EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

ANNUAL REPORT 2021

The European Medicines Agency's contribution to science, medicines and health in 2021

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 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 European Union (EU) Member States and the European Commission (EC) as partners in a European medicines regulatory network, the European Medicines Agency (EMA):

- provides independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines;
- applies efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the EC;
- implements measures for continuously monitoring and supervising the quality, safety and efficacy of all medicines authorised in the 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 alongside the Member States and the EC contributes to the harmonisation of regulatory standards at the international level.

Legal role

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 (March 2016 – March 2022)

I am delighted to introduce EMA's annual report for 2021 which highlights the Agency's important contributions to public health during the second year of the COVID-19 pandemic.

As chair of the EMA Management Board, I am particularly proud of the unparalleled coordination between EMA, the Member States and the European Commission that formed the basis for the joined-up response to the ongoing public health crisis. At the same time, the European medicines regulatory network's business continuity plan ensured that we, as a network, were also able to deal efficiently with the core regulatory activities needed to protect public and animal health.

EMA and the national experts worked tirelessly to fast-track the evaluation of COVID-19 vaccines and therapeutics that the European Union (EU) needed so urgently to fight the pandemic. This meant an unprecedented workload for EMA and the national competent authorities. The Management Board called for an increase in resources to ensure that rapporteur teams continued to be available to conduct assessments within the shortest possible timeframes.

COVID-19 was not the only topic that kept us occupied in 2021. The Agency, together with Member States and the European Commission, prepared for the implementation of two important pieces of new legislation that entered into force at the beginning of 2022: the Clinical Trials Regulation (CTR) and the Veterinary Medicinal Products Regulation.

The Clinical Trials Information System (CTIS), enabling the centralised application and management of clinical trial data in the EU, was developed by EMA with the support of the European medicines regulatory network and became a regular item on the agenda of the Management Board. During an extraordinary meeting in April, we discussed the outcomes of the independent audit of the new system and were able to set the go-live date of the system for 31 January 2022. CTIS will become the single entry point for sponsors and regulators for the submission and assessment of clinical trial applications. Its searchable database for healthcare professionals, patients and the general public will significantly increase transparency on clinical trials in Europe.

The new Regulation for Veterinary Medicinal Products, which became applicable on 28 January 2022, required the creation of a series of databases at EU level, and EMA led on their development and implementation. The Veterinary Regulation will stimulate innovation and increase the availability of and access to safe and high-quality veterinary medicines while also strengthening the EU's fight against antimicrobial resistance.

I also would like to highlight the progress made in harnessing the power of data analytics to support medicine regulation. First, the Big Data Steering Group delivered a strategy setting out principles to guide the definition, adoption and implementation of data standards for the European medicines regulatory network. Second, the Data Analysis and Real World Interrogation Network (DARWIN EU) took shape as a coordination centre that will provide evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real-world healthcare databases across the EU.

Finally, I would like to express my gratitude on behalf of the Board to colleagues across the network, to the European experts, the Commission and to EMA staff for all their hard work during the year. For me, it has been a great honour to lead the Board over the last six years, which have been the most challenging times the network ever encountered. The pandemic has not yet ended and we will have to continue to work closely together to further improve our response to this crisis and to ensure that we have efficient tools available to deal with any future public health emergencies.

I INTRODUCTION

by Emer Cooke

EMA Executive Director

In 2021, global efforts to tackle the COVID-19 pandemic continued, with the EU medicines network redoubling their efforts and delivering, one by one, the scientific recommendations Europe needed to protect the health of its citizens. Our experts worked extremely hard to ensure that EU citizens had access to much-needed vaccines and therapeutics. As a result of this collective effort, we ended 2021 with more medical tools to fight this pandemic.

After giving its first positive opinion for a COVID-19 vaccine at the end of 2020, EMA recommended four more vaccines for approval in 2021, which enabled the roll-out of the largest mass vaccination campaign ever in the EU. EMA also recommended five new COVID-19 treatments for approval, which brought therapeutic options for people who had contracted the virus. COVID-19 is a new disease and as our understanding of the virus and its effect on people grew, we updated our recommendations accordingly throughout the year: we recommended to extend vaccination to adolescents and children, provided advice on vaccine boosters and monitored closely the impact of each new variant of concern.

In parallel, we kept a very close eye on the safety of the new vaccines and treatments, acting swiftly as and when necessary. Due to the unparalleled extent of the vaccination campaigns - never before had we received such a large volume of safety information on vaccines or any other medicines in such a short time - we were able to build our safety recommendations based on the analysis of an extensive data set. The EU pharmacovigilance system demonstrated its strength, notably when we were the first to identify and immediately put in place measures to mitigate a very rare risk of a specific form of thrombosis with two of the vaccines.

We also worked tirelessly to help increase manufacturing capacity for COVID-19 vaccines. The number of approved manufacturing sites rose from 19 to 52 by the end of 2021, leading to a significant increase in vaccine supply, both in the EU and globally.

Due to its critical role in the global response to the pandemic, EMA found itself in the limelight of public and media attention during 2021. We fully understood the need to provide the public and our stakeholders with high quality, clear information about vaccines and to deliver on our commitment to transparency. We communicated every step of the way and published the full clinical data reviewed as part of the regulatory approval process for COVID-19 products. We also maintained at full speed our close collaboration with global regulators and other international partners through the International Coalition of Medicines Regulatory Authorities (ICMRA) in order to streamline and align regulatory requirements for medicine development and approval.

EMA's essential role in the COVID-19 pandemic was recognised by the European Commission, Parliament and Council in the form of a legislative proposal to extend the Agency's mandate developed throughout 2021. The extended mandate will give us new tools to tackle many of the challenges the medicines system in the EU is faced with, from coordinating national responses to shortages of critical medicines, to supporting innovation, particularly in crisis situations, but also in preparation for other emerging health threats. It will be my priority in 2022 to deliver on this ambitious vision.

Despite the focus on COVID-19, I am very proud that we have also made significant progress in other areas. 2021 was a very strong year for human and veterinary medicines overall. EMA recommended for approval 92 medicines for human use, including a first-in-class treatment for an aggressive form of breast cancer and the first cell-based gene therapy to treat multiple myeloma, to name but a few.

In the veterinary area, we recommended 12 new medicines for approval. These include a new vaccine for pigs, which has the potential to reduce the need for antimicrobial treatment in animals and could therefore limit the development of antimicrobial resistance – the 'silent' pandemic against which EMA continued to take action in 2021.

Throughout the year, EMA also worked hard to deliver on the implementation of two major legislative tasks by the end of January 2022: the Veterinary Medicines Regulation and the Clinical Trials Information System (CTIS) supporting the go-live of the Clinical Trials Regulation (CTR).

A long time in the making, the CTR and the IT system we have developed, CTIS, will support ambitious plans for clinical trials in the EU that will put Europe back on the map as an important global player in medical research. Concerning the Veterinary Medicines Regulation, EMA developed major new IT systems and supported the European Commission in putting in place a large body of implementing legislation. It will re-shape the regulation of medicines for animals, with a strong emphasis on making innovative medicines available, including for limited markets, and further foster prudent use of antimicrobials.

I would like to sincerely thank all those who have been part of this journey and who are at the heart of 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.

COVID-19: THE EUROPEAN MEDICINES REGULATORY NETWORK'S RESPONSE TO THE PANDEMIC

The COVID-19 pandemic continued to be the number one priority for EMA and the European medicines regulatory network in 2021. EMA recommended four more vaccines for approval in 2021 that formed the basis of the largest mass vaccination campaign ever seen in the EU. EMA also recommended five new COVID-19 treatments that brought much needed therapy options for people who had contracted the virus.

This also required intensive safety monitoring to enable quick action where needed.

The network's operation under these circumstances relied on the existing health threats preparedness plan, the mobilisation of experts from the COVID-19 EMA pandemic Task Force (COVID-ETF), and the close collaboration with international regulators and ECDC. The rapid scientific advice on the development of COVID-19 medicines and the accelerated agreement of paediatric development plans, both activated in 2020, continued to be deployed successfully throughout 2021.

Support to developers of COVID-19 vaccines and treatments

Scientific advice is one of EMA's key tools to support the sound development of medicines. During the pandemic, developers could send a request at any time to the Agency to receive expedited advice within a maximum of 20 days. Developers received guidance and direction from EMA on the best methods and study designs to generate robust information for their future medicine or vaccine.

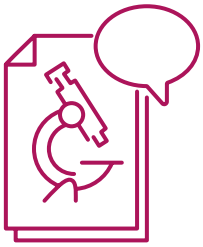
EMA provided a fast-track procedure for paediatric investigation plans (PIPs). A PIP describes how a COVID-19 vaccine or treatment will be studied in children and must be agreed with EMA ahead of any marketing authorisation application. This fast-track procedure enabled reduction of the timeline for PIP review from the usual 120 days down to 20 days, as needed.

KEY EVENTS IN 2021

JANUARY 06, 2021
EMA recommends granting a conditional marketing authorisation for COVID-19 Vaccine Moderna in people from 18 years of age.

JANUARY 12, 2021
EMA receives an application for conditional marketing authorisation for a COVID-19 vaccine developed by AstraZeneca and Oxford University.

COVID-19 procedures in 2021



77

scientific advice procedures

10

in the pipeline

32

paediatric investigation plans

24

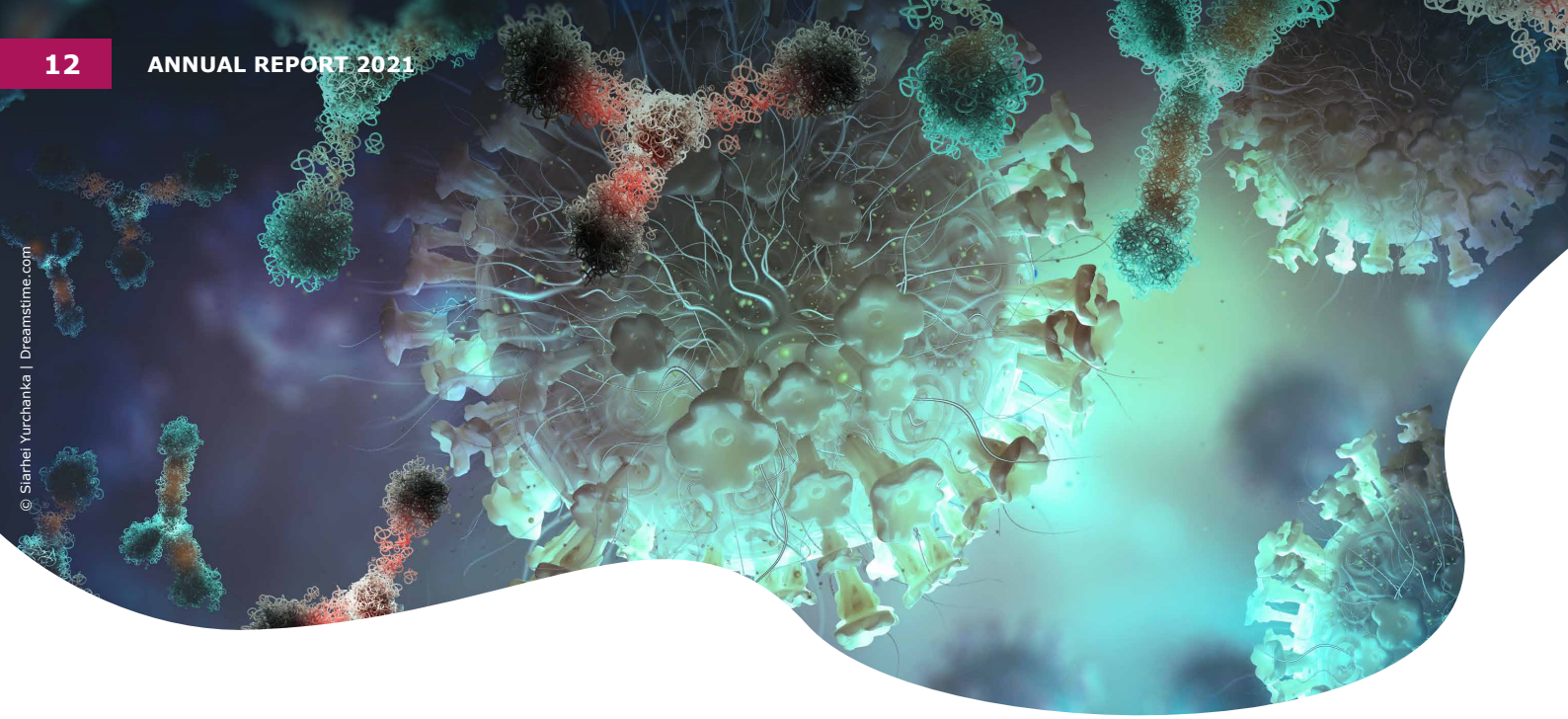
in the pipeline

JANUARY 19, 2021

EMA endorses a joint statement published by the International Coalition of Medicines Regulatory Authorities (ICMRA) to inform and help healthcare professionals answer questions about the evaluation, approval and monitoring of safe, effective and high-quality COVID-19 vaccines.

JANUARY 29, 2021

EMA releases its first safety update on a COVID-19 vaccine — Comirnaty.



Preparing for variants – guidance for vaccine developers

As the pandemic unfolded, SARS-CoV-2 evolved and several new variant strains were identified worldwide in 2021. Data indicated that variants could impact the level of protection against infection and disease provided by COVID-19 vaccines.

While the authorised vaccines remained effective in preventing severe disease and hospitalisation, it became an urgent public health priority to define an expedited regulatory process for adaptation of the vaccines to protect against variants, if needed. Based also on discussions at international level on how to approach variants and vaccines in a coordinated way, EMA issued guidance outlining the requirements for manufacturers' planning to modify their COVID-19 vaccines to address coronavirus variants.

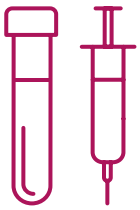
JANUARY 29, 2021
EMA recommends granting a conditional marketing authorisation for COVID-19 Vaccine AstraZeneca in people from 18 years of age.

FEBRUARY 01, 2021
EMA's human medicines committee (CHMP) starts a rolling review of data on a medicine known as REGN-COV2 antibody combination (casirivimab/imdevimab), for the treatment and prevention of COVID-19.

Rapid evaluation and approval processes

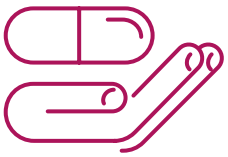
The use of rolling reviews continued to enable the rapid assessment of COVID-19 vaccines and treatments. Rolling review allows EU experts to scrutinise the evidence from studies on a medicine or a vaccine as soon as it becomes available, and before a formal marketing authorisation application is submitted. Once EMA decides that sufficient data are available, the company is invited to submit a formal application, which is then processed under a shortened timetable.

Four vaccines and five treatments were granted a marketing authorisation in 2021



COVID-19 vaccines

- **Spikevax** (Moderna)
- **Vaxzevria** (AstraZeneca)
- **COVID-19 Vaccine Janssen**
- **Nuvaxovid** (Novavax)



COVID-19 treatments

- **Regkirona** (regdanvimab)
- **Ronapreve** (casirivimab/imdevimab)
- **RoActemra** (tocilizumab)*
- **Xevudy** (sotrovimab)
- **Kineret** (anakinra)*

* The indication of this medicine has been extended to include the treatment of COVID-19.

FEBRUARY 03, 2021
EMA's human medicines committee (CHMP) starts a rolling review of NVX-CoV2373, a COVID-19 vaccine by Novavax.

FEBRUARY 04, 2021
EMA pilots a new 'OPEN' initiative to increase international collaboration on the evaluation of COVID-19 vaccines and therapeutics. The pilot started in December 2020.

Extending vaccine manufacturing capacity

One of the major challenges for the EU was to ensure an adequate supply of vaccines to support the large-scale roll-out in national vaccination campaigns. Throughout 2021, EMA was able to quickly approve new manufacturing sites and lines, additional suppliers of raw materials and other manufacturing changes to enable a rapid scale-up of the production of Comirnaty, Spikevax, Vaxzevria and COVID-19 Vaccine Janssen. This was done through proactive planning, communication and by following accelerated assessment timetables. The number of approved manufacturing sites rose from 19 to 52 during the year, leading to a huge increase in vaccine supply in the EU and in third countries through the COVID-19 Vaccines Global Access (COVAX) initiative.

Vaccination in children

All COVID-19 vaccines were initially approved in adults only. The approvals of two of the vaccines, Comirnaty and Spikevax, were extended to younger age groups during the course of 2021 as additional data became available. While these age groups are generally at low risk of severe infection, SARS-CoV-2 can also cause severe disease in younger people.

2021 milestones for COVID-19 vaccines in children and adolescents

FEBRUARY 04, 2021
EMA's human medicines committee (CHMP) is reviewing available data to support national decision-making on the possible use of monoclonal antibodies in COVID-19.

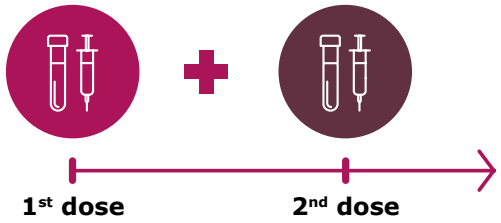
FEBRUARY 08, 2021
The International Coalition of Medicines Regulatory Authorities (ICMRA) emphasises the importance of international collaboration and sharing expertise and best practices on observational studies of real-world data to facilitate regulatory decision-making on COVID-19 treatments and vaccines.

Booster doses

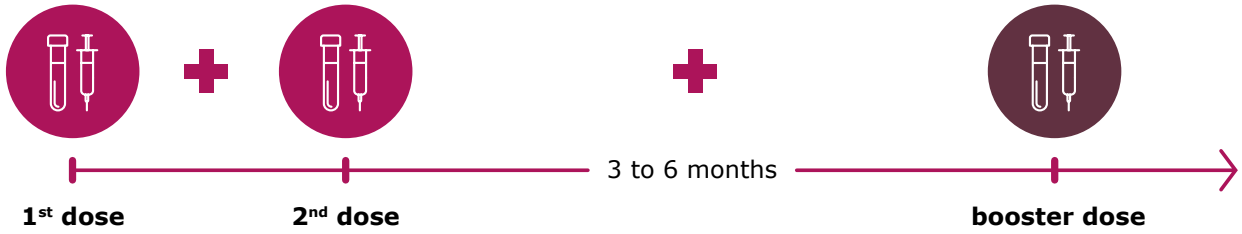
Available data showed that immunity against COVID-19 from initial vaccination waned gradually over time and that protection from infection and symptomatic disease also declined. Therefore, in 2021, boosters were authorised to restore the protection offered from primary vaccination. EMA provided timely recommendations on booster schedules for three of the authorised vaccines: Comirnaty, Spikevax and COVID-19 Vaccine Janssen.

Heterologous vaccination

Heterologous primary vaccination:



Heterologous boosting:



FEBRUARY 10, 2021
EMA is developing guidance for manufacturers planning changes to the existing COVID-19 vaccines to tackle the new virus variants.

FEBRUARY 12, 2021
EMA starts a rolling review of CVnCoV, a COVID-19 vaccine by CureVac.

FEBRUARY 16, 2021
EMA receives an application for conditional marketing authorisation for a COVID-19 vaccine developed by Janssen.

Safety monitoring of COVID-19 vaccines and treatments

The EU has a comprehensive safety monitoring and risk management system, which ensures that measures are in place for detecting any potential new risks, conducting rigorous scientific assessments of all safety data and introducing any necessary mitigating actions early on.

Throughout 2021, EMA issued monthly safety updates for every authorised COVID-19 vaccine. Safety updates reflect data collected and assessed since the vaccine's authorisation, including data from EudraVigilance (the EU's centralised database of suspected side effects), data from the companies' monthly safety reports required for COVID-19 vaccines, as well as from independent studies coordinated by European authorities. This allows regulators to swiftly assess data emerging from a range of different sources and take appropriate regulatory action to protect public health, if needed.

FEBRUARY 23, 2021
EMA starts evaluating an application to extend the use of Veklury (remdesivir) to include treating adults with COVID-19 who do not require supplemental oxygen.

FEBRUARY 24, 2021
EMA's human medicines committee (CHMP) starts a rolling review of data on the monoclonal antibody regdanvimab (also known as CT-P59), which is being developed by Celltrion, for the treatment of COVID-19.

EMA's main recommendations on safety issues following monitoring of COVID-19 vaccines and treatments:

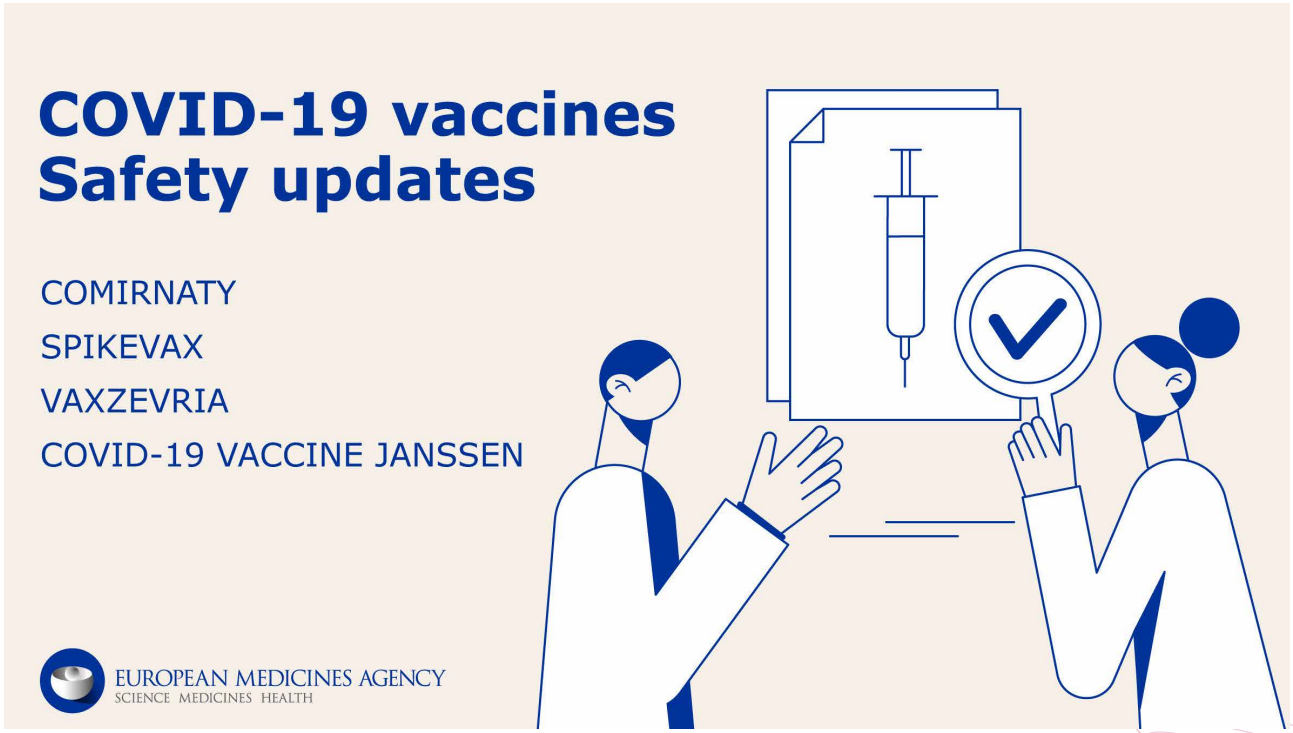
- **April**: EMA concluded that thrombosis with thrombocytopenia syndrome (TTS) (blood clots with low blood platelets) should be listed as a very rare side effect of Vaxzevria, formerly COVID-19 Vaccine AstraZeneca, and that TTS should be added as a new very rare side effect for COVID-19 Vaccine Janssen.
- **June**: EMA recommended that people with a medical history of capillary leak syndrome (CLS) must not be vaccinated with Vaxzevria, and that CLS should be included as a very rare side effect in the product information.
- **July**: EMA recommended listing Guillain-Barré syndrome as a very rare side effect of COVID-19 Vaccine Janssen and listing myocarditis and pericarditis as new side effects in the product information of Comirnaty and Spikevax. EMA also recommended that people with a medical history of CLS must not be vaccinated with COVID-19 Vaccine Janssen, and that CLS should be included as a very rare side effect in the product information.
- **August**: EMA recommended including immune thrombocytopenia as an adverse reaction for COVID-19 Vaccine Janssen.
- **September**: EMA recommended listing Guillain-Barré syndrome as a very rare side effect of Vaxzevria.
- **October**: EMA recommended listing venous thromboembolism (VTE) as a very rare side effect of COVID-19 Vaccine Janssen in the product information, to raise awareness especially in people with an increased risk of VTE. In addition, transverse myelitis was also listed as a side effect. EMA also recommended listing immune thrombocytopenia as a side effect in the product information of Vaxzevria.
- **December**: EMA assessed data on the known risk of myocarditis and pericarditis following vaccination with Comirnaty and Spikevax, including evidence from two large European epidemiological studies, and concluded that the risk for both of these conditions is overall very rare.

FEBRUARY 25, 2021
Regulators around the globe are committed to aligning their regulatory requirements and addressing knowledge gaps to facilitate the development, authorisation and monitoring of safe, effective and high-quality vaccines and medicines against COVID-19.

FEBRUARY 25, 2021
EMA issues guidance outlining the requirements for manufacturers planning to modify their COVID-19 vaccines in order to address coronavirus (SARS-CoV-2) variants.

EMA also took steps to use real-world data from clinical practice to monitor the safety and effectiveness of COVID-19 treatments and vaccines. EMA has contracted institutions specialised in observational research to conduct several research projects, which were still ongoing at the end of the year:

- safety monitoring of COVID-19 vaccines in the EU;
- natural history of coagulopathy and use of antithrombotic agents in COVID-19 patients;
- early safety monitoring of COVID-19 vaccines;
- impact of COVID-19 infection and medicines in pregnancy;
- multicentre cohort studies on the use of medicines in COVID-19 patients;
- infrastructure for the monitoring of the coverage, safety and effectiveness of COVID-19 vaccines.



FEBRUARY 26, 2021
EMA's human medicines committee (CHMP) completes its review on the use of the monoclonal antibodies casirivimab and imdevimab to treat patients with COVID-19. The Agency concluded that the combination also known as REGN-COV2 can be used for the treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

MARCH 02, 2021
EMA and Health Canada collaboratively publish the full clinical data reviewed as part of their authorisations of the Moderna COVID-19 vaccine.

Mobilising expertise from across the network

The unprecedented mobilisation of experts through the European medicines regulatory network continued throughout 2021 and proved to be one of the key success factors supporting fast-track development and marketing authorisations of safe, effective and high-quality medicines and vaccines for COVID-19.

EMA and its scientific committees were supported by COVID-ETF, a group bringing together experts from across the EU network to facilitate rapid and coordinated regulatory action on medicines and vaccines for COVID-19.

In 2021, the activities of the Task Force included:

- reviewing available scientific data on potential COVID-19 medicines and identifying promising candidates;
- requesting data from developers and engaging with them in preliminary discussions;
- offering scientific support to facilitate clinical trials conducted in the EU for the most promising medicines for COVID-19;
- providing feedback on development plans of COVID-19 vaccines and treatments when formal rapid scientific advice was not feasible;
- advising the Scientific Advice Working Party (SAWP) or the Committee for Medical Products for Human Use (CHMP) on formal scientific advice and assessments of COVID-19 medicinal products;
- contributing to the activities of the Pharmacovigilance Risk Assessment Committee (PRAC) on emerging safety issues related to COVID-19 vaccines and treatments;
- ensuring close cooperation with stakeholders and relevant European and international organisations.

MARCH 02, 2021
EMA is conducting a review of Celltrion's monoclonal antibody regdanvimab (CT-P59) to support national authorities who may decide on the use of this medicine for COVID-19 prior to authorisation.

MARCH 04, 2021
EMA's human medicines committee (CHMP) starts a rolling review of Sputnik V (Gam-COVID-Vac), a COVID-19 vaccine developed by Russia's Gamaleya National Centre of Epidemiology and Microbiology.

Transparency

In 2021, EMA continued to implement exceptional measures to maximise the transparency of its regulatory activities regarding vaccines and treatments for COVID-19 during evaluation and after approval.

EMA published the European public assessment reports for COVID-19 vaccines and treatments swiftly, only one or two days after authorisations were granted.

In addition, EMA and Health Canada worked collaboratively to publish the full clinical data reviewed as part of the regulatory approval process for COVID-19 vaccines and therapeutics. EMA and Health Canada are the only two regulators worldwide publishing such comprehensive information.

> ‘EMA and Health Canada’s joint commitment to openness and transparency support global research, allow for public scrutiny and reinforce society’s trust in COVID-19 vaccines as mass vaccination campaigns continue to be rolled out across the EU, Canada and the rest of the world.’
>
> **Emer Cooke**, EMA’s Executive Director

This international partnership showed the shared commitment of both authorities to ensuring that the public has as much information as possible to make decisions regarding vaccination and treatment.

> ‘During the COVID-19 pandemic, EMA is implementing exceptional measures to try and maximise the transparency of its regulatory activities on treatments and vaccines for COVID-19 that are approved or are under evaluation. EMA is doing this by shortening its standard publishing timeframes and publishing information it does not normally publish for other medicines.’
>
> **European Ombudsman** [1]

[1] This statement was provided by the European Ombudsman in her decision that refusal of public access to documents relating to the manufacturing of mRNA vaccines against COVID-19 did not constitute maladministration.

MARCH 05, 2021
EMA’s human medicines committee (CHMP) completes its review on the use of the monoclonal antibodies bamlanivimab and etesevimab to treat patients with COVID-19. This review was undertaken to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies prior to marketing authorisation.

MARCH 10, 2021
EMA’s safety committee (PRAC) investigates cases of thromboembolic events, and other conditions related to blood clots, reported post-vaccination with Vaxzevria (previously COVID-19 Vaccine AstraZeneca).

Crisis communication, tackling disinformation, stakeholder engagement

Social media has amplified an 'infodemic' where massive amounts of information are shared and disinformation and misinformation can easily spread. Mis- and disinformation around COVID-19 vaccines and treatments had a massive public health impact in 2021 as it undermined trust in authorised medicines, scientists, regulators and other public health authorities and limited the uptake of life-saving vaccines. In 2021, EMA intensified its media monitoring and social listening activities, carefully scrutinised public queries and closely collaborated with other EU entities and international public health bodies to identify harmful health advice and address concerns in a timely manner.

Providing the general public with factual, complete and up-to-date information about its activities to fight the pandemic remained a major goal for EMA in 2021. This was ensured through frequent updates on EMA's website for the general public, regular press briefings and media interviews with EMA key experts, as well as frequent social media posts that increased visitors' engagement.

Key figures on EMA's COVID-19 communication

- 18 press briefings were organised throughout 2021 to meet the huge media interest in EMA's COVID-19-related activities.
- Around 200 news announcements were published and 56 media interviews took place to inform the public about key milestones in medicine assessment or new initiatives related to the pandemic response.
- Approximately 1,000 updates were shared on EMA's official Twitter and LinkedIn accounts. The updates have been shown on users' news feeds almost 80 million times.
- More than 6,500 direct interactions between EMA and patients and healthcare professionals were registered.
- The COVID-19 related content on EMA's website attracted more than 10 million visits last year.

MARCH 11, 2021
EMA's human medicines committee (CHMP) starts a rolling review of data on the antibodies bamlanivimab and etesevimab which are being developed by Eli Lilly to be used in combination for the treatment of COVID-19.

MARCH 11, 2021
EMA recommends granting a conditional marketing authorisation for COVID-19 Vaccine Janssen to prevent COVID-19 in people from 18 years of age.

More than ever, EMA reached out to the public to respond to their questions and concerns. It engaged with patient and healthcare professional organisations and the general public through information sessions, public meetings and consultations to increase the effectiveness of its public health communications.

In 2021, EMA held three public meetings on COVID-19 to explain how the Agency assesses and monitors COVID-19 vaccines and heard directly from European citizens about their needs and concerns. The meetings were held virtually and broadcast live. They were attended by thousands of people, who had the opportunity to ask questions to EMA experts live.

Disinformation leading to judicial challenges

Despite EMA's unprecedented transparency efforts on COVID-19 vaccines, six legal challenges were initiated against the conditional marketing authorisations and/or an extension of indication for COVID-19 vaccines authorised in 2020 and 2021.

In all cases the European General Court sided with EMA and the European Commission, dismissing all actions for annulment as inadmissible.

MARCH 11, 2021
The position of EMA's safety committee (PRAC) is that the benefits of Vaxzevria (previously COVID-19 Vaccine AstraZeneca) continue to outweigh its risks and the vaccine can continue to be administered while investigation of cases of thromboembolic events is ongoing.

MARCH 12, 2021
The PRAC is reviewing all cases of thromboembolic events, and other conditions related to blood clots, reported post-vaccination with Vaxzevria (previously COVID-19 Vaccine AstraZeneca). Vaccine's benefits currently still outweigh its risks.

Coordinating the network's response to shortages

A global health emergency, such as the COVID-19 pandemic, can drive a sudden surge in demand for certain medicines necessary for specific treatments, which could lead to shortages.

In 2021, the EU network continuously monitored the supply of human and veterinary medicines in the EU and the impact of the increased production of COVID-19 medicines during the pandemic on the availability of other (non-COVID-19) medicines. In addition, the Agency has continuously monitored ongoing or anticipated shortages of medicines used to treat COVID-19 patients in intensive care units (ICUs) through the industry single points of contact known as 'i-SPOCs'. Information received from the i-SPOCs has been shared with the steering group for decision-making, when needed.

In June 2021, the EU Executive Steering Group on Shortages of Medicines Caused by Major Events adopted a reflection paper with recommendations to support forecasting of demand for human medicines across the EU in exceptional situations like the COVID-19 pandemic. The reflection paper is publicly available.

The document built on the experience gained by EU authorities in 2020, during the first wave of the pandemic, and presented a common methodology to predict the demand for medicines for use in intensive care units.

The EU network also launched a pilot phase to forecast demand data for a small number of medicines (five medicines used in ICU setting), based on the principles and methodology described in the reflection paper. The pilot phase proved to be successful in demonstrating the practical implementation of the approach for forecasting demand data. In addition, the aggregated results from the pilot were robust and representative of the actual demand in the EU or the European Economic Area (EEA).

MARCH 15, 2021
EMA investigates a number of events of blood clots in people who had received Vaxzevria (previously COVID-19 Vaccine AstraZeneca), as previously reported.

MARCH 16, 2021
The evaluation is looking at the available data related to all thromboembolic events reported after vaccination with Vaxzevria (previously COVID-19 Vaccine AstraZeneca). National agencies are providing additional support to gather missing and incomplete information as quickly as possible, particularly where it relates to these unusual cases.

International collaboration

As Chair of the International Coalition of Medicines Regulatory Authorities (ICMRA), EMA led the global efforts to streamline and align regulatory requirements for medicine development and approval. Throughout 2021, EMA chaired or co-chaired a series of workshops and strategic meetings to exchange information, develop joint approaches and provide recommendations on key aspects of medicine development and benefit-risk evaluation during the pandemic.

In December 2020, EMA started to pilot the 'OPEN' initiative to increase international collaboration on the EU rolling review and evaluation of COVID-19 vaccines and therapeutics. Regulators from Australia, Canada, Japan, Switzerland and the World Health Organization (WHO) participated in the pilot under the terms of existing confidentiality arrangements.

In 2021, all the vaccines and therapeutics against COVID-19 approved in the EU were assessed under OPEN, and more are currently under review.

The discussions under OPEN aimed to actively engage international partners, allowing regulators to accelerate and align on decisions. Through its partnership with WHO, EMA also contributed to global health by breaking down regulatory barriers and facilitating access and equity for COVID-19 vaccines and therapeutics.

MARCH 18, 2021
EMA's safety committee (PRAC) concludes its preliminary review of a signal of blood clots in people vaccinated with Vaxzevria (previously COVID-19 Vaccine AstraZeneca).

MARCH 22, 2021
EMA reviews the evidence on the use of ivermectin for the prevention and treatment of COVID-19 and concludes that the available data do not support its use for COVID-19 outside well-designed clinical trials.

Key ICMRA actions and recommendations in 2021

- **19 Jan**: Highlight the key role of healthcare professionals in strengthening confidence in COVID-19 vaccines: https://www.ema.europa.eu/en/news/global-regulators-highlight-key-role-healthcare-professionals-fostering-confidence-covid-19-vaccines.
- **8 Feb**: Agree to enhance collaboration on COVID-19 observational research: https://www.ema.europa.eu/en/news/international-regulators-working-together-enhance-collaboration-covid-19-observational-research.
- **25 Feb**: Propose alignment in three areas: responding to emerging COVID-19 virus variants; addressing knowledge gaps regarding COVID-19 vaccines and treatments in pregnant and breastfeeding women; and strengthening collaboration on safety monitoring of vaccines: https://www.ema.europa.eu/en/news/international-cooperation-align-approaches-regulation-covid-19-vaccines-medicines.
- **7 May**: Call for wider public access to clinical data: https://www.ema.europa.eu/en/news/international-regulators-who-call-wider-public-access-clinical-data.
- **11 June**: Publish a statement to boost trust in COVID-19 vaccines: https://www.ema.europa.eu/en/news/international-regulators-who-address-need-boost-covid-19-vaccine-confidence.
- **16 July**: Work towards alignment of regulatory processes for the development of new and adaptations of already-approved vaccines against COVID-19 variants: https://www.ema.europa.eu/en/news/international-regulators-work-towards-alignment-development-authorisation-second-generation-covid-19.
- **12 Oct**: Outline principles to increase manufacturing capacity during COVID-19: https://www.ema.europa.eu/en/news/global-approach-regulatory-flexibility-increase-manufacturing-capacity-during-covid-19.
- **10 Dec**: Urge researchers, the pharmaceutical industry, healthcare professionals, health research funding agencies and research institutions around the world to continue their focus on developing COVID-19 therapeutics: https://www.ema.europa.eu/en/news/international-regulators-stress-continued-need-covid-19-therapeutics.
- **13 Dec**: Publish reflections on the remote oversight of good clinical practice and good manufacturing practice during COVID-19: https://www.ema.europa.eu/en/news/international-regulators-reflections-remote-approaches-gcp-gmp-regulatory-oversight-during-covid-19.

MARCH 26, 2021
EMA's human medicines committee (CHMP) completes its review on the use of the monoclonal antibody regdanvimab (also known as CT-P59) to treat patients with COVID-19.

MARCH 26, 2021
EMA organises third public meeting to inform citizens on approval, safety and impact of COVID-19 vaccines in the EU.

MARCH 26, 2021
EMA's human medicines committee (CHMP) adopts several important recommendations that will increase manufacturing capacity and supply of COVID-19 vaccines in the EU.

Joint activities with ECDC

In 2021, EMA and the European Centre for Disease Prevention and Control (ECDC) kicked off a new initiative aimed at strengthening post-marketing monitoring of the safety, effectiveness and impact of COVID-19 vaccines in the EU and the EEA.

As part of this initiative, EMA and ECDC jointly coordinated and oversaw a number of observational studies funded from the EU budget and conducted in several European countries. In line with their respective mandates and in collaboration with EU/EEA countries, EMA led research on safety monitoring, and ECDC took the lead regarding studies on the effectiveness of the vaccines. Throughout the year, this work was supported by a Joint Advisory Board (JAB), composed of representatives of the European Commission, the EU/EEA National Immunisation Technical Advisory Groups (NITAGs)[2] collaboration organised by ECDC, members of the COVID-ETF, the CHMP and the PRAC. The JAB was established as a consultative body to advise on the prioritisation, design, conduct and interpretation of the independent post-authorisation observational studies. It provides guidance on operational aspects related to the implementation of these studies, as needed.

> ‘EMA and ECDC were ideally placed to coordinate such studies. In 2021, we worked very closely together to set up, execute and assess the data and we will continue to do so, alongside the European Commission and the Member States.’
>
> **Emer Cooke**, EMA’s Executive Director

As part of this collaboration, EMA and ECDC communicated regularly on the COVID-19 situation in the EU and made recommendations, among others, on the use of COVID-19 vaccine additional and booster doses. The expert recommendations published by the two EU Agencies were intended to help decision makers for national vaccination campaigns ensure that the maximum number of EU citizens were protected as quickly as possible against the virus.

As an example, EMA and ECDC reviewed available evidence and provided technical recommendations and advice on heterologous vaccination against COVID-19, either in the primary course or as a booster, to provide scientific grounds and flexibility to vaccination schemes.

[2] NITAGs have the role of making evidence-based recommendations to Member States to support national decisions around vaccines and their use.

MARCH 29, 2021
EMA convenes an ad hoc expert group meeting to provide further input into the ongoing assessment of very rare cases of unusual blood clots associated with low numbers of platelets.

APRIL 07, 2021
EMA’s safety committee (PRAC) concludes that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria. EMA confirms that the overall benefit-risk remains positive.

Lessons learned from the COVID-19 response

EMA and the European medicines regulatory network introduced a variety of measures and regulatory flexibilities as part of their response to the COVID-19 crisis. A lessons-learned exercise was initiated in 2021, and although this is still ongoing, several learnings have already emerged as important elements, some of which will be implemented as part of EMA's extended mandate:

- Provide rapid and coordinated feedback to medicine developers during a crisis.
- Establish a mechanism and resources to ensure sustainability of the COVID-ETF for future crisis preparedness.
- Establish a mechanism to enable rapid advice and approval of large, well-designed trials, to avoid fragmentation in clinical research.
- Establish pan-European research investigator networks with effective infrastructural support, to enable large trials by public research bodies or industry.
- Improve collection, coordination and analysis of health data across the EU.
- Enhance data analytics to support public confidence in the regulatory supervision of vaccines and therapeutics.
- Invest in real-world evidence to complement evidence from clinical trials.
- Reflect on the need to establish a framework on the use of labelling and serialisation flexibilities in public health emergencies.
- Support research to define optimal tools for risk communication and data visualisation.
- Strengthen collaboration and communication with ECDC, national public authorities and the NITAGs, who are national experts advising on vaccination programmes coordinated by ECDC.
- Strengthen international collaboration and explore ways to increase harmonisation and speed of data sharing.
- Coordinate and support Members States' activities in preventing and mitigating supply disruptions of critical medicines during crises.
- Support EU-level coordination and scientific, technical and clinical evaluation of certain medical devices and in-vitro diagnostics during emerging health threats.

APRIL 14, 2021
EMA's safety committee (PRAC) is reviewing very rare cases of unusual blood clots that occurred in the United States following the use of Janssen's COVID-19 vaccine.

APRIL 15, 2021
EMA is reviewing available data on the use of the monoclonal antibody VIR-7831 (also known as GSK4182136) in the treatment of patients with COVID-19. EMA is starting this review to support national authorities who may decide on the use of this medicine for COVID-19 prior to marketing authorisation.

Read more about EMA's response to the COVID-19 pandemic in these papers:

- Cavalieri M., Enzmann H., Straus S., Cooke E., The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines, The Lancet, 2021 January 13, doi: 10.1016/S0140-6736(21)00085-4
- Cavaleri M., Sweeney F., Gonzalez-Quevedo R., Carr M., Shaping EU medicines regulation in the post COVID-19 era, The Lancet Regional Health Europe, 2021 October 1, doi: 10.1016/j.lanepe.2021.100192

APRIL 19, 2021
EMA and Heads of Medicines Agencies (HMA) organise a joint workshop on AI in medicines regulation.

APRIL 20, 2021
EMA's safety committee (PRAC) concludes that a warning about unusual blood clots with low blood platelets should be added to the product information for COVID-19 Vaccine Janssen. The PRAC also concludes that these events should be listed as very rare side effects of the vaccine. EMA confirms overall benefit-risk remains positive.

CHAPTER 1

KEY ACHIEVEMENTS IN 2021

EVALUATION AND MONITORING OF MEDICINES: HIGHLIGHTS

Human medicines

Medicines recommended for approval

Authorisation of new medicines is essential to advancing public health as they bring new opportunities to treat certain diseases. In 2021, EMA recommended 92 medicines for marketing authorisation. Below is a selection of medicines approved in 2021 that represent significant progress in their therapeutic areas:

Abecma, the first cell-based gene therapy to treat adults with relapsed and refractory multiple myeloma who have received at least three previous therapies and whose cancer has worsened since receiving the last treatment.

Bylvay, the first treatment for progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

Enspryng, a treatment for neuromyelitis optica spectrum disorders (NMOSD) in patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

Evrysdi, the first oral treatment for patients with certain types of spinal muscular atrophy, a rare and often fatal genetic disease that causes muscle weakness and progressive loss of movement.

Imcivree, for the treatment of obesity and the control of hunger associated with genetic deficiencies of the melanocortin 4 receptor (MC4R) pathway.

Tavneos, a first-in-class medicine to treat adults with severe, active granulomatosis with polyangiitis or microscopic polyangiitis, a rare type of inflammation of the blood vessels.

Trodelvy, a first-in-class medicine to treat adults with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for advanced disease.

Voxzogo, to treat achondroplasia in patients two years of age and above whose epiphyses are not closed. Achondroplasia is a condition that impairs bone growth and causes dwarfism.

Spikevax, **Vaxzevria**, **COVID-19 Janssen vaccine** and **Nuvaxovid** – four vaccines for preventing COVID-19.

Regkirona, **Ronapreve** and **Xevudy** - three treatments for COVID-19.

APRIL 21, 2021
EMA's Management Board confirms that the clinical trial EU Portal and Database, one of the main deliverables of the Clinical Trial Regulation and the key component of the Clinical Trial Information System (CTIS), is now fully functional and on track to go live by 31 January 2022.

APRIL 23, 2021
Analysis of data on Vaxzevria (formerly COVID-19 vaccine AstraZeneca) puts risks of very rare blood clots in the context of benefits for different age groups and different rates of infection inform national decisions on vaccine roll-out.

EARLY ACCESS TO MEDICINES THAT ADDRESS PUBLIC HEALTH NEEDS

In 2021, **three medicines** received a recommendation for marketing authorisation following an **accelerated assessment**: **Bylvay**, **Evrysdi** and **Trodelvy**. This mechanism is reserved for medicines that are able to address unmet medical needs. It allows for faster assessment of eligible medicines by EMA's scientific committees (within a maximum of 150 days rather than 210 days).

The **four vaccines and three treatments for COVID-19** recommended for authorisation by EMA in 2021 were assessed under a rolling review – EMA can use this regulatory pathway during a pandemic to speed up the evaluation of medicines by assessing data as they become available from ongoing studies.

13 medicines received a recommendation for a **conditional marketing authorisation (CMA)**, one of the possibilities in the EU to give patients early access to new medicines: **Abecma**, **COVID-19 Janssen vaccine, Gavreto, Jemperli**, **Koselugo**, **Lumykras**, **Minjuvi**, **Nexpovio**, **Nuvaxovid**, **Pemazyre**, **Rybrevant**, **Spikevax**, **Vaxzevria**.

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) because the benefit of earlier patient access outweighs the potential risks of limited data. These authorisations are subject to specific obligations to generate complete data on the medicines after the authorisation.

Four medicines (**Bylvay**, **Evkeeza**, **Tecovirimat SIGA** and **Voraxaze**) were authorised under exceptional circumstances, a route that allows patient access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with 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. These medicines are subject to specific post-authorisation obligations and monitoring.

The enhanced development support provided by EMA's PRIority Medicines (PRIME) scheme aims at helping patients to benefit as early as possible from promising medicines that target an unmet medical need, by optimising the generation of robust data and enabling accelerated assessment. This year, **six medicines with PRIME designation** were recommended for approval (**Abecma**, **Bylvay**, **Evrysdi**, **Imcivree**, **Oxbryta** and **Skysona**[3]).

14 medicines under development were included in the scheme in 2021 in five medical specialties: oncology (6), neurology (3), haematology-haemostaseology (2), immunology-rheumatology-transplantation (2), and endocrinology-gynaecology-fertility-metabolism (1).

[3] The marketing authorisation has been withdrawn at the request of the marketing authorisation holder.

APRIL 26, 2021
The European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) kick off a new initiative aimed at strengthening post-marketing monitoring of the safety, effectiveness and impact of COVID-19 vaccines in the EU and the EEA.

APRIL 29, 2021
EMA starts evaluating an application to extend the use of Olumiant (baricitinib) to include treatment of COVID-19 in hospitalised patients from 10 years of age who require supplemental oxygen.

MEDICINES FOR RARE DISEASES

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.

Orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) at the time of approval to determine whether the information available to date allows maintaining the medicine's orphan status and granting the medicine ten years of market exclusivity. Among the 92 medicines recommended for marketing authorisation in 2021, **19 had orphan designation confirmed** by the end of the year.

At the time of marketing authorisation, the status of designated orphan medicines is reviewed. In 2021, the following six applications lost their orphan status before receiving marketing authorisation, which means they were still authorised but not as orphan medicinal products: **Brukinsa**, **Copiktra**, **Efmody**, **Nexpovio**, **Orladeyo** and **Sibnayal**. More information can be found in the COMP monthly reports.

NEW USES FOR EXISTING MEDICINES

89 extensions of indication were recommended in 2021. 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. Extensions of indication included:

Benlysta, the first centrally approved medicine for the treatment of active lupus nephritis.

Forxiga, to include the treatment of type 2 diabetes in children from 10 years of age whose condition is not controlled well enough.

Nucala, to include an add-on treatment for: i) relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis in patients aged 6 years and older; ii) inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause in adults; and iii) with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyps for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Saxenda, as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescents from the age of 12 years and above with obesity and body weight above 60 kg.

Volibris, to include the treatment of pulmonary arterial hypertension (PAH) in adolescents and children (aged 8 to less than 18 years).

RoActemra and **Kineret**, to include treatment of adults with COVID-19.

MAY 03, 2021
EMA starts evaluating an application to extend the use of the COVID-19 vaccine Comirnaty to include young people aged 12 to 15.

MAY 04, 2021
EMA's human medicines committee (CHMP) starts a rolling review of COVID-19 Vaccine (Vero Cell) Inactivated, developed by Sinovac.

NEGATIVE OPINIONS

The CHMP adopted a **negative opinion for five medicines** in 2021: **Aduhelm**, **Flynpovi**, **Ipique**, **Nouryant** and **Raylumis**.

When the Committee cannot reach an agreement on a positive benefit-risk balance, it issues a negative opinion on the marketing authorisation application and elaborates on the grounds for this opinion. Applicants have the right to request a re-examination of the negative opinion within 15 days of receipt of the notification.

87% of all opinions (positive and negative) **were reached by consensus** among the 27 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.

71% of applicants who were granted a positive opinion for their medicine had received scientific advice or protocol assistance 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. This encourages generation of more robust data for regulatory assessment, and thus protects patients from taking part in unnecessary or poorly designed clinical trials.

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MAY 06, 2021
EMA, the European Commission's DG Sante, and ANVISA Brazil sign a confidentiality arrangement, allowing the exchange of non-public information to enhance cooperation for the benefit of public health.

MAY 07, 2021
EMA's human medicines committee (CHMP) starts a rolling review of data on sotrovimab (also known as VIR-7831 and GSK4182136), a monoclonal antibody.

Keeping patients 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 the quality, safety and benefit-risk balance of the medicine used in clinical practice. This is to optimise how the medicine is used by patients to achieve its full benefit and to protect patients from avoidable side effects. Regulatory measures range from a change to the product information to the suspension or withdrawal of a medicine or recall of a limited number of batches.

Important new safety advice issued in 2021 included[4]:

- Recommended actions to minimise the risk of acute adrenal insufficiency in children that may occur when switching from conventional oral hydrocortisone formulations to **Alkindi** granules, due to potential inaccurate dosing with other oral hydrocortisone formulations.
- Update of the product information of **immune checkpoint inhibitors** (Tecentriq, Bavencio, Libtayo, Imfinzi, Yervoy, Keytruda, Opdivo) to include a class effect of immune-mediated, non-infectious cystitis.
- Update of the product information and EU reminder card of **infliximab** (Remicade and biosimilars) to include stricter recommendations on the administration of live vaccines to infants breastfed by mothers receiving infliximab due to infant exposure via breast feeding or during pregnancy.
- Update of product information of **Invanz** to consider discontinuation of treatment if Invanz-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness). Patients with renal impairment are at higher risk of Invanz-induced encephalopathy and the resolution may be prolonged.
- Update of product information of **Kadcyla** to include new recommendations and measures to closely monitor the infusion site for possible subcutaneous infiltration during drug administration, as cases of delayed epidermal injury or necrosis following extravasation have been observed.
- Update of the product information of **Ifosfamide solutions** to provide further details on the characteristics and risk factors of ifosfamide-induced encephalopathy, as well as highlighting the need to closely monitor patients receiving these medicines.

[4] Safety advice on treatments and vaccines for COVID-19 are included in the 'European Medicines Regulatory Network's response to COVID-19' section.

MAY 07, 2021

The International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO) urge pharmaceutical companies to publish clinical trial reports for new medicines and vaccines without redactions to ensure that research results are publicly accessible to all those involved in healthcare decision-making.

MAY 17, 2021

EMA's human medicines committee (CHMP) recommends a change to the approved storage conditions of Comirnaty, the COVID-19 vaccine developed by BioNTech and Pfizer. Stored in a fridge at 2-8°C, the vaccine can be kept for up to 31 days, instead of 5 days.

- Update of the product information of **Kineret** and **Ilaris** with recommendations and warnings on adverse drug reactions with eosinophilia and systemic symptoms (DRESS) predominantly in patients with systemic juvenile idiopathic arthritis (sJIA).
- Update of the product information of **Venclyxto** to include new recommendations and measures for the mitigation of the risk of tumour lysis syndrome (a serious complication with rapid break down of cancer cells).
- New recommendation to only use **Xeljanz** in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors and patients with other malignancy risk factors when no suitable treatment alternative is available.

The product information for 502 centrally authorised medicines was updated on the basis of new safety data in 2021. Every year, PRAC recommendations on safety warnings are also 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 INTEGRITY OF CLINICAL TRIAL CONDUCT AND THE MANUFACTURE AND SUPPLY OF MEDICINES

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

The identification by marketing authorisation holders of active substances and finished products at risk of N-**nitrosamine** formation or (cross-) contamination was completed. All human chemical and biological products for which a potential risk of nitrosamine contamination was identified are undergoing confirmatory testing. This applies to 16% of chemical and 1% of biological centrally authorised products (CAPs). Results are expected by September 2022 and July 2023, respectively. In March 2021, the European medicines regulatory network established the **Nitrosamine Implementation Oversight Group (NIOG)** to oversee the implementation of the CHMP's Article 5(3) opinion on nitrosamines in human medicines. The group includes representatives from the CHMP, the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), EMA working parties, the European Directorate for the Quality of Medicines and HealthCare (EDQM) and EMA staff. It also acts as the main interface for pharmaceutical industry stakeholders to discuss regulatory and scientific developments on nitrosamines with EMA and the European medicines regulatory network.

MAY 21, 2021

EMA's human medicines committee (CHMP) completes its review on the use of the monoclonal antibody sotrovimab to treat patients with COVID-19.

The Agency concludes that sotrovimab can be used to treat confirmed COVID-19 in adults and adolescents (aged 12 years and above and weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe COVID-19.

Throughout 2021, EMA continued to contribute to the **Nitrosamines International Steering Group (NISG)** and the **Nitrosamine International Technical Working Group (NITWG)**. The Agency shared information on substances at risk of containing nitrosamine impurities and discussed the approach for ensuring the safety and quality of such medicines. This also includes agreement on acceptable intake limits, or testing approaches. NISG was created in 2018 when the first case of presence of nitrosamines in sartan medicines was identified. The members of NISG and NITWG are: Australia, Brazil, Canada, Japan, Singapore, Switzerland, the United States of America, the EDQM, the World Health Organisation and EMA.

A system was put in place to ensure patient safety whilst avoiding shortages of critical medicines. A Nitrosamine Multidisciplinary Expert Group (NMEG) proposed interim safe limits for a limited duration of time whilst marketing authorisation holders (MAHs) implement their corrective and preventive actions. This system has facilitated the successful management of nitrosamine levels in **metformin and rifampicin**. Official medicines control laboratories (OMCLs) have tested products containing these active substances in order to independently evaluate the quality of distributed medicines.

EMA's CHMP carried out a review of the presence of a nitrosamine impurity, N nitroso-varenicline, in **Champix** (varenicline), a smoking cessation medicine. The CHMP concluded that the marketing authorisation holder has to fulfil certain quality requirements to ensure that Champix conforms to acceptable nitrosamine intake limits for EU medicines, calculated in line with the ICH M7 guideline. As a precaution, the marketing authorisation holder recalled several batches and paused distribution of Champix, as of June 2021.

Read more about the EU's regulatory response to nitrosamine impurities:

- Ruepp R, Frötschl R, Bream R, Filancia M, Girard T, Spinei A, Weise M and Whomsley R (2021) The EU Response to the Presence of Nitrosamine Impurities in Medicines. Front. Med. 8:782536. doi: 10.3389/fmed.2021.782536

MAY 27, 2021
EMA's COVID-19 taskforce (COVID-ETF) advises healthcare professionals that there is currently insufficient evidence that inhaled corticosteroids are beneficial for people with COVID-19.

MAY 28, 2021
EMA's human medicines committee (CHMP) recommends granting an extension of indication for the COVID-19 vaccine Comirnaty to include use in children aged 12 to 15.

JUNE 01, 2021
EMA and the European Network for Health Technology Assessment (EUnetHTA) publish a report on their achievements since 2017.

Veterinary medicines

New medicines to benefit animal health in Europe

In 2021, EMA recommended 12 veterinary medicines for marketing authorisation; seven of these contain a new active substance (i.e. not previously authorised in the EU). Among the 12 medicines recommended for marketing authorisation, five were vaccines. Of these, four were biotechnological vaccines.

A SELECTION OF KEY RECOMMENDATIONS IN 2021:

Fatrovax RHD, a new vaccine used to reduce mortality and signs of rabbit haemorrhagic disease (RHD). The active substances are obtained by means of biotechnology using *Trichoplusia ni pupae*, avoiding the use of rabbits in the production of the vaccine. This is in line with the so-called 3R principles (replace, reduce and refine animal use for the development, manufacturing and testing of medicines).

Felpreva, a new veterinary medicine for cats with, or at risk from, mixed parasitic infestations.

Strangvac, a vaccine given to horses from 8 months of age to reduce clinical signs of the acute stage of strangles.

Suiseng Diff/A, a new vaccine given to female pigs to protect their offspring from intestinal disease caused by toxins produced by the bacteria *Clostridioides difficile* (toxins A and B) and *Clostridium perfringens* type A (alpha toxin). This vaccine has the potential to reduce the need for antimicrobial treatment in animals and could therefore limit the development of antimicrobial resistance (AMR).

Fatrovax RHD, Felpreva and Strangvac 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 under current market conditions.

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JUNE 01, 2021
Virtual event on Big Data changing the focus from treating animals to preventing disease.

JUNE 03, 2021
The EU Executive Steering Group on Shortages of Medicines Caused by Major Events adopts a reflection paper which contains recommendations to support forecasting of demand for human medicinal products across the EU and also at the national level in exceptional situations like the COVID-19 pandemic, whenever such activity is undertaken.

Optimising the safe and effective use of veterinary medicines

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

IMPORTANT NEW SAFETY ADVICE ISSUED IN 2021

The product information for 27 medicines was updated on the basis of new safety data. The revised information is expected to help animal owners and healthcare professionals to make informed decisions when using or prescribing a medicine. This included:

- Addition of further information in the package leaflet on potential side effects following the administration of:
  - **Advocate spot-on solution for dogs**: ataxia (inability to co-ordinate muscle movements); muscle tremor (shaking);
  - **Bravecto spot-on solution for cats**: convulsions;
  - **Bravecto Plus**: ataxia;
  - **Cerenia tablets for dogs**: lethargy (lack of energy);
  - **Cerenia injection for solution for dogs and cats**: lethargy;
  - **Comfortis**: ataxia in cats; muscle tremor in cats;
  - **Cytopoint**: injection-site pain; injection-site swelling; immune-mediated diseases, such as haemolytic anaemia (excessive breakdown of red blood cells) or thrombocytopenia (low blood platelet counts, which can lead to bleeding and bruising);
  - **Felisecto Plus**: convulsions; ataxia; emesis (vomiting); diarrhoea;
  - **Fevaxyn Pentofel**: haematemesis (vomiting of blood); diarrhoea with bleeding;
  - **Galliprant**: elevated liver enzymes; elevated blood urea nitrogen (a marker for liver and kidney problems); elevated creatinine;
  - **Kriptazen**: diarrhoea (change of frequency from "very rare" to "rare");
  - **Letifend**: hypersensitivity reactions, such as anaphylaxis and skin manifestations, including oedema (swelling), urticaria (itchy rash), pruritus (itching);

JUNE 04, 2021
At the 6th ICMRA workshop on observational research, medicines regulators from around the globe discuss the importance of global collaboration on real-world evidence for regulatory decision-making on COVID-19 treatments and vaccines.

JUNE 07, 2021
EMA's COVID-ETF advises healthcare professionals in the EU to consider recommendations by learned societies when assessing people with signs and symptoms of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria and COVID-19 Vaccine Janssen.

- **Librela**: allergic reactions;
- **Osurnia**: application-site reactions, such as erythema (reddening of the skin), pain, pruritus, oedema and ulcer; hypersensitivity reactions, including facial oedema, urticaria and shock;
- **Prevomax**: lethargy;
- **Purevax RC**: emesis;
- **Purevax RCP**: emesis;
- **Purevax RCP FeLV**: emesis;
- **Purevax RCPCh**: emesis;
- **Purevax RCPCh FeLV**: emesis;
- **Simparica Trio**: vomiting; diarrhoea; lethargy, anorexia/inappetence; tremor; ataxia; convulsion;
- **Stronghold Plus**: convulsions; ataxia; emesis; diarrhoea;
- **Ubac**: anaphylactic-type reactions (sudden, severe allergic reactions), such as oedema;
- **Vectra Felis**: muscle tremors; lethargy;
- **Vectra 3D**: convulsions;
- **Vepured**: emesis; recumbency (inability to stand due to loss of consciousness, pain or inability to control the body); convulsions; lethargy; loss of consciousness;

- Addition of new special precautions to be taken by the person administering the following veterinary medicines to animals:
  - **Draxxin**: reddening of the skin (erythema) and/or dermatitis as a result of contact with the medicine. If there is suspicion of an allergic reaction following accidental exposure (recognised by itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting, etc.), appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.
  - **Kexxtone**: keep dogs away from treated animals. Accidental ingestion of active ingredient by dogs has resulted in fatal consequences. In case of suspected ingestion by dogs, seek veterinary advice immediately.
  - **Vectra 3D**: pregnant women and women suspected of being pregnant should not administer the product and should avoid direct contact with the application site until the application site is no longer noticeable.

JUNE 08, 2021
EMA starts evaluating an application to extend the use of the COVID-19 Vaccine Moderna to include young people aged 12 to 17.

JUNE 11, 2021
The International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO) jointly develop a statement to help healthcare professionals increase trust and confidence in COVID-19 vaccines and answer questions from patients about the development, regulatory review and safety monitoring of these vaccines.

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 limits (MRLs) recommended by EMA reflect the level of residues of the veterinary medicine in food derived from a treated animal that can be considered safe for consumption. The MRL is established before the medicine for food-producing animals is authorised in the EU.

In 2021, positive opinions were adopted recommending the establishment of MRLs for the following active substances:

- **Bambermycin** in poultry tissues;
- **Toltrazuril** in poultry eggs.

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

JUNE 11, 2021
EMA's safety committee (PRAC) concludes that people who have previously had capillary leak syndrome must not be vaccinated with Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).

JUNE 11, 2021
EMA's committee for human medicines (CHMP) approves a new manufacturing site for the production of Moderna COVID-19 vaccine finished product.

JUNE 22, 2021
EMA's committee for human medicines (CHMP) approves additional manufacturing sites for the production of Comirnaty, the COVID-19 vaccine developed by BioNTech and Pfizer.

REGULATION OF VETERINARY MEDICINES

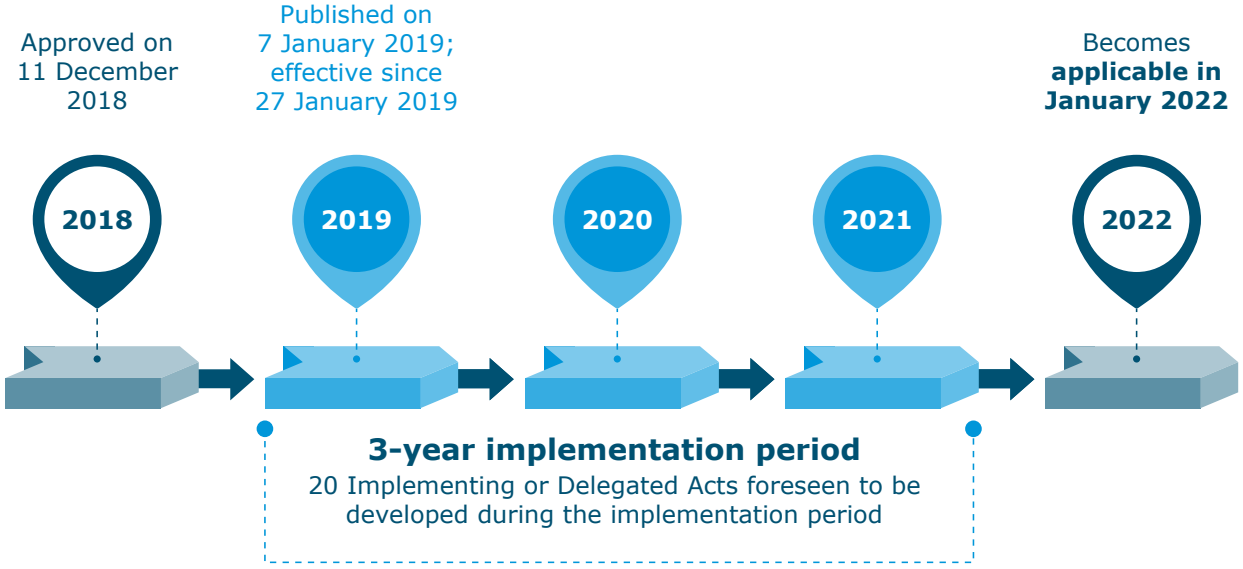
Preparing for the implementation of the Veterinary Medicinal Products Regulation

The implementation of the Veterinary Medicinal Products Regulation is the culmination of a process that started in 2018. EMA is responsible for coordinating and facilitating the work of the European medicines network on the implementation of the new legislation.

During the lead-up to the entering into application of the new Regulation, EMA revised procedures as well as regulatory and scientific guidance documents, to take account of the new rules. This was achieved through an open, constructive dialogue with the European Commission, national competent authorities and stakeholders on the practical implications of the new obligations and procedures. These regular meetings and exchanges with Member States and stakeholders also helped to prepare them for the changes brought by the Regulation at all levels.

2021 was a year in which the Agency reached many milestones that were needed for the new Regulation to become applicable on 28 January 2022.

Timeline



JUNE 25, 2021
EMA's committee for human medicines (CHMP) approves an additional manufacturing site for the production of COVID-19 Vaccine Janssen.

JUNE 28, 2021
EMA publishes a report highlighting the Agency's support for micro, small and medium-sized enterprises (SMEs) which develop and market medicines for human or veterinary use in the EU. The report covers the period from 2016 to 2020.

Development of new processes and IT systems required by the Veterinary Medicinal Products Regulation

The Regulation calls for the establishment of a number of databases at EU level. EMA has led the development and implementation of the information technology systems required by the Regulation:

- Union Product Database (UPD)
- Union Pharmacovigilance Database (EVV)
- Manufacturing and Wholesale Distribution Database (MWD)
- Antimicrobials Sales and Use data (ASU)

The Union Product Database (UPD) project was established at the start of 2020 to ensure timely implementation of the requirements arising from the new Regulation. It gathers information on all veterinary medicines authorised in EU/EEA countries and will enable some post-authorisation procedures. One of the main priorities for 2021 was the submission of legacy data on veterinary medicinal products already authorised in the EU into the UPD which started during the summer. Timely delivery of the UPD components to enable submission was pivotal to achieve this goal. The Implementation Guide on veterinary medicines product data was finalised in June. After July, EMA's efforts focused on providing support to national competent authorities (NCAs) for their upload of legacy data into the UPD. Weekly support sessions addressing practical questions and issues encountered while submitting data into the UPD were organised for all NCAs, as well as a tailored coaching programme to help NCAs to use the web user interface. By December 2021, 26,458 products had already been entered into the UPD. In parallel, the Agency developed the Veterinary Medicines information website, the public face of the UPD, which is the go-to source of information on all veterinary medicines in the EU/EEA.

The Union Pharmacovigilance Database (EVV) was developed as an enhanced and upgraded EudraVigilance Veterinary (EVVet3) system for the exchange and processing of suspected adverse reaction reports related to veterinary medicines authorised in the EEA. In January 2021, the Product Owners Group was expanded to include representatives from the veterinary pharmaceutical industry, ensuring that the views and needs of all relevant stakeholders are represented. An access policy was presented during the June 2021 meeting of the EMA Management Board and subsequently published on the EMA website. In September, the Project Group approved the final requirements for the recording of pharmacovigilance inspection outcomes and for signal management.

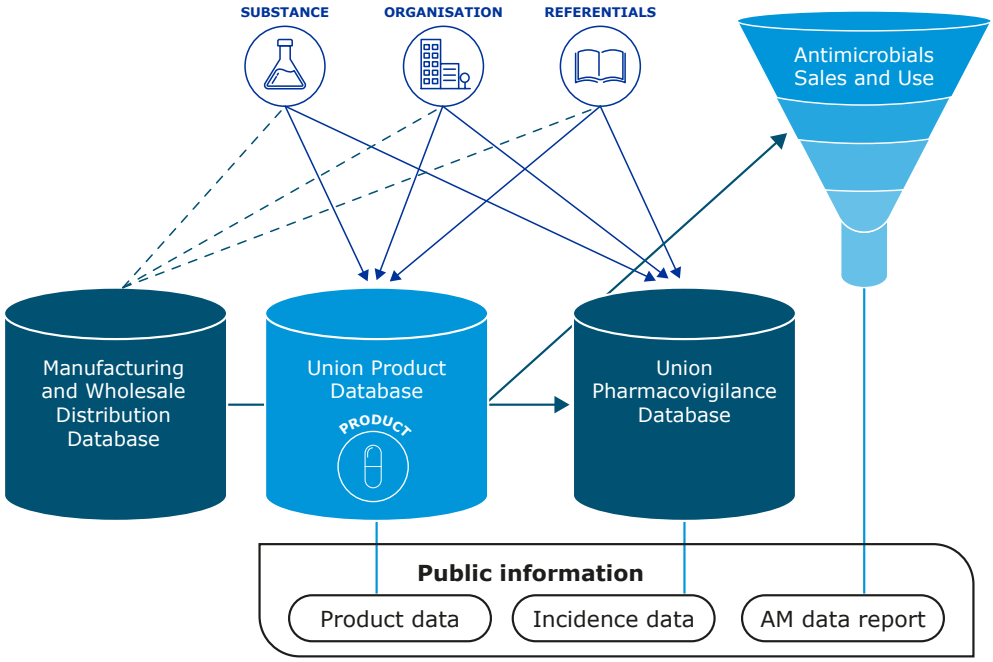
JUNE 30, 2021
Use of antibiotics has decreased and is now lower in food-producing animals than in humans, says the latest report published by the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).

JUNE 30, 2021
EMA's Deputy Executive Director Noël Wathion retires from the Agency, after 25 years of service.

Development of the **Manufacturers and Wholesale Distributors database (MWD)** started in July 2021 after the approval of the project vision and the finalisation of the detailed requirements. Most of the legislative requirements outlined by the new Regulation were covered by the existing EudraGMDP system, the EU database of manufacturing authorisations and certificates of good manufacturing practice. However, the existing system required some functionality extensions for full compliance. Four modules of EudraGMDP were impacted. EMA organised a first demonstration of the system under development to NCAs in September 2021. Webinars were held in October 2021 to support preparedness of NCAs and industry.

The new legislation also puts in place a range of measures to limit the development of AMR. At the heart of these efforts is the Collection of **Antimicrobial Sales and Use data (ASU)** project, which started in 2021. The ASU Project Group approved the final business case, project vision and implementation timeline throughout the year, and started working on gathering detailed requirements. In December, EMA and the Collection of ASU Project Group introduced the project to the members of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) network. This was the first of a series of meetings to update NCAs on the project progress and prepare them for the data submission expected to start in 2023. The Agency also published guidance and Q&As for marketing authorisation holders on how to submit data on the volume of sales.

Veterinary Medicines Regulation - IT systems



JULY 02, 2021
EMA's committee for human medicines (CHMP) approves a scale-up of the active substance manufacturing process at Janssen Biologics B.V. The plant, which is located in Leiden, the Netherlands, produces all active substance for the manufacture of the EU supply of COVID-19 Vaccine Janssen.

JULY 09, 2021
EMA's safety committee (PRAC) concludes that myocarditis and pericarditis can occur in very rare cases following vaccination with the COVID-19 vaccines Comirnaty and Spikevax (previously COVID-19 Vaccine Moderna).

Veterinary limited markets

In March 2021, EMA released the eleventh report on the MUMS and limited markets scheme for veterinary medicines. The report concluded that the scheme has been successful in terms of incentivising the submission of requests for classification of products as MUMS/limited market, resulting in new veterinary medicines becoming available to treat minor animal species and uncommon diseases in major animal species. Building on the success of EMA's experience applying this policy over the last ten years, the new veterinary regulation introduced specific provisions in the EU legislation to boost the development of new medicines for limited markets. In 2021, EMA issued several guidelines to replace those applicable under EMA's MUMS/limited market policy and to help applicants to consider the criteria for eligibility of products for a limited market authorisation and benefit from reduced data requirements introduced by the new Regulation.

JULY 09, 2021
EMA's safety committee (PRAC) recommends that people who have previously had capillary leak syndrome must not be vaccinated with COVID-19 Vaccine Janssen.

JULY 14, 2021
Joint EMA-ECDC statement on the current COVID-19 situation and urging EU citizens to get vaccinated and to complete their vaccination courses.

JULY 16, 2021
International regulators work towards alignment on development and authorisation of new or modified COVID-19 vaccines to address emerging coronavirus variants.

A new international standard format for reporting adverse events

With the implementation of the Union Pharmacovigilance Database, the data format previously used has been replaced by the pharmacovigilance reporting standards developed by the Veterinary International Conference on Harmonization (VICH). In October 2021, EMA released the EU adverse event report (VICH) implementation guide. This document aims to support stakeholders in the implementation of the Regulation on veterinary medicinal products, by providing guidance on the technical specifications and the process of transmission of adverse event reports (AERs). It is targeted at all stakeholders responsible for submitting AERs electronically to the Union Pharmacovigilance Database. It describes the rules that stakeholders must follow to ensure successful electronic communication between their own systems and EudraVigilance Veterinary (EVV).

JULY 19, 2021
EMA starts evaluating an application to extend the use of Kineret (anakinra) to include treatment of COVID-19 in adult patients with pneumonia who are at risk of developing severe respiratory failure (inability of the lungs to work properly).

JULY 20, 2021
EMA's human medicines committee (CHMP) starts a rolling review of Vidprevtyn, a COVID-19 vaccine developed by Sanofi Pasteur.

FIGHTING ANTIMICROBIAL RESISTANCE

AMR is a global threat to animal and human health that requires coordinated action across all government sectors and society. It threatens the effective treatment of infections caused by an ever-increasing range of bacteria and other microorganisms that have become resistant to available treatments. Tackling AMR continued to be a high priority for EMA and the European medicines regulatory network in 2021.

EMA supports a '**One Health' approach**, promoting close and integrated cooperation between the human and veterinary fields.

Responsible use of antimicrobials in animals

In January 2021, EMA's committee for veterinary medicines (CVMP) adopted a strategy on antimicrobials for 2021-2025. The strategy aims to secure the availability of effective antimicrobial medicines for the treatment of serious infectious diseases in animals, while minimising the risks to animals or people emerging from their use. It provides a status report on ongoing activities on antimicrobials and sets out proposed actions for the CVMP during the next 5 years.

The CVMP strategy on antimicrobials will deliver provisions in the Veterinary Medicines Regulation (Regulation (EU) 2019/6) that derive from the European 'One Health' action plan against antimicrobial resistance. The new Veterinary Medicines Regulation aims to increase the availability and safety of veterinary medicines, promotes responsible use of antimicrobials in animals and enhances EU action against antimicrobial resistance.

> 'Antimicrobial resistance is a silent pandemic that could have disastrous consequences for modern medicine. We need to act now to preserve antibiotics. At EMA, our experts are working relentlessly to ensure that effective antibiotics against infectious diseases in people and animals remain available to everyone in the EU.'
>
> **Emer Cooke**, EMA's Executive Director

JULY 22, 2021
Following an EMA review, Guillain Barré syndrome is listed as a very rare side effect for COVID-19 Vaccine Janssen.

JULY 23, 2021
EMA's human medicines committee (CHMP) recommends granting an extension of indication for the COVID-19 vaccine Spikevax (previously COVID-19 Vaccine Moderna) to include use in children aged 12 to 17 years.

Decrease in sales of veterinary antimicrobials

European countries have substantially reduced the use of antimicrobials in animals according to the annual **ESVAC report**, published by EMA in November 2021 and reporting data for 30 countries from the EEA and Switzerland. Data from the 25 countries that provided input for the full 2011-2020 period showed overall sales of veterinary antimicrobials in European countries were 43% lower in 2020 than in 2011. While an increase of 6% in overall sales for the 25 countries in 2020 compared to 2019 was registered, data for the next years are necessary to better understand this observation.

Sales of those antimicrobials that are considered critically important for use in humans noticeably decreased between 2011 and 2020 and accounted for only 6% of total sales in 2020.

Scientists, veterinarians and other animal healthcare professionals, risk assessors and policy makers in Member States use the results of the annual ESVAC report as a reference for antimicrobial policies and for guidance on the responsible use of antimicrobials. Under the new Veterinary Medicines Regulation, reporting data on sales and use of antimicrobials in animals will become a legal obligation for EU Member States and the Agency from 2023.

> ‘The decrease in sales of antimicrobials for use in animals over ten years shows that EU policy initiatives combined with guidance and national campaigns promoting prudent use of antimicrobials in animals are having a positive effect.’
>
> **Ivo Claassen**, EMA’s Deputy Executive Director and Head of Veterinary Medicines Division

JULY 30, 2021
EMA’s human medicines committee (CHMP) approves a scale-up of the active substance production process at Moderna’s COVID-19 vaccine manufacturing sites in the United States.

AUGUST 04, 2021
With the increasing circulation of the Delta variant of SARS-CoV-2 in EU/EEA countries, EMA and the European Centre for Disease Prevention and Control (ECDC) strongly encourage those who are eligible for vaccination but have not yet been vaccinated to start and complete the recommended COVID-19 vaccination schedule in a timely manner.

Joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) report

In June 2021, EMA, the European Food Safety Authority (EFSA) and ECDC published the third **JIACRA report**, which presented data on antibiotic consumption and development of AMR in Europe for 2016-2018. The report highlighted that the use of antibiotics has decreased and is now lower in food-producing animals than in humans.

The significant fall in antibiotic use in food-producing animals suggested that the measures taken at country level to reduce use are proving to be effective. However, the report also showed that the picture in the EU is diverse as the situation varied significantly by country and by antibiotic class.

AUGUST 06, 2021
EMA endorses recommendations developed by the International Coalition of Medicines Regulatory Authorities (ICMRA) to facilitate the use of track and trace systems at the global level.

AUGUST 16, 2021
The International Coalition of Medicines Regulatory Authorities (ICMRA) sets out recommendations to help regulators to address the challenges that the use of AI poses for global medicines regulation.

Supporting the international fight against AMR

EMA continued to work with its EU and international partners on a number of initiatives aiming to address the global public health problem of AMR. In 2021, these included contributing to the ICMRA campaign during World Antimicrobial Awareness Week in November and other global initiatives to combat antibiotic resistance, such as the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR).

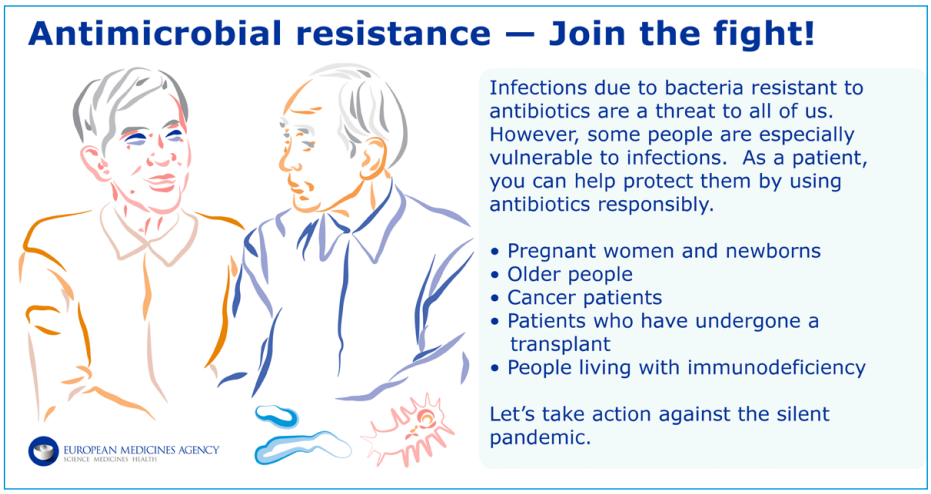
The progress of TATFAR and its achievements in tackling AMR were reviewed at a conference held on 14-15 September and are summarised in a 2016-2020 progress report. The report outlines the actions to fight AMR in three key areas: appropriate therapeutic use of antimicrobials in human and veterinary medicine; prevention of drug-resistant infections; and strategies for improving the pipeline of new antimicrobial medicines. As member of the taskforce, EMA has contributed to the implementation of strategies to encourage responsible use of antimicrobials in veterinary medicines and to foster research and development of new safe and effective human antibiotics.

AUGUST 16, 2021
EMA starts evaluating the anti-inflammatory medicine RoActemra (tocilizumab) to extend its use to include treatment of hospitalised adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation (breathing assisted by a machine).

AUGUST 24, 2021
EMA's human medicines committee (CHMP) adopts recommendations that will increase manufacturing capacity and supply of COVID-19 vaccines in the EU.

Fighting the silent pandemic

To mark **European Antibiotic Awareness Day** in 2021, EMA launched a social media campaign to highlight the importance of using antibiotics prudently. A collection of info-cards focused on what patients, healthcare professionals, veterinarians, public health leaders and the pharmaceutical industry in their respective roles can do to make sure that these important medicines remain available as effective treatments for EU patients.



SEPTEMBER 02, 2021

Based on current evidence, there is no urgent need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population, according to a technical report issued by the European Centre for Disease Prevention and Control (ECDC). The report also notes that additional doses should already be considered for people with severely weakened immune systems as part of their primary vaccination.

SEPTEMBER 06, 2021
EMA starts evaluating an application for the use of a booster dose of Comirnaty to be given 6 months after the second dose in people aged 16 years and older. Booster doses are given to vaccinated people (i.e. people who have completed their primary vaccination) to restore protection after it has waned.

SEPTEMBER 09, 2021
EMA's human medicines committee (CHMP) approves additional manufacturing sites for the production of Comirnaty, the COVID-19 vaccine developed by BioNTech and Pfizer.

Watch the EAAD 2021 message by EMA's Executive Director Emer Cooke

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In support of the **World Antimicrobial Awareness Week 2021**, EMA joined an ICMRA campaign aiming to raise awareness of the growing public health problem of AMR and the need to address it. The Agency disseminated a set of info-cards to call on global health leaders, healthcare professionals and patients to take action.

SEPTEMBER 27, 2021
EMA starts evaluating an application for the use of a booster dose of Spikevax (Moderna's COVID-19 vaccine) to be given at least 6 months after the second dose in people aged 12 years and older.

SEPTEMBER 29, 2021
EMA puts in place special support to developers to replace, reduce and refine animal use for the development, manufacturing and testing of human and veterinary medicines.

CLINICAL TRIALS IN THE EU – IMPROVING THE CLINICAL RESEARCH ENVIRONMENT

Preparing for the new clinical trials regulation

The Clinical Trials Information System (CTIS) development continued in 2021. Following a successful audit and a decision of EMA's Management Board, the European Commission confirmed that the entry into application of the Clinical Trials Regulation (CTR) and the go-live date for CTIS would take place on 31 January 2022.

The application of the CTR and the go-live of CTIS represents a major milestone for clinical research in the EU and the EEA. CTIS supports the harmonisation of the assessment and supervision processes for clinical trials and will be the single point of entry for all clinical trial applications in the EU/EEA. Throughout the development of the system, Member States and sponsors were engaged to ensure that the system meets user needs. Intensive testing was carried out to guarantee the timely delivery of CTIS.

Throughout 2021, EMA ran a programme of activities to make sure that sponsors and Member States were prepared for the CTIS go-live. This included two large information events for all stakeholders and two targeted training sessions organised for SMEs and academia, supported by a tailored online training module. An event on how sponsor organisations can prepare for CTIS took place on 29 July and was attended by more than 2,400 participants. In addition, a master trainer network was set up, a sponsor handbook and sponsor organisation modelling materials were created, organisation modelling sessions were held with Member States and an extensive online modular training programme was made available.

Finally, EMA, in collaboration with Member States and the European Commission, delivered safety monitoring and coordination tools for the clinical trial Safety Implementing Regulation, which also entered into application on 31 January 2022. The Safety Implementing Regulation lays down the rules for Member States' cooperation on safety assessment on the basis of the CTR.

SEPTEMBER 30, 2021
As member of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), EMA supports the international fight against antimicrobial resistance.

OCTOBER 04, 2021
EMA starts evaluating an application for marketing authorisation for the monoclonal antibody Regkirona (regdanvimab, also known as CT-P59) to treat adults with COVID-19 who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID-19.

Accelerating Clinical Trials in the EU (ACT EU)

In late 2021, the European Commission, the Heads of Medicines Agencies (HMA) and EMA agreed to launch the **Accelerating Clinical Trials in the EU (ACT EU) initiative** to transform how clinical trials are initiated, designed and run. ACT EU aims to further develop the EU as a focal point for clinical research and to better integrate clinical research in the European health system, for the benefit of patients.

ACT EU will help to achieve the ambitious goals for innovation in clinical trials as set out in the European medicines agencies network strategy to 2025 and the European Commission's Pharmaceutical Strategy.

The initiative uses the momentum of the CTR to further promote the development of high quality, safe and effective medicines. ACT EU will reinforce the European environment for clinical trials whilst maintaining the high level of protection of trial participants, data robustness and transparency that EU citizens expect.

The European Commission, EMA and HMA have agreed ten priority actions for 2022/2023, including enabling innovative trial methods, modernising oversight and supporting the modernisation of good clinical practice. One of the priority actions will be to establish a multi-stakeholder platform where all voices, including those of patients, can contribute to enabling better clinical research.

ACT EU is co-led by the European Commission, HMA and EMA. The Agency has overall responsibility for programme management.

OCTOBER 04, 2021
EMA's human medicines committee (CHMP) concludes that an extra dose of the COVID-19 vaccines Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna) may be given to people with severely weakened immune systems, at least 28 days after their second dose. The CHMP has evaluated data for Comirnaty showing a rise in antibody levels when a booster dose is given approximately 6 months after the second dose in people from 18 to 55 years old.

OCTOBER 07, 2021
EMA's human medicines committee (CHMP) approves an additional manufacturing site for the production of COVID-19 Vaccine Janssen in the US.

I DATA ANALYTICS AND METHODS

The Agency has an ambitious plan to build up capability and capacity within EMA and across the network to deliver robust evidence for benefit-risk decision-making. In 2021, EMA made progress in a number of projects and initiatives that will strengthen scientific advice on products under development, underpin support to marketing authorisation assessments and deliver expert methods advice and data analysis for medicines on the market.

DARWIN EU

The aim of the **Data Analysis and Real World Interrogation Network (DARWIN EU)** is to deliver real-world evidence from across Europe on diseases, populations and the uses and performance of medicines. This will enable EMA and national competent authorities in the European medicines regulatory network to use these data whenever needed throughout the lifecycle of a medicinal product.

In 2021, DARWIN EU made significant steps forward. EMA launched a tender procedure for the selection of a service provider to establish and run, under the guidance of the Agency, the Coordination Centre for the DARWIN EU network. The selection will be concluded in early 2022.

Also, the DARWIN EU Advisory Board was formed in June 2021. It is co-chaired by EMA's Executive Director Emer Cooke and Karl Broich from the German Federal Institute for Drugs and Medical Devices representing the HMA and includes representatives from key stakeholder groups such as patients and healthcare professionals, payer and health technology assessment (HTA) organisations, national medicines regulatory authorities, national data permit authorities, the European Commission and ECDC. The mandate of the board is:

- strategic advice and recommendations to the project team on establishing DARWIN EU and its use of the European Health Data Space (EHDS);
- coordination and alignment with relevant European and EU Member State initiatives and policies;
- supporting two-way communication on DARWIN EU with the EU Regulatory Network, stakeholders and the EHDS.

EMA will be a principal user of DARWIN EU as it will request studies to support its committees' scientific evaluations and regulatory decision-making. EMA's role in DARWIN EU is crucial as it is responsible for:

- linking real-world data studies to core benefit risk decision-making;
- providing strategic direction and setting standards;
- overseeing the coordination centre and monitoring its performance;
- ensuring close links to European Commission policy initiatives, particularly the EDHS, and delivering pilots.

DARWIN EU will also contribute to developing the EHDS and close collaboration took place with the joint action to deliver European principles for the secondary use of health data, **Towards the European Health Data Space (TEHDAS)**.

OCTOBER 11, 2021
EMA starts evaluating an application for marketing authorisation for the monoclonal antibody combination Ronapreve (casirivimab/imdevimab).

OCTOBER 12, 2021
The International Coalition of Medicines Regulatory Authorities (ICMRA) presents prerequisites for regulatory flexibility that can be applied to increase manufacturing capacity during COVID-19.

OCTOBER 12, 2021
EMA ends the rolling review of CVnCoV, CureVac AG's COVID-19 vaccine, after the company informed the Agency that it was withdrawing from the process.

Big data steering group work plan 2021-2023 and EU Big Data Stakeholder Forum

The **HMA-EMA joint Big Data Steering Group** adopted its multiannual workplan in June 2020 and updated it in August 2021. The workplan aims to increase the utility of big data in regulation, from data quality through study methods to assessment and decision-making. It is patient-focused and guided by advances in science and technology. The workplan includes eleven priority recommendations of the HMA-EMA Joint Big Data Task Force.

2021 deliverables included adoption of a Network Data Standardisation Strategy and a suite of stakeholder workshops including on artificial intelligence (AI), real-world meta-data, standards and real-world evidence. In December 2021, the European medicines regulatory network organised the second annual **Big Data Multi-Stakeholder Forum**. The Forum informed stakeholders on the delivery of the data pillar of the Network Strategy 2025 via the HMA-EMA joint Big Data Steering Group workplan, provided an opportunity to listen to stakeholders' views and feedback and discuss the areas for collaboration. 165 registered participants attended the Forum online and others could follow via the live stream on the web.

Read more about EMA's vision for the use of real-world evidence:

- Arlett P., Kjær J., Broich K., Cooke E., Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value, Clinical Pharmacology & Therapeutics, 2021 November 19, doi: https://doi.org/10.1002/cpt.2479

OCTOBER 14, 2021
EMA's human medicines committee (CHMP) starts a rolling review of Evusheld (also known as AZD7442), a combination of two monoclonal antibodies (tixagevimab and cilgavimab), which is being developed by AstraZeneca AB for the prevention of COVID-19 in adults.

OCTOBER 18, 2021
New manufacturing sites and new formulation approved for COVID-19 vaccine from BioNTech/Pfizer.

INFORMATION MANAGEMENT AND DIGITAL BUSINESS TRANSFORMATION

As with all public sector institutions, EMA needs to deliver a growing number of activities without a commensurate increase in staff. In this environment, the Agency is increasingly dependent on its ability to mobilise knowledge, technological skills and expertise and to improve the quality and speed of its own services. Digitalisation of interfaces, processes and services is a major tool in helping EMA to make best use of its limited resources.

Digital Innovation Lab

To accelerate digital transformation, EMA is building a **Digital Innovation Lab** (DigiLab) to discover, experiment and develop digital solutions that will support the core business and benefit the Agency, the network and other stakeholders.

In 2021, DigiLab designed a process to capture opportunities for digital innovation in order to prioritise the most promising ideas and business needs and turn them into potential solutions. Digital innovations that were initiated in 2021 included experimentation with virtual reality, such as a 360-degree interactive video aiming to deliver immersive training experiences.

DigiLab works closely with the Agency's Analytics Centre of Excellence to explore how AI, machine learning and robotics can be used to build pragmatic solutions to existing EMA business needs with the main objective of gaining efficiency. Examples of successful pilots during 2021 include:

- application of AI to speed up core business processes, such as the validation of Type I and Type II variation applications to marketing authorisations;
- identification and redaction of personal data in documents;
- automation of the triage of incoming requests for information;
- a chatbot to help stakeholders find information on the EMA website faster.

The deployment of these solutions has either started in 2021 or will start in 2022.

OCTOBER 18, 2021
EMA starts evaluating an application to extend the use of BioNTech/Pfizer's COVID-19 vaccine, Comirnaty, to children aged 5 to 11.

OCTOBER 25, 2021
EMA's human medicines committee (CHMP) starts a rolling review of the oral antiviral medicine molnupiravir (also known as MK 4482 or Lagevrio), for the treatment of COVID-19 in adults.

OCTOBER 25, 2021
EMA's human medicines committee (CHMP) concludes that a booster dose of the COVID-19 vaccine Spikevax (from Moderna) may be considered in people aged 18 years and above.

Information management at EMA

A major review of EMA's information management governance model (including the governance structure formerly known as EU Telematics) was carried out from end-2020 until end-Q1 2021. The review included interviews with key EMA internal as well as external stakeholders, both NCAs and industry. The review concluded that improvements could be made to a number of points: increase transparency on decision making and priority setting; simplify the existing structure and number of governance bodies; and clear allocation of ownership of outcomes. This led to a recommendation from the Executive Board and EMA's Management Board to change the model. In June 2021, they endorsed the adoption of an agile way of working and the implementation of agile governance principles across all layers of technology delivery (strategic, portfolio, execution) by adopting the Scaled Agile Framework (SAFe).

Across industry, Agile and SAFe are broadly considered as best practice, with benefits ranging from a faster delivery of technology, increased transparency, better alignment between business and IT and easier management of changing priorities. For EMA specifically, it is expected to deliver:

- a holistic portfolio management with a strong business value focus and quick and incremental delivery of IT systems that focus on improving end-user satisfaction and unlocking data;
- a reduction in steering committees and project boards, and thus reduced administrative burden and clearer accountability;
- increased transparency on how and why decisions are made and on the progress of implementation and their outcomes.

In July 2021, the old EU Telematics governance bodies were dissolved, and a **pilot to test the new way of working** was launched in September 2021. EMA established two new governance bodies in autumn 2021: the Network Portfolio Advisory Group (NPAG), comprised of HMA and Management Board members, and the Network ICT Advisory Committee, which includes four IT Directors and experts from the NCAs and a representative from the European Commission. EMA is currently operating a hybrid system, in which the new agile governance model and way of working is being rolled out progressively across the full portfolio of IT projects.

OCTOBER 28, 2021
EMA and the Heads of Medicines Agencies (HMA) launch a pilot project to support the repurposing of medicines as a follow-up to the European Commission's Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) discussions on a proposal for a medicines repurposing framework.

NOVEMBER 02, 2021
EMA ends the rolling review of bamlanivimab and etesevimab, two antibodies for the treatment of COVID-19 developed by Eli Lilly Netherlands BV, after the company informed the Agency that it was withdrawing from the process.

PROTECTING IT SYSTEMS AGAINST CYBERATTACKS

During 2021, EMA successfully strengthened its IT security systems after it had become the subject of a cyberattack in December 2020.

The Agency swiftly launched a full investigation, in close cooperation with Dutch police authorities, the Computer Emergency Response Team for the EU Institutions, bodies and agencies (CERT-EU) and Europol, the EU's law enforcement agency. To support the full investigation, EMA also engaged a specialised IT security company to advise and assess the additional security measures that were immediately put in place in response to the data breach. The Management Board, the European medicines regulatory network and the European Commission were informed promptly and received regular updates.

The criminal intrusion into EMA's IT systems was successfully contained. The Agency and the European medicines regulatory network remained fully functional, and timelines related to the evaluation and approval of COVID-19 vaccines and treatments were not affected.

The investigation showed that data was unlawfully accessed, including a limited number of documents belonging to third parties. Further evaluation revealed that the data breach was limited to one IT application and that the perpetrators primarily targeted data related to COVID-19 medicines and vaccines. This included internal/confidential email correspondence dating from November 2020, relating to evaluation processes for COVID-19 vaccines.

Some of the breached documents including email correspondence were leaked on the internet and picked up by some media outlets. Not all of the documents were published in their integral, original form and may have been taken out of context. Whilst individual emails were authentic, data from different users were selected and aggregated, screenshots from multiple folders and mailboxes were created and additional titles were added by the perpetrators.

Some of the unlawfully accessed documents contained personal data. EMA notified the European Data Protection Supervisor and jointly agreed follow-up actions. EMA also informed all concerned third parties of the breach to provide support, assess the nature of the personal data and notify the person concerned in relation to the risk identified. All requests by data subjects to access their data were granted.

The Agency enforced its cybersecurity insurance policy in place since 2019 and was able to recover 100% of all disbursements borne in connection with the cyberattack.

EMA has, as a result of the COVID-19-related cyberattack, **further strengthened its defensive cybersecurity capabilities**. The Agency has been dedicating resources and investing significantly to avoid cybersecurity issues. It has been enhancing its IT systems as a priority to protect against future attacks. A revision of EMA's information security strategy is also underway, with the aim of putting in place a three-year improvement road map in line with best practices for similar organisations.

NOVEMBER 03, 2021
The clinical data supporting the extension of indication for the use of Comirnaty in children from 12 to 15 published.

NOVEMBER 10, 2021
EMA starts evaluating an application to extend the use of Moderna's COVID-19 vaccine, Spikevax, to children aged 6 to 11.

NOVEMBER 11, 2021
EMA's human medicines committee (CHMP) recommends authorising Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab) for COVID-19.

REGULATORY SCIENCE AND INNOVATION

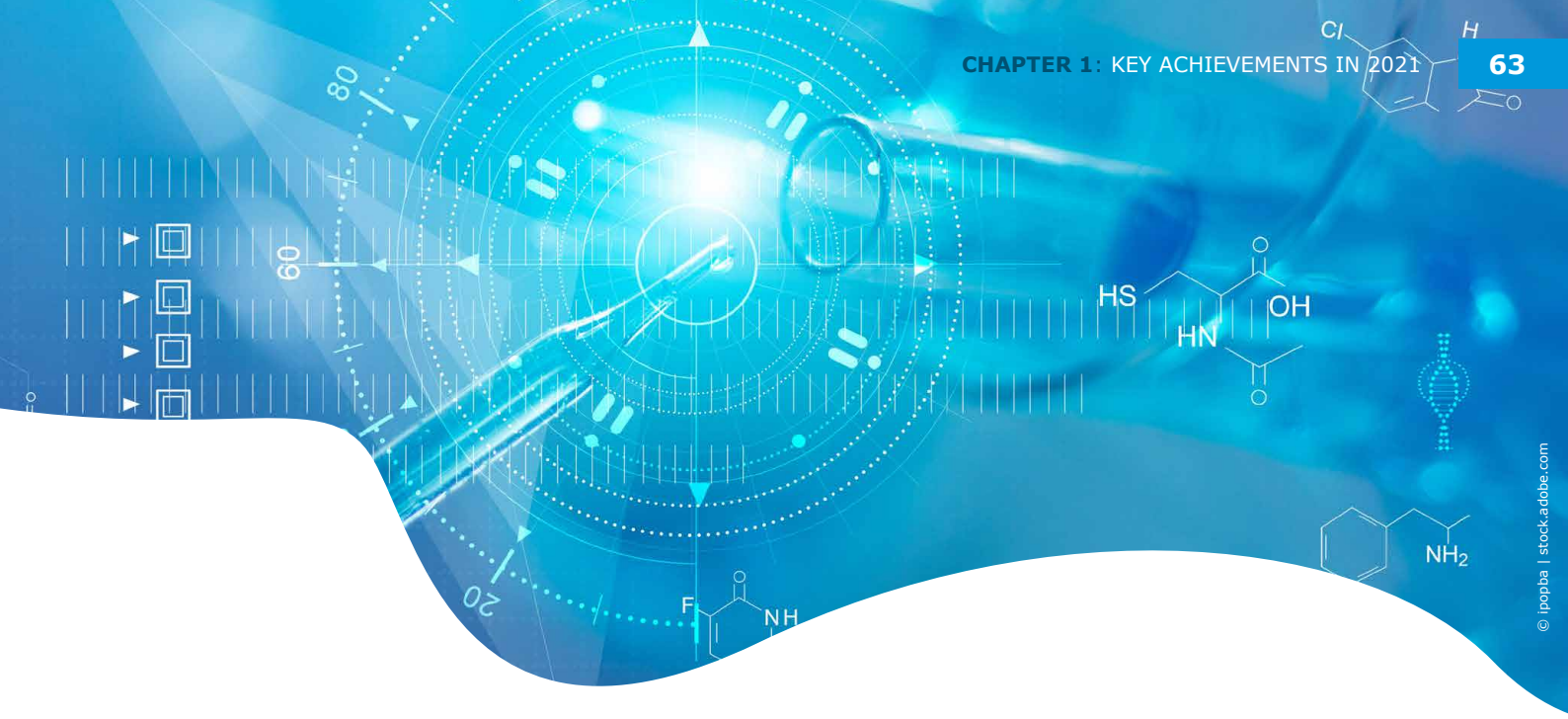
While addressing the immediate challenges of the COVID-19 pandemic, EMA continued with its efforts to 'future-proof' the Agency to ensure it is fit to tackle the scientific and technological challenges ahead and operates as efficiently as possible to deliver high-quality outputs for public and animal health.

Progress was made to fulfil the recommendations set in the Regulatory Science Strategy to 2025. Published in March 2020, this strategy aims at advancing regulatory science over the next five years, regarding both human and veterinary medicines. The strategy was developed together with the HMA as part of the 'European medicines agencies network strategy to 2025'. This translated into specific actions and work planning spanning until 2025.

Actions linked to the regulatory science strategy started to take shape across the Agency. This includes the establishment of the ACT EU initiative, priority focus on novel manufacturing technique and advanced therapies and personalised medicines' developments, investment in real-world evidence capabilities, various digital innovation initiatives, as well as work done on health threats as part of the pandemic response. Progress made in these areas is described in other sections of this annual report as well as outreach to academia and research funders, which is described below.

NOVEMBER 17, 2021
EMA starts evaluating an application for conditional marketing authorisation for Novavax's COVID-19 vaccine, Nuvaxovid (also known as NVX-CoV2373).

NOVEMBER 18, 2021
EMA starts evaluating an application for marketing authorisation for the monoclonal antibody Xevudy (sotrovimab).



Regulatory science research needs

In December 2021, EMA published the Regulatory Science Research Needs List, a list of regulatory science topics that need further research to close gaps and improve medicine development and evaluation to enable access to innovative medicines for patients. EMA identified around one hundred specific topics, in four categories relating both to human and veterinary medicines:

- integration of science and technology in medicine development;
- collaborative evidence generation to improve the scientific quality of evaluations;
- patient-centred access to medicines in partnership with healthcare systems;
- emerging health threats and availability/ therapeutic challenges.

With this list, the Agency has started to stimulate researchers and funding organisations to address these topics in their research agendas and share their findings and results with regulators. By engaging in the Regulatory Science Research Needs initiative, researchers and sponsors will be able to see the findings translated into regulatory practice, medicine development and public health. The Agency's proactive exchanges with funding organisations and involvement in externally funded research projects also contribute to closing the regulatory science gaps.

NOVEMBER 18, 2021
European Antibiotic Awareness Day (EAAD) is the annual European health initiative to support and promote the prudent use of antibiotics.

NOVEMBER 19, 2021
EMA is reviewing available data on the use of Paxlovid (PF-07321332/ritonavir), an oral treatment for COVID-19 developed by Pfizer. EMA starts this review to support national authorities who may decide on its early use for COVID-19, for example in emergency use settings, prior to marketing authorisation.

Innovation Task Force support for 3R methodologies

In September 2021, EMA opened up its Innovation Task Force (ITF) to the discussion of methodologies that minimise animal testing during medicine development. The ITF is a dedicated forum for early dialogue between regulators and developers of medicines to discuss innovative aspects such as emerging therapies, methods and technologies. The goal of this initiative is to facilitate the integration of the so-called 3Rs principles into the development and evaluation of medicinal products. The 3Rs are a set of principles supported by the Agency to replace, reduce and refine animal use for the development, manufacturing and testing of human and veterinary medicines.

This action facilitates the development and implementation of New Approach Methodologies that are in line with the European Union legislation on the protection of animals used for scientific purposes. It also supports a more adaptive regulatory system that will encourage innovation in human and veterinary medicine, as outlined in the Regulatory Science Strategy to 2025.

What are the 3Rs?

Replace
animal studies with non-animal methods

If not possible >

Reduce
animal studies to minimum required and necessary

In addition >

Refine
practices to minimise stress of study animals

NOVEMBER 19, 2021
EMA issues advice on the use of Lagevrio (also known as molnupiravir or MK 4482) for the treatment of COVID-19 to support EU countries who may decide on early use of the oral antiviral.

NOVEMBER 22, 2021
EMA starts evaluating an application for the use of a booster dose of COVID-19 Vaccine Janssen to be given at least two months after the first dose to people aged 18 years and older.

Borderline Classification Group

EMA and the HMA agreed in February 2021 the establishment of the Borderline Classification Group. This initiative, supported by the EU Innovation Network, aims to support a harmonised approach to the classification of innovative borderline products, i.e. products for which doubts arise as to whether they should be considered as medicinal products or fall under another regulatory framework, e.g. devices, food or cosmetics. This is to avoid situations where the same product could be classified differently depending on the approaches followed by each Member State, with consequences on the evidence requirements during development.

The Borderline Classification Group provides a multidisciplinary forum for informal discussions between competent authorities and other relevant groups at EU level, including the European Commission to enable scientific and regulatory feedback to innovative complex drug developers with regards to the classification of their products and consequently the applicable legal/regulatory framework for these products and the evidence requirements. The first meeting of this group took place in March 2021.

NOVEMBER 23, 2021
The annual report on the European Surveillance of Veterinary Antimicrobial Consumption published by EMA shows that European countries have substantially reduced the use of antimicrobials in animals.

NOVEMBER 23, 2021
EMA starts evaluating an application for marketing authorisation for the oral antiviral medicine Lagevrio (molnupiravir).

STRENGTHENING EMA'S ROLE IN CRISIS PREPAREDNESS AND MANAGEMENT OF PUBLIC HEALTH THREATS

The COVID-19 pandemic is an unprecedented 'stress test' of the resilience of European health systems. It has highlighted both strengths and limitations of the current EU health security framework, as well as the need for formalised preparedness and response tools.

The gaps in the public health preparedness and response exacerbated by the COVID-19 pandemic have been addressed in the European Commission's proposal to build a 'European Health Union' capable of better addressing public health emergencies, which was launched on 11 November 2020. EMA is one of the EU agencies at the core of EU's response to this global public health emergency.

The European Health Union package included a proposal for a Regulation reinforcing EMA's mandate in order to facilitate a coordinated EU-level response to future crises.

Throughout 2021, EMA followed closely the progress of the package drafted by the Commission as it advanced through the EU's legislative process in the Council of the European Union and the European Parliament.

EMA's extended mandate – Key dates

- 11 November 2020: Commission legal proposal adopted
- **15 June 2021:** Council agreement on a general approach
- **8 July 2021:** Parliament adopted its negotiating mandate
- **13 July 2021:** Trilogues between European Parliament, Council and European Commission started
- 20 January 2022: Ratification of final text by co-legislators
- 1 February 2022: Entry into force
- 1 March 2022: Date of application

NOVEMBER 25, 2021
EMA's human medicines committee (CHMP) recommends granting an extension of indication for the COVID-19 vaccine Comirnaty to include use in children aged 5 to 11.

NOVEMBER 25, 2021
A fourth public meeting provides an update on COVID-19 vaccines and therapeutics in the EU. It also addresses misinformation and highlights the current vaccination coverage in the EU.

How EMA prepared for the extended mandate

EMA set up an Extended Mandate Task Force (EMTF) to analyse the impact of the new legal mandate on the Agency's organisational structure and activities, as well as to draft a roadmap for the implementation of the new rules in order to be ready for their coming into operation on 1 March 2022.

The Agency also put in place a communication plan to inform its stakeholders and provide the necessary guidance on how the new tasks will be implemented.

DECEMBER 01, 2021
Global regulators meet to discuss challenges faced during the ongoing COVID-19 pandemic, but also antimicrobial resistance and medicines for use in pregnancy.

DECEMBER 02, 2021
EMA's human medicines committee (CHMP) starts a rolling review of VLA2001, a COVID-19 vaccine being developed by Valneva.

Main elements of EMA's extended mandate

The extended mandate puts structures and processes established by EMA during the COVID-19 pandemic on a permanent footing, while entrusting several new tasks to the Agency.

EMA will be tasked with the monitoring of events, including medicine shortages, which might lead to a crisis situation, as well as with the reporting of shortages of critical medicines during a crisis. The Agency will also coordinate responses of EU countries on shortages of critical medical devices and in-vitro diagnostics occurring in crisis situations, after an initial transition period.

EMA will set up, maintain and manage, by early 2025, a European Shortages Monitoring Platform to facilitate data collection and reporting by companies and Member States on shortages, supply and demand of critical medicines. EMA has also been given the responsibility to coordinate twelve EU expert panels to provide advice to Member States and the European Commission on high-risk medical devices and in-vitro diagnostic medical devices.

Under its extended mandate, EMA will also facilitate a coordinated EU-level response to public health emergencies by:

- reinforcing the activities of the COVID-ETF in providing scientific advice and reviewing available scientific evidence on medicines with the potential to address a public health emergency, and supporting existing EMA committees with their authorisation and safety monitoring of medicines;
- coordinating independent vaccine effectiveness and safety monitoring studies using relevant data held by public authorities;
- investing in and leveraging real-world evidence to support crisis preparedness and response. This includes the establishment of a pan-European network of real-world data, DARWIN EU, which will provide EMA's scientific committees with real-world evidence from healthcare databases across the EU.

HERA and EMA

The European Health Emergency preparedness and Response Authority (HERA) was established on 16 September. The role of HERA is to prevent, detect and rapidly respond to health emergencies. HERA will closely cooperate with EMA and ECDC and complement their work during and before emergencies in areas such as clinical trials, preparedness and response planning, and intelligence gathering. Emer Cooke, EMA's Executive Director, was invited to become an observer on the HERA Board.

DECEMBER 03, 2021
The International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO) review some of the practices applied by regulatory authorities worldwide to respond to the challenges faced during the COVID-19 pandemic.

DECEMBER 06, 2021
EMA's human medicines committee (CHMP) recommends extending the indication of RoActemra (tocilizumab) to include the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation.

MEDICAL DEVICES LEGISLATION

In May 2021, the Medical Devices Regulation came into force, one year later than originally planned due to the COVID-19 pandemic. This new piece of legislation introduced new responsibilities for EMA, NCAs and notified bodies. For instance, EMA is responsible for the overall evaluation of marketing authorisation applications for medicinal products containing a medical device as an integral part, while notified bodies are responsible for the review of the relevant general safety and performance requirements of medical devices that form an integral combination with a medicine.

To help developers prepare for submissions to EMA, the guideline on quality documentation for medicinal products when used with a medical device was finalised and published in July 2021. The guideline applies where a medicinal product and a medical device form an integral product, where they are packaged together or where the product information of a medicinal product refers to a specific medical device it needs to be used with.

The Medical Devices Regulation was approved together with the Regulation on In-Vitro Diagnostic Devices, which will apply from 26 May 2022.

The transition timelines were amended on the initiative of the European Commission in October 2021, also due to COVID-19. The original five-year transition period for different types of in-vitro diagnostic devices is now shorter for devices classified as higher risk (until May 2025) and longer for devices classified as lower risk (until May 2027). Before a notified body can issue a CE certificate for a companion diagnostic, it must seek a scientific opinion from EMA on the suitability of the diagnostic for the medicinal product concerned.

DECEMBER 07, 2021
A second annual multi-stakeholder forum on big data is hosted by EMA, the Heads of Medicines Agencies and the European Commission.

DECEMBER 07, 2021
EMA and ECDC share their recommendations on the possibility of using two different COVID-19 vaccines, either for the first and second doses of a primary course or using a third dose of a different COVID-19 vaccine as a booster.

INTERNATIONAL REGULATORY COOPERATION TO IMPROVE GLOBAL HEALTH

In an increasingly globalised pharmaceutical market and a world in which public health issues go beyond national borders, cooperation among medicine regulators has become key to supervising complex supply chains, avoiding duplication of regulatory work, aligning regulatory approaches and making best use of resources. In 2021, the Agency continued to work with its partners in Europe and beyond to contribute to the health of EU citizens and people around the world.

Bilateral interactions with non-EU regulators

EMA has bilateral confidentiality arrangements with a number of third-country regulators. These arrangements enable the parties to exchange confidential information and provide a framework for regulatory cooperation.

In March 2021, EMA and the European Commission's Directorate-General for Health and Food Safety (DG SANTE) signed a confidentiality arrangement with the Brazilian Health Regulatory Agency (ANVISA). This brings the number of standing confidentiality agreements to eight.

Country	Confidentiality agreement since
Australia	2012
Brazil	**2021**
Canada	2007
European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe	1995
Japan	2007
Switzerland	2015
United States	2003
World Health Organization (WHO)	2015

DECEMBER 08, 2021
Most suspected side effects after COVID-19 vaccination are not caused by the vaccine. This video shows how the safety of vaccines is monitored so they will protect us against death and hospitalisation.

DECEMBER 10, 2021
EMA endorses a statement by the International Coalition of Medicines Regulatory Authorities (ICMRA) that urges all stakeholders, including researchers, pharmaceutical industry, healthcare professionals, health research funding agencies and research institutions to continue their focus on developing therapeutics to treat and prevent COVID-19 in patients around the world.

Multilateral work – advancing the role of the International Coalition of Medicines Regulatory Authorities (ICMRA)

Throughout 2021, EMA, as chair of ICMRA, continued to spearhead global efforts to strengthen regulatory cooperation on issues that impact people worldwide. While priority was given to activities related to ensuring alignment of regulatory approaches to the COVID-19 response, ICMRA also covered a range of other activities.

> ‘The pandemic has increased the urgency for regulators to converge on responses both to existing regulatory challenges and complex new ones. ICMRA has proven its value during the COVID-19 response, both as a platform for sharing information and best practices and as a venue for providing strategic leadership, active information sharing, pragmatic solutions and regulatory convergence.’
>
> **Emer Cooke**, EMA’s Executive Director **and Chair of ICMRA**

DECEMBER 13, 2021
Key findings of a review of inspection practices applied by international regulatory authorities during the COVID-19 pandemic to enable remote oversight of good clinical practice (GCP) and good manufacturing practice (GMP).

DECEMBER 15, 2021
EMA’s human medicines committee (CHMP) concludes that a booster dose of COVID-19 Vaccine Janssen may be considered at least two months after the first dose in people aged 18 years and above.

WHO WE ARE

ICMRA is an informal group of leaders of medicines regulatory authorities that provides strategic directions for enhanced collaboration, improved communication and approaches to jointly address common challenges, such as the COVID-19 pandemic.

ICMRA
International Coalition of Medicines Regulatory Authorities

ICMRA STRUCTURE

- **ICMRA PLENARY**
- **EXECUTIVE COMMITTEE**
  - ICMRA Chair
  - ICMRA Vice-chairs
  - ICMRA Executive Committee members
- **ICMRA SECRETARIAT**
- **PROJECTS**

PROJECTS

- **AMR**
- **Communications**
- **Drug shortages**
- **Innovation**
  - Innovation Network
- **Pharmacovigilance**
  - Big data
  - Adverse events reporting
  - Vaccine confidence
- **Public health response**
- **Supply chain integrity**

EMA led a number of projects and working groups, including supply chain integrity, a horizon-scanning exercise in AI and communications, to achieve ICMRA's objectives.

In its role as chair of the ICMRA working group on supply chain integrity, EMA contributed to the development of a paper with recommendations to facilitate the use of track and trace systems at global level in 2021. The recommendations were developed in consultation with WHO, representatives from international medicines regulatory authorities and experts from the private sector.

EMA led a horizon-scanning exercise in AI carried out by the ICMRA Informal Network for Innovation working group. The group developed a report with specific recommendations to help regulators address the challenges that the use of AI poses for global medicines regulation.

The Coalition's visibility increased substantially during 2021, and with it the public awareness of its role in facilitating greater cooperation of international medicines authorities on shared regulatory issues and challenges. This was the result of efforts led by EMA for proactive communications, coordinated campaigns, regular information sharing and cross-channel promotion of ICMRA materials. The Agency published 15 news announcements to inform the public about joint ICMRA initiatives and activities, such as vaccine confidence, transparency and data integrity and regulatory flexibility. As a result, ICMRA was mentioned in 1.4M media articles published globally from January to December 2021.

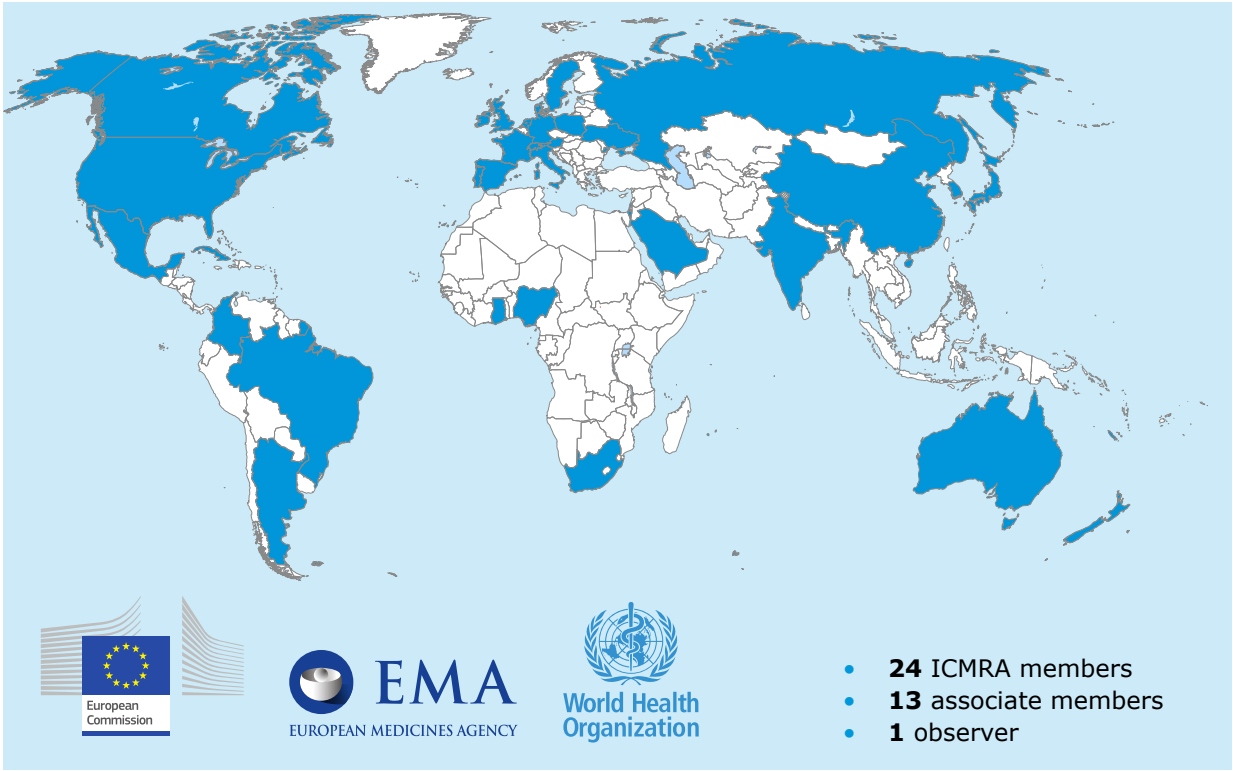
DECEMBER 15, 2021
For the first time, EMA issues a list of regulatory science topics that need further research to close gaps and improve medicine development and evaluation to enable access to innovative medicines for patients.

DECEMBER 15, 2021
A decade ago, EMA endorsed a framework for interaction to support access to expertise in clinical practice and enhance targeted communication.

Increasing ICMRA's global footprint

Six new members joined ICMRA in 2021, bringing the number up from 31 members in 2020 to 37 participating regulatory authorities representing every region of the world. In addition, WHO participates as an observer.

Country	Medicines regulatory authority
Argentina	National Administration of Drugs, Foods and Medical Devices (ANMAT)
Colombia	Colombia National Food and Drug Surveillance Institute (INVIMA)
Cuba	Center for State Control of Drugs, Equipment and Medical Devices (CECMED)
Ghana	Food and Drugs Authority (FDA)
Portugal	National Authority of Medicines and Health Products (INFARMED)
Ukraine	State Expert Centre of the Ministry of Health



ICMRA member/associate member

DECEMBER 16, 2021
EMA's human medicines committee (CHMP) recommends extending the indication of Kineret (anakinra) to include treatment of COVID-19 in adult patients with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure.

DECEMBER 16, 2021
EMA's human medicines committee (CHMP) recommends authorising the monoclonal antibody Xevudy (sotrovimab) for the treatment of COVID-19.

Cooperation with African regulators

EMA is committed to supporting global regulatory capacity building and contributing to the protection and promotion of public health beyond the EU.

In October 2021, EMA shared its assessment of the second Ebola vaccine (which consists of two components, Mvabea and Zabdeno) approved for use in the EU, as part of a review meeting facilitated by WHO. Twenty national regulatory authorities (NRAs) of the most concerned African countries were invited to attend the meeting. The objective of the meeting was to explain in detail EMA's regulatory assessment of this vaccine and to respond to any questions the invited regulators might have before they take their own regulatory decisions based on EMA's scientific assessment.

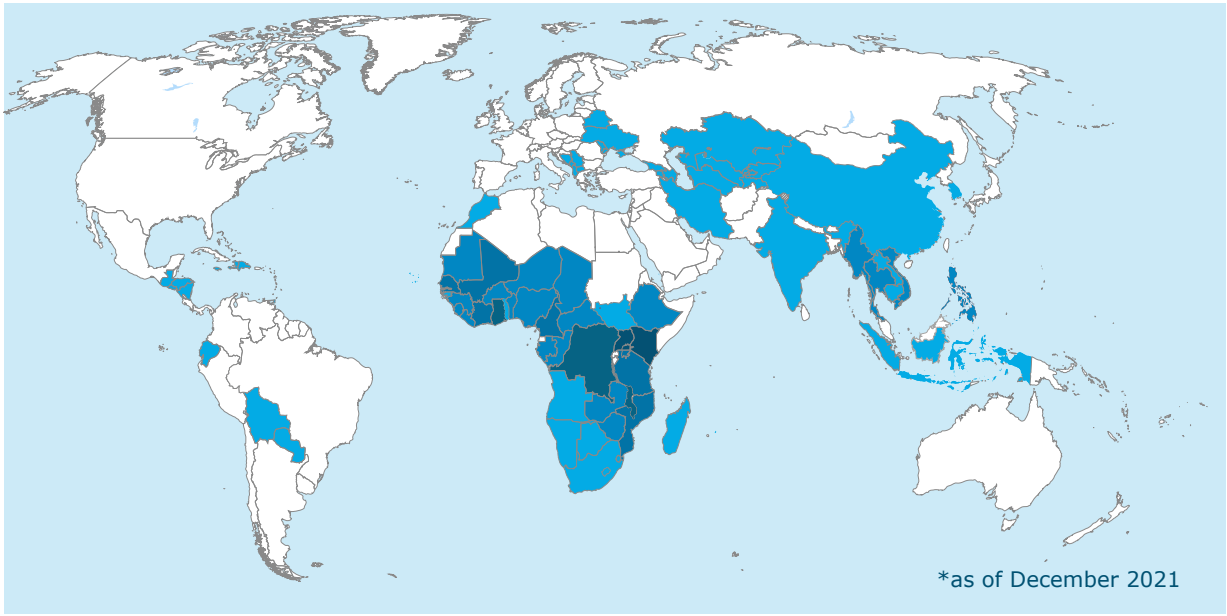
DECEMBER 16, 2021
EMA's human medicines committee (CHMP) issues advice on the use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19. The medicine, which is not yet authorised in the EU, can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe disease.

DECEMBER 16, 2021
EMA approves an additional manufacturing site for COVID-19 Vaccine Janssen and scale-up of processes for Spikevax (Moderna) and Comirnaty (BioNTech/Pfizer).

Facilitating access to medicines in low- and middle-income countries

In 2021, EMA analysed the list of approvals granted worldwide based on scientific opinions through the EU-M4all procedure (previously known as Article 58 procedure). This programme enables EMA, in close cooperation with WHO, to provide scientific opinions on medicines intended for markets outside the EU.

Between 2004 and 2021, EMA issued 12 positive opinions under the EU-M4all procedure, leading to 127 authorisations in 79 countries.



One product Two products Three products Four products Five products

EU-M4all combines EMA's scientific review capabilities with the epidemiology and disease expertise of WHO and experts from NRAs in the target countries to facilitate the assessment of high-priority medicines, such as new or improved therapies for unmet medical needs, which are intended to prevent or treat diseases of major public health interest.

DECEMBER 20, 2021
EMA recommends granting a conditional marketing authorisation for Novavax's COVID-19 vaccine Nuvaxovid (also known as NVX-CoV2373) to prevent COVID-19 in people from 18 years of age.

DECEMBER 21, 2021
On 21 December 2020, EMA recommended for authorisation the very first vaccine against COVID-19 for European citizens. Since then, we have made a lot of progress and have many more medical tools against COVID-19 than this time last year.

CHAPTER 2

KEY FIGURES IN 2021

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

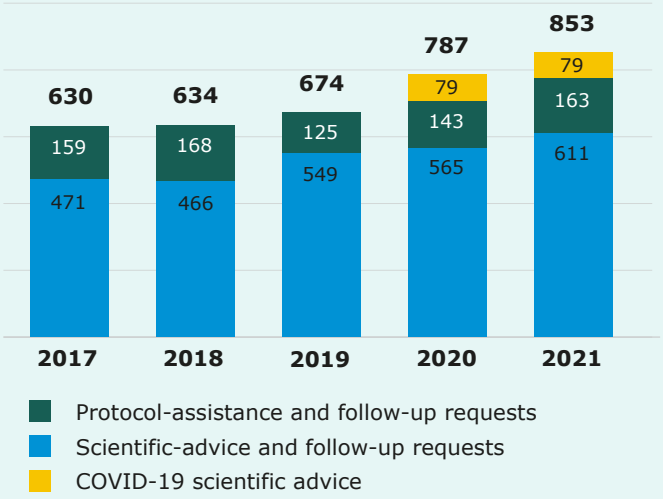
During a medicine's development, a developer can request guidance and direction from EMA on the best methods and study designs to generate robust information on how well a medicine works and how safe it is. This is known as scientific advice.

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.

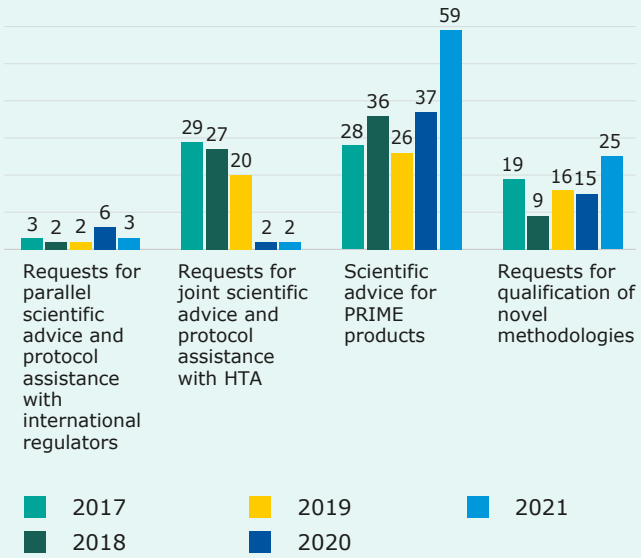
In 2021, EMA received a total of 690 requests for scientific advice. Among these, 79 were for COVID-19 medicines or vaccines, the same as in 2020.

Protocol assistance is the special form of scientific advice for developers of designated orphan medicines for rare diseases. The requests for protocol assistance increased by 14%, from 143 requests in 2020 to 163 in 2021.

Scientific-advice and protocol-assistance requests received - total



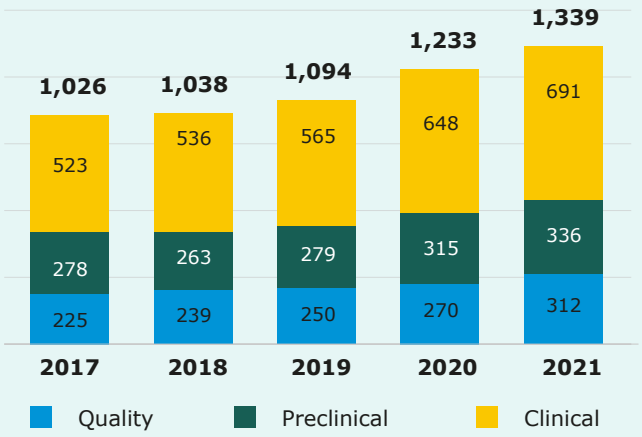
Scientific-advice and protocol-assistance requests received - special programmes



Scientific advice is the core of many of EMA's special programmes to encourage development and availability of new and innovative medicines. The Agency received 59 requests for scientific advice for PRIME products in 2021, the highest number since the scheme was launched in 2016.

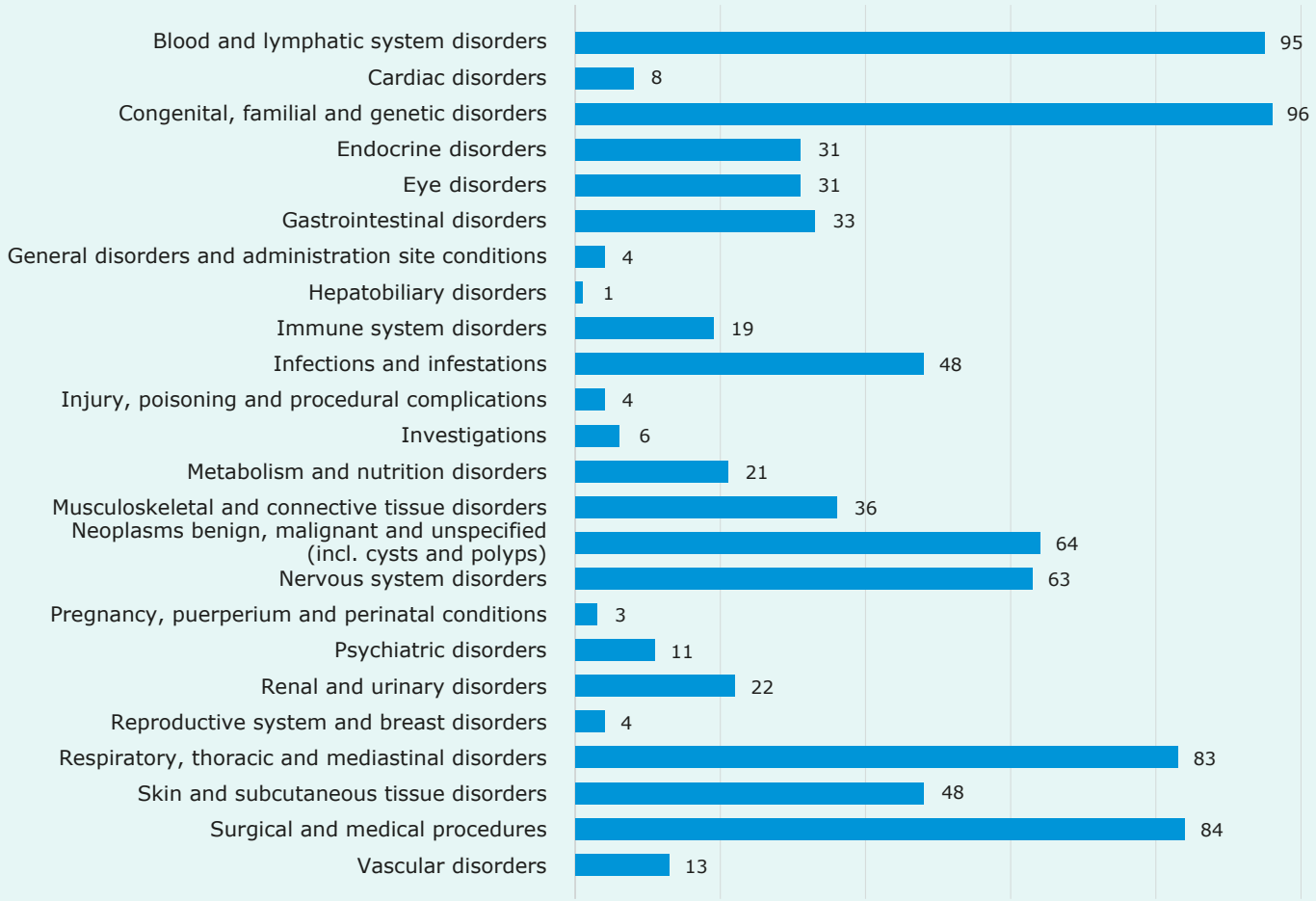
Requests for qualification of novel methodologies also increased significantly as a result of applications to qualify digital outcome measures, clinical trial modelling and simulation methods and machine-learning approaches.

Scientific-advice requests by topic



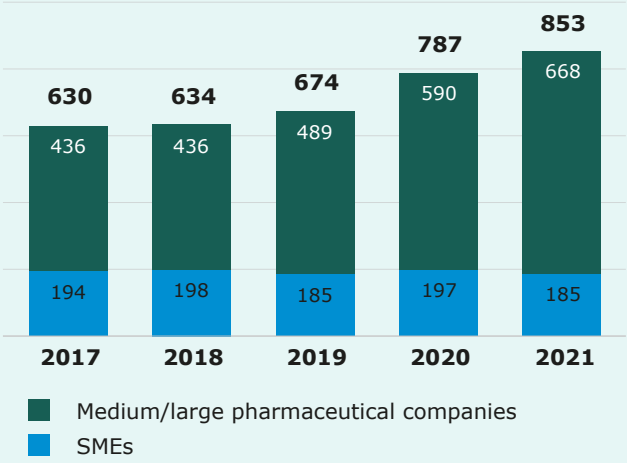
As in previous years, 81% of the requests for scientific advice included questions related to clinical issues, 39% to preclinical issues and 37% to quality issues. In terms of development stage, 63% of requests related to medicines in phase III, 23% to medicines in phase II, 12% to medicines in phase I and 2% to medicines in phase IV of their clinical development.

Scientific-advice requests by therapeutic area (2021)



22% of the total number of requests came from SMEs.

Scientific-advice requests by affiliation of requester



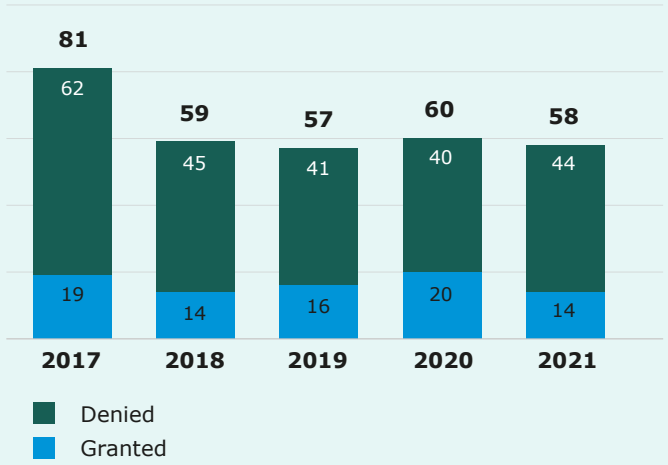
PRIME

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 2021, EMA received 52 PRIME eligibility requests and adopted 58 recommendations.

PRIME is meant 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 (14 out of 58 in 2021) are accepted into the scheme.

Six PRIME-designated medicines were recommended for approval (**Abecma**, **Bylvay**, **Evrysdi**, **Imcivree**, **Oxbryta** and **Skysona**) in 2021.

PRIME - eligibility recommendations



Support for SMEs

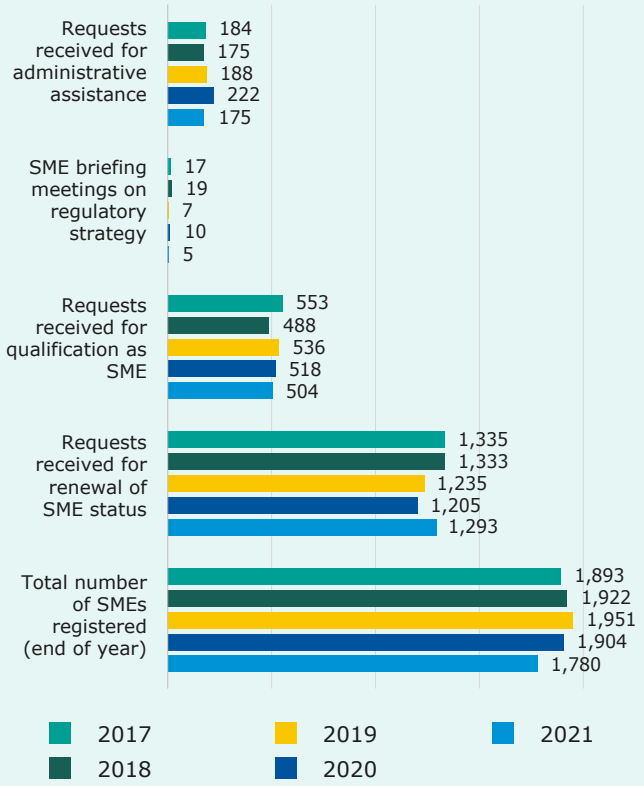
SMEs are recognised as a driver of innovation in the EU. The Agency promotes innovation and the development of medicines by SMEs through regulatory and administrative support to these companies. The Agency's SME office provides advice and guidance, organises topical workshops and produces a dedicated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

In 2021, the SME office received 175 requests for direct assistance on administrative or regulatory aspects and organised five briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. A total of 1,780 SMEs was registered at the Agency by the end of 2021.

In 2021, SMEs submitted ten marketing authorisation applications. This represents 9% of all applications received in 2021. Out of the ten applications, four were for orphan designated medicines.

The CHMP gave a positive opinion for 11 medicines developed by SMEs. This represents 12% of all positive opinions in 2021. Eight of these medicines developed by SMEs had a new active substance.

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



Initial evaluation applications and SMEs (human medicines)

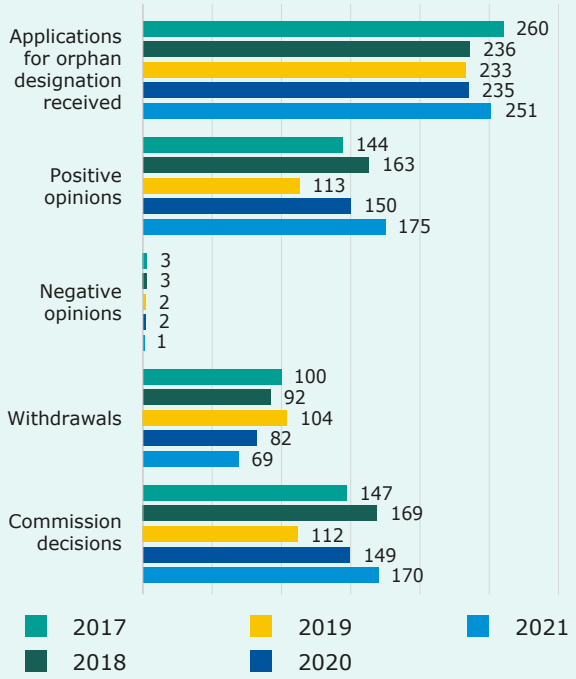
	2016	2017	2018	2019	2020	2021
Initial marketing authorisation applications submitted by SMEs	27	20	15	24	23	10
Positive opinions	4	12	13	8	16	11
Negative opinions	1	2	5	1	1	0
Withdrawals	5	7	5	3	1	4

Orphan medicine designation

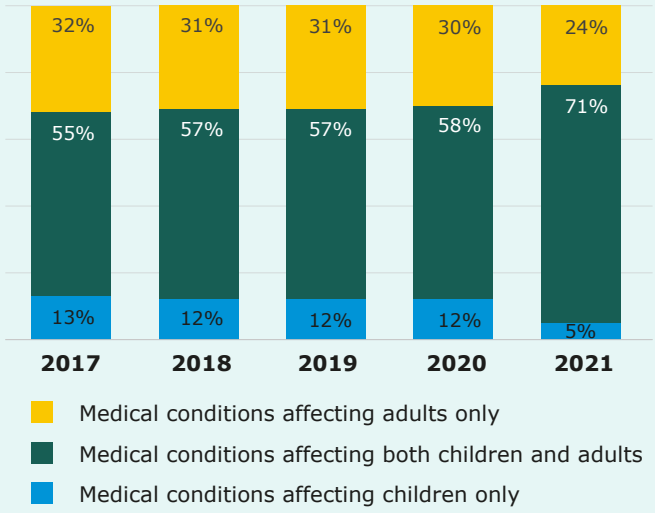
The EU framework for orphan medicines aims to encourage the development and marketing of medicines for patients with rare diseases by providing incentives for developers.

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



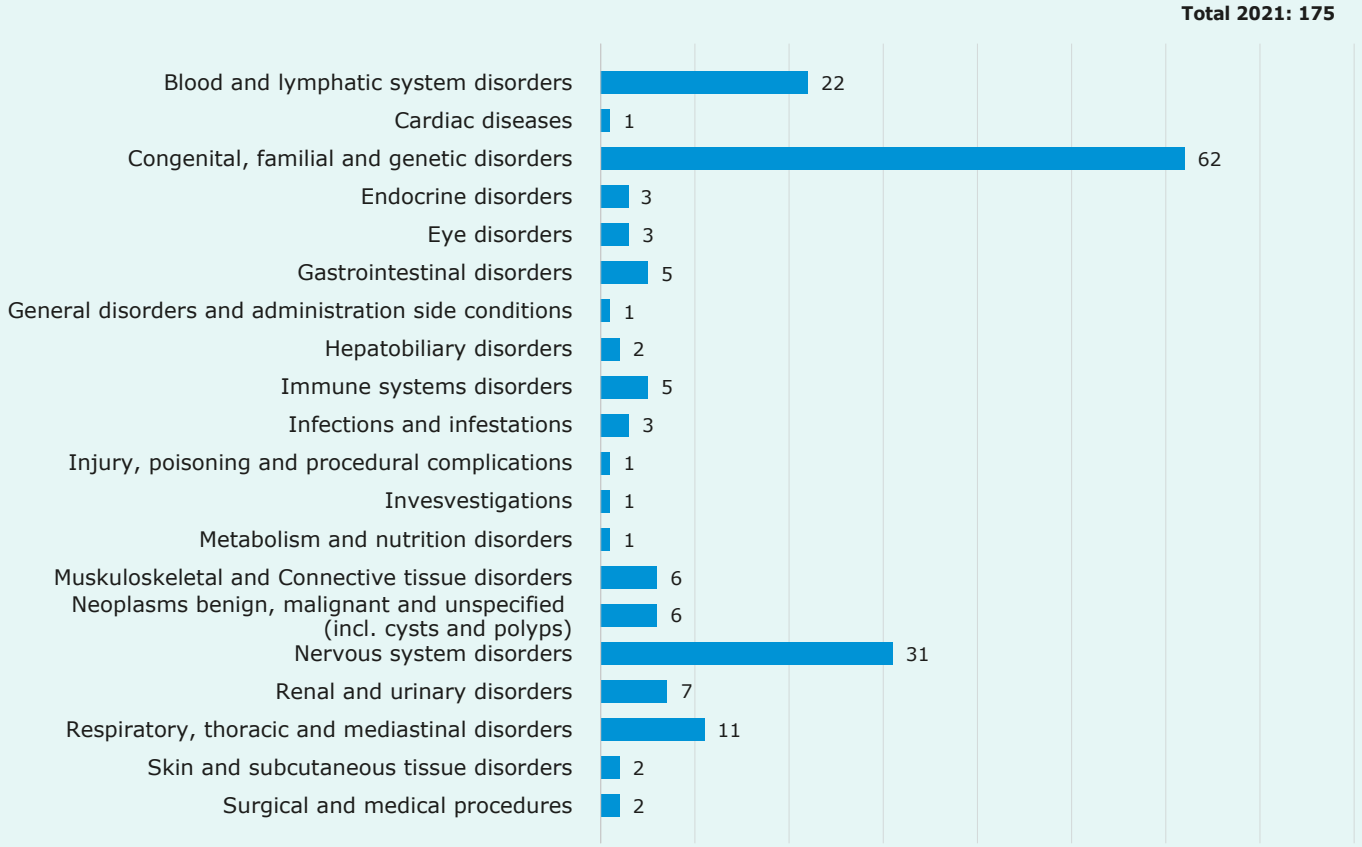
Designated orphan medicines for the treatment of children and adults



The number of applications for orphan designations was 251 in 2021, a similar number to previous years. Of these, 175 were granted a designation, allowing them to benefit from the incentives under the EU Orphan Framework. Sixty-nine applications were withdrawn, and one received a negative opinion from the COMP.

The European Commission supports the development of medicines for rare diseases financially, with €12,187,155 provided in 2021. More than 72% of the Commission's special contribution was used to provide protocol assistance to medicine developers and more than 21% for the assessment of applications for marketing authorisation.

Opinions on oprhan designation by therapeutic area (2021)



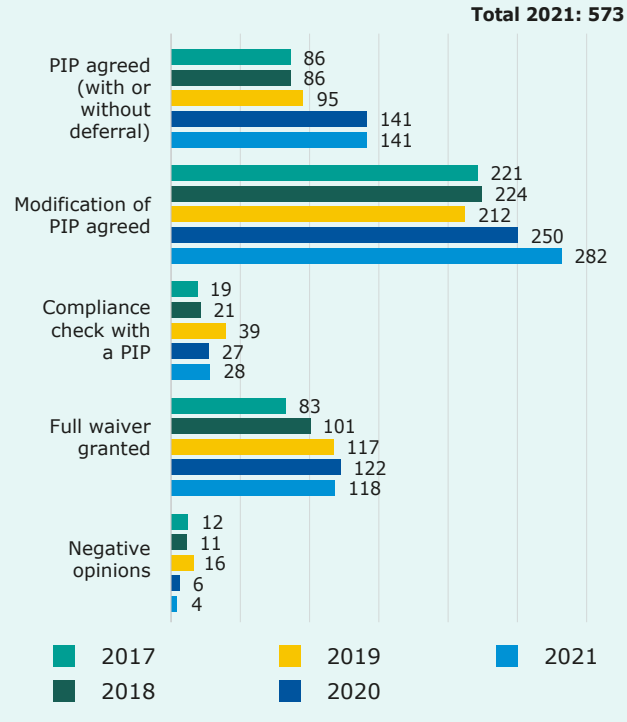
Medicines for children

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 the submission of a marketing authorisation. To support research and development of medicines in children, EMA provides the secretariat for the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).

A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children to support the authorisation of a medicine for children. Where studies in children are inappropriate or unnecessary, a waiver may be granted. In 2021, the PDCO agreed 141 initial PIPs.

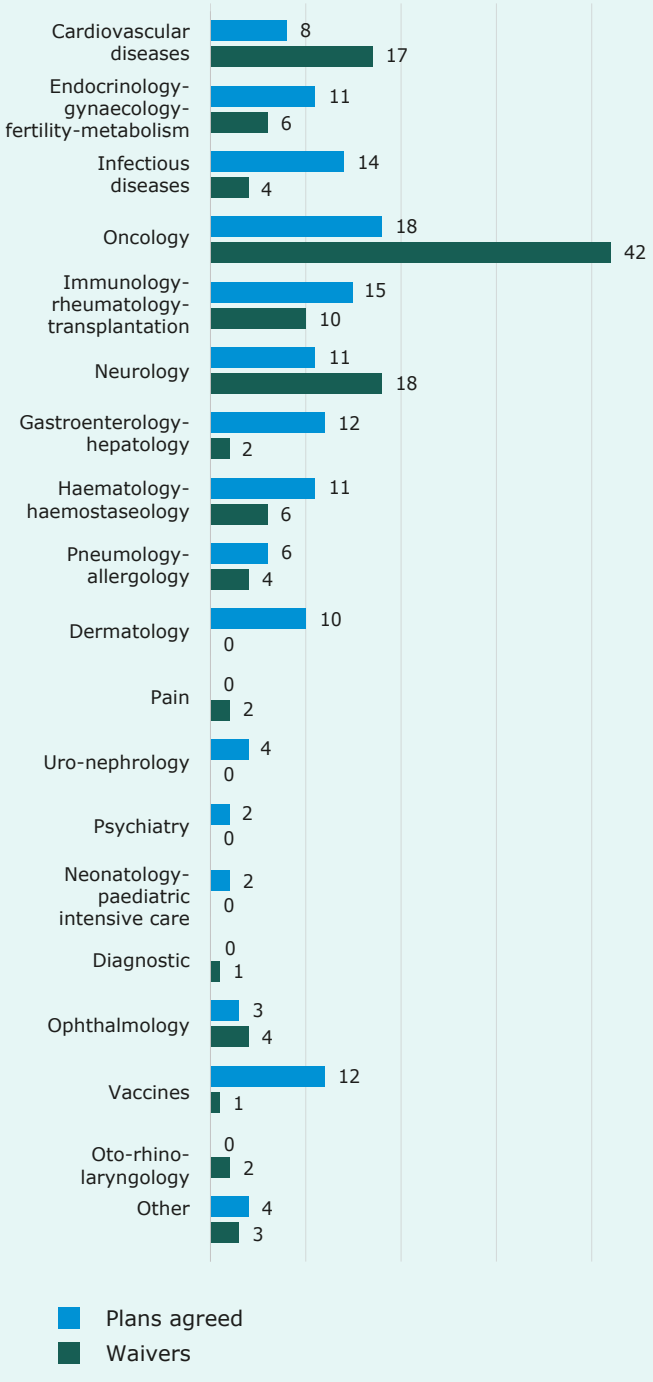
After a 9% decline in 2020, the number of requests for scientific advice on paediatric issues has risen slightly in 2021.

Opinions on PIPs and waivers



Article 46 of the Paediatric Regulation requires marketing authorisation holders to submit studies on the use of already authorised medicines in children to regulatory authorities. This ensures that all paediatric studies are assessed by the relevant competent authorities. In 2021, EMA assessed 129 paediatric studies in the context of article 46. These studies are available to the public through the EU Clinical Trials Register.

Paediatric investigation plans agreed and waivers granted (2021)

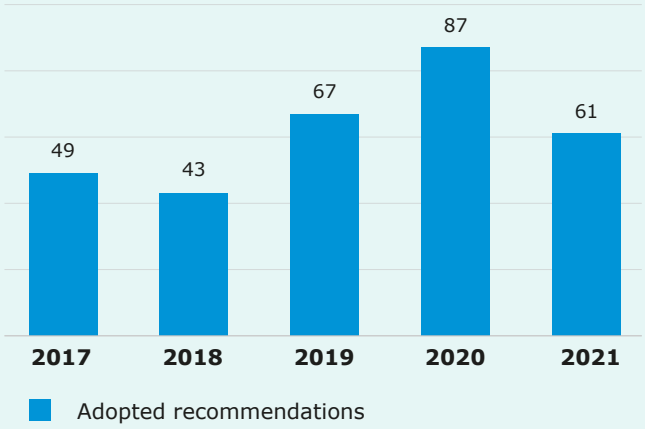


Advanced-therapy medicinal products

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.

Scientific recommendations on advanced therapy classifications



In 2021, the CAT received 66 requests for ATMP classification and adopted 61 recommendations. 26 recommendations were for medicines developed by SMEs.

Two ATMPs were recommended for marketing authorisation by the CHMP in 2021: **Abecma**, a first cell-based gene therapy to treat adult patients with multiple myeloma; **Skysona**, a first gene therapy to treat children with rare inherited neurological disease. For the latter, the marketing authorisation has subsequently been withdrawn at the request of the marketing authorisation holder.

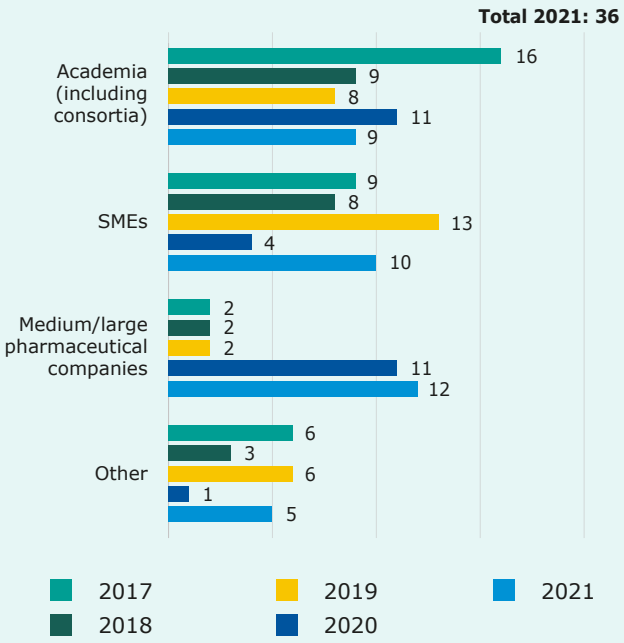
Innovation Task Force

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

The Agency held 36 ITF briefing meetings in 2021 (compared to 27 in 2020). Of these 36 meetings, 28% were requested by SMEs, another 25% by academia developers and 33% by large pharmaceutical companies.

A third of the requests received concerned innovative methods, e.g. statistics, manufacturing, software, biomarkers, and around 15% technologies, e.g. 3D printing, e-health. Innovations linked to COVID-19 discussed in 2021 included novel manufacturing methods and decentralised clinical trials. Further discussions on innovative developments included genome editing and biomaterials.

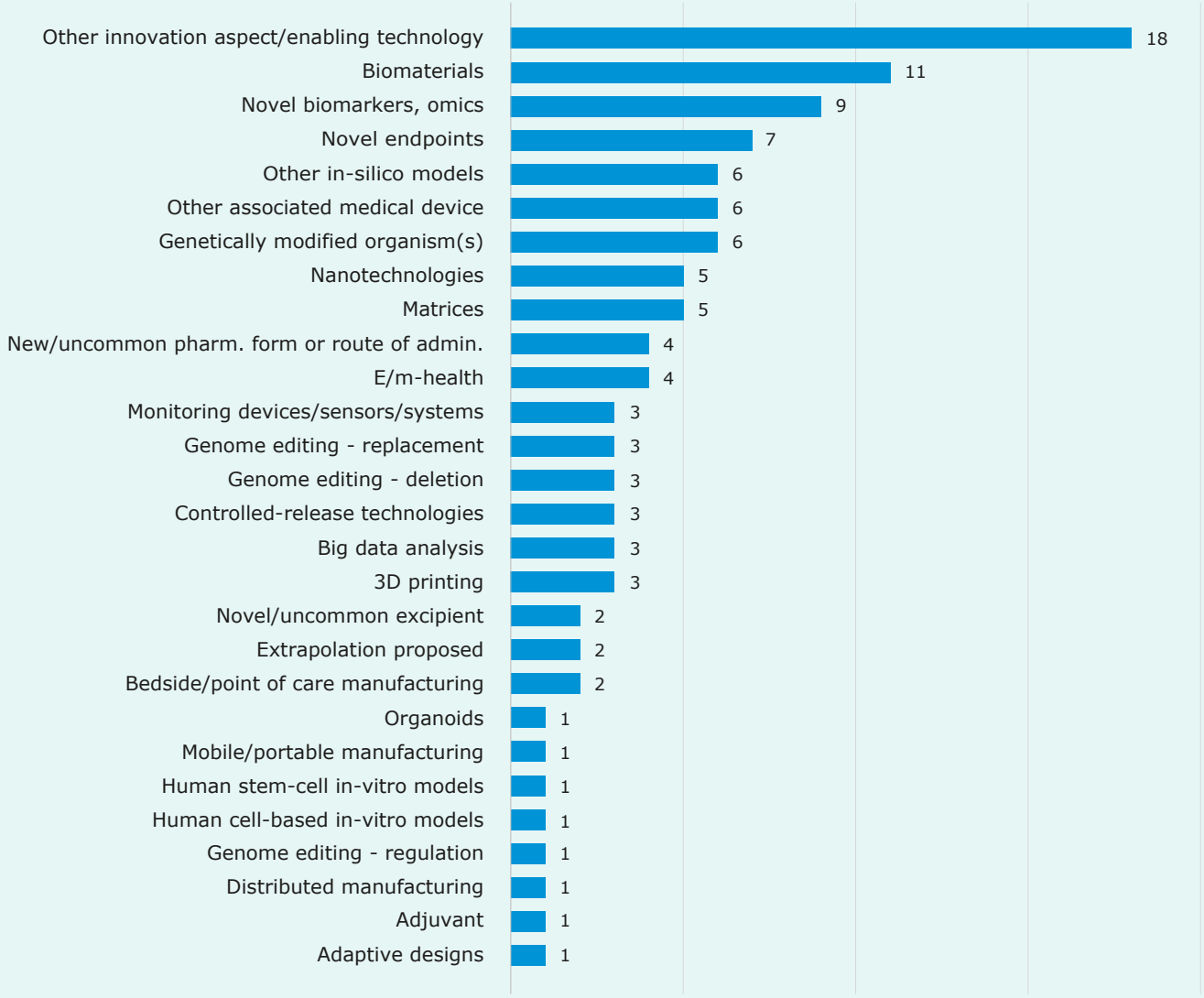
ITF briefing meetings by affiliation



REQUESTS RECEIVED BY ENABLING TECHNOLOGY

Each request could be associated with up to three of the categories in the table

Enabling technology



EMA and the Heads of Medicines Agencies (HMA) set up the EU Innovation Network (EU-IN) in 2015 to strengthen collaboration between national competent authorities (NCAs) and EMA on regulatory matters relating to emerging therapies and technologies. As part of the EU-IN, the ITF supports the delivery of the strategic goals of the network, in particular by identifying emerging trends through horizon scanning, taking part in borderline classification discussions and fostering collaboration with academic researchers including the Strengthening Training of Academia in Regulatory Science (STARS) and the medicines repurposing pilot projects.

Key scientific guidelines

The Agency develops scientific guidelines to provide advice to applicants or marketing authorisation holders, competent authorities and other interested parties on the most appropriate way to test and monitor the safety, efficacy and quality of medicines.

Guidelines are drafted by EMA working parties comprised of experts from across Europe. The objective is to reflect the latest scientific developments and experience gained through scientific advice and the evaluation and monitoring of medicines.

The Agency's work on guideline development and revision continued to be suspended or scaled back due to business continuity planning around COVID-19. A selection of reflection papers and guidance issued or revised in 2021 is listed below:

Topic	Content
Guidance outlining the requirements for manufacturers planning to modify their COVID-19 vaccines in order to address coronavirus (SARS-CoV-2) variants	This reflection paper outlines the quality, nonclinical and clinical data that would be required to support approval of a variant vaccine, whether monovalent or multivalent.
Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic	Guidance is available for clinical-trial sponsors on how they should adjust the management of clinical trials and participants during the COVID-19 pandemic. It covers how to deal with the extraordinary situations that the pandemic presents. These include, for example, the self-isolation or quarantine of trial participants, limited access to public places (including hospitals) due to the risk of spreading infections, and reallocation of healthcare professionals. It also advises on how to communicate these changes to the NCAs. The guidance also provides specific advice on clinical trials for COVID-19 treatments, including the need for large, multinational trial protocols.
Consideration on core requirements for PSURs of COVID-19 vaccine	Guidance is available for marketing authorisation holders on preparing periodic safety update reports (PSURs) for COVID-19 vaccines. The guidance complements the existing EMA's global guidelines on PSURs and on good pharmacovigilance practices, which apply to all medicines.
Guideline on quality documentation for medicinal products when used with a medical device	This guideline describes the information that should be presented in the Quality part of a marketing authorisation dossier for a medicinal product when it is used with a medical device, or device part. It focuses on product-specific quality aspects of a medical device, or device part, that may have an impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of a medicinal product.

Recommendations for marketing authorisation

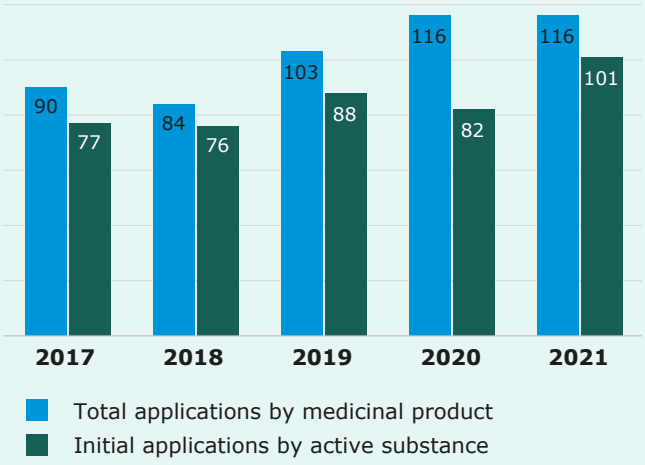
Applications for initial evaluation

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

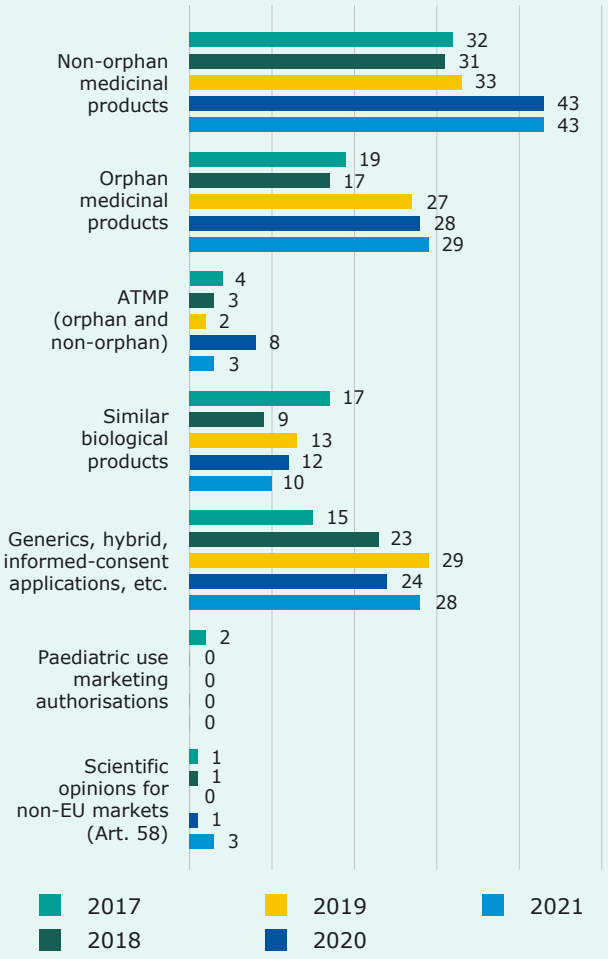
The initial evaluation covers all activities relating to the processing of marketing authorisation applications for new medicines which have never been assessed before, from the pre-submission discussion with future applicants, through to the evaluation by the CHMP and the granting of the marketing authorisation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

A total of 116 applications were received in 2021. Among these were three applications for scientific opinions for non-EU markets (art 58), the most ever received in a single year.

Initial-evaluation applications

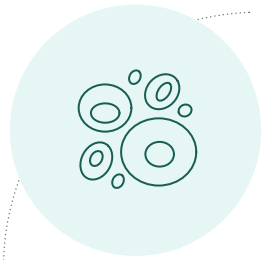


Initial-evaluation applications by type of application



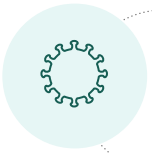
Outcome of initial evaluation

Cancer



Abecma ● ● ● ●
Abevmy ●
Abiraterone Accord
Abiraterone Krka
Abiraterone Mylan
Alymsys ●
Gavreto ●
Imatinib Koanaa
Jemperli ●
Lextemy* ●
Lumykras ●
Nexpovio ●
Oyavas ●
Padcev
Pemazyre ● ●
Qinlock ●
Rybrevant ●
Tepmetko
Trodelvy ●
Voraxaze ● ●

COVID-19



COVID-19 Vaccine Janssen ●
Nuvaxovid ●
Regkirona
Ronapreve
Spikevax ●
Vaxzevria ●
Xevudy

Cardiovascular

Kerendia
Rivaroxaban Mylan
Vazkepa
Verquvo

Metabolism

Evkeeza ●
Imcivree ● ●
Nexviadyme
Sapropterin Dipharma

Reproductive

Drovelis
Lydisilka
Ryeqo

Gastroenterology/ Hepatology

Bylvay ● ● ● ●

Neurology

Byfavo
Evrysdi ● ● ●
Fingolimod Mylan
Kesimpta
Koselugo ● ●
Ontilyv
Ontozry
Ozawade
Ponvory
Skysona* ● ● ●
Sugammadex Mylan
Vumerity
Vyepti

Endocrinology

Efmody
Lonapegsomatropin Ascendis Pharma ●
Ngenla ●
Sitagliptin SUN
Sitagliptin/Metformin hydrochloride Mylan
Sogroya ●
Wegovy
Yselty

Dermatology

Adtralza
Bimzelx
Cibinqo
Klisyri

Ophthalmology

Byooviz ●
Enspryng ●
Uplizna

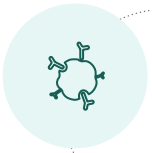
Infections

Artesunate Amivas ●
Tecovirimat SIGA ●

Diagnostic agents

Celsunax

Immunology/ Rheumatology/ Transplantation



Hukyndra ●
Icatibant Accord
Jayempi
Libmyris ●
Orladeyo
Saphnelo
Tavneos ●
Voxzogo ●

Haematology/ Haemostaseology

Aspaveli ●
Brukinsa
Copiktra
Evrenzo
Minjuvi ● ●
Onureg
Oxbryta ● ●
Thiotepa Riemser

Pneumology/ Allergology

BroPair Spiromax
Riltrava Aerosphere
Seffalair Spiromax

Vaccines

Apexxnar
Vaxneuvance

Psychiatry

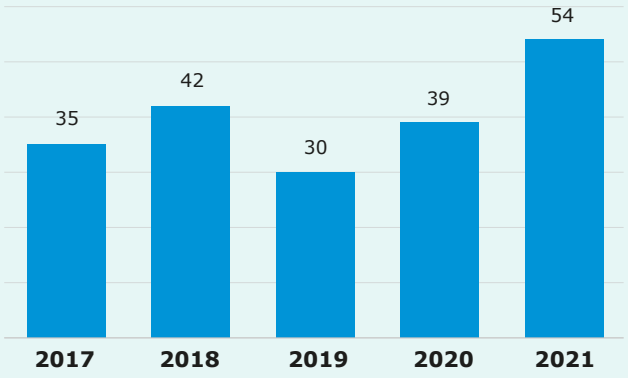
Okedi

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

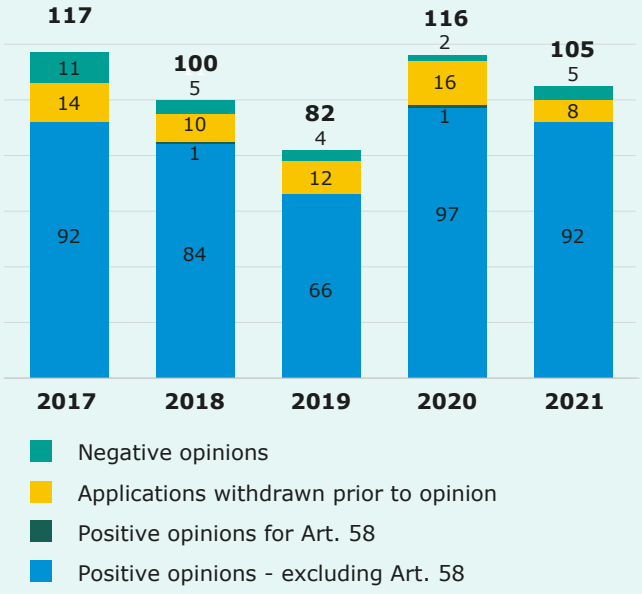
Medicines that contain a new active substance are highlighted in bold

* The marketing authorisation has been withdrawn at the request of the marketing authorisation holder.

Positive opinions - new active substances



Outcome of initial-evaluation applications



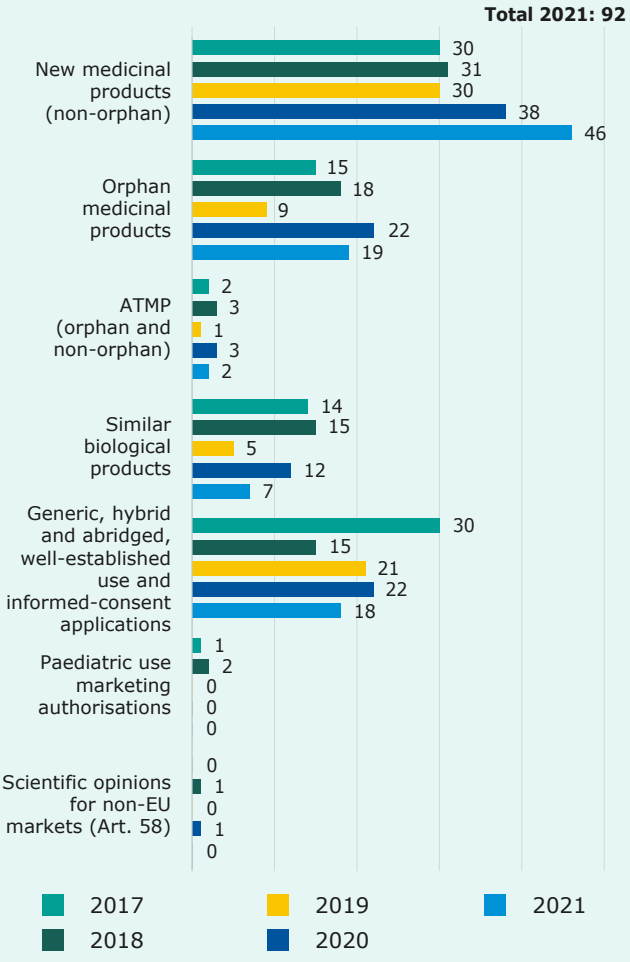
In 2021, EMA recommended 92 medicines for marketing authorisation. Of these, 54 had a new active substance which had never previously been authorised in the EU, an increase of 38% compared to 2020, and by far the highest number of the last five years.

The CHMP adopted negative opinions for five medicines in 2021: **Aduhelm**, **Ipique**, **Raylumis**, **Nouryant** and **Flynpovi**.

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

Applicants for 71% of the medicines granted a positive opinion by the CHMP in 2020 had received scientific advice during the development phase of their medicine.

Positive opinions by type of procedure



Conditional marketing authorisations

In 2021, 13 medicines received a recommendation for a conditional marketing authorisation (CMA), one of the possibilities in the EU to give patients early access to new medicines: **Abecma**, **Gavreto**, **Jemperli**, **Lumykras**, **Nexpovio**, **Pemazyre**, **Rybrevant**, **COVID-19 Vaccine Janssen**, **Nuvaxovid**, **Spikevax**, **Vaxzevria**, **Minjuvi**, **Koselugo**.

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 complete data on the medicines.

In 2021, one medicine (**Cometriq**) that had previously received a CMA was granted a recommendation for a full marketing authorisation by the CHMP after fulfilling its post-authorisation obligations.

Since the introduction of CMA in 2006, 24 medicines out of 72 have been granted a full marketing authorisation following a CMA. On average, it took around 3.5 years for companies to fulfil their post-authorisation obligations and get their products fully authorised.

CMA and switch to standard marketing authorisation (excluding withdrawals)

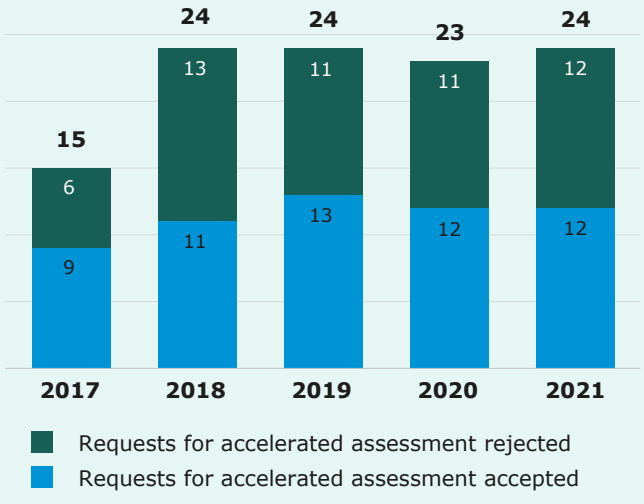
	2017	2018	2019	2020	2021
Positive opinions for CMAs	3	1	8	13	13
Opinions recommending switch of CMA to standard marketing authorisation	5	2	1	2	1

Accelerated assessment

Three medicines (**Trodelvy**, **Bylvay** and **Evrysdi**) received a recommendation for marketing authorisation following an accelerated assessment in 2021. This mechanism is reserved for medicines that can address unmet medical needs. It allows for faster assessment of eligible medicines by EMA's scientific committees.

In 2021, 12 requests from applicants for accelerated assessment of their medicine were accepted, 11 of which were PRIME products, and 12 requests were rejected. The main reasons for rejection were either that the unmet medical need the medicine is expected to address was not adequately justified, or that the data provided did not justify a major public health interest.

Accelerated assessment requests

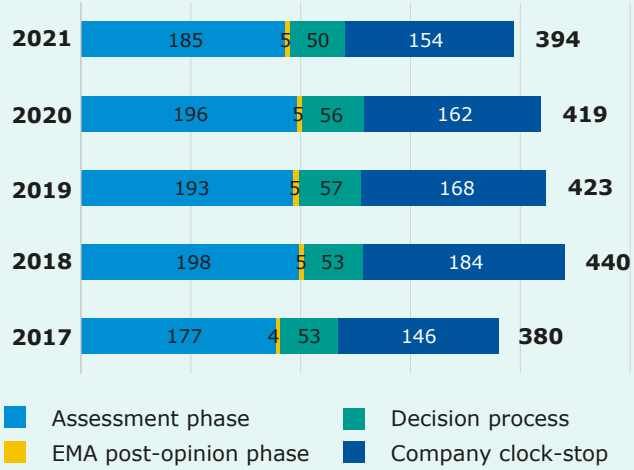


Average assessment time

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 is received, the counting of the days continues.

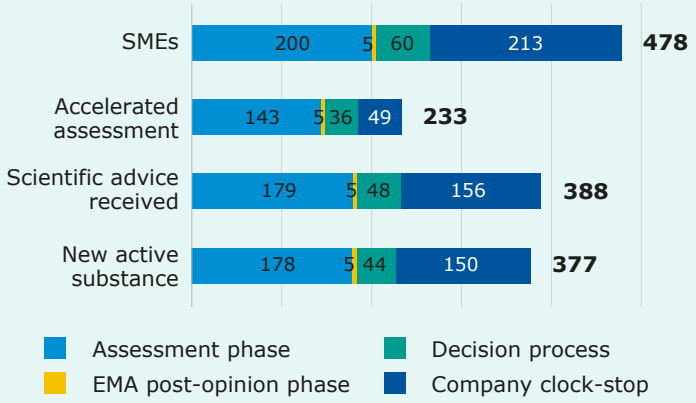
Once issued, the CHMP opinion is transmitted to the European Commission, which has the ultimate authority to grant a marketing authorisation and will take a decision within 67 days of receipt of the CHMP opinion.

Average number of days for centralised procedures - positive opinions



The overall total time required for the centralised procedure, from start of the evaluation process to the adoption of a decision by the European Commission, was an average of 394 days in 2021, 25 days less than in 2020.

Average number of days for centralised procedures - subset (2021)



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

For medicines evaluated under accelerated assessment, the total time from start of assessment until granting of authorisation was reduced by around 5.4 months (from 394 to 233 days), potentially facilitating the following decision-making steps at a national level and ultimately patient access.

Post-authorisation activities

In 2021, the CHMP gave 89 positive recommendations for extension of the therapeutic indication of already authorised medicines. Almost one third of these extensions of indication related to cancer medicines.

Important extensions of indication included:

- **Volibris**, to include the treatment of pulmonary arterial hypertension (PAH) in adolescents and children (aged 8 to less than 18 years).
- **Forxiga**, to include the treatment of type 2 diabetes in children from 10 years of age whose condition is not controlled well enough.
- **Saxenda**, as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years with obesity and body weight above 60 kg.
- **Benlysta**, to include the treatment of active lupus nephritis.
- **Nucala**, as an add-on treatment for relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis in patients aged 6 years and older.
- **RoActemra**, to include treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation.
- **Kineret**, to include treatment of COVID-19 in adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure.
- **Veklury**, to include treatment of adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

In line with previous years, in 2021 EMA received applications for:

- 3,809 type-IA variations;
- 3,102 type I-B variations;
- 1390 type-II variations;
- 27 extensions of marketing authorisations.

The product information for 502 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 (CAPs), managing assessment procedures, e.g. for periodic safety update reports (PSURs), and the operation and maintenance of the EudraVigilance system.

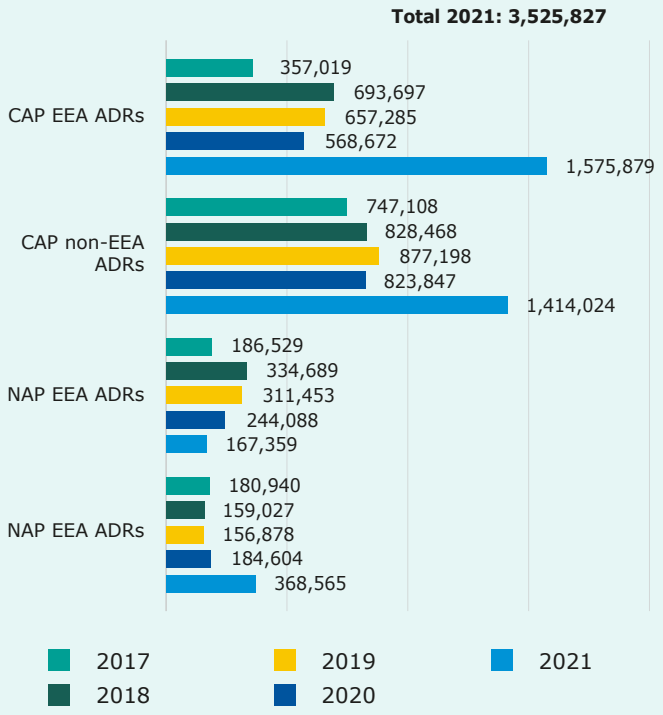
EudraVigilance

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.

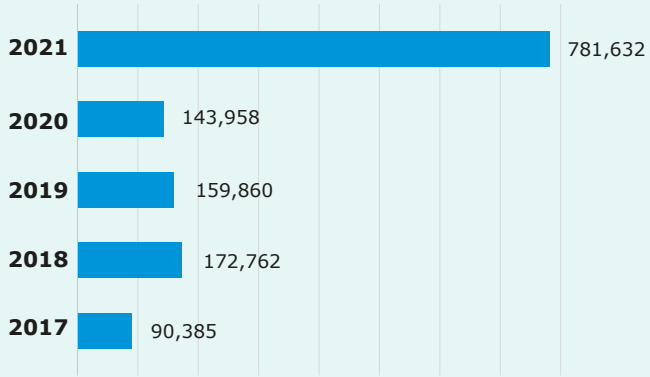
Over 3.5 million ADR reports were submitted to EudraVigilance in 2021, representing a 94% increase compared with 2020.

Over 45% of all reports in EudraVigilance originated in the EEA. The number of reports submitted by European patients and consumers is five times higher compared to previous years. This increase is due to the unprecedented roll-out of COVID-19 vaccines to hundreds of millions of EU citizens who have been encouraged to report all side effects to the authorities.

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, 2019, 2020 and 2021 include reports of non-serious suspected adverse drug reactions.

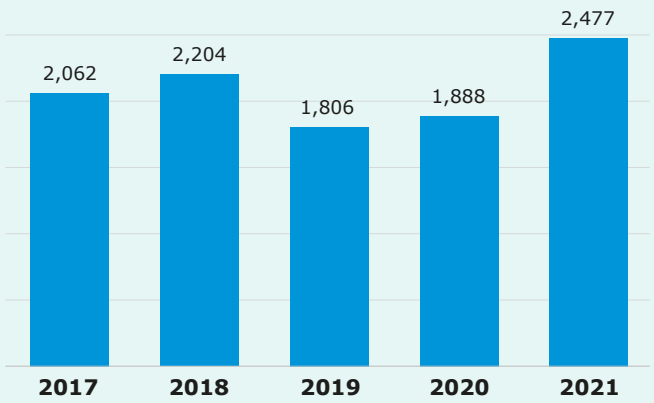
Signal detection

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 2021, 2,477 potential signals were reviewed by EMA, an increase of 31% compared to 2020. Approximately 89% of these signals originated from monitoring the EudraVigilance database, highlighting its central role for safety monitoring. The PRAC assessed 86 signals and of these, EMA validated 55. The number of signals validated by Member States and assessed by the PRAC significantly decreased (31 vs 42). 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.

Signals peer-reviewed by EMA



OUTCOME OF SIGNAL ASSESSMENT

2,477 potential signals reviewed by EMA

↓

86 confirmed signals were prioritised and assessed by the PRAC

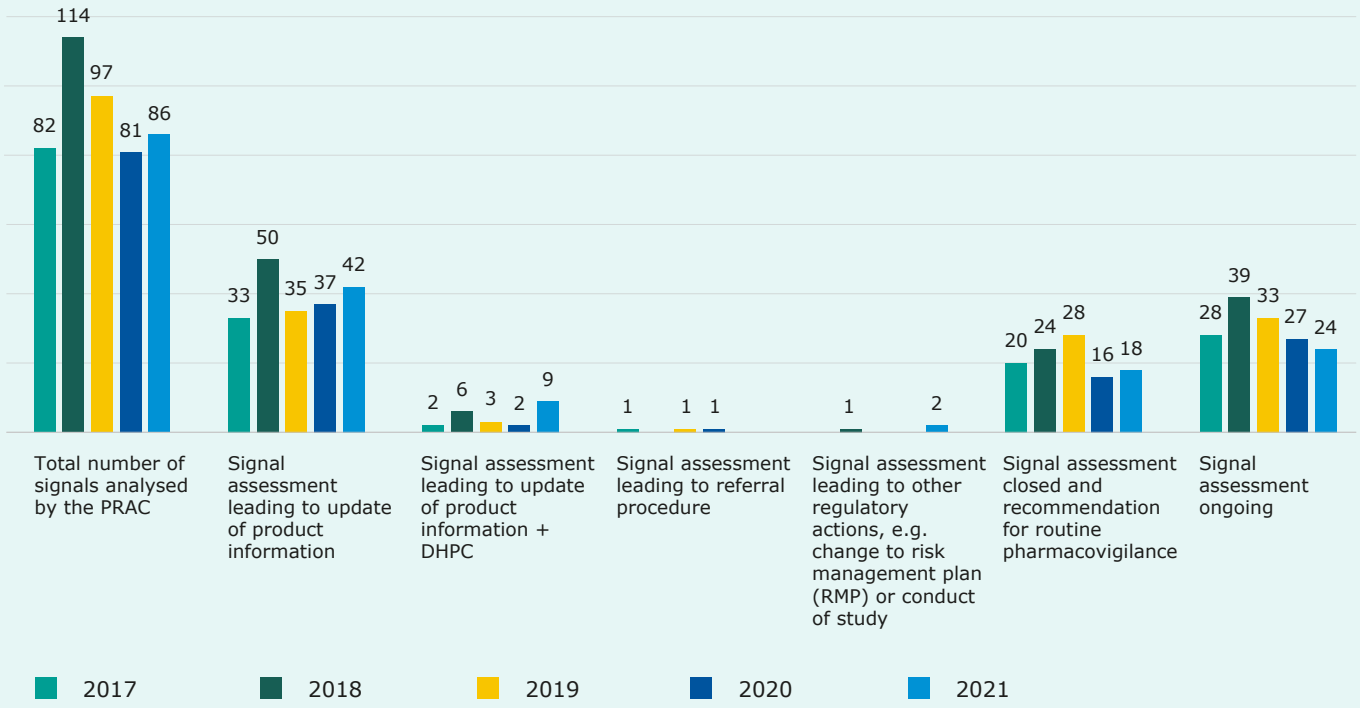
Of these, 55 signals were detected and validated by EMA	31 signals were detected and validated by EU Member States

↓

Out of 86 confirmed signals

↓	↓	↓	↓
42 signals led to a product information update; 9 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers	18 signals led to a recommendation for routine pharmacovigilance	24 signals were still under review by the PRAC at the end of 2021 as further data were required	2 signals led to other regulatory actions, e.g. change to risk management plans (RMPs) or conduct of study

Signal assessment



Periodic safety update reports (PSURs)

Marketing authorisation holders 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 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 assessments or PSUSAs.

In 2021, the PRAC started the assessment of 890 PSURs and PSUSAs, of which 30% represent single assessments of active substances only contained in NAPs. 911 recommendations were issued by the PRAC based on the assessment of PSURs and PSUSAs, of which 31% consisted of single assessments of active substances only contained in NAPs.

Close to the half of 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	2017	2018	2019	2020	2021
PSURs - standalone (CAPs only) finalised	540	537	558	516	575
PSURs – single assessment finalised	302	364	270	258	336
PSURs – single assessment (CAPs with NAPs) finalised	39	43	48	49	49
PSURs – single assessment (NAPs only) finalised	263	321	222	209	287
Total outcomes	**842**	**901**	**828**	**774**	**911**

PRAC outcomes of PSURs and PSUSAs	2017	2018	2019	2020	2021
Maintenance	**680**	**735**	**655**	**630**	**748**
NAPs only	207	245	166	161	226
CAPs/NAPs and CAPs only	473	490	489	469	522
CHMP Variation	**162**	**166**	**173**	**144**	**163**
NAPs only	56	76	56	48	61
CAPs/NAPs and CAPs only	106	90	117	96	102
Total outcomes	**842**	**901**	**828**	**774**	**911**

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 RMP assessments.

In 2021, the PRAC assessed 15 imposed PASS protocols that were requested to obtain further information on a medicine's safety, which was in line with 2020. The Committee assessed 226 non-imposed PASS protocols.

In addition, the PRAC started to assess the results of 11 imposed PASS, a number almost triple that for 2020.

Post-authorisation safety studies					
	2017	**2018**	**2019**	**2020**	**2021**
Imposed PASS protocol procedures started	6	17	12	17	22
Imposed PASS protocol procedures finalised	5	9	13	13	23
Non-imposed PASS protocol procedures started	333	195	144	158	143
Non-imposed PASS protocol procedures finalised	265	196	180	167	226
PASS amendment	11 (started), 10 (finalised)	11 (started), 11 (finalised)	11 (started), 9 (finalised)	19 (started), 14 (finalised) + 9 follow up amendments (started) and 7 (finalised)	17 (started), 18 (finalised) + 15 follow up amendments (started) and 11 (finalised)
Imposed PASS result procedures started	6	8	3	4	11
Imposed PASS result procedures finalised	3	8	3	2	6
PASS scientific advice through SAWP	0	3	3	1	1

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 eight 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					
	2017	**2018**	**2019**	**2020**	**2021**
PAES (imposed)	19	4	9	8	8
PAES (non-imposed)	1	2	0	0	0

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 CAPs, 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 17% between 2020 and 2021.

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 2021, 372 medicines were subject to additional monitoring, an increase of 8% compared to 2020. These medicines are identified by an inverted black triangle on their packaging.

The EU **incident management plan** is coordinated by EMA and aims to ensure that concerned bodies in the EU take appropriate action whenever new events or information (known in this context as incidents) arise concerning human medicines. It covers medicines authorised centrally, nationally and through the decentralised and mutual-recognition procedures. The plan's operation involves representatives from EMA, the European Commission and regulatory authorities in the Member States. In 2021, four 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 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 2021, 20 non-urgent information or rapid alert notifications were submitted via EPITT, in line with 2020.

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 2021, 9,193 Individual Case Safety Reports (ICSRs) resulted from EMA's medical literature monitoring (MLM) service, a slight decrease compared to 2020.

Other pharmacovigilance activities	2017	2018	2019	2020	2021
Cumulative number of products on the list of products to be subject to additional monitoring	336	351	342	343	372
Number of incident management plans triggered	4	11	3	6	4
Number of non-urgent information or rapid alert notifications submitted through EPITT	61	44	43	15	20
Number of external requests for EudraVigilance analyses	32	17	13	15	30
Number of MLM ICSRs created	14,193	13,275	9,676	9,550	9,193

Referral procedures

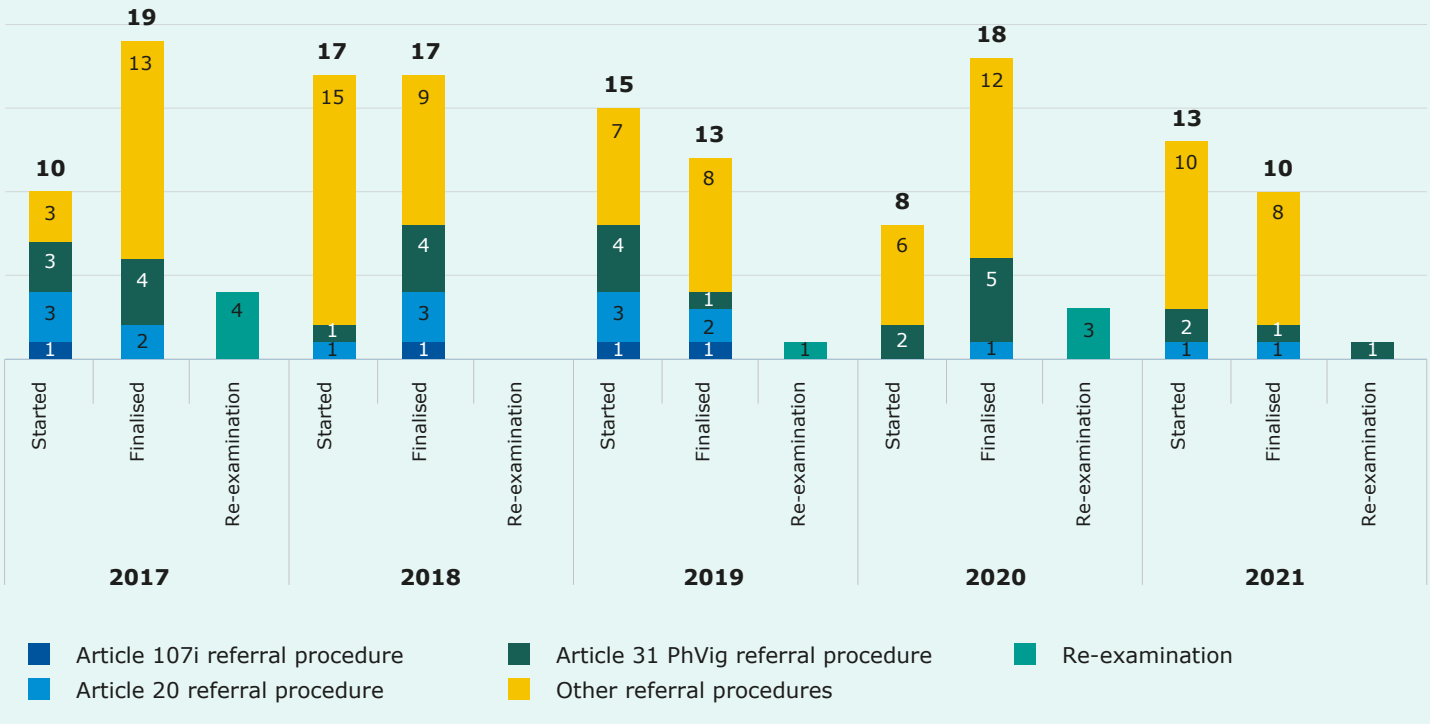
Referral procedures are initiated to address concerns over the safety or benefit-risk balance of a medicine, as well as to deal with disagreement among Member States on the use of a medicine. In a referral, EMA is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine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

In 2021, ten referral procedures were finalised, of which two were related to the safety of medicines, initiated under articles 31, 20 or 107i of the pharmacovigilance legislation. One led to changes in the product information, and one resulted in the suspension of the marketing authorisation.

The remaining eight referral procedures aimed 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.

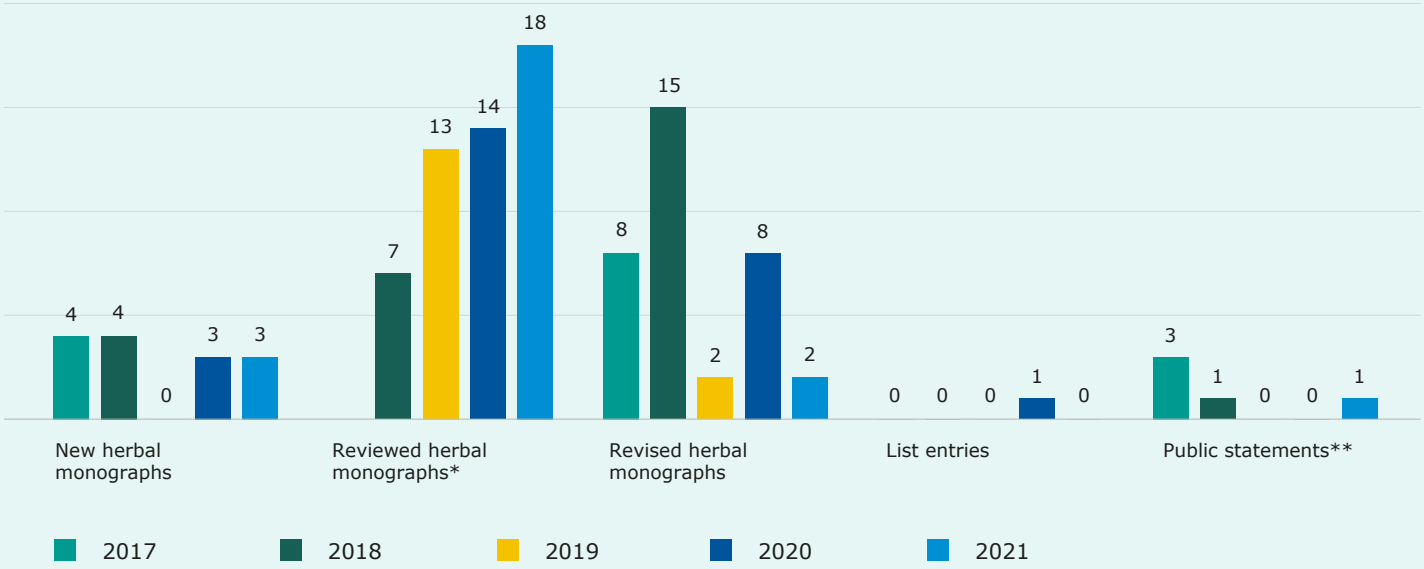
Referrals for human medicines finalised or re-examinations



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 2021, 18 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.

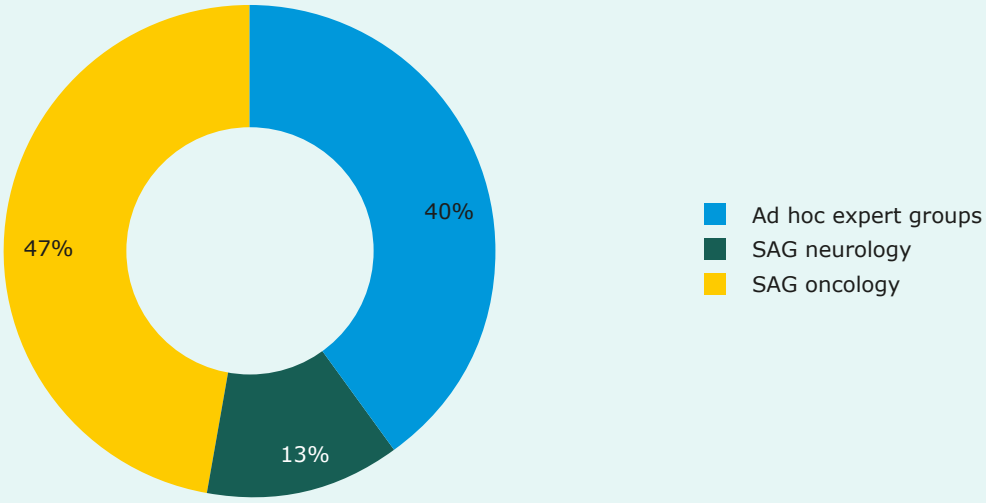
Note: A complete list of recommendations on herbal medicines can be found in the annexes.

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 15 consultations took place in 2021 in the form of SAG meetings, about 50% less than in 2020.

Areas of discussions - SAGs and ad hoc expert group meetings (2021)



Procedures with Scientific Advisory Group or ad hoc expert group involvement (number of consultations)	2017	2018	2019	2020	2021
Marketing authorisation (new MAA, new MAA re-examination, Art 58)	14	19	15	18	11
Extension of indication (including line extensions)	3	10	3	7	2
Referral (including re-examination)	11	3	6	0	1
Guideline	1	0	1	0	0
Other topics (renewal, PSUR, signal, class review)	1	0	2	3	1
Total	**30**	**32**	**27**	**28**	**15**

Involvement of patients and healthcare professionals

Patients and healthcare professionals are involved in a wide range of EMA activities. They bring a valuable real-life perspective to scientific discussions on medicines, which is expected to lead to better outcomes of 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)	2017	2018	2019	2020	2021
Scientific advice/protocol assistance	158	107	143	97	90
SAGs/ad hoc expert meetings	46	37	46	42	25
Scientific committee/working party consultations	104	112	355	227	122
Patient membership in Management Board, committees, working parties	59	59	57	57	56
EMA Management Board	2	2	2	2	2
Scientific committees	15	15	11	14	13
Patients' and Consumers' Working Party	42	42	44	41	41
Document reviews conducted by patients and consumers	176	178	169	203	192
EPAR summaries	39	43	40	50	55
Package leaflets	79	75	101	123	112
Safety communications	24	35	11	16	25
Herbal summaries	34	25	17	14	n/a
Total cases of patient/stakeholder engagement in EMA activities	**950**	**493**	**770**	**594**	**485**

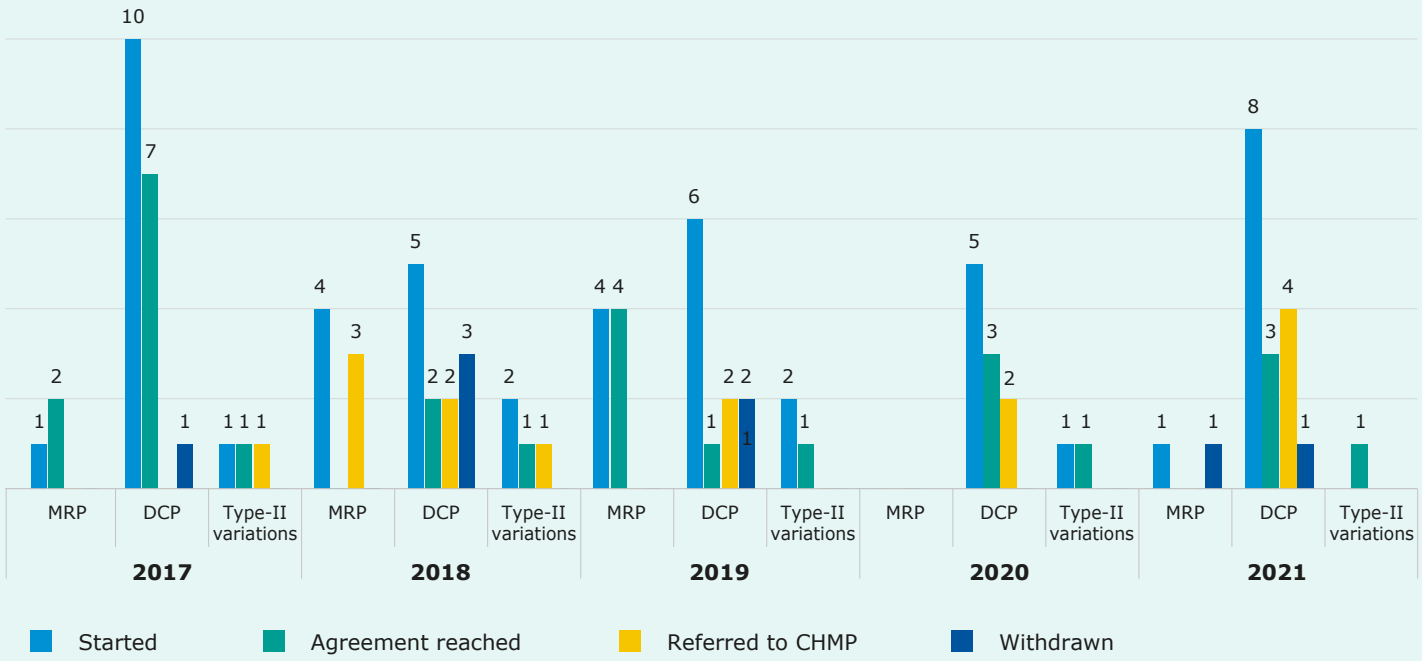
Healthcare-professional involvement in EMA activities (interactions)	2017	2018	2019	2020	2021
Scientific advice/protocol assistance	1	0	2	1	4
SAGs/ad-hoc expert meetings	40	31	36	39	21
Scientific committee/working party consultations	74	47	68	28	94
Healthcare-professional membership in Management Board, committees, working parties	54	54	58	62	57
EMA Management Board	2	2	2	2	2
Scientific committees	12	12	12	12	12
Healthcare Professionals' Working Party	40	40	44	48	43
Document reviews conducted by healthcare professionals	33	80	48	46	26
Safety communications	20	40	35	42	20
DHPCs	13	40	13	4	6
Total cases of healthcare-professional engagement in EMA activities	**450**	**212**	**212**	**176**	**202**

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.

Detailed information about the work of the CMDh in 2021 in relation to pharmacovigilance and referrals can be found on the HMA website.

Applications referred to the CMDh



VETERINARY MEDICINES

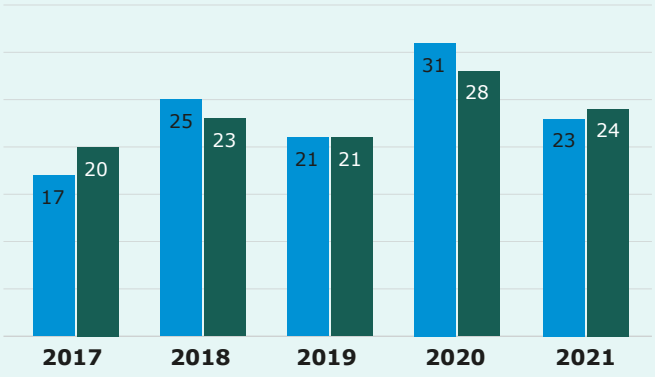
Activities supporting research and development

The Agency provides pre-authorisation support to medicine developers to boost innovation and research and to 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. Activities in many areas slightly decreased in 2021, most likely because developers of veterinary medicines were waiting for the implementation of the new Veterinary Medicinal Products Regulation.

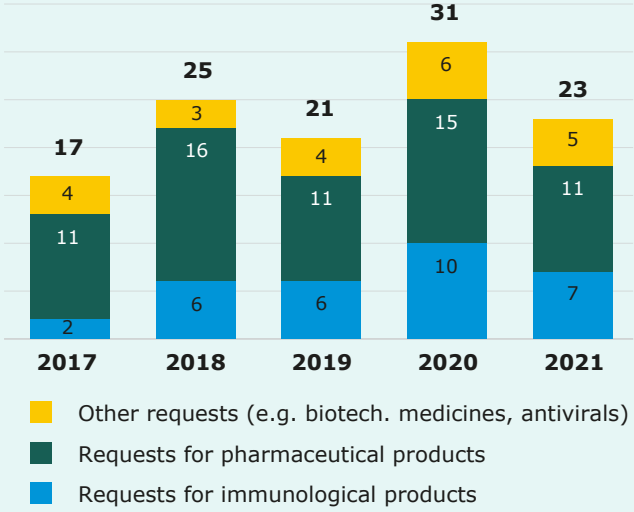
Scientific advice

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. In 2021, EMA received 23 requests for scientific advice and finalised 24, including some pending from 2020. Almost a third of all scientific advice requests received were for immunologicals, including vaccines. These types of medicine play a major role in protecting animal health by preventing and controlling serious epizootic diseases. They also have an impact on human health by ensuring safe food supplies and preventing animal-to-human transmission of infectious diseases. In addition, veterinary vaccines can be an efficient tool in reducing the need to use antibiotics in animals, thereby contributing to the fight against AMR.

Scientific-advice requests received and finalised



Scientific-advice requests received by area



Minor use minor species

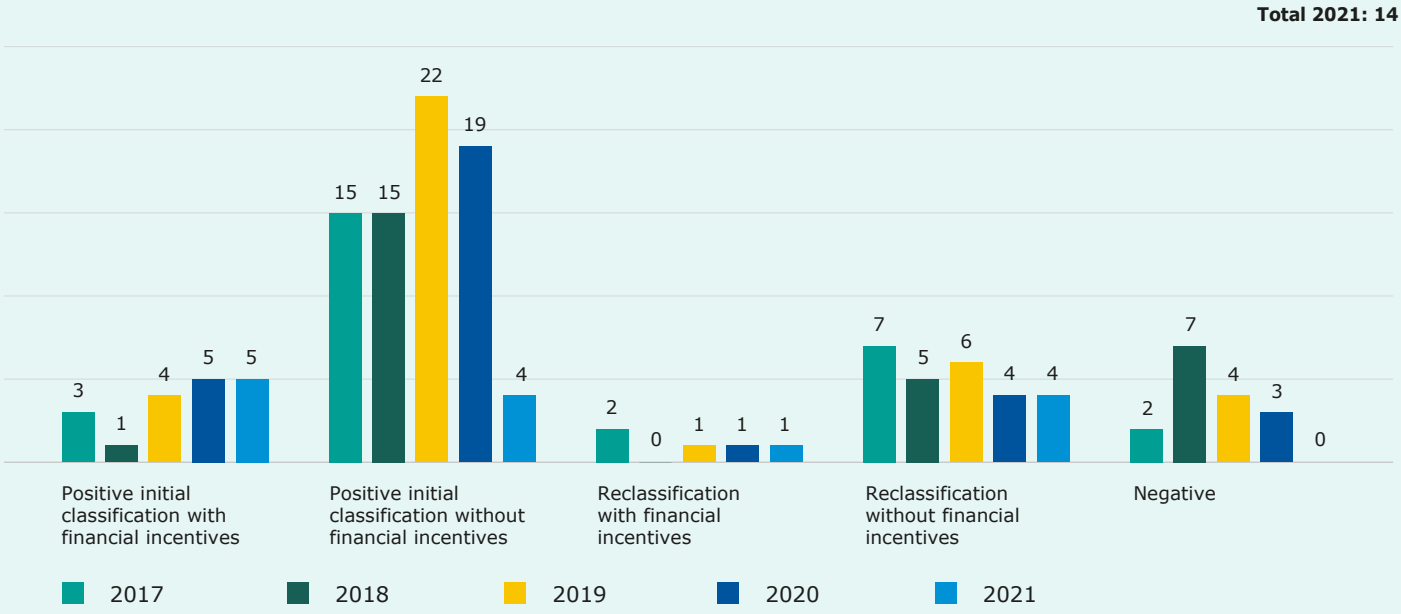
The Agency's minor use minor species (MUMS)/ limited market policy aims to assist companies with the submission of applications for products for limited markets. The goal is to stimulate the development of veterinary medicines for minor species, and for rare diseases in major species, which would otherwise not be developed in the current market environment. In 2021, the Agency received a total of 14 new requests for the (re)classification of veterinary medicines intended for MUMS/limited markets.

Among the 14 outcomes in 2021, eight 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 six requests.

Of the medicines classified previously as MUMS/ limited market, three products were recommended by the CVMP for marketing authorisation in 2021:

- **Fatrovax RHD**, a new vaccine used to reduce mortality and signs of rabbit haemorrhagic disease;
- **Felpreva**, a new veterinary medicine for cats with, or at risk from, mixed parasitic infestations;
- **Strangvac**, a new vaccine given to horses from 8 months of age to reduce clinical signs of the acute stage of strangles (an infection of the upper respiratory tract and regional lymph nodes of horses caused by the bacterium *Streptococcus equi*).

MUMS/limited market (re)classification requests outcome



Support to SMEs

EMA's SME office promotes innovation and development of medicines by SMEs. It provides regulatory assistance and financial incentives to SMEs for the development and authorisation 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. Out of the 1,780 SMEs registered with EMA at the end of 2021, 61 were developing veterinary products and 78 both human and veterinary products. An SME submitted one of the nine applications for marketing authorisation for veterinary medicines in 2021. The CHMP gave a positive opinion for two medicines developed by SMEs. The Agency received six new requests for scientific advice relating to the quality, safety or efficacy of medicines for veterinary use submitted by SME applicants, which represent 26% of the total requests.

Innovation Task Force

The ITF is a multidisciplinary group that includes scientific, regulatory and legal expertise from across the EU. 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. Two ITF meetings were held in 2021 concerning the development of veterinary medicines.

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 the development of medicines and ensure that they are safe, effective and of high quality. Guidelines are drafted by EMA working parties comprising experts from across Europe.

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

A selection of reflection papers and guidance issued or revised in 2021 is listed below:

Topics	Content
Antimicrobial resistance	Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances
	Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products in the EU
	Reflection paper on the use of aminopenicillins and their beta-lactamase inhibitor combinations in animals in the European Union: development of resistance and impact on human and animal health
Efficacy of veterinary medicines	Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6
Environmental risk assessment	Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products
Immunologicals	Guideline on clinical trials with immunological veterinary medicinal products
	Guideline on data requirements for authorisation of immunological veterinary medicinal products under exceptional circumstances
	Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6
Pharmacovigilance	Guideline on veterinary good pharmacovigilance practices (VGVP) Collection and recording of suspected adverse events for veterinary medicinal products
	Guideline on veterinary good pharmacovigilance practices (VGVP) Controls and pharmacovigilance inspections
	Guideline on veterinary good pharmacovigilance practices (VGVP) Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files
	Guideline on veterinary good pharmacovigilance practices (VGVP) Signal management
	Guideline on veterinary good pharmacovigilance practices (VGVP) Veterinary pharmacovigilance communication
Quality of veterinary medicines	Guideline on Manufacture of the Veterinary Finished Dosage Form
Safety of veterinary medicines	Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6
	Concept paper for the revision of residues guidelines to align with the definitions for withdrawal periods provided in Regulation (EU) 2019/6
	Concept paper on the development of a guideline on determination of the need for an MRL evaluation for biological substances

Note: A full list of reflection papers and guidelines issued in 2021 can be found in the annexes.

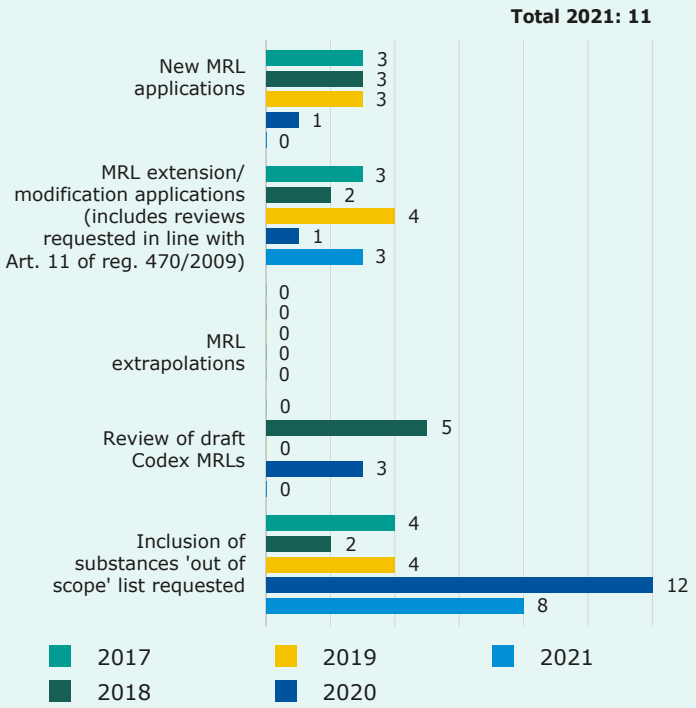
In addition, the CVMP adopted revised guidelines, including administrative changes made to align them with the new definitions and terminology provided by Regulation (EU) 2019/6. The references to the applicable legislation and other scientific guidelines were also updated in 2021. As no changes were made to the scientific content, no concept papers and no public consultation were deemed necessary. The revised guidelines came into effect on 28 January 2022.

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 European Commission on the basis of a recommendation from the CVMP. In 2021, the CVMP received applications for the extension or modification of existing MRL classifications for three substances.

Non-active ingredients considered not to exert pharmacological effects, including many excipients, are considered to fall outside the scope of the MRL Regulation. The CVMP determines on a case-by-case basis whether a non-active ingredient exhibits pharmacological effects and poses a risk to the consumer. If the CVMP concludes that no MRL evaluation is required, EMA includes the substance in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In 2021, the CVMP reviewed eight requests for the inclusion of substances in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009.

Evaluation of maximum residue limits

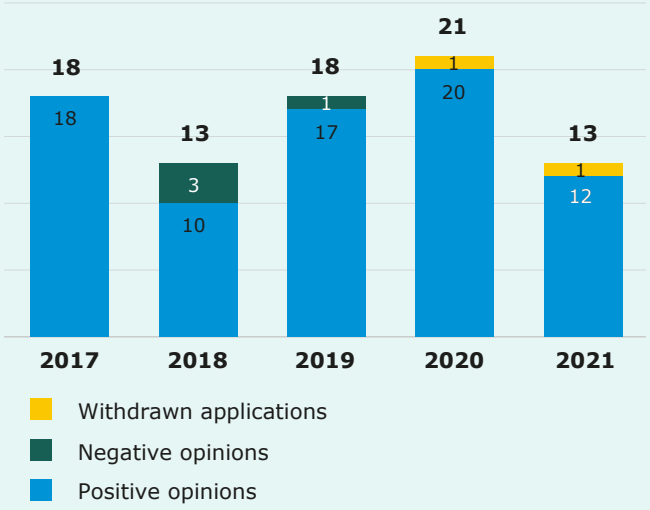


Recommendations for marketing authorisations

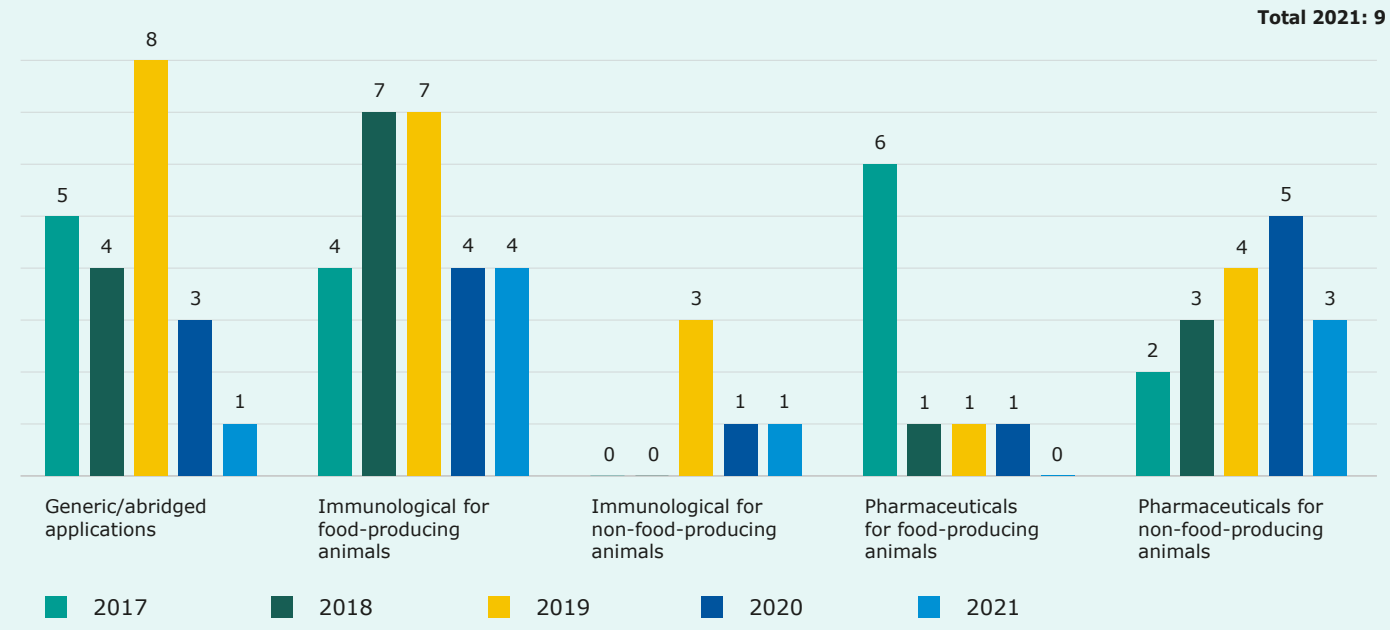
Applications for initial evaluation

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 to evaluation by the CVMP and the granting of marketing authorisation by the European Commission. A total of nine applications were received in 2021. More than half of the applications were submitted for immunologicals. Four applications were for immunological products for food-producing animals.

Outcome of initial-evaluation applications



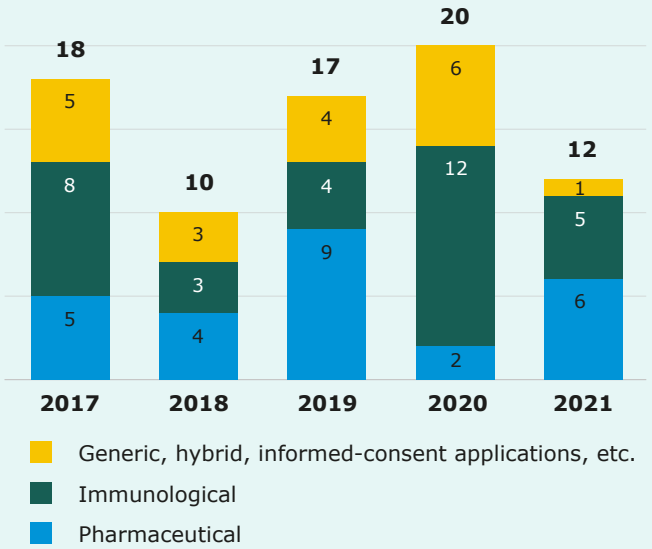
Applications for initial evaluations received



RECOMMENDATIONS FOR AUTHORISATION

In 2021, 12 new veterinary medicines were granted a positive opinion. Of these, seven had a new active substance. Five were vaccines, including four new biotechnological vaccines. This demonstrates the animal health industry's continued strong interest in developing vaccines. Vaccines are an alternative option for combating infectious diseases and by reducing the need for antimicrobials, they also indirectly reduce the risk of AMR in food-producing animals.

Positive opinions for veterinary medicines



Medicines recommended for approval in 2021

Dogs

Credelio Plus
Daxocox
Imoxat
Tessie
Zenalpha

Cats

Bonqat
Felpreva
Imoxat

Pigs

CircoMax
Suiseng Diff/A

Chickens

Ultifend ND IBD

Ferrets

Imoxat

Horses

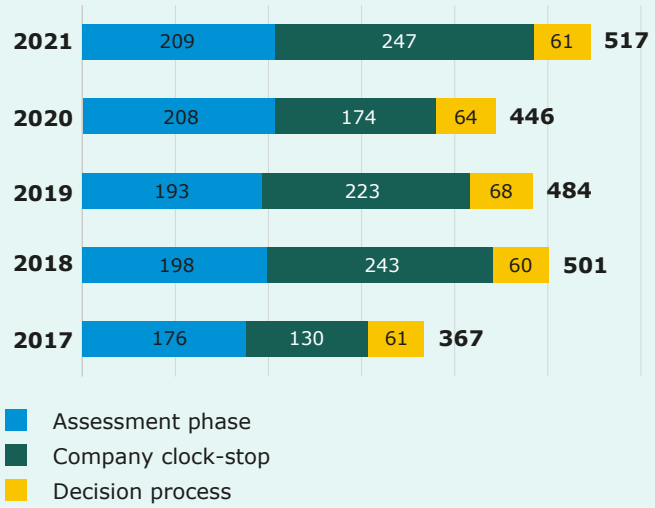
Strangvac

Rabbits

Fatrovax RHD

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 slightly increased compared to the past years, mostly due to longer clock-stops.

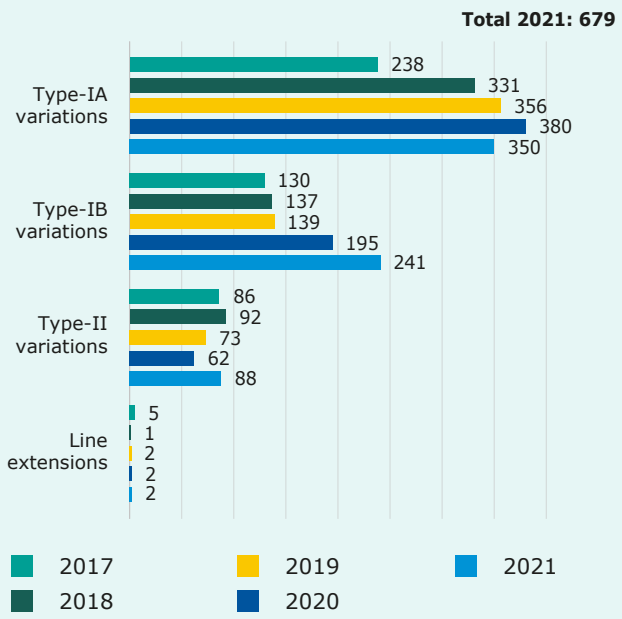
Post-authorisation activities

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 2021, the overall number of post-authorisation applications increased by more than 6% due to the availability of more products on the market.

The use of five known products was expanded in 2021:

- **Bravecto**, also to be used for reduction of the risk of infection with *Babesia canis canis* via transmission by Dermacentor reticulatus for up to 12 weeks in dogs.
- **Cortavance**, also to be used for alleviation of clinical signs associated with atopic dermatitis in dogs.
- **Improvac**, also to be used for suppression of oestrus in female pigs.
- **NexGard Combo**, also to be used for the treatment of notoedric mange (caused by *Notoedres cati*), the treatment of infections with *Aelurostrongylus abstrusus* (L3, L4 larvae and adults) and prevention of aelurostrongylosis in cats.

Post-authorisation applications received



- **Suvaxyn CSF marker**, also to be used for active immunisation of breeding sows in order to reduce infection of their unborn piglets by classical swine fever virus (CSFV).

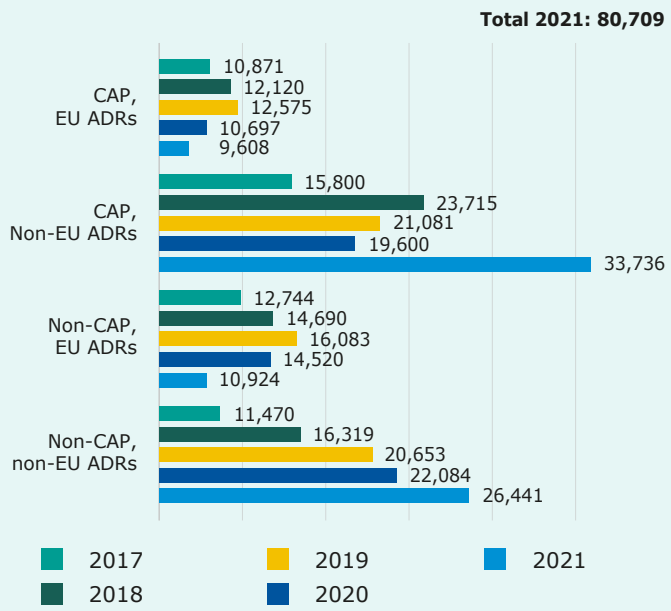
Safety monitoring of medicines

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

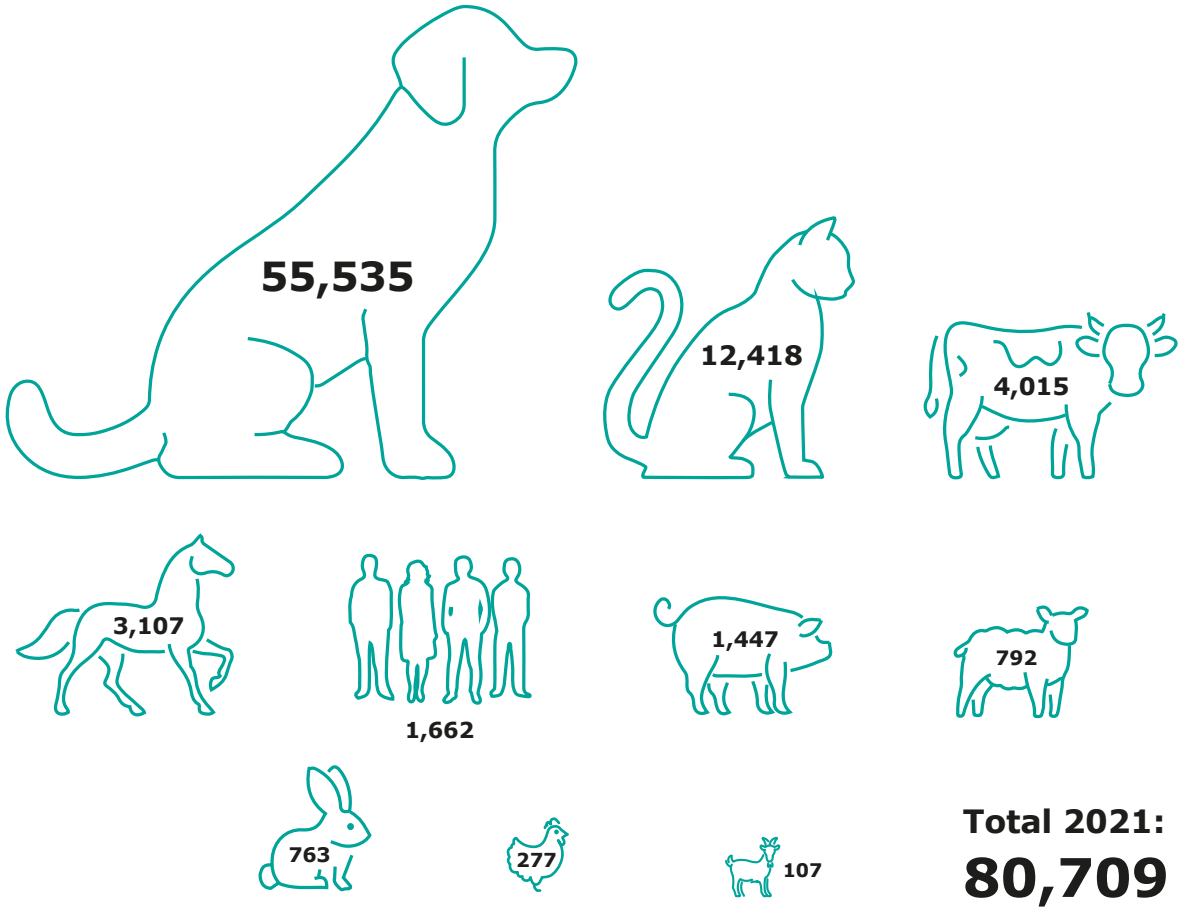
EudraVigilance

There was an increase of 21% in the number of AE reports received in the EudraVigilance system in 2021 compared to 2020. A growth in reporting can be expected due to the increased number of centrally authorised veterinary medicinal products and the improved awareness among veterinarians of the value of pharmacovigilance reporting, as well as greater control by regulators of the implementation of pharmacovigilance requirements by the veterinary pharmaceutical industry.

Adverse-event reports in animals



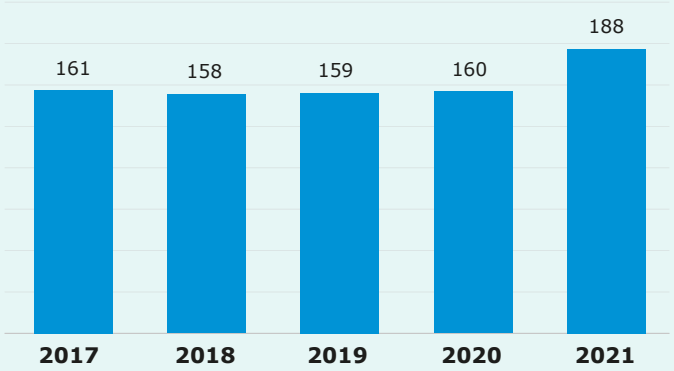
Number of adverse-event reports per species



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 related studies carried out (in authorised and unauthorised indications). The CVMP started the assessment of 188 PSURs in 2021. This number of PSURs reflects the progressive accumulation of products authorised through the centralised procedure.

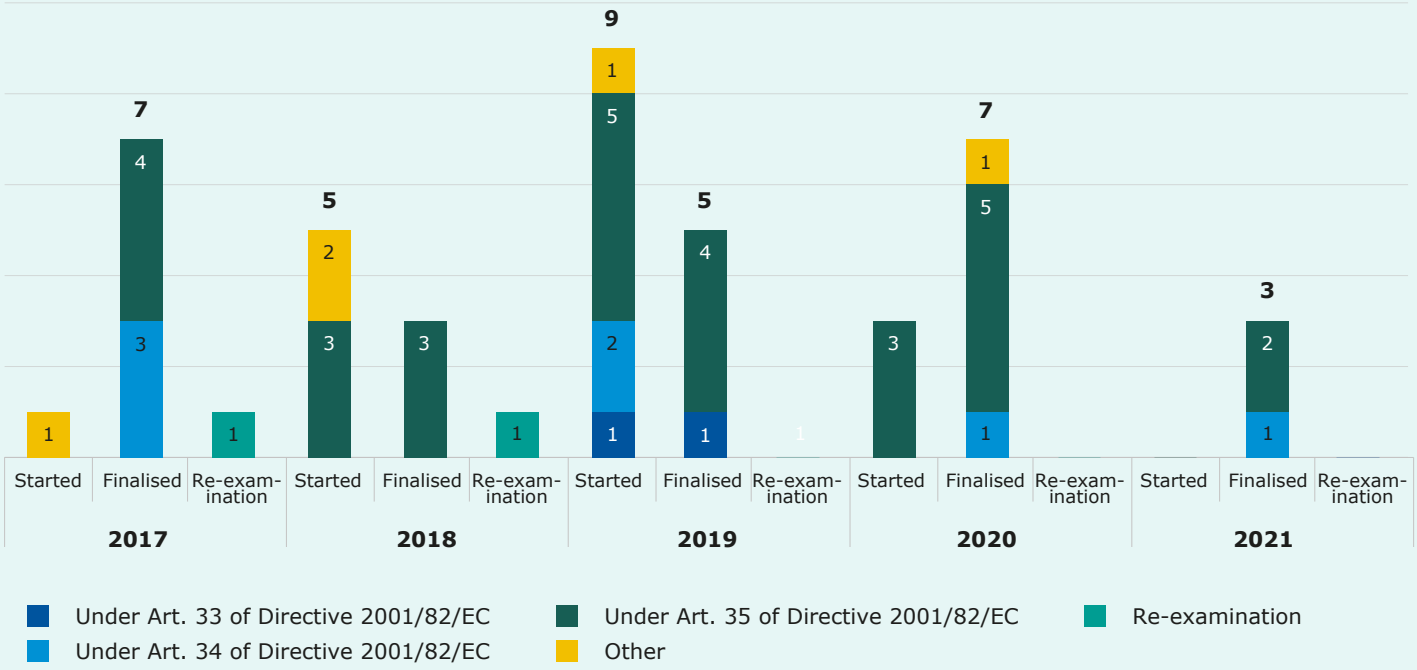
Periodic safety update reports



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 European Commission. Three referral and arbitration procedures related to veterinary medicinal products were finalised in 2021. Among these, two were safety- or efficacy-related (under Article 35 of Directive 2001/82/EC).

Arbitration and referrals for veterinary medicines

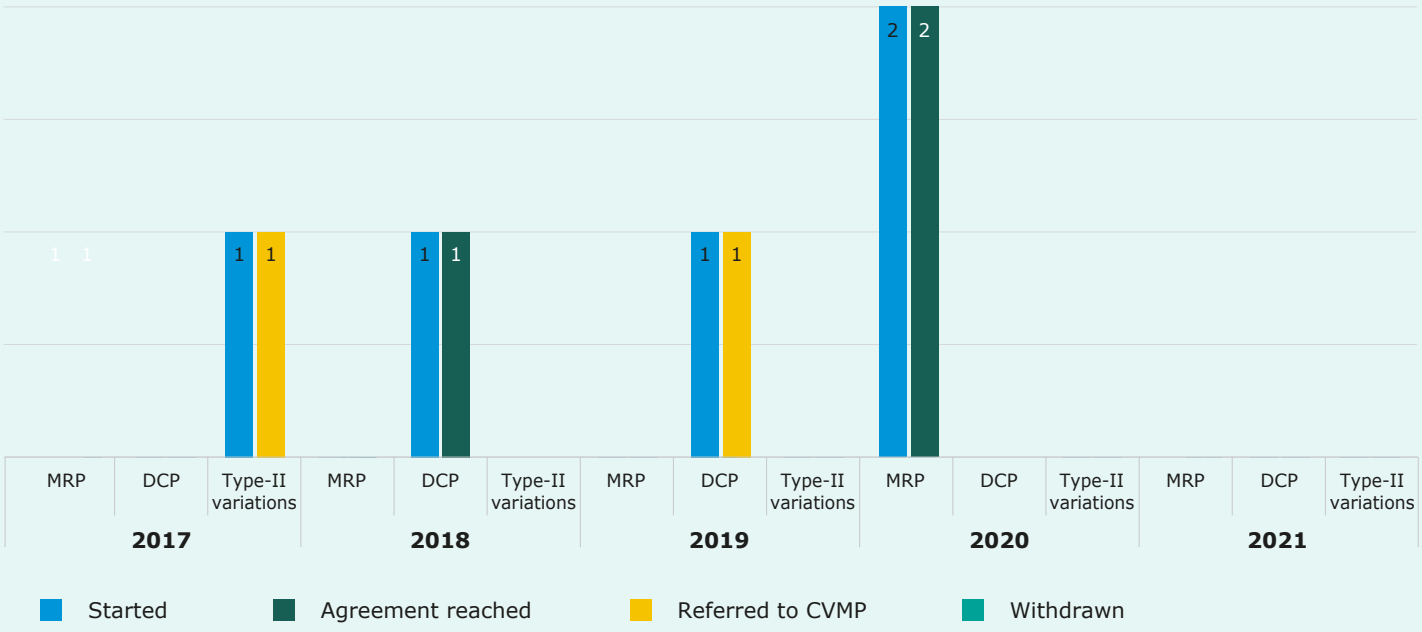


Note: Complete information on referral procedures can be found in the annexes.

Mutual recognition and decentralised procedures

The Agency provides secretarial support to the 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, which constitute the primary routes for veterinary medicines entering the EU market.

Applications referred to the CMDv



EUROPEAN MEDICINES REGULATORY NETWORK

The European medicines regulatory network – a partnership between EMA, the European Commission and 50 medicines regulatory authorities in the EU and the EEA – is the basis of the success of EMA.

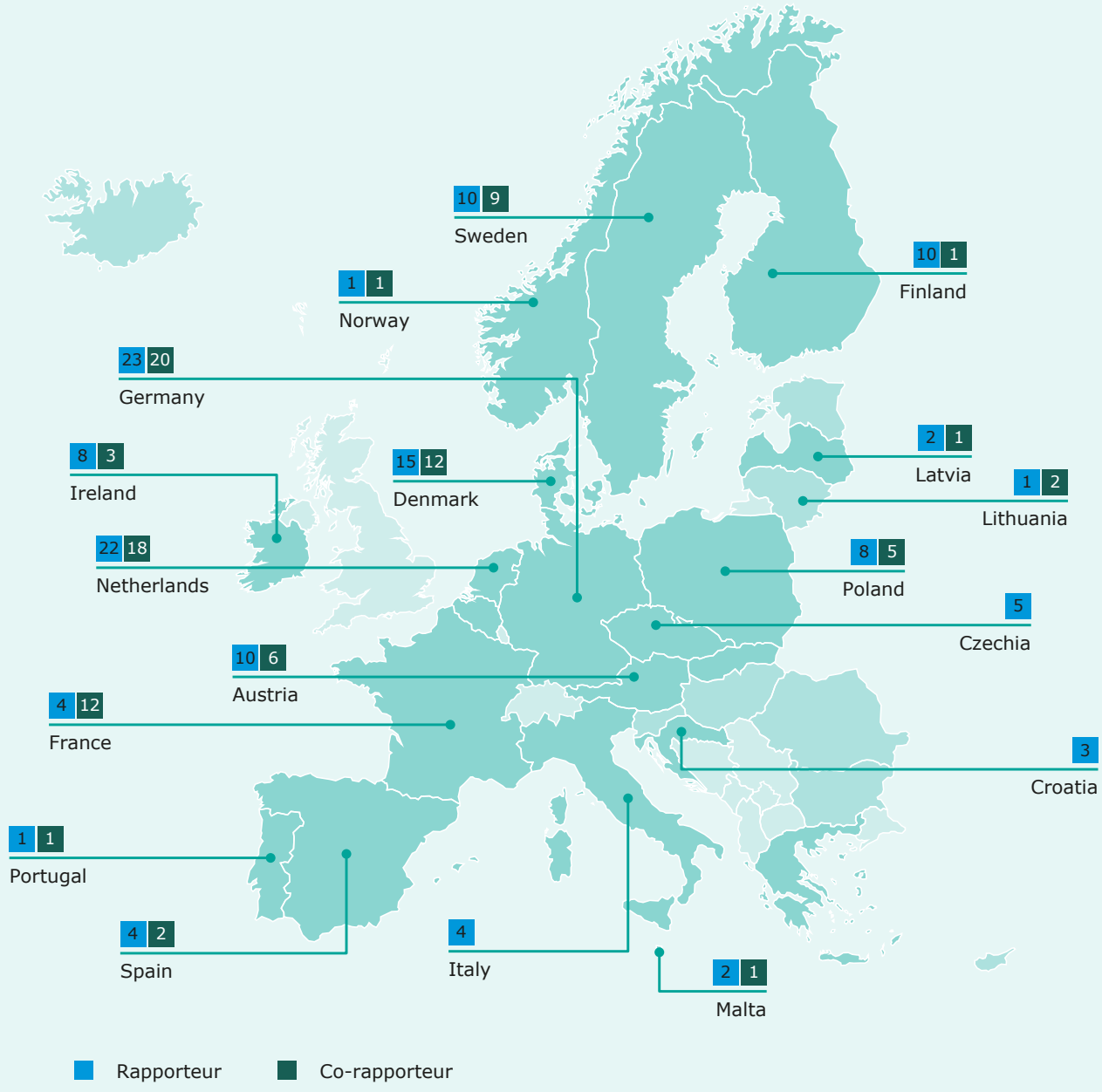
The network gives the Agency access to a pool of over 4,000 experts, who provide the best available scientific expertise for the regulation of medicines in the EU. Experts participate in the work of the Agency as members of its committees, working parties, Scientific Advisory Groups (SAGs) and a number of ad hoc advisory groups as well as members of the assessment teams carrying out the evaluation of medicines (see annex for further information on these groups).

Rapporteurships 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.

PRAC rapporteurs/co-rapporteurs appointed in 2021

PRAC rapporteurs/co-rapporteurs appointed in 2021
(for initial marketing autorisation applications)



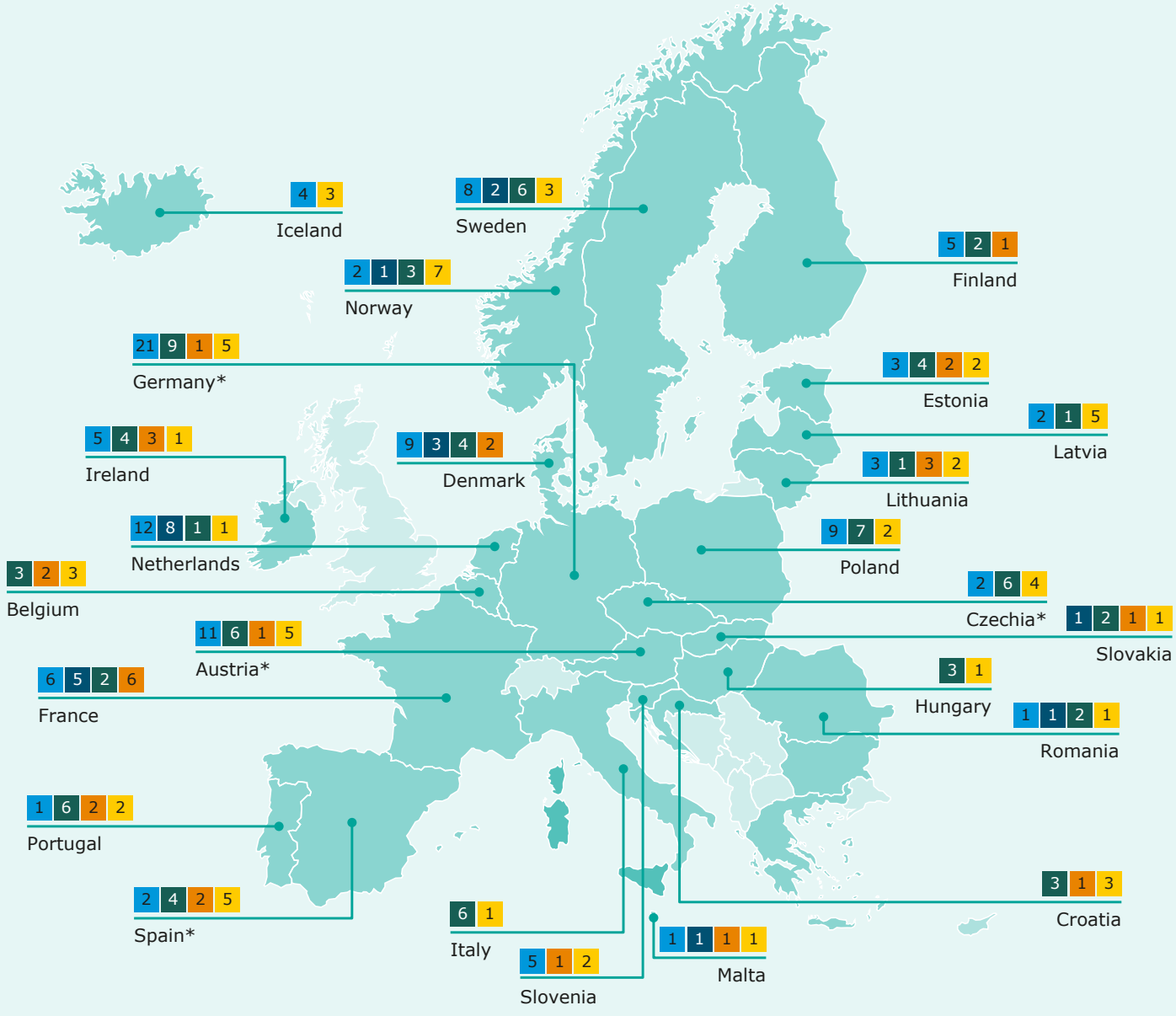
CHMP rapporteurships/co-rapporteurships

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

The table below presents the number of procedures for which each country in 2021 was appointed 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 2021

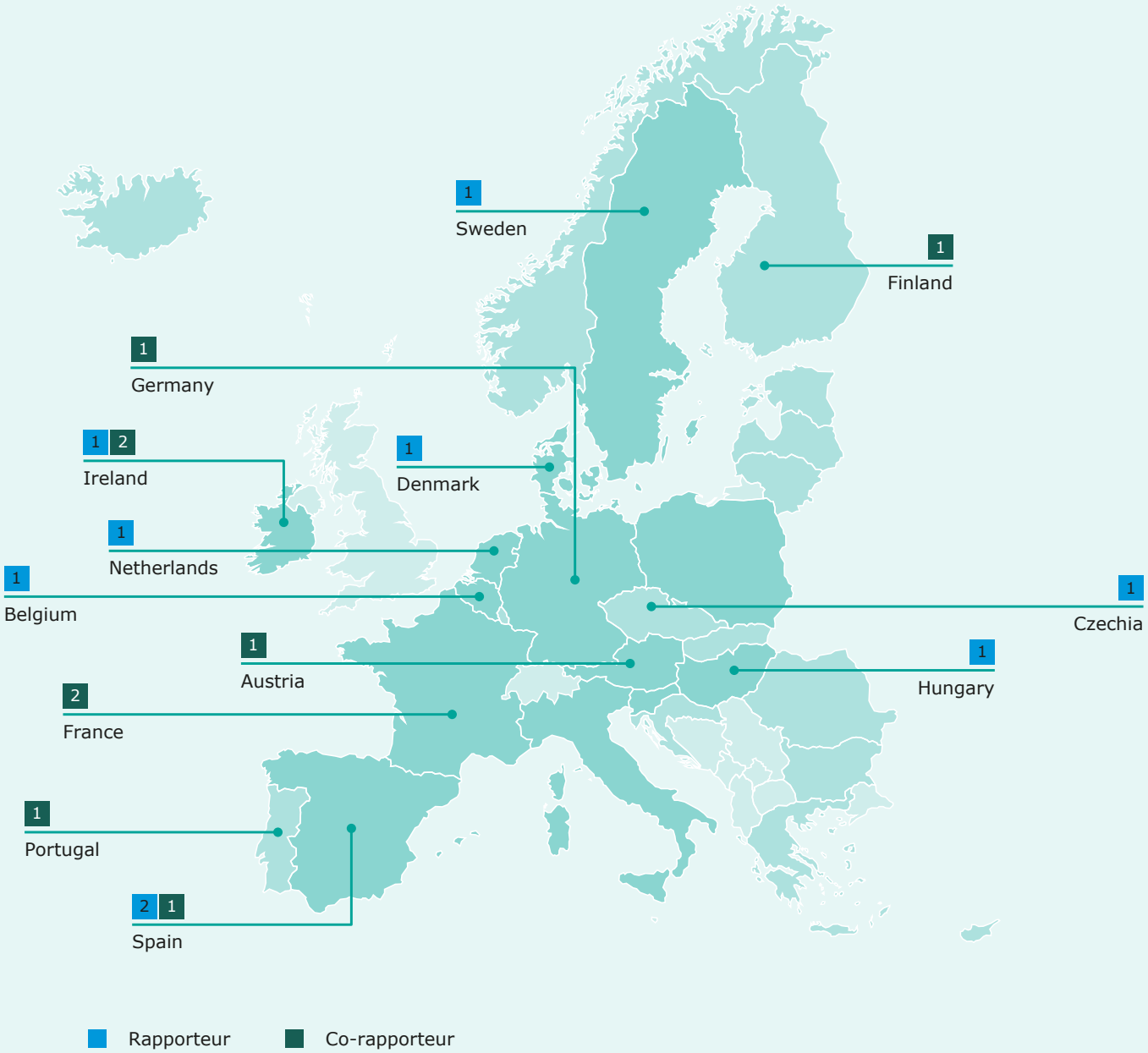
(for initial marketing autorisation applications, including generics)



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

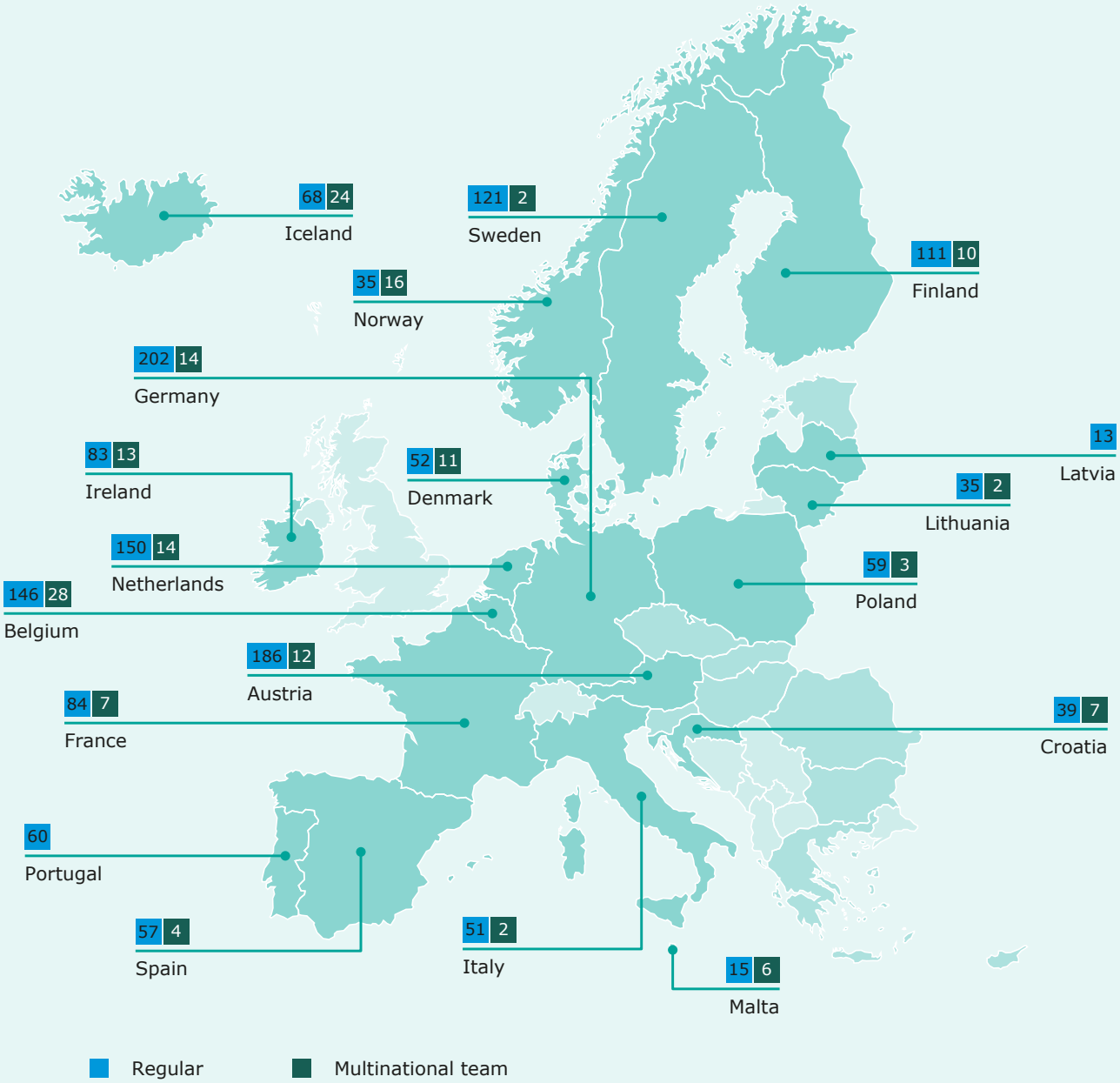
CVMP rapporteurships/co-rapporteurships

CVMP rapporteurs/co-rapporteurs appointed in 2021
(for initial marketing autorisation applications, including generics)



Scientific advice working party (SAWP)

SAWP coordinators appointed in 2021



Working parties: revised role, structure and scope

EMA's Management Board has endorsed a new operational model for EMA Working Parties to rationalise their structure and operations. It foresees five strategic oversight bodies, known as Domains, quality, non-clinical safety, methodology, clinical and veterinary. Domains are composed of (vice) chairs of relevant committees, working parties and SAGs. They will perform STORES (Strategic, Tactical, Operational, Reactive, Educational, Stakeholder) functions and produce three-year rolling strategic plans on the dynamic implementation of the Network and Regulatory Science Strategies to 2025. Domains will coordinate and oversee activities within the organisation entities reporting to them.

Four organisational entities will report to the Domains:

- European Specialised Expert Communities (ESECs), composed of experts in a given topic area, are the source of expertise when constituting tDGs, OEGS and working parties.
- Temporary Drafting Groups (tDGs) responsible for drafting guidelines.
- Operational Expert Groups (OEGs), which will provide advice to the CHMP/SAWP and the PRAC on ongoing scientific advice and product assessments as required.
- Working parties will continue to perform certain tasks associated with the drawing up of scientific opinions or the work of the Committees.

The new model will deliver strategic priorities, be adaptable to future needs, reach out to stakeholders, and ultimately make the EU more competitive in global drug development. It will redistribute expertise in a more agile structure such as OEGs and tDGs and thus reduce the number and membership of standing working parties. ESECs will increase efficiency and consistency by providing information flow to the network, training development and expertise.

EU network training centre

The EU network training centre (EU NTC) is a joint initiative of EMA and the NCAs to address the training needs of the EU medicines regulatory network on both human and veterinary medicines. The table below highlights its key activities from when it was established in 2015 to 2021.

	2015	2016	2017	2018	2019	2020	2021
New scientific, regulatory and telematics curricula developed	1	8	0	2	2	2	1
Number of training events advertised to the EU Network	105	140	100	60	40	46	77
Number of reimbursed training events for the EU Network	7	25	20 (14 by EU NTC)	8 (5 by EU NTC)	12	1	0
Number of NCAs that have opened their training for inclusion in EU NTC Learning Management System	6	14	8	7	10	7	15
Number of users registered to the EU NTC Learning Management System		2,117	3,583	4,424	5,121	5,290	5,916
Number of NCA experts registered to the EU NTC Learning Management System		1,225	2,668	3,480	4,143	4,297	4,872

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 requested by the CHMP or CVMP in the context of the assessment of marketing authorisation applications and/or matters referred to these committees in accordance with EU legislation.

The responsibility for carrying out inspections rests with EU NCAs but EMA plays a coordinating role.

EMA also coordinates the preparation and maintenance of risk-based inspection programmes to verify compliance with the principles of GMP, GCP and pharmacovigilance at the EU level, in the following:

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

In the area of inspections, EMA ensures the best use of resources by promoting mutual reliance and work-sharing with other international authorities. For GMP inspections, there are several mutual-recognition agreements in place. EMA and its European and international partners 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 active pharmaceutical ingredients (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 within the EU and internationally, to strengthen global supply chains and improve access to authorised medicines. The delivery of training and capacity building on inspection-related activities for inspectors and assessors, including non-EU regulators, is one focus area for EMA. The Agency is the primary contact point for notification of suspected quality defects for CAPs and coordinates their investigation, evaluation and follow-up. It also operates a sampling-and-testing programme to supervise the quality of CAPs placed on the market and to check compliance of these products with their authorised specifications.

Inspections

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

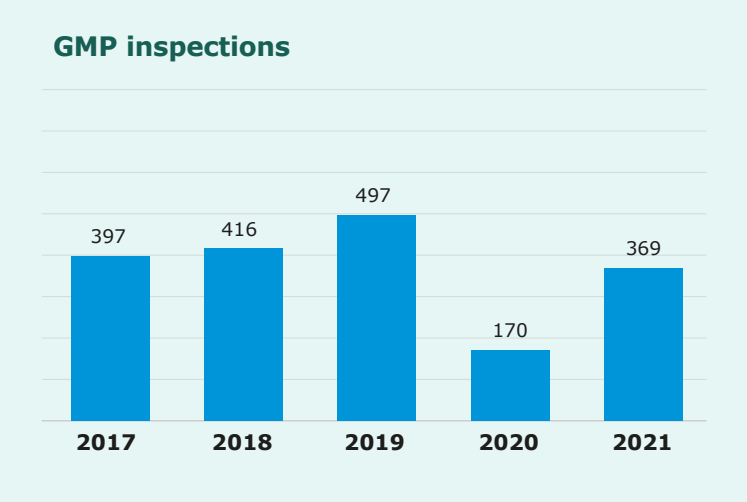
- the evaluation of marketing authorisation applications submitted to regulatory authorities across the EU;
- the oversight of manufacturers importing medicines into the EU;
- the oversight of the conduct of clinical trials in Europe;
- the oversight of compliance with pharmacovigilance obligations.

GMP inspections

The number of GMP inspection requests within the context of the centralised authorisation procedure has increased by 117% compared to 2020.

Five 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.

EEA authorities issued 2 statements of GMP non-compliance relating to CAPs either in connection to the active substance or the finished product, however no recalls were necessary. When inspections lead to findings, companies have to implement corrective action plans agreed with the inspecting authorities.



GMP certificates and non-compliance statements issued by EEA authorities										
	2017		2018		2019		2020		2021	
	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement	GMP certificate	GMP non-compliance statement
EEA/EU	2,115	7	2,213	6	2,235	11	1,695	1	1,825	5
China	39	1	66	4	51	4	11	0	24	0
India	119	7	112	5	105	1	64	0	29	0
USA	106	0	27	0	127	0	35	0	52	0
Rest of the world	97	2	84	1	108	0	38	0	52	0
Total	**2,476**	**17**	**2,502**	**16**	**2,626**	**16**	**1,843**	**1**	**1,982**	**5**

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 2017 and 2021. It includes GMP inspections requested by the CHMP or the CVMP.

GCP inspections

The number of GCP inspections decreased in the last year, from 59 GCP inspections in 2020 to 36 in 2021 due to travel and safety restrictions caused by the global pandemic.

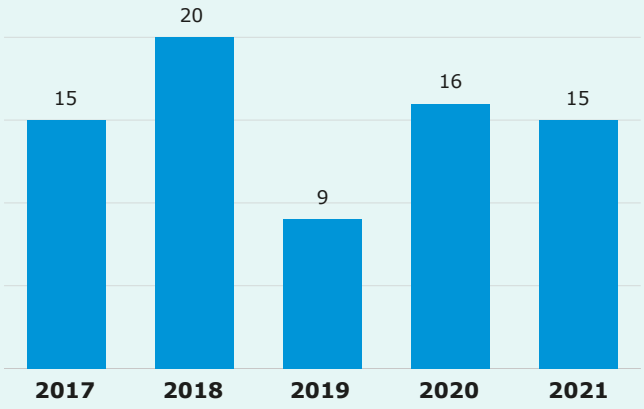
Pharmacovigilance inspections

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

In 2021, 15 pharmacovigilance inspections were requested by the CHMP or CVMP, which is in line with the number of pharmacovigilance inspections requested in 2020.

Most EU/EEA pharmacovigilance inspections (over 90%) are conducted under the national pharmacovigilance inspection programmes, which relate to marketing authorisation holders with product authorisations of all types (including CAPs).

Number of pharmacovigilance inspections



Market surveillance and quality defects

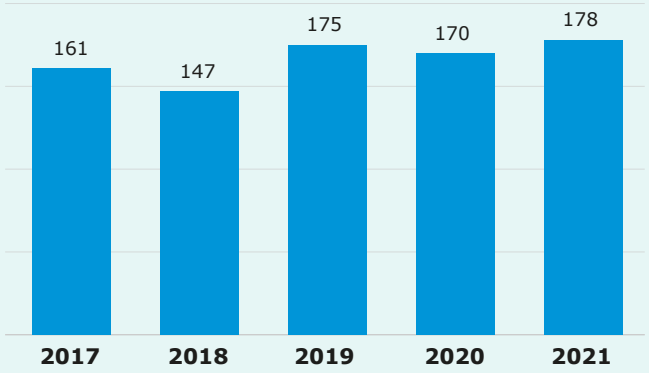
Manufacturers are required to inform authorities of quality defects in batches of a manufactured product. This can lead to a recall of batches from the market or prevention of their release by the manufacturer.

Where a defect is considered to be a risk to public or animal health, the marketing authorisation holder is requested to withdraw the affected batches of the CAP 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 2021, the Agency received 178 suspected quality defect notifications. Of these, 164 cases were confirmed quality defects and led to batch recalls of 10 CAPs.

Number of quality defect notifications received



Recalls due to reported quality defects

	2018	2019	2020	2021
Recalls	27	15	15	10
Class 1	3	3	3	1
Class 2	17	3	3	7
Class 3	7	9	9	2

The main reasons for recall of CAPs in 2021 are summarised in the following table:

2021	Manufacturing laboratory control issues	Product contamination and sterility issues	Product label issues	Product packaging issues	Product physical issues
Class 1				1	
Class 2	2	4		1	
Class 3			2		

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

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

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

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

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

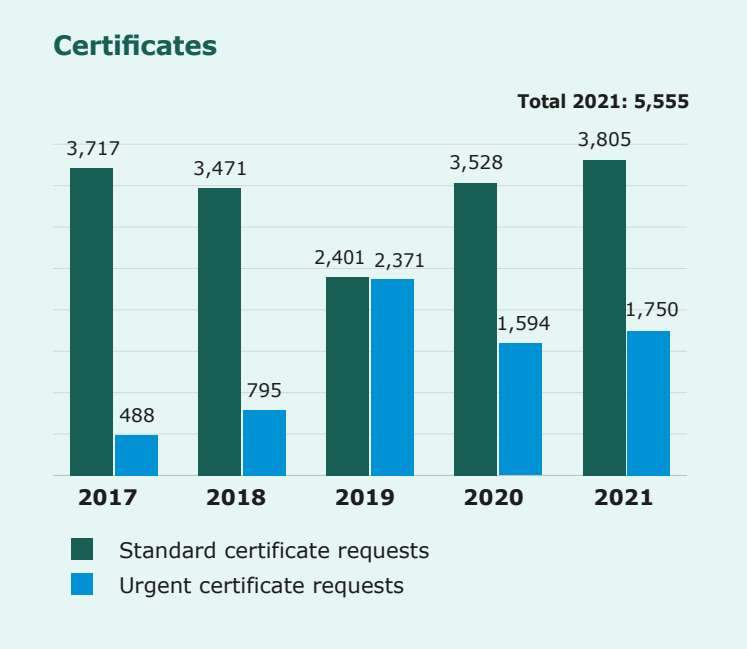
Parallel distribution

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

Parallel distribution notifications received					
	2017	2018	2019	2020	2021
Initial notifications	2,639	2,304	2,468	3,172	2,555
Notifications of change	1,975	2,184	2,103		0
Notifications of bulk change	6	11	12	10	19
Annual updates	5,843	5,245	4,270	11,624	4,816
Total	**10,463**	**9,744**	**8,853**	**14,806**	**7,390**

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.



Requests for certificates

	2017		2018		2019		2020		2021	
	Received	Finalised	Received	Finalised	Received	Finalised	Received	Finalised	Received	Finalised
Standard certificate requests	4,023	3,717	3,703	3,471	2,565	2,401	3,115	3,528	3,753	3,805
Urgent certificate requests	531	488	1,069	795	2,399	2,371	1,647	1,594	1,659	1,750
Total	**4,554**	**4,205**	**4,772**	**4,266**	**4,964**	**4,772**	**4,762**	**5,122**	**5,412**	**5,555**

COMMUNICATION AND STAKEHOLDERS

External communication

EMA's response to the COVID-19 pandemic was of significant interest in 2021.

Overall, in 2021, EMA organised 56 media interviews, all related to COVID-19. The interviews featuring EMA's Executive Director and EMA experts appeared in media outlets across Europe.

EMA held a total of 18 virtual press briefings in 2021, all on COVID-19 topics.

In May 2021, EMA organised its first regular press briefing to provide updates to the media and the public on its most recent activities in the context of the COVID-19 pandemic. Virtual technical briefings for the media were organised on a regular basis. By the end of 2021, EMA had held 13 regular bi-weekly COVID-19 press briefings.

COVID-19 press briefings were regularly attended by journalists from across the EU and further afield, from media outlets including Politico, Reuters, AFP, Bloomberg, MedNous, NOS from Netherlands, EF.SIN from Greece and many more.

In 2021, EMA held three public stakeholder meetings to provide an update on COVID-19 vaccines and therapeutics in the EU.

Around 200 news announcements were published to inform the public about key milestones in medicines assessment or new initiatives about the pandemic (an increase of more than 100% compared to 2020).

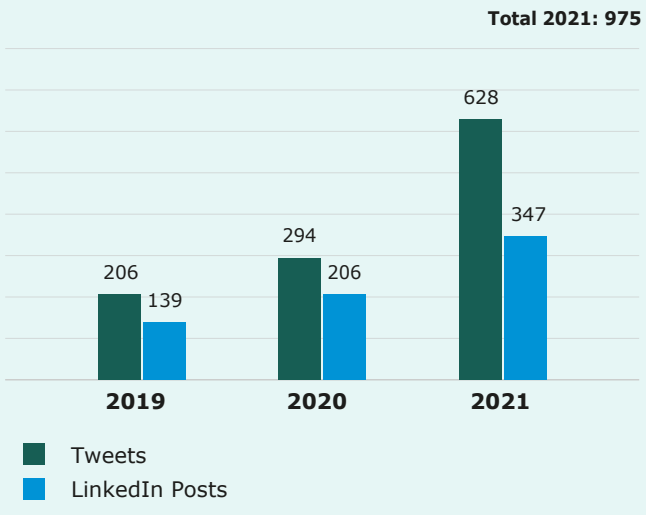
More than 6,500 direct interactions between EMA and patients and healthcare professionals were registered.

EMA published and updated 3,064 webpages on the EMA website in 2021.

Social media

By the end of December, EMA had nearly 110,000 followers on Twitter (an 83% increase compared to 2020) and over 214,000 followers on LinkedIn (a 38% increase compared to 2020). The number of social media posts on EMA's Twitter and LinkedIn profiles increased significantly in 2021. Throughout the year, the Agency ran several social media campaigns to highlight various topics, including campaigns on the safe use of COVID-19 vaccines, European Antibiotic Awareness Day and World Antimicrobial Awareness Week.

Social media posts



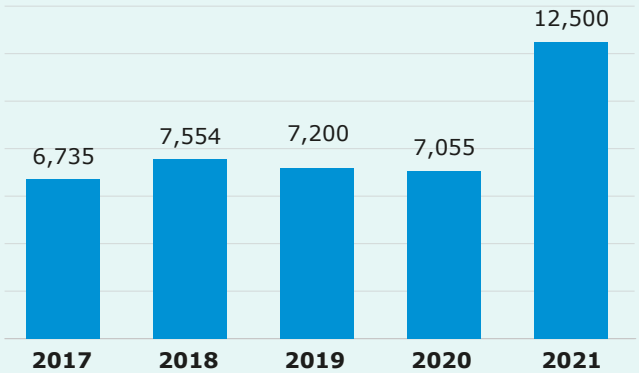
Requests for access to documents

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.

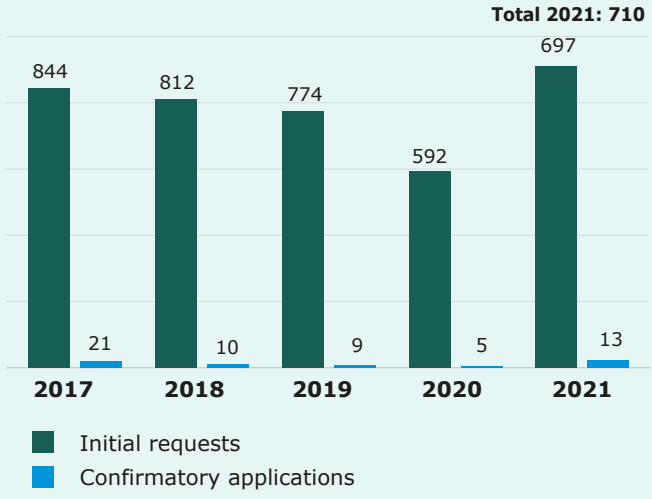
In 2021, EMA received 710 requests for access to documents.

The number of requests for information increased substantially by 77% in 2021, underlining the Agency's enhanced visibility in recent years, especially in view of the roll-out of COVID-19 vaccines across Europe.

Requests for information received

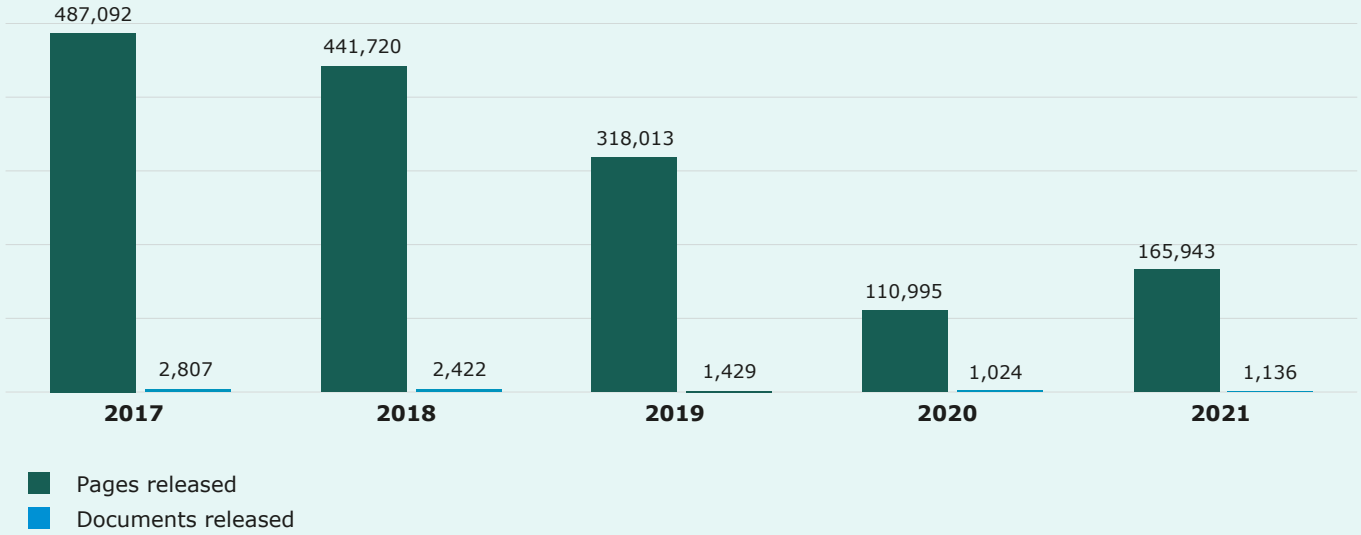


Requests received for access to documents

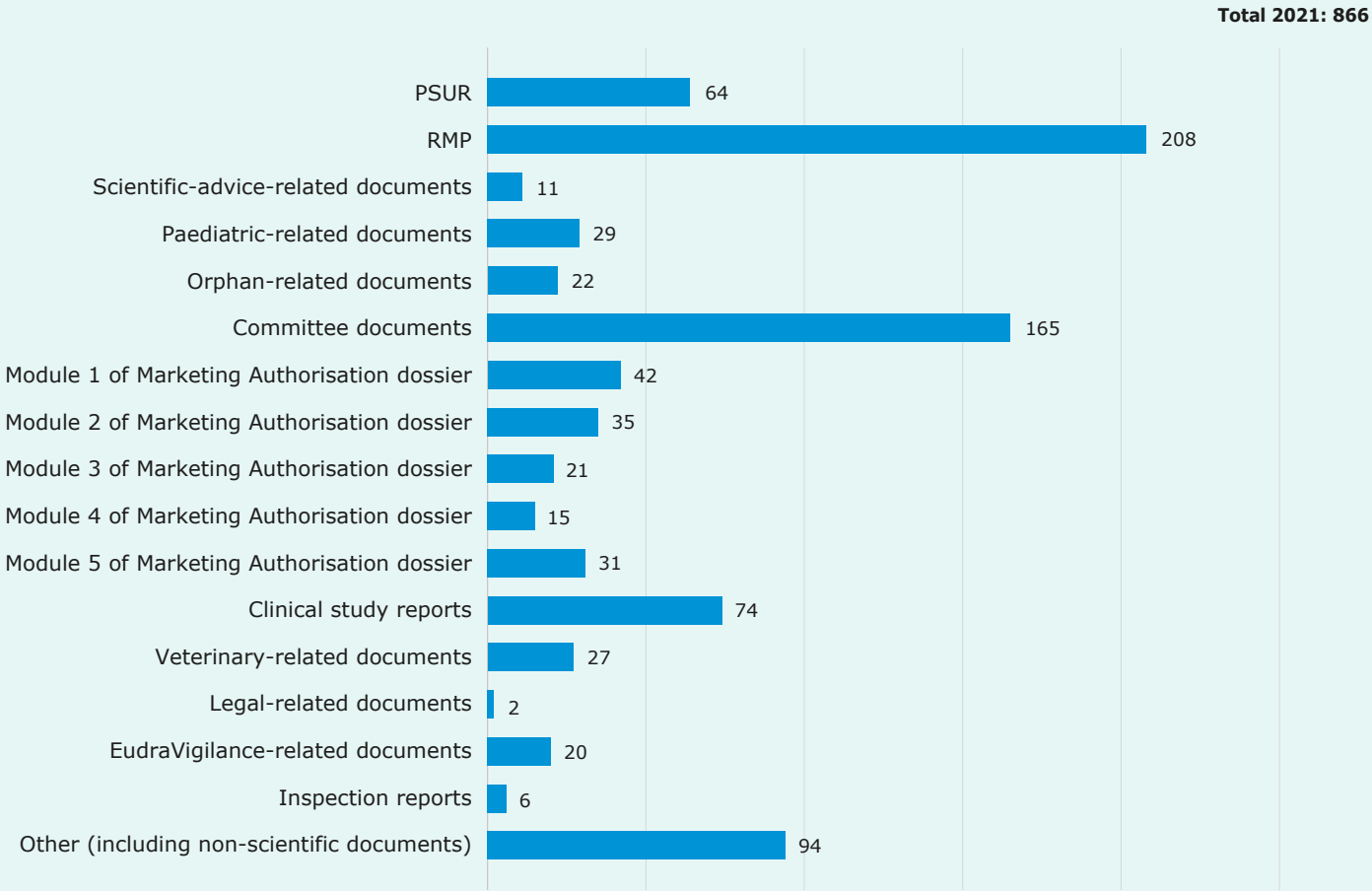


In 2021, the number of documents and pages released increased slightly compared to 2020, when the impact of the implementation of new data protection rules (EUDPR) led to a significant fall.

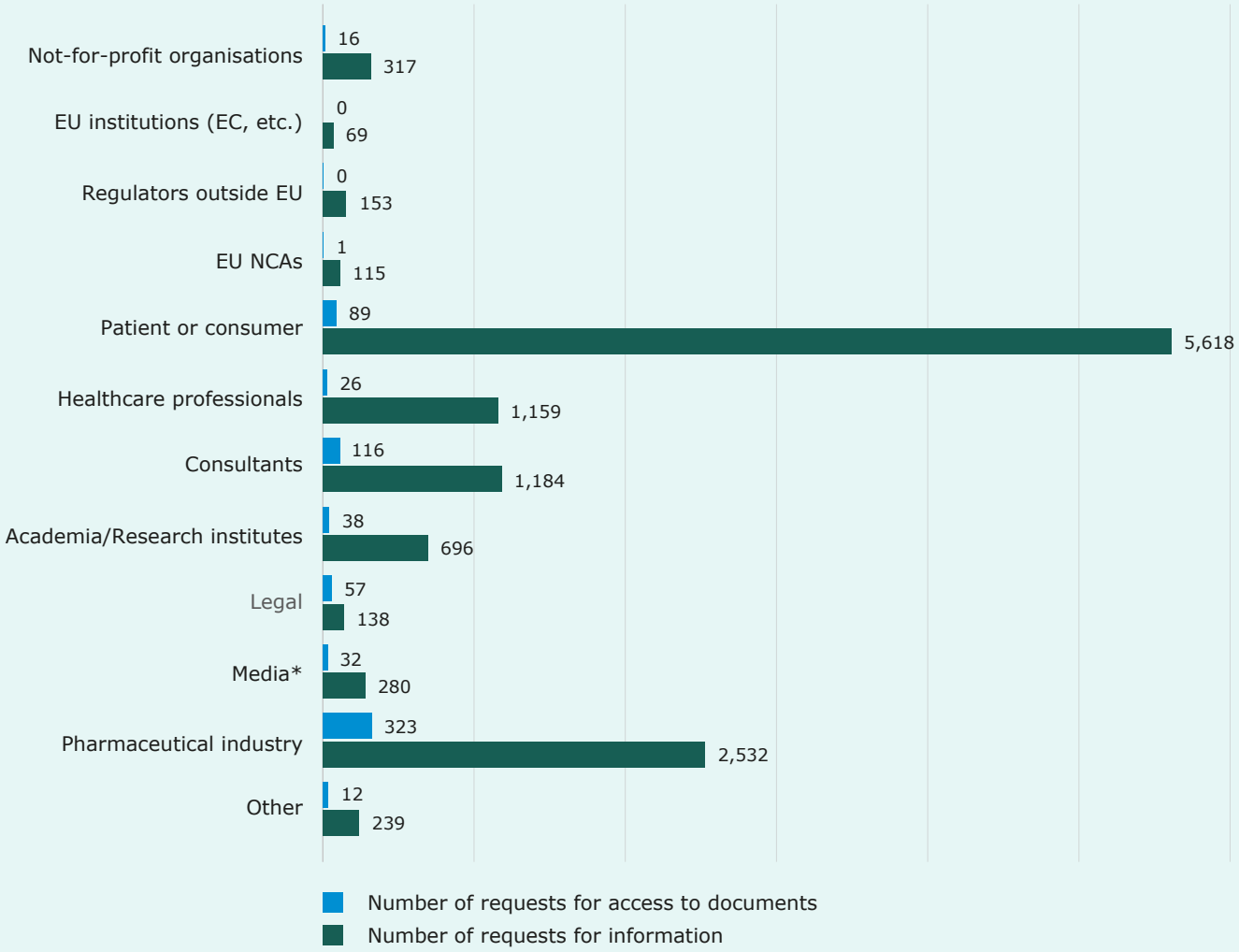
Documents and pages released following access to document requests



Access to documents by type of document (2021)



Affiliation of requestors of access to documents and of information (2021)



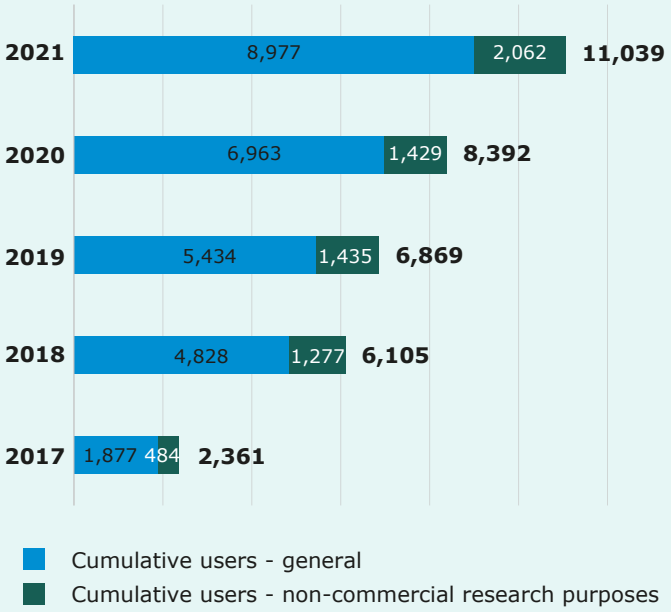
* Requests from media submitted via EMA's online form; does not include requests sent directly to the EMA press office.

Publication of clinical data

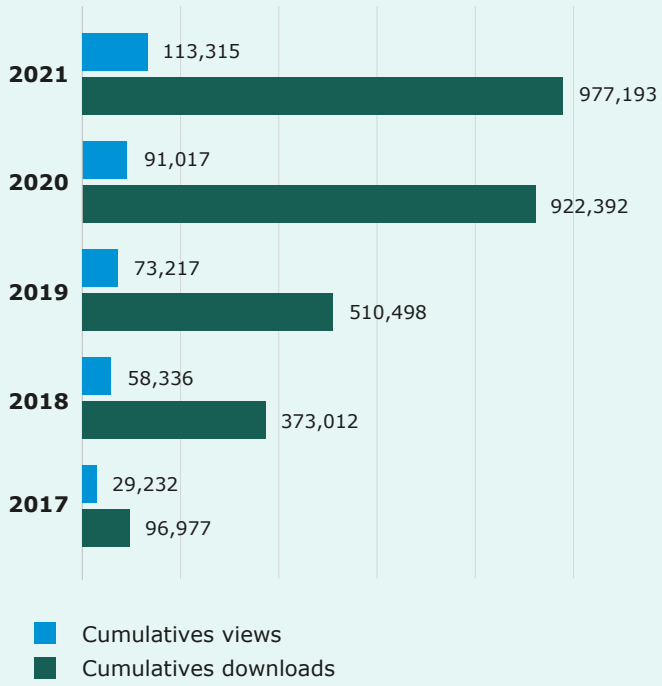
In October 2016, EMA became the first regulatory authority to give open access to clinical data submitted by companies in support of their marketing authorisation applications. EMA had to temporarily suspend all new activities related to clinical data publication in 2018 to ensure business continuity linked to preparations for Brexit and the Agency's relocation from London to Amsterdam.

While overall, clinical data publication remains suspended due to business continuity measures linked to the ongoing pandemic, EMA decided to publish clinical data for COVID-19 medicines in line with its exceptional transparency measures for COVID-19. By the end of 2021, EMA had published the clinical data supporting the authorisation of Moderna and Comirnaty COVID-19 vaccines. Once business continuity measures are lifted, a strategy will be agreed by EMA for resourcing and relaunching the clinical data publication policy, with enhanced collaboration with other international partners.

Clinical data website - users



Clinical data website - usage

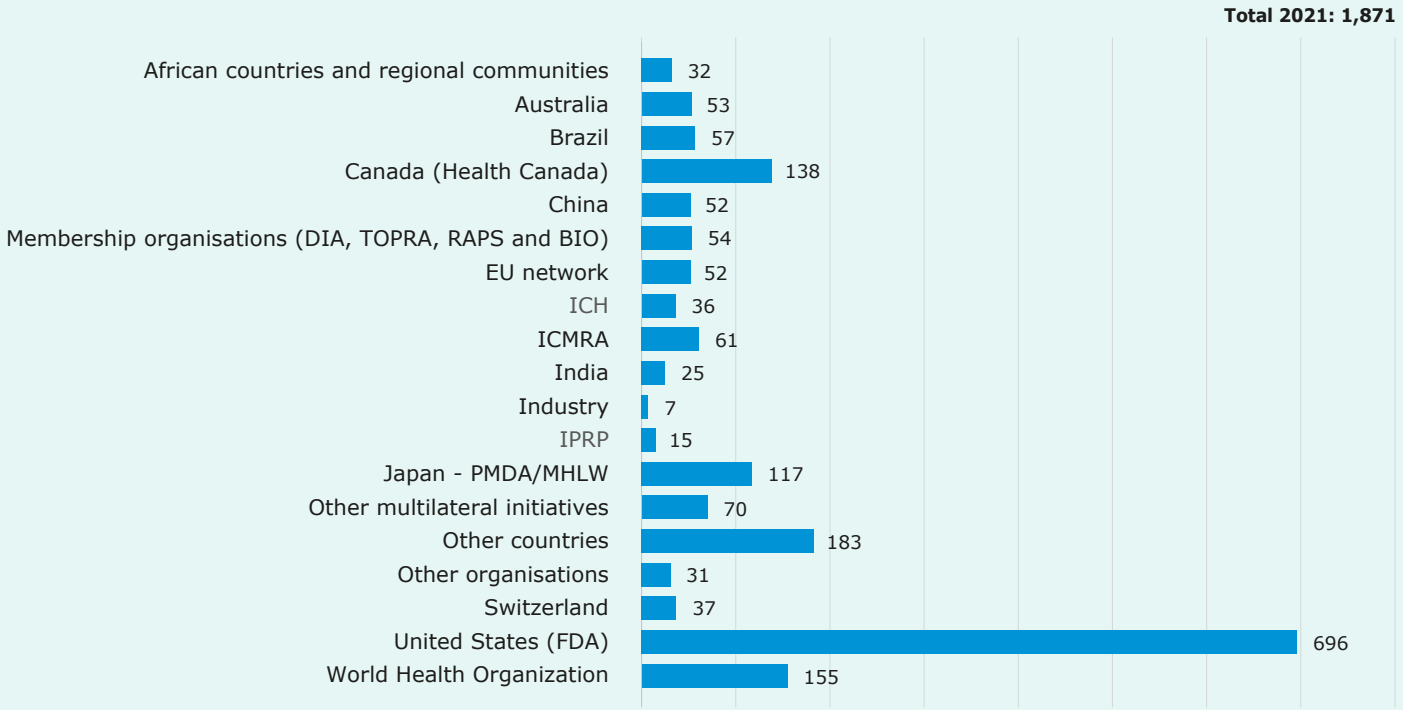


Interaction with international stakeholders

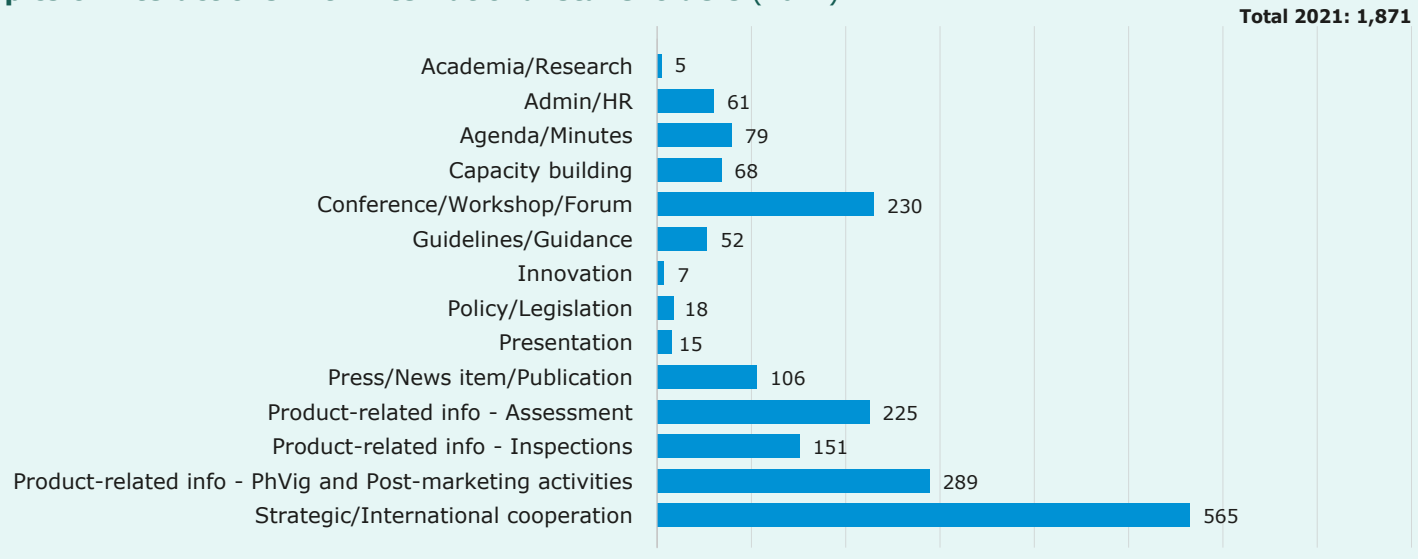
EMA has had an international role since its creation in 1995. Its founding regulation gives the Agency a specific responsibility to provide technical and scientific support for the evaluation of medicines. Today, international cooperation is moving from 'harmonisation' of technical requirements towards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

In 2021, EMA had a total of 1,871 interactions with international stakeholders through its International Affairs department (AF-IA).

Number of interactions per stakeholder (2021)



Topics of interactions with international stakeholders (2021)



ADMINISTRATIVE ASPECTS

Budget – total revenue

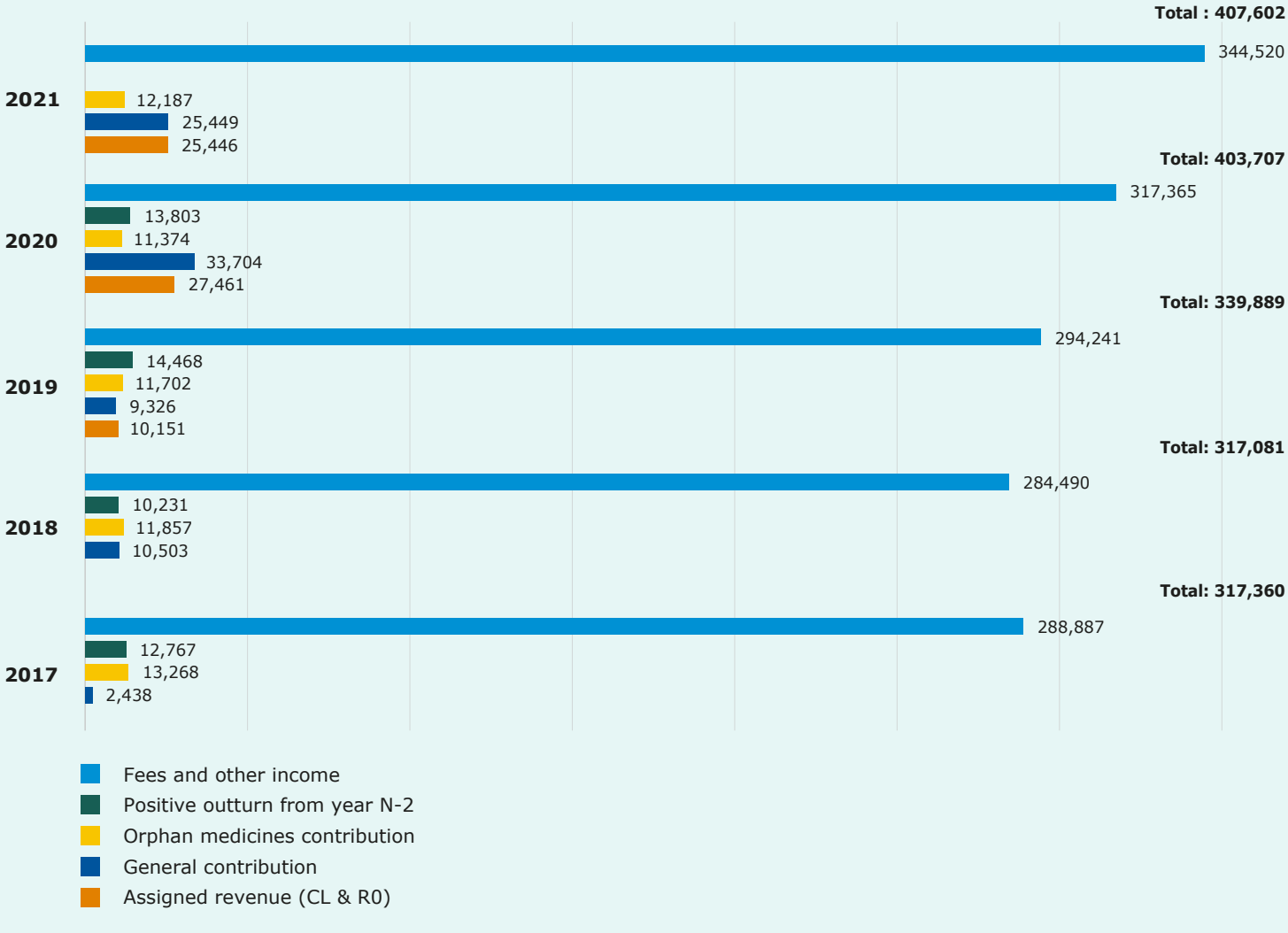
The Agency's total revenue in 2021 was €407.602 million compared to €403.707 million in 2020.

The revised Financial Regulation, which came into effect in 2019, introduced two new funding 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 2021, the assigned revenue received amounted to €25.446 million.

Revenue (in € thousands)



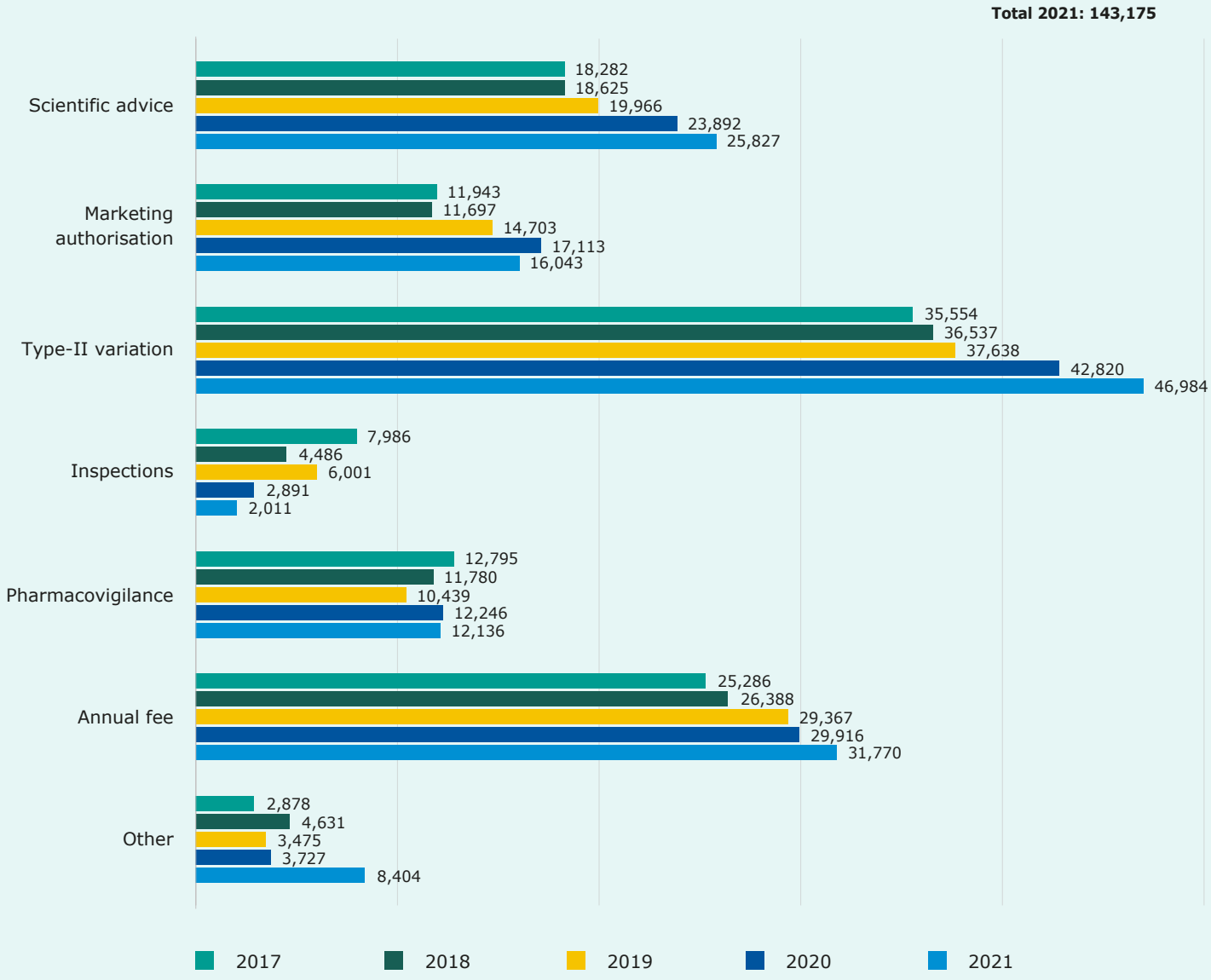
Remuneration to national competent authorities

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

In 2021, EMA paid a total of €143.175 million to the NCAs, compared to €132.605 million in 2020.

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.

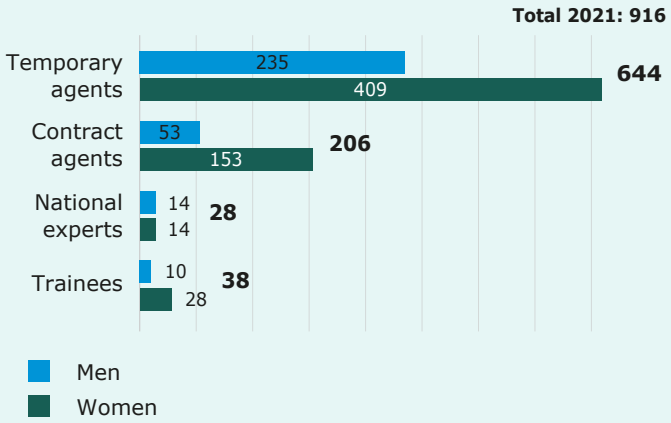
Remuneration to NCAs per fiscal year (in € thousands)



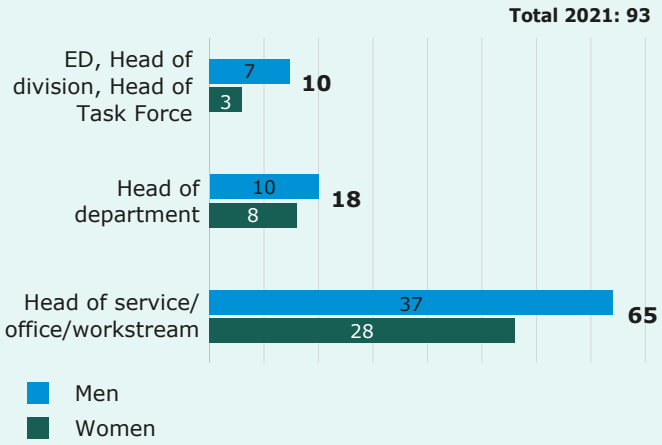
Agency staff

As of 31 December 2021, Agency staff numbered 916: 604 women and 312 men.

Agency staff
(as of 31 December 2021)



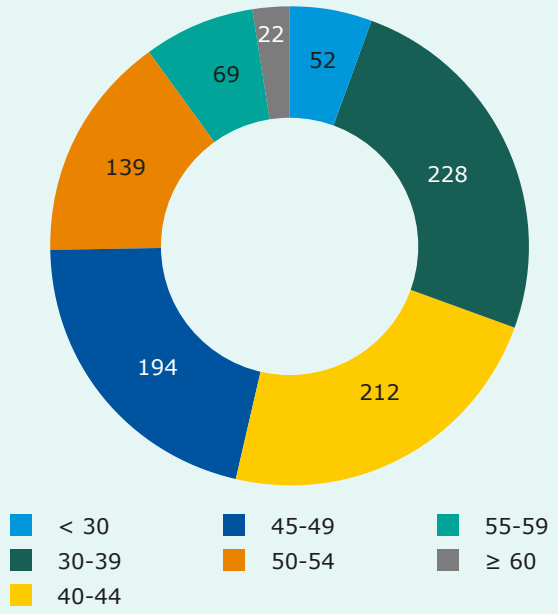
Gender balance of Agency management
(as of 31 December 2021)



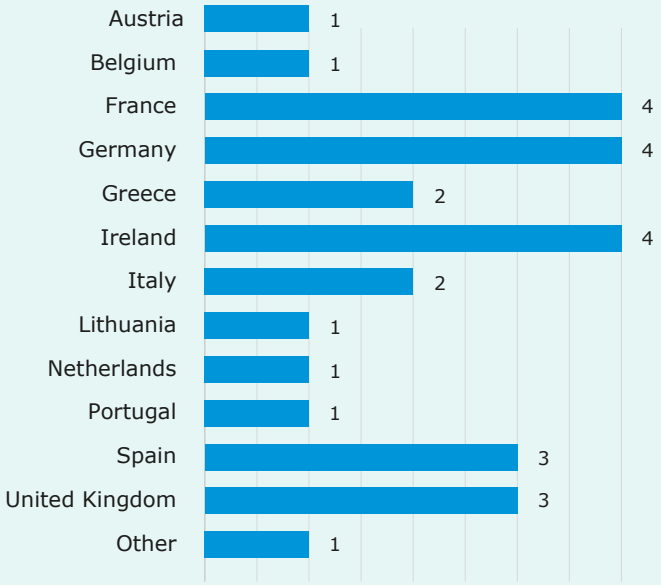
Gender balance of Agency staff in 2021

Status	Category AD (administrators)		Category AST (assistants)		TA/CA - all grades	
Temporary agents	201	204	34	205	235	409
Contract agents	29	69	24	84	53	153
Total	**230**	**273**	**58**	**289**	**288**	**562**
Total in %	**46%**	**54%**	**17%**	**83%**	**34%**	**66%**

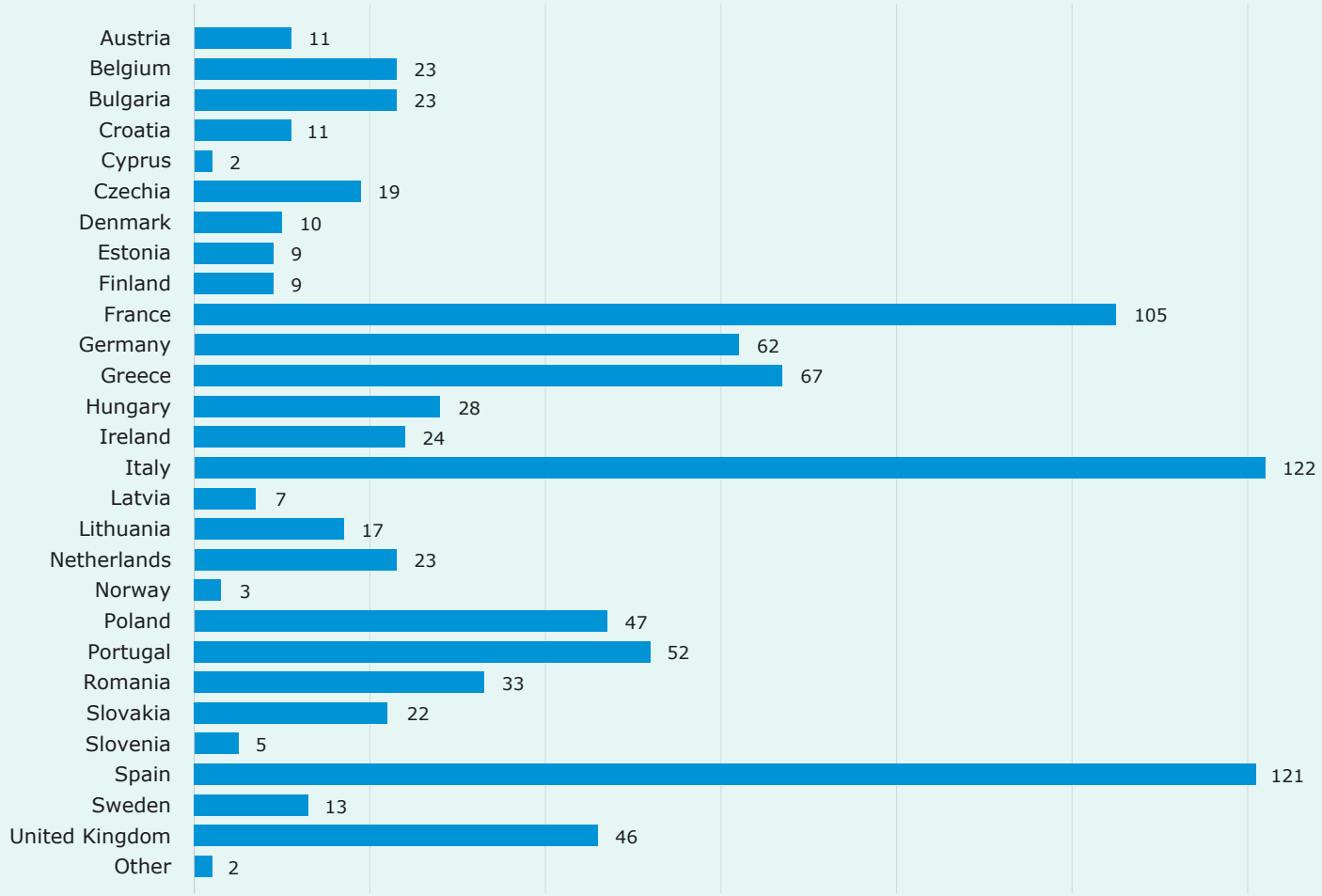
Age-range statistics (31 December 2021)



National origins of Agency management
(as of 31 December 2021)



National origins of Agency staff (as of 31 December 2021)



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 2021

Annex 11 – Guidelines and concept papers adopted by CHMP

Annex 12 – CVMP opinions on medicinal products for veterinary use in 2021

Annex 13 – Guidelines and concept papers adopted by CVMP in 2021

Annex 14 – COMP opinions on designation of orphan medicinal products in 2021

Annex 15 – HMPC European Union herbal monographs in 2021

Annex 16 – PDCO opinions and EMEA decisions on paediatric investigation plans and waivers in 2021

Annex 17 – Referral procedures overview 2021 – human medicines

Annex 18 – Arbitrations and referrals in 2021 – veterinary medicines

Annex 19 – Budget summaries 2020-2021

Annex 20 – European Medicines Agency establishment plan

Annex 21 – Litigation activities of EMA in 2021

Annex 22 – Access to documents requests

Annex 23 – Clinical Data Publication

Annex 24 – Publications by Agency staff members and experts in 2021

The annexes are available on EMA's website.

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