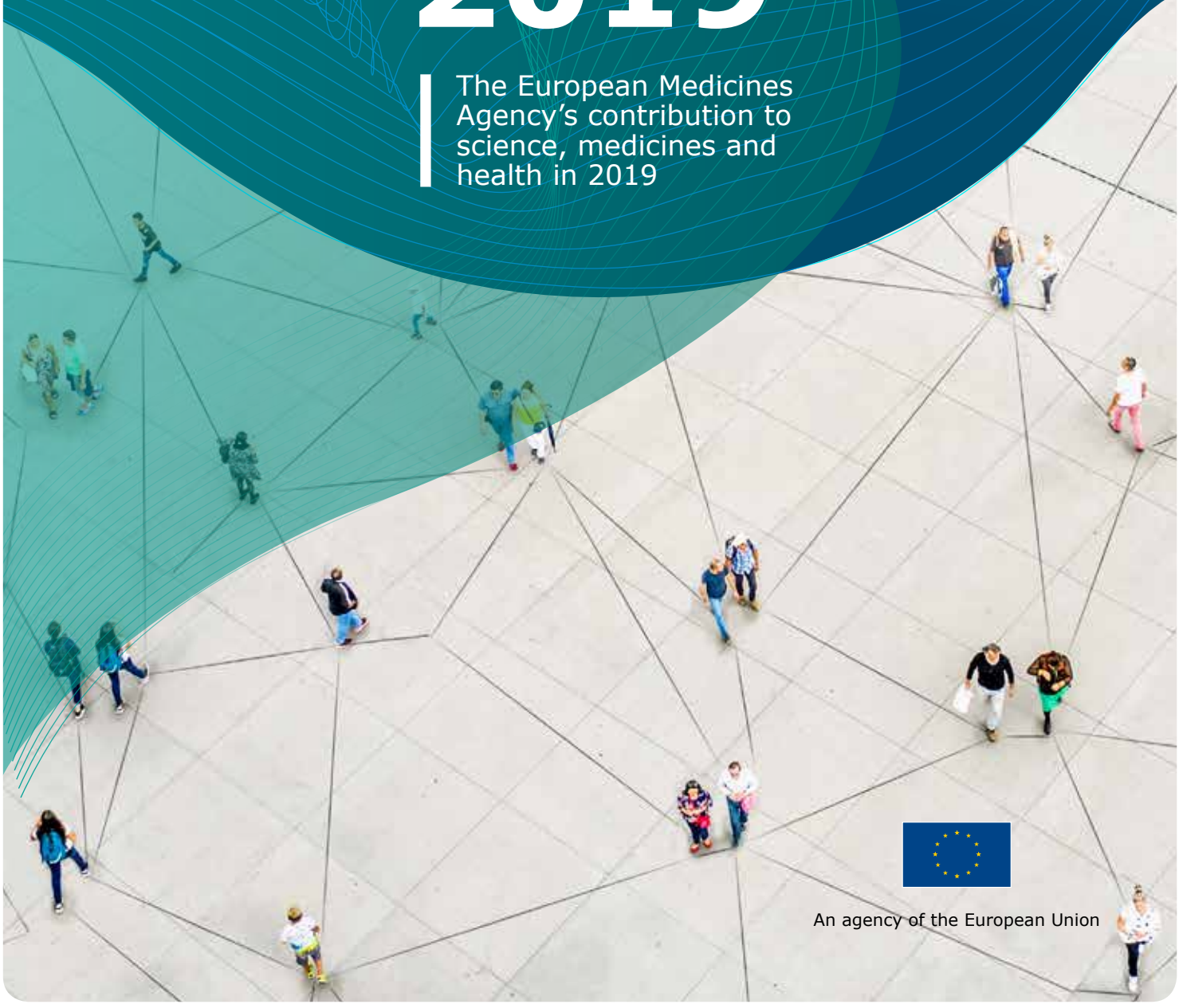
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ANNUAL REPORT 2019

The European Medicines Agency's contribution to science, medicines and health in 2019



An agency of the European Union

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I 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

- provides independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines;
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the EC;
- implements measures for continuously monitoring and supervising the quality, safety and efficacy of all medicines authorised in the European Union (EU) to ensure that their benefits outweigh their risks;
- provides scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines;
- recommends safe limits for residues of veterinary medicines used in food-producing animals, for the establishment of maximum residue limits by the EC;
- involves representatives of patients, healthcare professionals and other stakeholders in its work to facilitate dialogue on issues of common interest;
- publishes impartial and comprehensible information about medicines and their use;
- develops best practice for medicines evaluation and supervision in Europe, and contributes alongside the Member States and the EC to the harmonisation of regulatory standards at the international level.

Legal role

The EMA is the EU body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

The Agency provides the Member States and the EU institutions with the best-possible advice on any questions relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.

I FOREWORD

by Christa Wirthumer-Hoche

Chair of EMA Management Board

It is my pleasure to introduce EMA's annual report for 2019.

I would like to congratulate EMA on its relocation from London to Amsterdam. This was a huge administrative, logistical and managerial challenge, made even more complicated by the need to move twice within the space of one year. It was only thanks to its impressive business continuity planning that the Agency was able to continue all core activities related to the evaluation, maintenance and supervision of medicines which continued throughout this period.

At the end of 2019, the Agency was in as good a shape as it could have been following its move. However, the Board remains concerned about the longer-term prospects for the Agency's full recovery if the ongoing resource constraints cannot be addressed. The challenges of the move and the associated staff losses had made it necessary to put some activities on hold as 2019 began. EMA was only able to reinstate some of these activities. Important areas of the Agency's work, such as working parties and guideline development, remained largely suspended throughout the year, creating a significant impact on the European medicines regulatory network overall.

On top of this, the discovery of nitrosamine impurities in some medicines put further strain on the Agency. The Board praises EMA for its public-health-driven handling of the issue and for its part in developing and coordinating a strong EU-wide response to the possible presence of these carcinogenic substances in medicines. Managing this issue will continue to be an increasingly resource-demanding topic in the years to come.

Another area that absorbed a significant number of EMA resources was the implementation of new pieces of legislation. In particular, the New Veterinary Regulation has put a lot of time pressure not only on EMA staff but also on experts and the network as whole. Although this has been managed very well by EMA, which provided scientific and technical recommendations to the Commission to support them with implementation of the Regulation, it remains an area of concern that the Board will continue to monitor.

Despite the challenges, 2019 was also a year in which progress was made in important areas.

To prepare for the UK's withdrawal from the European Union (EU), the EU27 Member States and EMA redistributed the UK's portfolio of over 370 centrally authorised medicines to other EU Member States, plus Iceland and Norway. By 1 July 2019, I was glad to see that the new rapporteurs and co-rapporteurs were fully responsible for these medicines.

EMA and the network neared completion of the Regulatory Science Strategy to 2025, the plan for advancing engagement with regulatory science over the next few years. The Agency organised two further workshops with stakeholders which offered an excellent platform to move discussions forward. Once adopted by the Board in 2020, this strategy will form the backbone of the work of the Agency and network in the coming years.

The Regulatory Science Strategy will then feed into the development of the next joint EU network strategy, which will guide the work carried out by EMA and the national agencies. This covers important topics for the network,

such as the availability and accessibility of medicines, supply chain challenges, data analytics and artificial intelligence. It is important that we have one overarching strategy with the Heads of Medicines Agencies (HMA) over the whole EU network to help address these complex topics.

The EU network training centre continued to play a key role in making sure that the right expertise is available across the network. We now have more experts from national agencies than ever who are registered with the learning management system and moving forward. It will be important to continue the development of curricula on real-world data sources and to develop modules in big data and for telematics projects.

During 2019, there was much discussion in the Board concerning the Clinical Trials Information System, which is necessary for the new Clinical Trials Regulation to come into force. This is one of the most complex and ambitious IT developments ever undertaken by EMA, which needs to integrate systems and processes in place in all Member States into one virtual workspace that works for all. We have set up a governance structure to closely monitor progress. The system has yet to be finalised but we are on the right track now and I look forward to the start of the audit in December 2020.

On a personal note, it was a great honour to be re-elected as chair of the Board in March. I thank you for your trust and look forward to leading the Board for a further three years.

And, finally, on behalf of the Board, my heartfelt thanks go to colleagues across the network, to the Commission and to EMA staff for all the work achieved during what was a challenging year.

March 2020

I INTRODUCTION

by Guido Rasi

EMA Executive Director

2019 defined a critical turning point for EMA, as we entered a final phase of business continuity planning and undertook a major move from London to Amsterdam.

The move itself went smoothly, and we successfully focused our efforts on sustaining core activities for the evaluation and supervision of medicines. In addition to good planning, this was largely thanks to close collaboration with the Dutch authorities and the resilience of EMA staff. Our move was complex: on arrival in the Netherlands, we settled in temporary offices in the Sloterdijk area of Amsterdam as we continued preparations for our second move into our tailor-made new building, in Amsterdam Zuidas. The Dutch government delivered EMA's final building on 15 November as planned, and we started the move into our final home as 2019 drew to a close.

Logistics was one important element, staffing was another. Overall, including short-term staff who could not be transferred, we lost 159 people in 2019 which put our operations under pressure. A successful recruitment drive attracting over 5,000 candidates has helped to redress some of this loss, but recruitment – and in particular finding the right expertise – will remain a focus area for the Agency.

Preparing the pharmaceutical sector for the UK's withdrawal from the EU continued to consume significant resources from EMA and the European medicines regulatory network. Assuring the continuity of the supply of medicines to patients in the EU became the focus of our work. Together with the European Commission and the Member States, we gave guidance and actively encouraged companies marketing human and veterinary medicines in the EU to prepare their development and manufacturing arrangements for Brexit. Our proactive approach paid off: the risk of shortages for centrally approved medicines in case of a no-deal Brexit was very low at the end of 2019. The preparations will continue in 2020 until the end of the transition period.

However, these achievements came at a cost for the Agency. Most of the activities we had to postpone and suspend in 2018 in anticipation of the physical move remained on hold in 2019. These included guideline development, engagement in international activities, the majority of working party meetings and the Agency's landmark policy on the proactive publication of clinical data. We were also faced with new activities that absorbed significant resources, including implementation of major pieces of legislation – for veterinary medicines, medical devices and data protection. In addition, the detection of nitrosamine impurities in some medicines presented a new challenge that required prompt, transparent and coordinated action by EMA and the national competent authorities.

Thus, we were only able to reinstate a few activities in the second half of 2019. These mainly concerned projects to improve efficiency, such as enhancing those IT systems supporting the medicines evaluation process and the digitalisation of administrative processes.

Despite all the challenges of 2019, I am proud that EMA remained firmly focused on its public health mission. Altogether, EMA recommended the authorisation of 66 new medicines for human use, some of them presenting scientific advances that can make a real difference to people's lives, such as a new gene therapy for the treatment of beta-thalassaemia and the first Ebola vaccine. EMA continued to closely monitor the safety of medicines on the market and take action when needed. A good example of this is that, in 2019, the product information for 405 centrally authorised medicines was updated on the basis of new safety data.

EMA also recommended 15 new veterinary medicines for marketing authorisation, including five new active substances and four vaccines. The fight against antimicrobial resistance (AMR) remained a priority in this area.

We made progress across the EU in handling shortages of medicines. A new information-sharing system for EU regulators, piloted in 2019, supports the prevention and management of shortages and shows yet again how much we can gain in the EU through cooperation and mutual reliance.

Another important network initiative concerned developing key principles for the development and use of electronic product information (ePI) for human medicines in the EU. By seizing the opportunities of digitalisation, we can increase citizens' access to information on medicines.

Given the importance we place on early dialogue with medicines developers to generate high-quality data for scientific assessment, I was pleased that the European Ombudsman publicly recognised the value and need for scientific advice in her conclusions of an enquiry into our pre-submission activities. The progress EMA made in better explaining the rationale and process behind its work in the early phases of medicines development has certainly helped to shift the debate.

With all the challenges we are facing, getting fit for the future became a top priority in 2019. We progressed our strategy for advancing regulatory science to 2025 in dynamic discussions with our stakeholders through a public consultation and two workshops. This will allow us to finalise a strategy that can deliver high value in both the human and veterinary sectors and improve the way we regulate medicines in the EU. One of the areas where innovative approaches are needed is big data: here, the recommendations made by the Big Data Task Force pave the way towards creating a broader evidence base for regulatory decision-making coming from big data.

Being ready for the future whilst making best use of available resources also led us to rethink EMA's internal organisation. The more agile organisation we hope to achieve through the "future-proofing" exercise that started in 2019 should help EMA strengthen its ability, together with our partners in the network, to innovate and perform new activities.

I approach 2020 with the hope that we can now finally close the chapter of our relocation and focus on the future. This will be my last year at the helm of EMA, an organisation that has been my privilege to lead, and it is my ambition to leave it fully prepared to embrace the scientific and technological advances ahead for better human and animal health.

Before I present this year's annual report, I would like to thank all those who have been part of our journey and who contribute to EMA's work: the members of its scientific committees, the working parties and scientific advisory groups, the Management Board and the national experts, our stakeholders and, of course, EMA's staff.

March 2020

CHAPTER 1

KEY ACHIEVEMENTS IN 2019

EVALUATION AND MONITORING OF MEDICINES: HIGHLIGHTS

Human medicines

Medicines recommended for approval

New, innovative medicines are essential to advancing public health as they bring new opportunities to treat diseases, particularly those that target an unmet medical need or a rare condition. In 2019, EMA recommended 66 medicines for marketing authorisation. Below is a selection of medicines approved in 2019 that represent significant progress in their therapeutic areas. More information and figures on the approval of medicines is available in chapter 2.

Vitrakvi, the first 'histology-independent' treatment in the EU for solid tumours with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. NTRK gene fusions occur very frequently in a number of rare cancers.

Ondexxya, an antidote for adult patients taking the anticoagulant medicines apixaban or rivaroxaban, when reversal of their action is needed due to life-threatening or uncontrolled bleeding.

Baqsimi, the first treatment for severe hypoglycaemia (low blood sugar level) that can be administered without an injection in patients with diabetes aged four years and older.

Zynquista, an oral adjunct to insulin for certain patients with type 1 diabetes. Zynquista blocks the action of two proteins known as glucose transporters (SGLT1 and SGLT2) which are found in the intestine and kidneys.

Zynteglo, an advanced therapy medicinal product (ATMP) for the treatment of beta-thalassaemia, a rare inherited blood condition that causes severe anaemia. Zynteglo is intended for adult and adolescent patients 12 years and older who need regular blood transfusions to manage their disease and have no matching donor for a stem-cell transplant.

Epidyolex, for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, two rare forms of epilepsy. Epidyolex is the first medicine with an active substance derived from cannabis, that received a positive opinion in the EU centralised procedure.

Sixmo, a substitution treatment for opioid dependence. Sixmo is an implant that releases low levels of buprenorphine into the patient's body for six months.

KEY EVENTS IN 2019

JANUARY 09, 2019

The Dutch authorities officially hand over the temporary building in Amsterdam Sloterdijk.

The first Ebola vaccine – Supporting the response to a public health emergency

In October 2019, EMA's human medicines committee (CHMP) recommended granting a conditional marketing authorisation in the EU for Ervebo (rVSVΔG-ZEBOV-GP), the first vaccine for active immunisation of individuals aged 18 years and older at risk of infection with the Ebola virus.

Ebola virus disease is a rare but severe illness caused by the Ebola virus. Death rates have varied from 25% to 90% in past outbreaks. The largest outbreak to date occurred in West Africa between 2014 to 2016 with more than 11,000 deaths. Ervebo is a genetically engineered, replication-competent, attenuated live vaccine. Data from clinical trials and compassionate use programmes have shown that Ervebo protects against Ebola virus disease in humans after the administration of a single dose.

EMA is working with regulatory authorities around the world to support the World Health Organization (WHO) and advise on possible pathways for the development, evaluation and approval of medicines and vaccines to fight Ebola. Erbevo benefitted from support of the PRIME scheme and was assessed following an accelerated timetable.

EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

In 2019, **three medicines** (Ervebo, Xospata and Zynteglo) were recommended for marketing authorisation following an **accelerated assessment**. This mechanism is reserved for medicines that address unmet medical needs. It allows for the assessment of eligible medicines by EMA's scientific committees within a maximum of 150 days rather than the usual 210 days.

Eight medicines received a recommendation for a **conditional marketing authorisation**, one of the possibilities provided in the EU to give patients early access to new medicines: Ervebo, Libtayo, Lorviqua, Ondexxya, Polivy, Vitrakvi, Waylivra and Zynteglo.

As these medicines address unmet medical needs, the conditional authorisation allows for early approval on the basis of less complete clinical data than normally required (products for use in emergency situations may have less complete pharmaceutical or non-clinical data). These authorisations are subject to specific post-authorisation obligations to generate further data on the medicines.

JANUARY 14, 2019

EMA publishes a revised guideline on the evaluation of human medicines indicated for the treatment of bacterial infections for a six-month public consultation.

JANUARY 31, 2019

A public consultation on key principles for the ePI of EU medicines is launched.

One medicine (Dectova) was authorised under **exceptional circumstances**. This route allows for patients' access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because very few patients have the disease, or the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge.

Dectova is an antiviral medicine used to treat complicated and potentially life-threatening influenza (flu) caused by either the influenza A or B virus in adults and children from 6 months of age. Medicines authorised under exceptional circumstances are subject to specific post-authorisation obligations and monitoring.

MEDICINES FOR RARE DISEASES

The EU framework for orphan medicines provides incentives for developers to encourage the development and marketing of medicines for patients with rare diseases. A medicine that was granted an orphan designation during its development can benefit from ten years of market exclusivity after its marketing authorisation, provided EMA's Committee for Orphan Medicinal Products (COMP) confirms its orphan status at the time of approval.

Among the medicines recommended for marketing authorisation, **seven had had their orphan designation confirmed** by the end of the year: Epidyolex, Isturisa, Palynziq, Polivy, Waylivra, Xospata and Zynteglo.

In 2019, the following applications lost their orphan status before receiving marketing authorisation, which means they were still authorised as medicinal products but not as orphan medicinal products: Trecondi, Cufence, Esperoct, Ultomiris, Vitrakvi and Revlimid. More information can be found in the COMP monthly reports.

NEW USES FOR EXISTING MEDICINES

Sixty extensions of indication were recommended in 2019. The extension of the use of a medicine that is already authorised for marketing in the EU can also offer new treatment opportunities for patients. Important extensions of indication included:

Forxiga and its duplicate **Edistride** as an oral adjunct treatment with insulin for certain patients with type 1 diabetes.

Victoza, to include the treatment of children and adolescents aged ten years or older with type 2 diabetes.

Dupixent as an add-on maintenance treatment for patients aged 12 years and older with certain forms of severe asthma.

NEGATIVE OPINIONS

The CHMP adopted negative opinions for four[1] medicines in 2019: Cabazitaxel Teva, Doxolipad, Hopveus and Vanflyta.

When the Committee finds that the benefits of a medicine do not outweigh its risks, it issues a negative opinion on the marketing authorisation application and elaborates on the grounds. Applicants have the right to request a re-examination of the negative opinion within 15 days of receipt of the notification.

89% of all opinions (positive and negative) **were reached by consensus** among the 28 CHMP members, which means that, following in-depth discussions, the experts agreed on all aspects of the marketing authorisations and there were no divergent opinions.

[1] This figure does not include the initial negative opinions adopted by the CHMP on Xyndari (glutamine) in May and Evenity (romosozumab) in June 2019. The applicant for Xyndari withdrew its application for marketing authorisation in September 2019. The initial negative opinion for Xyndari was under re-examination at the company's request at the time of withdrawal. The applicant for Evenity requested re-examination of the Committee's negative opinion and, after considering the grounds for this request, the CHMP recommended granting marketing authorisation for this medicine in October 2019.

FEBRUARY 01, 2019

Sartan medicines: companies are required to review manufacturing processes to avoid presence of nitrosamine impurities.

FEBRUARY 05, 2019

EMA opens public consultation on its updated risk classification of antimicrobials used in animals.

Around **59% of applicants who were granted a positive opinion for their medicine had received scientific advice** from EMA during their product's development phase. This early engagement with developers allows EMA to clarify what kind of evidence is required to later evaluate a medicine for authorisation on the basis of the then generated data, and thus protects patients from taking part in unnecessary or poorly designed clinical trials.

Keeping medicines safe

MONITORING MEDICINES AFTER THEIR AUTHORISATION – OPTIMISING SAFE AND EFFECTIVE USE

Once a medicine has been authorised, EMA and the EU Member States continuously monitor its quality and benefit-risk balance. This helps to optimise the use of a medicine to achieve its full benefit and to protect patients from avoidable side effects. If new safety information becomes available, EMA's safety committee (PRAC) can take regulatory measures ranging from a change to the product information to the suspension or withdrawal of a medicine or the recall of already distributed medicines.

Important new safety advice issued in 2019 included:

- Recommendation to add new measures to prevent serious and potentially fatal errors with the dosing of **methotrexate** for treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. A dedicated stakeholders' meeting supported the Agency's safety recommendation.
- Recommendation to revoke the marketing authorisations for **fenspiride medicines** following a review that confirmed that these cough medicines could cause heart rhythm problems.
- Recommendation to restrict the use of the multiple sclerosis medicine **Lemtrada** (alemtuzumab) due to reports of rare but serious side effects, including deaths.
- Recommendation of new risk minimisation measures for **Xeljanz** (tofacitinib) to protect patients at high risk of blood clots. The review concluded that the medicine could increase the risk of blood clots in the lungs and in deep veins in patients who are already at high risk.
- Recommendation to restrict the use of the multiple sclerosis medicine **Gilenya** (fingolimod) in pregnant women and in women able to have children who are not using effective contraception. The review confirmed that the medicine can harm the unborn child.

FEBRUARY 08, 2019

EMA launches checklist to facilitate validation of initial marketing authorisation applications.

FEBRUARY 08, 2019

New safety features come into effect for medicines sold in the EU.

- Warning to healthcare professionals that **light-exposed intravenous nutrition products containing amino acids and/or lipids** may lead to severe adverse effects in premature newborn babies. These products (containers and administration sets) should be protected from light.

- Direct acting oral anticoagulants **Eliquis** (apixaban), **Pradaxa** (dabigatran etexilate), **Lixiana** (edoxaban), **Roteas** (edoxaban) and **Xarelto** (rivaroxaban) should not be used in patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, a disorder that causes an increased risk of blood clots.

- Recommendation not to use **Xarelto** (rivaroxaban) to prevent thrombosis (formation of blood clots in the blood vessels) in patients who have recently undergone transcatheter aortic valve replacement.

The product information for 405 centrally authorised medicines was updated on the basis of new safety data in 2019. 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. It is important for regulators to ensure that EU standards are adhered to, no matter where clinical trials or manufacturing take place.

In 2019, one centralised marketing authorisation application was withdrawn as a result of non-compliance with good clinical practice (GCP).

The CHMP concluded its review of sartan medicines which set strict new manufacturing requirements for these medicines. The review was initiated due to the presence of nitrosamine impurities, including N-nitrosodimethylamine (NDMA), in a number of these medicines used to control high blood pressure. Subsequently, a nitrosamine impurity was also detected in batches of ranitidine, and the CHMP started a review of medicines containing this active substance. Ranitidine medicines are widely used to reduce the production of stomach acid in patients with conditions such as heartburn and stomach ulcers.

In September 2019, EMA initiated a wider review to provide guidance to marketing authorisation holders (MAHs) on how to avoid the presence of nitrosamines impurities in human medicines. As part of this review, the CHMP has requested MAHs for human medicines containing chemically synthesised active substances to review their medicines for the possible presence of nitrosamines and to test all products at risk. More information on this review is available in the section on nitrosamine impurities later in the report.

EMA and NCAs continue to monitor the presence of nitrosamines impurities in medicines, in cooperation with regulators from outside the EU.

More information and figures on inspections and safety monitoring of medicines is available in chapter 2.

FEBRUARY 11, 2019

Two additional countries, Poland and Slovenia, to benefit from EU-US mutual recognition agreement for inspections.

FEBRUARY 11, 2019

EMA launches new online platform for parallel distribution notifications.

Veterinary medicines

New medicines to benefit animal health in Europe

In 2019, EMA recommended 15 veterinary medicines for marketing authorisation – an increase of 50% compared to 2018. Of these, five had new active substances which had not previously been authorised for use in animals. Four were vaccines, one of which had been developed by means of recombinant DNA technology.

Aservo EquiHaler, Nobivac Myxo RHD Plus and Stelfonta were recommended for marketing authorisation under EMA's minor-use-minor-species (MUMS)/limited market programme. This scheme aims to stimulate development of new veterinary medicines for minor species and for rare diseases in major species that would otherwise not be developed.

Aservo EquiHaler is a medicine for the treatment of horses with clinical signs of severe equine asthma. Nobivac Myxo RHD Plus is a live recombinant vaccine intended for the active immunisation of rabbits from five weeks of age against myxomatosis and rabbit haemorrhagic disease. Stelfonta is a medicinal product for the treatment of non-resectable, nonmetastatic cutaneous and subcutaneous mast cell tumours in dogs.

Optimising the safe and effective use of veterinary medicines

Important new safety advice issued in 2019

The product information for 15 medicines was updated on the basis of new safety data. The revised information is expected to help animal owners and veterinarians to make informed decisions when using or prescribing a medicine.

- Addition of further advice in the product information for Bravecto on potential side effects following administration in dogs, in relation to neurological signs.
- Inclusion of special precautions and warnings in the product information for Bravecto Plus to ensure the safety of the person handling and administering the treatment. Further advice on potential side effects following administration of Bravecto Plus in cats, such as neurological signs, was also included.
- Amendment of the product information on potential side effects affecting vision following administration of Broadline in cats.
- Addition of further advice in the product information for Coxevac on potential side effects following administration in cattle, such as systemic reactions.
- Inclusion of further advice in the product information for Credelio on potential side effects following administration in dogs and cats, such as neurological reactions.
- Addition of further advice in the product information for Cytopoint on potential side effects following administration in dogs, such as neurological reactions.

FEBRUARY 15, 2019

HMA-EMA Joint Big Data task force publishes a report and launches a consultation on the role of big data for evaluation and supervision of medicines in the EU.

- Amendment of the product information for Draxxin, to include additional special precautions.
- Amendment of the product information on potential side effects following administration of Eravac in rabbits to include lethargy and/or inappetence.
- Amendment of the product information on potential side effects following administration of Letifend in dogs, such as lethargy, vomiting, diarrhoea and hyperthermia.
- Addition of further advice in the product information for Nexgard Spectra on potential side effects following administration in dogs, such as erythema and neurological signs.

FEBRUARY 21, 2019

EU and Switzerland improve information sharing on good manufacturing practice through use of the EudraGMDP database.

- Amendment of the product information for Osurnia to include special precautions relating to off-label use of the product in cats.
- Addition of further advice in the product information on potential side effects following administration of Simparica and MiPet Easecto in dogs in relation to neurological signs.
- Amendment of the product information on potential side effects following administration of Suprelorin in dogs and ferrets, in relation to weight gain and neurological signs.
- Addition of further advice in the product information for Zycortal on potential side effects following administration in dogs, such as injection site reactions.

The CVMP adopted six positive opinions for extensions of existing authorisations, broadening the use of the medicines concerned.

PROTECTING CONSUMERS

If a medicine is intended to be used in a food-producing animal, it needs to be safe for people to eat the food that comes from this animal. The maximum residue limit (MRL) recommended by EMA reflects the level of veterinary medicine residues in food derived from a treated animal that can be considered safe for consumption. In 2019, MRLs were established for the following active substances:

- Bambermycin in medicines for rabbits
- Ciclesonide in medicines for horses.

More information and figures on veterinary medicines is available in chapter 2.

FEBRUARY 28, 2019

EMA publishes the first in a series of guidance documents to help applicants prepare for obligations stemming from the new EU regulations on medical devices.

RELOCATION TO THE NETHERLANDS AND PREPARATIONS FOR BREXIT

EMA's relocation to Amsterdam

On 20 November 2017, EU Member States decided to relocate EMA to Amsterdam in the Netherlands as a result of the UK's decision to withdraw from the EU. The announcement of EMA's new location marked the next phase of the challenging relocation project and the Agency immediately began working with the Dutch authorities to prepare for the move and take up its operations in Amsterdam. 2019 was a critical year for EMA as it was important to avoid major disruptions while the Agency and a large majority of its employees had to leave its premises in London and reinstate operations in its new home, in a two-step approach, the first step being the move to its temporary premises in 2019.

Key relocation milestones in 2019 are outlined in the following timeline:

- **1 January** - EMA's temporary premises, the Spark building in Amsterdam Sloterdijk is fully operational.
- **1 March** - Last working day in the London premises.
- **4-8 March** - All EMA staff telework.
- **11-15 March** - Staff gradually move into the Spark building.
- **30 March** - Amsterdam formally becomes the new seat of EMA.
- **March-December** - EMA operates out of the Spark building.
- **15 November** - The Dutch authorities confirm practical completion of the fully fitted and furnished EMA building which is tailor-made to the requirements of its operations. The premises are located in the Zuidas area of Amsterdam.
- **Nov-Dec 2019** - Installation and testing of IT and AV technical equipment makes the new building operational; furniture is moved from the temporary premises to the new building.
- **Looking ahead to 2020** - Staff will gradually move into the final premises as of 13 January 2020 and the first meetings will take place in the same week.

The move into the EMA building marks the final step of the Agency's relocation journey to the Netherlands.

TRACKING TOOL

Because of its important role in safeguarding public and animal health in the EU, EMA committed to giving stakeholders and the public full visibility of its relocation project. A tracking tool on the EMA website enabled interested parties to track progress made during the relocation project.

MARCH 11, 2019

EMA starts operating from Amsterdam.

MARCH 21, 2019

EMA's Management Board re-elects Christa Wirthumer-Hoche as chair.

The EMA building – key facts and figures:

- The EMA building is located in the business district of Amsterdam Zuidas.
- It was commissioned by the Dutch government represented by the Central Government Real Estate Agency (CGREA) as the developer and future landlord under a design-build-maintain contract with a consortium of two Dutch construction companies.
- It has 1,300 working spaces with a total net lettable area of approximately 33,000 square metres.
- It has a BREEAM 'Excellent' rating and an Energy Label A++.
- It has been built with high environmental awareness and an ambition to contribute to the future green corridor through Amsterdam Zuid.
- It is a nearly-zero-energy building.
- It has a conference centre with an auditorium where public hearings can be held (with seats for approximately 300 people).

'The new EMA building provides tailor-made, state-of-the-art working spaces, into which the Agency can grow in the future. It is a symbol of stability and security for all EMA colleagues, after our long relocation journey. Seeing this building gives me reassurance that we can continue advancing our public health mission and can meet the challenges ahead with confidence and enthusiasm.'

Guido Rasi, Executive Director of the Agency

EMA CONFIRMED THE SUBLEASE OF ITS LONDON PREMISES AT 30 CHURCHILL PLACE

EMA reached an agreement with Canary Wharf Ltd over its premises at 30 Churchill Place, London, in accordance with the EU budgetary authority's decision. EMA sublet its 26,450 sqm at 30 Churchill Place to a subtenant who took a sublease from EMA until the expiry of EMA's lease in June 2039.

MARCH 26, 2019

EMA publishes a question-and-answer document on EU authorities' preparatory work to prevent medicine shortages due to Brexit.

MARCH 27, 2019

EMA's annual report on EudraVigilance is published.

Business continuity planning

EMA's move to Amsterdam forced the Agency to re-prioritise its activities and amend its workplan. To enable the Agency to deal with the logistical and administrative challenges of the relocation and to cope with the loss of staff, EMA implemented phase 4 of its business continuity plan at the beginning of 2019. This enabled the Agency to continue focusing its efforts to safeguard core activities related to the evaluation, maintenance and supervision of medicines.

Most activities that were temporarily suspended or reduced at the end of 2018 as part of phase 3 of EMA's business continuity plan (BCP) remained on hold in 2019: for example, guideline development (unless exceptions were agreed), engagement in international activities, most working party meetings, and the Agency's proactive publication of clinical data.

From June 2019, the Agency was able to reinstate a small number of activities, mainly those aimed at ensuring that the Agency is fit for purpose in the longer term. These included, for example, IT systems supporting the medicines evaluation process and the digitalisation of administrative processes.

In addition, some of the EU network working groups directly contributing to EMA's core activities restarted. Specifically, meetings of the Good Manufacturing and Distribution Practice, the Inspectors Working Group, the Good Clinical Practice Inspectors Working Group, the Pharmacovigilance Inspectors Working Group, the Quality Working Party, and the Process Analytical Technology (PAT) team resumed their work in September 2019.

Similarly, meetings of the Patients and Consumers Working Party (PCWP) and the Healthcare Professionals Working Party (HCPWP) restarted as of September 2019.

IMPACT OF RELOCATION ON STAFF NUMBERS

By the end of the year, the Agency's available workforce was 775 – significantly less than at the end of 2017 when EMA's relocation plans took shape.

The Agency's major recruitment drive continued in 2019 to make sure that staff who decided not to relocate to Amsterdam or were unable to could be replaced as soon as possible.

FUTURE-PROOFING EMA

To help the Agency make best use of available resources and to be best prepared for future challenges, EMA initiated an in-depth review of its organisation in 2019. This 'future-proofing' exercise will help EMA to strengthen its ability to perform important new activities together with the European medicines regulatory network and tackle important challenges ahead, such as big data, digitalisation and new scientific methods and technologies.

Operations in the area of human medicines will be integrated to strengthen the therapeutic focus throughout a medicine's life cycle, with the ultimate aim of assuring the quality of scientific opinions and further enhancing support to EMA's scientific committees. Four task forces will focus on areas that are also key priorities for the network, such as digital business transformation, data analytics and methods, regulatory science and innovation, and clinical trials and manufacturing strategy.

The new structure will come into effect in Q1 2020.

MARCH 28, 2019

A report summarising the main achievements of the sampling and testing programme for the EU over the past 20 years is published.

APRIL 30, 2019

Bulgaria and Cyprus to benefit from EU-US mutual recognition agreement for inspections.

Preparing for Brexit

Brexit-related guidance for companies

EMA, the European Commission and the Member States continued to work closely together to provide guidance to help companies marketing human and veterinary medicines in the EU to prepare for the UK's withdrawal from the EU and minimise the impact on the supply of medicines. This was aimed at ensuring that companies would be ready to take the necessary steps to enable undisrupted supply of their medicines in the EU for the benefit of patients, based on the assumption that the UK would become a third country after Brexit.

Despite the proactive approach taken by EMA and the network, there was still the risk of supply issues with some centrally authorised medicines if the UK were to leave the EU without a withdrawal agreement, in particular around the three Brexit deadlines of 31 March, 12 April and 31 October 2019. Consequently, the Agency closely monitored the evolving situation and continuously liaised with pharmaceutical companies about their Brexit preparedness.

By the end of 2019, good progress had been made by companies to take the required steps to ensure that their centrally authorised medicines could remain on the EU market. Just one marketing authorisation transfer for a human medicine was still pending. Good progress was also made for products with qualified persons for pharmacovigilance (QPPVs) still based in the UK (58 still to be transferred) and pharmacovigilance master files (PMFs) based in the UK (64 still to be transferred).

Redistribution of UK portfolio of medicines

In preparation for Brexit, the EU27 Member States and EMA had started the redistribution of the UK's portfolio of medicines to other EU Member States in 2018. By 1 July 2019, the appointed rapporteurs and co-rapporteurs from the EU27 plus Iceland and Norway took over full responsibility for more than 370 centrally authorised products which previously had UK rapporteurs or co-rapporteurs.

MAY 06, 2019

EMA launches a social media campaign to highlight how the European medicines regulatory network keeps medicines available in Europe safe and effective.

NEW EU LEGISLATION APPLICABLE TO EMA

EMA's work is determined by its legal framework and throughout its history new pieces of legislation have often transformed the Agency's remit and scope of activities. In 2019, EMA also had to work on the implementation of important pieces of new legislation together with the European Commission, the NCAs for medicines regulation, and other EU partners.

Veterinary medicines

The **new Veterinary Medicines Regulation** (Regulation (EU) 2019/6), which will become applicable on 28 January 2022, will modernise the existing rules on the authorisation and use of veterinary medicines to take account of the innovation taking place in the sector by, for example, reducing the administrative burden for applicants. It is aiming to increase the availability and safety of veterinary medicines and enhances EU action against antimicrobial resistance.

In 2019, EMA worked on the preparation of scientific and technical recommendations to feed into the delegated and implementing acts the EC is preparing as part of implementation of the Regulation. These are legally binding acts that supplement or amend EU laws (for example, defining detailed measures) and set conditions that ensure EU legislation is applied uniformly.

EMA's recommendations are prepared by ad-hoc expert groups comprising members of the European network of experts and EMA staff, in collaboration with other EU bodies such as the European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA), where necessary.

Some of the topics covered by the Agency's recommendations last year were new requirements for the collection of data on the sales and use of antimicrobials in animals, which will complement the work already carried out by countries in the European Economic Area[2] (EEA) and Switzerland. This includes gathering data on sales of antibiotics, or developing an EU product database on veterinary medicines, which will provide information on all approved veterinary medicines and their availability in EU Member States.

To help stakeholders keep track of the upcoming changes, EMA launched a new webpage with information on EMA's scientific and technical recommendations, as well as updates on other activities such as the preparation for implementation progress.

> 'We prioritised work on the new veterinary legislation, despite EMA having to operate under business continuity conditions to safeguard core activities related to the evaluation and supervision of veterinary medicines. However, progress might be affected as the Agency will not only need time to rebuild its workforce after the relocation but may also have to absorb the new activities without a corresponding staffing increase.'
>
> **Ivo Claassen, Head of EMA's Veterinary Medicines Division**

[2] The European Economic Area comprises the Member States of the EU and Iceland, Liechtenstein and Norway.

MAY 24, 2019

EMA opens up the early dialogue available through its ITF to medicine developers who work on therapeutic approaches for the treatment or prevention of bacterial and fungal infections, to help combat AMR.

Medical devices

Medical devices are regulated at the Member State level. The two **new EU Regulations on medical devices** – Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in-vitro* diagnostic medical devices – have given EMA and the NCAs new roles and more responsibilities. In February 2019, EMA published the first of a series of guidance documents to help applicants prepare for obligations stemming from the new Regulations, which will come into full effect in May 2020 and May 2022, respectively.

This first questions and answers (Q&A) document, developed jointly by EMA and the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), in close collaboration with the European Commission, focuses on implementation of Article 117 of the medical devices Regulation which stipulates that marketing authorisation applications for medicines with an integral medical device must include the results of the device's assessment of conformity by a notified body.

Approximately one in four centrally authorised medicines includes a medical device component, and the majority of these involve an integral device. Examples include pre-filled syringes and pens, patches for transdermal drug delivery and pre-filled inhalers.

> 'With the ever-increasing pace of innovation and the blurring of traditional boundaries between medicines and devices, it is inevitable for the Agency to assume new responsibilities in regulating complex medicines with a medical device component. The big challenge we face is to ensure we have the appropriate expertise and resources to adequately carry out these new tasks.'
>
> **Guido Rasi, Executive Director of the Agency**

JUNE 03, 2019

EMA releases a draft guideline on the quality requirements for medical devices in combination products for public consultation.

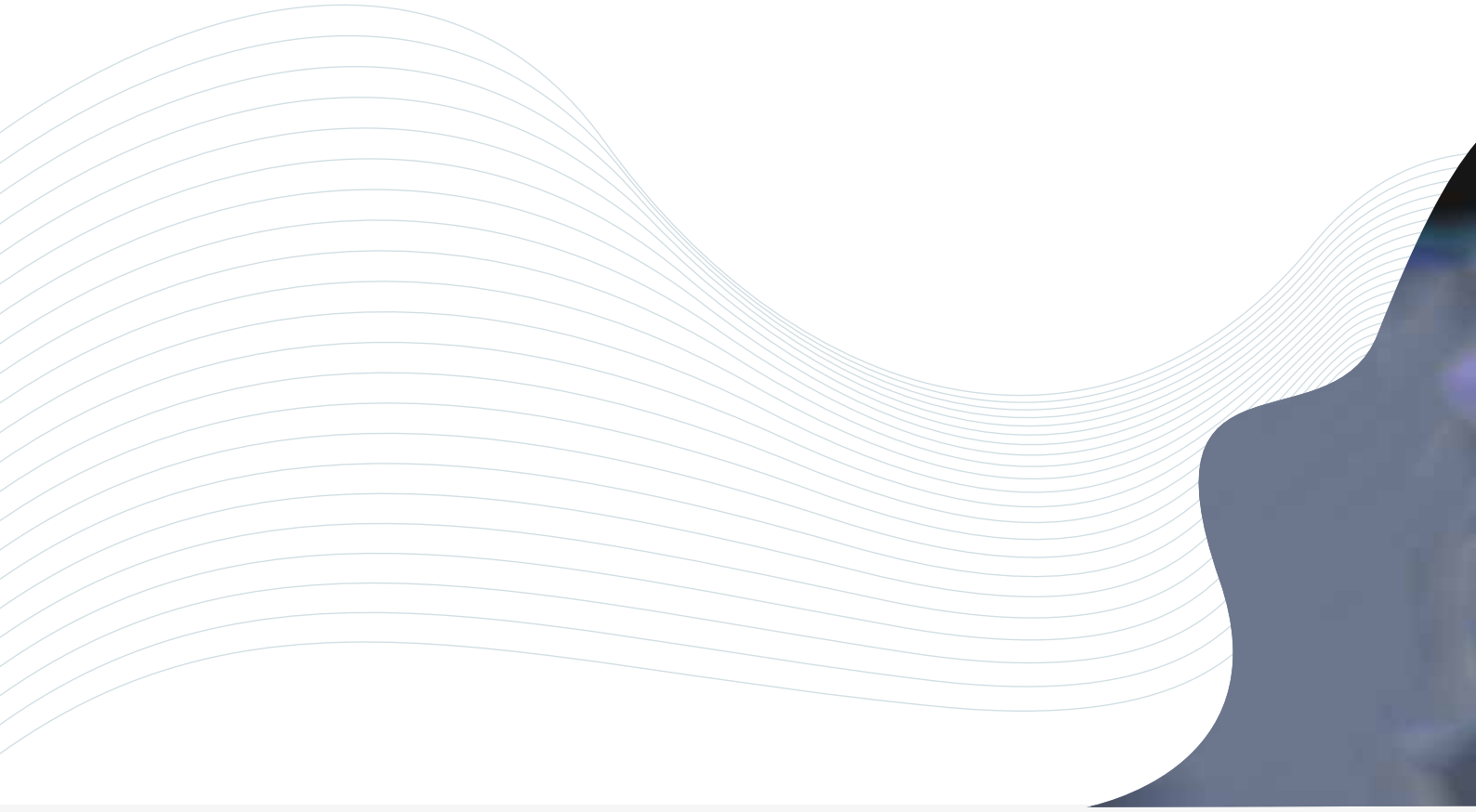
Data protection

The **new Data Protection Regulation for EU institutions and bodies** (Regulation (EU) 2018/1725), also known as EU DPR, entered into force on 11 December 2018. It ensures that the standards of data protection within EU institutions are in line with those provided for in the General Data Protection Regulation (GDPR), applicable to the public and private sector in the Member States.

EMA is reviewing its procedures to ensure that personal data processing activities are carried out in accordance with the new Regulation. In 2019, the Agency updated its privacy statements and the Data Processing Register, a repository of all data processing activities under its responsibility. These documents are available on EMA's website and provide citizens with information on how their personal data is handled and how to exercise their rights. Of note, upon request by the European Data Protection Supervisor (EDPS), EMA has amended and published the privacy statement concerning our access-to-document procedures.

In October, a new cookie consent banner was also published on the website. Through the banner, users can choose which cookies they want to allow and find more information on how these are used by the Agency. EMA also implemented new technical measures to improve the security of the server where the website is hosted.

A new set of internal rules concerning restrictions of certain rights of data subjects (Article 25 of the EU DPR) in the context of administrative inquiries



JUNE 06, 2019

EMA signs a joint statement with the two major organisations representing general practitioners (GPs) and family physicians in Europe and the major organisation representing primary care professionals in Europe, committing to strengthening their interactions.

and disciplinary proceedings conducted by EMA was also approved and published in the Official Journal of the European Union. New implementing rules clarifying the role of the Data Protection Officer under the EU DPR were finalised. Moreover, EMA entrusted an external analyst to examine the security of its systems from a data protection perspective; recommendations for improvements have been received and will be analysed in 2020.

Training materials for staff dealing with personal data, including guidelines on how to manage a data breach and how to carry out data protection impact assessments, were developed throughout 2019.

In cooperation with the European Commission and in consultation with the EDPS, the Agency is undertaking an in-depth analysis of the legal basis for important processing activities, such as the secondary use of health data, the use of big health data and of artificial intelligence for regulatory purposes. The availability of adequate resources for full implementation of the EU DPR provisions remains a serious challenge and will be further discussed with the European Commission in 2020.

JUNE 11, 2019

Luxembourg and the Netherlands to benefit from EU-US mutual recognition agreement for inspections.

JUNE 27, 2019

Germany to benefit from EU-US mutual recognition agreement for inspections.

SHORTAGES AND AVAILABILITY OF MEDICINES

Improving the availability of medicines authorised in the EU is a key priority for the European medicines regulatory network. In 2016, to better address potential problems with the supply of medicines, EMA and the HMA established a joint task force. Since its creation, it has developed and coordinated actions to facilitate the prevention, identification, management of and communication about shortages.

In 2019, the task force launched the Single Point of Contact (SPOC) system to improve information sharing on important shortages of medicines between Member States, EMA and the European Commission. This platform allows Member States to share information on availability problems with medicines as well as information on medicines that could be used as an alternative and are available in other Member States. This could help prevent and better manage shortages.

Its operation is currently being piloted (in two phases) to fine-tune operational aspects prior to full implementation in 2020. The first phase of the pilot, which ran from April to August 2019, tested the functioning and usefulness of the information exchange in the SPOC system. During this phase, 52 notifications of shortages were circulated within the SPOC network. During phase one of the pilot, 24 Member States made use of this system to share information on shortages. A second phase is foreseen for 2020, during which additional responsibilities of the SPOC system will be tested to further improve the handling of shortages.

REPORTING AND COMMUNICATING SHORTAGES

In July 2019, the task force published guidance for MAHs on detecting and reporting medicine shortages (Guidance on detection and notification of shortages of medicinal products for MAHs in the Union) and guidance to NCAs and EMA on good practices in communicating to the public on medicines' availability issues (Good practice guidance for communication to the public on medicines' availability issues).

Both documents lay the foundations for an improved and harmonised EU approach in reporting of and communication on medicine shortages and availability issues. These are key deliverables of the task force which have undergone extensive consultations with stakeholder groups, including at a multi-stakeholder workshop in November 2018. They are listed in the work programme of the task force for 2018-2020, which was updated in 2019.

JULY 03, 2019

The European Commission, EMA and the HMA co-sign a letter reminding sponsors of EU clinical trials of their reporting obligations.

JULY 04, 2019

EMA confirms sublease of its London premises; EMA also settles court case with Canary Wharf Group.

Brexit-related guidance

The uncertainties regarding the date and terms of the UK's withdrawal from the EU led to concerns about the impact on the supply of medicines if the UK should leave the EU without a withdrawal agreement (a 'no-deal scenario').

EMA, the European Commission and Member States prepared a series of guidance documents to help companies take the necessary regulatory steps to enable continued supply of their medicines in the EU for the benefit of patients. The guidance is based on the assumption that, in January 2021, the UK will become a third country where EU laws will cease to apply.

In March 2019, EMA and HMA published a questions-and-answers document for patients, healthcare professionals and the general public on the preparatory work that EU authorities have been doing to prevent medicine shortages due to Brexit.

JULY 04, 2019

The EU task force set up to address problems with medicines supply publishes two documents to improve reporting and communication of shortages.

JULY 08, 2019

Guido Rasi elected chair of International Coalition of Medicines Regulatory Authorities (ICMRA).

REGULATORY SCIENCE STRATEGY TO 2025

PREPARING FOR THE FUTURE – REGULATORY SCIENCE TO 2025

Regulatory science is at the foundation of everything that EMA does to make medicines available for the benefit of public and animal health. EMA supports the development of regulatory science and aims to ensure that advances in knowledge translate in a timely way into new, safe and effective treatments for patients and animals.

In 2019, a priority for EMA was to shape its plan for advancing regulatory science over the next five to ten years, in both human and veterinary medicines.

Regulatory science includes all the scientific disciplines necessary to assess the quality, safety and efficacy of medicines and to inform regulatory decision-making throughout the lifespan of a medicine. It encompasses basic and applied biomedical and social sciences and contributes to the development of regulatory standards and tools.

GROUNDWORK LAID FOR THE REGULATORY SCIENCE STRATEGY TO 2025

Following a dynamic period of reflection on scientific and technological advances in the pharmaceutical arena and the future challenges EMA's scientific committees and working parties will face due to these developments, the Agency focused on building consensus on future priorities and resource allocation.

> 'The Regulatory Science Strategy is the most comprehensive reflection we have conducted as an Agency since its origin. We have reflected on how we are going to engage with various challenges that new science and technology present in terms of medicines regulation, not only in Europe but also globally.'
>
> **Anthony Humphreys, Head of Regulatory Science and Innovation Task Force**

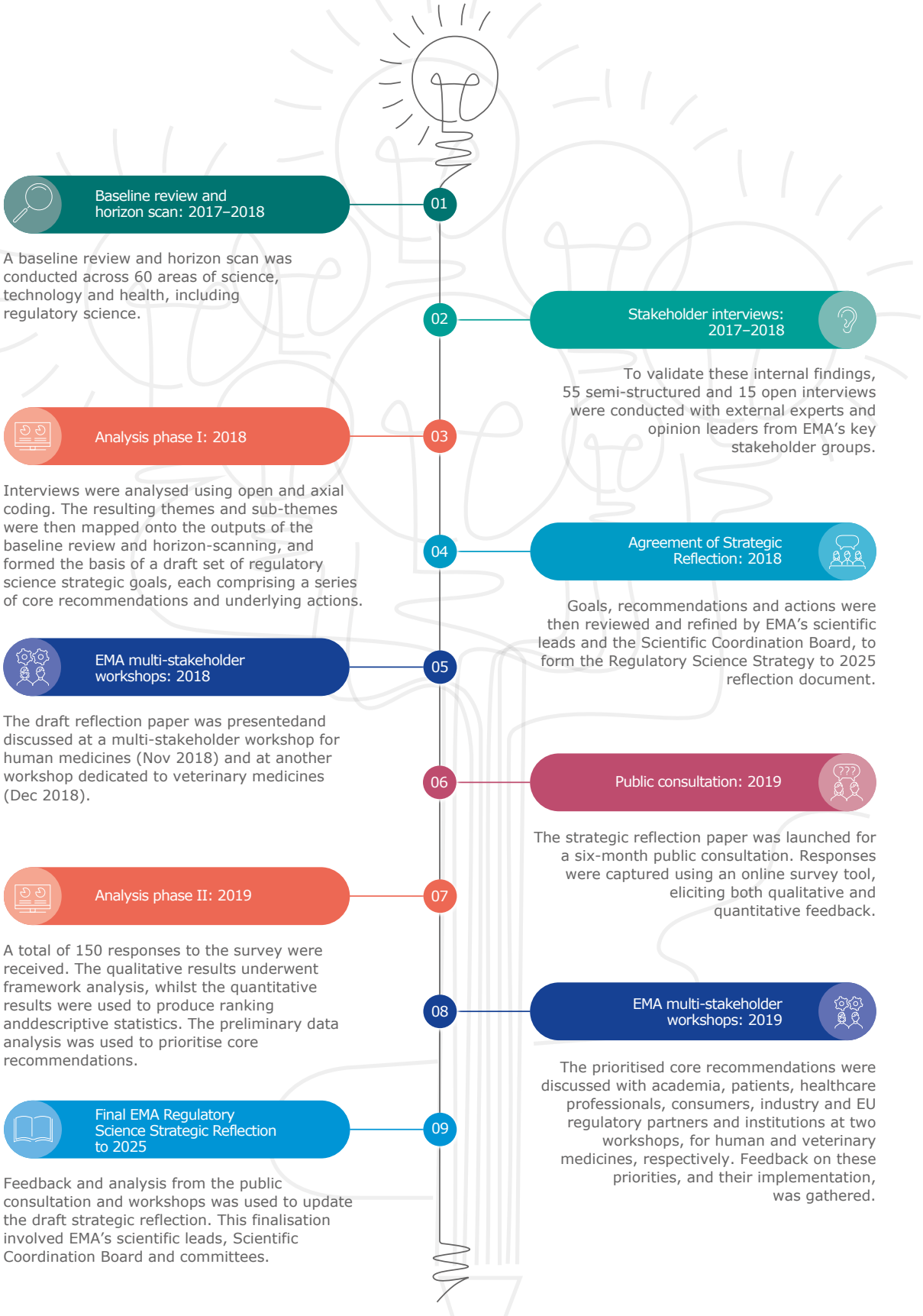
JULY 12, 2019

With the recognition of Slovakia, the EU and US complete the implementation of the MRA for inspections of manufacturing sites in their respective territories.

JULY 19, 2019

EMA takes note of the European Ombudsman's decision on pre-submission activities.

DEVELOPMENT OF THE REGULATORY SCIENCE STRATEGY TO 2025



This image is taken from: Philip A. Hines, Rosanne Janssens, Rosa Gonzalez-Quevedo, Apolline I.O.M. Lambert, Anthony J. Humphreys; A future for regulatory science in the European Union: the European Medicines Agency's strategy, Nature Review Drug Discovery, Comment 31 March 2020. (doi:10.1038/d41573-020-00032-0)

SEEKING STAKEHOLDERS' VIEWS

In the first half of 2019, EMA completed an extensive public consultation process to refine and prioritise key areas. The Agency reached out to a wide range of public health stakeholders and experts at all levels of medicine development, including patients, healthcare professionals, pharmaceutical industry, academia, and other regulatory bodies.

The purpose of the public consultation was to seek the widest possible views on whether the proposed core recommendations and supporting actions address stakeholders' needs.

> 'The Regulatory Science Strategy comes at the right time. As we implement the new Veterinary Medicines Regulation, it can support us in developing a science-based regulatory tool-box to improve the evaluation of benefits and risks of veterinary medicines.'
>
> **Ivo Claassen, Head of Veterinary Medicines Division**

OUTCOME OF PUBLIC CONSULTATION

EMA received constructive feedback on its draft strategy from over 150 respondents from a broad range of stakeholder groups, including academia, healthcare professionals, and the pharmaceutical industry that participated in this exercise and provided comments. Stakeholders used the opportunity to help guide the future strategic application of financial and human resources to address the greatest needs. The figure below shows an overview of stakeholder views on which areas required prioritisation.

STAKEHOLDER VIEWS ON WHICH AREAS REQUIRE PRIORITISATION

Overall, stakeholders found the draft regulatory science strategy comprehensive and recognised that it addresses relevant issues. They stressed the importance of stakeholder engagement for its implementation and acknowledged the Agency's efforts to collaborate with the wider stakeholder community, including patients, healthcare professionals, the pharmaceutical industry, other regulators and health technology assessment bodies and payers. All inputs from the public consultation, strategic reflections and discussions will be distilled into a comprehensive document that will be published in early 2020.

STRATEGIC REFLECTIONS ON THE REGULATORY SCIENCE STRATEGY TO 2025

Following the public consultation, the Agency hosted two multi-stakeholder workshops on human and veterinary medicines in November and December 2019. The meetings served to reach agreement on key areas where changes are required in the coming years. The finalised strategy post consultation will be a key element of the next European Regulatory Network Strategy to 2025. This will be developed together with the Member States and the European Commission and will feed directly into the Agency's multiannual work programme and the work plans of its committees and working parties.

JULY 24, 2019

EMA's Paediatric Committee elects Koenraad Norga as its new chair.

JULY 31, 2019

EMA and FDA publish a report following their joint workshop discussing how to support medicine developers in generating quality data packages in early access approaches (PRIME and breakthrough therapies).

CORE RECOMMENDATIONS THOUGHT TO DELIVER THE MOST SIGNIFICANT CHANGE IN THE REGULATORY SYSTEM

Stakeholders

PUBLIC HEALTH STAKEHOLDERS WHO PARTICIPATED IN EMA'S PUBLIC CONSULTATION PROCESS

Patients

- Individual member of the public
- Patient or consumer organisation
- Advocacy group

Healthcare Professionals

- Healthcare professional organisation
- Healthcare professional
- Veterinarian

Research Institutions

- European research infrastructure
- Academic researcher Learned society
- Other scientific organisation

Public Bodies

- EU regulatory partner/EU institution
- Health technology assessment body
- Payer

Industry

- Pharmaceutical industry (trade association, individual company, SME)

Top recommendations for human & veterinary medicines regulation

NUMBER OF TIMES RECOMMENDATIONS WERE IDENTIFIED AS FIRST, SECOND OR THIRD MOST IMPORTANT FOR DELIVERING CHANGE

Human medicines

- Foster innovation in clinical trials — 35 (7, 2, 13, 13)
- Promote use of high-quality real-world data (RWD) in decision-making — 30 (2, 3, 6, 3, 16)
- Reinforce patient relevance in evidence generation — 26 (4, 13, 4, 5)
- Contribute to HTA's preparedness and downstream decision-making for innovative medicines — 25 (2, 9, 3, 5, 6)
- Support developments in precision medicine, biomarkers and 'omics' — 23 (4, 4, 7, 1, 7)

Veterinary medicines

- Transform the regulatory framework for innovative veterinary medicines — 14 (1, 4, 4, 2, 3)
- Develop new approaches to improve the benefit-risk assessment of veterinary medicinal products — 8 (1, 2, 3, 2)
- Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance — 6 (1, 1, 1, 3)

Expert views on the development of the Regulatory Science Strategy

Anthony Humphreys, Head of Regulatory Science and Innovation Task Force

WHAT ARE THE OUTCOMES OF THE PUBLIC CONSULTATION ON THE REGULATORY SCIENCE STRATEGY TO 2025?

We were extremely pleased with the diversity of engagement across all of our various stakeholder groups. We received substantial input from healthcare professionals, patient groups, academia, industry, other EU institutions, NCAs and downstream decision-makers. That has allowed us to converge on what are seen as the most significant changes we could make as a system over the next five years that would deliver real value to improve the regulation of medicines in Europe.

WHAT ARE THE KEY TAKEAWAYS FROM THE MULTI-STAKEHOLDER DISCUSSIONS?

When digesting all the feedback we received from stakeholders, we converged on a number of very important points: fostering innovation and clinical trials; looking into real-world evidence, real-world data sources and how they can be used in benefit-risk decision-making; and trying to increase patient involvement throughout the whole development life cycle to ensure the medicines being delivered meet patient needs and expectations. We have also recognised that we can leverage and collaborate with our academic colleagues better to help us address regulatory challenges. We must also engage with the challenges of the new biology and personalised precision medicines. It is a very exciting time as regards the potential this offers patients, but it is also very challenging. How do we really engage with the extent of this interesting, challenging science that is coming through? That's at the very heart of this reflection on regulatory science.

WHAT ARE THE MOST IMPORTANT LESSONS LEARNT FROM THE PUBLIC CONSULTATION?

Having benefitted from the very extensive six-month consultation process, we really were in a listening mode and willing to receive input from our stakeholders, to adapt what we will focus on in the future, and to deliver what we anticipate to be the greatest changes needed to ensure the most impact.

WHO ARE THE KEY ACTORS WHO NEED TO BE INVOLVED IN IMPLEMENTING THE ACTIONS OUTLINED IN THE RSS?

Having listened to our stakeholders and agreed on a common set of priorities and underlying actions to deliver change in a given area, we have to work together to try to make it happen. It is this spirit of collaboration and cooperation as we go forward that is at the very heart of the exercise. It is going to be one of the most critical success factors to deliver the strategy.

CONSIDERING THE PROGRESS MADE IN 2019, WHAT ARE THE NEXT STEPS?

We held major workshops at the end of 2018 and, after a very extensive public consultation, we drew that reflection to a close in the last quarter of 2019 with both human and veterinary workshops. We are now writing up all that valuable feedback with a view to formal adoption by our Management Board in March 2020.

At the same time, this regulatory science reflection is not a stand-alone exercise. Many critical changes will have to be delivered together with our network partners as part of the EU Network Strategy to 2025 which we are now actively putting together with the heads of agencies of the NCAs.

HOW WILL THE REGULATORY SCIENCE STRATEGY BE IMPLEMENTED?

The Regulatory Science Strategy underlines the need for EMA experts and staff to keep pace with technological and scientific developments in order to assess innovative and increasingly complex medicines that are intersecting many different technologies. Throughout 2019, as we developed the strategy, we realised that our current organisation would need to be modified to meet these future challenges. The primary outcome of that future-proofing exercise has been the consolidation of the three human medicines divisions into a single division. This will focus on delivering the necessary changes in maintaining and improving the core business, together with the constitution of four task forces on digital business transformation, data analytics and methods, regulatory science and innovation, and clinical trials and manufacturing strategy. At the heart of their origin is delivering on the changes needed on one or more of the key strategic areas of the Regulatory Science Strategy.

Tjalling van der Schors, hospital pharmacist, board member at the European Association of Hospital Pharmacists (EAHP), Director of Professional Development

The Regulatory Science Strategy 2025 is well designed to reach the very-much-needed changes to ensure that medicines of the future will be safe and effective. The complexity requires difficult choices in the balance between evidence and progress. Patients need reliable medicines. The evidence to achieve this should not result in an unwanted increase of administrative burden for healthcare professionals.

Thomas Kanga-Tona, project manager at the International Association of Mutual Benefit Societies (AIM)

WHAT DOES THE REGULATORY SCIENCE STRATEGY TO 2025 MEAN TO YOU?

Overall, AIM subscribes to the EMA strategy and welcomes the fact that the Regulatory Science Strategy to 2025 highlights the need for closer collaboration/engagement with payer organisations and their needs. EMA's Regulatory Science Strategy is the opportunity for the Agency to clearly state its priorities for the next five years, with regards to its core tasks: making sure that safe, quality and efficacious medicines reach European markets.

WHAT IS THE IMPORTANCE OF THE REGULATORY SCIENCE STRATEGY TO 2025 FOR HEALTH TECHNOLOGY ASSESSMENT BODIES AND PAYERS?

For AIM, as a payers' organisation, the Regulatory Science Strategy to 2025 is the opportunity to provide feedback to the regulator about our insights on key trends we have noticed in recent years. We think that EMA should ensure there is strong data evidence at the time of marketing approval. It would help reduce uncertainty and allow for more timely access as it could improve the relevance of the end points. We would very much welcome EMA taking into account the concerns AIM has already raised about the accelerated pathways for drug approval. If more data needs to be collected after market access, EMA should be more stringent regarding the follow-up of requirements set for companies against the background of increasing the relevance of end points and ensuring that only safe and effective medicines are used in the EU. In general, when evaluating new technologies (especially ATMPs) we would like to ask EMA to also consider the impact on the healthcare setting/patient treatment process as a whole. Situations where technologies would only be available in certain centres in Europe, and fragile patients (and their families) would need to travel far from home and stay in foreign hospitals for months might have an important impact for the patient outcomes (including quality of life).

WHAT DID YOU THINK OF THE CONSULTATION PROCESS?

AIM replied to the public consultation and attended the community event which took place in November. However, we have heard little so far about how the final strategy will look, which topics will feature in it, as well as how they will be chosen. The overall timeline for the adoption of the strategy is quite opaque, too.

Anton Ussi, Operations and Finance Director of the European Infrastructure for Translational Medicine (EATRIS)

WHAT DOES THE REGULATORY SCIENCE STRATEGY TO 2025 MEAN TO YOU?

We are very optimistic about both the strategy and opportunities it affords the academic community. Recognition of the ever-increasing complexity of health innovations calls for a multi-stakeholder effort and structural interaction among these. The strategy has put this need front and centre, and deeper collaboration with academia will be an important element of this.

WHAT IS THE IMPORTANCE OF THE REGULATORY SCIENCE STRATEGY TO 2025 FOR ACADEMIA?

While academia has always been a pillar of the innovation process, we see academics playing a central role in innovation more often and going further downstream towards clinical application more often than ever before, especially in advanced therapies. As a community, we need to be able to understand from the regulator what is expected of us, as well as to be able to share our knowledge of these emerging technologies so that regulatory clarity can be achieved quickly. The strategy recognises that this two-way communication is essential and charts a clear path to facilitate it.

WHAT DO YOU THINK OF THE CONSULTATION PROCESS?

The consultation was open, transparent and extremely well executed. We were given the opportunity to provide in-depth responses, and the EMA was very active in ensuring that the consultation was broadly disseminated and utilised. After collation, the face-to-face workshop was deeply satisfying as we had a genuine sense of openness, and the feeling that the Agency is in listening mode. This bodes well for the future of the strategy. Hats off to the Agency for continuing apace with these developments in the midst of making an historical transition to Amsterdam.

Jean-Pierre Orand, Director of the French Agency for Veterinary Medicines (ANMV)

WHAT DOES THE REGULATORY SCIENCE STRATEGY TO 2025 MEAN TO YOU?

The Regulatory Science Strategy is an opportunity to reinforce the network, especially the relationship between regulator and academia, and to answer to the challenges we are confronted with.
The European medicines network of agencies has to be prepared for future problems of animal and human health. One of the regulator's strategic objectives is to adapt the available scientific and regulatory expertise both in terms of capacity and capability to cope with changing demands.
We will develop the capability to regulate novel products of the future, consider greater use of real-world databases and increase transparency about the data that underpin regulatory decisions.

Regulatory science will promote innovation to respond to therapeutic gap and be a tool to facilitate the registration of novel and innovative medicines, taking into account the specificities of the veterinary sector and considering the social and economic context.

So, the Regulatory Science Strategy to 2025 is a way to prepare for these challenges for the benefit of human and animal health.

WHAT IS THE IMPORTANCE OF THE REGULATORY SCIENCE STRATEGY TO 2025 FOR VETERINARIANS?

Animal health has a direct impact on human health; it is the concept of the One Health approach. Most of the diseases are zoonosis, and animals remain the principal source of protein for human consumption.

At the same time, the veterinary medicines sector faces different constraints compared to the human medicines sector. On one hand, there are many therapeutic gaps due to the high number of species and lots of minor use. On the other hand, the development of veterinary medicines will take into account economical aspects with the need for return of investment and low prices, environmental risk management, societal consideration (animal welfare, etc.) and an increase in animal health outbreaks in the world due to the globalisation of the market and the increasing circulation of people and goods, and climate change.

So, regulatory science might bring answers to all these constraints by developing another approach for increasing the availability of veterinary medicines, not only through innovation but also by developing new approaches for improving the benefit-risk assessment or application of the latest scientific knowledge.

A new legal framework has just been adopted for veterinary medicines and with the Regulatory Science Strategy there is an opportunity to develop a better environment for the authorisation of veterinary medicines.

WHAT DID YOU THINK OF THE REGULATORY SCIENCE STRATEGY CONSULTATION PROCESS?

The consultation process was very interesting as lots of stakeholders had a chance to share their views with transparency and openness.
The face-to-face workshop organised after the written phase was really satisfying as it was an opportunity to have fruitful exchanges with all stakeholders and to clarify certain opinions or ideas that came up during the written phase.

Nancy De Briyne, Deputy Executive Director of the Federation of Veterinarians of Europe (FVE)

WHAT DOES THE REGULATORY SCIENCE STRATEGY TO 2025 MEAN TO YOU?

The Regulatory Science Strategy for me is a vision and strategy document. It shows the road that legislators in the field of veterinary medicine need to take to keep up with rapidly changing societal and technological developments. It aims to make sure that health professionals will be able to continue to have the best medicines available to treat their patients and that we are prepared for emerging health threats.

"The best way to predict the future is to create it." (Lincoln)

WHAT IS THE IMPORTANCE OF THE REGULATORY SCIENCE STRATEGY TO 2025 TO VETERINARIANS?

The availability of effective, safe and affordable veterinary medicines is extremely important for veterinary surgeons to safeguard the health and welfare of their patients. Many of the issues impacting the daily work of veterinarians are covered in this strategy, e.g. how to regulate innovative medicines such as immunomodulators and phages; how to ensure the availability of medicines for all animals and in all EU countries; how to make the best use of precision medicine; how to control AMR; and how to prepare for emerging diseases due to climate change. All these important topics are dealt with in the strategy.

WHAT DID YOU THINK OF THE REGULATORY SCIENCE STRATEGY CONSULTATION PROCESS?

EMA did not try to rush the exercise but took extensive time to consult widely with all the stakeholders involved. FVE had an ample opportunity to collect the views of European veterinarians, attended several consultation meetings and gave input at several time frames. As such, FVE very much appreciates the consultation process.

A DECISIVE YEAR FOR BIG DATA IN MEDICINES REGULATION: TOWARDS DATA-DRIVEN DECISION-MAKING

In 2019, EMA and NCAs took major steps towards unlocking the potential of big data for medicines regulation in the EU. The joint HMA/EMA Big Data Task Force, which is composed of experienced medicines regulators and data experts appointed by the national competent authorities, EMA and the European Commission, worked intensively throughout the year, leading to concrete recommendations on steps the European medicines regulatory network could take to evolve its approach on how to use evidence from big data for regulatory decision-making.

Massive amounts of data are generated daily through wearable devices, electronic health records, social media, clinical trials or spontaneous adverse reaction reports. To complement the evidence from clinical trials and fill knowledge gaps regarding a medicine, insights derived from this data will increasingly be used by regulators to assess the benefits and risks of medicines across their whole life cycle. However, in order to benefit from and make prudent use of the data collected, regulators recognised they need to better understand the data landscape and identify the optimal analytical methods.

In **phase one** of its work, the HMA/EMA Big Data Task Force published a report in February 2019 which reviewed the big data landscape from a regulatory perspective and identified opportunities for improvements in the operation of medicines regulation. This report also included surveys of national regulatory agencies and the pharmaceutical industry on their perspectives, available expertise and possible obstacles. This helped to develop an understanding of the challenges and the current state of expertise in the regulatory network. The report, on which stakeholders were invited to comment, provided for the first time a definition of big data in medicines regulation:

> **Big data** are 'extremely large datasets which may be complex, multidimensional, unstructured and heterogeneous, which are accumulating rapidly, and which may be analysed computationally to reveal patterns, trends and associations. In general, big data sets require advanced or specialised methods to provide an answer within reliable constraints.'

AUGUST 30, 2019

Stakeholders are invited to register to attend a global public meeting on the revision of the ICH guideline on clinical trials.

AUGUST 30, 2019

EMA provides the first set of recommendations to the EC concerning the new veterinary regulation implementation.

Having identified the opportunities for improvement, in **phase two** of its work, the Big Data Task Force focused on mechanisms to achieve this. A second report, which was adopted by EMA's Management Board in December 2019, identified practical steps to be taken by the European medicines regulatory network to increase its capacity to deal with big data. The task force identified **ten priority actions** for European regulators, the most ambitious being the establishment of an EU platform to access and analyse healthcare data from across the EU (Data Analysis and Real World Interrogation Network, or DARWIN).

The European medicines regulatory network is now considering how to implement the task force's recommendations, in consultation with the European Commission. The recommendations will inform strategic decision-making and planning by the HMA and EMA and contribute to the development of the five-year EU Network Strategy to 2025.

SEPTEMBER 13, 2019

EMA's Executive Director asks the CHMP to provide guidance on avoiding the presence of nitrosamine impurities in human medicines containing chemically synthesised active substances.

Three questions on DARWIN to Peter Arlett, Head of Data Analytics and Methods Task Force at EMA and co-chair of the Big Data Task Force

WHAT IS DARWIN?

The creation of the Data Analysis and Real World Interrogation Network is the top recommendation from the Big Data task force. While the EU is fortunate in the richness of its healthcare data, which stems from universal healthcare coverage, it currently lacks the means to fully exploit it. The proposal is to create a European platform to access and analyse healthcare data of known quality and content using the highest levels of data security. This platform would initially focus on analysing electronic health records to support regulatory decision-making on the benefits and risks of medicines although, over time, it could include other healthcare data including claims and registry data.

WHY IS ITS DEVELOPMENT SEEN AS A PRIORITY BY THE BIG DATA TASK FORCE?

This is because the benefits for public health and stakeholders are very significant. DARWIN could support better regulatory decision-making on medicines by informing those decisions with robust evidence from healthcare. Once a medicine has been authorised, it could support the monitoring of the performance of medicines on the market (both effectiveness and safety). In the context of the authorisation of new medicines, it could complement data from randomised clinical trials with evidence from healthcare practice. With access to such data, regulators will also be able to validate claims made by the pharmaceutical industry through independent analysis and address public health challenges that cut across individual products, such as antimicrobial resistance or the safe and effective use of different classes of medicines.

WHAT ARE THE NEXT STEPS?

The Big Data Task Force has developed an initial business case with concrete proposals to deliver this ambitious project. Together with the HMA Task Force co-chair, Nikolai Brun, I am very grateful for the constructive discussions which took place within the task force and beyond with stakeholder groups. These discussions led to a proposal which balances well the needs of regulators and other decision-makers, both at the national and European level.

We will now need to build on this business case and secure support and resources to establish and maintain DARWIN. There is a need to establish both technology and, importantly, robust governance, including data security. By establishing DARWIN, we can deliver better medicines regulation by using evidence from the delivery of healthcare. The platform could also have benefits for many partners and stakeholders who take decisions that could be informed by such data accessed from across Europe.

SEPTEMBER 13, 2019

EMA starts a review of ranitidine medicines following the detection of NDMA.

SEPTEMBER 23, 2019

EMA publishes a new webpage to summarise the Agency's work on the new veterinary regulation.

PRIORITY RECOMMENDATIONS OF THE HMA-EMA JOINT BIG DATA TASK FORCE

01 Deliver a sustainable platform to access and analyse healthcare data from across the EU.

Data Analysis and Real World Interrogation Network - DARWIN. Build the business case with stakeholders and secure funding to establish and maintain a secure EU data platform that supports better decision-making on medicines by informing those decisions with robust evidence from healthcare.

02 Establish an EU framework for data quality and representativeness.

Develop guidelines, a strengthened process for data qualification through scientific advice, and promote across Member States the uptake of electronic health records, registries, genomics data, and secure data availability.

03 Enable data discoverability.

Identify key metadata for regulatory decision-making on the choice of data source, strengthen the current ENCePP resources database to signpost to the most appropriate data, and promote the use of the FAIR principles (Findable, Accessible, Interoperable and Reusable).

04 Develop EU network skills in big data.

Develop a big data training curriculum and strategy based on a skills analysis across the network, collaborate with external experts including academia, and target recruitment of data scientists, omics specialists, biostatisticians, epidemiologists, and experts in advanced analytics and AI.

05 Strengthen EU network processes for big data submissions.

Launch a 'big data learnings initiative' where submissions that include big data are tracked and outcomes reviewed, with learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods.

06 Build EU Network capability to analyse big data.

Build computing capacity to receive, store, manage and analyse large data sets including patient level data (PLD), establish a network of analytics centres linked to regulatory agencies, and strengthen the network's ability to validate AI algorithms.

07 Modernise the delivery of expert advice.

Build on the existing working party structure to establish a Methodologies Working Party that encompasses biostatistics, modelling and simulation, extrapolation, pharmacokinetics, real world data, epidemiology and advanced analytics, and establish an Omics Working Party that builds on and reinforces the existing pharmacogenomics group.

08 Ensure data are managed and analysed within a secure and ethical governance framework.

Engage with initiatives on the implementation of EU data protection regulations to deliver data protection by design, engage with patients and healthcare professionals on data governance, and establish an Ethics Advisory Committee.

09 Collaborate with international initiatives on big data.

Support the development of guidelines at international multilateral fora, a data standardisation strategy delivered through standards bodies, and bilateral collaboration and sharing of best practice with international partners.

10 Create an EU big data 'stakeholder implementation forum'.

Dialogue actively with key EU stakeholders, including patients, healthcare professionals, industry, HTA bodies, payers, device regulators and technology companies. Establish key communication points in each agency and build a resource of key messages and communication materials on regulation and big data.

NITROSAMINE IMPURITIES: THE NETWORK'S RESPONSE

In June 2018, the European medicines regulatory network became aware of the presence of nitrosamine impurities (N-nitrosamines) in a class of medication used to control high blood pressure, known as 'sartans'. Regulatory actions were instituted across the EU, including the recalls of some medicines from pharmacies and measures to prohibit the use of active pharmaceutical ingredients from certain manufacturers.

EMA's CHMP subsequently conducted a review of sartans, which finished in January 2019. While the network was looking at the lessons to be learnt from dealing with the sartans, impurities in a small number of other medicines were detected. This chapter describes the regulatory actions and measures taken throughout the year to protect public health, and the causes and consequences of nitrosamine impurities.

Focus on nitrosamines

N-nitrosamines are substances that are formed in certain chemical reactions in the environment; most people are exposed to them in small amounts in some foods as well as in drinking water. They are classified as probable human carcinogens (i.e. substances that could cause cancer in humans), on the basis of animal studies. The current regulatory guidelines set very strict limits.

JANUARY 2019: CHMP CONCLUDES THE REVIEW OF SARTANS

The CHMP found that the risk from the N-nitrosamine impurities was low. In the vast majority of sartan medicines, nitrosamine impurities were either not detected or were present at very low levels. Given the greater risk to patients from stopping their treatments, the Committee advised patients not to stop their sartan treatments without consulting their healthcare professionals.

The review concluded that the use of a certain solvent (dimethylformamide) together with sodium nitrite in the presence of an acid led to the formation of N-nitrosamines during the manufacture of sartan active pharmaceutical ingredients (APIs). There was also a potential for contamination from other sources, including solvents, reagents and manufacturing equipment already contaminated with N-nitrosamines.

Therefore, the review set out new requirements for MAHs of sartan medicines, including the requirement to test their products for N-nitrosamines and make the necessary changes to their API manufacturing processes.

The CHMP also set interim limits for two N-nitrosamine impurities (NDMA[3] and NDEA) in APIs valid for a two-year transitional period. After this period, all companies must have implemented the necessary changes to their manufacturing processes to minimise the risk of nitrosamines contamination, with the goal of having no quantifiable N-nitrosamines in sartans.

[3] N-Nitrosodimethylamine and N-Nitrosodiethylamine.

SEPTEMBER 25, 2019

EMA's Patients' and Consumers' Working Party (PCWP) re-elects Kaisa Immonen of the European Patients' Forum (EPF) as co-chair.

SEPTEMBER 25, 2019

EMA's Healthcare Professionals' Working Party (HCPWP) elects Ulrich Jäger of the European Hematology Association (EHA) as new co-chair.

Lessons learnt from the presence of nitrosamine impurities in sartans

The European medicines regulatory network and the European Directorate for the Quality of Medicines & HealthCare (EDQM) launched a 'lessons learnt exercise' in order to look at possible approaches to prevent unexpected impurities such as N-nitrosamines from being present in human medicines and to improve management of such incidents, should they occur in the future. The publication of a report, including recommendations and a technical analysis, is envisaged for mid-2020.

APRIL 2019: DETECTION OF N-NITROSAMINES IN PIOGLITAZONE

Following the detection of low quantities of a nitrosamine impurity in a few batches of the diabetes medicine pioglitazone manufactured in India, EMA called on companies to test their products and check their processes to rule out contamination.

SEPTEMBER 2019: CHMP STARTS REVIEW OF NITROSAMINE IMPURITIES IN RANITIDINE MEDICINES

After tests showed nitrosamine impurities in some batches of ranitidine, the European Commission asked EMA to conduct a regulatory review of these medicines[4]. Ranitidine-containing medicines are widely used to treat and prevent conditions caused by excess acid in the stomach, such as heartburn and stomach ulcers.

The CHMP started reviewing all available data with the aim of issuing recommendations in early 2020.

SEPTEMBER 2019: GUIDANCE TO MAHS ON HOW TO AVOID THE PRESENCE OF NITROSAMINES

As nitrosamine impurities had been detected in a number of medicines by September 2019, EMA's Executive Director asked the CHMP[5] to provide guidance to MAHs on how to avoid the presence of nitrosamines impurities, on the basis of what was known about their origins.

As a matter of precaution, the CHMP requested that MAHs for human medicines containing chemically synthesised active substances review their medicines for the possible presence of nitrosamines, perform a risk evaluation and test all products that might be at risk.

The CHMP has given companies six months from the start of the review to complete the risk evaluation and three years to complete the testing. The European medicines regulatory network plans to complete this exercise by 26 September 2022.

[4] under Article 31 of Directive 2001/83/EC.
[5] under Article 5(3) of Regulation (EC) No 726/2004.

SEPTEMBER 26, 2019

EMA advises companies on steps to take to avoid nitrosamines in human medicines.

OCTOBER 14, 2019

The European Network of Paediatric Research at EMA (Enpr-EMA) elects Pirkko Lepola of the Finnish Investigators Network for Pediatric Medicines (FinPedMed) as the new chair of its Coordinating Group.

Coordinating international efforts

Since the presence of nitrosamines in medicines was first discovered, it was clear that this issue would have global ramifications. This is a consequence of the close integration of the pharmaceutical global supply chain, with the lion's share of APIs being produced in China and India.

To provide an adequate response to this challenge, the European medicines regulatory network enhanced its cooperation with international partners. Beginning with the sartans, an international strategic group was set up to coordinate the activities of the different regulators and facilitate the rapid exchange of information.

The close cooperation is ongoing with international partners such as Health Canada, US Food and Drug Administration, Japan's Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency, Australia's Therapeutic Goods Administration, Singapore's Health Science Authority, and Swissmedic.

OCTOBER 15, 2019

The new ESVAC report shows that European countries continue to reduce the use of antibiotics in animals.

OCTOBER 17, 2019

The first vaccine to protect against Ebola is recommended for approval.

How the EU network manages incidents

The EU medicines regulatory network has set up the Incident Management Plan to establish procedures on how to deal with emerging information related to medicines safety in the EU. One of the main objectives is to have a coordinated approach at the EU level to manage incidents affecting the safety, quality or supply of medicines.

Within the context of the nitrosamine incidents, the EU network has utilised several organisational structures:

- the Quality Defect rapid Alert system, which was established to circulate information concerning the recall of medicinal products due to quality defects or which are falsified within the network and to international partners and organisations;
- the Incident Review Network (IRN), a virtual advisory network that reviews incidents and advises the network on approaches to take. The composition of the IRN includes staff members from the EMA, the EC and NCAs.

This approach has been reinforced by measures agreed in December 2019 with the network and pending the outcome of the article 5(3) review being undertaken by CHMP.

OCTOBER 21, 2019

The CHMP develops a paper to strengthen consistency when defining therapeutic indications in medicines product information.

OCTOBER 25, 2019

The Deputy Commissioner of the Chinese National Medical Product Administration (NMPA), Dr Chen Shifei, visits EMA together with a delegation.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is an increasingly serious public health threat. It threatens the effective treatment of an ever-increasing range of infections caused by bacteria and other microorganisms.

In 2019, EMA contributed to the global fight against AMR by:

- supporting the development of new antimicrobial agents;
- collecting data on consumption of veterinary antimicrobials;
- encouraging and advising on responsible use of antimicrobials.

SUPPORTING THE DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS

EMA supports the development of new medicines and treatment approaches, especially for patients with multi-drug resistant bacteria. In 2019, two new antibacterial agents received a positive opinion from CHMP: Quofenix (delafloxacin) is an antibiotic used in adults to treat bacterial infections of the skin and underlying tissues; Recarbrio (Imipenem/cilastatin/relebactam) is intended for the treatment of infections due to certain bacteria (aerobic Gram-negative bacteria).

EARLY DIALOGUE WITH MEDICINE DEVELOPERS

Fostering the development of new medicines to treat resistant infections is one of the main pillars in the fight against the global threat of AMR and is a high priority for EMA and the EU medicines regulatory network.

In May 2019, EMA opened the Innovation Task Force (ITF), its platform for early dialogue, to all medicine developers working on medicines for the treatment or prevention of life-threatening microbial infections to help strengthen the industry's drug-development pipeline for new antimicrobials. Based on the initial experience with product-specific discussions in this new framework, the initiative facilitates greater interaction between developers and the regulator streamlining and optimising respective drug developments in the AMR field and, as such, is facilitating their way to the patients. Promising drug candidates will have the opportunity for further interactions through the various development support measures offered by EMA.

A COMMON APPROACH FOR NEW ANTIBIOTIC DEVELOPMENT

EMA also published a revision of its guideline on the evaluation of human medicines indicated for the treatment of bacterial infections. The revision is the result of cooperation between the Agency and its international partners in the United States and Japan which aims to align the data requirements as much as possible between the three regions. The revised guideline was published for a six-month public consultation in July 2019.

EMA, the US FDA and the Japanese PMDA continued their cooperation throughout the year. In their fourth tripartite meeting, held on 24 and 25 September 2019 in Tokyo, the discussions revolved around the design of clinical trials that could meet the data requirements of different regulators. For the first time, the meeting also included a discussion on antifungal agents, an area increasingly affected by AMR and where clinical development programmes can be challenging.

OCTOBER 31, 2019

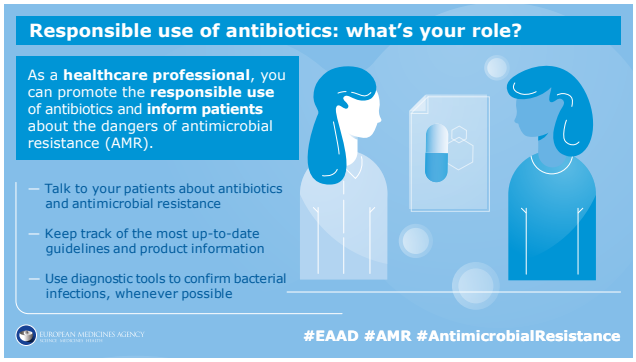
EMA provides a further recommendation to the EC concerning the new veterinary regulation implementation: criteria for antimicrobials to be reserved for human use.

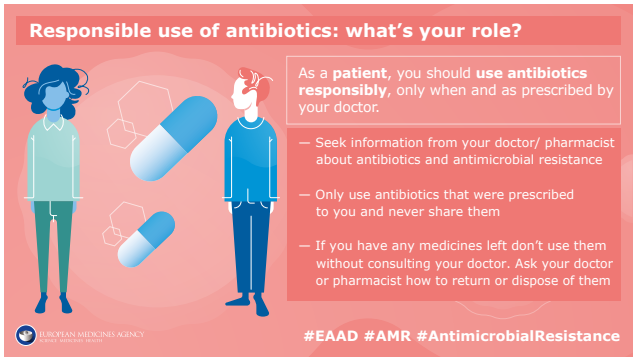
NOVEMBER 15, 2019

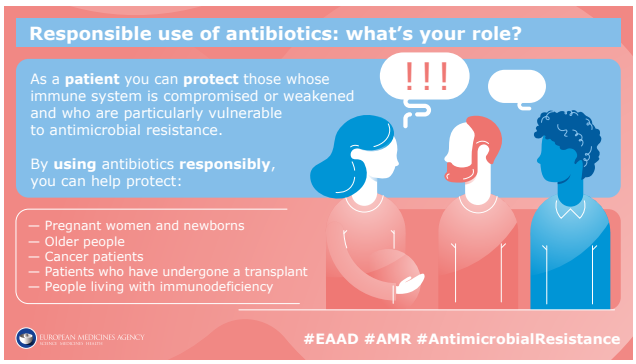
The Dutch authorities hand over EMA's final building in Amsterdam.

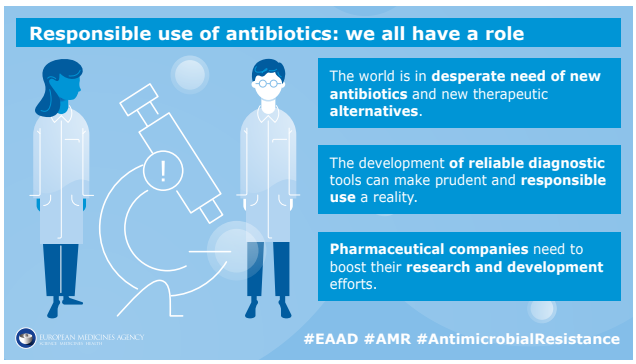
What does responsible use mean for you - European Antibiotic Awareness Day 2019

To mark European Antibiotic Awareness Day in 2019, EMA launched a social media campaign to highlight the importance of using antibiotics responsibly. A set of info-cards focused on what responsible use means for patients, healthcare professionals, veterinarians, health leaders and the pharmaceutical industry.









DECEMBER 17, 2019

EMA and its European and international partners launch a pilot programme to increase their cooperation in the inspection of manufacturers of sterile medicines for human use.

DATA SHOW DECREASE IN THE SALES OF VETERINARY ANTIMICROBIALS

The 9th European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report, published by EMA in October 2019 and reporting 2017 sales data for 31 participating countries, showed encouraging results on the sales of veterinary antibiotics. For the 25 countries that contributed data between 2011 and 2017, the sales of antibiotics for animal use decreased overall by 32%. The report is used by risk assessors and risk managers in Member States as a reference for antimicrobial policies and for guidance on the responsible use of antimicrobials.

While the situation across EU Member States remains variable, the report gives reason for optimism that the substantial reduction in the sales of antimicrobials for food-producing species observed in some countries indicates the potential for a similar decrease in others, especially in those where consumption is still high.

The ESVAC network has grown from nine countries reporting data for its first report published in 2011 to 31 countries from the European Economic Area and Switzerland providing data from 2017 in the report published in 2019.

Reduction in sales is the result of combined efforts of veterinarians, farmers, other actors in the livestock sector, EU Member States, the European Commission and EMA. National campaigns for prudent use of antibiotics in animals, sales targets and restriction of use of some antimicrobials in food-producing animals, as well as EU guidance, have helped to reduce the sales of veterinary antimicrobials across Europe.

RESPONSIBLE USE OF ANTIBIOTICS IN ANIMALS PROTECTS PEOPLE AND ANIMALS

In 2019, EMA launched a public consultation on its updated scientific advice on the categorisation of antimicrobials. The scientific advice ranks antibiotics by considering both the risk that their use in animals causes to public health through the possible development of AMR and the need to use them in veterinary medicine.

The update took into account the experience gained since the initial publication of the categorisation of antimicrobials in 2014. It now addresses all classes of antibiotics, including those classified as Critically Important Antimicrobials (CIA) for human health by the World Health Organization. The classification comprises four categories, from A to D: Avoid (A), Restrict (B), Caution (C) and Prudence (D).

Veterinarians are encouraged to check and consider EMA's updated scientific advice on the categorisation of antibiotics when prescribing these medicines for animals in their care. The categorisation can also be used as a tool for the preparation of treatment guidelines.

A JOINT ENDEAVOUR

The above-mentioned scientific advice was prepared by the Antimicrobial Advice Ad Hoc Expert Group (AMEG), comprising representatives and experts from the CVMP and the CVMP's Antimicrobials Working Party, the CHMP and the CHMP's Infectious Diseases Working Party, the EFSA, the ECDC, and the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) working group. It was adopted by both CVMP and CHMP in December 2019 in line with EMA support for a 'One Health' approach that promotes close and integrated cooperation between human and veterinary medicine.

DECEMBER 17, 2019

Four-year overview of pharmacovigilance activities in the EU: a report shows that the EU pharmacovigilance system is strong and adaptable and has had a positive impact on public health.

CATEGORISATION OF ANTIBIOTIC CLASSES FOR VETERINARY USE
(WITH EXAMPLES OF SUBSTANCES AUTHORISED FOR HUMAN OR VETERINARY USE IN THE EU)

A — AVOID

Amdinopenicillins
mecillinam
pivmecillinam

Ketolides
telithromycin

Monobactams
aztreonam

Rifamycins (except rifaximin)
rifampicin

Carboxypenicillin and ureidopenicillin, including combinations with beta lactamase inhibitors
piperacillin-tazobactam

Carbapenems
meropenem
doripenem

Lipopeptides
daptomycin

Oxazolidinones
linezolid

Riminofenazines
clofazimine

Sulfones
dapsone

Streptogramins
pristinamycin
virginiamycin

Drugs used solely to treat tuberculosis or other mycobacterial diseases
isoniazid
ethambutol
pyrazinamide
ethionamide

Other cephalosporins and penems (ATC code J01DI), including combinations of 3rd-generation cephalosporins with beta lactamase inhibitors
ceftobiprole
ceftaroline
ceftolozane-tazobactam
faropenem

Glycopeptides
vancomycin

Glycylcyclines
tigecycline

Phosphonic acid derivates
fosfomycin

Pseudomonic acids
mupirocin

Substances newly authorised in human medicine following publication of the AMEG categorisation
to be determined

B — RESTRICT

Cephalosporins, 3rd- and 4th-generation, with the exception of combinations with β-lactamase inhibitors
cefoperazone
cefovecin
cefquinome
ceftiofur

Polymyxins
colistin
polymyxin B

Quinolones: fluoroquinolones and other quinolones
cinoxacin
danofloxacin
difloxacin
enrofloxacin
flumequine
ibafloxacin
marbofloxacin
norfloxacin
orbifloxacin
oxolinic acid
pradofloxacin

C — CAUTION

Aminoglycosides (except spectinomycin)
amikacin
apramycin
dihydrostreptomycin
framycetin
gentamicin
kanamycin
neomycin
paromomycin
streptomycin
tobramycin

Aminopenicillins, in combination with beta lactamase inhibitors
amoxicillin + clavulanic acid
ampicillin + sulbactam

Cephalosporins, 1st- and 2nd-generation, and cephamycins
cefacetrile
cefadroxil
cefalexin
cefalonium
cefalotin
cefapirin
cefazolin

Amphenicols
chloramphenicol
florfenicol
thiamphenicol

Lincosamides
clindamycin
lincomycin
pirlimycin

Pleuromutilins
tiamulin
valnemulin

Macrolides
erythromycin
gamithromycin
oleandomycin
spiramycin
tildipirosin
tilmicosin
tulathromycin
tylosin
tylvalosin

Rifamycins: rifaximin only
rifaximin

D — PRUDENCE

Aminopenicillins, without beta-lactamase inhibitors
amoxicillin
ampicillin
metampicillin

Tetracyclines
chlortetracycline
doxycycline
oxytetracycline
tetracycline

Aminoglycosides: spectinomycin only
spectinomycin

Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)
cloxacillin
dicloxacillin
nafcillin
oxacillin

Natural, narrow-spectrum penicillins (beta lactamase-sensitive penicillins)
benzathine benzylpenicillin
benzathine phenoxymethylpenicillin
benzylpenicillin
penethamate hydriodide
pheneticillin
phenoxymethylpenicillin
procaine benzylpenicillin

Sulfonamides, dihydrofolate reductase inhibitors and combinations
formosulfathiazole
phthalylsulfathiazole
sulfacetamide
sulfachlorpyridazine
sulfaclozine
sulfadiazine
sulfadimethoxine
sulfadimidine
sulfadoxine
sulfafurazole
sulfaguanidine
sulfalene
sulfamerazine
sulfamethizole
sulfamethoxazole
sulfamethoxypyridazine
sulfamonomethoxine
sulfanilamide
sulfapyridine
sulfaquinoxaline
sulfathiazole
trimethoprim

Cyclic polypeptides
bacitracin

Steroid antibacterials
fusidic acid

Nitroimidazoles
metronidazole

Nitrofuran derivatives
furaltadone
furazolidone

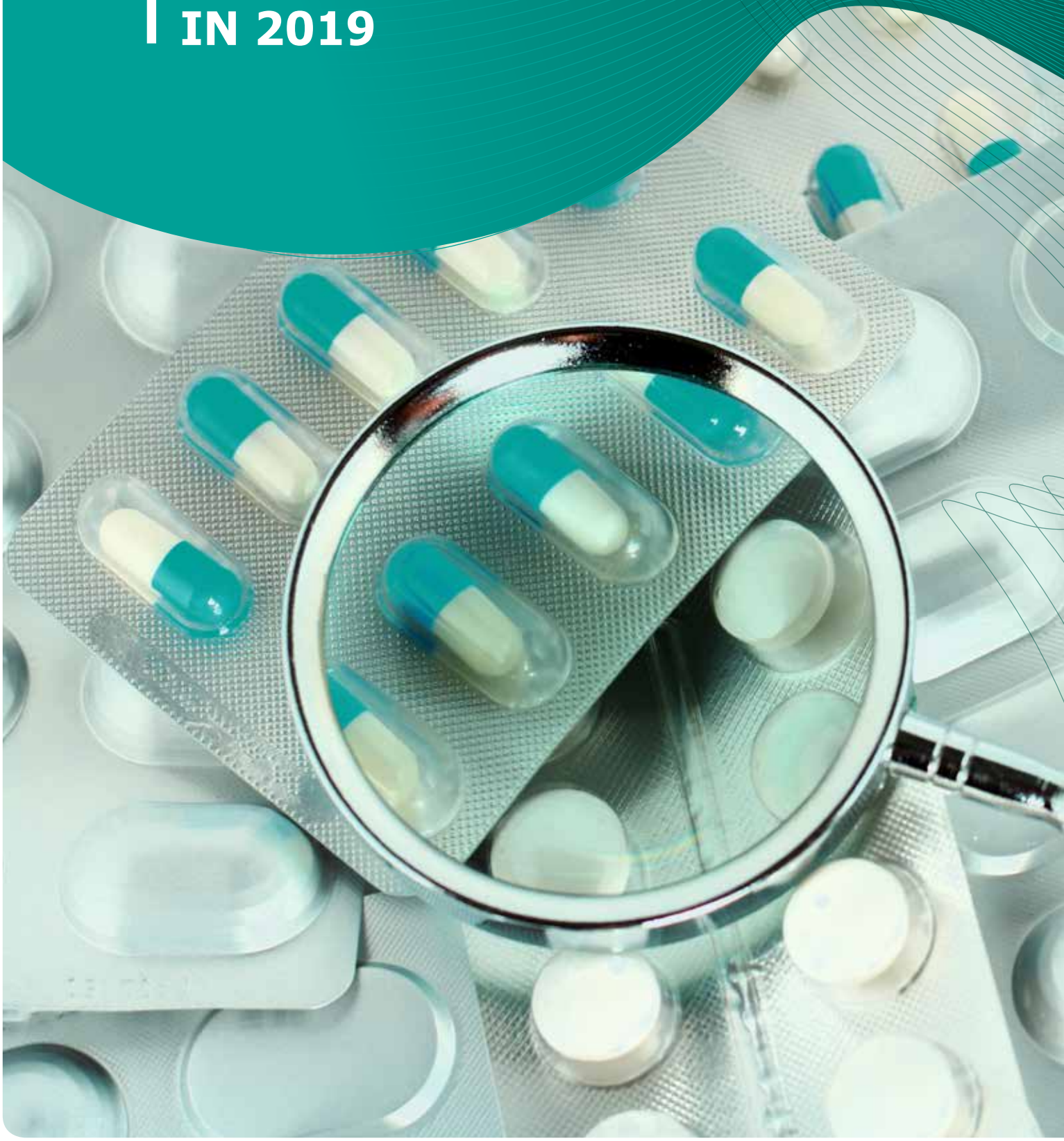
Other factors to consider

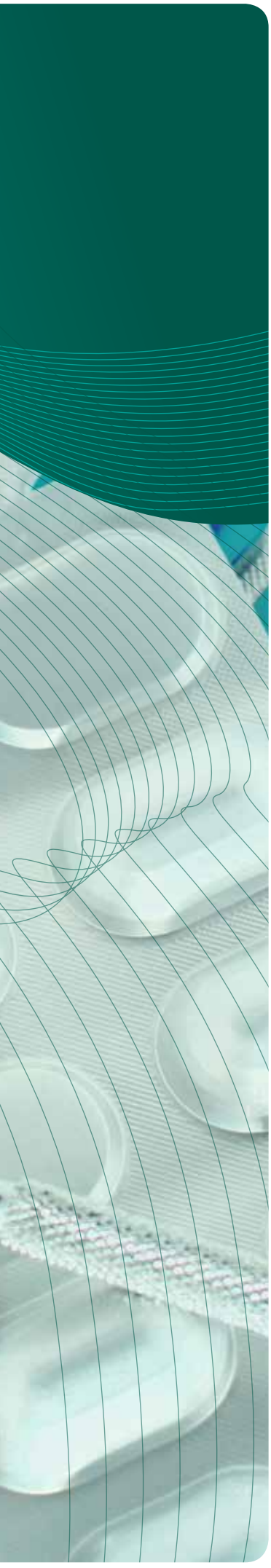
The **route of administration** should be taken into account alongside the categorisation when prescribing antibiotics. The list below suggests routes of administration and types of formulation ranked from the lowest to the highest estimated impact on antibiotic resistance.

Local individual treatment (e.g. udder injector, eye or ear drops)
Parenteral individual treatment (intravenously, intramuscularly, subcutaneously)
Oral individual treatment (i.e. tablets, oral bolus)
Injectable group medication (metaphylaxis), only if appropriately justified
Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified
Oral group medication via feed or premixes (metaphylaxis), only if appropriately justified

CHAPTER 2

KEY FIGURES IN 2019





HUMAN MEDICINES

Supporting research and development

EMA provides guidance and support to medicine developers. This includes scientific and regulatory information on how to design and run clinical trials, compliance standards, and obligations and incentives for developers of specialised medicines.

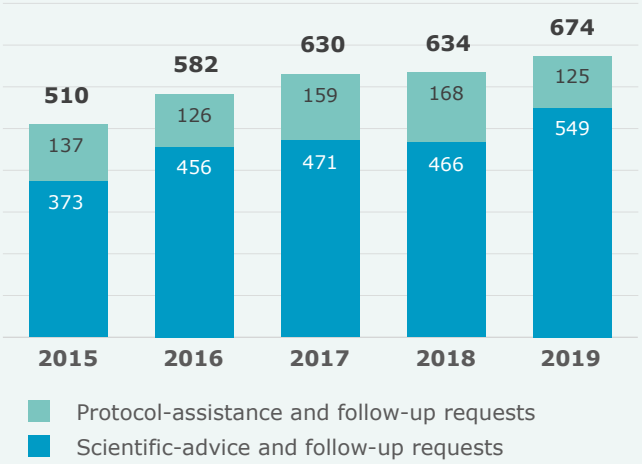
Scientific advice

During a medicine's development, a developer can request guidance and direction from EMA on the best methods and study designs to generate robust information on how well a medicine works and how safe it is. This is known as scientific advice.

Scientific advice is one of the Agency's key instruments for supporting the development of high-quality, effective and safe medicines, for the benefit of patients. 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 generate data that are relevant to support the evaluation of a marketing authorisation application or extension of indication.

In 2019, the European Ombudsman concluded a strategic enquiry into EMA's scientific advice activities. The Ombudsman's recognition of the value and need for scientific advice and her recommendations are in line with EMA's ongoing initiatives to further increase transparency. Early interactions with medicine developers and the provision of scientific advice are well-established processes with demonstrated added value in medicines regulation, and contribute positively to public health by helping to bring new, safe and effective medicines to patients. At the same time, EMA recognises the importance of guaranteeing the independence of the medicine assessment which takes place at a later stage. The Ombudsman's suggestions for further improvements are being addressed by the Agency and will be implemented in 2020.

Scientific advice and protocol-assistance requests received - total

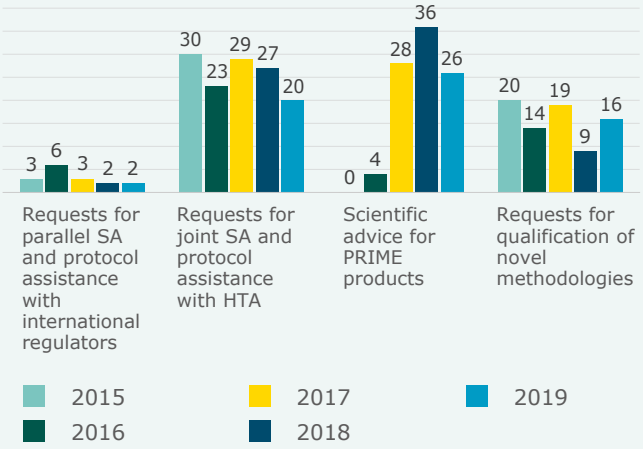


In 2019, EMA received a total of 549 requests for scientific advice, which represents an increase of 18% compared to 2018.

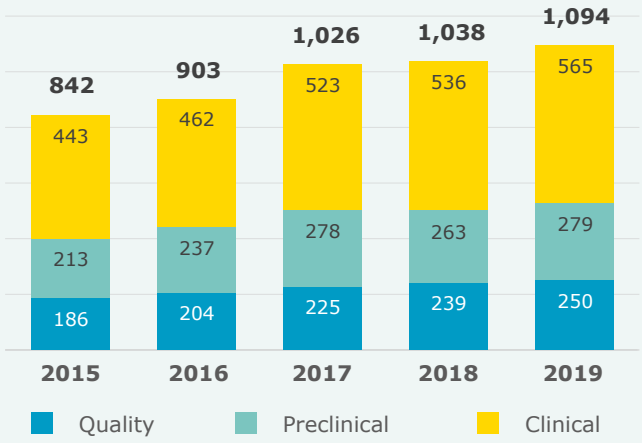
Patients participated as experts in several scientific advice procedures. A total of 143 patients were involved in 134 procedures.

Protocol assistance is the special form of scientific advice for developers of designated orphan medicines for rare diseases. The requests for protocol assistance fell by 26%, from 168 in 2018 to 125 in 2019. This decrease is in line with an overall decline in orphan designations in 2019.

Scientific advice and protocol-assistance requests received - special programmes



Scientific advice requests by topic

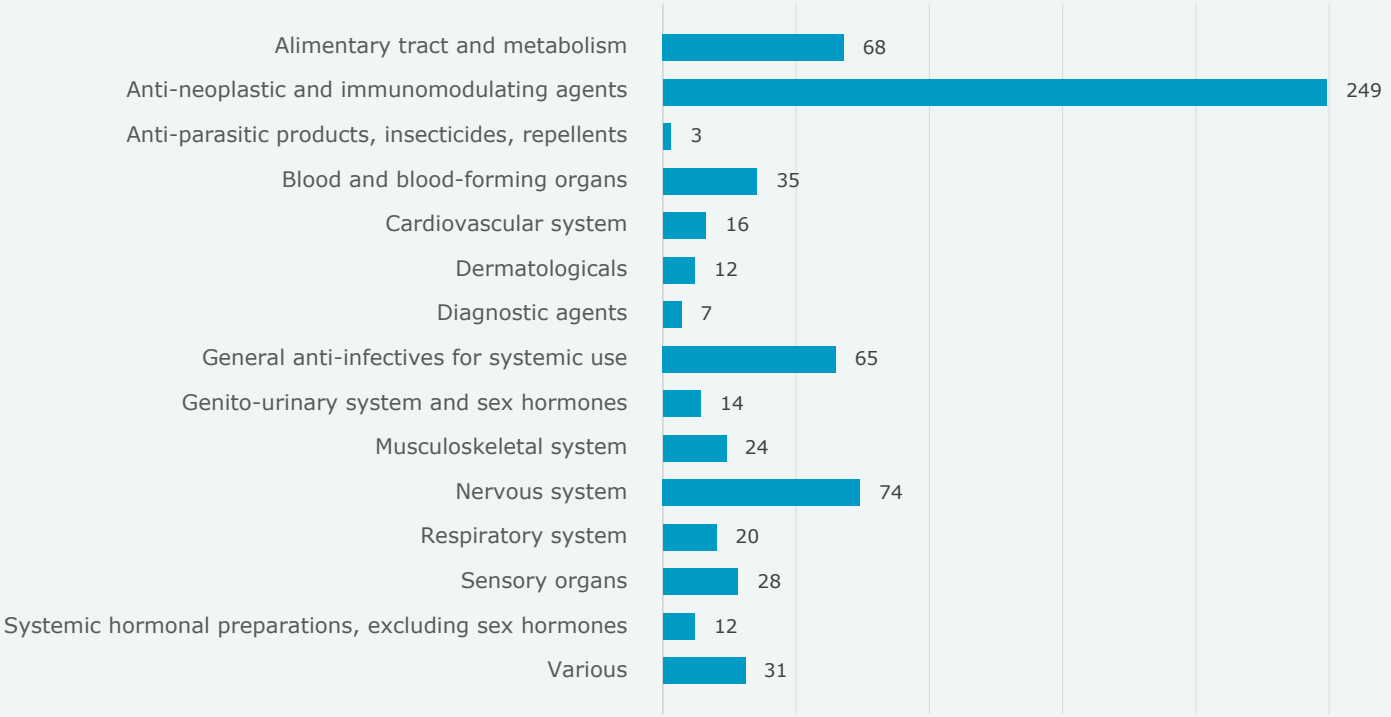


Scientific advice is the core of many EMA special programmes to encourage development and availability of new and innovative medicines. The Agency received 16 requests for qualification of novel methodologies, 11 of them from SMEs.

The requests for scientific advice for PRIME products decreased for the first time since the launch of the scheme in 2016, owing to a lower number of PRIME designations in the last two years, compared to 2017.

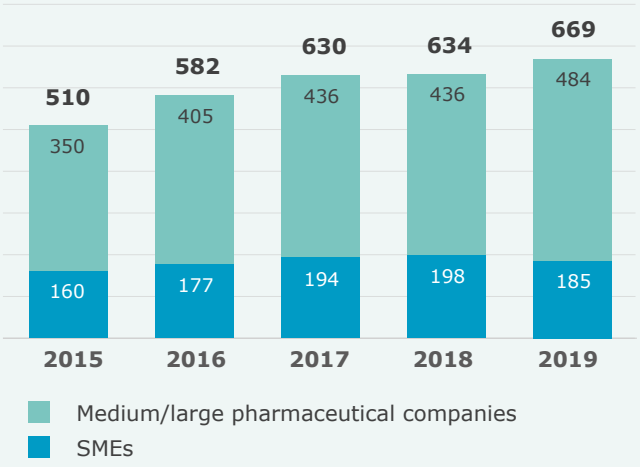
As in previous years, more than half of the requests for scientific advice related to clinical issues, 26% to preclinical issues and 23% to quality issues. In terms of development stage, 57% of requests related to medicines in phase III, 29% to medicines in phase II, 11% to medicines in phase I, and 3% to medicines in phase IV of their clinical development.

Scientific advice requests by therapeutic area (2019)



28% of the total number of requests came from SMEs.

Scientific advice requests by affiliation of requester



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.

In 2019, 20 requests for parallel advice were submitted, 26% fewer than in 2018. The requests were from the following therapeutic areas:

- Alimentary tract and metabolism - 3
- Anti-neoplastic and immunomodulating agents - 8
- Blood and blood-forming organs - 2
- Cardiovascular system - 1
- Musculoskeletal system - 3
- Nervous system - 2
- Sensory organs - 1

Seven requests were for advance therapies, six for orphan medicines, two for PRIME, and three came from SMEs.

In terms of development stage, 50% of requests related to medicines in phase III, 25% to medicines in phase II, 20% to medicines in phase IV, and 5% to medicines in phase I of their clinical development.

EMA and HTA bodies continued their efforts to facilitate an exchange of views on product-specific evidence, once generated. This occurs mainly in the context of joint relative effectiveness assessments by the European network for health technology assessment (EUnetHTA). In 2019, four such interactions took place between regulatory rapporteurs and HTA authors, based on the final CHMP opinion.

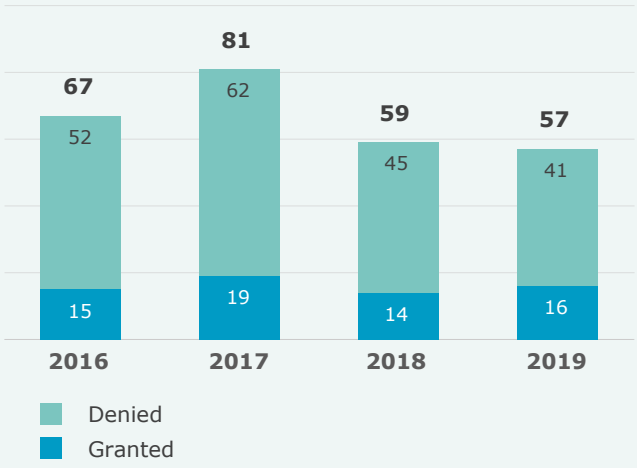
PRIME

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 2019, EMA received 60 PRIME eligibility requests and adopted 57 recommendations.

2018 and 2019 showed stable numbers in eligibility requests, after the peak in 2017 that followed the launch of the scheme.

PRIME is intended for the most promising medicines and EMA focuses its attention on medicines that have the potential to bring a major therapeutic advantage. That is why only a limited number of applications (16 out of 57 in 2019) are accepted into the scheme. The rate of products granted access to the scheme was slightly higher in 2019, with 28% compared to 23% in 2018.

PRIME - eligibility recommendations



Support for SMEs

SMEs are recognised as drivers 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 those SMEs registered with EMA. These companies also have access to various fee incentives to support their medicine-development programmes.

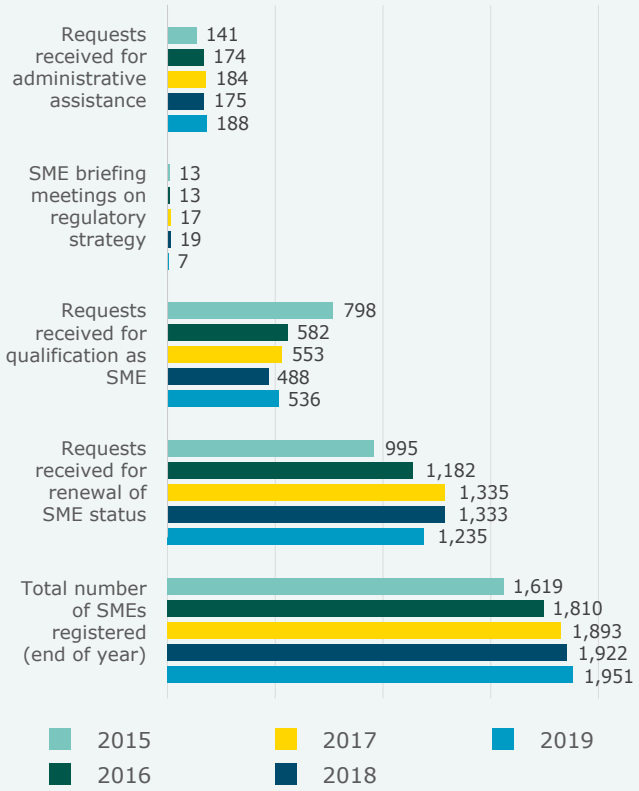
In 2019, the SME office received 188 requests for direct assistance on administrative or regulatory aspects and organised 9 briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. A total of 1,951 SMEs were registered with the Agency by the end of 2019.

In 2019, SMEs submitted 24 marketing authorisation applications. This is the highest number since 2016 and represents 20% of all applications received in 2019.

Of the 24 applications, 13 were for orphan designated medicines, which is the highest number in the past five years.

The CHMP gave a positive opinion for 8 medicines developed by SMEs, half of which had a new active substance. This represents 12% of all positive opinions in 2019.

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



Initial evaluation applications and SMEs (human medicines)

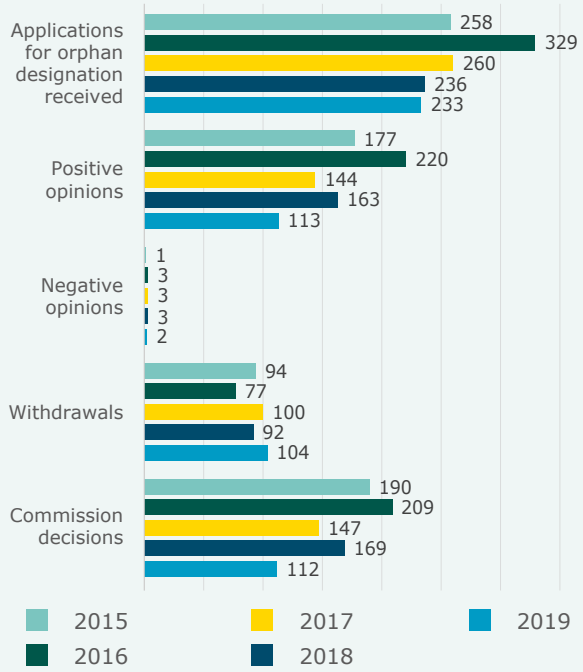
	2015	2016	2017	2018	2019
Initial marketing authorisation applications submitted by SMEs	15	27	20	15	24
Positive opinions	9	4	12	13	8
Negative opinions	2	1	2	5	1
Withdrawals	1	5	7	5	3

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.

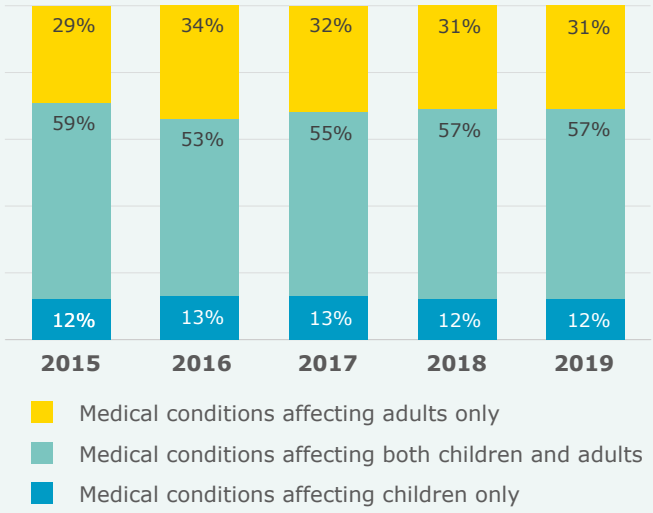
Medicines with an EU orphan designation benefit from ten years of market exclusivity if they are granted a marketing authorisation. During the development of an orphan medicine, other incentives, such as a fee reduction for scientific advice (protocol assistance), are also available for medicine developers. EMA's COMP is responsible for assessing orphan designation applications.

Orphan medicine designation procedures



* The figure on applications for orphan designation received in 2018 (236) has been amended.

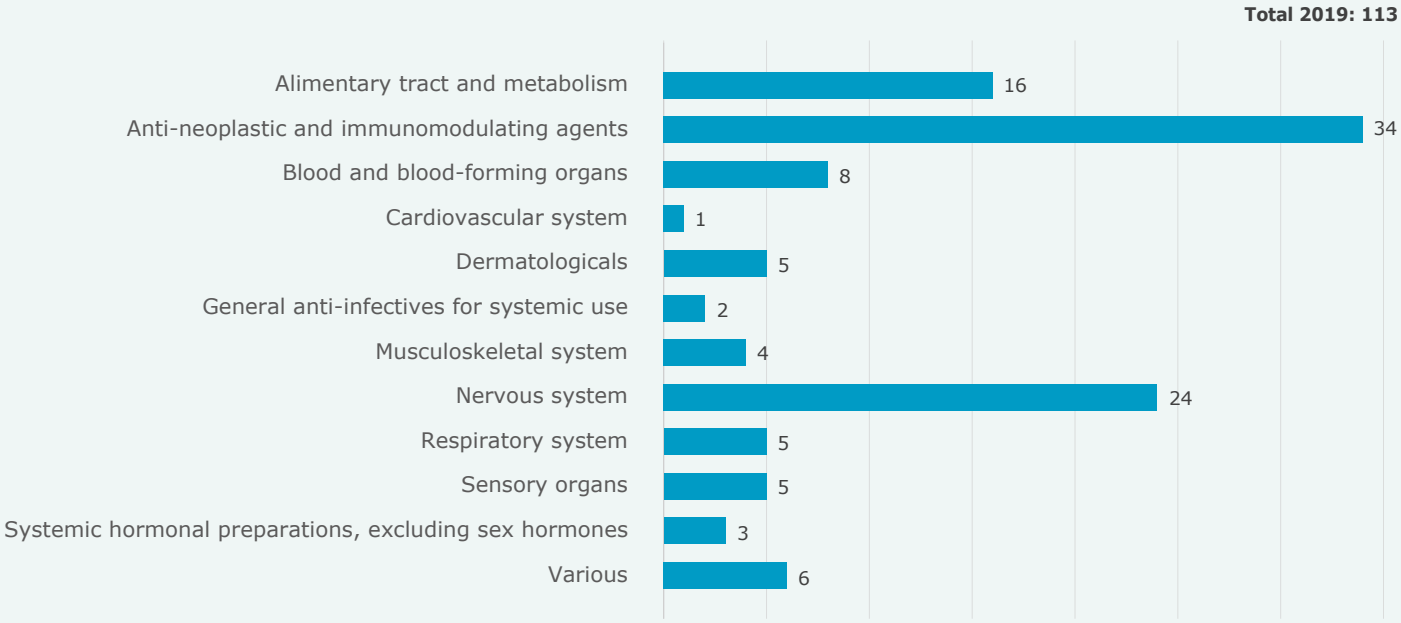
Designated orphan medicines for the treatment of children and adults



The number of applications for orphan designations was 233 in 2019, reflecting the steady identification of new targets to treat orphan diseases. Of these, 113 were granted a designation, allowing them to benefit from the incentives under the EU Orphan Framework. 104 applications were withdrawn and 2 received a negative opinion from the COMP.

The EC supports the development of medicines for rare diseases financially, with €11.7 million provided in 2019. More than 53% of the Commission's special contribution was used to provide protocol assistance to medicine developers and 32% for the assessment of applications for marketing authorisation.

COMP opinions by therapeutic area (2019)



Medicines for children

The Agency also promotes the development of medicines for children. EMA's Paediatric Committee (PDCO) assesses and agrees paediatric investigation plans (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 a marketing authorisation submission. To support research and development of medicines in children, EMA provides the secretariat for Enpr-EMA.

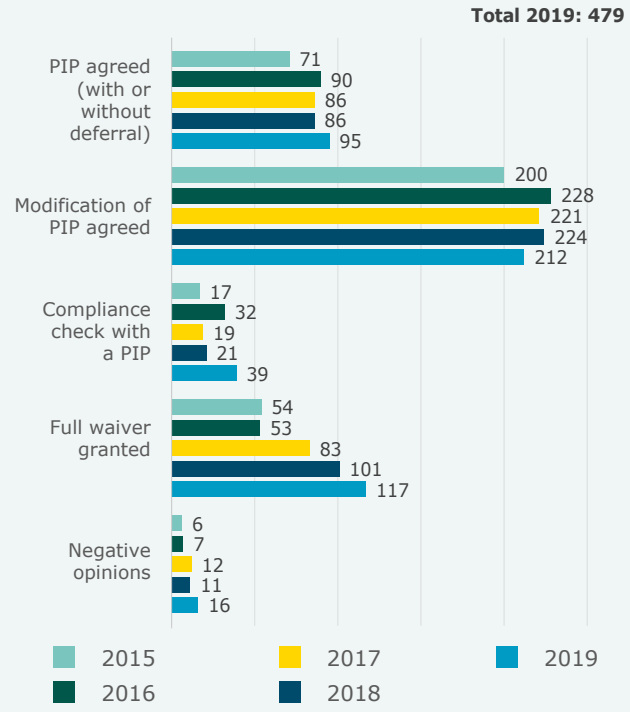
A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children to support the authorisation of a medicine for them. Where studies in children are inappropriate or unnecessary, a waiver may be granted. In 2019, the PDCO agreed 94 initial PIPs, the highest number in the past five years.

There were fewer modification requests, suggesting that applicants are submitting PIPs of better quality which reduce the need for changes.

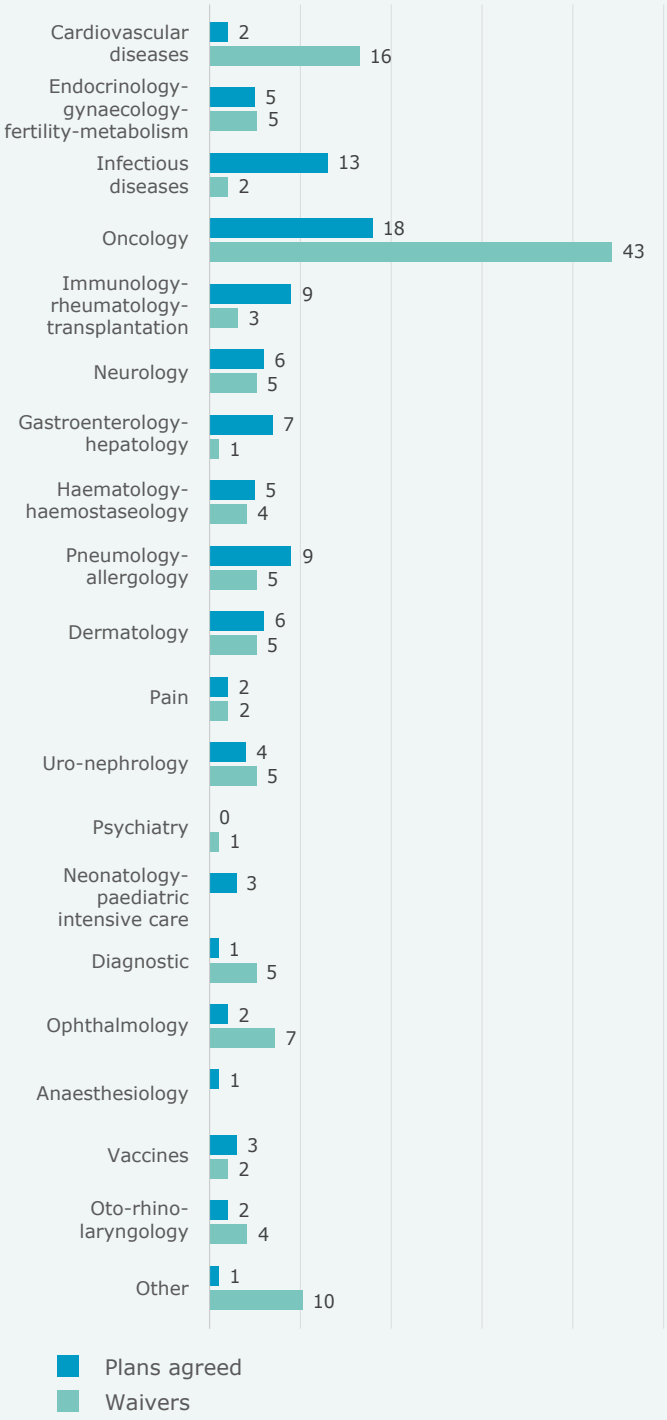
Requests for scientific advice on paediatric issues remained stable with 161 procedures in 2019.

Article 46 of the Paediatric Regulation requires MAHs 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 2019, EMA assessed 137 paediatric studies in the context of article 46. These studies are available to the public through the EU Clinical Trials Register.

Opinions on PIPs and waivers



Paediatric investigation plans agreed and waivers granted (2019)



Advanced-therapy medicinal products

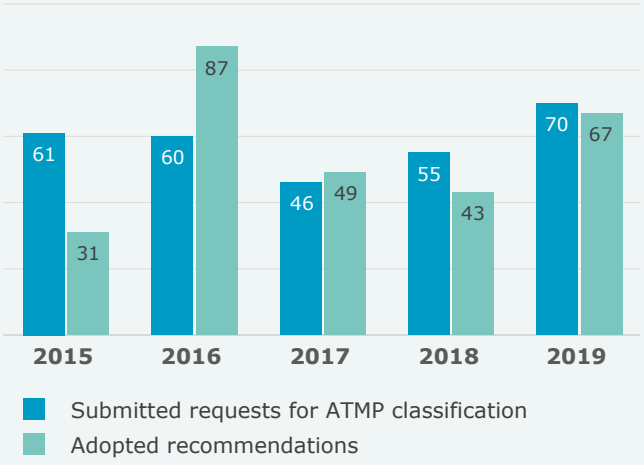
ATMPs are medicines based on genes or cells that have the potential for ground-breaking new treatments. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate.

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.

In 2019, the CAT received 70 requests for ATMP classification (27% more than in 2018) and adopted 67 recommendations, an increase of 56% compared to 2018.

One ATMP, Zynteglo, was recommended for marketing authorisation by the CHMP in 2019. Zynteglo is intended for the treatment of transfusion-dependent β-thalassaemia.

Scientific recommendations on advanced therapy classifications

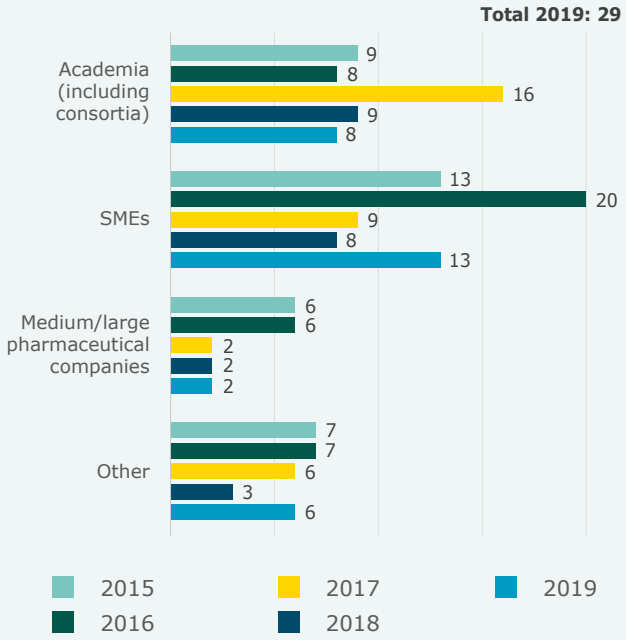


Innovation Task Force

The 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.

The Agency received 35 requests for briefing meetings and held 29 meetings in 2019 (compared to 22 in 2018). Almost half of these were attended by SMEs and nearly a third by academic developers (13 and 8 meetings, respectively). 31% of the meetings concerned biological medicines, 24.14% were related to biomarkers, and 20% to innovative methods to support the development of medicines.

ITF briefing meetings by affiliation



Key scientific guidelines

The Agency develops scientific guidelines to provide advice to applicants or MAHs, 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 comprising 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 2019, the Agency's work on guideline development and revision continued to be suspended or scaled back due to EMA's Brexit preparedness plans.

Guidelines launched or revised in 2019 are listed below:

Topic	Content
Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations	This document aims to help applicants prepare for obligations stemming from the new EU regulations on medical devices.
Guideline on the investigation of subgroups in confirmatory clinical trials	This document provides guidance for assessors in European regulatory agencies on assessment of subgroup analyses in confirmatory clinical trials. It should also be useful for clinical trial sponsors and assessors engaged in providing scientific advice.

Recommendations for marketing authorisation

Applications for initial evaluation

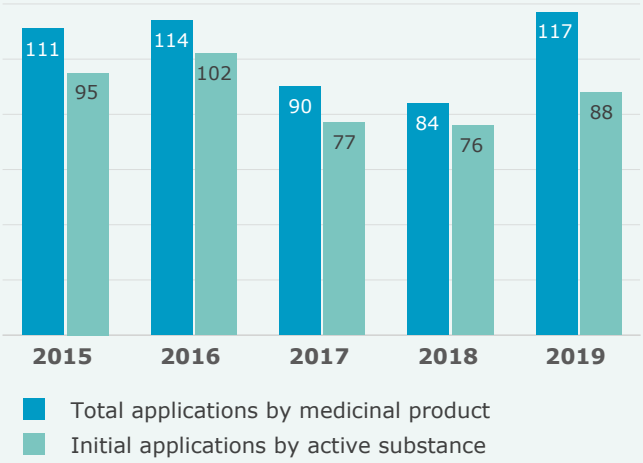
EMA's scientific committees carry out robust scientific evaluations of medicines and issue recommendations for the EC which ultimately decides whether or not to authorise a medicine for marketing throughout the EU.

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.

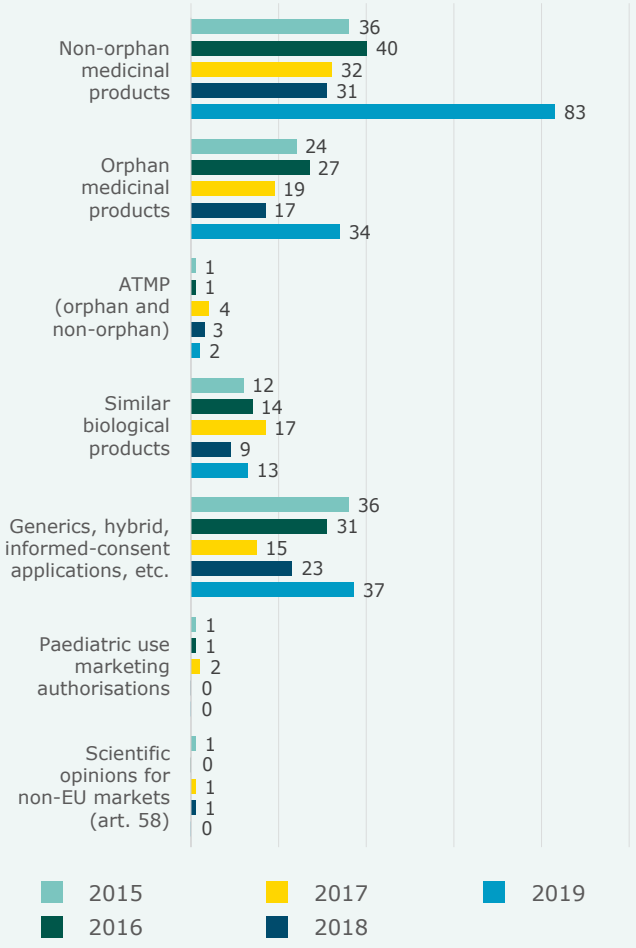
EMA received a total of 117 applications for initial evaluation in 2019, 39% more than in 2018. This increase breaks the downward trend observed in the previous two years.

The number of applications for orphan medicines doubled in 2019 (from 17 applications in 2018 to 34 in 2019). The applications for biosimilar medicines rose by 44%. There were two applications for ATMPs, compared with three received in the previous year.

Initial-evaluation applications



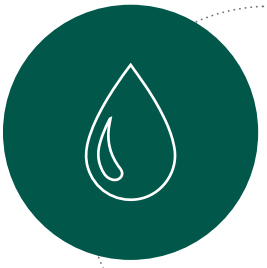
Initial-evaluation applications by type of application



Outcome of initial evaluation

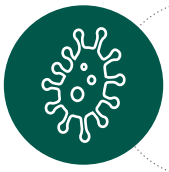
Medicines recommended for approval

Haematology/ Haemostaseology



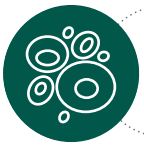
Arsenic trioxide Accord
Azacitidine Accord
Azacitidine Celgene
Bortezomib Fresenius Kabi
Deferasirox Accord
Deferasirox Mylan
Doptelet
Esperoct
Grasustek
Ivozall
Polivy
Tavlesse
Ultomiris
Xospata
Xromi
Zynteglo

Infections



Atazanavir Krka
Dectova
Dovato
Posaconazole Accord
Posaconazole AHCL
Quofenix
Recarbrio
Trogarzo

Cancer



Libtayo
Lorviqua
Pazenir
Talzenna
Vizimpro
Vitrakvi

Neurology

Ajovy
Epidyolex
Inbrija
Lacosamide UCB
Mayzent
Striascan

Endocrinology

Baqsimi
Isturisa
Evenity
Qtrilmet
Zynquista

Immunology/ Rheumatology/ Transplantation

Amsparity
Idacio
Kromeya
Pegfilgrastim Mundipharma
Rinvoq

Cardiovascular

Ambrisentan Mylan
Clopidogrel/Acetylsalicylic acid Mylan
Giapreza
Ondexxya

Psychiatry

Dexmedetomidine Accord
Sixmo
Spravato
Sunosi

Uro-nephrology

Febuxostat Krka
LysaKare
Senstend

Dermatology

Nuceiva
Skyrizi

Metabolism

Palynziq
Waylivra

Ophthalmology

Beovu
Rhokiinsa

Hepatology/ Gastroenterology

Cufence

Pneumology/ Allergology

Temybric Ellipta

Vaccines

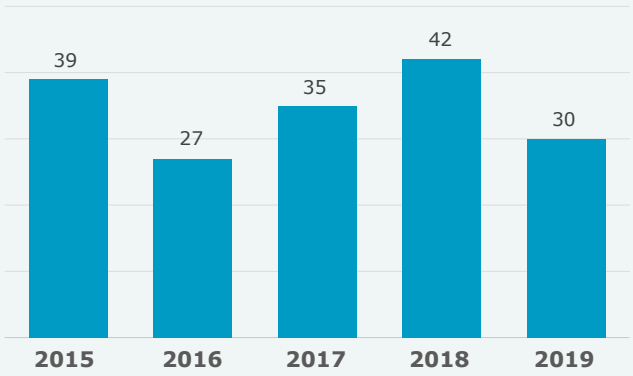
Ervebo

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

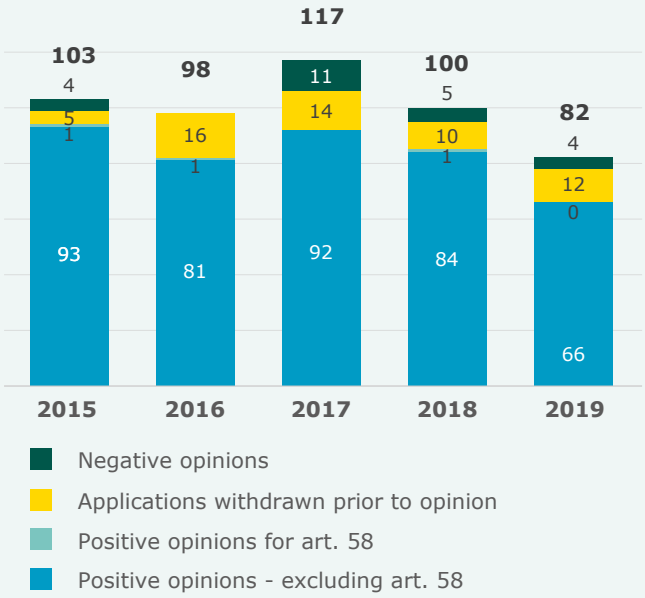
Medicines that contain a new active substance are highlighted in bold

These figures reflect EMA's recommendations which are sent to the European Commission for the adoption of an EU-wide marketing authorisation.
* This figure refers to medicines that had their orphan designation confirmed by 31 December 2019. At time of approval, orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) to determine whether the information available allows maintaining the medicine's orphan status.

Positive opinions - new active substances



Outcome of initial-evaluation applications



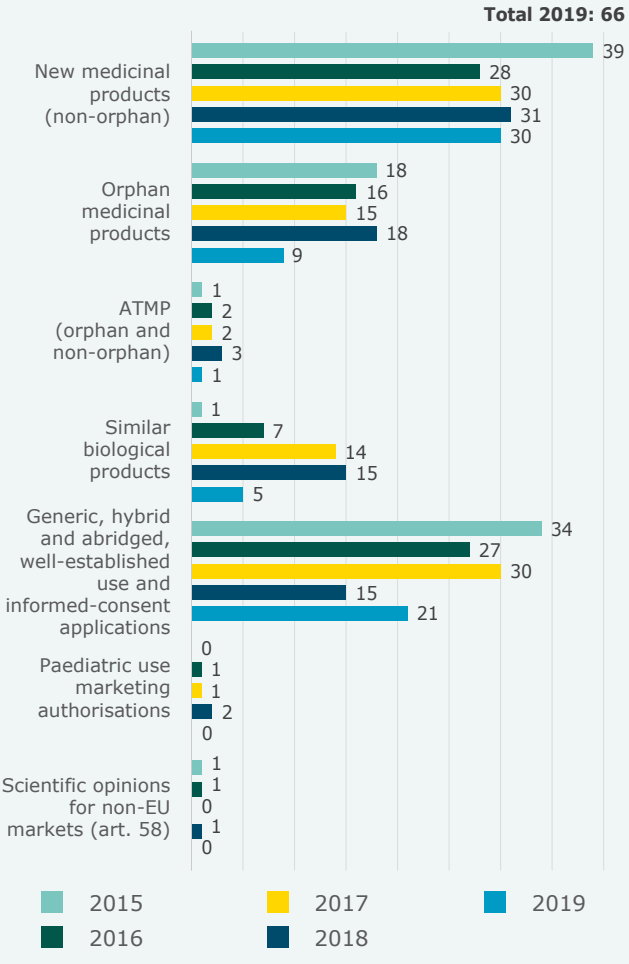
In 2019, EMA recommended 66 medicines for marketing authorisation. Of these, 30 had a new active substance which had never previously been authorised in the EU.

The CHMP refused to recommend marketing authorisations for four medicines in 2019. This figure does not include the initial negative opinions adopted by the CHMP on Xyndari (glutamine) in May and Evenity (romosozumab) in June 2019. The applicant for Xyndari withdrew its application for marketing authorisation in September 2019. The initial negative opinion for Xyndari was under re-examination at the company's request at the time of withdrawal. The applicant for Evenity 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 this medicine in October 2019.

Applications for 12 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 marketing authorisation.

Applicants for 59% of the medicines granted a positive opinion by the CHMP in 2019 had received scientific advice during the development phase of their medicine.

Positive opinions by type of procedure



Conditional marketing authorisations

In 2019, eight medicines received recommendations for a conditional marketing authorisation (CMA), one of the possibilities in the EU to give patients early access to new medicines: Ervebo, Libtayo, Lorviqua, Ondexxya, Polivy, Vitrakvi, Waylivra and Zynteglo.

As these medicines address unmet medical needs, the CMA allows for early approval on the basis of less complete clinical data than normally required (products for use in emergency situations may have less complete pharmaceutical or non-clinical data). These authorisations are subject to specific post-authorisation obligations to generate complete data on the medicines.

In 2019, one medicine (Pixuvri) which had previously received a CMA was granted a recommendation for a full marketing authorisation by the CHMP after fulfilling its post-authorisation obligations. For another medicine, Lartruvo, the CMA was revoked following the assessment of results of the requested post-authorisation studies.

Since the introduction of CMA in 2006, 21 medicines out of 47 have been granted a full marketing authorisation following a CMA. On average, it took around three and a half years for companies to fulfil their post-authorisation obligations and get their products fully authorised.

CMA and switch to standard marketing authorisation (excluding withdrawals)

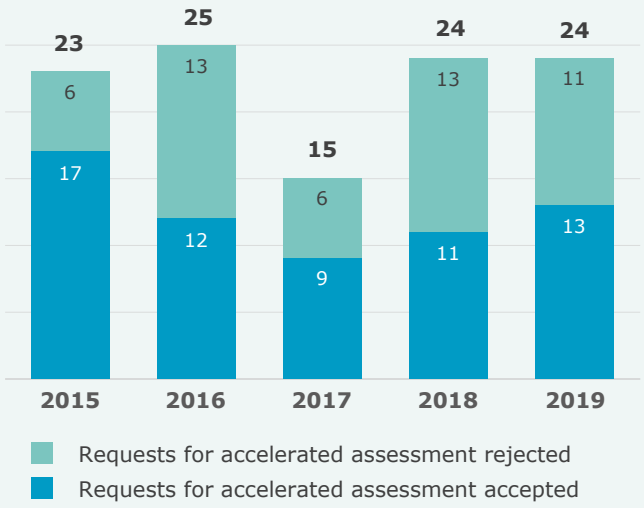
	2015	2016	2017	2018	2019
Positive opinions for CMAs	3	8	3	1	8
Opinions recommending switch of CMA to standard marketing authorisation	2	2	5	2[6]	1

Accelerated assessment

Three medicines (Ervebo, Xospata and Zynteglo) received a recommendation for marketing authorisation following an accelerated assessment in 2019. This mechanism is reserved for medicines that can address unmet medical needs and enables faster assessment of eligible medicines by EMA's scientific committees.

In 2019, 13 requests from applicants for accelerated assessment of their medicine were accepted and 11 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.

Accelerated assessment requests



[6] Corrected from the 2018 Annual Report which only counted one recommendation.

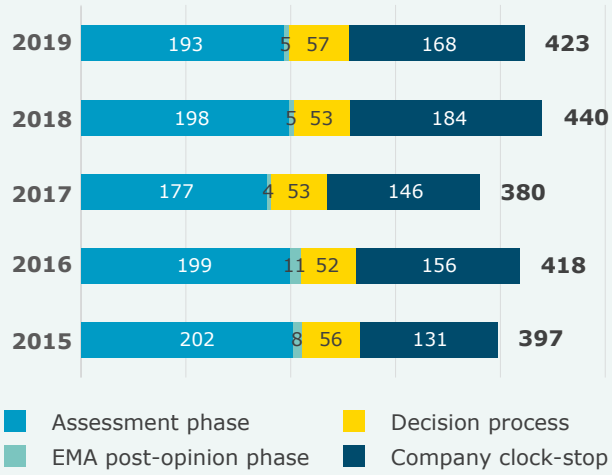
Average assessment time

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 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 has been received, the counting of the days continues.

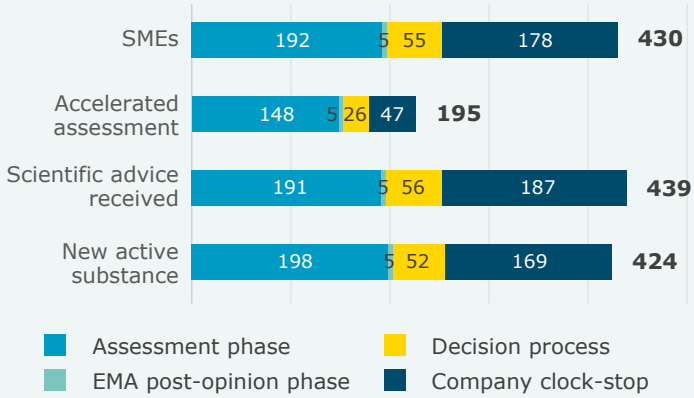
Once issued, the CHMP opinion is transmitted to the EC, which has the ultimate authority to grant a marketing authorisation and will take a decision within 67 days of receipt of the CHMP opinion.

The total time required for the centralised procedure, from start of the evaluation process to the adoption of a decision by the EC, was an average of 423 days in 2019, 17 days less than in 2018.

Average number of days for centralised procedures - positive opinions



Average number of days for centralised procedures - subset (2019)



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

For medicines evaluated under the accelerated procedure, the total time from start of assessment until granting of authorisation was reduced by around 6.5 months (from 423 to 226 days), potentially facilitating the following decision-making steps at a national level and ultimately patient access to medicines fulfilling unmet medical needs.

Post-authorisation activities

In 2019, the CHMP gave 60 positive recommendations for extension of the therapeutic indication of already authorised medicines. Almost half of these extensions of indication related to cancer medicines.

Important extensions of indication included:

- Forxiga and its duplicate Edistride as an oral adjunct treatment with insulin for certain patients with type 1 diabetes.
- Victoza, to include the treatment of children and adolescents aged ten years or older with type 2 diabetes.
- Dupixent as an add-on maintenance treatment for patients aged 12 years and older with certain forms of severe asthma.

In line with previous years, in 2019, EMA received applications for:

- 3,886 type-IA variations
- 2,425 type I-B variations
- 1,123 type-II variations
- 27 extensions of marketing authorisations

In the context of type-II variations, the product information for 405 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 on an indication that a medicine's safety profile or benefit-risk balance 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 covers all aspects of safety monitoring and risk management.

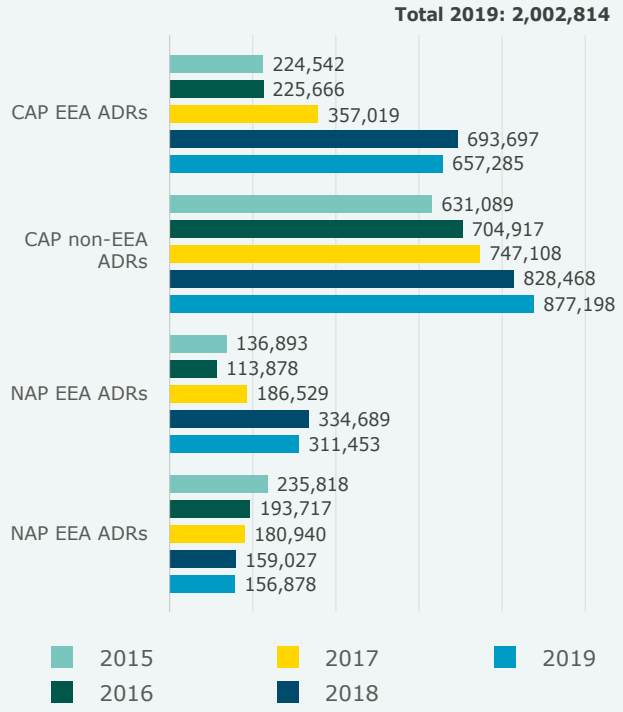
The Agency's main responsibilities in relation to the safety-monitoring of medicines include coordination of the European pharmacovigilance system, setting standards and guidelines for pharmacovigilance, provision of information on the safe and effective use of medicines, detecting new safety issues for centrally authorised products, managing assessment procedures, e.g. for periodic safety update reports (PSURs), and the operation and maintenance of the EudraVigilance system.

EudraVigilance – collecting suspected adverse drug reaction reports

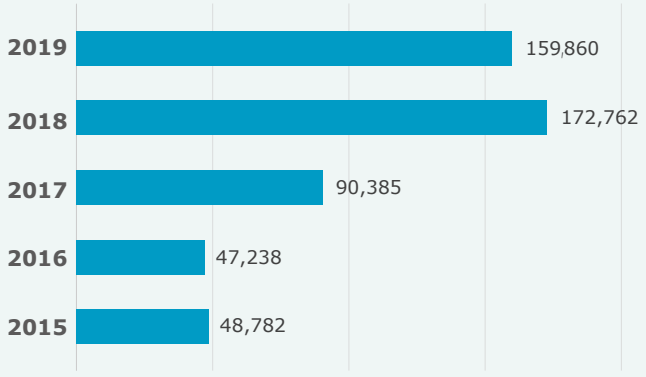
Both EMA and the NCAs are legally required to continuously monitor the adverse drug reaction (ADR) data reported to EudraVigilance to determine whether new or changed risks have been identified and whether these risks have an impact on a medicine's overall benefit-risk balance.

More than 2 million ADR reports were submitted to EudraVigilance in 2019, in line with 2018. Close to half of all reports in EudraVigilance originated in the EEA. The number of reports submitted by European patients and consumers nearly reached the record level seen in 2018. The reporting rates in 2018 and 2019 represent a significant expansion over the last five years. This shows patients' commitment to reporting side effects as a result of EU and national information campaigns and, since November 2017, the inclusion of non-serious EEA reports in EudraVigilance.

EEA and non-EEA ADR reports received



Number of reports from patients



Note: Following the launch of the new EudraVigilance system in November 2017, figures in 2017, 2018 and 2019 include reports of non-serious suspected adverse drug reactions.

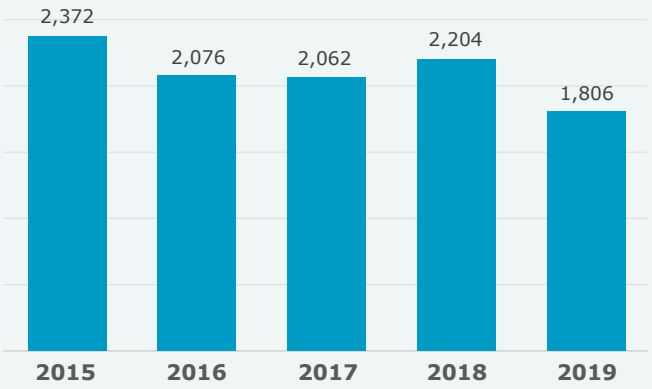
Signal detection

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 a safety signal is a routine pharmacovigilance activity to establish whether 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 mainly comprises changes in the information on medicines available for patients (in the package leaflet) and prescribers (in the summary of product characteristics).

In 2019, 1,806 potential signals were reviewed by EMA, approximately 78% of which originated from monitoring the EudraVigilance database, highlighting its central role for safety monitoring. This represents a decrease of 18% compared to 2018, where the number of signals assessed was particularly high. There was a small drop in the number of signals validated by EMA and assessed by the PRAC (50 signals in total), but a slight increase in the signals which were validated by Member States (46). In addition to signal detection activities and assessments at PRAC level, experts from the NCAs, in collaboration with EMA, provided a major contribution to the development of signal detection methods and continuous process improvement.

Signal reviewed by EMA



OUTCOME OF SIGNAL ASSESSMENT

1,806 potential signals reviewed by EMA

↓

97 confirmed signals were prioritised and assessed by the PRAC

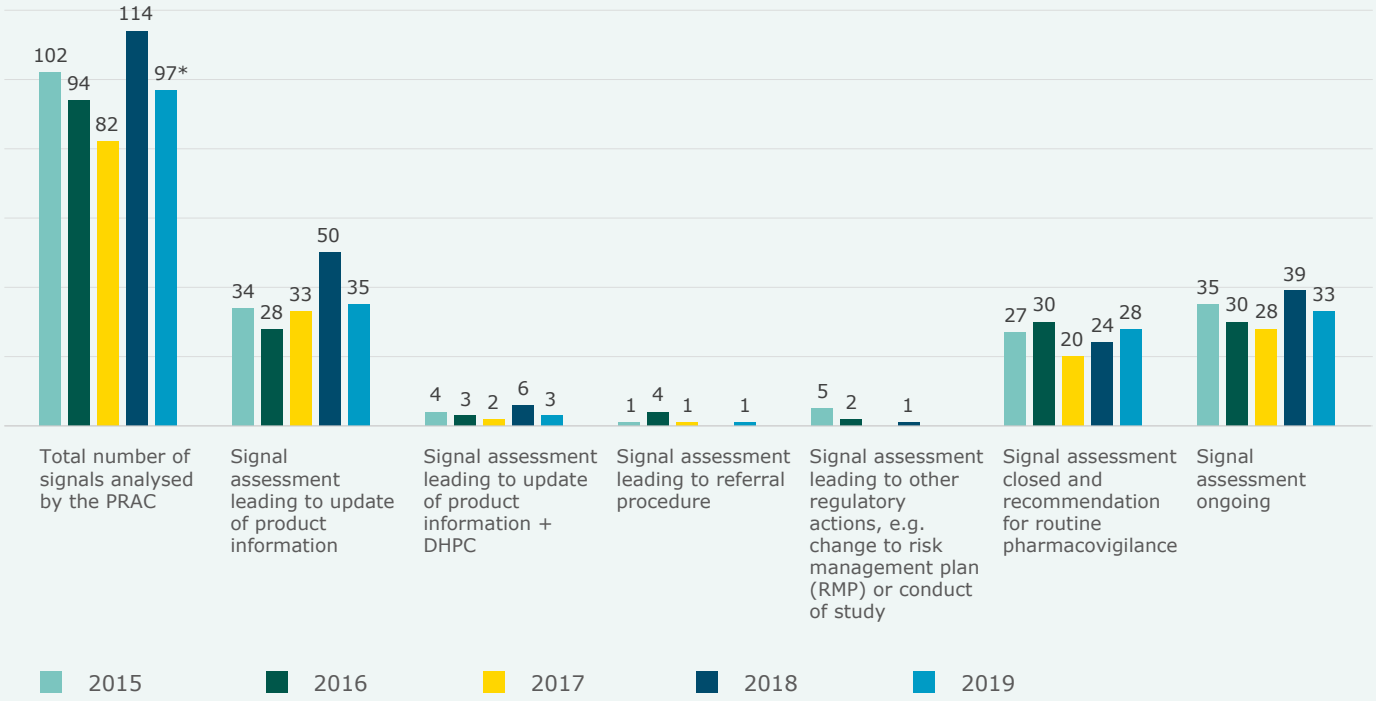
Of these, 50 signals were detected and validated by EMA	46 signals were detected and validated by EU Member States

↓

Out of 97 confirmed signals

35 signals led to a product information update; 3 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers	28 signals led to a recommendation for routine pharmacovigilance	33 signals were still under review by the PRAC at the end of 2018 as further data were required	1 signal led to a referral procedure to further investigate the issue

Signal assessment



* This includes one signal originating from an MAH in the context of a pilot on signal detection in EudraVigilance.

Periodic safety update reports (PSURs)

MAHs are required to submit a report on the evaluation of a medicine's benefit-risk balance to the regulatory authorities at regular, predefined intervals following the authorisation of a 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 both centrally authorised products (CAPs) and for nationally authorised medicines (NAPs) that are authorised in more than one Member State. These reports are called 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 or PSUSA.

In 2019, the PRAC started the assessment of 800 PSURs and PSUSAs, of which a quarter represent single assessments of active substances only contained in NAPs. 828 recommendations were issued by the PRAC based on the assessment of PSURs and PSUSAs, of which a quarter consisted of single assessments of active substances only contained in NAPs.

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	2015	2016	2017	2018	2019
PSURs stand-alone (CAPs only) finalised	470	511	540	537	558
PSURs single assessment (CAPs with NAPs) finalised	27	16	39	43	48
PSURs single assessment (NAPs only) finalised	136	264	263	321	222
Total outcomes	**633**	**791**	**842**	**901**	**828**

PRAC outcomes of PSURs and PSUSAs	2015	2016	2017	2018	2019
Maintenance	**500**	**637**	**680**	**735**	**655**
NAPs only			207	245	166
CAPs/NAPs and CAPs only			473	490	489
Variation	**133**	**154**	**162**	**166**	**173**
NAPs only			56	76	56
CAPs/NAPs and CAPs only			106	90	117
Total outcomes	**633**	**791**	**842**	**901**	**828**

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 MAHs as part of their post-authorisation obligations. The PRAC is responsible for assessing the protocols of imposed PASS and their results. The PRAC also reviews protocols of large numbers of voluntarily submitted PASS in the context of risk management plan assessments.

In 2019, the PRAC assessed 13 imposed PASS protocols that were requested to obtain further information on a medicine's safety, a slight increase compared to 2018. The Committee assessed 180 non-imposed PASS protocols.

In addition, the PRAC started to assess the results of three imposed PASS, the same number as assessed in 2018.

Post-authorisation safety studies					
	2015	2016	2017	2018	2019
Imposed PASS protocol procedures started	20	12	6	17	12
Imposed PASS protocol procedures finalised	20	10	5	9	13
Non-imposed PASS protocol procedures started			333	195	144
Non-imposed PASS protocol procedures finalised			265	196	180
PASS amendment	1	12 (started), 7 (finalised)	11 (started), 10 (finalised)	11 (started), 11 (finalised)	11 (started), 9 (finalised)
Imposed PASS result procedures started	2	3	6	8	3
Imposed PASS result procedures finalised	0	3	3	8	3
PASS scientific advice through SAWP	0	3	0	3	3

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 nine PAES on companies in order to collect further data on the benefits of medicines while they are used by patients in real life.

Post-authorisation efficacy studies					
	2015	2016	2017	2018	2019
PAES (imposed)	23		19	4	9
PAES (non-imposed)			1	2	0

Notification of withdrawals

Companies are 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 12% between 2018 and 2019. This increase was driven by commercial reasons; only 8% of these withdrawals were due to issues around quality, safety or efficacy.

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 2019, 342 medicines were subject to additional monitoring, in line with 2018. These medicines are identified by an inverted black triangle on their packaging.

The EU **incident management plan** is coordinated by the 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 and mutual-recognition procedures. The plan's operation involves representatives from EMA, the EC and regulatory authorities in the Member States. In 2019, three incidents triggered the plan. Overall, a declining trend in the numbers of Incident Review Network meetings related to safety issues has been observed in recent years. This is probably associated with the robust tools and processes introduced with the revised pharmacovigilance legislation, which enabled most incidents to be managed by using routine, established pathways.

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. EPITT helps medicines regulatory authorities in the EEA and EMA to track signals at EU level. In 2019, 43 non-urgent information or rapid alert notifications were submitted via EPITT.

Scientific and medical literature is an important source of information to identify suspected adverse reactions with medicines authorised in the EU. EMA is responsible for monitoring a number of substances and selected medical literature to identify suspected adverse reactions with such medicines, and for entering the relevant information into the EudraVigilance database. In 2019, 9,676 Individual Case Safety Reports (ICSRs) resulted from EMA's medical literature monitoring (MLM) service.

Other pharmacovigilance activities	2016	2017	2018	2019
Cumulative number of products on the list of products to be subject to additional monitoring	301	336	351	342
Number of incidents triggering incident management plan	7	4	11	3
Number of non-urgent information or rapid alert notifications submitted through EPITT	49	61	44	43
Number of MLM ICSRs created	8,495	14,193	13,275	9,676

Referral procedures

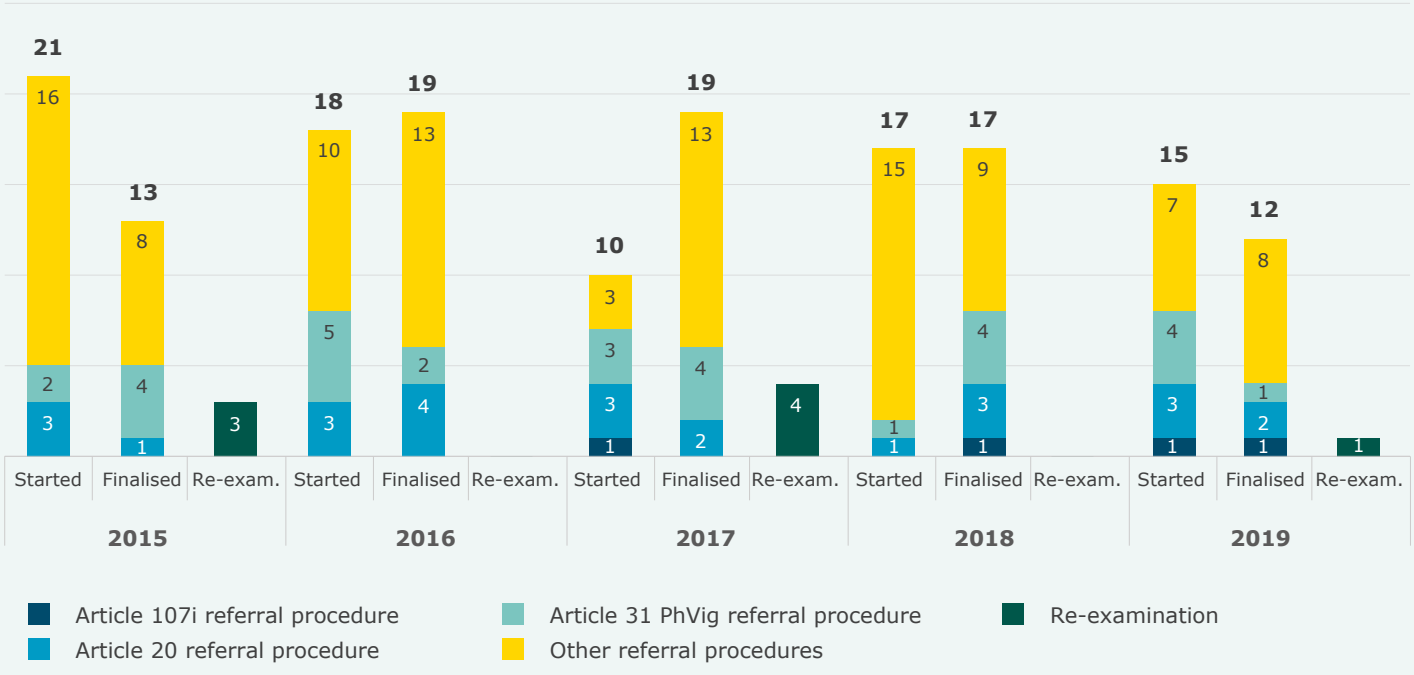
Referral procedures are initiated to address concerns over the safety or benefit-risk balance of a medicine, as well as to deal with disagreement among Member States on the use of a medicine. In a referral, EMA is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine 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 nationally authorised products are concerned, the decision is taken by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). In cases where the CMDh position is agreed by majority (not by consensus), the EC will issue a final decision applicable throughout the EU.

In 2019, 12 referral procedures were finalised, of which four were related to the safety of medicines, initiated under articles 31, 20 or 107i of the pharmacovigilance legislation. Three led to changes in the product information, and one resulted in the revocation of the marketing authorisation.

The remaining eight referral procedures were initiated to address either:

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

Referrals for human medicines finalised or re-examinations

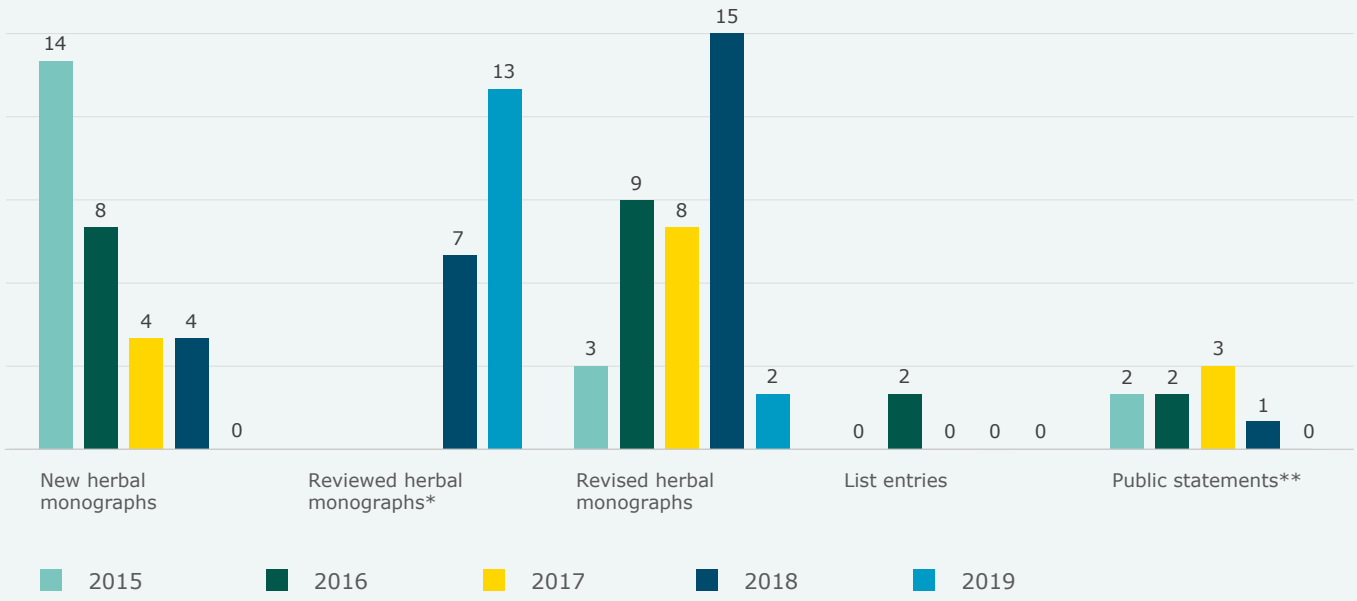


Herbal medicines

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.

In 2019, 13 monographs were updated following a systematic review of newly available data.

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



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

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

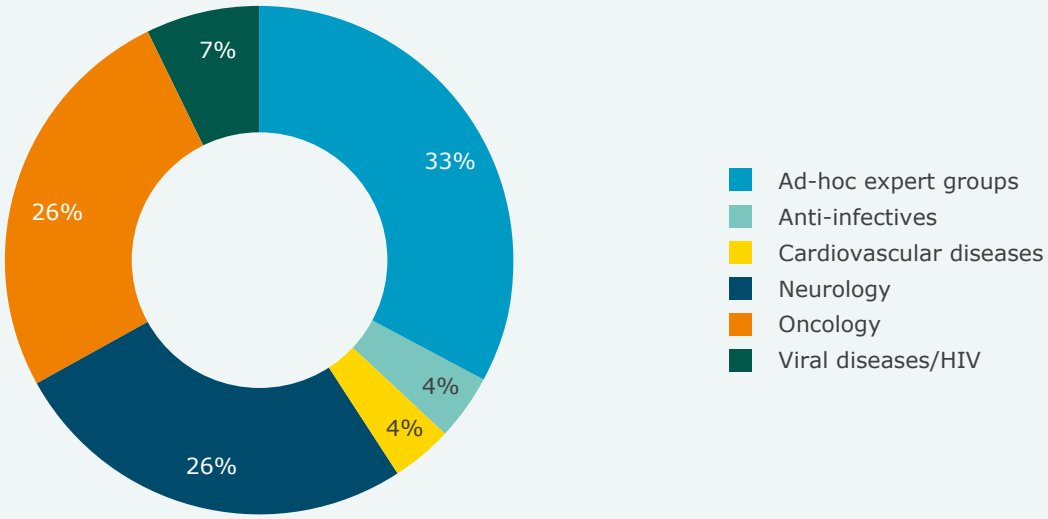
Note: A complete list of recommendations on herbal medicines can be found in the annexes.

Contribution of experts, patients and healthcare professionals to scientific assessments

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

A total of 27 consultations took place in 2019 in the form of SAG meetings, compared to 32 in 2018 and 30 in 2017. 25 of these consultations included patients or carers, with a total of 46 patients/carers involved.

Areas of discussions - SAGs and ad-hoc expert group meetings (2019)



Procedures with SAG or ad-hoc expert group involvement (number of consultations)	2015	2016	2017	2018	2019
Marketing authorisation (new MAA, new MAA re-examination, art. 58)	7	8	14	19	15
Extension of indication (including line extensions)	2	6	3	10	3
Referral (including re-examination)	3	5	11	3	6
Guideline	1	0	1	0	1
Other topics (renewal, PSUR, signal, class review)	3	0	1	0	2
Total	**16**	**19**	**30**	**32**	**27**

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)	2015	2016	2017	2018	2019
Scientific advice/protocol assistance	76	82	158	107	143
SAGs/ad-hoc expert meetings	23	28	46	37	46
Scientific committee/working party consultations	24	50	104	112	355
Workshops	115	141	138	N/A*	N/A*
Working groups and other ad-hoc activities	313	290	269	N/A*	N/A*
Patient membership in MB, committees, working parties	55	58	59	59	57
Document reviews conducted by patients and consumers	137	120	176	178	169

* Following implementation of EMA's Business Continuity Planning in 2018, quantification of these activities has been discontinued.

HCP involvement in EMA activities (interactions)	2015	2016	2017	2018	2019
Scientific advice/protocol assistance	1	1	1	0	2
SAGs/ad-hoc expert meetings	21	26	40	31	36
Scientific committee/working party consultations	47	31	74	47	68
Workshops	59	106	83	N/A*	N/A*
Working groups and other ad-hoc activities	184	129	160	N/A*	N/A*
HCP membership in MB, committees, working parties	47	51	54	54	58
Document reviews conducted by healthcare professionals	29	55	33	80	48

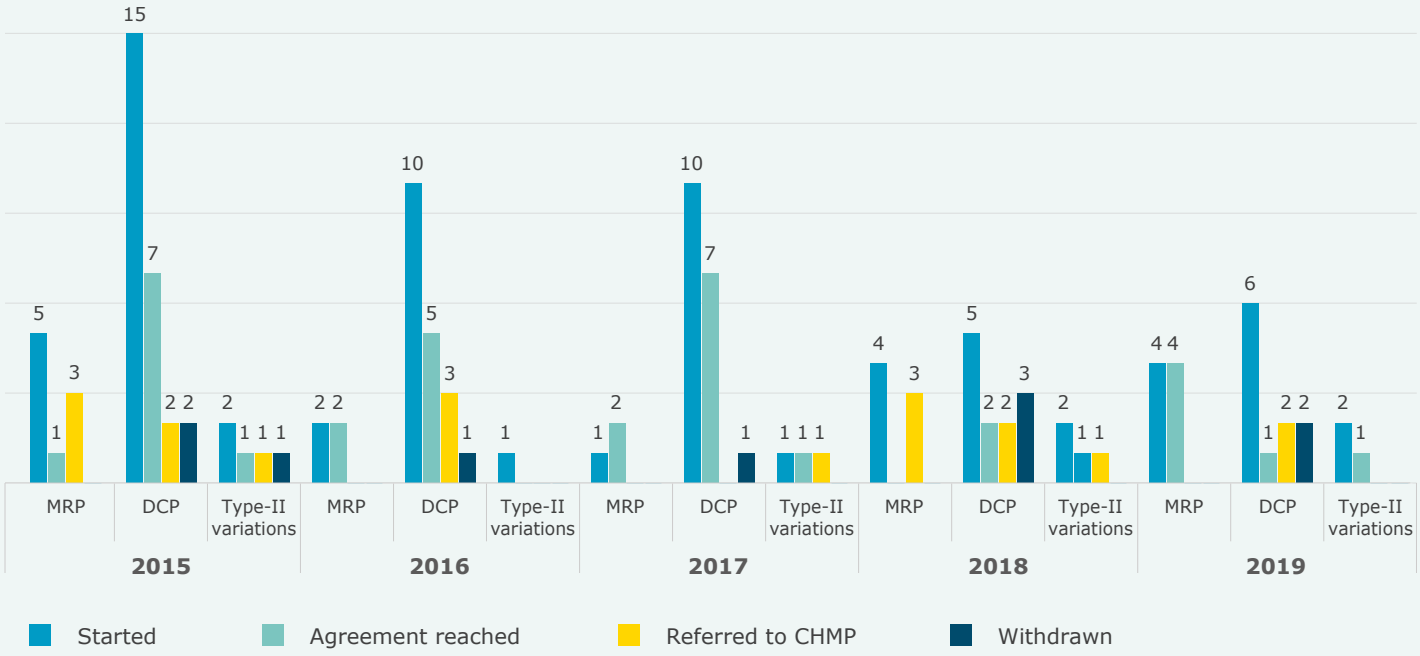
* Following implementation of EMA's Business Continuity Planning in 2018, quantification of these activities has been discontinued.

Mutual-recognition and decentralised procedures

90% of the medicines entering the EU market are nationally authorised. These are mainly generics which reach the market through the mutual recognition procedure (MRP) and the decentralised procedure (DCP), the primary authorisation routes for generic applications within the EU. The CMDh, 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, EMA promoted consistency of scientific requirements applied by EU Member States through the publication of 14 product-specific bioequivalence guidelines based on CMDh requests.

Detailed information about the work of the CMDh in 2019 in relation to pharmacovigilance and referrals can be found on the HMA website.

Applications referred to the CMDh



VETERINARY MEDICINES

Activities supporting research and development

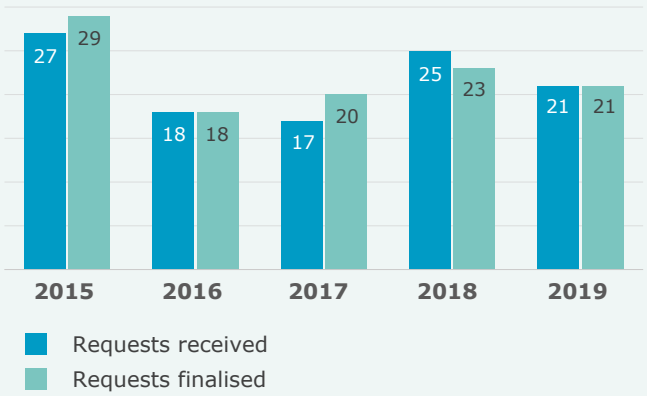
The Agency provides pre-authorisation support to medicine developers to boost innovation and research and enhance the availability of safe and effective veterinary medicines. This is achieved through activities and incentives offered to companies prior to submitting an application for marketing authorisation.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

Scientific advice

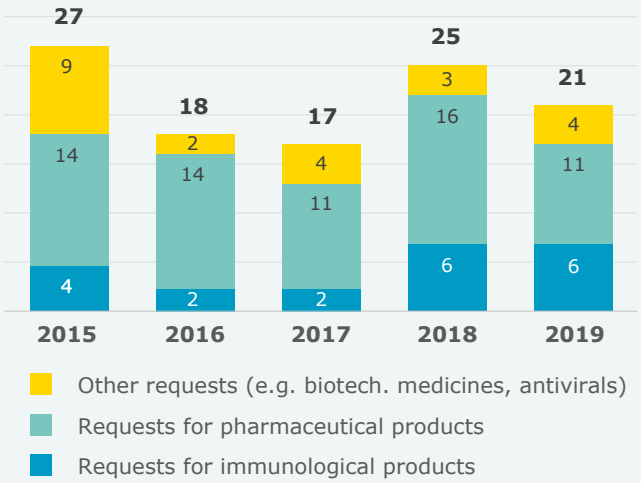
Scientific advice is provided on any aspect of research and development relating to the quality, safety or efficacy of medicines for veterinary use, and to the establishment of maximum residue limits. Scientific advice is a means of facilitating and improving the availability of new veterinary medicines.

EMA received 21 requests for scientific advice in 2019 and finalised 21, including some pending from 2018. More than a quarter of all scientific advice requests received were for immunologicals, including vaccines.

Scientific-advice requests received and finalised



Scientific-advice requests received and finalised



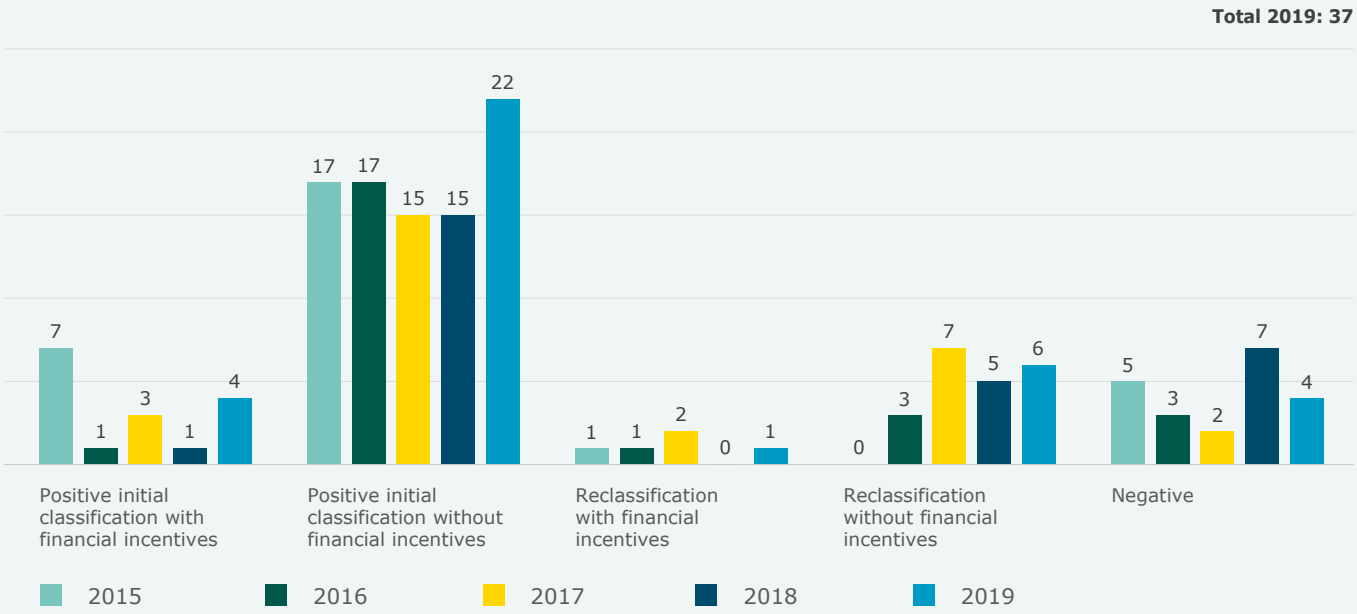
Minor use minor species

The Agency's minor use minor species (MUMS)/ limited market policy aims to assist companies with the submission of applications for products for limited markets. The objective is to encourage the development of veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment.

In 2019, the Agency received a total of 34 new requests (the highest number of requests received in a year) for the (re)classification of veterinary medicines intended for MUMS/limited market, indicating greater interest from medicine developers in developing products for minor uses or minor species.

Among the 37 outcomes in 2019, 28 were classified or reclassified as MUMS, and benefited from reduced data requirements. Financial incentives, such as access to free scientific advice and reduced application fees, were granted in response to five requests.

MUMS/limited market (re)classification requests outcome



Support to SMEs

EMA's SME initiative promotes innovation and development of medicines by SMEs. The SME office provides active regulatory, financial and administrative incentives to SMEs in the development of their medicines. Support takes the form of individual guidance and more general advice through the SME user guide, topical workshops and a dedicated newsletter.

Of the 1,951 SMEs registered with EMA at the end of 2019, 4% were developing veterinary products and 4% both human and veterinary products. In 2019, the Agency received a total of 14 new requests for scientific advice relating to the quality, safety or efficacy of medicines for veterinary use submitted by SMEs. The number of requests has grown after a decline in the previous three years, indicating more interest from medicine developers in engaging early with the Agency.

Innovation Task Force

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

Four ITF meetings were held in 2019 concerning the development of veterinary medicines, showing a stable interest in this activity.

Key scientific guidelines

The Agency develops scientific guidelines to provide advice to applicants or MAHs, competent authorities and other interested parties on the most appropriate way to test and monitor the safety, efficacy and quality of medicines. This is a key activity to support medicines development and ensure that they are safe, effective and of high quality. Guidelines are drafted by EMA working parties comprising experts from across Europe.

EMA issues new guidelines and revises existing ones every year to reflect the latest scientific developments and experience gained through scientific advice and the evaluation and monitoring of medicines. In 2019, the Agency's work on guideline development and revision continued to be suspended or scaled back due to its Brexit preparedness plans.

A selection of reflection papers and scientific advice issued or revised in 2019 is listed below:

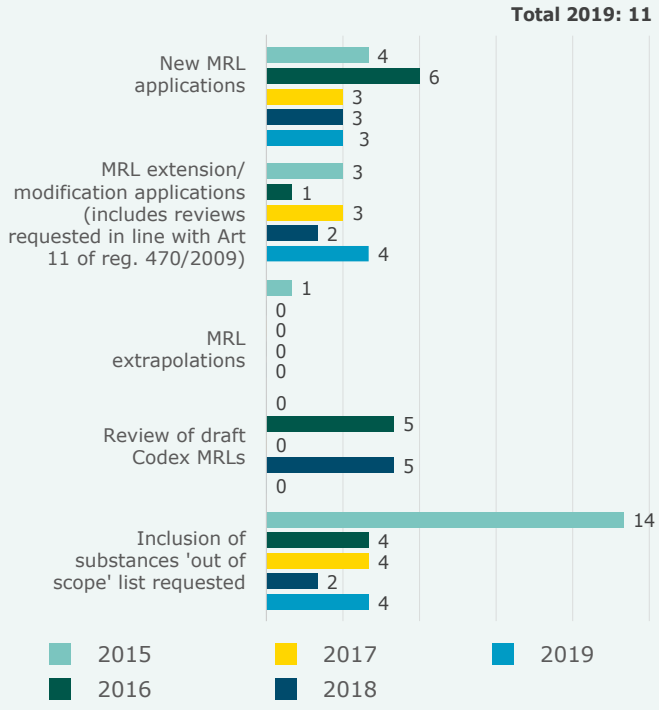
Topics	Content
Antimicrobial resistance	Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU. This draft reflection paper has been developed to identify additional measures that could be implemented to promote the authorisation of alternatives to antimicrobials in the EU and is available for public consultation until 30 April 2020.
Antimicrobial resistance	Response to the request from the EC to update the scientific advice on the impact on public health and animal health of the use of antibiotics in animals: (i) Preliminary risk profiling for new antimicrobial veterinary medicinal products (ii) Categorisation of antibiotics for use in animals.

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 for pharmacologically active substances in veterinary medicinal products used to treat food-producing animals. The objective is to ensure the safety of foodstuffs of animal origin, such as meat, fish, milk, eggs and honey. EMA has a parallel responsibility for recommending MRLs for pharmacologically active substances in biocidal products used in animal husbandry. MRLs are formally established by the EC on the basis of a recommendation from the CVMP.

Three applications for the establishment of MRLs for new substances were received in 2019. In addition, the CVMP received applications for the extension or modification of existing MRL classifications for four substances.

Evaluation of maximum residue limits



Recommendations for marketing authorisations

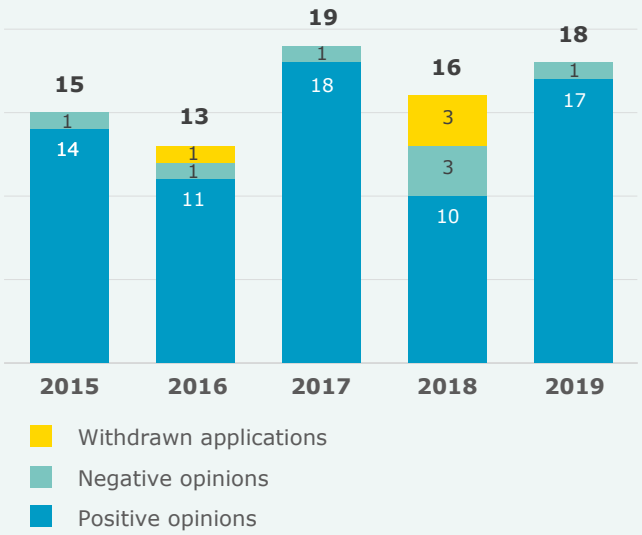
Applications for initial evaluation

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 marketing authorisation by the EC.

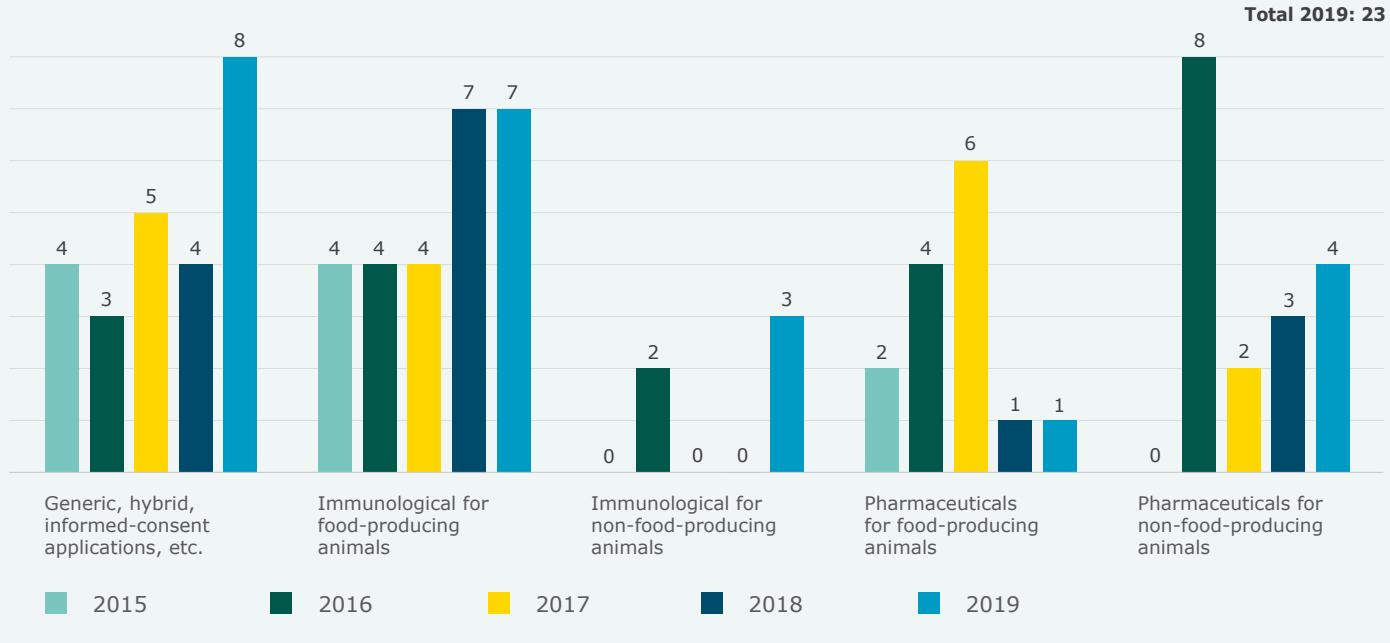
A total of 23 applications were received in 2019, marking an increase of over 50% compared to 2018. Almost 50% of the applications submitted were for immunologicals.

Seven applications were for immunological products for food-producing animals. Vaccines are an alternative option to combat infectious diseases; by reducing the need for antimicrobials, they also indirectly reduce the risk of AMR in food-producing animals.

Outcome of initial-evaluation applications



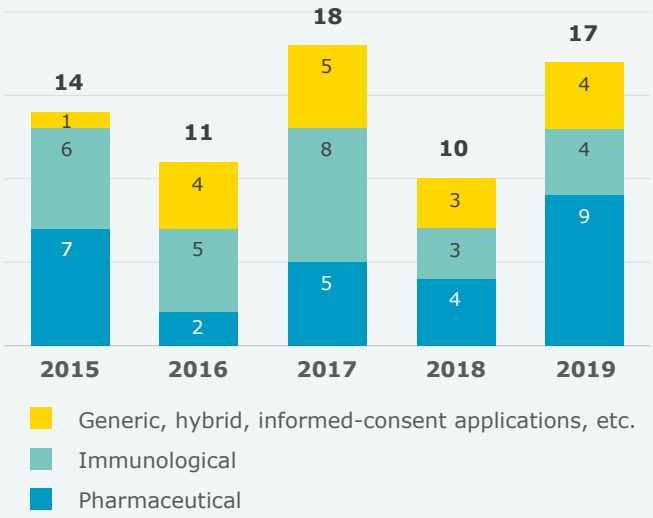
Applications for initial evaluations received



RECOMMENDATIONS FOR AUTHORISATION

In 2019, 15 new veterinary medicines were granted a positive opinion, a significant increase (50%) compared to 2018. Following re-examination, two products evaluated in 2018 were also recommended for approval. Five medicines had a new active substance and four are vaccines, including one vaccine developed by means of a biotechnological process.

Positive opinions for veterinary medicines



Medicines recommended for approval in 2019

New veterinary medicines

Dogs

Afoxolaner Merial
Chanhold
Evicto
Neptra
Simparica Trio
Stelfonta

Cats

Chanhold
Evicto
Felisecto Plus
Mirataz

Pigs

Baycox Iron
Forceris
ReproCyc ParvoFLEX

Cattle

Nasym

Horses

Aservo EquiHaler

Chickens

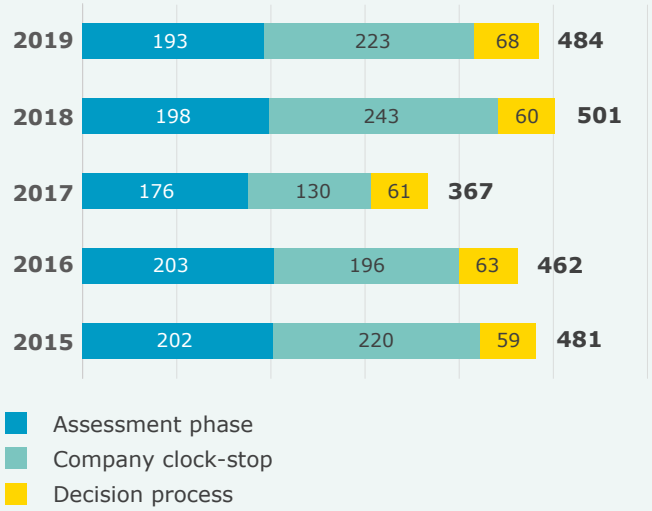
Gumbohatch

Rabbits

Nobivac Myxo RHD Plus

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

Average number of days for initial authorisations



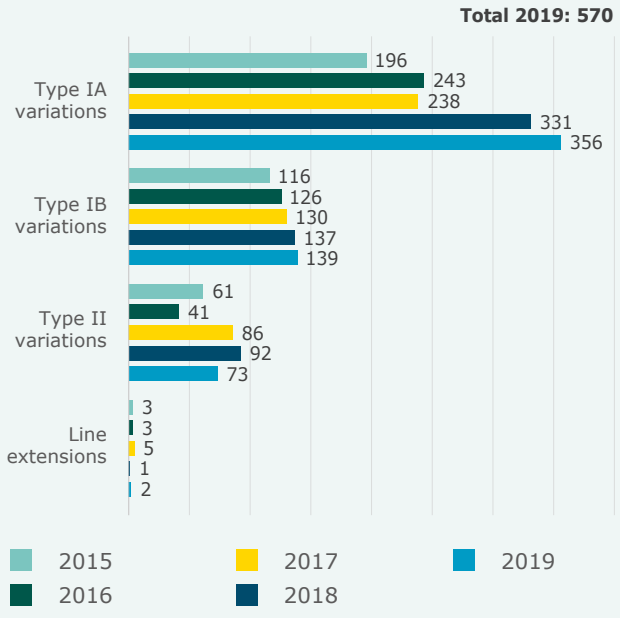
The average number of days taken for initial evaluations fell slightly compared to 2018 due to certain shorter procedures, such as informed consent applications. An informed consent application makes use of data from the dossier of a previously authorised medicine, with the MAH of that medicine giving consent for the use of their data in the application.

Post-authorisation activities

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

The total number of post-authorisation procedures continues to increase year-on-year, broadly in line with the number of products authorised through the centralised procedure. In 2019, the overall number of post-authorisation applications increased slightly compared to 2018.

Post-authorisation applications received



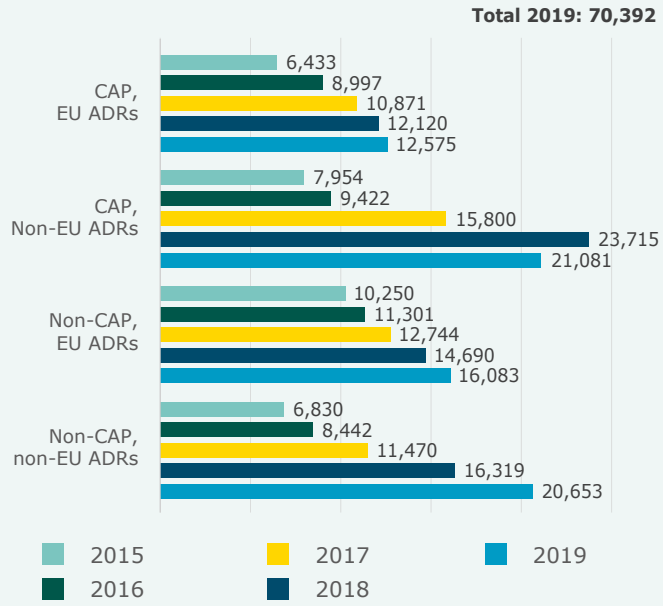
Safety monitoring of medicines

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

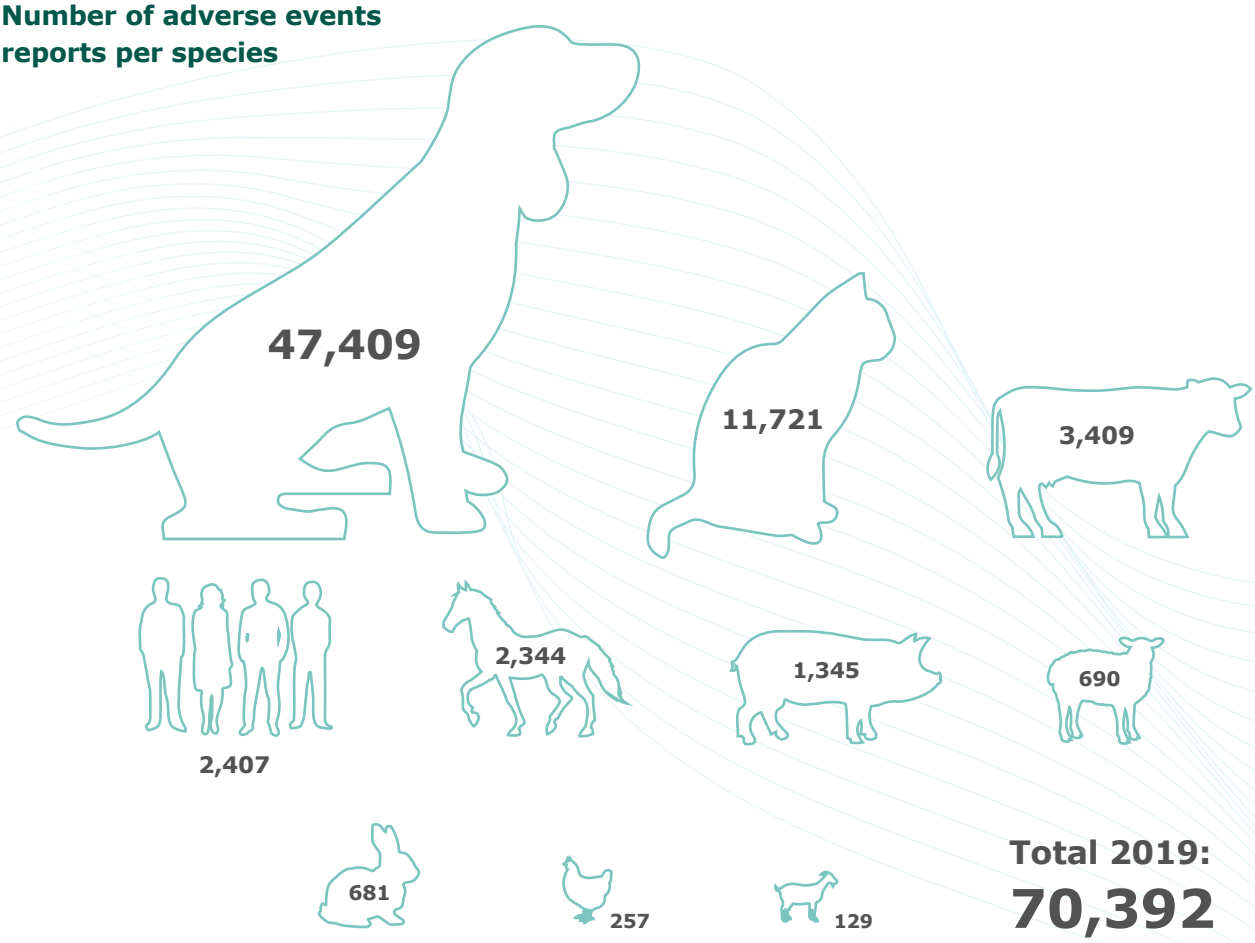
EudraVigilance

The number of AE reports received in the EudraVigilance system is steadily growing year on year. This long-term trend towards increased reporting is due to more centrally authorised veterinary medicinal products and better 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.

Adverse events reports in animals



Number of adverse events reports per species

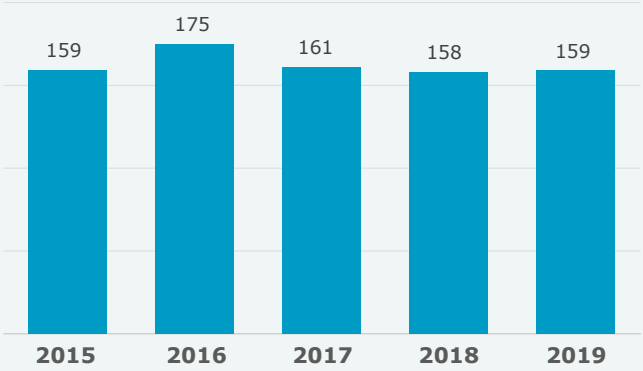


Periodic safety update reports (PSURs)

A PSUR provides an evaluation of a medicine's benefit-risk balance, which is submitted by MAHs at predefined times following a medicine's authorisation. PSURs summarise data on the benefits and risks of a medicine and include the results of all studies carried out on it (in authorised and unauthorised indications).

The CVMP started the assessment of 159 PSURs in 2019. This number of PSURs reflects the progressive accumulation of products authorised through the centralised procedure.

Periodic safety update reports

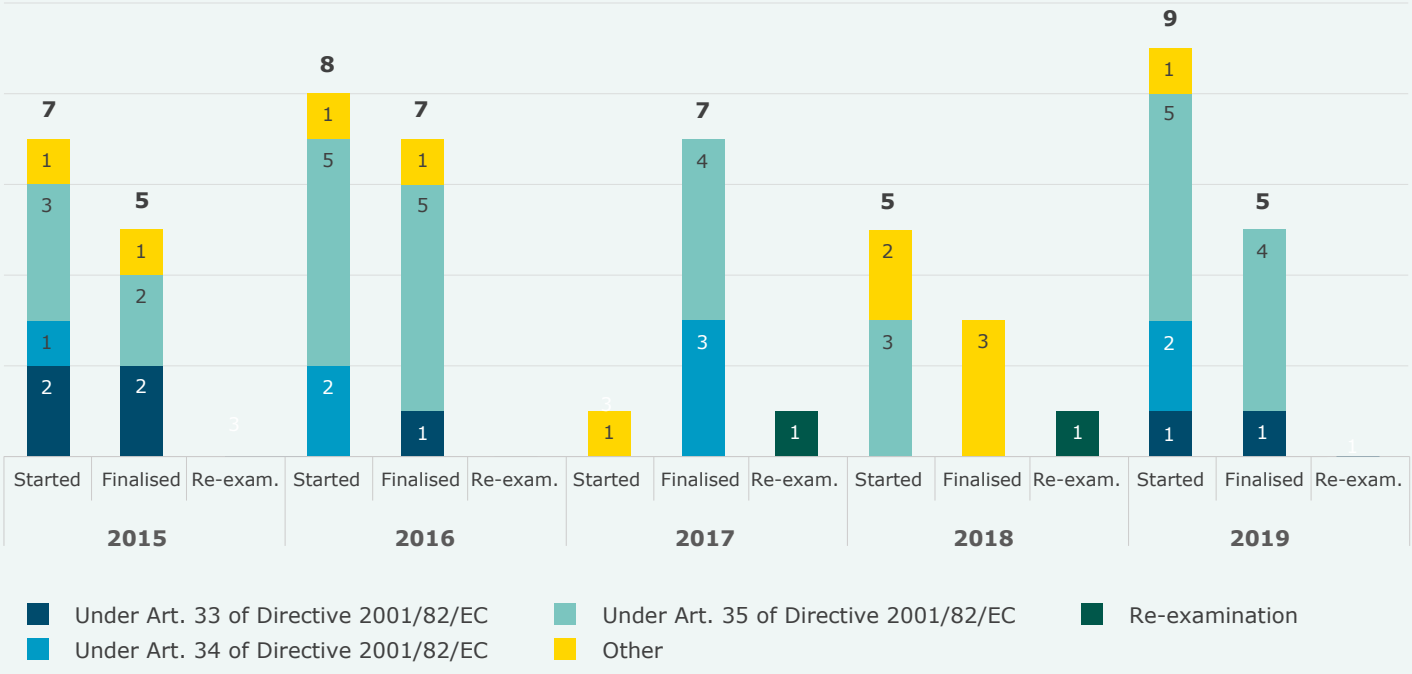


Referral procedures

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

Nine referral and arbitration procedures related to veterinary medicinal products began in 2019 and five procedures were finalised. Among these, five were safety- or efficacy-related (under Article 35 of Directive 2001/82/EC or under Article 45 of Regulation (EC) 726/2004).

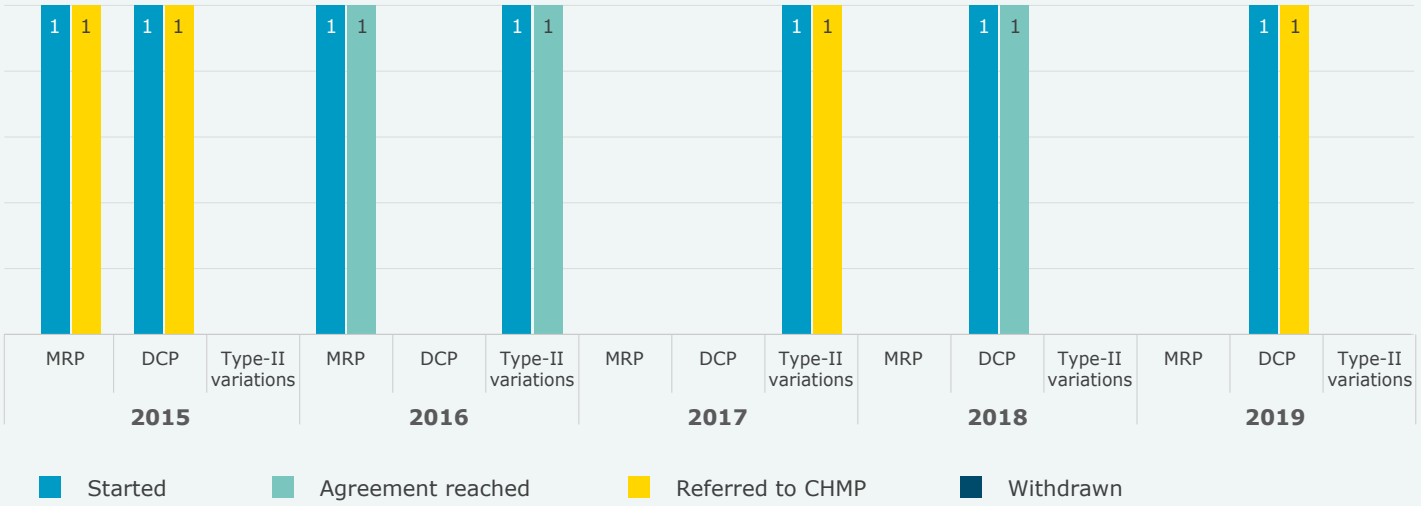
Arbitration and referrals for veterinary medicines



Mutual-recognition and decentralised procedures

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

Applications referred to the CMDv



EUROPEAN MEDICINES REGULATORY NETWORK

The European medicines regulatory network – a partnership between EMA, the EC and 50 medicines regulatory authorities in the EU and Liechtenstein, Iceland and Norway – is the basis of the EMA'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 committees, working parties, SAGs and ad-hoc advisory groups as well as members of the assessment teams carrying out medicine evaluations (see annex for further information on these groups).

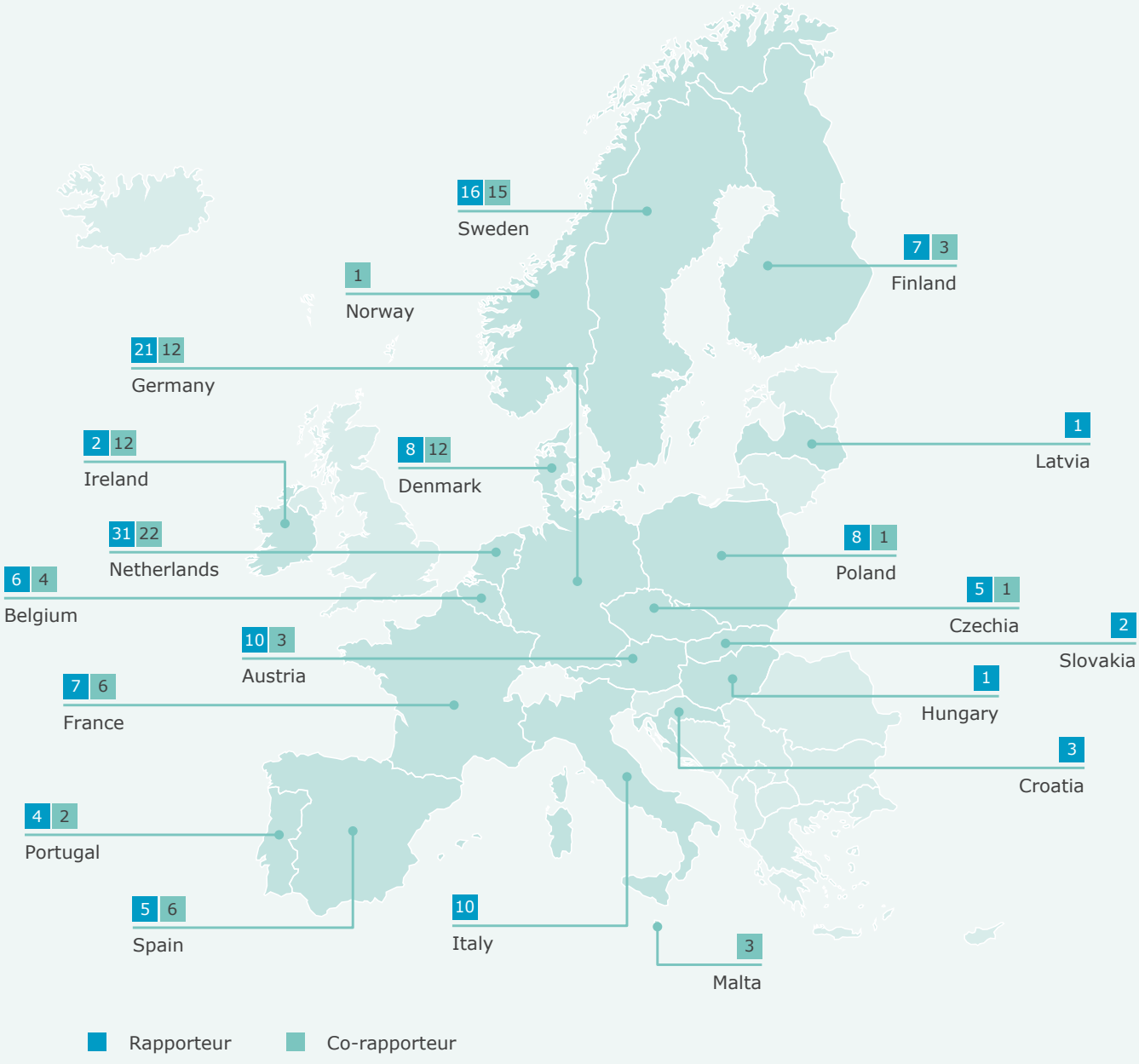
Rapporteurships and co-rapporteurships

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 possible 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 preparation for Brexit, the EU27 Member States and EMA redistributed the UK's portfolio of medicines to other EU Member States. This involved transferring over 370 centrally authorised products to rapporteurs and co-rapporteurs from the EU27 plus Iceland and Norway.

The new rapporteurs and co-rapporteurs were fully responsible for these medicines since 1 July 2019. No centrally authorised medicines had UK (co)-rapporteurs after that point.

PRAC rapporteurs/co-rapporteurs appointed in 2019
(for initial Marketing autorisation applications)



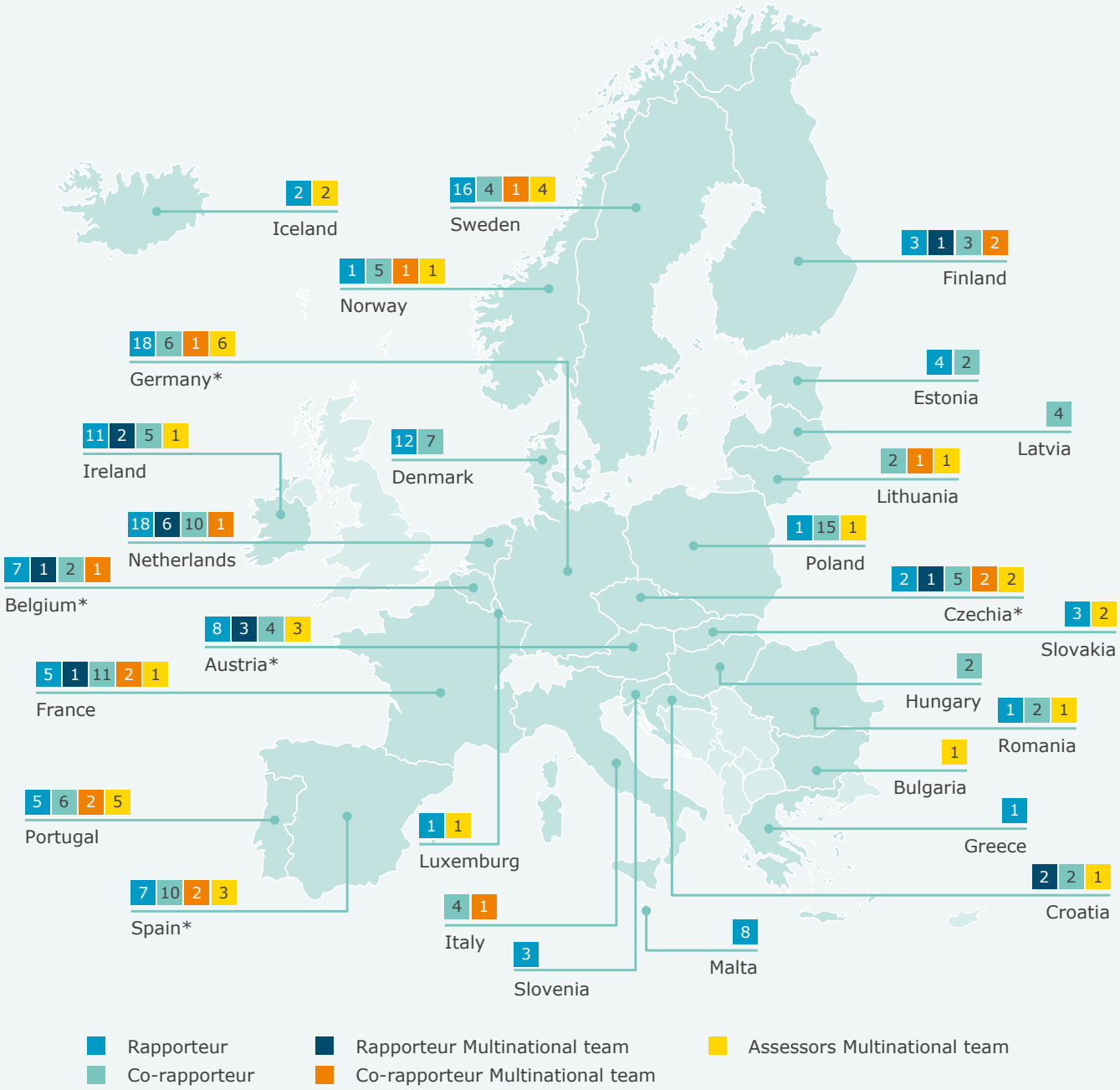
CHMP RAPPORTEURSHIPS/ CO-RAPPORTEURSHIPS

CHMP rapporteurs and co-rapporteurs can create multinational teams for the initial assessment of marketing authorisation applications.

The table below presents the number of procedures in which each country was involved in 2019, either as a regular rapporteur or co-rapporteur, as a rapporteur or co-rapporteur leading a multinational team, or as an assessor of part of a multinational team.

CHMP rapporteurs/co-rapporteurs appointed in 2019

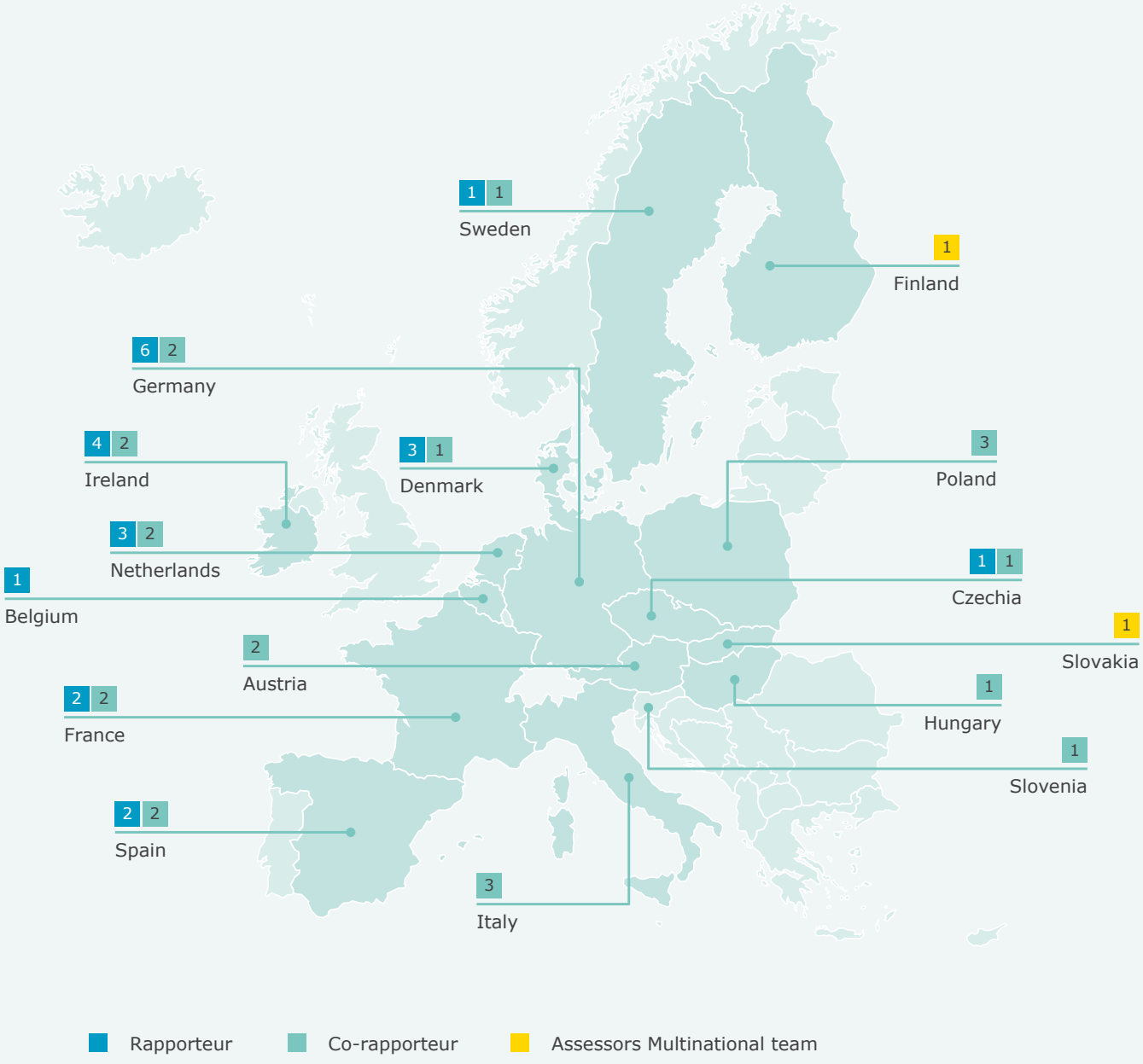
(for initial Marketing autorisation applications, including generics)



* co-opted members included under the country of affiliation/provenance

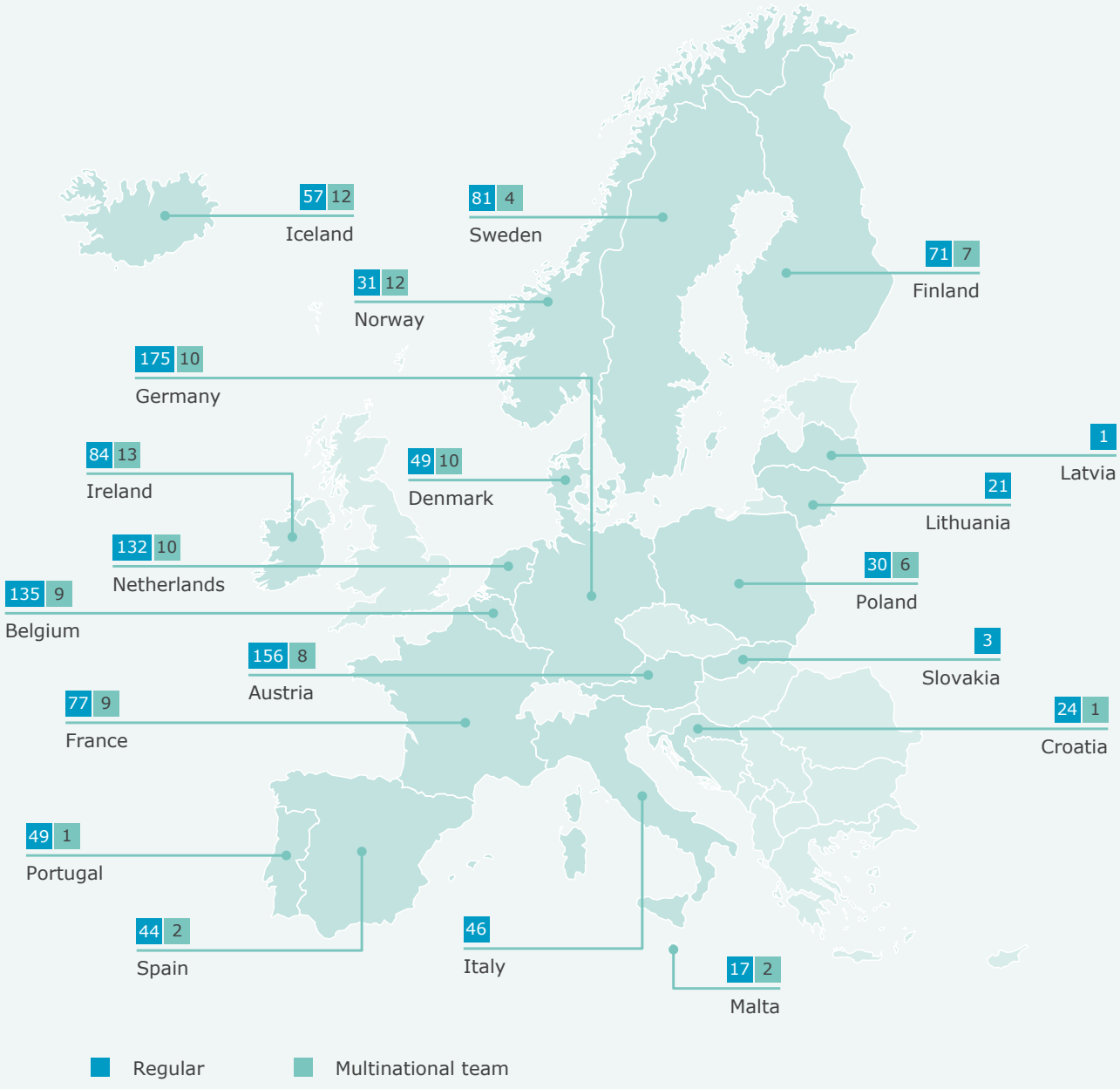
CVMP rapporteurs/co-rapporteurs appointed in 2019

(for initial Marketing autorisation applications, including generics)



Scientific advice working party (SAWP)

SAWP coordinators appointed in 2019



EU network training centre

The EU network training centre is a joint initiative of EMA and the NCAs to address the training needs of the EU medicines regulatory network regarding both human and veterinary medicines. The table below highlights its key activities from when it was established in 2015 to 2019.

	2015	2016	2017	2018	2019
New scientific, regulatory and telematics curricula developed	1	8	0	2	2
Number of training events advertised to the EU network	105	140	100	60	40
Number of reimbursed training events to the EU network	7	25	20 (14 by EU NTC)	8 (5 by EU NTC)	12
Number of NCAs that have opened their training for inclusion in EU NTC Learning Management System	6	14	8	7	10
Number of users registered in the EU NTC Learning Management System		2,117	3,583	4,424	5,121
Number of NCA experts registered in the EU NTC Learning Management System		1,225	2,668	3,480	4,143

INSPECTIONS AND COMPLIANCE

EMA coordinates the verification of compliance with the principles of good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), good pharmacovigilance practices (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 as 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, although 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 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;
- 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 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).

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, several mutual-recognition agreements are in place with Australia, Canada, Israel, Japan, New Zealand, Switzerland and the United States.

In 2019, the EU and the United States fully implemented the mutual recognition agreement for inspections of manufacturing sites for certain human medicines in their respective territories. In addition, as part of the mutual recognition agreement between the EU and Switzerland, the Swiss Agency for Therapeutic Products (Swissmedic) started to enter information on GMP compliance and manufacturing authorisations related to Swiss manufacturers in the EudraGMDP database. EudraGMDP is a database operated by EMA which supports the exchange of information on GMP compliance, as well as on manufacturing and importation authorisations.

EMA and its European and international partners also launched a pilot programme to increase their cooperation in the inspection of manufacturers of sterile medicines for human use. This new initiative built on the success of and experience gained from a similar collaboration, the international APIs inspection programme.

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 both within the EU and internationally, to strengthen global supply chains, and to improve access to authorised medicines.

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 number of the total 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 requested by the CHMP or CVMP within the context of the centralised authorisation procedure increased by almost 20% in 2019, from 416 GMP inspections in 2018 to 497 in 2019.

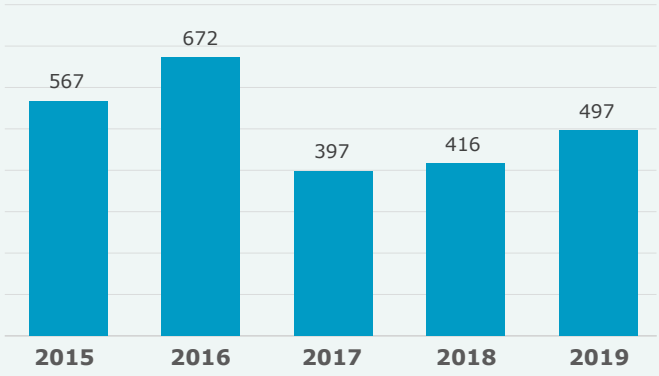
EudraGMDP holds all the data collected in inspections conducted by EU/EEA authorities, including those requested by the CHMP and CVMP.

In 2019, 16 GMP inspections conducted by EEA authorities led to the issuing of a non-compliance statement. This means that medicines manufactured at a site with such a non-compliance statement cannot be sold in the EU.

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

EEA authorities issued three statements of non-compliance relating to CAPs, in relation either to the active substance or the finished product.

GMP inspections



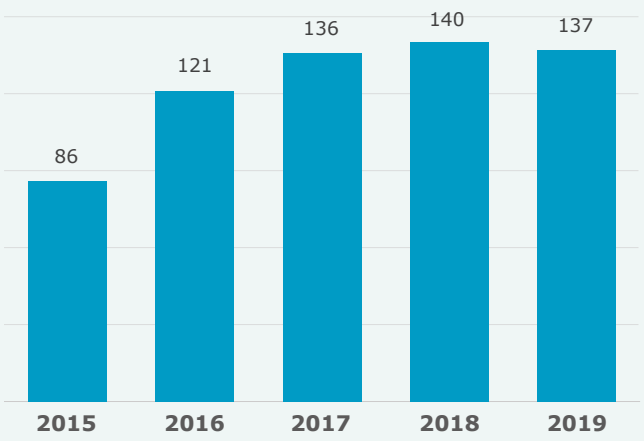
GMP certificates and non-compliance statements issued by EEA authorities										
	2015		2016		2017		2018		2019	
	GMP certificate	GMP non-compliance	GMP certificate	GMP non-compliance	GMP certificate	GMP non-compliance	GMP certificate	GMP non-compliance	GMP certificate	GMP non-compliance
EEA/EU	2,310	5	1,951	5	2,115	7	2,213	6	2,235	11
China	72	6	55	4	39	1	66	4	51	4
India	135	6	96	12	119	7	112	5	105	1
USA	110	1	86	3	106	0	27	0	127	0
Rest of the world	119	0	81	0	97	2	84	1	108	0
Total	**2,746**	**18**	**2,269**	**24**	**2,476**	**17**	**2,502**	**16**	**2,626**	**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 2015 and 2019. It includes GMP inspections requested by the CHMP or the CVMP.

GCP inspections

The number of GCP inspections requested by the CHMP has been consistent in recent years. In 2019, 137 GCP inspections were requested.

In 2019, the highest number of GCP inspections requested by the CHMP was conducted in the USA, followed by the EU/EEA/EFTA and the Middle East/Asia/Pacific regions, which have the highest number of patients, investigator sites and pivotal clinical trials included in marketing authorisation applications for CAPs.



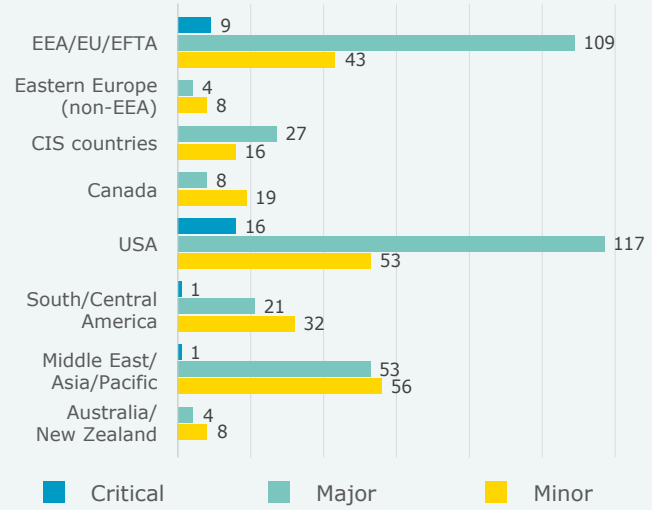
The classification of findings per region is presented in the adjacent chart.

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 well-being 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 2019, GCP non-compliance contributed to two application withdrawals.

Type of findings of CHMP-requested GCP inspections finalised by EEA authorities (2019)



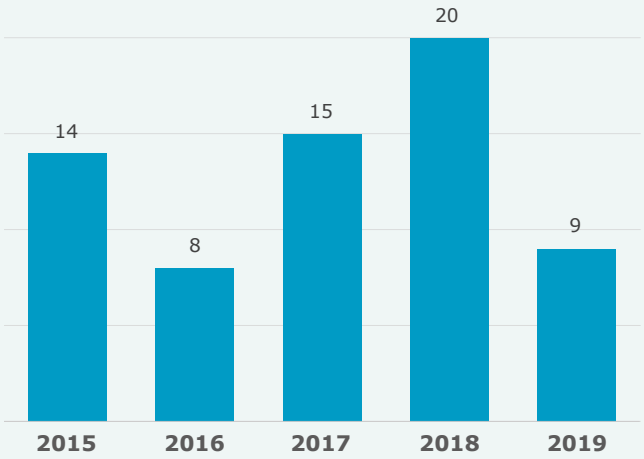
Pharmacovigilance inspections

EMA, in cooperation with competent authorities in the Member States, maintains a risk-based programme for routine pharmacovigilance inspections of MAHs 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 2019, nine pharmacovigilance inspections were requested by the CHMP or the CVMP. Although there was a reduction in the number of pharmacovigilance inspections requested in 2018, the 2019 figure is comparable with the number of inspections requested in 2016. The fluctuation in the number of pharmacovigilance inspections requested by the CHMP or CVMP reflects the three-year cycle of the risk-based programme for routine pharmacovigilance inspections of MAHs of centrally authorised products rather than indicating a change in the number of inspections.

The pharmacovigilance inspections requested by the CHMP or CVMP are only a small part of the total number of pharmacovigilance inspections in the EU. Most of the EU/EEA pharmacovigilance inspections (over 90%) are conducted under the national pharmacovigilance inspection programmes which relate to MAHs with product authorisations of all types (including CAPs).

Number of pharmacovigilance inspections



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 MAH 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 addition, as a result of the detection of nitrosamines in some batches of medicines (e.g. ranitidine, nizatidine), EMA worked with NCAs to coordinate recalls of affected medicines in the EU. EMA also collaborated with EDQM to organise related testing activities with the network of official medicines control laboratories (OMCLs).

Recalls due to reported quality defects

	2015	2016	2017	2018	2019
Recalls	15	16	17	27	15
Class 1	1	3	2	3	3
Class 2	3	9	8	17	3
Class 3	11	4	7	7	9

The main reasons for recall of CAPs in 2019 are summarised in the following table:

	Manufacturing laboratory control issues	Product contamination and sterility issues	Product label issues	Product packaging issues	Product physical issues
Class 1			1	2	
Class 2	1		1		1
Class 3		1	3	1	4

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).

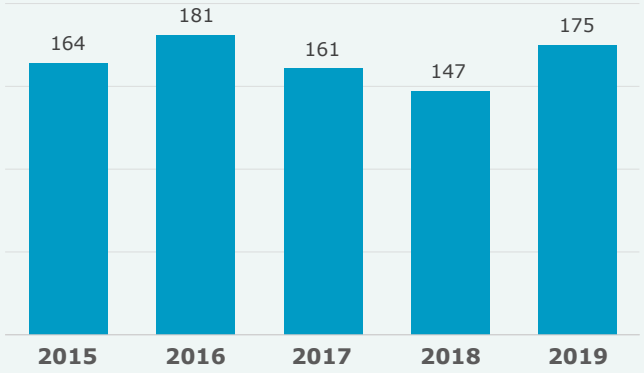
Product physical issues relate to incorrect product physical properties (e.g. friability, size/shape, leakage).

Market surveillance testing

In 2019, the Agency received 175 suspected quality defect notifications. Of these, 134 cases were confirmed quality defects and led to batch recalls of 15 centrally authorised medicines.

One quality defect was identified following sampling from the EU market and testing by an OMCL 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 MAH is compliant with the rules.

Parallel distribution notifications received

	2015	2016	2017	2018	2019
Initial notifications	2,838	2,850	2,639	2,304	2,468
Notifications of change	2,096	1,847	1,975	2,184	2,103
Notifications of bulk change	13	8	6	11	12
Annual updates	3,990	5,138	5,843	*5,245	4,270
Total	**8,937**	**9,843**	**10,463**	**9,744**	**8,853**

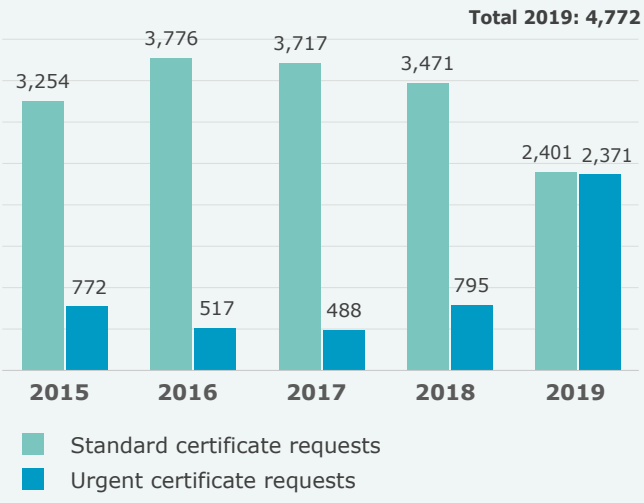
* This is the value after the final revision of annual updates.

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.

A delay in processing standard certificates due to EMA's resource constraints in 2019 led to a high number of urgent certificates being processed during the year.

Certificates



COMMUNICATION AND STAKEHOLDERS

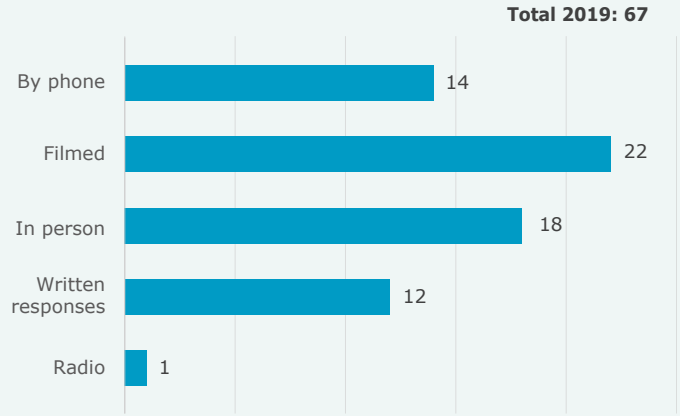
External communication

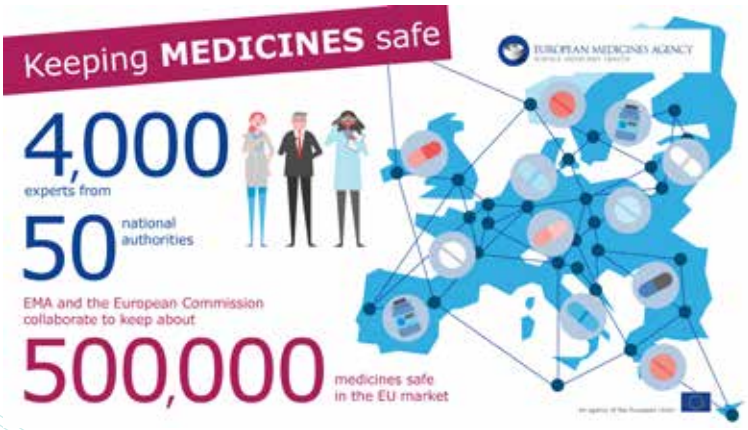
EMA's preparations for Brexit and the Agency's relocation from London to the Netherlands in March 2019 were of significant interest to the media. EMA staff members engaged in interviews on their move to the Netherlands in several outlets including Finnish TV, Euronews TV and the Dutch newspaper *De Telegraaf*.

Overall, in 2019, EMA organised 67 media interviews on a broad range of topics. Apart from Brexit, another topic that attracted substantial media interest was the discovery of nitrosamine impurities in some medicines and the subsequent safety reviews carried out by EMA.

In June, EMA organised a media seminar to establish good relations with media operating in the Netherlands and in the Brussels area. The event attracted 11 journalists, including eight working for Dutch newspapers and specialised publications. Participants heard presentations from EMA senior managers on what EMA does, how medicines are approved in the EU and how the Agency works.

2019 interviews





SOCIAL MEDIA

By the end of December, EMA had over 45,200 followers on Twitter (an 18% increase compared to 2018) and nearly 110,00 followers on LinkedIn (a 110% increase compared to 2018).

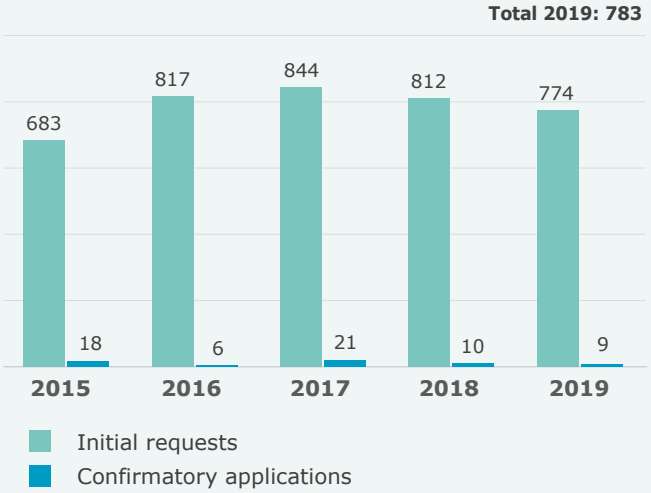
Throughout the year, the Agency ran a number of social media campaigns to highlight various topics, including the safety monitoring of medicines in the EU as well as campaigns for European Immunization Week in April and European Antibiotic Awareness Day in November.

EMA published an interactive tool describing **the journey of a medicine** for human use authorised through EMA, from initial research to discussions on patient access to medicines across the EU. The initiative aimed to improve understanding of how EMA works.

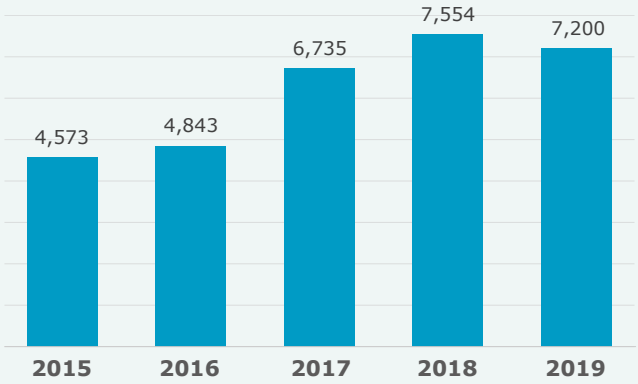
Requests for access to documents

EU citizens have the 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 Regulation (EC) No 1049/2001 and its policy on access to documents.

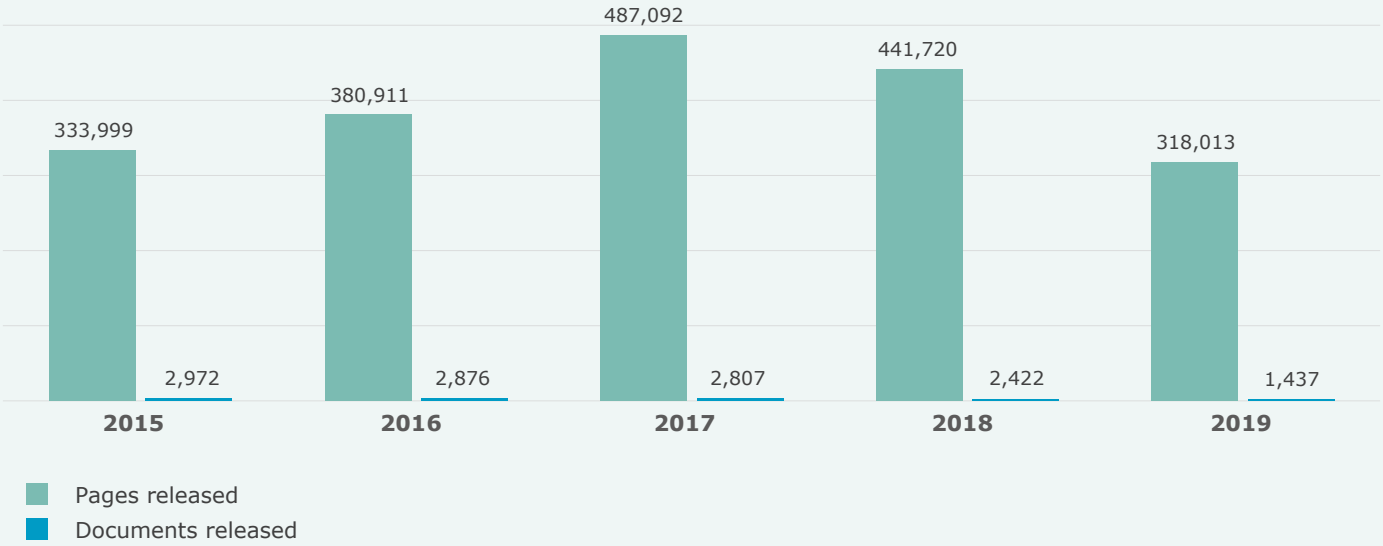
Requests received for access to documents



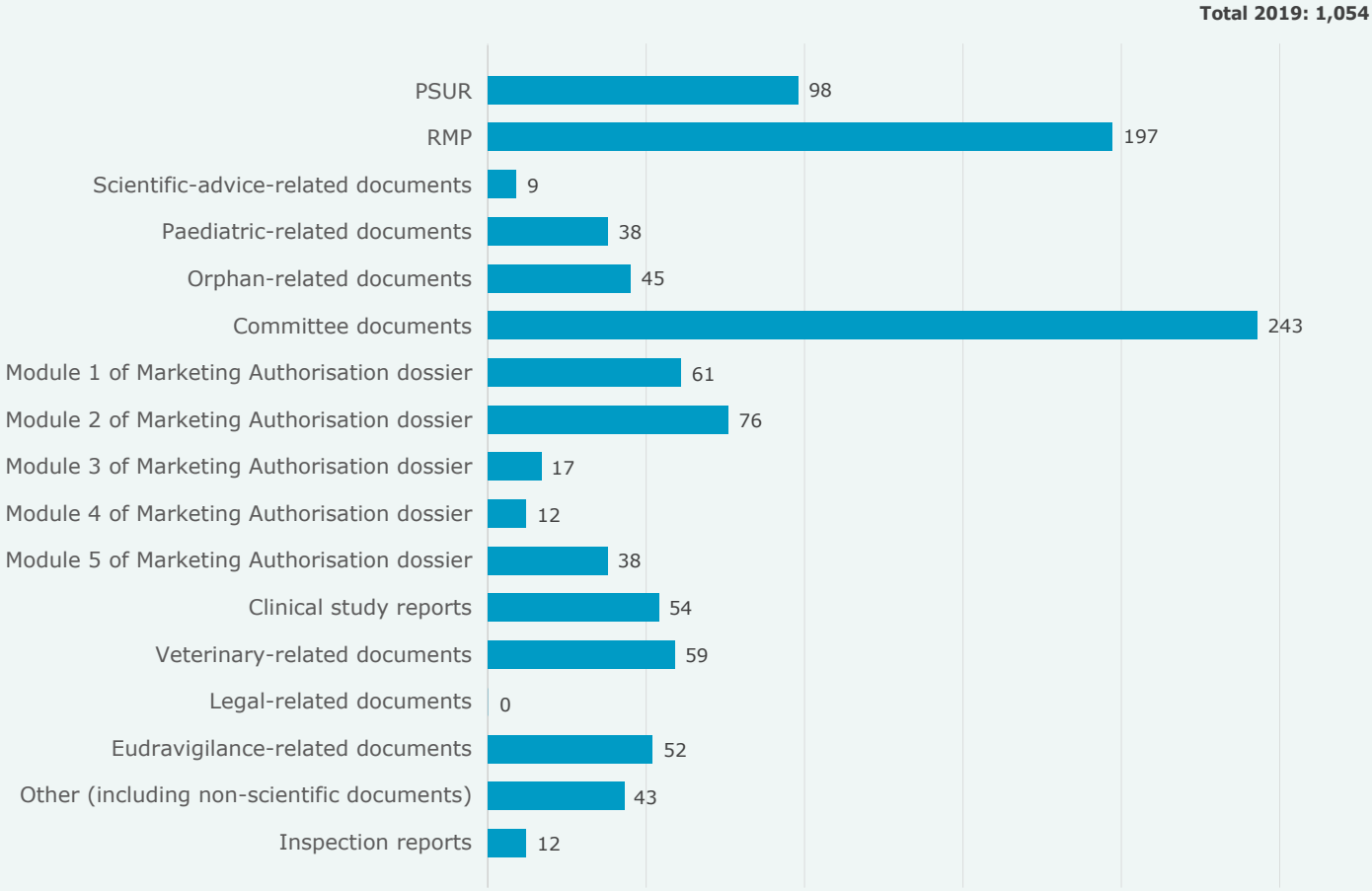
Requests for information received



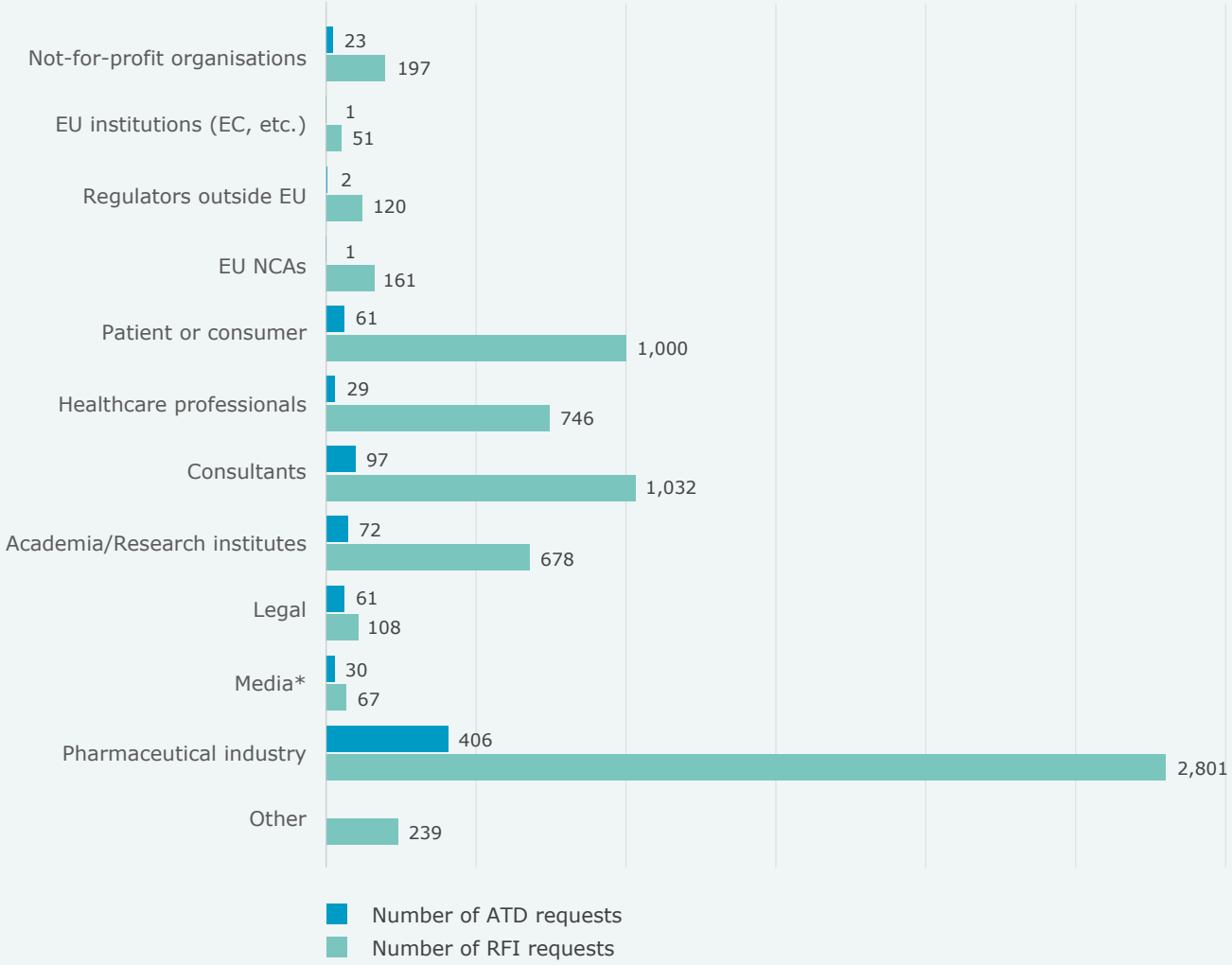
Documents and pages released following requests for access to documents



Access to documents by type of document (2019)



Affiliation of requestors of access to documents and of information (2019)



* Requests from media submitted via EMA's online form; does not include requests sent directly to the EMA press office.

Requests for access to document closed – initial requests and confirmatory applications

Decision	2015		2016		2017		2018		2019	
	Initial re-quests	Confir-matory appl.	Initial re-quests	Confir-matory appl.	Initial re-quests	Confir-matory appl.	Initial re-quests	Confir-matory appl.	Initial re-quests	Confir-matory appl.
Fully granted	446	5	542	3	580	5	562	5	436	1
Partially granted (with redactions)	8	1	17	1	14	0	18	0	7	0
Refused	48	10	44	4	43	3	40	2	27	6
Total	**502**	**16**	**603**	**8**	**637**	**8**	**620**	**7**	**470**	**7**

COURT OF JUSTICE UPHOLDS EMA'S APPROACH TO TRANSPARENCY

In September 2019, Advocate-General Hogan released his Opinions on two access-to-documents cases that were pending before the Court of Justice of the European Union. These two court cases were brought against EMA by two pharmaceutical companies and concerned EMA's policy on access to documents (based on Regulation (EC) No 1049/2001) and the rules the Agency applies to grant access to the documents it holds on human and veterinary medicines.

The companies challenged EMA's decision to release toxicology and clinical study reports requested by third parties claiming that the disclosure of the studies would undermine their commercial interests. These documents had been submitted by the companies in their centralised applications for marketing authorisation. In February 2018, the General Court endorsed the Agency's approach to transparency and upheld EMA's decision to disclose the study reports. The companies appealed the judgments of the General Court before the Court of Justice in March 2018.

In his review of the cases, Advocate-General Hogan supported the companies' claims and proposed that the two cases be sent back to the General Court for a new legal reassessment.

EMA's stakeholders were concerned by the Advocate-General's Opinions, arguing that making available to the public most data submitted to the Agency for the purpose of marketing authorisations generates trust in the EU regulatory network, broadens the scientific knowledge base, fosters the development of medicines, and ultimately benefits public health. Over 30 organisations also offered their support to EMA in its fight for transparency and published an open letter.

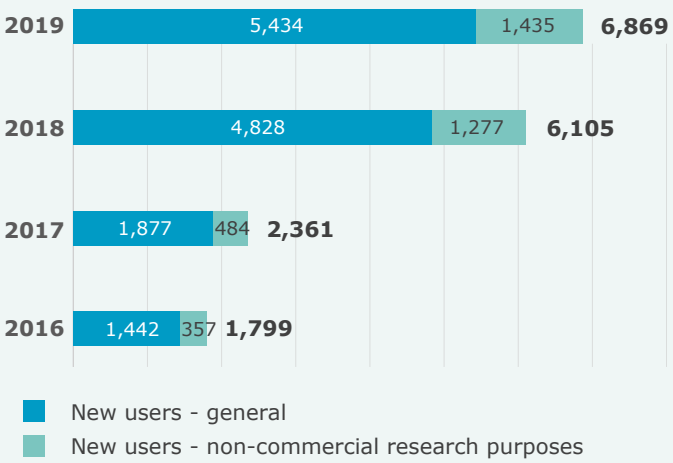
On 22 January 2020, the Court of Justice dismissed the appeals and upheld EMA's approach to transparency. The judges reiterated the principle of the widest possible public access to documents held by Union institutions, bodies, offices and agencies. An exception to that principle may be applied for the protection of commercial interests only if it is proven by the MAH/applicant that the disclosure of documents would pose the risk of concrete harm to the commercial interests of those concerned. The Court of Justice agreed with EMA that such harm was not established in respect of the disclosure of the clinical study and toxicology reports at stake.

Publication of clinical data

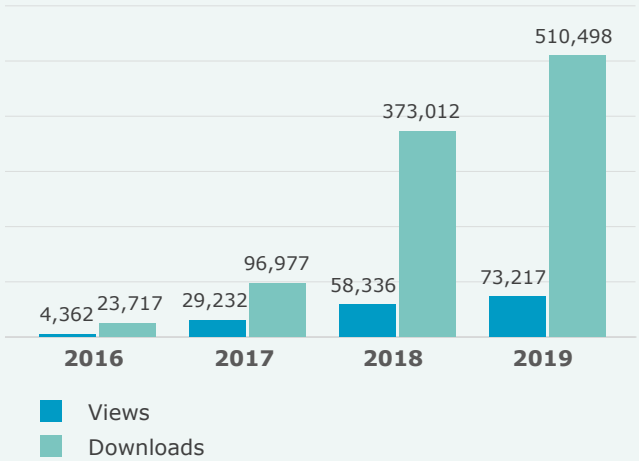
In October 2016, EMA became the first regulatory authority to provide open access to clinical data submitted by companies in support of their marketing authorisation applications. The charts below indicate the use of the clinical data website from its launch in October 2016 to the end of 2019.

In August 2018, due to business continuity planning resource constraints, EMA suspended all new activities related to clinical data publication in order to free up resources to focus on its core activities of medicines evaluation and supervision. This suspension continued throughout 2019.

Clinical data website - users



Clinical data website - usage

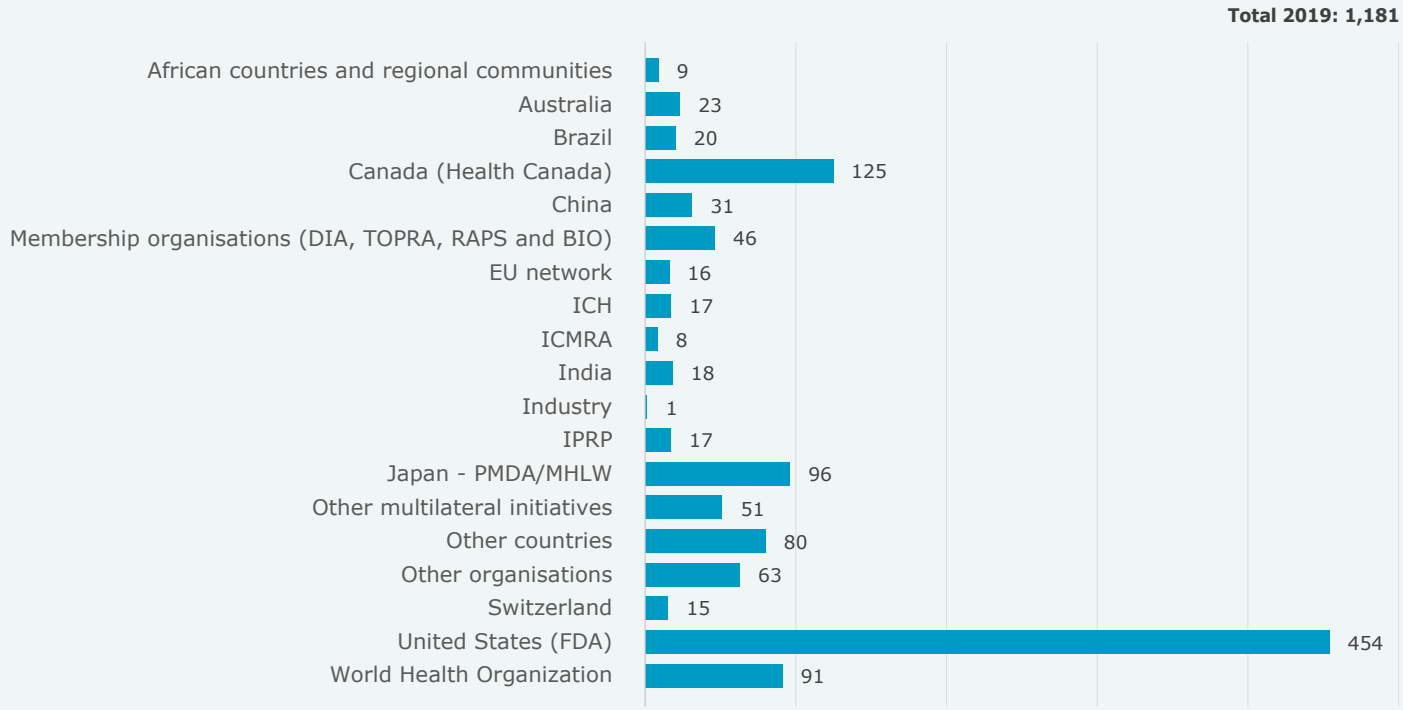


Interaction with international stakeholders

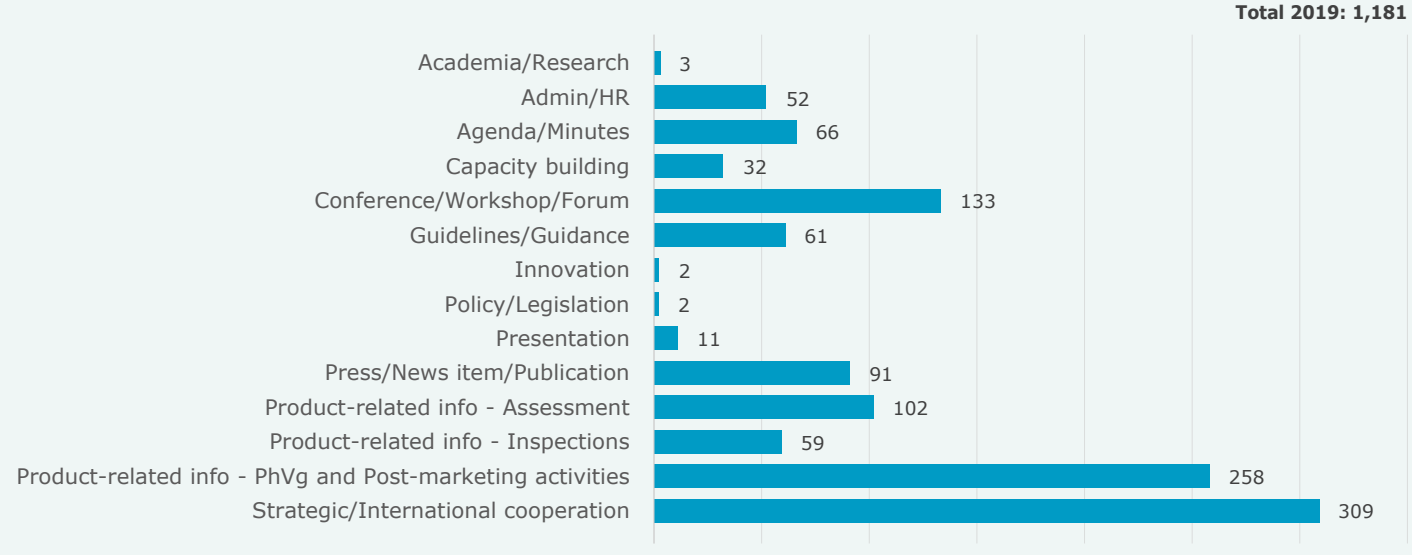
EMA has had an international role since its creation in 1995. Its founding regulation gives the Agency a specific responsibility to provide technical and scientific support to the evaluation of medicines. Today, international cooperation is moving from 'harmonisation' of technical requirements towards more mutual reliance and work-sharing through multilateral cooperation and coalitions.

In 2019, EMA had a total of 1,181 interactions with international stakeholders through its International Affairs department.

Number of interactions per stakeholder (2019)



Topics of interactions with international stakeholders (2019)



ADMINISTRATIVE ASPECTS

Budget

Total revenue

In 2019, the Agency's total revenue was €339.889 million compared to €317.081 million in 2018.

The revised Financial Regulation, which came into effect on 1 July 2019, introduced two new fund sources for handling assigned revenue: R0 for external assigned revenue (inducements related to the EMA building in Amsterdam) and CL for internal assigned revenue (rent and building charges received from the Agency's subtenant in London).

In view of the long-term nature of this revenue stream, it is now included as a separate category in the table below.

In 2019, assigned revenue received amounted to approximately €10.15 million.

Revenue (in € thousands)

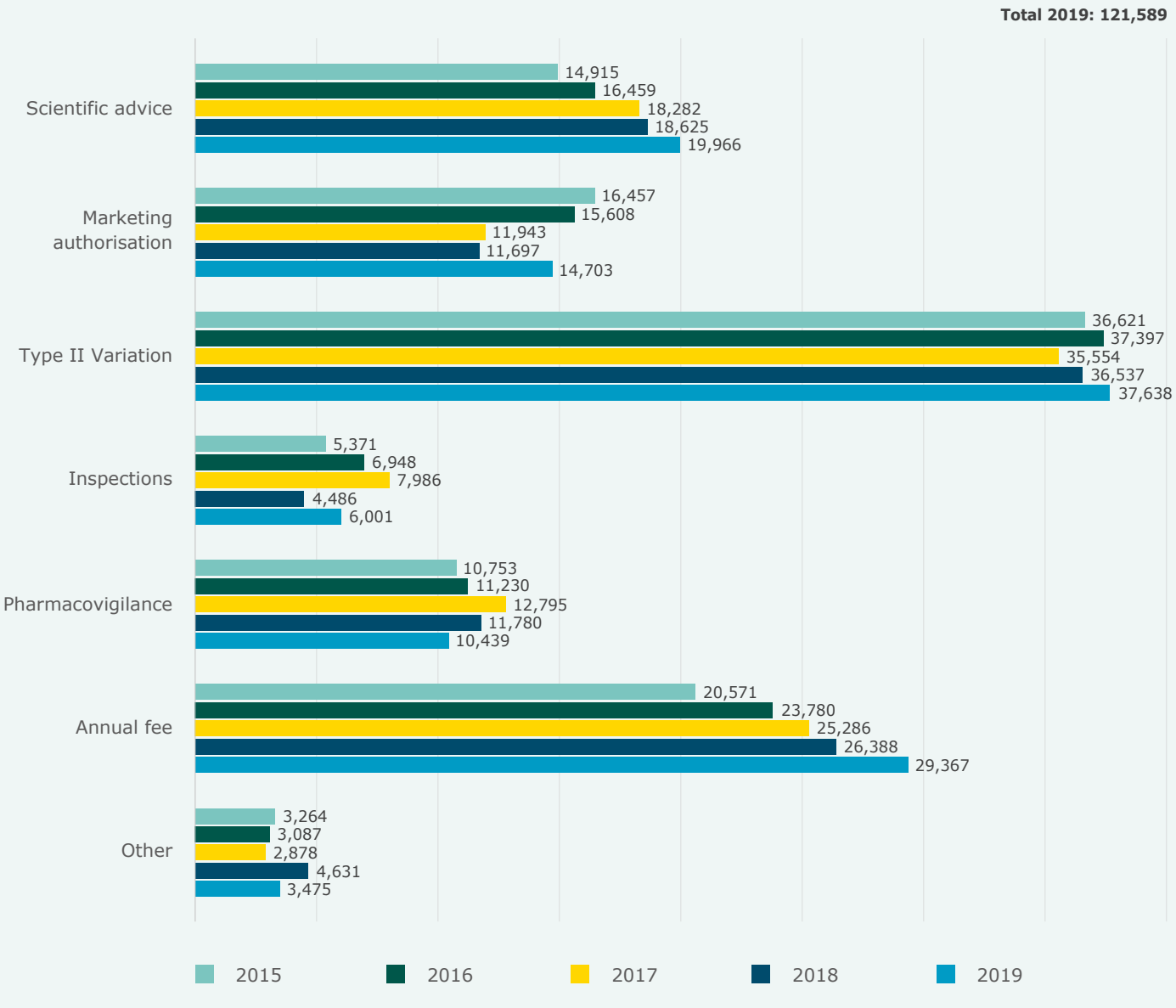
Remuneration to national competent authorities

NCAs in the EU Member States receive part of the fee revenue for the assessments they carry out on behalf of the Agency.

In 2019, EMA paid a total of €121.6 million to the national competent authorities, compared to €114.1 million in 2018.

This figure includes payment for pharmacovigilance procedures, including the assessment of PSURs, PASS protocols and study results, and of pharmacovigilance-related referrals. Fees are charged to companies whose medicines, whether authorised centrally or nationally, are included in these procedures.

Remuneration to NCAs per fiscal year (in € thousands)

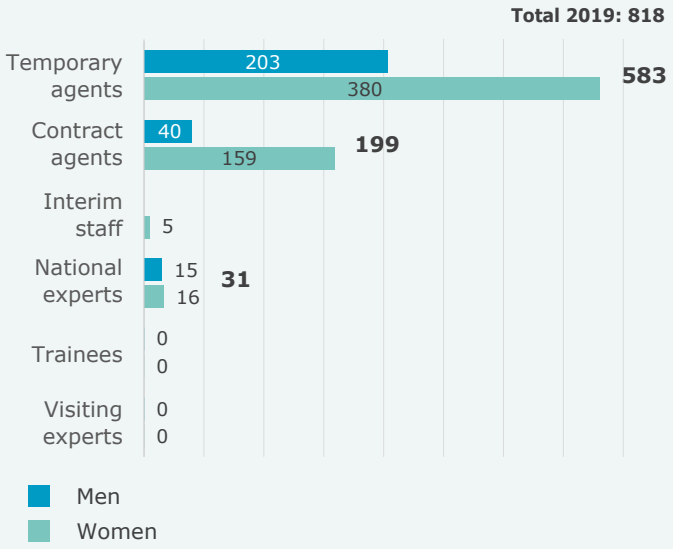


Agency staff

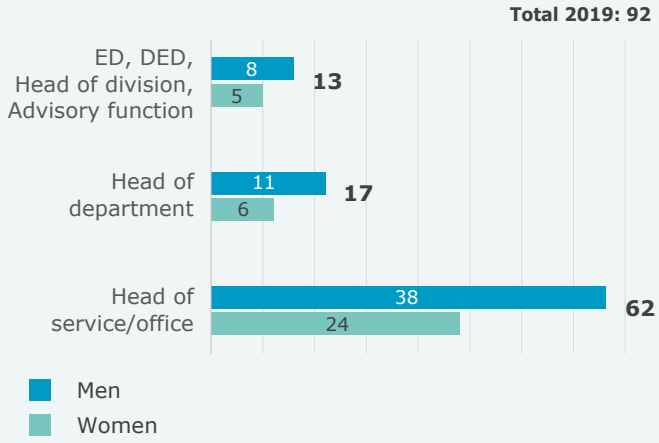
As of December 2019, Agency staff numbered 818: 560 women and 258 men.

Due to long-term absences, such as maternity or parental leave or long-term sick leave, the Agency's total available workforce was 775 at the end of the year.

Agency staff
(as of 31 December 2019)



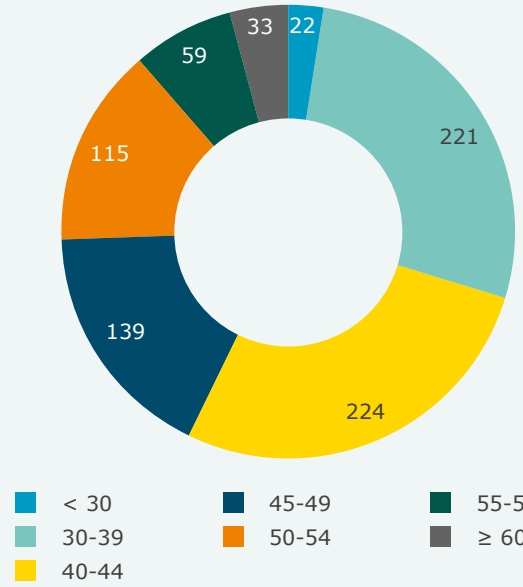
Gender balance of Agency management
(as of 31 December 2019)



Gender balance of Agency staff 2019

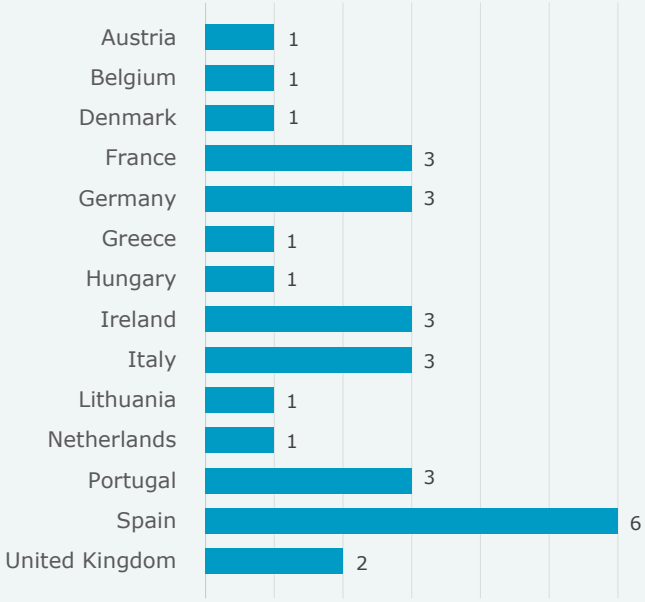
Status	Category AD (administrators)		Category AST (assistants)		All grades	
						
Temporary agents	50%	50%	13%	87%	35%	65%
Contract agents	26%	74%	15%	85%	20%	80%
Total	**45%**	**55%**	**14%**	**86%**	**31%**	**69%**

Age-range statistics (31 December 2019)



This chart includes temporary agents, contract agents and national experts only.

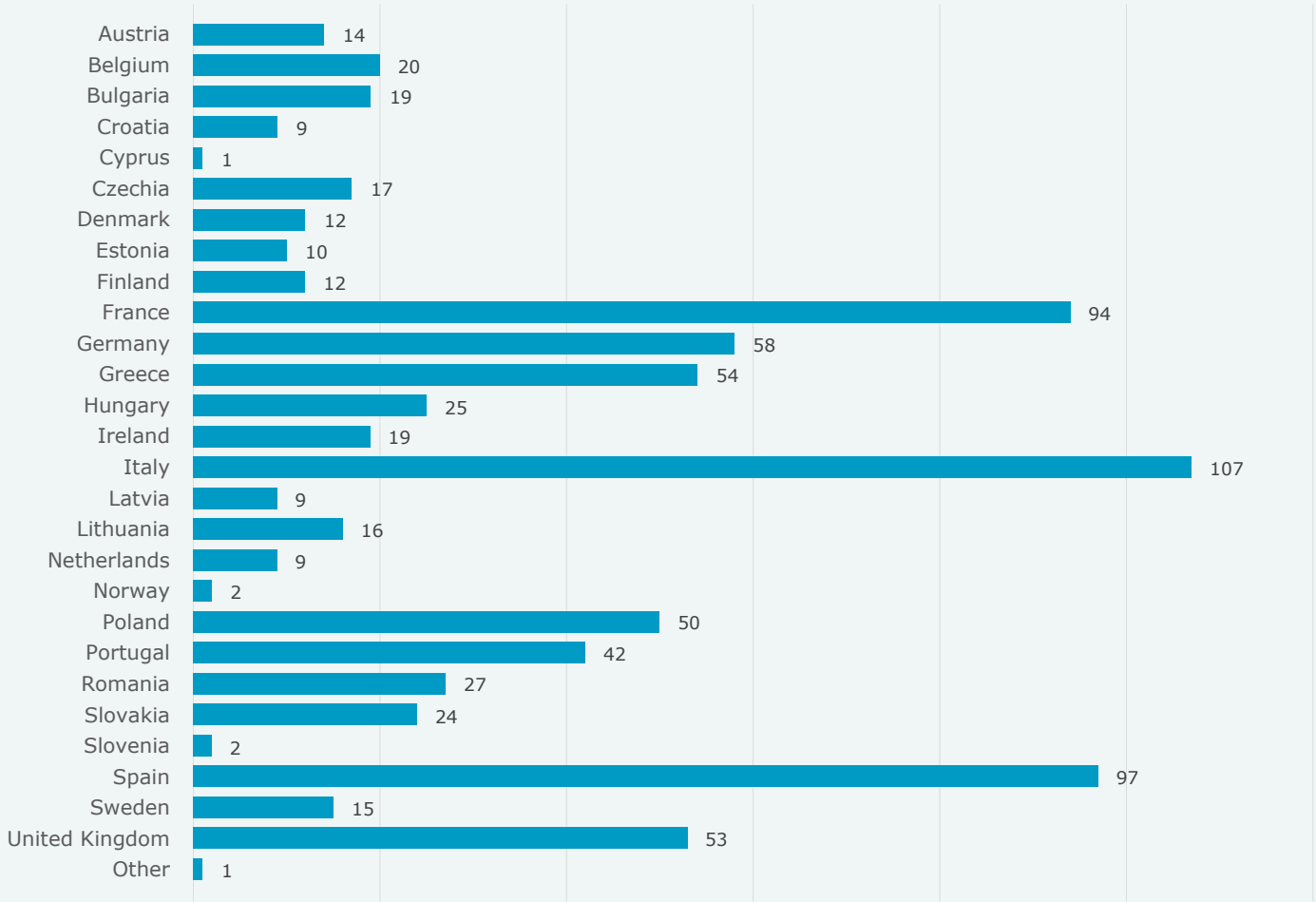
National origins of Agency management (as of 31 December 2019)



This chart excludes Heads of service/office.

National origins of Agency staff (as of 31 December 2019)

Total 2019: 818



ANNEXES

Annex 1 – Members of the Management Board

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

Annex 3 – Members of the Pharmacovigilance Risk Assessment Committee

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

Annex 5 – Members of the Committee on Orphan Medicinal Products

Annex 6 – Members of the Committee on Herbal Medicinal Products

Annex 7 – Committee for Advanced Therapies

Annex 8 – Members of the Paediatric Committee

Annex 9 – Working parties and working groups

Annex 10 – CHMP opinions on initial evaluations and extensions of therapeutic indication in 2019

Annex 11 – Guidelines and concept papers adopted by CHMP

Annex 12 – CVMP opinions on medicinal products for veterinary use in 2019

Annex 13 – Guidelines and concept papers adopted by CVMP in 2019

Annex 14 – COMP opinions on designation of orphan medicinal products in 2019

Annex 15 – HMPC European Union herbal monographs in 2019

Annex 16 – PDCO opinions and EMA decisions on paediatric investigation plans and waivers in 2019

Annex 17 – Referral procedures overview 2019 – human medicines

Annex 18 – Arbitrations and referrals in 2019 – veterinary medicines

Annex 19 – Budget summaries 2018–2019

Annex 20 – European Medicines Agency establishment plan

Annex 21 – Access to documents requests in 2019

Annex 22 – Publications by Agency staff members and experts in 2019

The annexes are available on EMA's website.

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Annual report 2019