

Designed by Bobby Gunthorpe with assistance from Jamie Hearn & Chris Wells

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Mission statement

The mission of the European Medicines Agency (EMA) 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 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 of our partners and stakeholders to our work.

We assure continual improvement of our processes and procedures, in accordance with recognised quality standards.

We adhere to high standards of professional and personal integrity.

We communicate in an open, transparent manner with all of our partners, stakeholders and colleagues.

We promote the well-being, motivation and ongoing professional development of every member of the Agency.

Principal activities

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

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



Legal role

The European Medicines Agency is the 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 institutions of the EU the best-possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.

Foreword

by Sir Kent Woods

Chair of the Management Board



"I would like to pay tribute to the commitment and hard work of Agency staff and external experts during 2012. As this report shows, much has been achieved through their efforts on behalf of the citizens of Europe."

It is a pleasure to introduce the annual report of the Agency for 2012. This year the format has been revised with the intention of making it more accessible to readers. While it summarises the broad spread of the Agency's activities during the year, there is also a particular focus on a small number of topics of current interest.

In three short essays, jointly written by Agency staff and external experts from our scientific committees, attention is given to the use of best evidence in drug regulation, the approval of the first gene-therapy medicinal product, and antimicrobial resistance. They give a taste of the Agency's close engagement with both the science base and the public-health context of its work.

Within the healthcare system, medicines regulation sits at the point of contact between innovative biomedical science, clinical practice and wider society. In order that currently unmet medical needs – human or veterinary – should be better met in the future, the Agency has a strong interest in supporting innovation and keeping abreast of developments which can be translated into practical applications. After market authorisation, our understanding of the benefit-risk profile of medicines continues to be refined by information gathered in larger and more diverse populations of patients than can be included in clinical trials. That expansion of knowledge is a joint enterprise of clinicians, industry, patients, academia and regulators.

In carrying out their public-health task, the staff

of the Agency are able to draw on scientific and clinical expertise from the whole EU; not only in the national agencies of the Member States and our scientific committees, but also from a large network of external experts. The scale and diversity of these activities are evident in this annual report.

For the Agency's Management Board, a major theme during the year has been the transparent and rigorous handling of potential conflicts of interests. Policies have been carefully reviewed in relation to Agency staff, scientific experts and members of the Management Board itself. Public confidence in the regulatory system is essential, and I believe that the policies and procedures in place amply justify that confidence. A closely related issue is transparency; here too the Agency is making important progress to meet changing public expectations.

I would like to pay tribute to the commitment and hard work of Agency staff and external experts during 2012. As this report shows, much has been achieved through their efforts on behalf of the citizens of Europe.

Introduction

by Professor Guido Rasi
Executive Director



The year 2012 was characterised by great changes for the European Medicines Agency against a backdrop of continuing austerity and increased public scrutiny.

Legislative changes brought many new activities for the Agency and the European medicines system as a whole, but given the economic climate of austerity, these activities had to be absorbed by the existing resources of the Agency and the national competent authorities.

Changes were also initiated at the Agency's architecture level, both as a direct consequence of the new pharmacovigilance legislation and to increase the efficiency of the Agency's operations. It was also a year of change in terms of handling conflicts of interests, in order to tighten the policies in place, and in terms of openness and transparency – two major priorities of the Agency. Once again, the European medicines network was the source of the Agency's success. The network – a partnership between the European Medicines Agency, the European Commission and more than 40 medicines regulatory authorities in the EU and the European Economic Area (EEA) – makes available the members of the scientific committees and gives the Agency access to a pool of experts, allowing it to source the best-available scientific expertise for the regulation of medicines in the EU.

I am grateful for the hard work, dedication and support of all of the Agency's staff, the members of its committees, working parties and working

groups, and the Management Board, who enabled the Agency to meet its commitments successfully, despite increases in workload throughout the year. The year 2012 was my first full year as Executive Director of the Agency. It gives me great pleasure to present our achievements in protecting and improving public and animal health to the Agency's Management Board.

"It was a year of change in terms of handling conflicts of interests, in order to tighten the policies in place, and in terms of openness and transparency – two major priorities of the Agency."

1 | Agency highlights in 2012: a year of change

1.1 | Changes to the legal framework

The year 2012 saw the introduction of fundamental changes to the Agency's legal framework, stemming from the implementation of the new pharmacovigilance legislation. In addition, the Agency prepared for the implementation in 2013 of the new falsified-medicines legislation.

The new pharmacovigilance legislation

The new pharmacovigilance legislation became operational on 1 July 2012. This new legislation is an opportunity to improve public-health promotion and protection and, consequently, its implementation was a key priority for the Agency in 2012. The Agency, together with its partners in the national competent authorities and in the European Commission, worked to put in place key processes and structures to allow the efficient operation of the new legislation, including the following:

- Creation of the Pharmacovigilance Risk Assessment Committee (PRAC), which held its inaugural meeting on 19 July 2012. The PRAC provides for the first time for dedicated, expert oversight of all areas of pharmacovigilance at EU level, and has responsibility for assessing all aspects of the risk-management of medicines for human use.
- Establishment of the Article 57 database – the first EU database of all authorised medicines. Pharmaceutical companies started to submit information on their marketing authorisations in accordance with an agreed format and an IT tool supplied by the Agency in April 2012. By the end of 2012, over 300,000 records were entered into the database, creating a powerful tool that has the potential to allow, once fully populated, regulators in Europe to pinpoint with greater accuracy and rapidity medicines for which public-health concerns exist, whether these are due to pharmacovigilance or issues related to the manufacturing or the supply chain of a medicine.

- Contributions to the Commission's Implementing Measures (Commission Implementing Regulation (EU) No 520/2012, adopted as final on 19 June 2012), which provide the technical details to be observed in the daily practice of applying the new legislation.

- Provision of guidance on all key processes in the form of good-pharmacovigilance-practice guides, published in June 2012.

One of the biggest challenges of the new legislation for the Agency and the national competent authorities is securing enough human and financial resource to deliver the implementation and the operation of the new measures.

During the implementation of this piece of legislation, the Agency involved and consulted stakeholders at an unprecedented level through a series of stakeholders' forums and through periodic updates and discussions in the Agency's Patients and Consumers Working Party (PCWP) and Healthcare Professionals' Working Group (HCP WG).

Falsified-medicines legislation

The Agency also worked on preparing for the implementation of the falsified-medicines legislation, in preparation for its entry into force on 2 January 2013. This new piece of legislation is the EU's response to the public-health threat of falsified medicines. The Agency has an important supporting role to the European Commission and the Member States. Some of its key activities in 2012 are summarised here:

- Extension and update of the EudraGMP database – the database on good manufacturing practice – in order to fulfil new legislative requirements, such as: distribution authorisation; good-distribution-practice (GDP) certificates; registration of active-pharmaceutical-ingredient (API) manufacturers, importers and distributors.

27
Jan



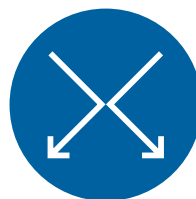
Agreement signed for greater cooperation with the European Food Safety Authority

16
Feb



Luc Verhelst starts as new Head of Information and Communications Technology

29
Feb



EMA starts to publish more information on conflicts of interests of experts and management

1
Mar



EMA starts to publish information on human medicines under evaluation

- Preparation of a revised GDP guideline, which has undergone public consultation and is being finalised by the European Commission.

The new legislation foresees that, from 2 July 2013, APIs imported from third countries will need to be accompanied by a 'written confirmation' from the competent authority of that country, confirming among other things that the GMP applied are at least equivalent to the EU ones. This provision depends largely on the cooperation of third countries. The European Commission, the Member States and the Agency therefore made big efforts to effectively communicate the new EU legislative requirements to authorities in the major exporting countries.

As part of these efforts, the European Commission is in the process of establishing a list of equivalent third countries for which this requirement can be waived. By the end of 2012, four countries had applied to be listed: Switzerland, Israel, Australia and Singapore.

In order to avoid potential shortages of medicines, which could arise due to countries not applying EU-equivalent GMP on 2 July 2013, when this aspect of the new legislation comes into force, the Agency has developed a risk-ranking methodology for centrally authorised medicines, which can be used to prioritise inspections of active-substance manufacturers in third countries. This methodology is applicable to centralised products and has been shared with Member States that can use it or adapt it to their specific situations to assess the risk of shortages for non-centralised medicinal products.

13
Mar



EU-wide survey for veterinarians on prescribing habits for antimicrobials launched

22
Mar



Workshop on development of vaccines to protect cattle against the Schmallenberg virus

26
Mar



EU Clinical Trials Register information now available through the WHO's International Clinical Trials Registry Platform

27
Mar



EMA and national competent authorities agree a common, Europe-wide approach for the identification of commercially confidential information and personal data

1.2 | Changes to the Agency's architecture

There were changes to the Agency's architecture as a direct consequence of the new pharmacovigilance legislation. The new Pharmacovigilance Risk Assessment Committee (PRAC) brings the number of Agency scientific committees up to seven, adding to an already complex system of committees, their working parties and advisory groups.

Launching the Scientific Coordination Board

In April 2012, the Agency launched the new Scientific Coordination Board. The group, which is chaired by the Agency's Executive Director, is composed of the chairs of the Agency's scientific committees, the scientific advice working parties, the Co-ordination Groups for Mutual Recognition and Decentralised Procedures (Human and Veterinary) and relevant senior management staff from the Agency's secretariat. Its mission is to ensure that there is sufficient coordination between the committees, so that the standards they set for the development of medicines are consistent across the whole product lifecycle, for increased robustness and predictability of the benefit-risk assessment of medicines.

The group is also tasked to look at other factors that are putting the system under pressure, including: difficulties in sourcing appropriate experts, due to the continuous strengthening of the rules on allowable conflicts of interests of the Agency's experts; the increase in the number and level of activities of all committees; and challenges from new scientific developments, for instance advanced therapies or personalised medicines, which require an integrated scientific and regulatory approach.

Reviewing internal processes in preparation for reorganisation

Following its review of the way the Agency's committees and their working parties interact, the Agency turned to look inward, at the processes at the level of the secretariat. In December 2012, it began a review of its operations and processes,

focused on increasing the efficiency of its scientific activities and IT operations. A key focus will be on the support provided to the Agency's scientific committees, to help them deliver high-quality, consistent opinions, based on the best-available evidence.

The ultimate aim of this exercise, which is expected to result in a reorganisation of the Agency, is to improve the Agency's processes and its use of resources, not least to ensure that it is better prepared for future legislative and policy challenges.

Streamlining information technology

The Agency adopted a new information and communications technology strategy that seeks to set in place the technological foundations needed to support the Agency in its core activities. It increases efficiency and effectiveness by addressing key points such as technological change, communication with stakeholders, organisational structure and work processes, and the way data are managed at the Agency. Some of the key deliverables:

- Decommissioning of duplicate technologies, which will lead to a significant reduction of ICT running costs.
- Development of a new data architecture vision, to further facilitate data integration and elimination of redundant data stores. This supports a more efficient and effective handling of the Agency's and its stakeholders' current and future data usage demands.
- The new telematics governance approved by the Management Board Telematics Committee, which provides a framework to foster collaboration across the European medicines network and to maximise efficiency in communication around the development and operation of IT for the network.

11
Apr



EMA proposes a way forward for proactive publication of clinical-trial data

16
Apr



EMA publishes reflection paper on ethical and good clinical practice (GCP) aspects of clinical trials of medicinal products for human use conducted outside the EU

27
Apr



Approval of 100th Community herbal monograph

31
May



Launch: www.adrreports.eu - online publication of suspected-side-effect reports boosts EU transparency

1.3 | Changes to the handling of conflicts of interests

A fundamental overhaul of the way the Agency deals with conflicts of interests of its experts, committee members, Management Board members and staff was brought to a preliminary conclusion in 2012. The Agency takes the issue of potential conflicts of interests of its staff and scientific experts extremely seriously, taking care to ensure that they do not have any financial or other interests that could affect their impartiality.

The new approach provides for more robust rules about what constitutes a conflict of interests, underpinned by increased levels of transparency. Achievements in 2012 included the following:

- Further tightening of the Agency's rules on handling of conflicts of interests (3 April 2012).
- Updates to the list of European experts, to display each expert's risk level on the Agency's website. A risk level corresponds to an expert's declared interests in the pharmaceutical industry, and is used to determine each expert's permitted level of involvement in the Agency's activities (29 February 2012).

- Publication of profiles for all of the Agency's management staff and of their declarations of interests (29 February 2012).
- Introduction of a new breach-of-trust procedure, setting out a procedure for how the Agency deals with incorrect or incomplete declarations of interests by experts and committee members (3 April 2012).
- Two review exercises provided reassurance that the updated rules on conflicts of interests are working.

The comprehensive measures the Agency has taken over the past year in relation to strengthening its handling of conflicts of interests were not only acknowledged by the European Parliament in its decision to grant the Agency discharge for its 2010 budget, but also by a review by the European Court of Auditors of the management of conflicts of interests in four independent EU agencies, which found that the EMA now has some of the most advanced policies and procedures for declaring, assessing and managing potential conflicts of interests in place.

The main challenge in operating the new procedures now is to find the right balance between ensuring the impartiality and independence of experts involved in the Agency's work versus the need to secure the best-possible scientific expertise to continue to deliver top-quality scientific assessments.

8
Jun



Management Board completes improved and tightened framework for conflicts of interests

7
Jun



Adoption of 1,000th orphan designation

1
Jul



Pharmacovigilance legislation becomes operational

1
Jul



Enrica Alteri joined the Agency as Head of the Safety and Efficacy of Medicines Sector

16
Jul



EMA publishes policy on changing scope of paediatric investigation plans

1.4 | Changes to the Agency's approach to transparency

The year 2012 was also notable for the progress the Agency made in its approach to transparency. The European Parliament, in its discharge decision, highlighted the measures introduced to improve transparency.

- In March 2012, the Agency started publishing a list of all new human medicines under evaluation by the Committee for Medicinal Products for Human Use (CHMP). The Agency updates the list every month.
- In May 2012, the Agency began publishing suspected-side-effect reports for centrally authorised medicines on a new public website: www.adrreports.eu. The reports come directly from EudraVigilance, the EU database on adverse drug reactions. The launch of the new website is part of the implementation of the EudraVigilance access policy.
- In July 2012, the Agency's committees started publishing their agendas and minutes. The Paediatric Committee (PDCO) was the first to publish agendas and minutes, followed by the PRAC and the Committee for Orphan Medicinal Products (COMP).

A phased approach to the publication of minutes and agendas of the remaining four committees is being adopted, which will result in systematic publication of all of the Agency's committees' agendas and minutes before the end of 2013.

- At a workshop in November 2012, the Agency launched a process towards proactive publication of clinical-trial data. The event was preceded by the Agency's decision, taken earlier in the year, that clinical-trial data should be made proactively available, once the marketing-authorisation process has ended. The workshop allowed the Agency to gather the views, interests and concerns from a broad range of institutions, groups and individuals. The Agency has now embarked on a process to establish policies in close dialogue with its stakeholders in five different areas identified during the workshop.

The Agency's efforts to increase the transparency of its operations and processes were underpinned by overall improvements in its communications activities. The Agency adopted a communications strategy to guide its activities in this area up to 2015. As part of this, the Agency adopted a new roadmap for its online activities, aimed at optimising and rationalising the Agency's online presence.

19
Jul



First meeting of the Pharmacovigilance Risk Assessment Committee

18
Jul



EMA starts to publish agendas and minutes of scientific committees

20
Jul



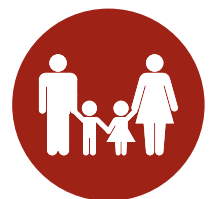
CHMP recommends first gene therapy for approval

7
Sep



EMA enhances cooperation with EU drug-monitoring agency on psychoactive and abused medicines

17
Sep



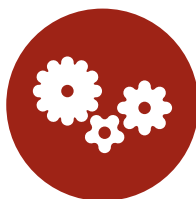
Consultation on involvement of children and young people in assessments performed by the Paediatric Committee

1.5 | Other achievements

In addition to these major themes of change, the Agency has achieved progress in a number of other areas:

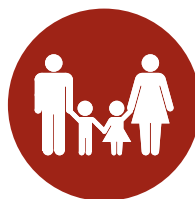
- The occurrence of shortages of medicines has increased over the last few years, owing to a large extent to the globalisation of manufacturing and supply chains. The Agency, in collaboration with the national competent authorities and the European Commission, developed a short- and medium-term plan to help the European medicines regulatory network prevent, mitigate and manage shortages of important medicines resulting from manufacturing problems. This plan was published in November 2012.
- The first gene-therapy medicine was recommended for approval in the European Union. Glybera offers a new medical treatment for patients with severe or multiple pancreatitis attacks due to lipoprotein lipase deficiency.
- The Agency held a workshop on vaccines development against the Schmallenberg virus, a new, emerging livestock disease discovered in late 2011. There is currently no vaccine against this disease and the workshop was intended to encourage the development of an appropriate vaccine.
- The Agency carried out end-user research during the year to understand the needs of its stakeholders in relation to the Agency's websites and to establish clear business requirements for future developments. This included surveys, interviews and workshops. The Agency will continue to work with patients, consumer and healthcare-professional organisations, as well as with other stakeholders, on user-experience research during the coming years.
- The Agency prepared a report to the European Commission on its experience with the application of the Paediatric Regulation since it entered into force in 2007. The report summarises the areas of success and lessons learned of the implementation of the Regulation, but also identifies areas for improvement, stating that some paediatric therapeutic areas that predominantly affect children have been neglected in terms of pharmaceutical research. In September 2012, the European Commission launched a public consultation on the experience gained with the Paediatric Regulation, open until 28 November 2012.
- In the area of involvement of civil society, the Agency moved forward in 2012 by establishing a procedure for systematic participation of patients in scientific advisory group (SAG) meetings. This represents the first pillar in the involvement of civil society in the benefit-risk evaluation at the EMA. The publication of the 5th annual report on the interaction with patients' and consumers' organisations saw a big increase in participation (423 interactions as compared to 307 in the previous year).
- The Agency started implementing its framework for interaction with healthcare professionals, adopted by the Management Board in December 2011. Eligibility criteria for selection of organisations have been established and, as of December 2012, 21 organisations have been acknowledged as 'eligible' on the EMA website.

28
Sep



EMA announces that it will accept biosimilar reference medicines sourced outside the European Economic Area

29
Sep



Launch of Commission consultation on experience gained with the Paediatric Regulation

15
Oct



Second ESIVAC report: Sales of veterinary antimicrobial agents in 19 EU/EEA countries in 2010

23
Oct



Start of infringement procedure to investigate Roche's alleged non-compliance with pharmacovigilance obligations

- On 26 March, the EU Clinical Trials Register information was made available through the WHO's International Clinical Trials Registry Platform. By the end of the year, more than 19,000 entries were included.
- The Agency started an infringement procedure against Roche Registration Ltd, following a request from the European Commission, to investigate allegations that the company has failed to comply with pharmacovigilance obligations. This is the first such procedure conducted by the Agency.
- The guidance for pharmaceutical companies on biosimilar medicines was updated to reflect the European Commission's confirmation that it intends to accept batches of reference medicines sourced from outside the EEA in the future. This aims to facilitate the global development of biosimilars and avoid the unnecessary repetition of clinical trials.

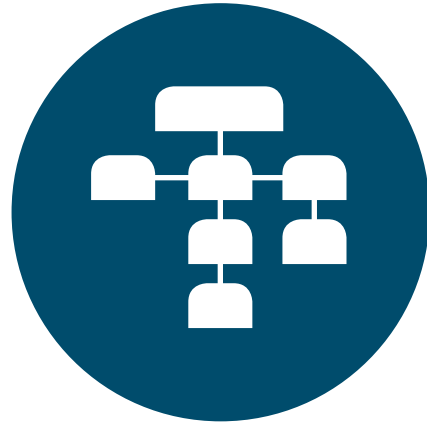
- The Agency implemented the amended Variation Regulation by 2 November 2012. The decision-making process for variation procedures for centrally authorised products was modified so that changes that are critical for public health are reflected in the marketing authorisation within 2 months, while other changes are reflected in periodic updates (within 1 year). Also, a statement on compliance with the agreed, completed paediatric investigation plan is now included in the marketing authorisation.
- Major progress was made in preparing the move of the Agency to new premises in 2014. Designs were signed off by the beginning of the year and building works started towards the middle of the year.

22
Nov



Workshop on access to clinical-trial data and transparency kicks off process towards proactive publication of data

19
Dec



EMA starts preparations for reorganisation of its operations and activities

26
Nov



Publication of reflection paper and implementation plan to help deal with manufacturing-related medicines shortages

15
Dec



EudraGMP planning model goes live

30
Dec



EMA receives the 350,000th structured medicinal product entry in the extended EudraVigilance Medicinal Product Dictionary

31
Dec



The EudraVigilance database receives the 3,648,000th case of a suspected medicine side effect, available for analysis by the EU regulatory network

2 | Advancing public and animal health in 2012

This chapter provides engaging thoughts on three topics of major importance in science, medicines and health in 2012. The three essays introduce high-profile actors of the Agency and their views on best evidence, access to innovative treatments, and antimicrobial resistance. This chapter is articulated around the 'three pillars' on which all of the Agency's work is based:

Science

representing the scientific expertise that guides the Agency in all of its regulatory decision-making;

Medicines

representing the Agency's focus on assessing and monitoring medicines to ensure their quality, safety and efficacy;

Health

representing the purpose for which the Agency was created, namely to protect and improve public and animal health.



"The new vision of regulatory decision-making is based on the continuous assessment of the benefit-risk balance of medicines throughout their lifecycle." **Tomas Salmonson**

Peter Arlett (left), Tomas Salmonson (right)

2.1 Science

Best evidence – bringing real-life data into regulatory science

Peter Arlett, Head of Pharmacovigilance and Risk Management

Tomas Salmonson, Chair of the Committee for Medicinal Products for Human Use (CHMP)

Randomised controlled trials, although recognised as a gold standard for establishing efficacy, operate in a well-defined environment and measure efficacy and safety in selected populations.

When it comes to the benefits and risks of medicines in the reality of everyday medical practice, as well as in subpopulations, such as the elderly or patients with multiple diseases treated with multiple therapies, the results of such trials will not be fully applicable. The new vision of regulatory decision-making is therefore based on the continuous assessment of the benefit-risk balance of medicines throughout their lifecycle, including in real clinical life.

This process involves the integration of multiple data sources, not just the industry studies that traditionally have dominated the assessment of benefits and risks of medicines, but also academic studies, studies from electronic health records, studies using pharmacoepidemiology methods, and modelling and simulations. In addition, more and more adverse reaction data reported directly by patients will be included in assessments in the future.

Generating, searching and integrating diverse sources of evidence to support decision-making must be supported by regulatory science to continuously improve methods and processes, along with capacity-building to develop knowledge and expertise. Regulatory science aims to improve the decision-making process by looking at and validating new techniques, methodologies or approaches. Substantial work has been done in this area. For instance, the Innovative Medicines Initiative-funded EU PROTECT project was initiated to develop and improve methods for the early detection and assessment of safety issues and for the integration and presentation of data on benefits and risks of medicines. These methods are tested in real-life situations. At another level, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) strengthens the post-authorisation monitoring of medicines

and facilitates post-authorisation studies through research capacity building by setting standards for the conduct of studies, sharing best practice and enabling collaboration and connectivity between European academics; so does the European network of paediatric research at the European Medicines Agency (Enpr-EMA) in the area of clinical research in children.

A number of tools were put in place or strengthened in 2012 to address the need of generating relevant new sources of evidence. These tools now need to be systematically utilised and further integrated to deliver continuous knowledge generation. This concept of continuous knowledge generation, which is enabled by a lifecycle approach to data collection and improved scientific and regulatory methods, will support robust and high-quality regulatory decision-making for the benefits of public and animal health. A challenge for the next couple of years will be to allow all stakeholders to fully leverage the data, information and knowledge generated. A change to the summary of product characteristics or package leaflet needs to be translated into changes in prescriber, dispenser and consumer behaviour to fully realise the benefits for public health. The new pharmacovigilance legislation provides new tools to support this vision. On the one hand, it gives regulators a mandate to increase accessibility of stakeholders to knowledge about medicines. On the other hand, it provides a framework for the measurement of the effectiveness of risk-minimisation, to ensure that actions taken deliver the intended health benefits in real life. The implementation of these tools provides challenges and opportunities, but ultimately will ensure that regulation fully delivers for the patients and consumers of Europe.

2.2 Medicines

The approval of Glybera – a story of continuous learning

Christian Schneider, Chair of the Committee for Advanced Therapies

Hans-Georg Eichler, Senior Medical Officer

In July 2012, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the marketing authorisation of Glybera (alipogene tiparovec), a gene therapy for lipoprotein lipase (LPL) deficiency, a very rare inherited disorder. This is the first gene-therapy medicine to be recommended in the EU.

The evaluation of this application, which involved a close collaboration between the Agency's Committee for Advanced Therapies and the CHMP, was complex and the decision-making process was scientifically challenging for several reasons. The scientific evaluation of Glybera involved a new type of medicine with no past regulatory experience, a disease with a fluctuating rather than a continuously progressing clinical course, making the data difficult to analyse and interpret, and a limited dataset from a small patient population. Glybera was finally recommended for use under exceptional circumstances in a more restricted indication than initially applied for, which targets the patient population with greatest need for treatment.

The lessons learnt from this case are multiple and pave the way for approval of similarly complex medicines in the future, as more gene therapies for rare diseases, personalised medicines and nanomedicines are on their way. The evaluation of Glybera illustrated the difficulty of balancing important but divergent public-health interests. On the one hand, we want to allow timely access to innovative therapies for unmet medical needs. We also want to enable and incentivise development of potentially beneficial innovative treatments. On the other hand, we owe patients medicines with robust evidence that their benefits outweigh their risks.

The Glybera story also illustrated the need for an evolving regulatory framework, different from the dichotomous unapproved/approved current paradigm. The Agency is committed to exploring new ways that would facilitate timely access to innovative treatments. In this matter, progressive marketing authorisation (sometimes called adaptive licensing) is an option mentioned in the Agency's

road map to 2015. Such licensing pathways – which are based on stepwise learning under conditions of acknowledged uncertainty, and involve iterative phases of data-gathering and regulatory evaluation – would allow approval to align more closely with patients' needs for timely access to innovative medicines. These new approaches are needed not only for advanced therapies, but wherever there are unmet medical needs and promising new therapeutic options.

The assessment of Glybera also highlighted the fact that, in complicated regulatory situations, expert committees working on the same dossier and dataset can have complementary viewpoints and objectives. It is perfectly acceptable in science that, in borderline situations, two scientific experts can indeed come to different conclusions when balancing certainties and uncertainties of a marketing authorisation application dossier. The positive outcome of the Glybera assessment sends a positive message to developers of future medicines. This case showed that even a very small company with a complex medicine and very limited but still comprehensive dataset can go through the European regulatory process and get a positive outcome.



"The lessons learnt from the Glybera story are multiple and pave the way for approval of similarly complex medicines in future." **Christian Schneider**

Christian Schneider (left), Hans-Georg Eichler (right)



"To stimulate drug development, specific regulatory pathways that would allow rapid approval of new classes of antibiotics are needed." **Anja Holm**

Marco Cavaleri (left), Anja Holm (right)

2.3 Health

Antimicrobial resistance – reversing the trend for the protection of human and animal health

Anja Holm, Chair of the Committee for Medicinal Products for Veterinary Use (CVMP)

Marco Cavaleri, Head of Anti-Infectives and Vaccines

In humans, as in animals, emergence of antimicrobial resistance, or the ability of micro-organisms to become resistant to treatment, is an unavoidable phenomenon. As long as antimicrobials are used, resistance to these medicines will develop, and this can only be slowed down by a more rational use of antibiotics. The increasing emergence of pan-drug-resistant pathogens is a major global issue in human medicine today. New antimicrobial agents are missing for several key human pathogens, and very few new classes of antibiotics are under development. In the veterinary area, where multidrug resistance seems less widespread, development of new antibiotic classes is almost non-existent. Pharmaceutical companies have progressively abandoned development of new classes of antibiotics, considering that the latter may not provide a sufficient return on investment compared to other medicines. Indeed, the price of antibiotics is traditionally low and the duration of treatment is usually short.

What needs to be done to reverse the trend? Actions are needed on various fronts. First, the use of antibiotics needs to be rational, to preserve as much as possible the effectiveness of the current arsenal. Despite increasing awareness, antibiotics are still overused in certain situations in both the human and veterinary worlds. The use of antibiotics needs to be brought under control so that treatment options for coming generations are not compromised. On this matter, a global approach is required, since antimicrobial resistance travels with people, animals and foodstuffs across the world. Public-health policies are needed at country level, and also at each hospital, to define the most appropriate use of each antibiotic, based on epidemiologic data.

A severe infection requires prompt action; today, the treatment of acute infections is empirical, which can lead to improper antibiotic use. For adequate treatment of acute infections for both humans and animals, point-of-care diagnostics are needed to allow the rapid identification of the pathogen causing

the infection and the immediate use of the most appropriate treatment.

The second point of action lies in the area of regulation. To stimulate drug development, specific regulatory pathways that would allow rapid approval of new classes of antibiotics for human use are needed. This is where the Agency plays a lead role. Very successful workshops on this topic took place in 2011 and 2012. In this matter, the Agency is looking at innovative clinical-study designs that would alleviate the size of human clinical trials while still allowing an acceptable level of evidence around the benefit-risk profile to be gathered. Harmonisation of regulatory requirements across the world is also critical, given that clinical-trial plans are global.

Another crucial point is the development of legislative and community incentives to produce a sustainable research and development infrastructure. In the human field, public-private partnerships need to be strengthened and innovative approaches to marketing antibiotics, such as stock-piling, should be further considered. With respect to veterinary medicine, a clear message to the animal-health industry needs to be given whether or not to invest in developing new antibiotics for use in animals, and potential incentives and conditions may need to be considered.

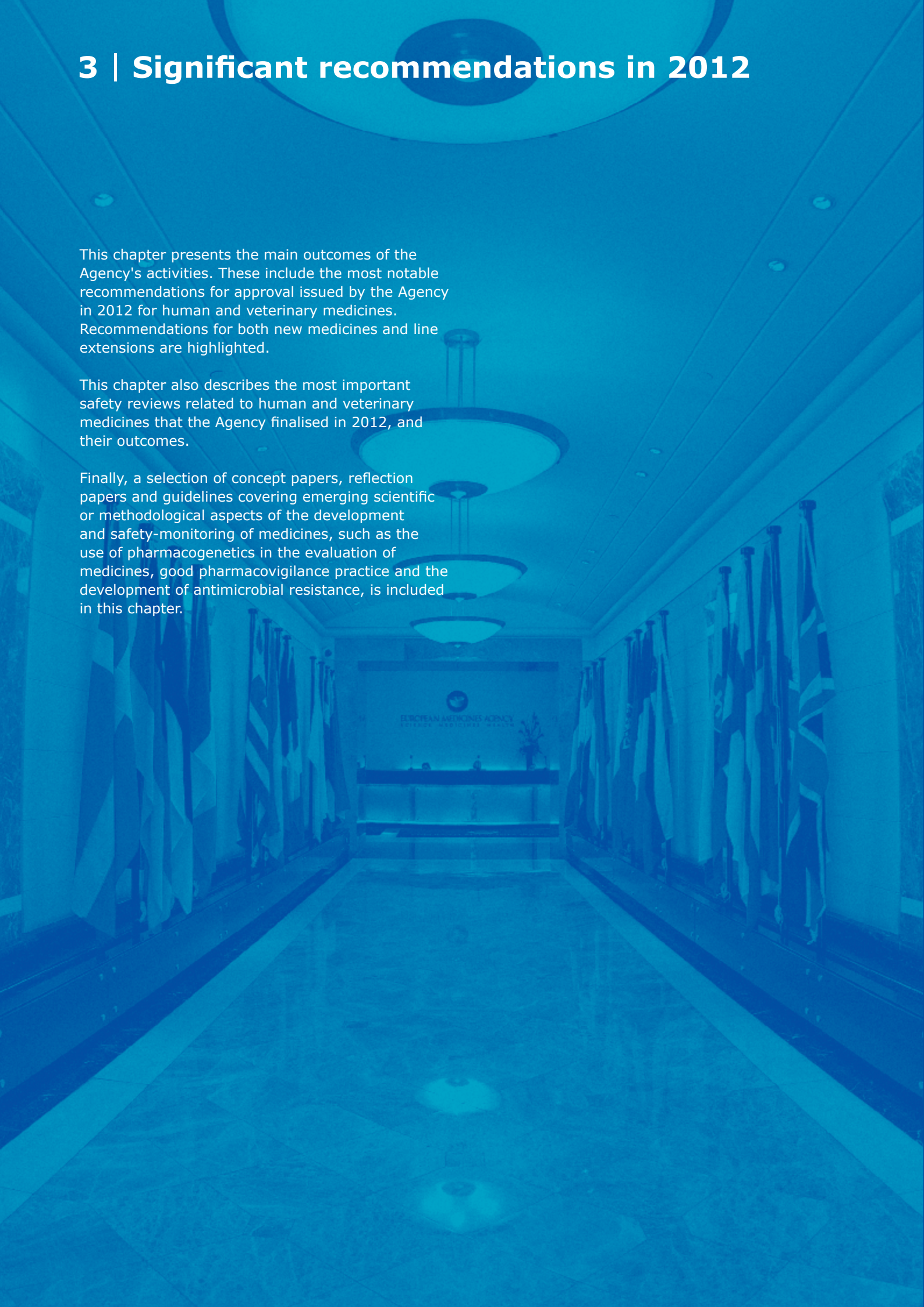
Last but not least, we, the Agency, need to look at all the therapeutic options available, including innovative medicines such as bacteriophages or nanomedicines, and also to envisage the development of vaccines for hospital-acquired infections, livestock-production diseases or resistant pathogens. It is essential that we focus our efforts on expanding the available arsenal against infections caused by resistant bacteria. The Agency and its scientific committees are ready to explore new frontiers with an open mind, to address in a sustainable way such an important public-health need.

3 | Significant recommendations in 2012

This chapter presents the main outcomes of the Agency's activities. These include the most notable recommendations for approval issued by the Agency in 2012 for human and veterinary medicines. Recommendations for both new medicines and line extensions are highlighted.

This chapter also describes the most important safety reviews related to human and veterinary medicines that the Agency finalised in 2012, and their outcomes.

Finally, a selection of concept papers, reflection papers and guidelines covering emerging scientific or methodological aspects of the development and safety-monitoring of medicines, such as the use of pharmacogenetics in the evaluation of medicines, good pharmacovigilance practice and the development of antimicrobial resistance, is included in this chapter.



3.1 | Human medicines

Recommendations for approval

In 2012, the Agency issued 59 positive opinions recommending marketing authorisation for new medicines, including three opinions recommending conditional marketing authorisation and one that involved an accelerated assessment.

The most notable new medicines for human use recommended for marketing authorisation by the Agency's Committee for Medicinal Products for Human Use (CHMP) in 2012 include the following:

- **Signifor** (pasireotide) for the treatment of Cushing's disease in patients who cannot have surgery or for whom surgery has not been successful. Signifor is the first approved medical treatment for patients who cannot be cured by surgery. A number of medicines are being used off-label to treat the disease, but the available data on their safety and efficacy are limited. The approval of Signifor is the first step in making a medicine available to European patients that has been studied in the indication and for which doctors and patients are provided with specific information about its use.
- **Pyramax** (pyronaridine tetraphosphate / artesunate) for the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax*. Pyramax is the first anti-malaria treatment for which the CHMP adopted a scientific opinion in the framework of Article 58 of Regulation (EU) 726/2004. This legal provision allows the CHMP to review medicines that are intended entirely for use outside the EU. Applicants can use the CHMP's scientific opinion as a basis when applying for a marketing authorisation in countries outside the EU.
- **Pixuvri** (pixantrone) for monotherapy treatment of patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. Pixuvri received a conditional marketing authorisation because it is the first approved treatment for this stage of the disease and the public-health benefits of making this medicine available immediately, without full data, was considered to outweigh the risks inherent in the fact that additional data are required.
- **Forxiga** (dapagliflozin) for the treatment of type-2 diabetes mellitus in adults. Forxiga is a novel diabetes treatment that works by inhibiting the sodium-glucose co-transporter 2 (SGLT2), a transporter protein in the kidneys that allows glucose to be reabsorbed into the bloodstream. Its mechanism of action allows improvement of glycaemic control in type-2 diabetes without increasing insulin secretion.
- **Kalydeco** (ivacaftor) for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a G551D mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. Kalydeco, an orphan medicine, is the first medical treatment that targets the underlying mechanism of the disease, by restoring the function of the mutated CFTR protein. Currently available therapies for patients with cystic fibrosis only address the consequences of the disease, not the underlying defect. Kalydeco was reviewed by the CHMP under accelerated assessment, to speed up access by patients to this new medicine.
- **Revestive** (teduglutide) for the treatment of adult patients with short bowel syndrome (SBS). Revestive, an orphan medicine, is the first medical treatment approved in Europe in this rare but seriously debilitating condition. It has shown that it can additionally reduce parenteral nutrition requirements in patients with the condition.
- **Hexaxim** for the vaccination of infants and toddlers from six weeks to 24 months of age against six World Health Organization (WHO) priority diseases: diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b. Hexaxim is the first vaccine for which the CHMP adopted a scientific opinion in the framework of Article 58 of Regulation (EU) 726/2004. By offering protection against these



diseases, Hexaxim promises to relieve the burden of these diseases in regions outside the EU, where they continue to cause unacceptable levels of illness and death.

- **Glybera** (alipogene tiparvovec) for the treatment of patients diagnosed with lipoprotein lipase deficiency and suffering of severe or multiple pancreatitis attacks. Glybera is the first gene-therapy medicinal product approved in the EU. Gene-therapy medicines have the potential to cure genetic disorders by replacing a defective gene with a working copy, thus helping the body to recover functionality. Glybera uses an adeno-associated virus vector as the delivery vehicle to add working copies of the LPL gene into muscle cells to enable production of the enzyme in the cells.
- **NexoBrid** (concentrate of proteolytic enzymes enriched in bromelain) for removal of eschar in adult patients with deep partial- and/or full-thickness thermal burn wounds. Nexobrid consists of a mixture of enzymes that are extracted from the stem of the pineapple plant. It is the first pharmacological debriding agent for the removal of necrotic tissue from severe burn wounds, a treatment that still rests mainly on surgical intervention.
- **Constella** (linaclotide) for the treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Constella is the first medicine authorised specifically for irritable bowel syndrome in the EU, giving patients an alternative to the available treatments, which are limited to lifestyle modifications such as reducing stress or altering diet, psychological interventions and general symptomatic treatments such as laxatives, antidiarrhoeals and antispasmodics, or unapproved medicines. It is estimated that irritable bowel syndrome affects up to 20% of the Western population.
- **Amyvid** (florbetapir) for positron emission

tomography (PET) diagnostic imaging of β -amyloid neuritic plaque density in the brain. Amyvid is the first radiopharmaceutical for PET imaging of β -amyloid neuritic plaque density. It is used as a diagnostic agent in patients who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. A negative Amyvid PET scan can rule out the presence of AD, and is expected to reduce the frequency of false-positive diagnoses.

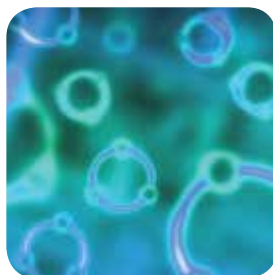
- **Bexsero** (Meningococcal group B vaccine (rDNA, component, adsorbed)) for vaccination against invasive disease caused by *N. meningitidis* group B strains. Bexsero is the first vaccine for meningitis B in the EU. The disease mainly affects infants and young children, but could also occur in older children and young adults. Despite the availability of medical treatment and effective antibiotics, 8% of European patients die and some 11–19% of survivors suffer life-long consequences, including permanent brain damage, learning disabilities and hearing loss. The authorisation of a vaccine meets a great unmet medical need by offering effective protection.
- **Adcetris** (brentuximab vedotin) for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma. Adcetris is an antibody-drug conjugate, which means that it combines both an antibody and an active substance. The antibody can direct the medicine to a specific target on lymphoma cells known as CD30, allowing a selective delivery of the active substance to tumor cells.

Extensions of existing indications

A total of 17 extensions of marketing authorisations were finalised in 2012.

The following medicines are some of the most noteworthy to have had their indications extended to include new populations in 2012:

- **Intence** (etravirine): extension of the therapeutic indication for the treatment of human immu-





odeficiency virus type-1 (HIV-1) infection in antiretroviral-treatment-experienced paediatric patients from 6 years of age, in combination with a boosted protease inhibitor and other antiretroviral medicinal products. The product was previously approved in adults only.

- **Viread** (tenofovir disoproxil): extension of the therapeutic indication for the treatment of adolescents aged 12 to 18 years old with chronic hepatitis B. In this indication, the product was previously approved in adults only. Extension of the indication for the treatment of HIV-1 to include treatment-experienced adolescents 12 to < 18 years of age to enable continuity of treatment with Viread across all age ranges from 2 years of age, through adolescence to adulthood.
- **Prezista** (darunavir): extension of the therapeutic indication for the treatment of previously treated HIV-positive children aged 3–6 years. The product was previously approved in adults only.
- **Eliquis** (apixaban): prevention of stroke and systemic embolism in certain adult patients. Eliquis was already indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- **Afinitor** (everolimus): treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. Afinitor was already indicated for the treatment of neuroendocrine tumours of pancreatic origin and for the treatment of advanced renal cell carcinoma.

Safety reviews

The Agency carried out a number of safety reviews in 2012. The scientific review for some of the most

notable safety reviews finalised in 2012 resulted in the following:

- New contraindications for aliskiren-containing medicines in patients with diabetes or moderate to severe renal impairment who take angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In addition, new warnings that the combination of aliskiren and ACE inhibitor or ARB is not recommended in all other patients because adverse outcomes cannot be excluded against the use of aliskiren in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers in patients with diabetes mellitus or renal impairment.
- Confirmation of positive benefit-risk balance for orlistat-containing medicines and harmonisation of information on possible very rare liver-related side effects.
- New advice for Gilenya to better manage the risk of adverse effects on the heart.
- Modifications to product information for clearer guidance with Pradaxa on how to reduce and manage the risk of bleeding associated with this medicine. These included more specific guidance on when Pradaxa must not be used as well as advice on managing patients and reversing the anticoagulant effect of Pradaxa if bleeding occurs.
- New advice for doctors treating patients with Doribax for nosocomial pneumonia, in order to allow the use of a higher dose in certain patients with hospital-acquired pneumonia and to clarify the recommendations and warnings on the use of Doribax in different types of bacterial infection.
- Restriction of the indications for calcitonin, which will no longer be used for the treatment of osteoporosis.



- New contraindications for strontium-ranelate-containing medicines in immobilised patients or patients with history of venous thromboembolism (VTE). In addition, an update on the warnings to advise patients to immediately stop treatment if they develop allergic reactions, and the need to re-evaluate continued treatment in patients over 80 years of age at risk of VTE.

- Restriction of the indication for tolperisone-containing medicines given orally for the treatment of adults with post-stroke spasticity.

- New contraindications and warnings for trimetazidine-containing medicines, as well as restriction of the indication to add-on to existing treatments in patients who are not adequately controlled by, or who are intolerant to, other medicines for angina pectoris.

- Continued review of Pandemrix and development of narcolepsy. The hypothesis from preliminary research on differences in the immunological response triggered by different pandemic influenza vaccines was reviewed, but the evidence was preliminary and insufficient to allow conclusion on the role of the Pandemrix antigen and its adjuvant on the association between Pandemrix and narcolepsy.

- A review of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular (CV) risk. For diclofenac, the latest study results were in line with previous evidence of an increased CV risk. Since the data consistently indicated that this risk is higher for diclofenac, this matter will now be assessed by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC), to determine the need to update the existing treatment advice for patients and prescribers. For naproxen and ibuprofen, the possibility of a small increased risk of thrombotic events cannot be excluded, which is in line with previous reviews on the CV risk for these medicines. For most other non-selective NSAIDs, there were not enough data for the CHMP to reach firm conclusions,

and the possibility of an increased CV risk with these medicines cannot be excluded.

- Suspension of oral medicines containing meprobamate, because of serious side effects, including confusion, loss of consciousness and risk of addiction.

In addition, the Agency finalised quality-related referral procedures resulting in recommendations to deal with the quality shortcomings at Ben Venue Laboratories and Roche Carolina.

Guidelines

The Agency prepares scientific guidelines to provide advice to applicants or marketing-authorisation holders, competent authorities and/or other interested parties on the best or most appropriate way to fulfil an obligation laid down in EU pharmaceutical legislation.

In 2012, the Agency finalised, or opened public consultation for, revised scientific guidelines that provide guidance on all stages of clinical drug development in specific therapeutic areas, including acute heart failure, schizophrenia, Parkinson's disease, cancer and multiple sclerosis. These revisions include the latest scientific developments in the respective therapeutic areas.

In addition to these revisions, the Agency also initiated or finalised the development of guidance or guidelines covering emergent scientific or methodological aspects of the development and safety-monitoring of medicines. Here is a selection of these initiatives:

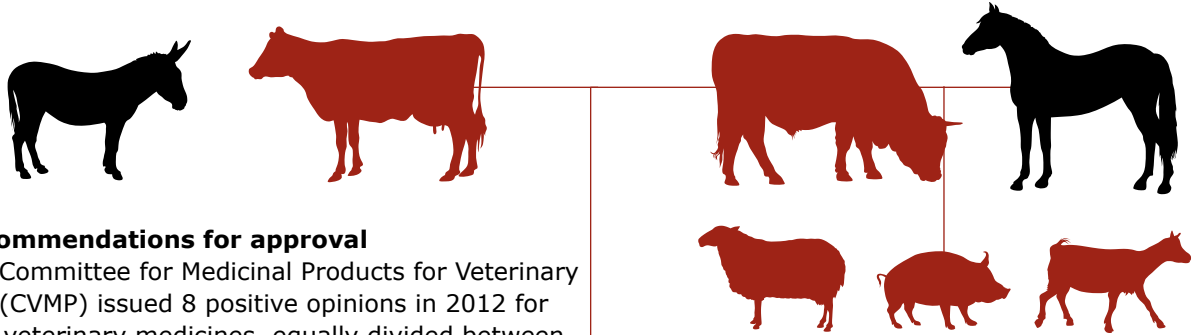
- Concept paper on pharmacogenomics in safety-monitoring of medicines: describes how the use of pharmacogenomics methodologies in the pharmacovigilance evaluation of medicines can help identify individuals at risk of side effects, unexpected complications or lack of efficacy, and therefore contribute to the development of strategies to optimise the use of medicines. Public consultation closed.

- Reflection paper on ethical and good clinical practice (GCP) aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing-authorisation applications to the EU regulatory authorities: aims to strengthen existing processes to provide assurance to regulators and stakeholders that clinical trials meet the required ethical and GCP standards, no matter where in the world they have been conducted.
- Reflection paper on classification of advanced therapies: clarifies the legal basis for the classification of medicines as advanced therapies and provides information on how these medicines are classified as gene-therapy, somatic-cell-therapy, tissue-engineered or combined medicines. Some borderline cases and areas where scientific knowledge is limited or evolving rapidly are also discussed.
- Guideline on use of pharmacogenetics in pharmacokinetic evaluation of medicines: describes how to integrate the study of genetic variability between patients during the development of medicines and the evaluation of their pharmacokinetic profile, and how to translate the knowledge acquired from these studies into treatment recommendations for genetic subpopulations. Guideline adopted.
- First set of guidelines on good pharmacovigilance practices: contains a set of measures to facilitate the performance of pharmacovigilance in the EU. These guidelines, which apply to marketing-authorisation holders, the Agency and medicines regulatory authorities in EU Member States, aim to improve safety for patients by strengthening the monitoring of the safety of medicines across the EU. Guidelines adopted.
- Guidance on medicines containing monoclonal antibodies: provides information on the non-clinical and clinical requirements for companies developing medicines containing monoclonal antibodies that are

similar to medicines already authorised. The guidance contains answers to questions frequently asked by companies with an interest in developing similar biological monoclonal antibodies. Guideline adopted.



3.2 | Veterinary medicines



Recommendations for approval

The Committee for Medicinal Products for Veterinary Use (CVMP) issued 8 positive opinions in 2012 for new veterinary medicines, equally divided between pharmaceuticals and immunologicals. One positive opinion was also granted for a generic.

- **Zulvac 1+8 Bovis** (inactivated bluetongue virus, serotype 1 and 8, strain BTV-1), a vaccine for the active immunisation of cattle for the prevention of viraemia caused by bluetongue virus, serotype 1 and 8. The vaccine will only be used in an emergency situation as part of an approved national disease programme, as control of bluetongue is the responsibility of national veterinary authorities, in consultation with the European Commission. This product benefited from the accelerated procedure.
- **Poulvac E. coli**, a vaccine for the active immunisation of chickens to reduce mortality and lesions associated with *E. coli* serotype 078. Colibacillosis can cause lesions in the sac that surrounds the heart, the sac surrounding the liver and the 'air sacs', the specialised bags within the bird's body where air is stored during breathing (airsacculitis). The vaccine also helps to reduce deaths caused by this infection.
- **Porcilis ColiClos**, a vaccine for the passive immunisation of piglets against *E. coli* and *C. perfringens*. The benefits of Porcilis ColiClos are to reduce mortality and clinical signs in piglets during the first days of life, caused by these bacterial strains.
- **Nobivac L4**, a vaccine for dogs containing inactivated *Leptospira* strains and indicated for the active immunisation of dogs to reduce infection and/or urinary excretion caused by *Leptospira* strains. Leptospirosis disease in dogs results in bleeding, hepatitis and jaundice or nephritis. The main infection source is from urine or urine-contaminated water or soil. The vaccine also reduces the excretion of the virus into the urine by the infected dog, thereby reducing the risk of transmission.

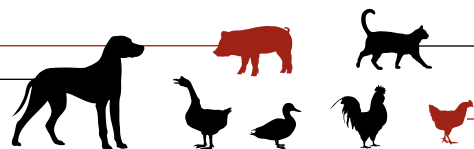
- **Cardalis tablets** (benazepril and spironolactone), indicated for the treatment of congestive heart failure in dogs. This is a type of heart disease where the heart cannot pump enough blood around the body. Cardalis is used for congestive heart failure caused by long-term damage to the heart valves.

- **Contacera** (meloxicam), an anti-inflammatory and anti-rheumatic indicated for use in cattle, pigs and horses. Contacera is a generic. It has different uses depending on the animal species.

- **Kexxtone** (monensin), indicated for reduction of the incidence of ketosis in the periparturient dairy cow/heifer. Kexxtone is used to reduce the incidence of ketosis in dairy cows and heifers that are expected to develop ketosis in the period around calving. Ketosis is a metabolic disturbance in which blood-glucose levels are low and substances called ketones accumulate in the blood.

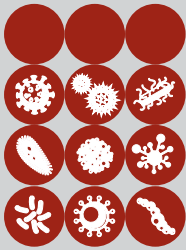
- **Semintra** (telmisartan), indicated for the treatment of chronic kidney disease in cats. Semintra decreases the mean arterial blood pressure and proteinuria associated with chronic kidney disease.

- **Pexion** (imepitoin), indicated for the control of epilepsy in dogs. The benefits of Pexion are its potential safety benefit in comparison with the standard treatment and the increase in range of available treatment possibilities for idiopathic epilepsy.





Safety reviews



In 2012, the CVMP received 12 referrals related to veterinary medicinal products for food-producing animals. Nine of these referrals concerned products containing antimicrobial substances.

This reflects the high level of concern within the EU to ensure that such products are authorised with appropriate conditions of use, in order to reduce as much as possible the risk of antimicrobial resistance development. In particular, the CVMP started assessing referral procedures on the following:

- Veterinary medicines containing enrofloxacin. The aim of the referral is to consider the indications, dosage regimens and withdrawal periods for chickens and turkeys, in order to ensure consumer safety and efficacious treatment in chickens and turkeys, as well as to lower the risk of development of antimicrobial resistance to enrofloxacin.
- Veterinary medicines containing doramectin. The aim of the referral is to harmonise the withdrawal periods for all identical or similar injectable doramectin products and the environmental risk mitigation measures for all injectable and pour-on products containing doramectin across the EU.

Some of the most notable referral recommendations issued in 2012:

- Recommendation on prudent-use warnings for veterinary medicinal products containing systemically administered (parenteral or oral) third- and fourth-generation cephalosporins intended for use in food-producing species.

- Recommendation on withdrawal periods for veterinary medicinal products containing active substances belonging to the class of flukicides for which no maximum residue limit has been established in milk and which are intended for use in ruminants producing milk for human consumption.

Guidelines

A number of guidelines and guidance documents were adopted for consultation or published in 2012. They relate to the quality, safety, environmental risk assessment and efficacy of medicines for veterinary use. Several documents provide particular guidance on immunological veterinary medicinal products.

Two reflection papers related to the use of antimicrobials:

- Draft reflection paper on the use of pleuromutins in food-producing animals in the European Union: development of resistance and impact on human and animal health. Adopted for consultation, December 2012.
- Draft reflection paper from the Agency project for European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals. Adopted for consultation, December 2012.

Also, three documents refer to the application of '3Rs' (replacement, refinement and reduction) in animal testing, as a European directive aiming to improve the welfare of laboratory animals and to anchor the 3Rs principle took full effect on 1 January 2013:

- Guideline on data requirements for removing the target-animal batch-safety test for immunological veterinary medicinal products in the EU. Adopted January 2012.
- Recommendation to marketing-authorisation holders, highlighting the need to ensure compliance with 3Rs methods described in the European Pharmacopoeia. Adopted July 2012.
- Concept paper on the need for revision of the position on the replacement of animal studies by in vitro models. Adopted for consultation, July 2012.

In the area of pharmacovigilance, the CVMP adopted several working documents, including:

- Reflection paper on risk-management plans for centrally authorised veterinary medicinal products. Adopted February 2012.
- Concept paper for the revision of the CVMP guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products. Adopted for consultation, July 2012.



4 | Key figures in 2012

This chapter presents the key figures of the Agency's activities in 2012 through four topics:

- **Human medicines**
- **Veterinary medicines**
- **Inspections and compliance**
- **Budget and staff**

It also highlights the major trends and changes observed over the past few years.

4.1 | Human medicines

4.1.1. Initial evaluation

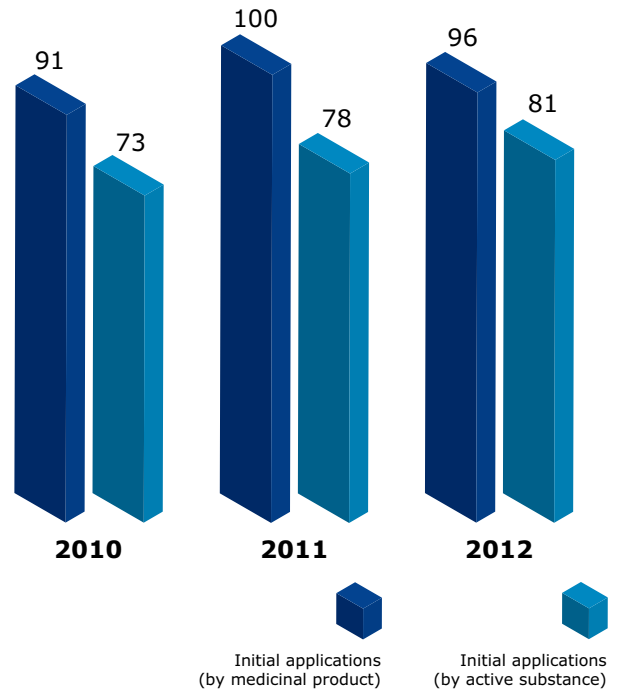
Initial evaluation covers activities relating to the processing of marketing-authorisation applications for medicines, from pre-submission discussion with future applicants, through evaluation by the CHMP, to the granting of a marketing authorisation by the European Commission.

For the last few years, the Agency has received a stable number of applications for initial evaluation of medicines for human use, with 96 applications received in 2012. The number of new active substances has continuously increased for the last three years.

A significant increase in the number of applications for medicines with orphan designation was observed in 2012: a 36% increase compared with 2011. An increase in the number of applications from micro, small and medium-size enterprises (SMEs) was also observed in 2012: almost 30% of initial-evaluation applications were submitted by SMEs. The increase is particularly significant for applications for medicines with orphan designation, as 68% of these applications were submitted by SMEs, compared to just 27% in 2011.

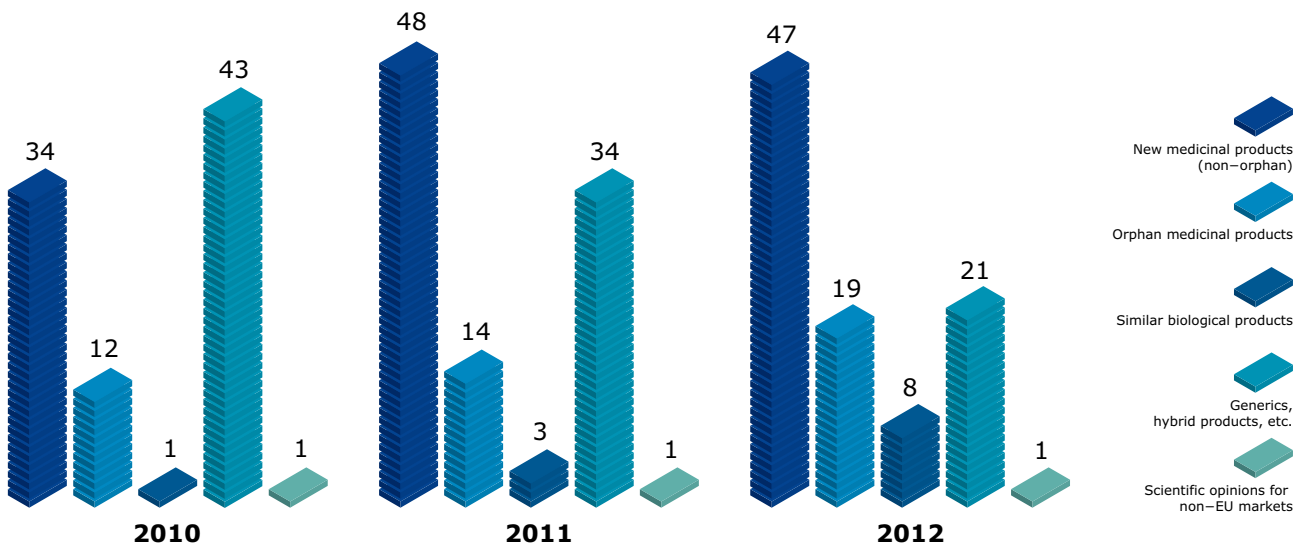
A significant decrease in applications for generics and hybrid products was observed in 2012 compared with 2011 (36% decrease). This trend can be explained, among other reasons, by the restricted possibility for the submission of duplicate or multiple generic applications via the centralised procedure, based on Article 82(1) of Regulation (EC) 726/2004.

Initial-evaluation applications 2010–2012



96 applications for medicines for human use were received in 2012

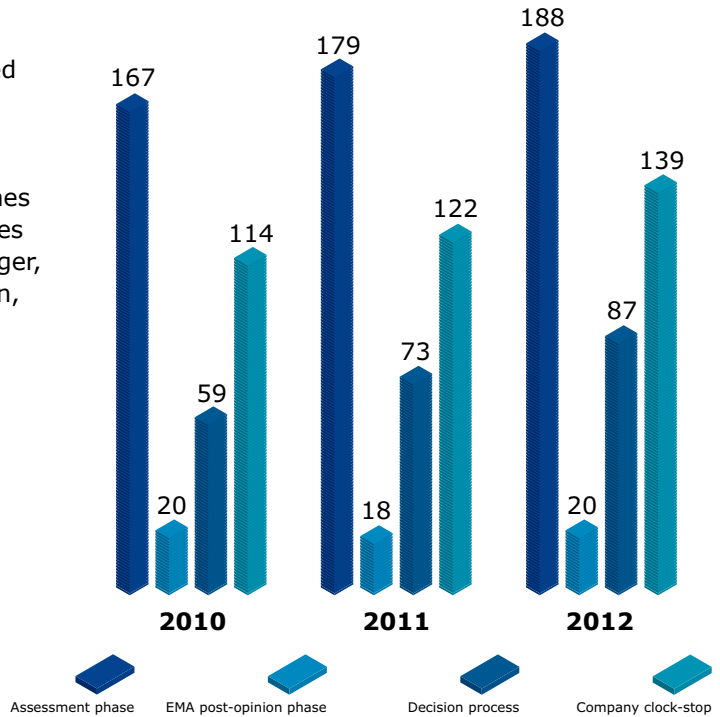
Initial-evaluation applications by type of application 2010–2012



Average number of days for centralised procedure – positive opinions 2010–2012

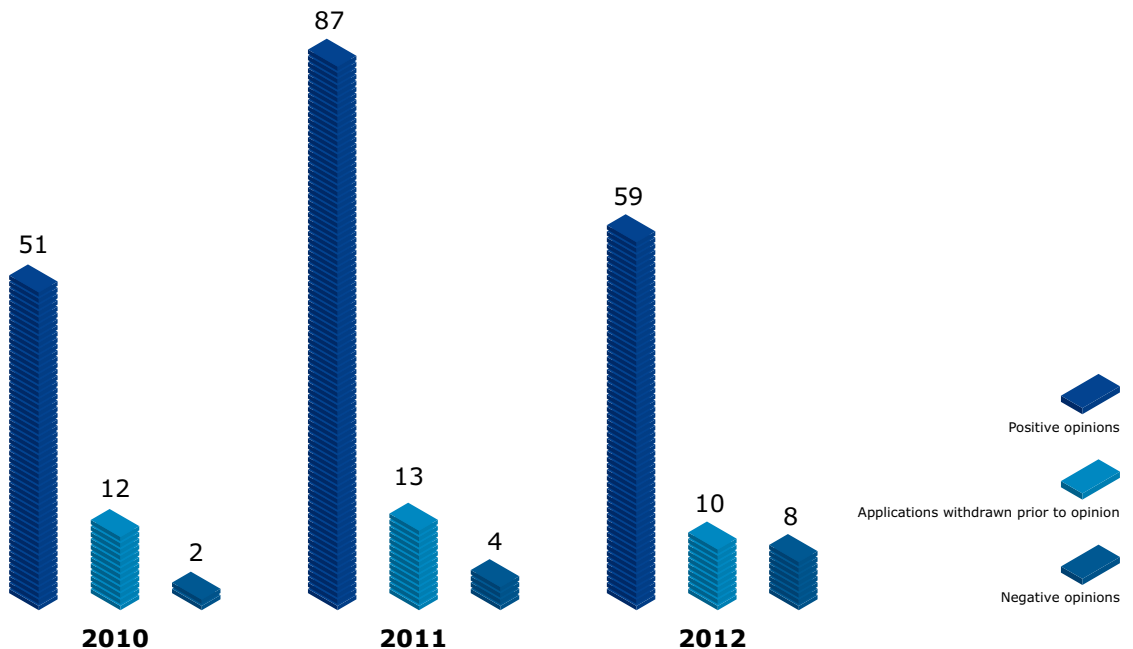
Average assessment time and outcome of initial-evaluation applications

An increase in the Agency's average assessment time of initial-evaluation applications was observed in 2012. This increase reflects the change in the distribution of the applications: a decrease in the number of generic and hybrid applications and an increase in the number of applications for medicines with orphan designation. The same principle applies to company clock-stops, which are on average longer, due to more complex applications under evaluation, requiring clarification and additional data.



The number of positive and negative opinions and withdrawn applications varies from one year to the next, and depends on a number of factors such as the type and complexity of the products under evaluation, the robustness of the data in the application, and the type of applicant, e.g. non-SME versus SME. The figures for 2012 are in line with the increase of the average assessment time, showing an increased complexity of the applications assessed.

Outcome of initial-evaluation applications 2010–2012



4.1.2. Scientific advice

The Agency provides scientific advice and protocol assistance to sponsors during the phase of research and development of medicinal products. Scientific advice is considered as a means to facilitate and improve earlier availability of medicinal products to patients and healthcare professionals, and as a means to promote innovation and research.

The total number of scientific-advice requests decreased slightly in 2012 compared to 2011, while protocol assistance continues to increase over the years.

The mean duration for scientific-advice procedures was stable, with 3 days for validation and 72 days for assessment in 2012.

One in two requests concerned clinical advice and 63% of the requests were received for products undergoing phase III evaluation.

Seeking scientific advice and complying with it has been associated with a greater chance of receiving a positive opinion, as shown by an analysis of data collected between 2004 and 2007 (inclusive) and published in 2010 (Regnstrom J et al., Eur J Clin Pharmacol, 2010 Jan.).

64% of registered SMEs requested scientific advice compared to 41% in previous years

4.1.3. Support to small and medium-sized enterprises (SMEs)

The Agency put the SME initiative in place in December 2005 to promote innovation and development of medicines by SMEs. This initiative provides active regulatory, financial and administrative support to these companies in the development of their medicines. The support takes the form of individual guidance and more general advice through the SME user guide, topical workshops and a dedicated newsletter.

In 2012, the number of companies assigned SME status by the Agency increased by 58% compared to the previous year, with a cumulative total of 1,098 active SMEs registered with the Agency at year end. The significant increase was primarily due to companies registering for the electronic submission of product information (under Article 57(2) of Regulation (EU) No 1235/2010) and for access to MedDRA fee incentives. The Agency granted a total of nearly €6.5 million in fee reductions to SMEs, excluding additional reductions granted for designated orphan medicines.

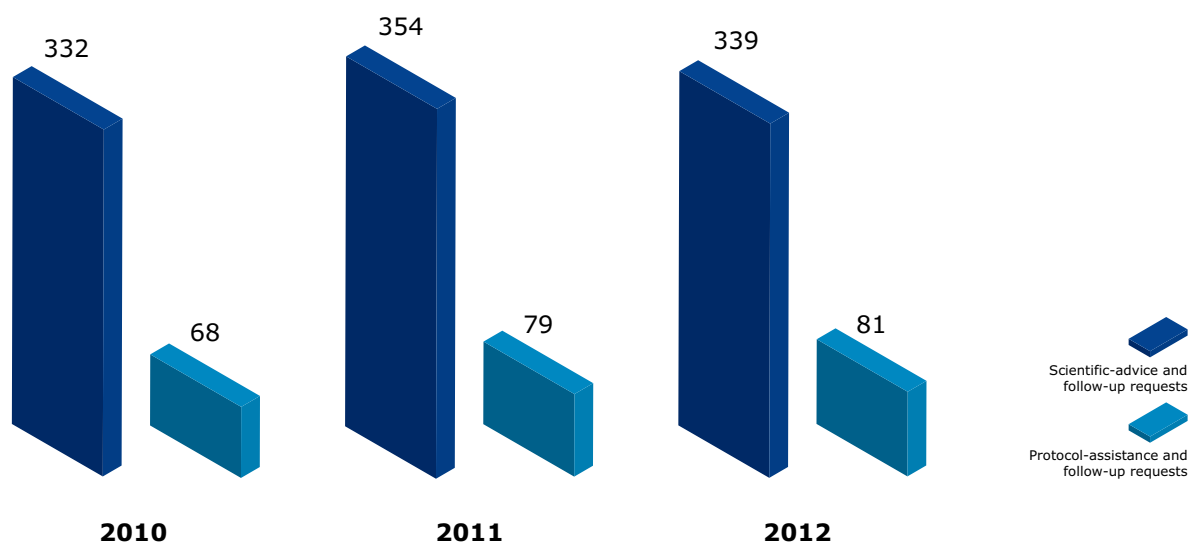
SMEs and scientific advice

The 2012 annual report from the Agency's SME Office highlighted the fact that over the past two years, there has been a significant increase in the number of SMEs seeking scientific advice prior to filing a marketing-authorisation application (64% compared to 41% in previous years).

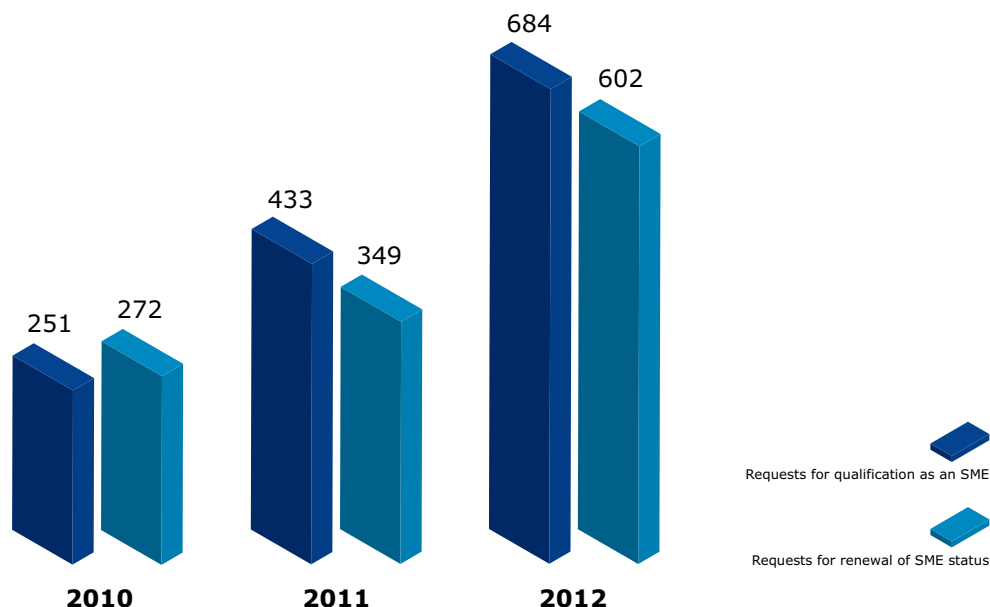
In 2012, for the first time, an SME requested biomarker qualification, another tool that supports the development of medicines that the Agency provides to companies, large and small.

Also of interest in 2012, 2 of the 6 parallel scientific-advice procedures with health-technology-assessment bodies were initiated by SMEs. This parallel advice procedure allows identification of the criteria and endpoints in clinical trials that are useful to these important stakeholders when reviewing relative effectiveness.

Scientific-advice and protocol-assistance requests received 2010–2012



Initial SME qualifications and renewals 2010–2012



4.1.4. Orphan-medicine designations

Orphan medicines are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union, or where for economic reasons such medicines would not be developed without incentives.

The most-represented therapeutic areas were oncology (35%) and metabolic diseases (17%).

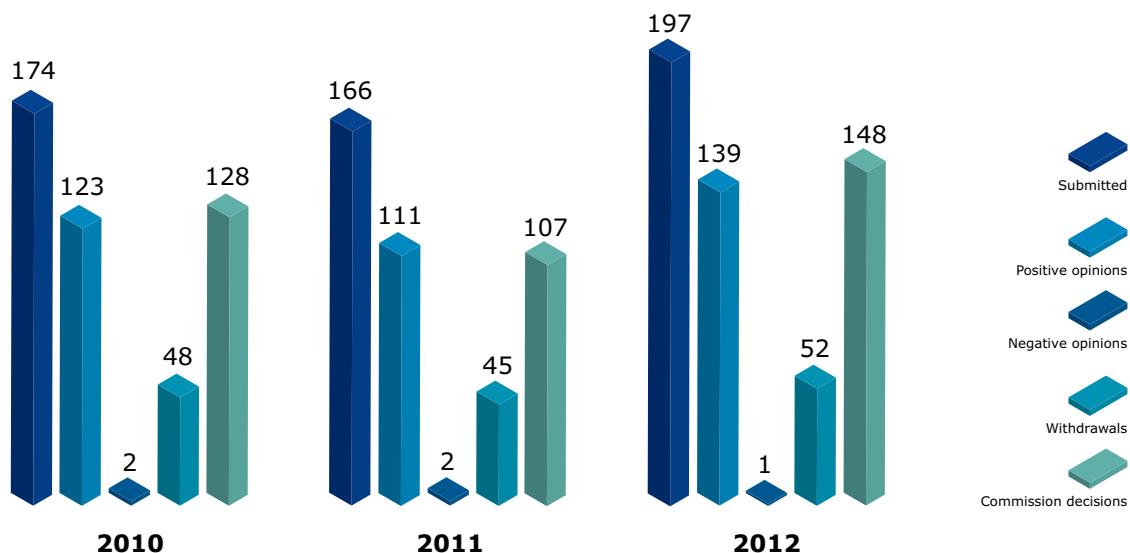
In 2012, the Agency processed a total of nearly €7.5 million in fee reductions for designated orphan medicinal products.

The number of orphan-designation applications rose by more than 18% in 2012 compared to 2011. In line with this trend, there was a 25% increase between 2011 and 2012 in the number of positive opinions for orphan designations issued by the Committee for Orphan Medicinal Products (COMP). Among these positive opinions:

- 42% concerned medical conditions affecting children only;
- 30% concerned medical conditions affecting children and adults;
- 28% concerned medical conditions affecting adults only.

There was a 25% increase between 2011 and 2012 in the number of positive opinions for orphan designations issued by the COMP

Orphan-medicinal-product-designation procedures 2010–2012



4.1.5. Medicines for children

This area covers the Agency's activities relating to the assessment and agreement of, and verification of compliance with, paediatric investigation plans (PIPs) and waivers by the Paediatric Committee (PDCO).

A slight decrease in the number of PIP applications, including waivers and deferrals, was observed in 2012 compared with 2011. In 2012, a number of PIP applications were submitted at later stages in the product development, leading to delays and contributing to a lower number of applications received compared to the initial forecast. The total number of clinical indications in PIP applications that were assessed in 2012 remained stable compared to 2011, while the number of modifications of agreed PIPs continued to increase.

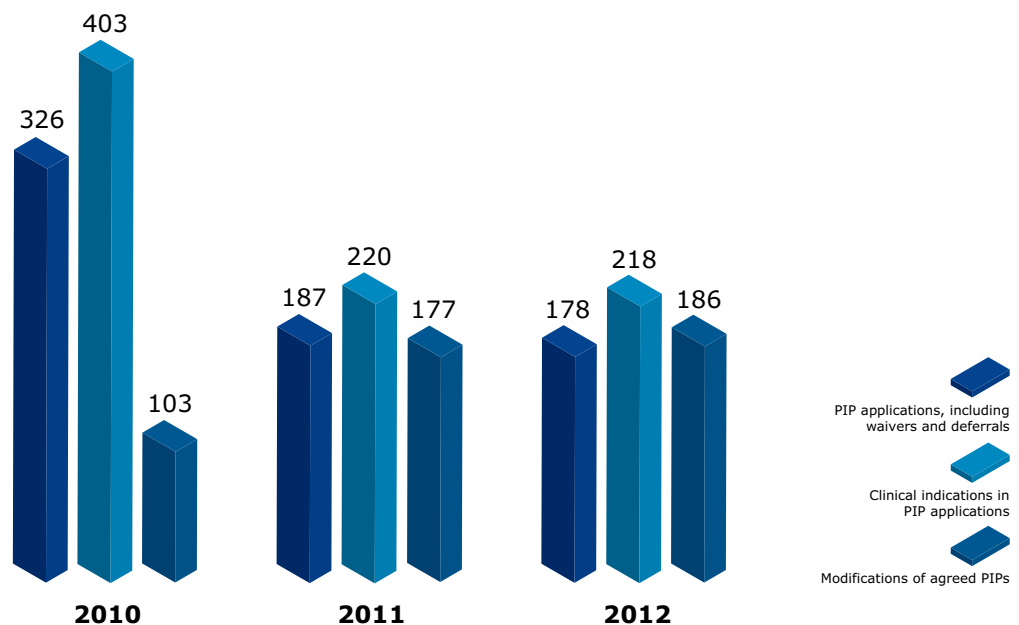
4.1.6. Advanced-therapy medicinal products

The Agency's Committee for Advanced Therapies (CAT) prepares a draft opinion on each advanced-therapy medicinal product (ATMP) application, before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion for the medicine concerned. The CAT also participates in Agency procedures for the certification of quality and non-clinical data for small and medium-sized enterprises developing ATMPs, and for the provision of scientific recommendations on the classification of ATMPs.

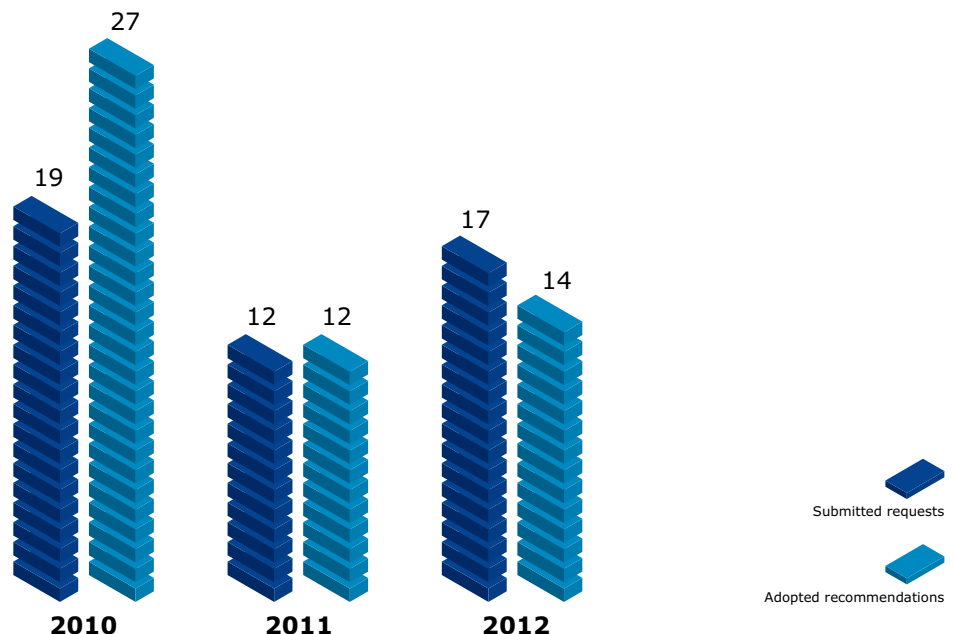
In 2012, 3 applications for ATMPs were submitted. The CAT adopted a draft opinion for Glybera, the first gene-therapy medicine approved in the EU.

One application for certification of quality and non-clinical data from an SME applicant was received, and the CAT adopted its second recommendation on certification on the quality data of a tissue-engineered product.

Paediatric and PIP applications 2010–2012



Scientific recommendations on advanced-therapy classification 2010–2012



4.1.7. Herbal medicines

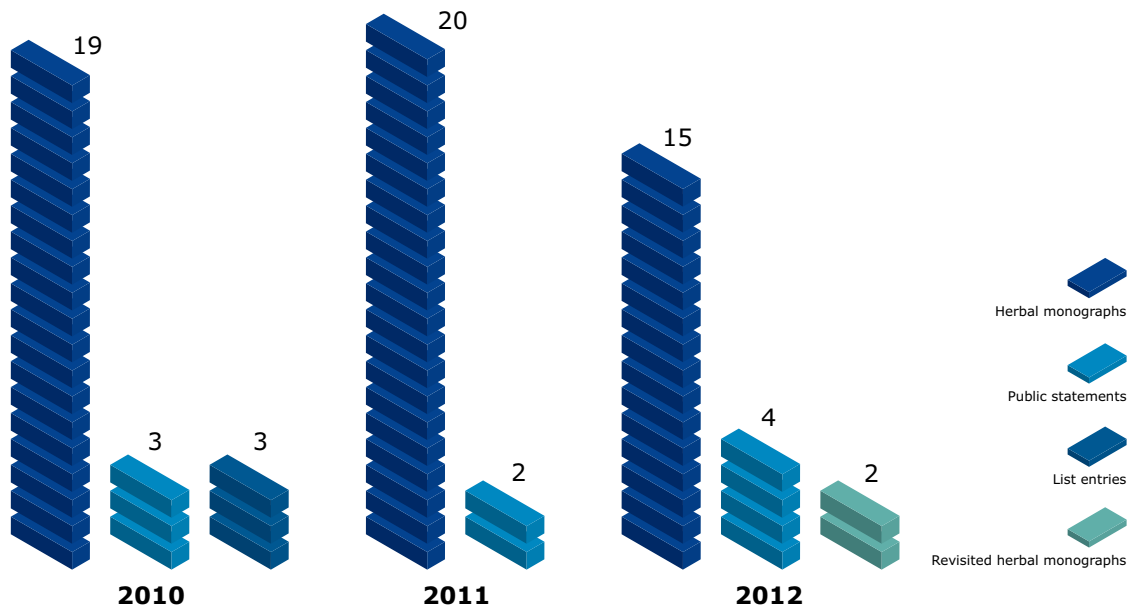
The Agency's Committee on Herbal Medicinal Products (HMPC), with a view to promoting an increasingly harmonised process for licensing and information on herbal substances across the EU, establishes Community herbal monographs for traditional and well-established herbal medicines, as well as a draft list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

- In 2012, 15 final Community herbal monographs were approved and 7 draft monographs were released for public consultation. In addition, 4 final

public statements on assessment work that could not lead to the establishment of a monograph were finalised and 2 draft public statements were released for public consultation.

- Despite a reduced forecast of 5, no list entries were released or finalised in 2012, as there were no suitable genotoxicity data available to the Committee for the assessment work to be undertaken for the preparation of such list entries. Even though discussions were held at the level of the HMPC to find an alternative solution, no such solution has been found so far.

Herbal monographs and list of herbal substances, preparations and combinations thereof 2010–2012

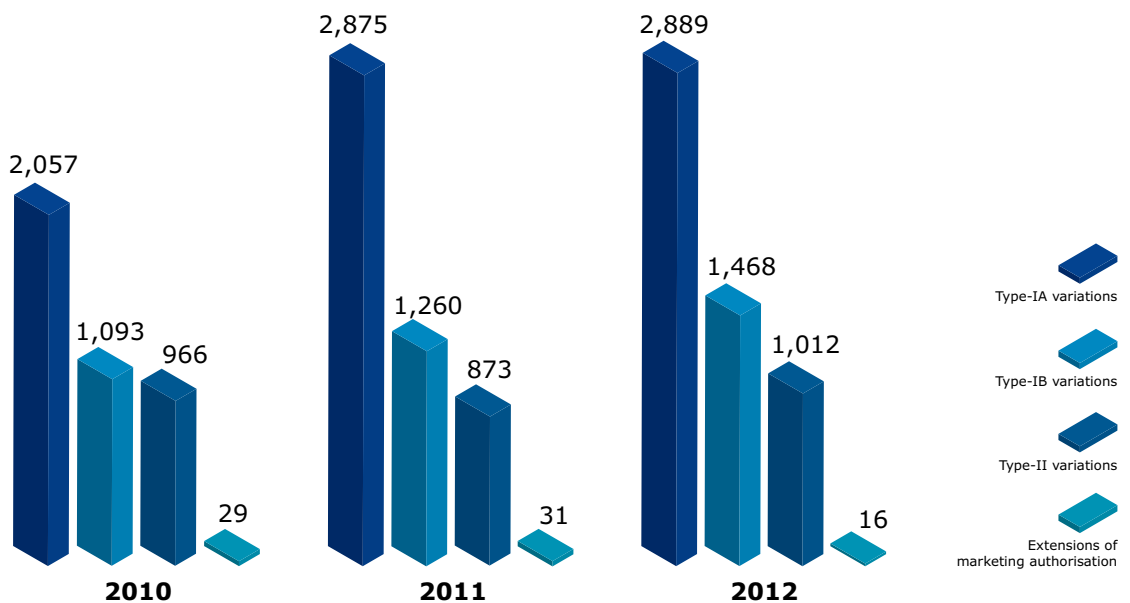


4.1.8 Post-authorisation activities

Evolution of post-authorisation applications received

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

Post-authorisation applications received 2010–2012



Pharmacovigilance and maintenance activities

Pharmacovigilance covers the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions (ADRs) or any other drug-related problem. This includes the management of suspected ADRs in the pre- and post-authorisation phases, periodic safety-update reports (PSURs), signal detection, risk-management plans (RMPs) and post-authorisation safety and efficacy/effectiveness studies.

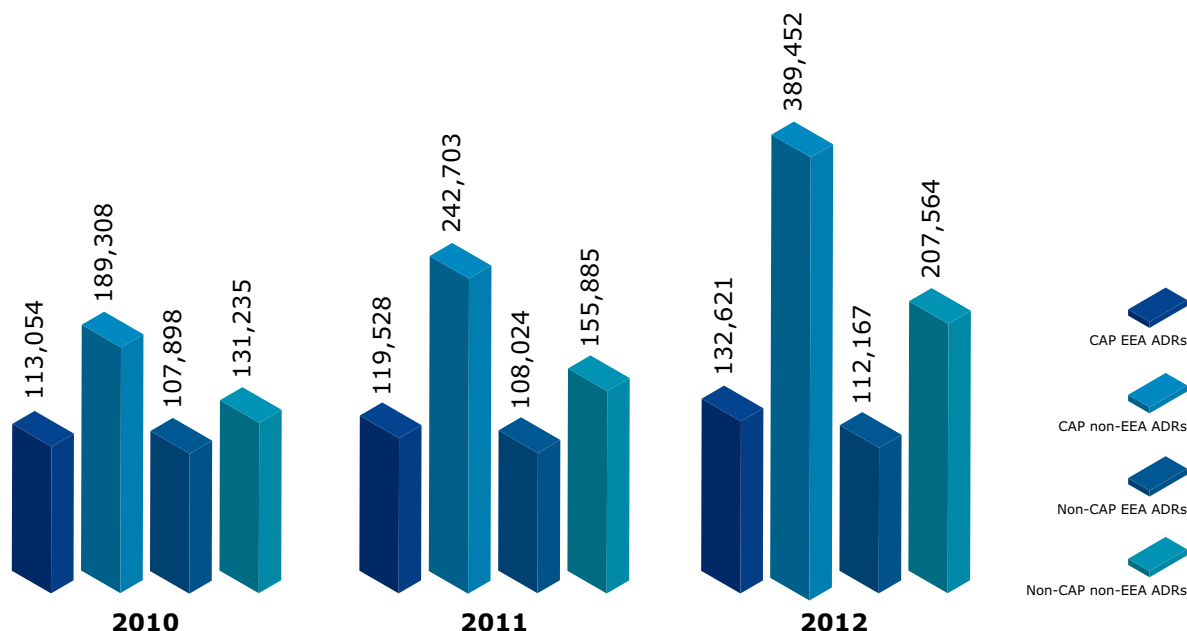
In 2012, the total number of ADR reports received increased by 34% compared with 2011, with a particularly important increase in the number of reports coming from countries outside the European Economic Area (EEA) for centrally authorised products (CAPs) (60% increase). The increase of non-EEA ADR reports relates to the extended scope of adverse-drug-reaction reporting as set out in the new pharmacovigilance legislation, specifically the extension of reporting requirements from serious unexpected adverse reactions to reporting of all serious adverse drug reactions and the inclusion of spontaneous reports submitted directly by patients and consumers, without previous confirmation by a healthcare professional.

The general increase in adverse-event reports indicates an increased commitment of stakeholders to providing all available data. A similar trend is observed with veterinary products.



In 2012, the total number of ADR reports received increased by 34% compared with 2011

EEA and non-EEA ADR reports received 2010–2012

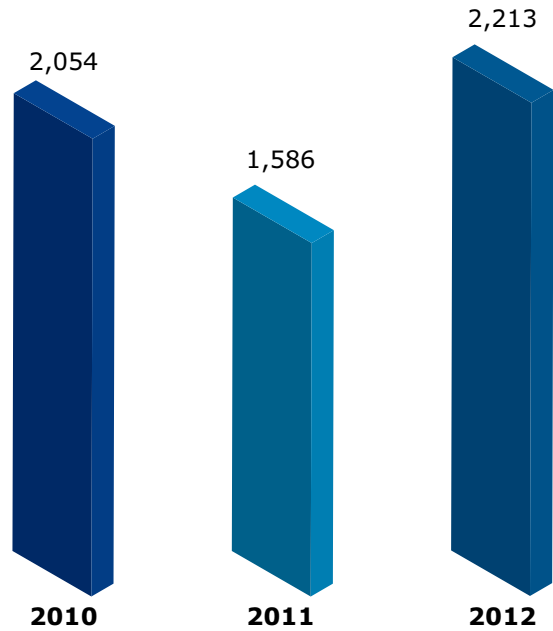


Signal detection

Signal detection – the identification and evaluation of new and emerging information on the safety profile of a medicine in the context of spontaneous reporting – is part of the Agency's pharmacovigilance activities.

A total of 2,213 potential safety issues were detected in 2012, out of which 52 signals were validated. This means that the signal may have a causal relationship with the medicine, which requires further exploration. All validated signals were reported to the rapporteurs of the medicines concerned, who carried out further investigations.

Signal detection 2010–2012

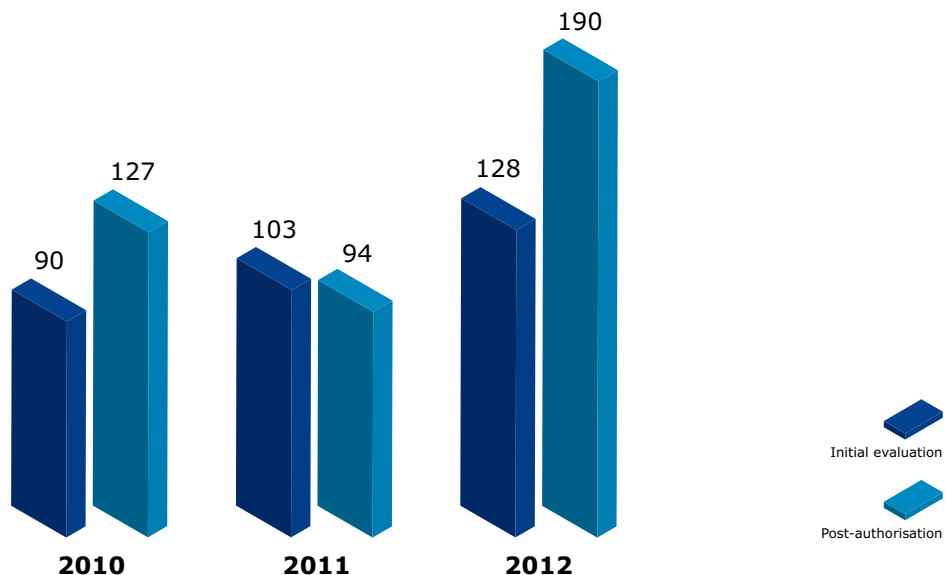


The number of risk-management plans for initial-marketing authorisation rose by 24%

Risk-management plans

The number of peer-reviewed risk-management plans increased substantially. The number of risk-management plans for initial-marketing authorisations rose by 24%, while for post-authorisation the number more than doubled, highlighting the effects of the new pharmacovigilance legislation.

Risk-management plans peer reviewed as part of initial evaluation and post-authorisation 2010–2012



4.1.9. Referral procedures

Referral procedures are used to resolve concerns over the safety or benefit-risk balance of a medicine, or disagreements among Member States on the use of a medicine. In a referral, the Agency is requested to conduct, on behalf of the European Union, a scientific assessment of a particular medicine or class of medicines, to agree on a recommendation for a harmonised position across the EU. A recommendation subsequently results in a legally binding decision issued by the European Commission throughout the EU.

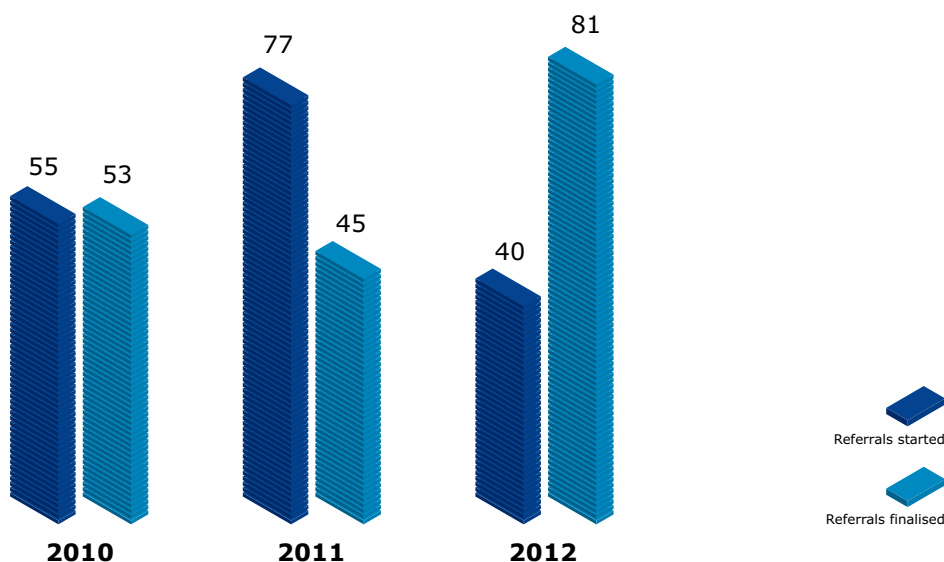
- The number of referrals started in 2012 was lower than that in 2011 as there were no quality-shortcoming-related Article 20 referrals affecting several centrally authorised products in 2012, while there were 21 in 2011.
- In 2012, only 2 Article 5(3) referrals were started where the CHMP was requested to draw up an opinion on a scientific matter, compared to 7 in 2011.
- As the number of referrals started in 2011 was high, the number of referrals finalised in 2012 was also high. Five referral procedures started in 2010, 48 referral procedures started in 2011, and 28 started in 2012 were finalised in 2012.
- The entry into force of the EU pharmacovigilance legislation in July 2012 introduced new types of referral procedures.
- Also, as of July 2012, pharmacovigilance-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC), and then either by the Committee for Medicinal Products for Human Use (CHMP) or, for nationally authorised medicines, by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human. All other referrals on human medicines are assessed by the CHMP only. By the end of 2012, 6 pharmacovigilance-related Article 31 referral procedures were started at the level of the PRAC.

4.1.10. Mutual-recognition and decentralised procedures

The Agency provides secretarial support to the Co-ordination Group for Mutual-recognition and Decentralised Procedures – Human (CMDh) and its subgroups/working groups, in accordance with the approved rules of procedure. The work of the CMDh is essential for the effective authorisation and maintenance of more than 90% of medicines entering the EU market. The mutual-recognition procedure (MRP) and the decentralised procedure (DCP) are the primary authorisation routes for generic applications within the EU.

- 7 MRP and 20 DCP initial applications and 6 applications for type-II variations were referred to the CMDh in 2012.
- Agreement was reached for 3 MRP and 15 DCP referrals (5 of the 15 DCP referrals were referred to the CMDh in 2011) and for 5 referrals for type-II variations.
- 3 MRPs and 5 DCPs were referred to the CHMP for the adoption of an EU-wide scientific opinion under Article 29(4) of Directive 2011/83/EC (1 of the 3 MRP and 3 of the 5 DCP referrals were referred to the CMDh in 2011), as was 1 application for a type-II variation under Article 13 of Commission Regulation (EC) No 1234/2008.
- With regard to work-sharing for the assessment of paediatric studies submitted according to Articles 45 and 46 of the Paediatric Regulation, 42 active substances under Article 45 and 45 submissions of paediatric studies under Article 46 were processed. 45 public assessment reports according to Article 45 (including 1 updated report), 12 public assessment reports according to Article 46 and 1 assessment report from the previous work-sharing project were published on the CMDh website.
- With regard to the revised Variations Regulation, the CMDh gave recommendations on 8 requests for recommendation according to Article 5.

Referrals started and finalised 2010–2012

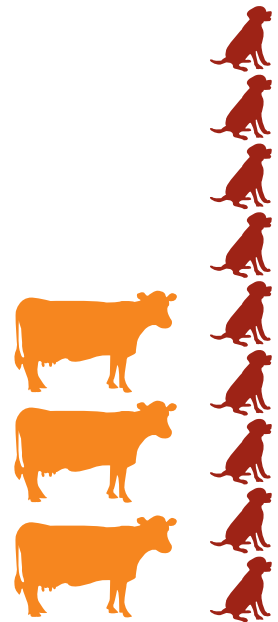


4.2 | Veterinary medicines

4.2.1. Initial evaluation

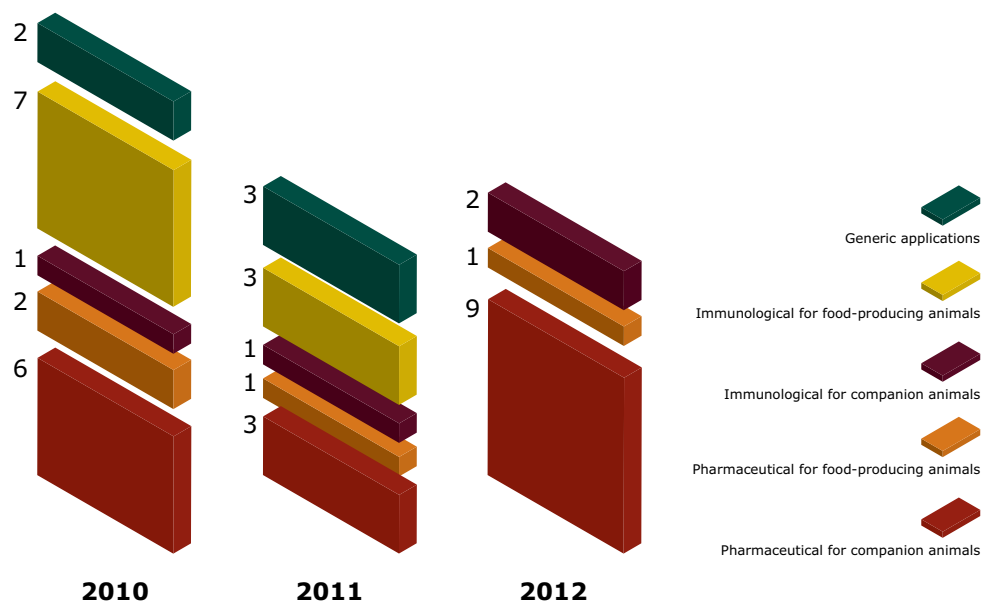
The initial-evaluation phase covers activities relating to the processing of marketing-authorisation applications for veterinary medicines, ranging from pre-submission meetings with future applicants, through evaluation by the Committee for Medicinal Products for Veterinary Use (CVMP), to the granting by the European Commission of the marketing authorisation.

The CVMP received 12 applications for the initial evaluation of new veterinary products in 2012. While in the past the numbers of applications for vaccines and pharmaceuticals were similar, with approximately half of the products intended for food-producing species, in 2012, 83% of applications concerned pharmaceuticals. Nine out of the 12 applications were for medicines for companion animals. These products are often adaptations of human medicines or new fixed-dose combinations. A large proportion (75%) of the products for companion animals were for the treatment or prevention of parasites. In total, only 25% of applications were for food-producing animals.



Nine out of the 12 applications were for medicines for companion animals

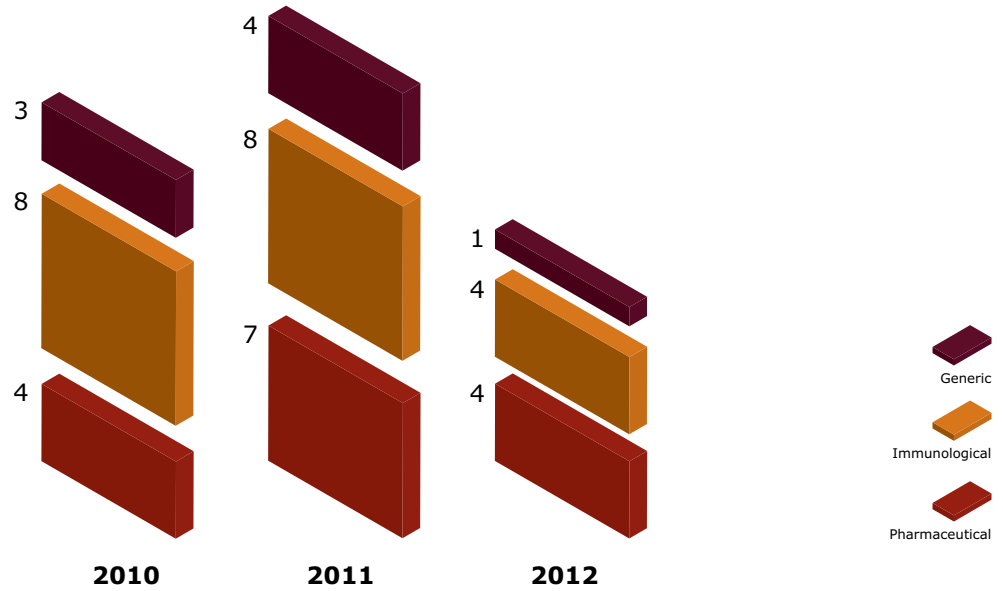
Applications for veterinary medicines received 2010–2012



Options for veterinary medicines adopted

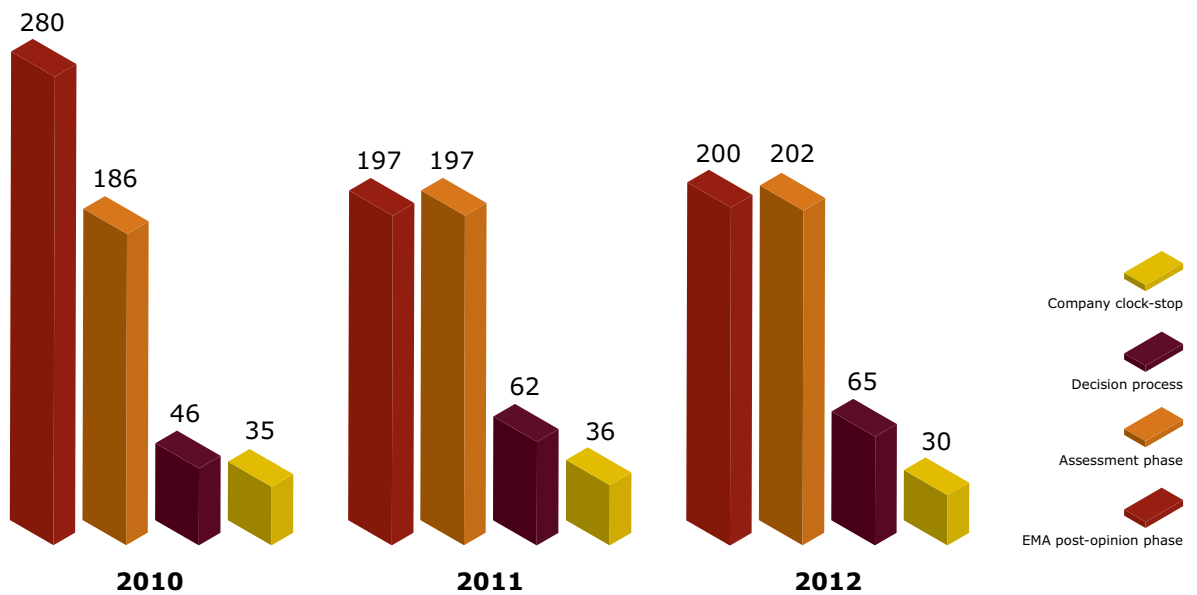
In 2012, the CVMP issued 9 positive opinions for veterinary medicines: 4 for new pharmaceuticals, 4 for new immunological products and 1 for a generic.

Opinions for veterinary medicines adopted 2010–2012



The average number of days for centralised procedures is stable, with an average of 297 days in total for the assessment phase, the EMA post-opinion phase and the decision process; company clock-stop represents 200 days on average.

Average number of days for centralised procedure 2010–2012



4.2.2. Scientific advice

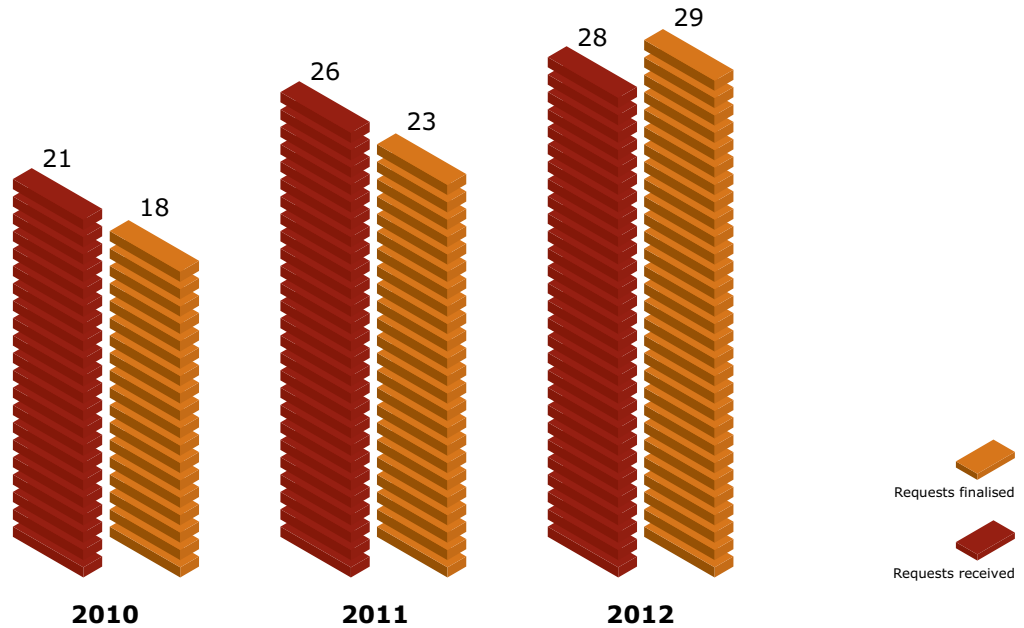
Scientific advice is provided on any aspect of research and development relating to the quality, safety or efficacy of medicines for veterinary use, and to the establishment of maximum residue limits. Scientific advice is considered as a means to facilitate and improve earlier availability of veterinary medicines, and as a means to promote innovation and research.

The number of applications submitted for scientific advice continues to increase, with 28 requests received in 2012. Applications were processed in line with the timetables agreed and covered all areas of the dossier. In 2012, more applications were received than predicted, and this is to some extent a result of the incentives offered to SME companies (90% fee waiver) and to products classified under the MUMS/limited-markets policy, which may also receive fee incentives. This positive trend shows signs of continuing, and more requests for follow-up advice were received in 2012 than previously.



**28 requests
received in 2012
for scientific advice**

Scientific-advice requests received and finalised 2010–2012



4.2.3. 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 establishes maximum residue limits (MRLs) for pharmacologically active substances used to treat animals, to provide for the safe use of foodstuffs of animal origin, including meat, fish, milk, eggs and honey.

As a reflection of the very low number of new active pharmaceuticals being developed for food-producing animals, only 1 application for maximum residue limits for a new substance was received in 2012. The interest in extensions of MRLs to other species continues to be slightly higher, thereby increasing the potential availability of veterinary medicines for a wider range of species. Five extension applications were submitted in 2012.

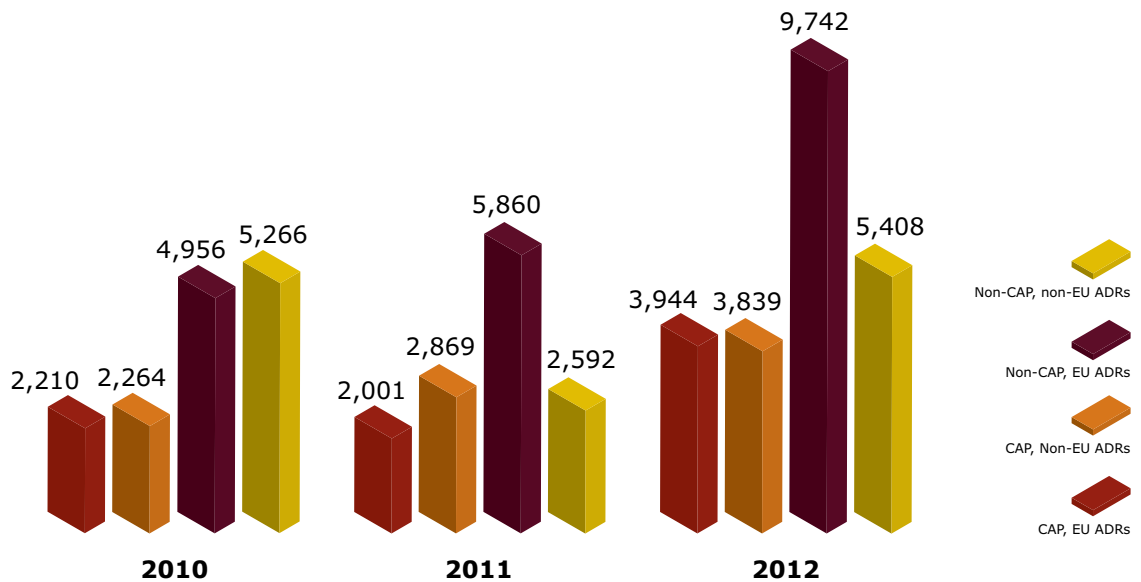
4.2.4. Post-authorisation activities

Pharmacovigilance and maintenance activities

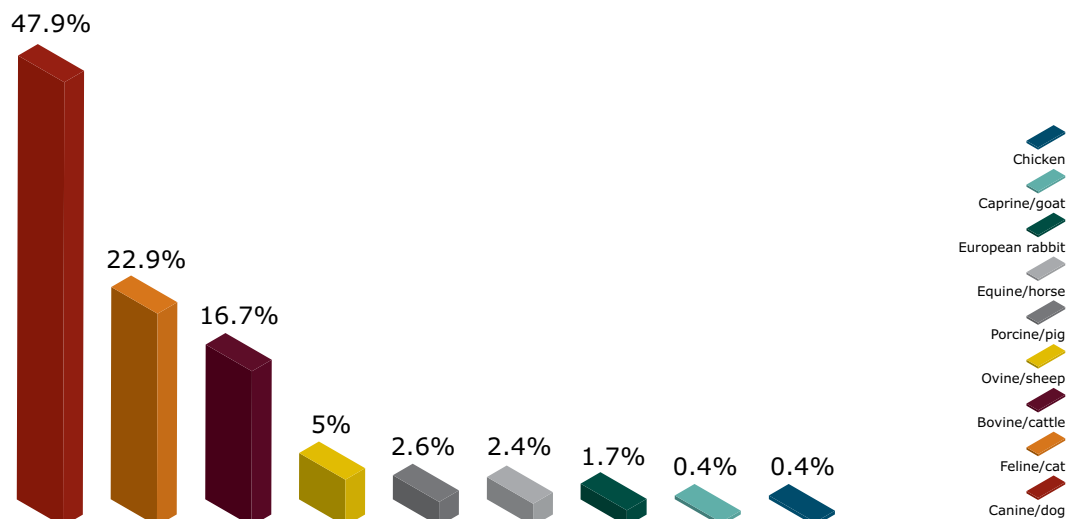
Pharmacovigilance covers activities relating to the detection, assessment, understanding and prevention of adverse drug reactions (ADRs) or other drug-related problems. It aims at ensuring that post-authorisation monitoring and effective risk-management are continuously applied to veterinary medicines throughout the EU.

As observed for human medicines, the total number of adverse-event reports increased in 2012 compared with 2011 (increase by 72%). Increases were observed for all the categories of reports. The increase in adverse-event reports indicates an increased commitment of stakeholders to providing all available data.

Reports on suspected adverse reactions in animals and reports on human reactions 2010–2012



Percentage of reports per species in EudraVigilance Veterinary 2012

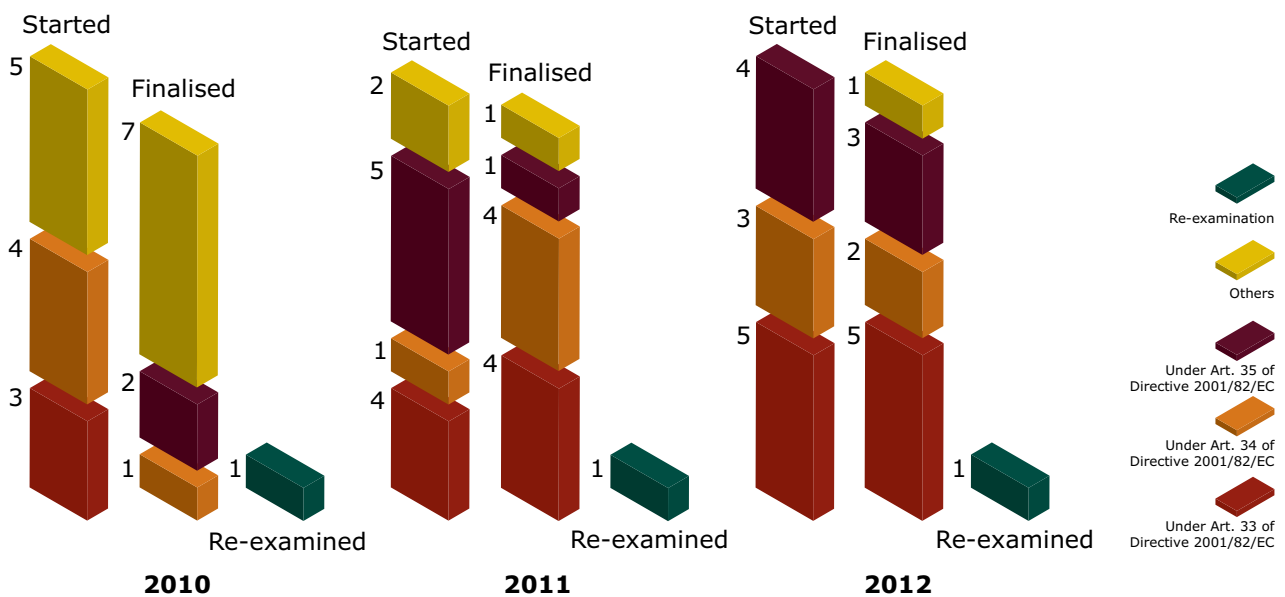


4.2.5. Referral procedures

Referral procedures are used to resolve disagreements and address concerns among EU Member States. In a referral, the Agency is requested to conduct, on behalf of the European Union, a scientific assessment of a particular medicine or class of medicines, to agree on a recommendation for a harmonised position across the EU.

Nine of the 12 referrals received in 2012 concerned products containing antimicrobial substances for food-producing animals. This reflects the high level of concern within the EU to ensure that such products are authorised with appropriate conditions of use, in order to reduce the risk of antimicrobial-resistance development as much as possible.

Referrals started and finalised 2010–2012



4.2.6. Mutual-recognition and decentralised procedures

The Agency provides the secretariat for the Co-ordination Group for Mutual-recognition and Decentralised Procedures – Veterinary (CMDv) and its working groups, in accordance with the approved rules of procedure. The work of the CMDv is essential for the effective authorisation and maintenance of the majority of veterinary medicines entering the EU market. The mutual-recognition procedure (MRP) and the decentralised procedure (DCP) are the primary authorisation routes for veterinary generics within the EU, which currently account for the vast majority (80%) of new marketing-authorisation applications.

- 213 MRPs/DCPs were finalised in 2012 – a decrease of 7.5% compared to 2011.
- 8 initial applications, as well as 1 line extension and 1 type-II variation, were referred to the CMDv in 2012. 50% of the referrals to the CMDv ended in disagreement and were further referred to the CVMP for final arbitration. The CVMP accepted 100%

of the procedures referred by the CMDv and the final outcome was that 75% of these referrals were overruled, i.e. the concerns of the referring Member State(s) were not upheld.

- The CMDv handled approximately 35 work-shared variations. The task of updating the CMDv's best-practice guide on variations following the revision of the Variations Regulation was begun.
- Within the context of the veterinary-legislation review, the CMDv collaborated intensively with stakeholders in sending proposals to the European Commission on the simplification of current labelling requirements.
- The CMDv, with support from the secretariat, successfully took over responsibility from the European Commission of the information on national requirements previously held in the Notice to Applicants.

4.3 | Inspections and compliance

The Agency coordinates the verification of compliance with the principles of good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), good pharmacovigilance practice (GVP) and certain aspects of the supervision of authorised medicinal products in use in the European Union. It does this through inspections requested by the CHMP or CVMP in connection with the assessment of marketing-authorisation applications and/or the assessment of matters referred to these committees in accordance with EU legislation.

The Agency also checks compliance of parallel distribution of centrally authorised medicines that are distributed from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder. Finally, the Agency 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.

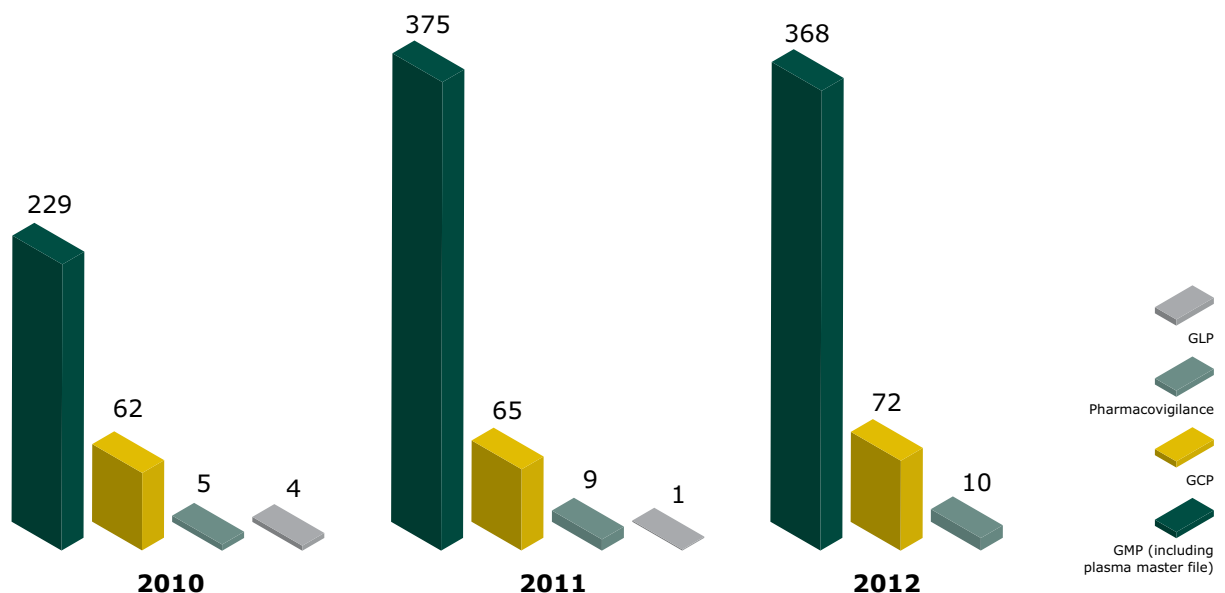
Inspections

There has been an overall increase in GMP inspections over the years; however, the high figures for 2011 were due to unplanned inspections related to non-compliance and unforeseen API (active pharmaceutical ingredient) inspections in third countries.

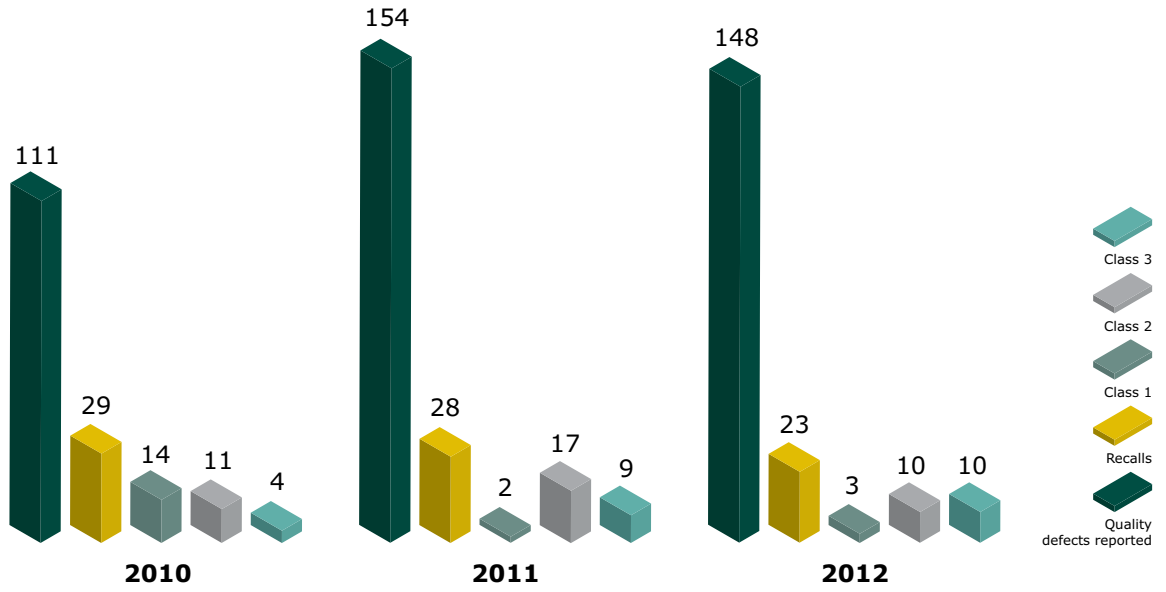
Number of quality defects

The number of quality defects reported following inspections has been very high for the past two years (see opposite).

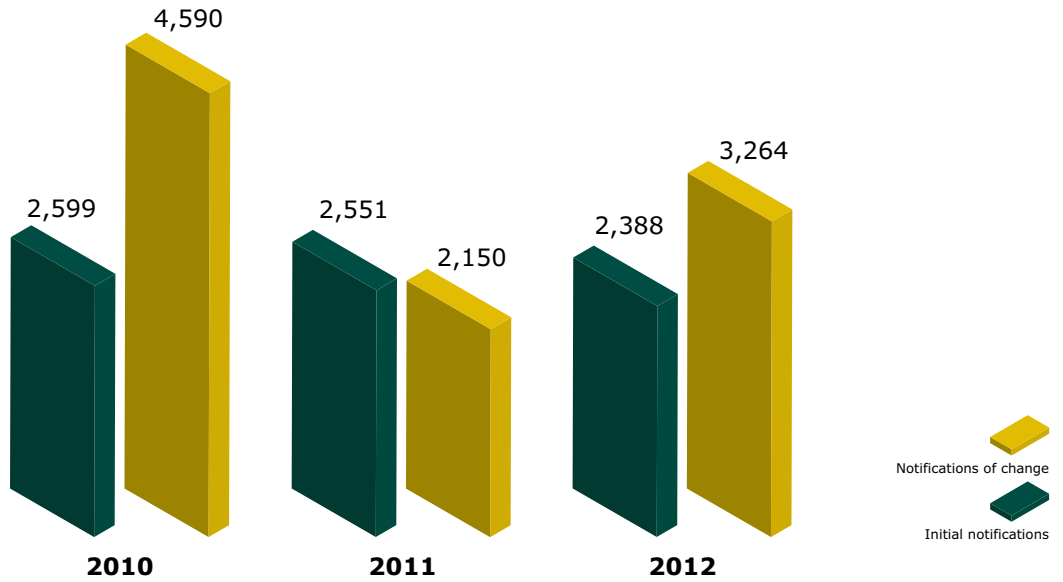
Number of inspections 2010–2012



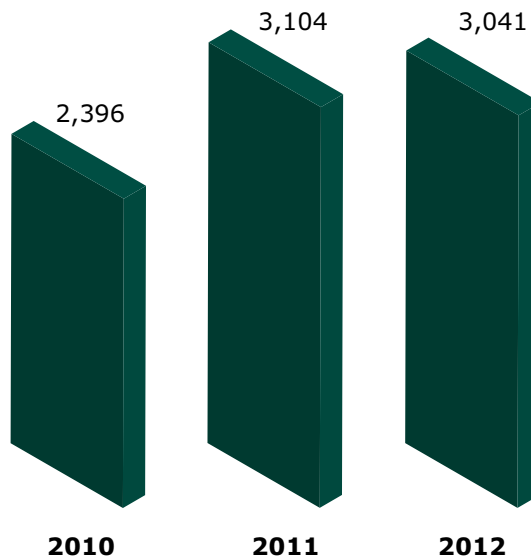
Number of quality defects reported 2010–2012



Parallel distribution notifications – notifications of change 2010–2012



Certificate requests 2010–2012



4.4 | Budget and staff

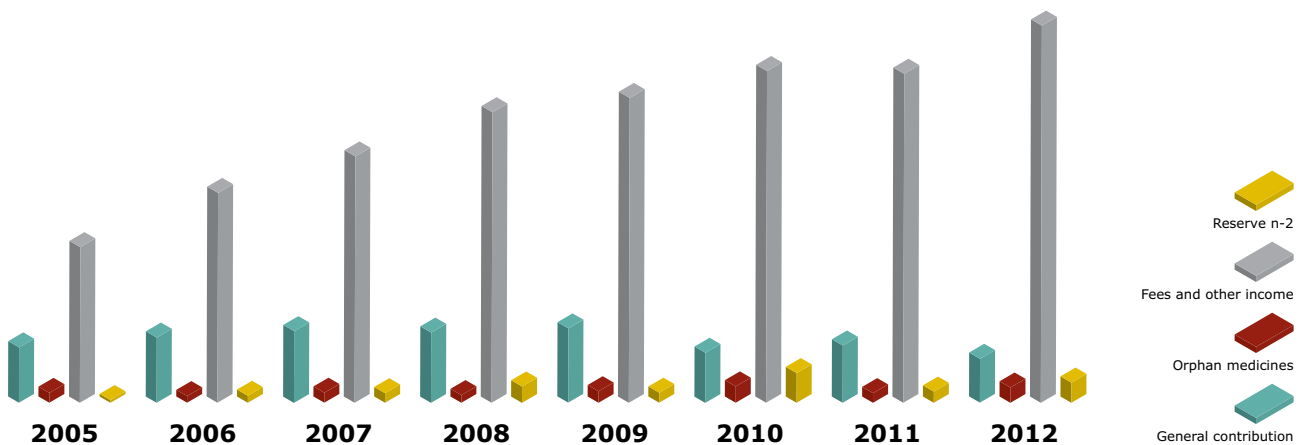
Budget composition: revenue

The total budget of the Agency in 2012 was €222,489,000, representing a 12% increase compared with 2011. The EU general contribution was 10% of the total budget.

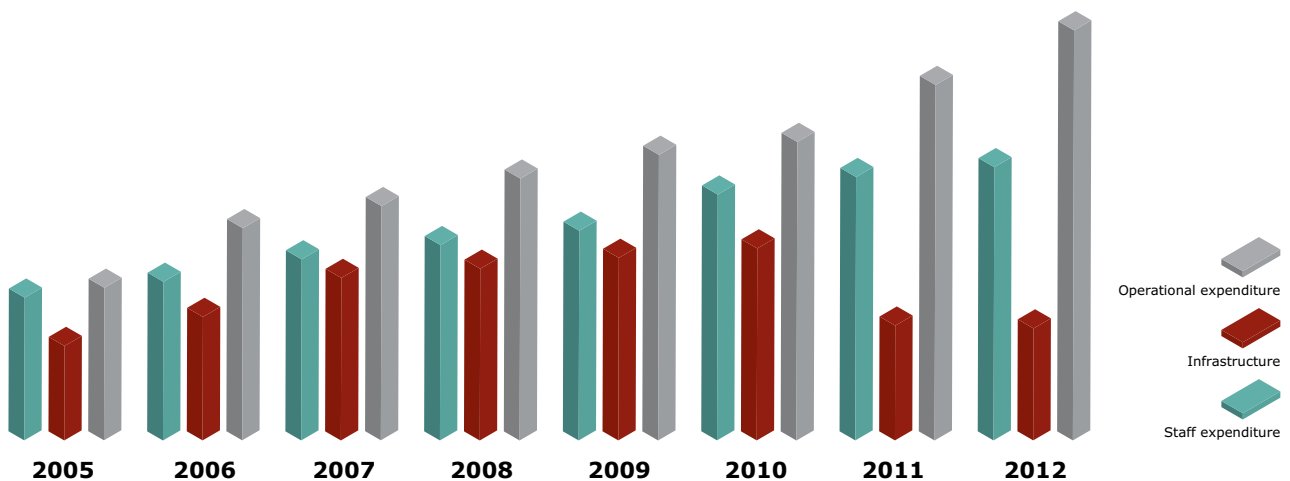
Budget composition: expenditure

Operational expenditure makes up over half of the Agency's total expenditure. This includes a total of €82,181,000 paid to Member States for the evaluation of medicines.

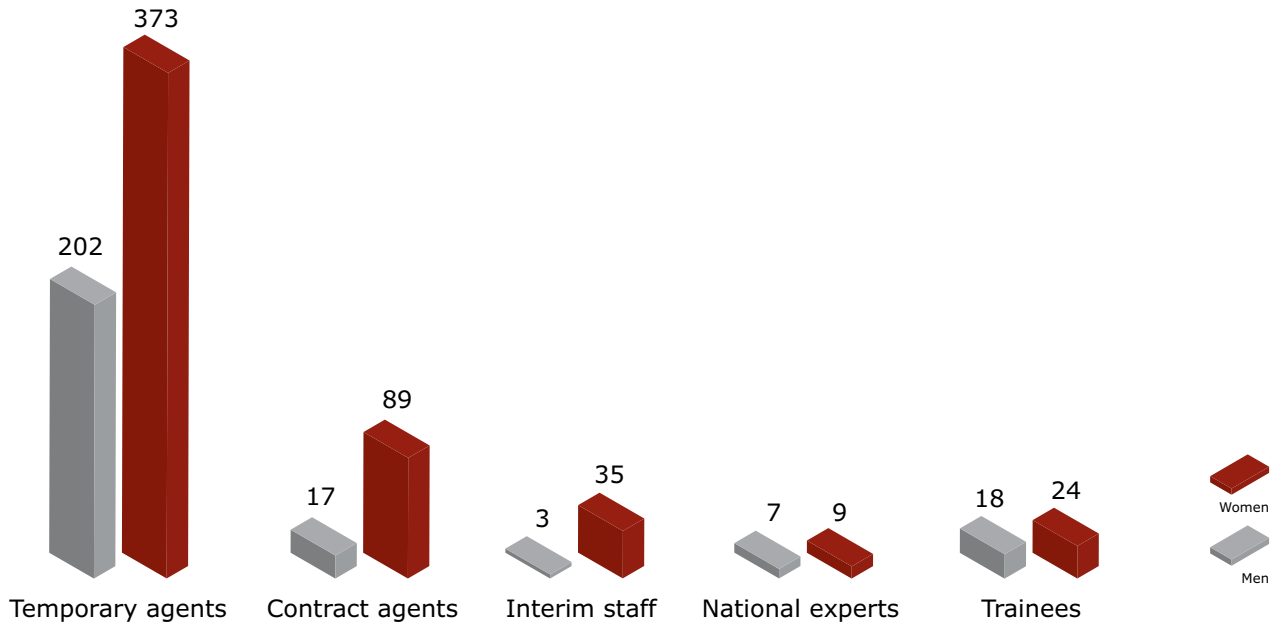
Revenue 2012



Expenditure 2012



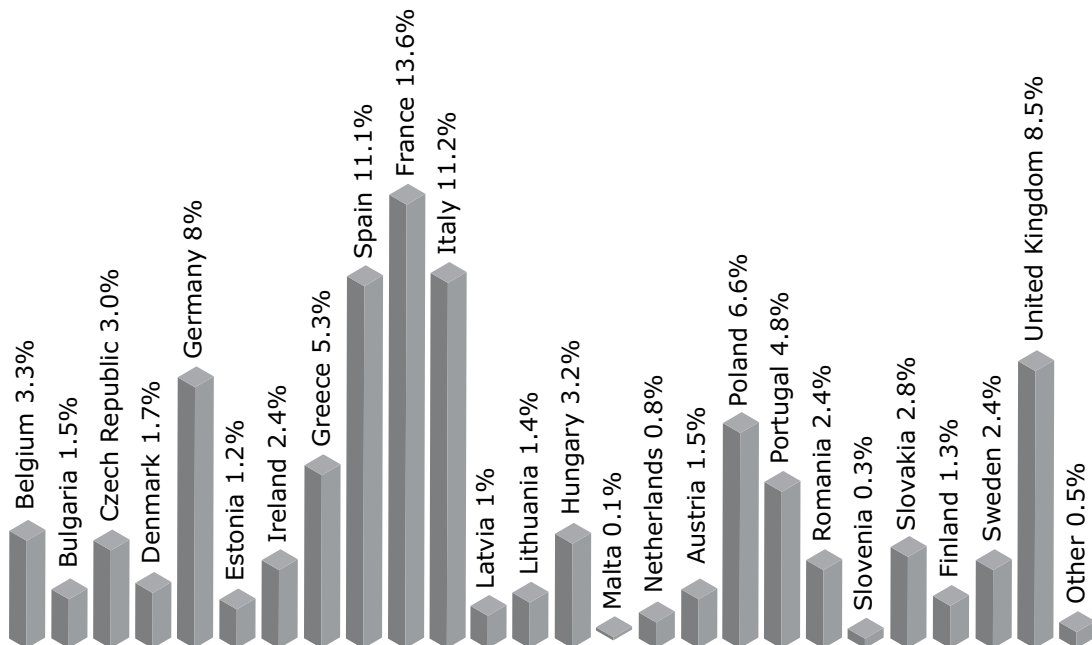
Agency staff



Gender balance

Status	Category AD (administrators)		Category AST (assistants)	
	Men	Women	Men	Women
Ratio men/women for temporary agents	158 (50%)	157 (50%)	44 (17%)	216 (83%)
Ratio men/women for contract agents	14 (35%)	26 (65%)	3 (5%)	63 (95%)
Total	172 (48%)	183 (52%)	47 (15%)	278 (85%)

National origins of Agency staff December 2012



Annexes

Annex documents are available on the Agency's website (www.ema.europa.eu) via:
About us > How we work > Core management documents > Annual reports

European Medicines Agency

7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Telephone +44 (0)20 7418 8400

Facsimile +44 (0)20 7418 8416

E-mail info@ema.europa.eu

www.ema.europa.eu

Annual report 2012

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