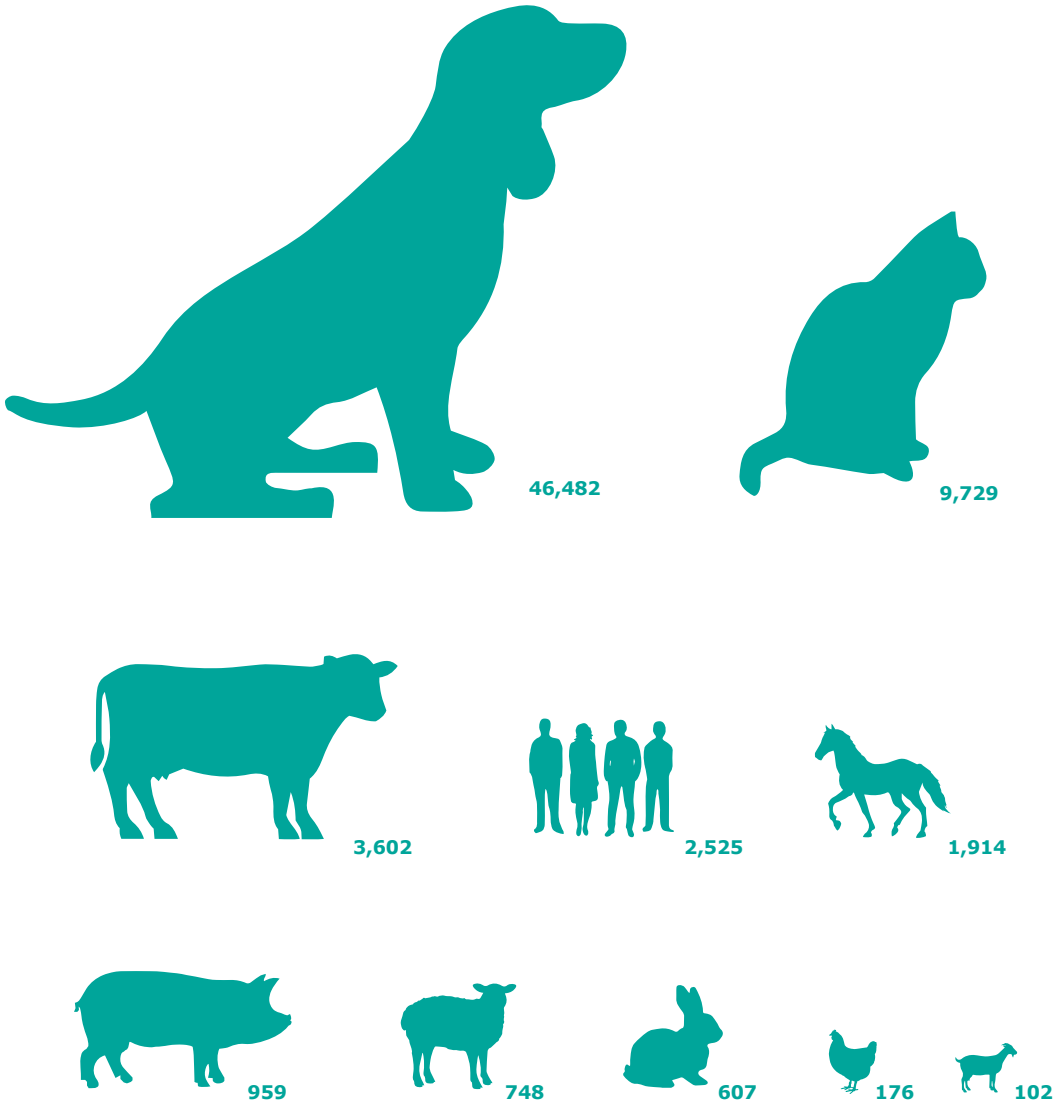
EudraVigilance

The number of AE reports received in the EudraVigilance system is steadily growing year on year.



A significant increase (30%) in the overall number of adverse event reports received in EudraVigilance was observed, similarly to the situation already seen in 2017. A steady growth in reporting, year on year, can be expected due to the increased number of centrally authorised veterinary medicinal products and the improved awareness among veterinarians of the value of pharmacovigilance reporting, as well as greater control by regulators of the implementation of pharmacovigilance requirements by the veterinary pharmaceutical industry. In addition, during the last two years, an increase of voluntary submission by marketing authorisation holders of non-serious reports has been noted. In 2018 in particular, there was a significant increase in voluntary electronic reporting of non-serious adverse events from some non-EU countries (50%) by marketing authorisation holders implementing the CVMP revised recommendation for the basic surveillance of EVVet data for CAPs.

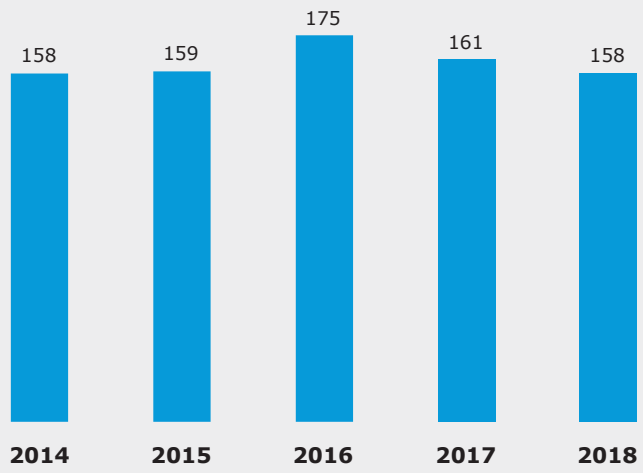
Number of adverse reports per species



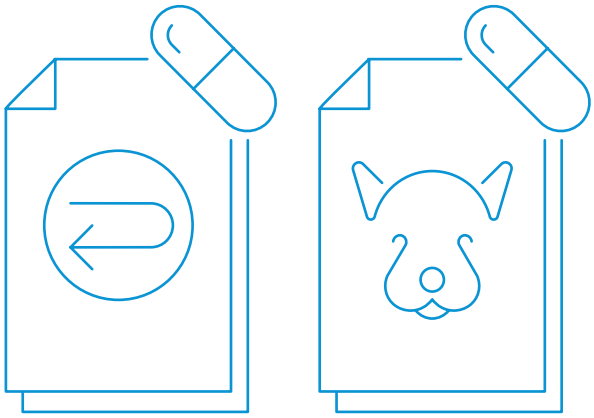
Periodic safety update reports

A PSUR provides an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at pre-defined intervals 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



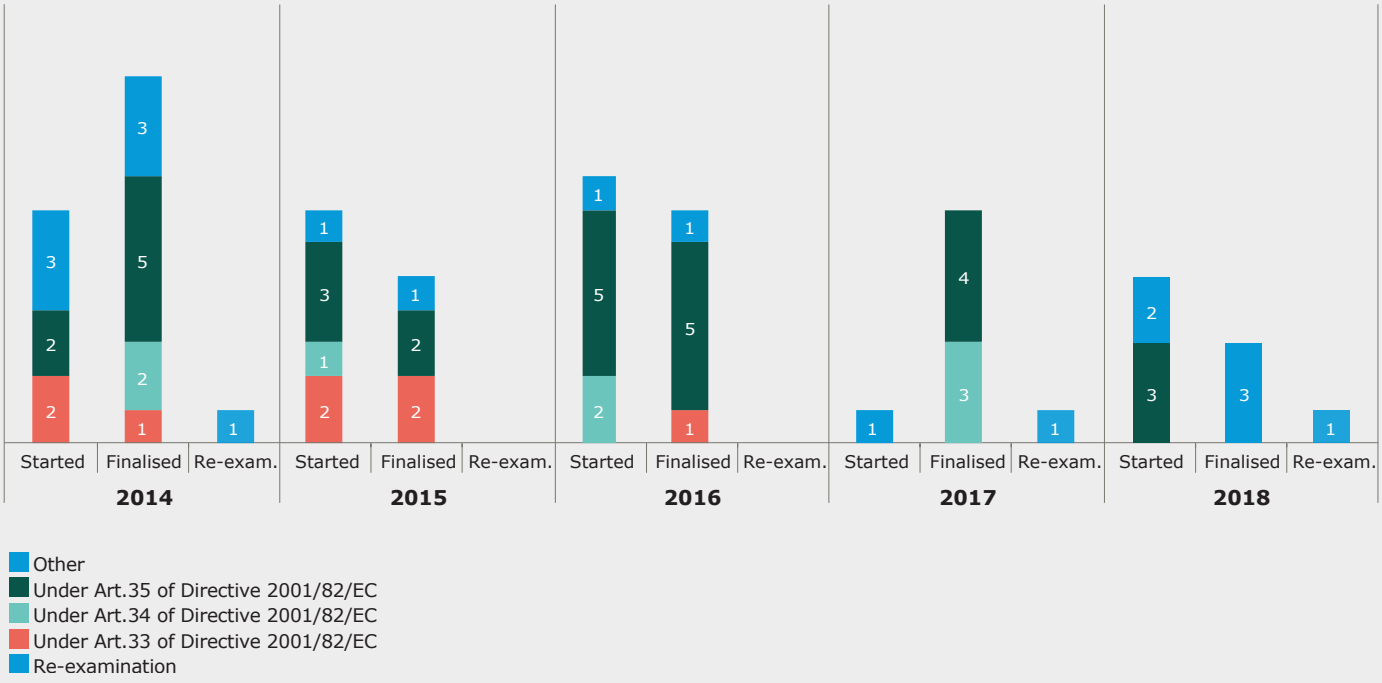
Referral procedures



Referral procedures are initiated to address concerns over the quality, safety, efficacy or benefit-risk balance of a veterinary medicine, or deal with 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 issue a cross-EU recommendation. The recommendation subsequently results in a legally-binding decision throughout the EU adopted by the EC.

In 2018, 3 referral procedures were finalised. All of them were triggered by disagreement between Member States in the context of the mutual-recognition or decentralised authorisation procedure (under Article 33 of Directive 2001/82/EC).

Arbitration and referrals for veterinary medicines

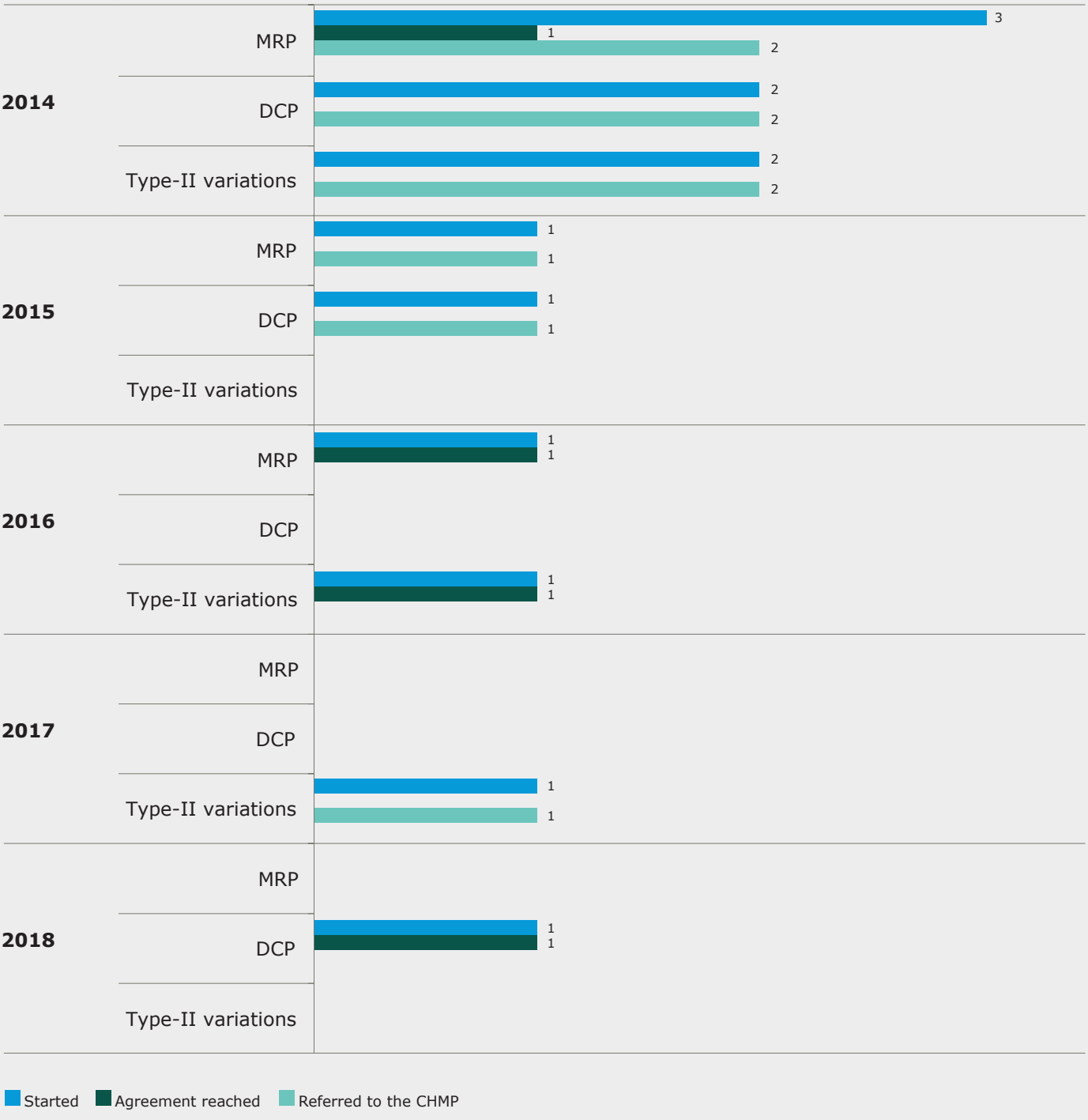


Note: Complete information on referral procedures can be found in the annexes.

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 the 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 4,000 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, twenty-six working parties, nine SAGs and a number of other ad-hoc advisory groups as well as members of the assessment teams carrying out the evaluation of medicines (see the annex for further information on these groups).

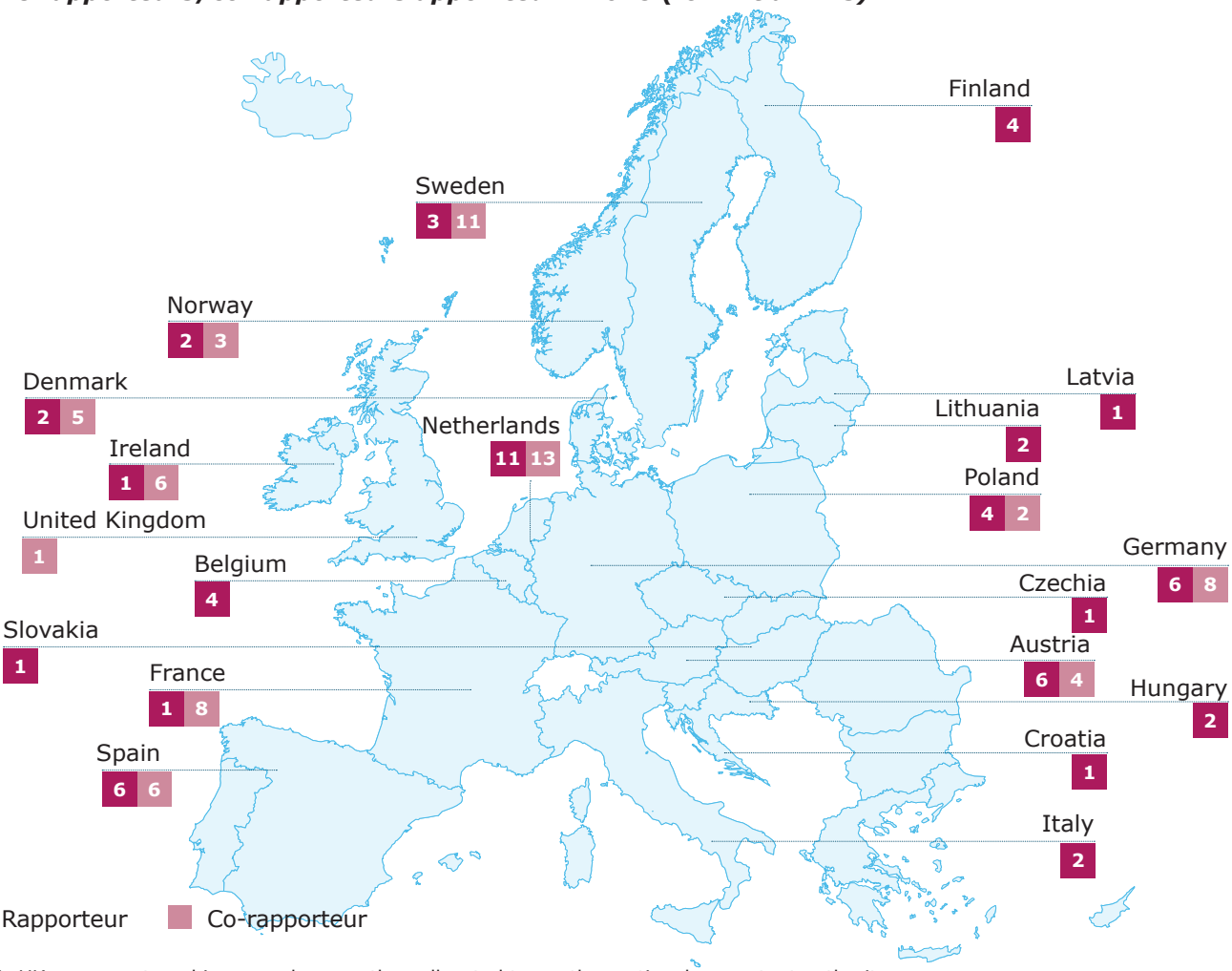
Rapporteurships/co-rapporteurships

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. The appointment is made on the basis of the best available expertise for the particular product. Rapporteurs work through assessment procedures and also take the lead in evaluating any new information on the medicine that may become available.

In April 2018, in preparation for the UK's withdrawal from the EU, the EU27 Member States and EMA completed the reallocation of the medicines for which the UK's MHRA and VMD were rapporteur or co-rapporteur.

Over 370 CAPs were transferred to new rapporteurs and co-rapporteurs from the EU27 Member States, plus Iceland and Norway, following a methodology developed by EMA's working groups on committees' operational preparedness for human and veterinary medicines whereby products were transferred based on the expertise and resources of the Member State.

PRAC rapporteurs/co-rapporteurs appointed in 2018 (for initial MAs)



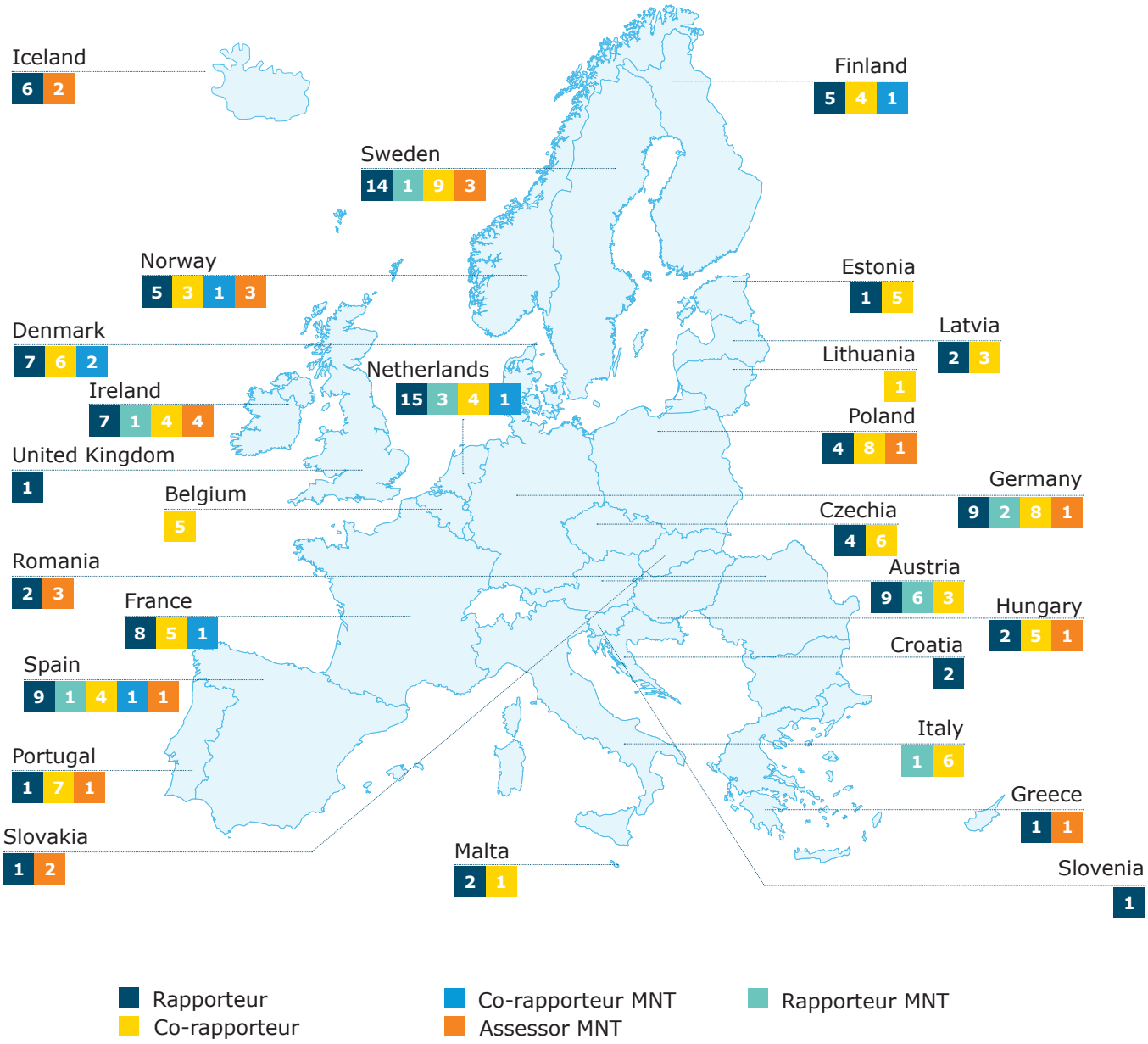
*This UK co-rapporteurship was subsequently reallocated to another national competent authority.

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 table below presents the number of procedures in which each country was involved in 2018 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.

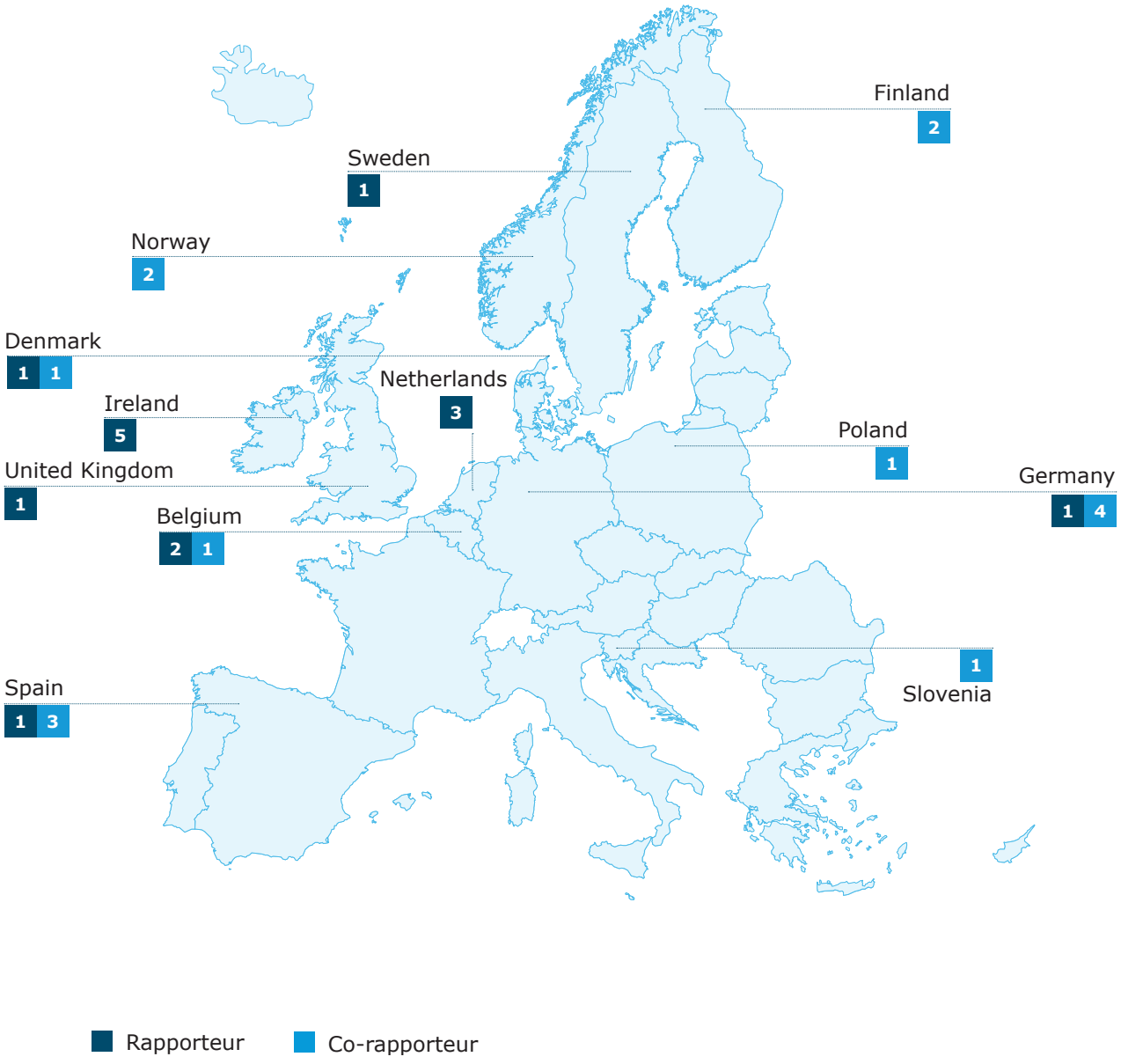
CHMP rapporteurs/co-rapporteurs appointed in 2018 (for initial marketing authorisations, including generics)



*This UK rapporteurship was subsequently reallocated to another NCA.

CVMP rapporteurships/co-rapporteurships

CVMP rapporteurs/co-rapporteurs appointed in 2018 (for initial marketing authorisations, including generics)

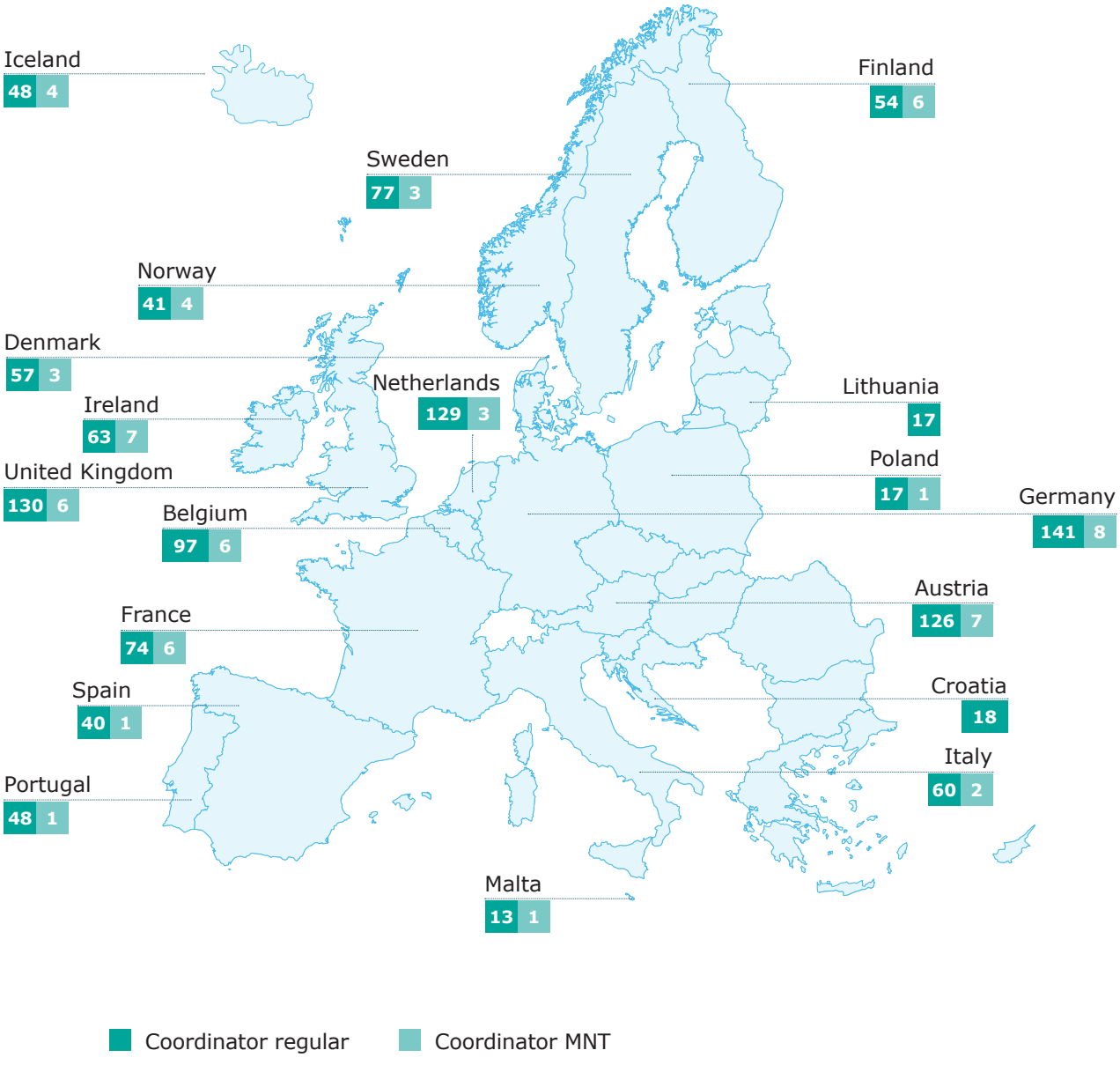


*This UK rapporteurship was subsequently reallocated to another NCA.

Scientific advice coordinators

The concept of multinational teams has also been introduced in the CHMP SAWP.

SAWP coordinators appointed in 2018

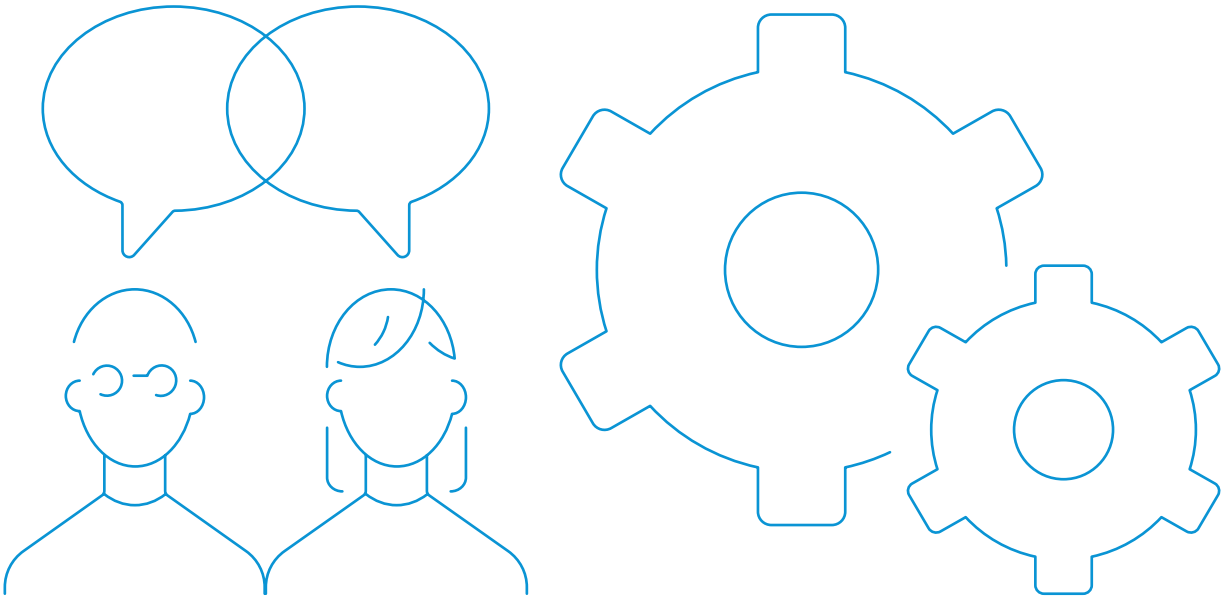


The SAWP stopped appointing coordinators from the UK as of November 2018. The maximum length of a scientific advice produced is 70 days, meaning that all scientific advice procedures with a UK coordinator will be finalised before 29 March 2019.

EU network training centre

The EU NTC is a joint initiative of EMA and the NCAs to address the training needs of the EU medicines regulatory network on both human and veterinary medicines. The table below highlights the key activities of the EU NTC from 2015 to 2018.

Activity	2015	2016	2017	2018
New scientific, regulatory and telematics curricula developed	1	8	0	2
Number of training events advertised to the EU network	105	140	100	60
Number of reimbursed training events to the EU network	7	25	20	8
Number of NCAs that have opened their training for inclusion in the EU NTC Learning Management System	6	14	8	7
Number of users registered in the EU NTC Learning Management System		2,117	3,583	4,424
Number of NCA experts registered in the EU NTC Learning Management System		1,225	2,668	3,480



Inspections and compliance

EMA coordinates the verification of compliance with the principles of GMP, GCP, GLP, GVP and certain aspects of the supervision of authorised medicinal products in the EU. The main verification tool is inspection, 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 the EU level, in the following:

- a risk-based programme of GMP inspections based on the results of inspections by trusted authorities;
- a 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);
- a risk-based programme of routine pharmacovigilance inspections in relation to CAPs (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 2018, work continued on trade agreements covering recognition of GMP inspections: the MRA between the EU and the US (the EU-US MRA) and the Comprehensive Economic Trade Agreement with Canada (CETA). In addition, in 2018, the scope of the EU-Japan MRA was extended to include biologicals, sterile products and APIs (see Section 1.5.2).

EMA and its European and international partners have also successfully strengthened their interactions to improve the oversight of API manufacturers worldwide. This international collaboration allows EMA, several European Union national authorities (France, Denmark, Ireland, Italy, and the United Kingdom), the EDQM, the FDA, Australia's TGA, Health Canada, the Japanese MHLW and PMDA, and the WHO to share information on GMP inspections of API manufacturers that are located outside the participating countries (see section 1.5.2).

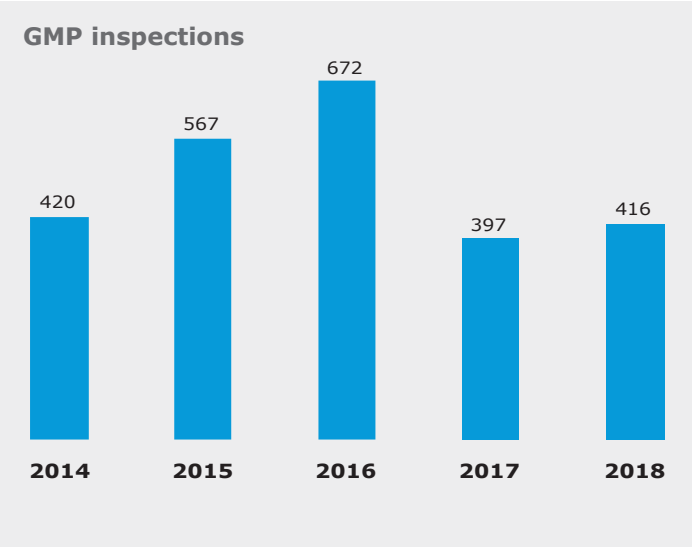
GCP inspections include specific initiatives such as the EMA-FDA joint GCP inspections initiative, which the PMDA has also joined as observer, and the EMA-FDA-seven EU Member States regulatory authorities (Austria, France, Germany, Italy, Netherlands, Spain, UK) joint initiative to collaborate on the 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, GLP and GVP. This helps to 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 medicines and coordinates their investigation, evaluation and follow-up. It also operates a sampling-and-testing programme to supervise the quality of centrally authorised medicines placed on the market and to check compliance of these products with their authorised specifications.

Inspections

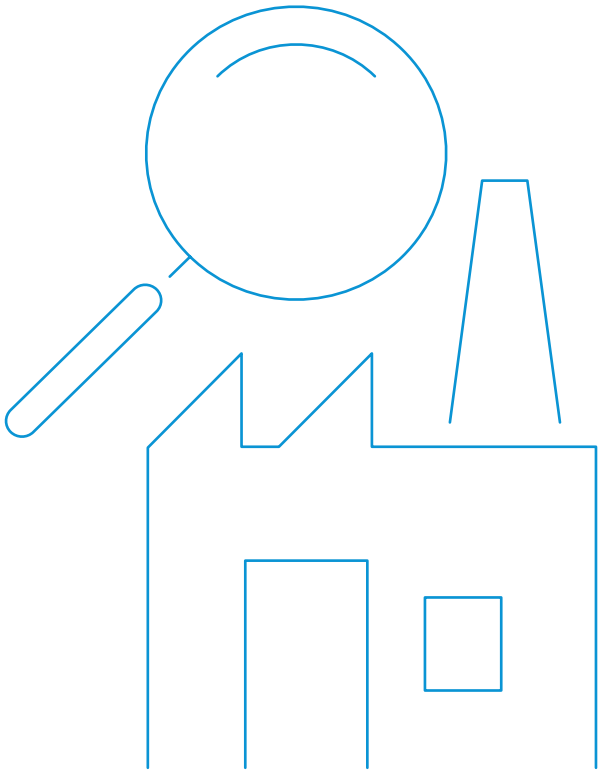
GMP, GCP, GLP and pharmacovigilance inspections requested by the CHMP or CVMP for medicines that are subject to centralised authorisation procedures take place worldwide. However, they represent just a small part of the total number of inspections performed by the EU/EEA inspectors, who also carry out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

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



GMP inspections

The number of GMP inspections requests within the context of the centralised authorisation procedure remained at a similar level to that of 2017, when the requests had declined as a consequence of the implementation of the EU-US MRA. This MRA is based on the mutual recognition of the inspections carried out in each other's territory, reducing the need for duplication of inspections.



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 2018, 16 GMP inspections conducted by EEA authorities led to the issuing of a non-compliance statement.

When inspections lead to findings, companies have to implement corrective action plans agreed with inspectors.

EEA authorities issued 3 statements of non-compliance relating to CAPs either in relation to the active substance or the finished product, which resulted in the following actions:

- For 1 case an EU wide recall of impacted products was performed.
- For 2 cases, a submission of a variation to replace the impacted manufacturer in the marketing authorisation dossier was required.

GMP certificates and non-compliance statements issued by EEA authorities

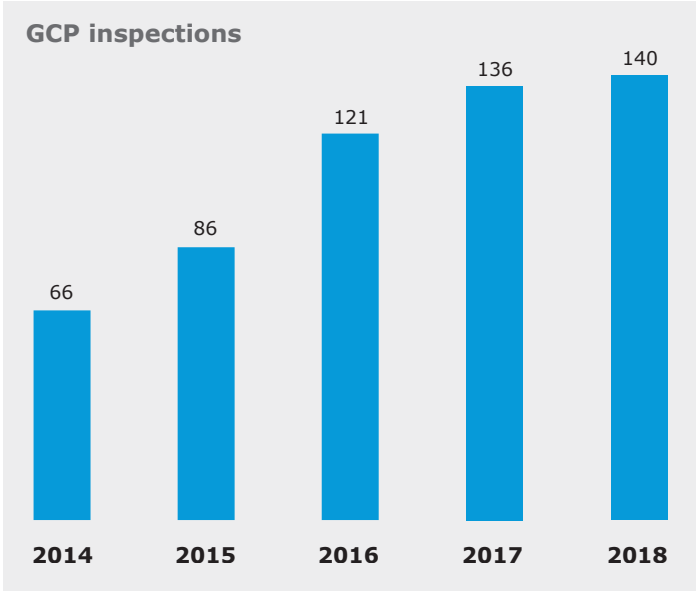
	2015		2016		2017		2018	
	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement
EEA/EU	2,310	5	1,951	5	2,115	7	2,213	6
China	72	6	55	4	39	1	66	4
India	135	6	96	12	119	7	112	5
USA	110	1	86	3	106	0	27	0
Rest of the world	119	0	81	0	97	2	84	1
Total	2,746	18	2,269	24	2,476	17	2,502	16

Note: This table shows the number of GMP certificates and non-compliance statements issued by EEA authorities as an outcome of GMP inspections conducted between 2014 and 2018. It includes GMP inspections requested by the CHMP or the CVMP.

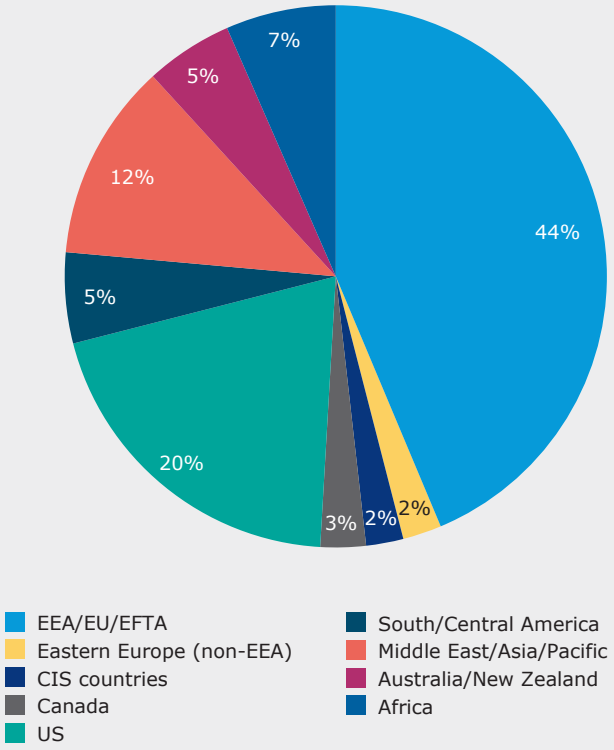
GCP inspections

The number of GCP inspections slightly increased compared to 2017, with 140 in 2018 compared to 136 in 2017.

In 2018, the highest number of GCP inspections requested by the CHMP was conducted in the EU/EEA/EFTA, followed by the US and the Middle East/Asia/Pacific regions, which have the highest number of patients, investigator sites and pivotal clinical trials included in marketing authorisation applications for CAPs. Nevertheless, compared to 2017, the number of inspections taking place outside the EU/EEA/EFTA and US have increased to ensure greater geographical coverage in GCP inspections. The decrease in the number of GCP inspections in the US region was possible due to close collaboration and sharing of information within the GCP initiative.

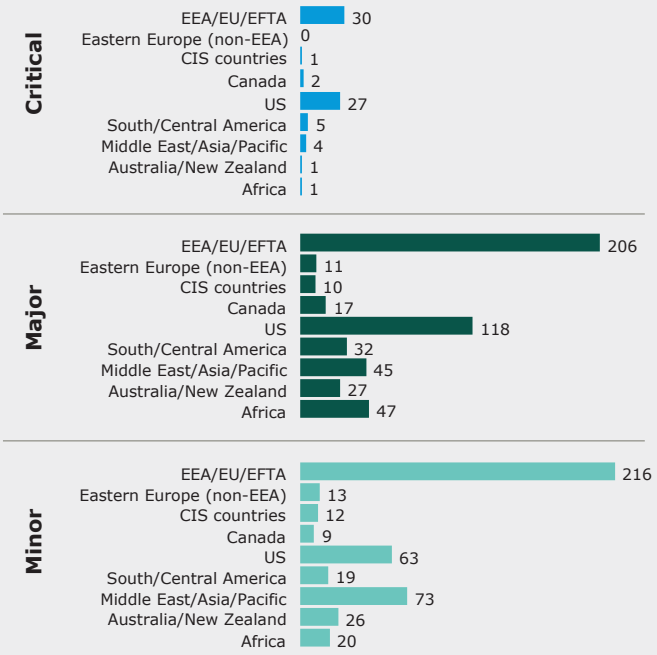


CHMP-requested GCP inspections finalised by EEA authorities (2018)



The classification of findings per region is presented in the chart below.

Type of findings of CHMP-requested GCP inspections finalised by EEA authorities (2018)



Where GCP inspections report critical and/or major findings on 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 and on the rights, safety and wellbeing of clinical trial subjects.

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 2018, GCP non-compliance contributed to 1 CHMP negative opinion and 5 application withdrawals.

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 CAPs 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 2018, 20 pharmacovigilance inspections were requested by the CHMP or CVMP, a third more than in 2017, when 15 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 CAPs).

Market surveillance and quality defects

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

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

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

In 2018 the Agency received 147 suspected quality defect notifications. Of these, 123 cases were confirmed quality defects and led to batch recalls of 27 centrally authorised medicines.

In May 2018, the Agency updated the template used for reporting suspected defective medicinal products. The new format of the template makes use of a standardised quality defect vocabulary extracted from the Medical Dictionary for Regulatory Activities (MedDRA). This allows a consistent analysis of quality defects and their root causes.

Additionally, as a result of the contamination of some batches of sartan blood pressure medicines (also known as angiotensin II receptor blockers) with nitrosamine impurities, EMA worked with NCAs and EDQM to coordinate recalls of affected medicines in the EU, including one centrally authorised medicine (See section 1.1.1).

Quality defects reported

	2014	2015	2016	2017	2018
Recalls	14	15	16	17	27
Class 1	2	1	3	2	3
Class 2	8	3	9	8	17
Class 3	4	11	4	7	7

The main reasons for recall of CAPs in 2018 are summarised in the following table.

Reason for recalls in 2018					
	Manufacturing laboratory control issues	**Product contamination and sterility issues**	**Product label issues**	**Product packaging issues**	**Product physical issues**
Class 1	1			2	
Class 2	3	5	5	2	2
Class 3	3		1	3	
Total	7	5	6	7	2

Manufacturing laboratory control issues include out-of-specification results obtained during quality control testing.

Product contamination and sterility issues include chemical, microbiological or physical contamination of the medicinal product.

Product label issues include issues related to labelling of the medicinal products (e.g. missing or incorrect batch number).

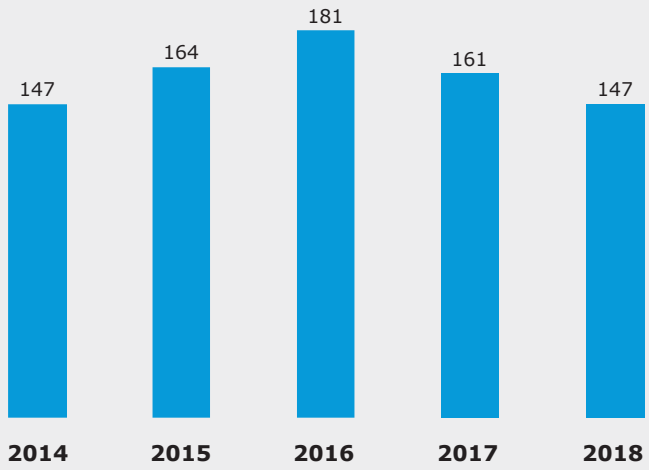
Product packaging issues relate to physical issues (e.g. a mix-up or a damaged container).

Product physical issues relate to incorrect product physical properties (e.g. friability, size/shape, leakage).

Market surveillance testing

A total of 2 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.

Number of quality defect notifications received



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.

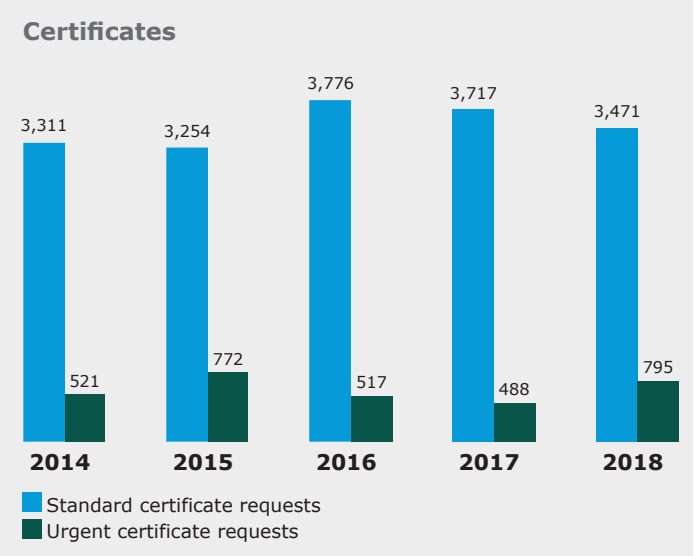
Parallel distribution notifications received

	2014	2015	2016	2017	2018
Initial notifications	2,492	2,838	2,850	2,639	2,304
Notifications of change	1,295	2,096	1,847	1,975	2,184
Notifications of bulk change	9	13	8	6	11
Annual updates	2,899	3,990	5,138	5,843	6,000*
Total	6,695	8,937	9,843	10,463	10,499

*Estimated end-of-year figure

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 2018, EMA published 183 press releases and news items.

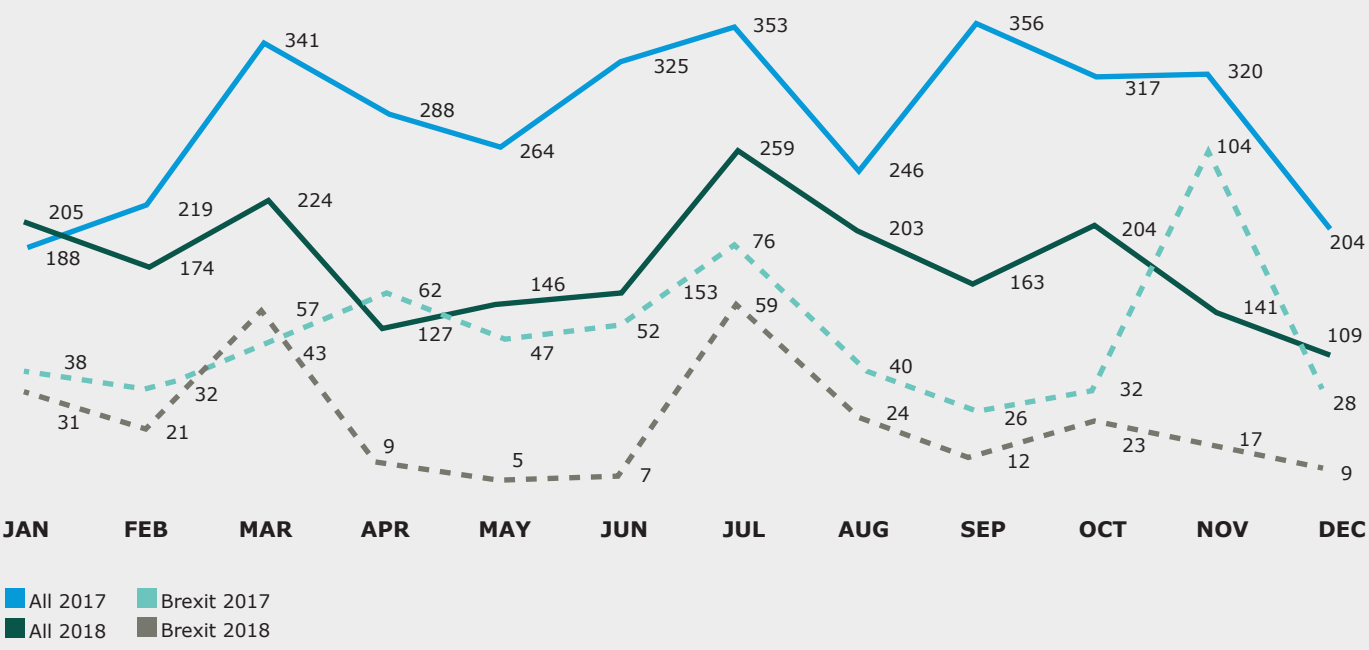
EMA's preparations for Brexit and its relocation to Amsterdam continued to be of significant interest to the media. Of particular interest was the outcome of EMA's industry survey, which was launched in January 2018 to identify centrally authorised medicines potentially at risk of supply shortages as a result of Brexit.

Another hot topic in 2018 was EMA's review of sartan blood pressure medicines.

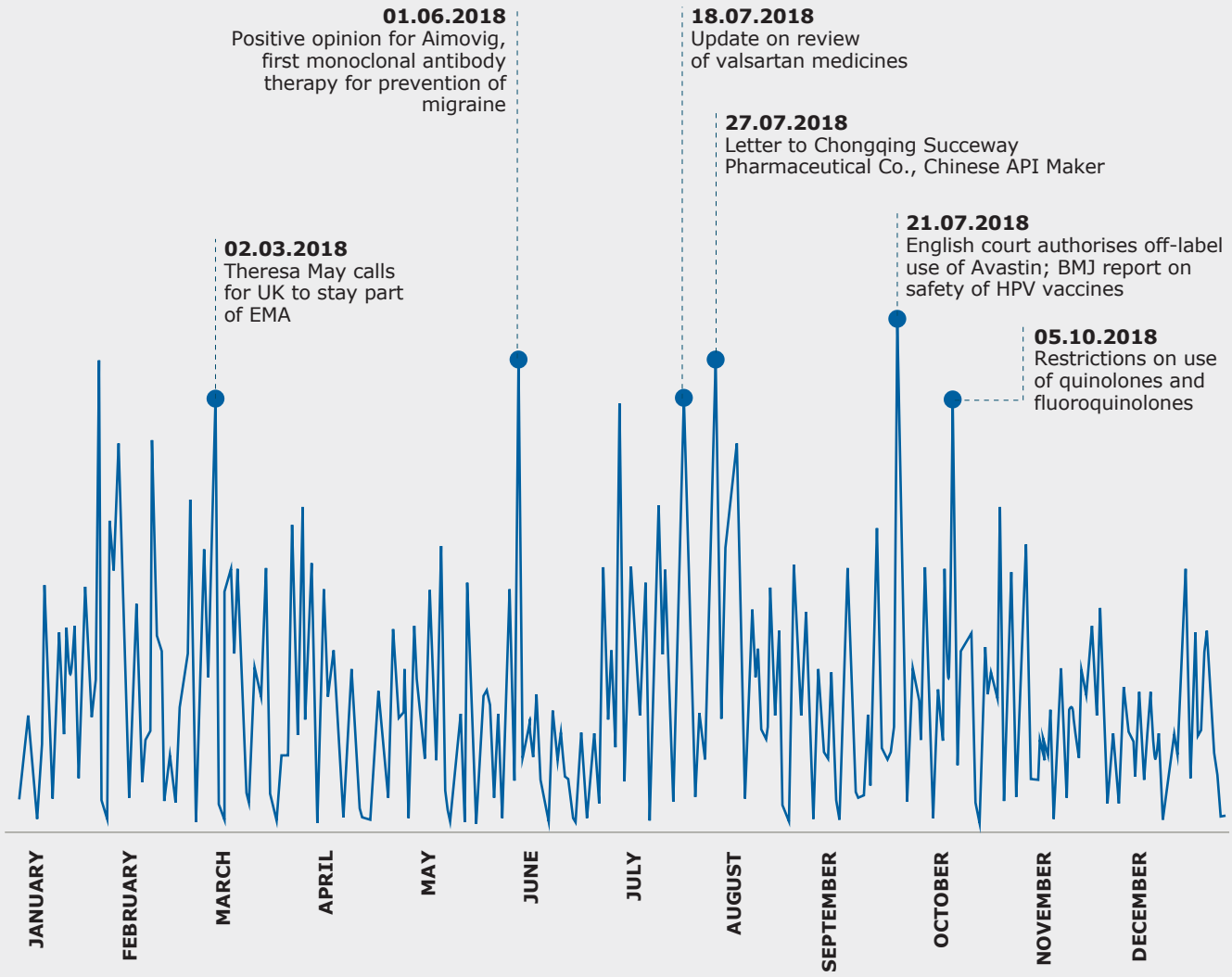
The Agency's public hearing on quinolones and fluoroquinolones, which took place in June 2018, also generated a lot of media coverage.

At the end of 2018, EMA had over 38,000 followers on Twitter, an increase of 17% compared to 2017. EMA's LinkedIn profile had over 52,500 followers at the end of 2018, an increase of 76% compared to 2017 (over 29,900 followers).

Number of news articles mentioning EMA

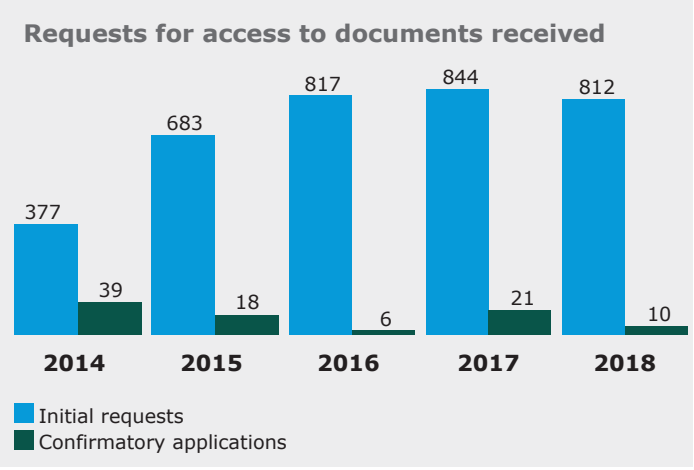


EMA in the media 2018

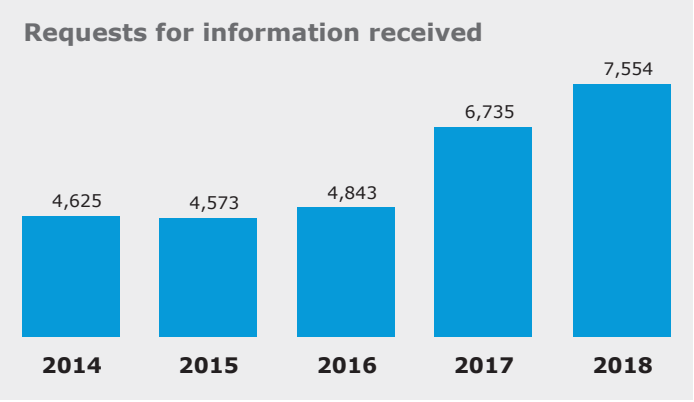


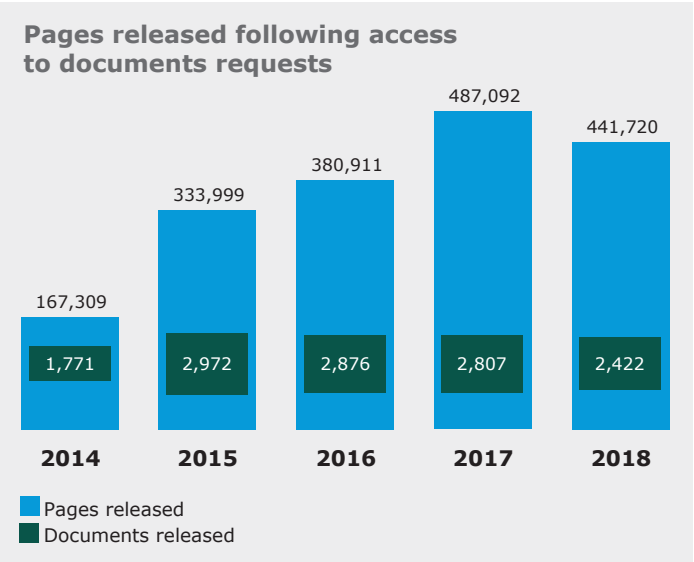
Requests for access to documents

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.



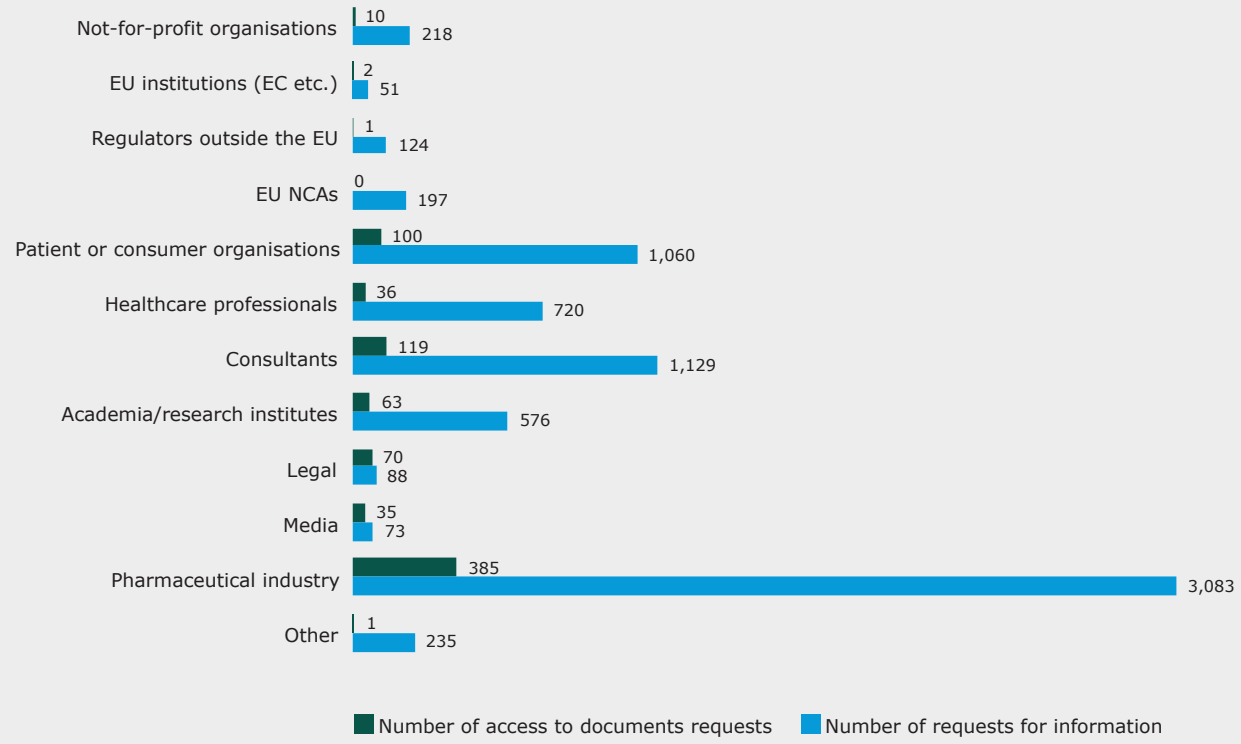
The number of requests for information increased by 12% in 2018, underlining the Agency's enhanced visibility in recent years.





ATD received in 2018	
Type of document	**%**
PSUR	7
RMP	17
Scientific Advice related documents	1
Paediatric related documents	2
Orphan related documents	6
Committee Documents	24
Module 1 of Marketing Authorisation dossier	3
Module 2 of Marketing Authorisation dossier	6
Module 3 of Marketing Authorisation dossier	2
Module 4 of Marketing Authorisation dossier	0
Module 5 of Marketing Authorisation dossier	2
Clinical study reports	7
Veterinary related documents	9
Legal related documents	0
Eudravigilance related documents	8
Other (include non scientific documents)	5
Inspection reports	1
Total	**100.00**

Affiliation of requestors of access to documents and of information (2018)



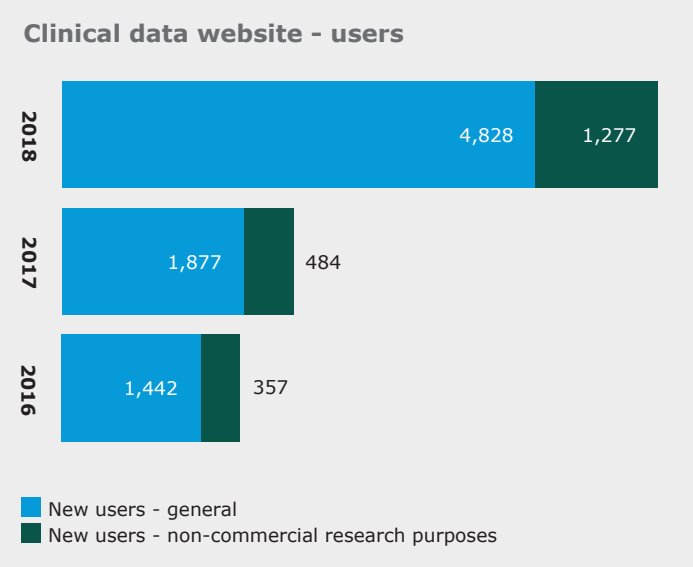
Note: More information on access to documents can be found in the annexes.

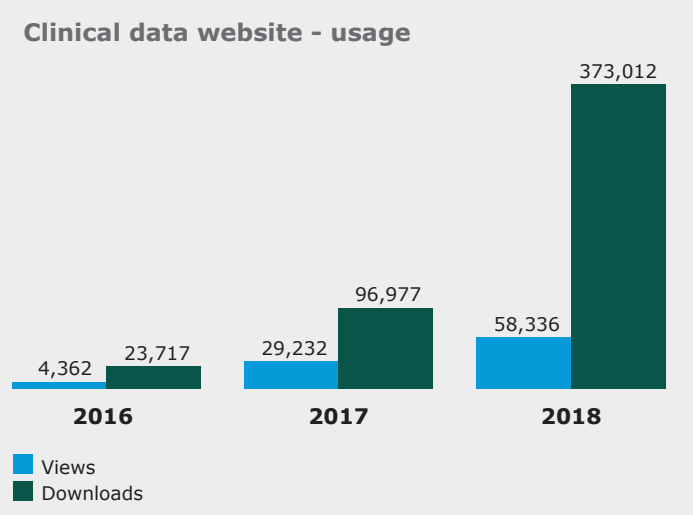
Requests for access to documents closed

Decision	2014		2015		2016		2017		2018	
	Initial	Confir-matory applica-tion	Initial	Confir-matory applica-tion	Initial	Confir-matory applica-tion	Initial	Confir-matory applica-tion	Initial	Confir-matory applica-tion
Fully granted	236	25	446	5	542	3	580	5	562	5
Partially granted	13	1	8	1	17	1	14	0	18	0
Refused	62	16	48	10	44	4	43	3	40	2
Total	311	42	502	16	603	8	637	8	620	7

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 below charts capture the usage of the clinical data website from its launch in October 2016 to the end of 2018.



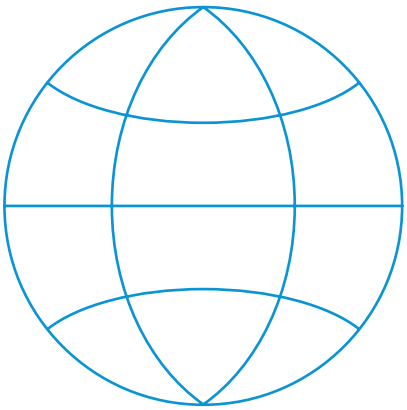


In addition, a total of 142 clinical dossiers for 133 products were published. This includes opinions and withdrawals for initial applications, line extensions and extensions of indication.

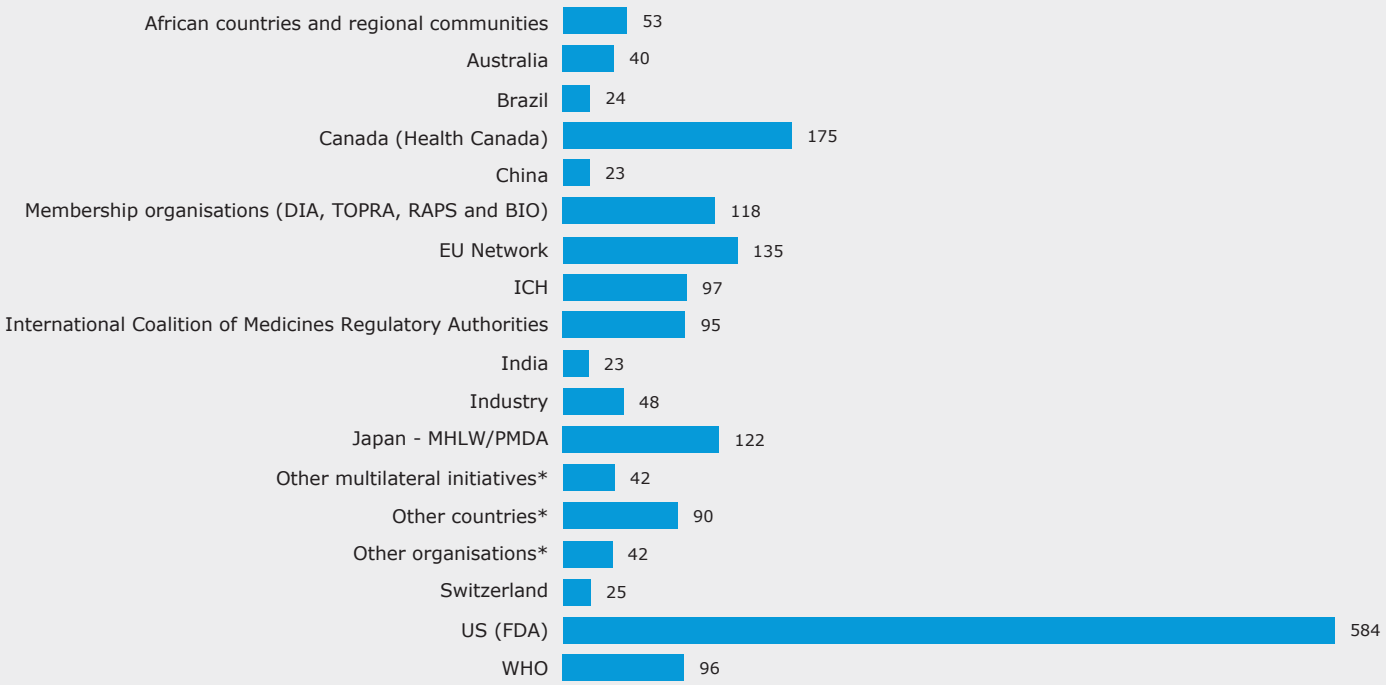
Publication of new dossiers was temporarily stopped in August 2018 due to the Agency's Brexit business continuity planning.

Interactions with international stakeholders

EMA has had an international role since its creation in 1995. Its founding regulation gives the Agency a specific responsibility to provide technical and scientific support to international organisations on issues related to the evaluation of medicinal products. Today, international cooperation is moving from 'harmonisation' of technical requirements towards more mutual reliance and work-sharing through multilateral cooperation and coalitions. In 2018, EMA had a total of 1,832 interactions with international stakeholders through its International Affairs department.

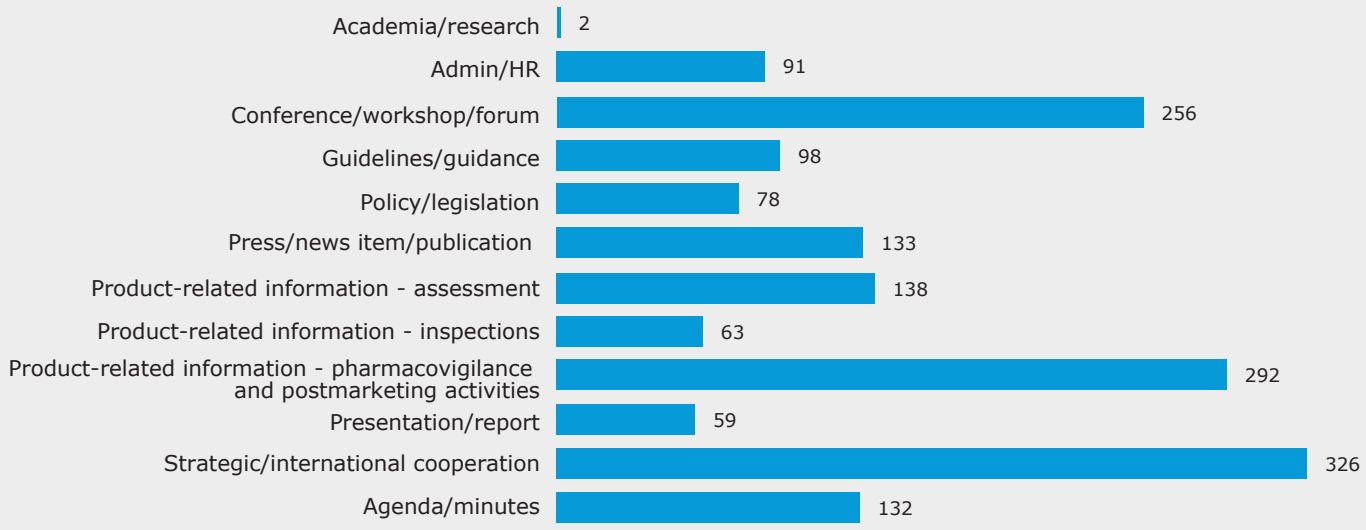


Number of interactions per stakeholder (2018)



* Countries, organisations and initiatives worldwide that are not listed in the figure and for which less than ten interactions have been recorded in 2018

Topics of interactions with international stakeholders (2018)

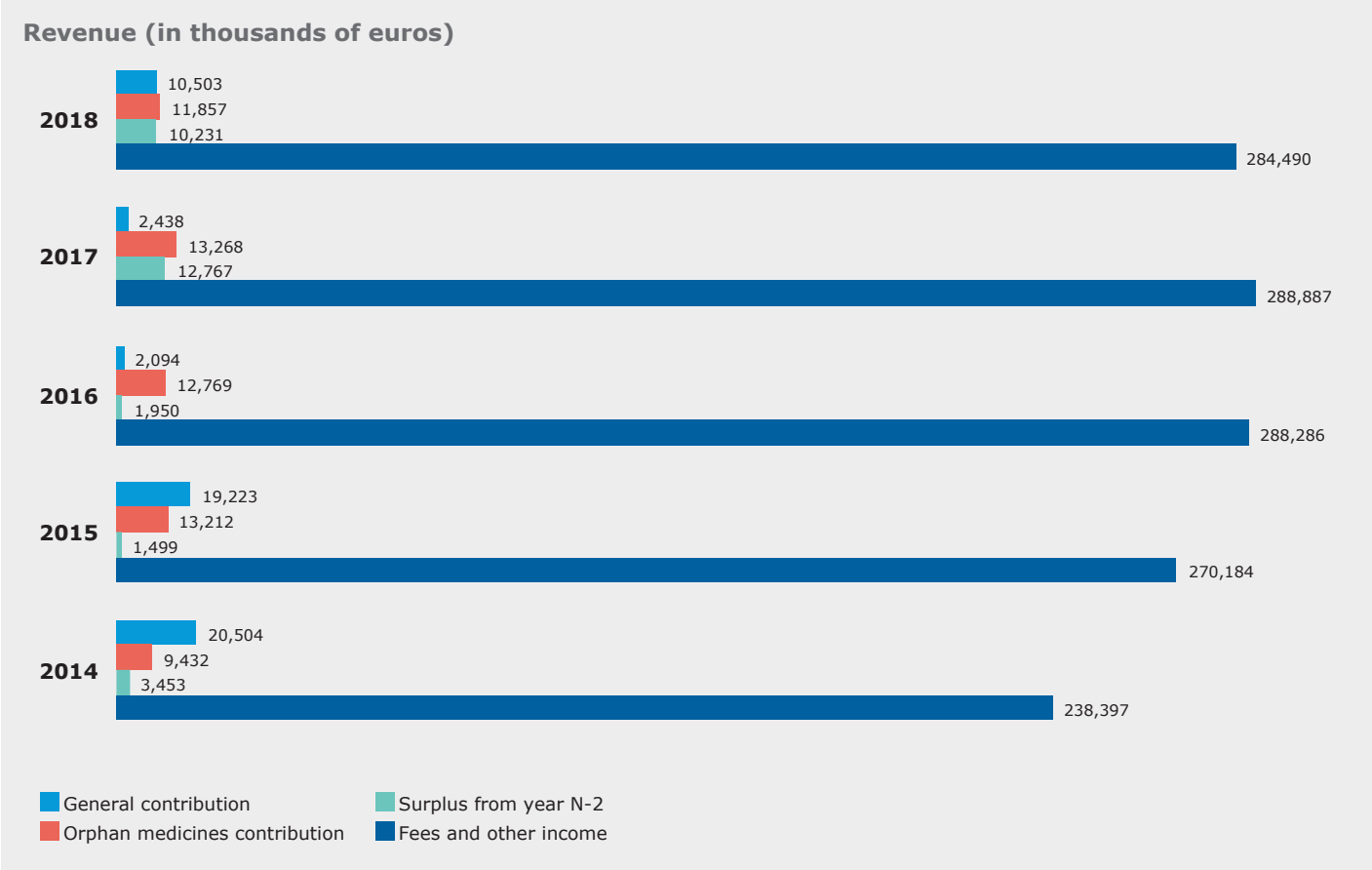


Administrative aspects

Budget

Total revenue

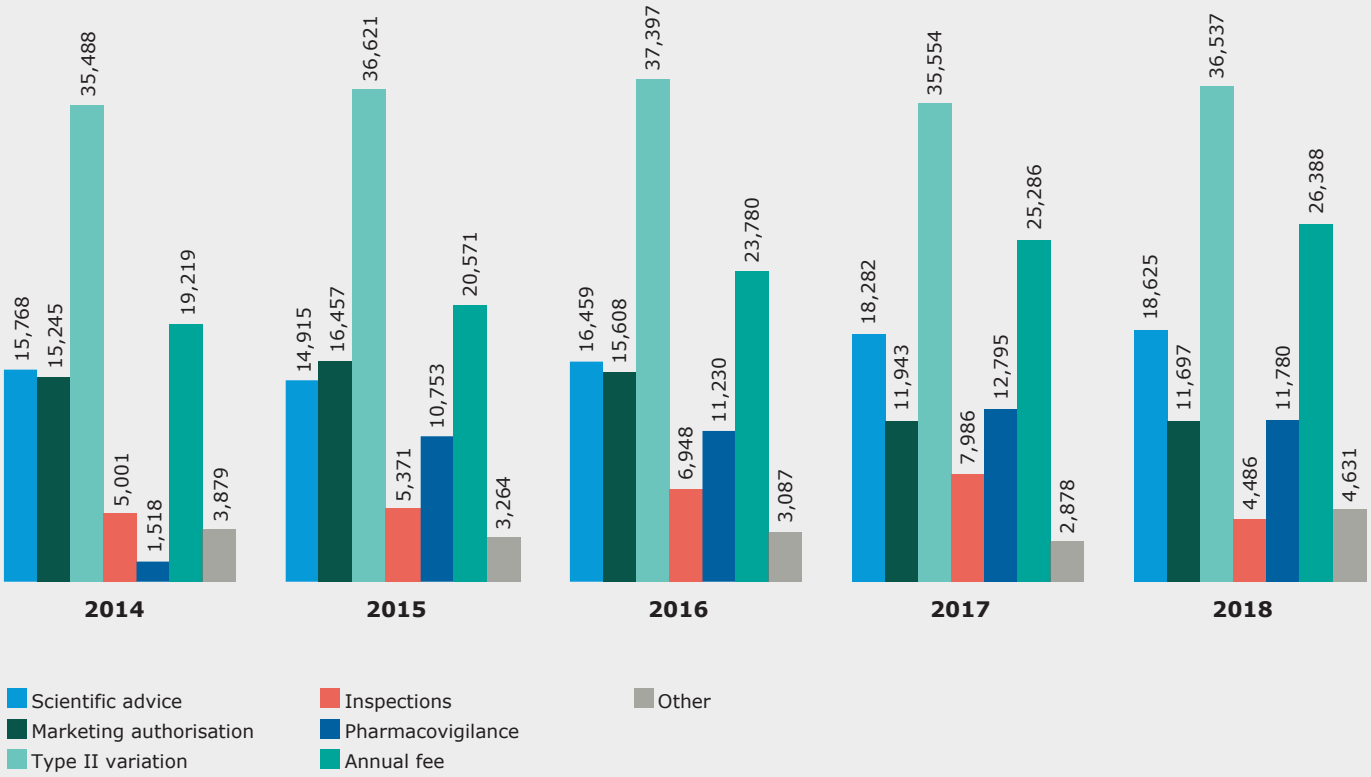
The Agency's total revenue in 2018 was €317,081 million compared to €317,360 million in 2017.



Remuneration to national competent authorities

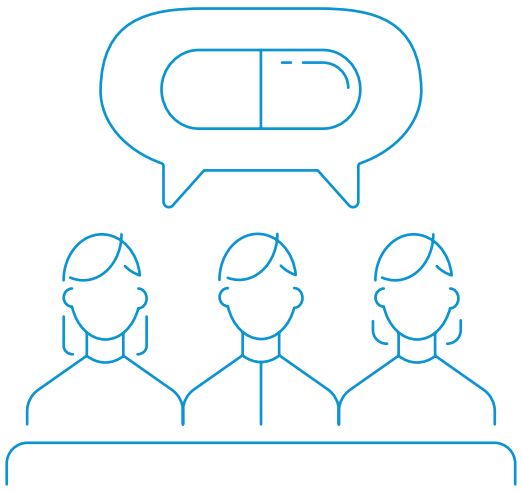
The NCAs in the EU Member States receive a share of EMA's revenue from fees for the assessments they carry out on behalf of the Agency.

Remuneration to NCAs per fiscal year (in thousands of euros)



In 2018, EMA paid a total of €114,143,746 million to the NCAs, compared to €114,724,000 million in 2017.

This figure 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

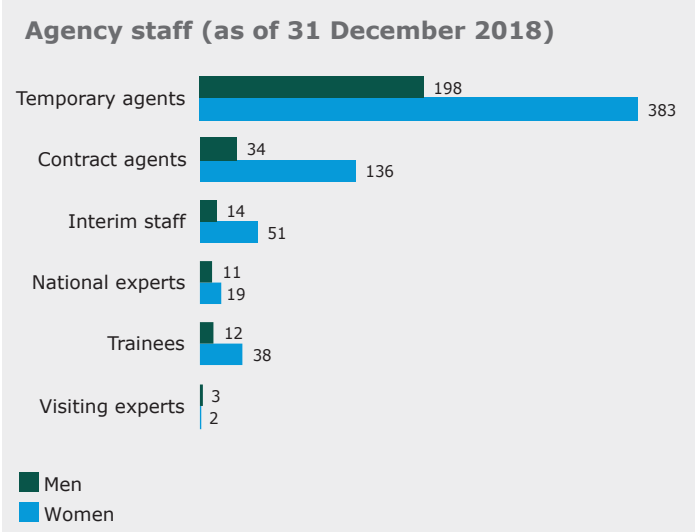
EMA's office building at 30 Churchill Place in Canary Wharf, London includes many environmentally friendly features, such as photovoltaic (or solar) cells and a 'green' roof to enhance biodiversity. It has achieved a new standard for environmental performance and energy efficiency in London and the design 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	2014	2015	2016	2017	2018
Energy efficiency	Electricity consumption	kWh	3,069,676	3,546,829	3,266,036	3,087,933	2,998,597
		kWh/m2	147	145	133	126	122
Resource efficiency	Water consumption	m3	2,585	2,607	1,345	1,525	1,413
	Paper consumption	metric tons	41	27	23	20	18
Waste management	Recycled waste	metric tons	53	73	46	51	40
	Non-recyclable waste	metric tons	59	54	32	36	35
Carbon footprint	Greenhouse gas emissions	tons CO2e	2,724	2,843	2,854	2,956	2,551

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

Agency staff

As of December 2018, Agency staff numbered **901: 629** women and **272** men.

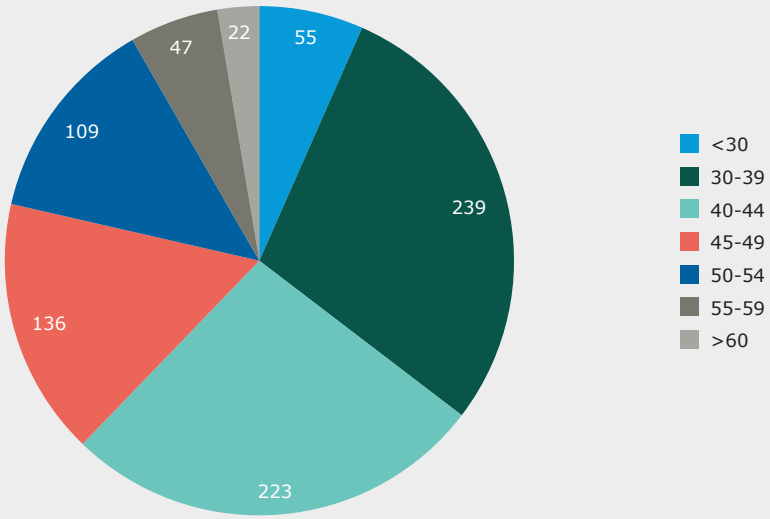


Gender balance of Agency staff 2018

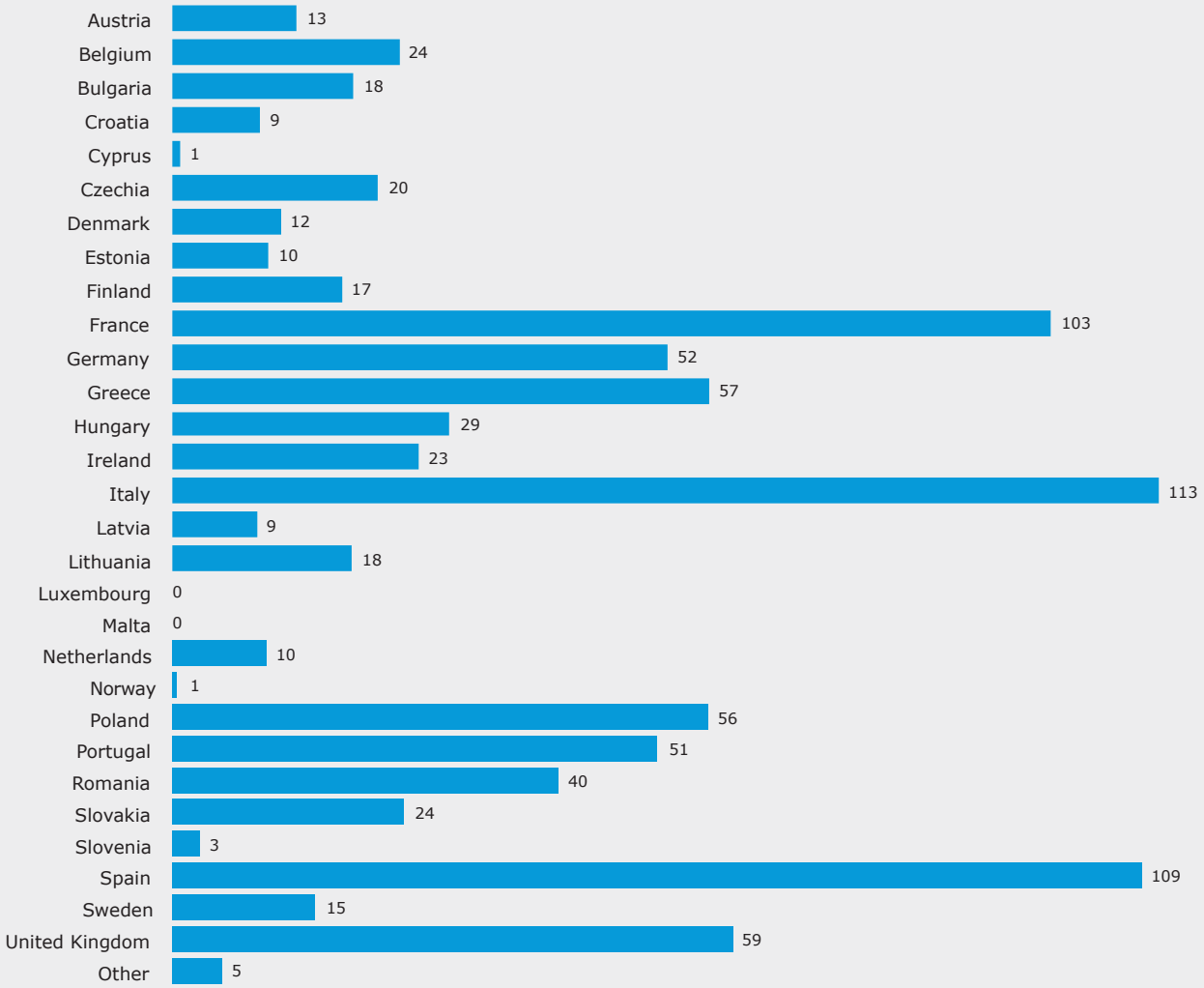
Status	Category AD (administrators)		Category AST (assistants)		All grades	
	Men	Women	Men	Women	Men	Women
Temporary agents	49%	51%	13%	87%	34%	66%
Contract agents	28%	72%	15%	85%	20%	80%
Total	45%	55%	14%	86%	44%	69%

Gender balance of the Agency management 2018

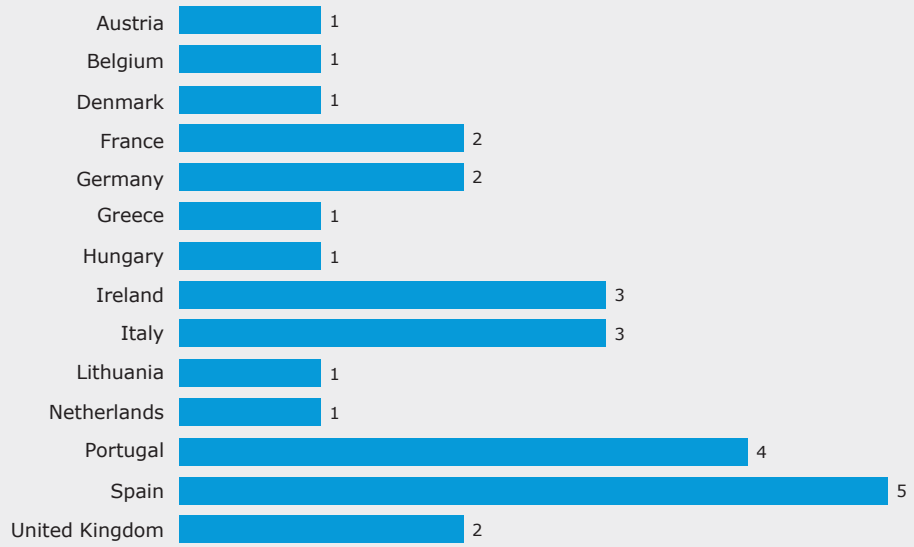
Age-range statistics (31 December 2018)



National origins of Agency staff (2018)



National origins of Agency management (2018)



Agency management includes the Agency's Executive Director, the Deputy Executive Director, heads of division, heads of department, EMA's Senior Medical Officer and heads of advisory functions.

Annexes

Annex 1 – Members of the Management Board

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

Annex 3 – Members of the Pharmacovigilance Risk Assessment Committee

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

Annex 5 – Members of the Committee on Orphan Medicinal Products

Annex 6 – Members of the Committee on Herbal Medicinal Products

Annex 7 – Members of the Committee for Advanced Therapies

Annex 8 – Members of the Paediatric Committee

Annex 9 – Working parties and working groups

Annex 10 – CHMP opinions on initial evaluations and extensions of therapeutic indication in 2018

Annex 11 – Guidelines and concept papers adopted by CHMP in 2018

Annex 12 – CVMP opinions on medicinal products for veterinary use in 2018

Annex 13 – Guidelines and concept papers adopted by CVMP in 2018

Annex 14 – COMP opinions on designation of orphan medicinal products in 2018

Annex 15 – HMPC European Union herbal monographs in 2018

Annex 16 – PDCO opinions and EMEA decisions on paediatric investigation plans and waivers in 2018

Annex 17 – Referral procedures overview 2018 – human medicines

Annex 18 – Arbitrations and referrals in 2018 – veterinary medicines

Annex 19 – Budget summaries 2017–2018

Annex 20 – European Medicines Agency Establishment Plan

Annex 21 – Access to documents requests in 2018

Annex 22 – Publications by Agency staff members and experts in 2018

European Medicines Agency

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Annual report 2018