



GOBIERNO
DE ESPAÑA

MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

 agencia española de
medicamentos y
productos sanitarios

AEMPS

AGENCIA ESPAÑOLA
DE MEDICAMENTOS
Y PRODUCTOS SANITARIOS

How are Medicines
and Medical Devices
regulated in Spain?

How are Medicines and Medical Devices regulated in Spain?



First edition: **2010**

Second edition: **2014**

Published and distributed by: ©**AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS**
C/ Campezo 1. 28022. Madrid

NIPO: **681-14-002-7**

Legal Deposit: **M-27561-2014**

TABLE OF CONTENTS

1. The Agencia Española de Medicamentos y Productos Sanitarios, AEMPS: Who we are	2
Mission and vision	3
Summary of activity	4
The human team	6
Structure	7
2. How are medicines assessed and authorised?	8
Medicines Research Stages	10
Authorisation	12
Authorisation procedures	13
How are medicines assessed: the dossier for authorisation	14
Summary of product characteristics, package leaflet and public assessment report	15
Veterinary medicines: establishment of maximum residue limits, withdrawal period and environmental risk assessment	16
Access to medicines in exceptional circumstances	18
3. How are authorised medicines followed up?	20
The Pharmacovigilance System	21
Quality controls and inspections	24
Guarantees of supply	26
Combating illegal medicines	28
Procedures on medicines sold on the Internet	29
4. How are Medical Devices regulated?	30
5. Cosmetics and Personal Care Products	34
Cosmetics	35
Personal Care Products	38
6. AEMPS on the international stage	40
7. Information for the public and professionals	42

1.

The Agencia Española de Medicamentos y Productos Sanitarios, AEMPS: Who we are

The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), a state agency within the Spanish Ministry of Health, Social Services and Equality, is the body which guarantees quality, safety, efficacy and accurate information on medicines and medical devices marketed in Spain.

Since the AEMPS started its activities in 1999, it has developed a wide range of activities to meet the demand of citizens for the guarantee of medicines and medical devices. This high level of requirement, together with new needs such as ensuring access to these, agility and flexibility in the availability of new treatments and the rational use of medicines, are some of the challenges that the AEMPS, on behalf of the Spanish Public Administration, faces.

The transformation of the AEMPS into a State Agency in 2011 responds to the aspirations of modernity and rationalisation of the Spanish Public Administration, with a view to more efficient management and transparency in the specialised and complex tasks undertaken by the Agency, and with the agility needed to assume legislative advances at a European level.

The most important legislation governing the activities of the AEMPS is the Law 29/2006, of 26th of July, on guarantees and rational use of medicines and medical devices, modified by the Law 10/2013, of 24th of July, and the different royal decrees regulating each area of intervention, as well as the Royal Decree 1275/2011, of 16th of September, by which the State Agency “Agencia Española de Medicamentos y Productos Sanitarios” is created and its Statute approved.



AEMPS protects public health by means of previous authorisations, registration and controls of manufacturing and marketing carried out on medicines for human use, veterinary medicines, medical devices, cosmetics and personal care products, and support of clinical research.

Mission and vision

As a public service, the mission of the AEMPS is to give guarantees to the general public on the quality, safety, efficacy and accurate information on medicines and medical devices, in the widest remit, from research to end use, to protect and promote health in both human beings and animals. Its vision is to strengthen the reference health authority for citizens and healthcare professionals with regard to guarantees of quality, safety, efficacy, information and accessibility of medicines and medical devices.

Summary of activity

AEMPS develops a wide range of activities, within the framework of;

Medicine assessment and authorisation for human and animal use.

Authorisation of clinical trials with medicines and clinical investigation with medical devices.

Continuous monitoring of medicine safety once medicines go on the market.

Quality control.

Authorisation and inspection of pharmaceutical laboratories and active ingredient manufacturers.

Supervision of medicine supplies and their supply to the public.

State roles and responsibilities of inspection and surveillance in the framework of narcotic drugs and psychotropic substances.

Certification, control and supervision of medical devices.

Combating illegal and falsified medicines and medical devices.

Monitoring safety procedures for cosmetics and personal care products.

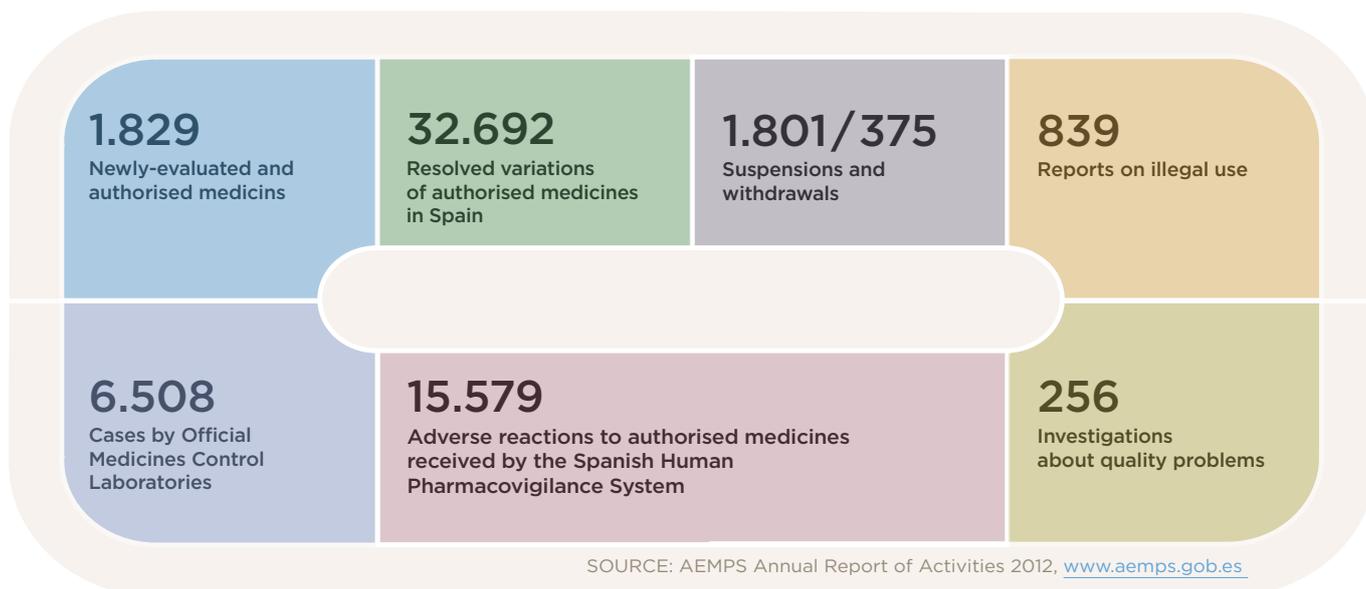
Providing all relevant information to the public and healthcare professionals.

Public health and the well-being of citizens are the basic objectives steering the work of the AEMPS.

Public health and the well-being of citizens are the basic objectives steering the work of the AEMPS. Through its work, the AEMPS interacts with a great variety of agents: patients, healthcare professionals, pharmaceutical and health technology industries and cosmetic industries, other Spanish and foreign health and non-health authorities, researchers, scientific associations, the media and the general public.

Ongoing monitoring of the BENEFIT-RISK BALANCES of authorised medicines for human use

SUMMARY OF ANNUAL ACTIVITY IN MEDICINES FOR HUMAN USE



In all its actions the AEMPS bases its work on the most advanced and rigorous scientific knowledge and maintains principles of objectivity, independence, transparency and accessibility.

In all its actions the AEMPS bases its work on the most advanced and rigorous scientific knowledge and maintains principles of objectivity, independence, transparency and accessibility.

Society demands rapid access to new products. To facilitate this, the AEMPS supports investigation and innovation as well as collaborating with public and private organisations and institutions so as to improve the availability of new treatments and diagnostic tools in an agile and safe manner.

Another important task of the AEMPS is to provide information to the public, healthcare professionals and researchers, on all aspects pertaining to medicines, medical devices and any incidents occurring after they are put on the market. The website www.aemps.gob.es is the main tool used to carry out this activity.

With a view to improving in its work, the AEMPS has drawn up a General Strategic Plan for 2009-2012, extended to 2013, with six general objectives, which are supported by specific strategies and developed in more than 100 projects. The main objective of the plan is to maintain the highest scientific rigour in medicine and medical devices regulation, which will be proportionate to risks, agile, transparent, and foreseeable within response timescales, guaranteeing public health in the face of challenges presented by new therapies and new assessment methodologies, new challenges in safety or brought on through the globalisation of medicines and medical devices manufacturing.



The human team

The human team of the AEMPS is made up of more than 500 highly qualified professionals with degrees and doctorates in Pharmacy, Medicine, Veterinary Science, Biology, Chemistry, Law, Computer Engineering, etc.

The AEMPS is further supported by scientific committees and specialised coordination committees in the main areas of intervention, as well as a network of external experts.

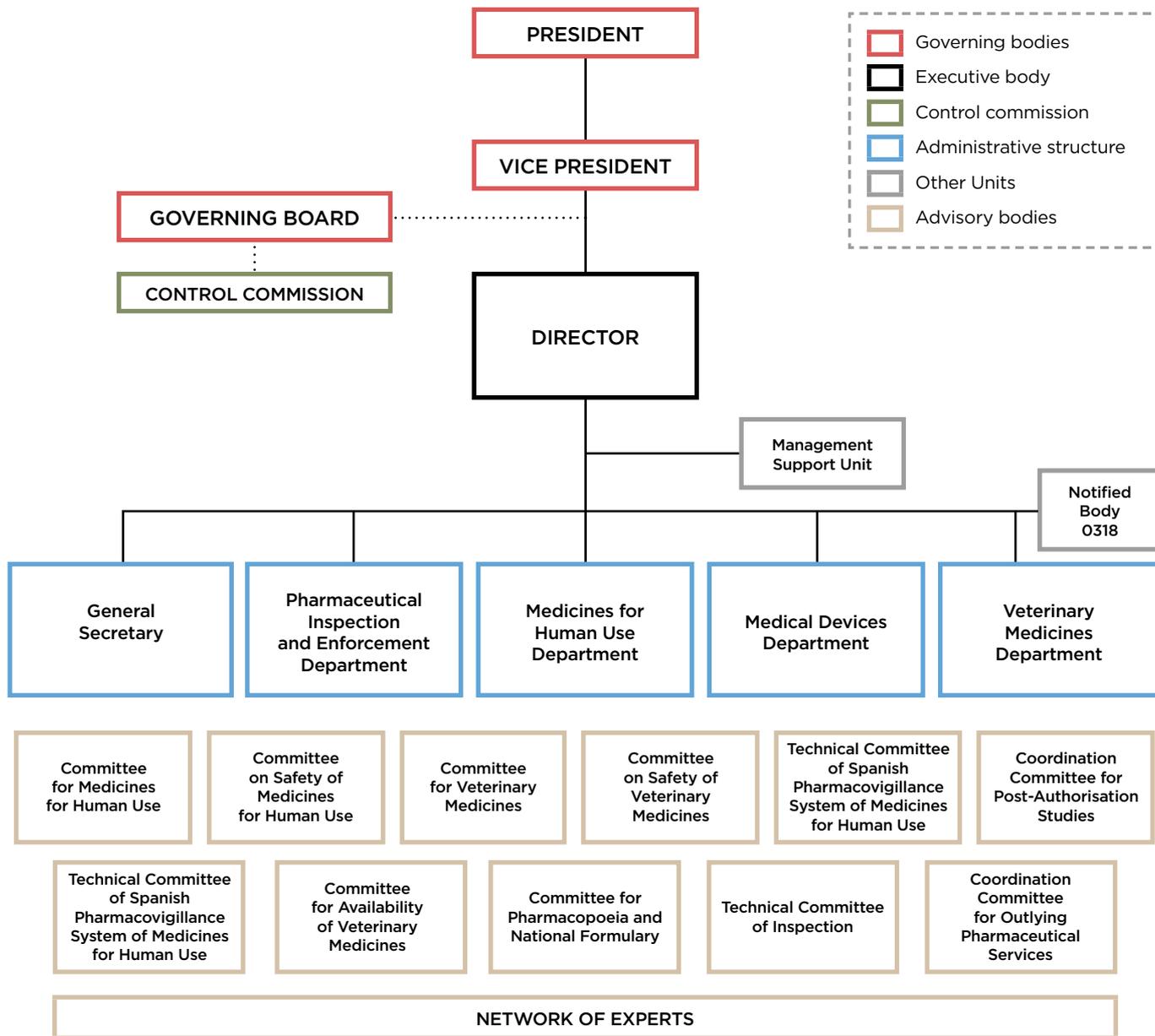
The scientific committees are consultancy bodies, guaranteeing transparency and independence of AEMPS activities. They are multiagency bodies, which include responsible AEMPS personnel and eminent experts in the field, as well as representatives of consumer and user associations, and professional medical, pharmaceutical and veterinary associations.

There are also AEMPS committees in coordination with the authorities in Autonomous Communities and outlying pharmaceutical inspection services.

One of AEMPS' strengths is undoubtedly its interaction with expert professionals in the Spanish Health System and the Spanish universities through the AEMPS network of experts, which provides scientific and clinical advisory services in specific areas of knowledge. More than a hundred of these specialists have at some time been designated expertise of the European Medicines Agency.

Structure

Bodies and structure of the Agencia Española de Medicamentos y Productos Sanitarios.



2.

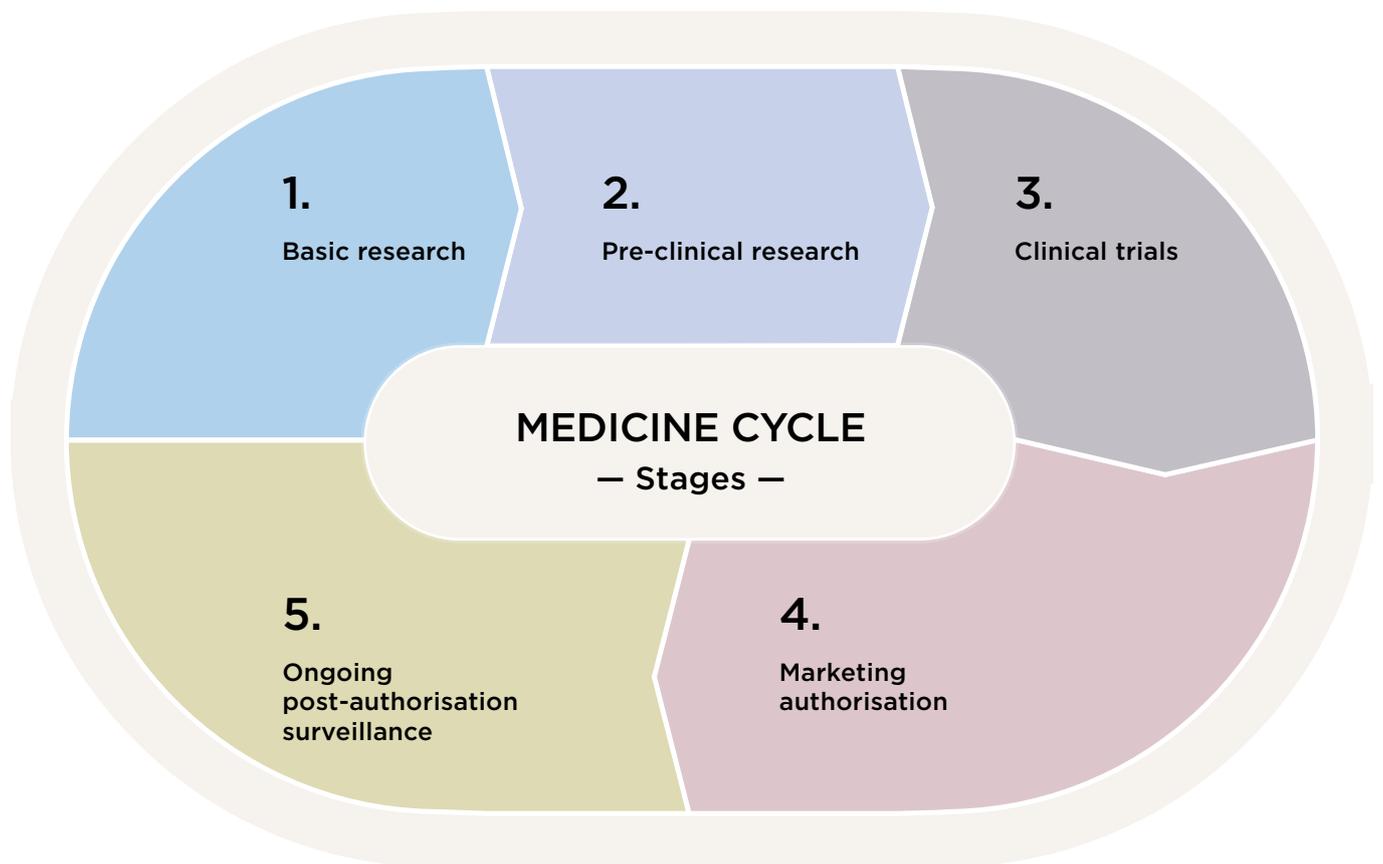
How are medicines assessed and authorised?

A medicine is a substance or combination of substances, presented as possessing properties to treat or prevent diseases among human beings and animals; to be used to restore, correct or modify physiological functions through pharmacological, immunological or metabolic action; or to establish medical diagnosis.

Medicines are regulated throughout their entire lifecycle. All medicines used in Spain must obtain a marketing authorisation, which AEMPS will grant after assessing their quality, safety and efficacy. Likewise, any other variation of the medicine must be authorised or reported to AEMPS. These assessments allow us to ensure a positive relation between the benefit and risk of the medicine throughout its progress on the market.

Medicines regulated by the AEMPS include diverse products ranging from chemical or biotechnological medicines, blood products, vaccines, plant-based medicines, homeopathic medicine, and contrast media for radiological exploration to cell therapies.

All medicines authorised by the AEMPS can be found on the online AEMPS Medicine Information Centre (under the Spanish acronym CIMA), available on the Internet at www.aemps.gob.es which gives continually updated information.





Medicines Research Stages

For a medicine to be authorised, it has to undergo various stages in research which are aimed at verifying the quality, efficacy and safety of the medicine. The research process on medicines encompasses the initial basic research, pre-clinical trials or animal-evaluation and clinical trials on humans. Any clinical trials on human beings must be authorised by the AEMPS before they are carried out.

BASIC RESEARCH

The discovery of a new medicine implies processes such as identification of candidates, synthesis, description, tracking and tests of therapeutic efficacy. Despite advances in technology and knowledge in biological systems, it is still a long process with a very low success rate.

It is estimated that for every 10,000 molecules of medicines studied in the basic initial research, only 250 molecules proceed to the next stage - the pre-clinical tests.

PRE-CLINICAL STUDY

After the basic research, the most promising molecules are studied in animals or laboratory models to assess their safety and biological activity. These studies are intended to establish the effects of the medicine in different doses on different organs and systems, and how it is distributed or eliminated in the organism. Chemical and pharmaceutical studies are carried out on the compound to establish how stable or pure it is, manufacturing tests are also carried to find out the viability of grand scale production and further studies to prepare the appropriate formula for its use.

The main objective of these studies is to carry out rigorous tests on the safety of the compound and the efficacy expectations before starting trials on human beings. This phase can take three years or more, and thousands of compounds never progress to the next stage. It is estimated that for every 250 compounds at the pre-clinical stage, only five progress to the next stage - the clinical trials.

Altogether, the time required for the basic research and pre-clinical tests is approximately six years.

CLINICAL TRIALS

Clinical trials are necessary to establish if the behaviour of the medicine in human beings (in the case of medicines for human use) or in different target animal species (in the case of veterinary medicines) is suitable and if it is truly effective in the treatment of the disease for which it is intended with an acceptable profile of adverse reactions.

To start clinical trials on individuals, companies must present applications for authorisation to regulatory Agencies, such as the AEMPS in Spain. These applications must include results of earlier research stages and a detailed plan on how the clinical trials will be conducted.

In the case of medicines for human use, in addition to the authorisation by the AEMPS, both the design and form in which the trials will be conducted are supervised by ethical committees on clinical research, which guarantees respect for the rights and well-being of the participants.

The clinical research is divided into three phases, whose main features, depending on whether medicines for human use or veterinary medicines are used, are as follows:

PHASE I

TRIALS IN HUMAN PHARMACOLOGY: Traditionally, these are carried out on a small number of healthy subjects (between 20 and 100 people), to ascertain dose range (from the lowest effective dose to the highest that can be administered without causing harm) and medicine behaviour in the body with regard to absorption, distribution, metabolism and elimination.

TRIALS IN VETERINARY PHARMACOLOGY: These are pre-clinical/pharmacokinetic studies, safety in the laboratory, MRL/withdrawal period in food-producing animals. They are usually small groups of animals.

PHASE II

EXPLORATORY TRIALS: These are effectiveness exploratory trials and are carried out on hundreds of patients with the aim of establishing a test to assess the efficacy of the treatment, and at the same time assessing side effects, appropriate doses and establishing the length of required treatment.

TRIALS IN VETERINARY MEDICINES: These are studies of selection and confirmation of dose. We are referring to studies which involve a reduced number of animals and that can be carried out both under laboratory or field conditions.

PHASE III

CONFIRMATORY TRIALS: These are effectiveness confirmatory trials that are carried out in a significant number of patients (several thousand), divided into groups according to whether they are exposed to a new medicine, or to an already known medicine to treat a specific illness (or by placebo), to obtain evidence or definite proof of efficacy and safety. The trials usually take between one to four years.

TRIALS OF VETERINARY MEDICINES: These are studies carried out in the target species (not in experimental animals) to establish therapeutic effects and safety during the use of the product in field conditions and are conducted according to good clinical practice. The number of animals involved is very high and the studies take between one to three years.

Authorisation

No medicine can be marketed or sold in Spain without prior authorisation from the AEMPS or the European Commission.

Marketing authorisation is given on the basis of scientific criteria on the quality, safety, and efficacy of the medicine. These three criteria allow us to assess the relationship between medicine benefits and risks for disease and contexts for which the medicine has been approved.

For years, there have been common technical criteria within the EU for medicine assessment and authorisation.

This allows Europe-wide authorisation procedures where a medicine can have national authorisation, valid within one member state or authorisation in more countries within the EU, thereby increasing the efficacy and efficiency of the European Medicine Agencies Network.

After obtaining authorisation, the medicine needs to be subjected to ongoing surveillance for new risks and uses, so that at any time said authorisation can be reviewed. Any desired change introduced in a medicine after it has already been authorised must be subjected to assessment, following procedures for its original authorisation.

Authorisation procedures

FRAMEWORK FOR AUTHORISATION PROCEDURES:

1	National procedure
2	Decentralised procedure
3	Mutual-recognition procedure
4	Centralised procedure

NATIONAL PROCEDURE. The applicant presents a dossier for authorisation to the AEMPS with all the information required for the marketing authorisation in Spain.

DECENTRALISED PROCEDURE. The applicant presents an application for authorisation simultaneously in several EU member countries. Different agencies will assess the medicine in a coordinated manner, with one agency assuming the coordination or key role. At the end of the process, each agency will issue an identical authorisation which will be valid for its area of jurisdiction.

MUTUAL-RECOGNITION PROCEDURE. This occurs when a medicine has already received a marketing authorisation within the EU. The holder of this authorisation may present an application for recognition of the authorisation in other EU Member States, notifying both the Member State which has issued authorisation (the key Member State) and the European Medicines Agency (EMA). The key Member State will send the medicine assessment report to the states involved, which in turn will recognise the initial authorisation for marketing and sale.

CENTRALISED PROCEDURE. The applicant applies for authorisation in all the EU Member States at the same time. In this case, the European Medicines Agency will take responsibility for the administrative process, and the scientific assessments will be carried out by two Member States (rapporteur and co-rapporteur) who will send their reports to the other Member States. A scientific committee, subsidiary of the European Medicines Agency, takes responsibility for preparing reports on any question pertaining to the medicine assessment. Once a positive technical report has been issued, the European Commission will grant the applicant authorisation for marketing and sale of the medicine, which will be valid throughout the EU.

Out of approximately 1,800 new authorisations granted each year, about 55% follow decentralised or mutual-recognition procedures, 33% follow national procedures, and around 12% follow the centralised procedure.

All procedures involve the same teams of assessment experts, and follow the same technical criteria.



How are medicines assessed: the dossier for authorisation

Having successfully concluded the above-mentioned research stages, when a marketing authorisation for a medicine is requested, it is necessary for applicants to submit a dossier with all research results on the medicine, data on its manufacture, risk management plan and, in general, all documentation showing compliance with the requirements necessary for its authorisation.

During the assessment process, AEMPS reviews all data available from both the pre-clinical phase and clinical trials, and all information on its manufacture and chemical and pharmaceutical controls, thereby subjecting for further analysis the medicine, its raw materials or intermediary products at the official evaluation laboratories of the Agency, or inspection of facilities where the medicine or their active ingredients were manufactured.

When the assessment carried out on the medicine is favourably concluded, a marketing authorisation is issued, which includes conditions set down by the AEMPS for appropriate use (for example, dosage, warnings and contraindications). These conditions are included in the information on the use of the medicine, destined for healthcare professionals (available in the summary of product characteristics) and for patients (in the package leaflet).

Summary of product characteristics, package leaflet and public assessment report

From the assessment of all information on the medicine, the AEMPS prepares three documents aimed at giving information on its use: a summary of product characteristics, a package leaflet and a public assessment report.

The summary of product characteristics is the document authorised by the AEMPS, in which the conditions for authorised use of the medicine are set out (indications, dosage and dose intervals, warnings, contraindications, adverse reactions, use in special conditions), and includes necessary scientific information for doctors and other healthcare professionals (clinical data summaries, pharmacological properties, and pre-clinical data on safety).

The package leaflet is the information accompanying the medicine, which is destined for the patient or user. It includes information on medicine composition and instructions on its administration, use and storage, as well as adverse reactions, interactions and contraindications, all with the aim of achieving its correct use and the observance of prescribed treatment. It is written in clear and easily understandable language to allow patients and users to be able to use it, and where necessary with the help of healthcare professionals.

The AEMPS also publishes a public assessment report for each medicine for human use that has been authorised since March of 2013. These reports contain all the scientific information assessed by the AEMPS in order to issue a marketing authorisation, including, for example, clinical or bioequivalence studies presented by the marketing authorisation holder. This information can be found in the online AEMPS Medicine Information Centre, together with its package leaflet and summary of product characteristics.

The text and other features of the labelling and the package leaflet require authorisation from the AEMPS.

Any change in the summary of product characteristics, package leaflet and public assessment report also has to be assessed and authorised by the AEMPS, and made available with constant updating on its website, inside the AEMPS online Medicine Information Centre (under the Spanish acronym CIMA).



From the assessment of all information on the medicine, the AEMPS prepares three documents aimed at giving information on its use: a summary of product characteristics, a package leaflet and a public assessment report.



Veterinary medicines: establishment of maximum residue limits, withdrawal period and environmental risk assessment

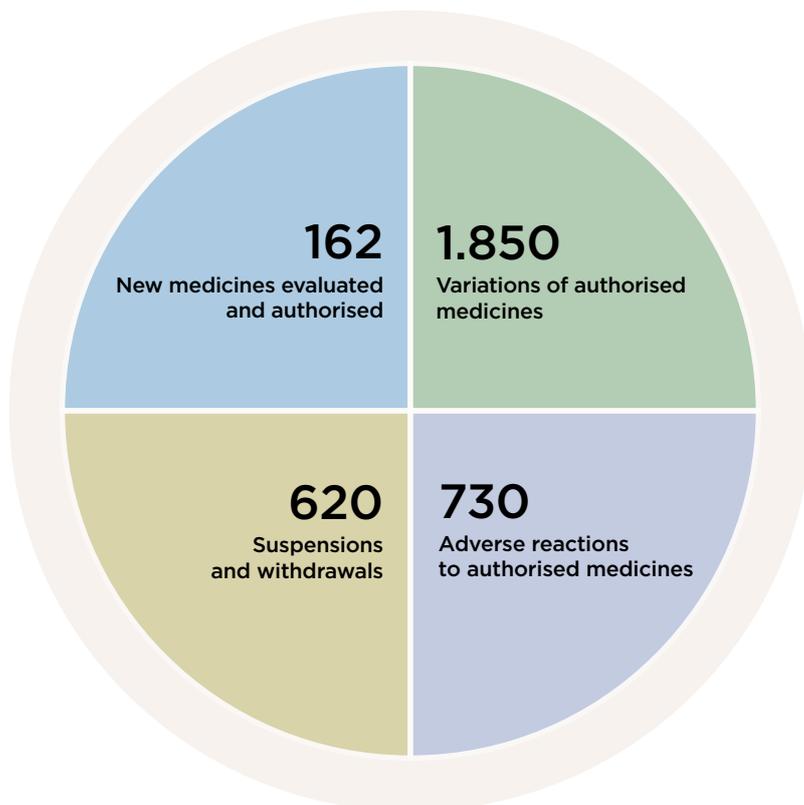
Veterinary medicines are aimed at preventing, treating or diagnosing animal diseases.

The procedure for assessing and authorising these medicines is the same as for human beings. In addition, for purposes pertaining to their use, veterinary medicines must also deal with consequences to public and animal health, as well as to the environment.

To ensure public health, for veterinary medicines aimed at food-producing animals, maximum residue limits (MRL) are set out along with the withdrawal period between treatment of animals and the harvesting of food products from them, thereby ensuring they will be fit for human consumption.

Ongoing monitoring of the BENEFIT-RISK BALANCE of authorised veterinary medicines

SUMMARY OF ANNUAL ACTIVITY IN VETERINARY MEDICINES



SOURCE: AEMPS Annual Report of Activities 2012, www.aemps.gob.es

The assessment of the environmental impact of veterinary medicines and their metabolite substances is another constraint in the authorisation process for marketing and sale.

The assessment of the environmental impact of veterinary medicines and their metabolite substances is another constraint in the authorisation process for marketing and sale.

The veterinary pharmaceutical sector in Spain occupies the third position in the EU and the seventh of the global turnover. Livestock occupies one of the prime positions in the EU, with great diversity of species and different production systems.

The demand on the market for immunological medicines in this area is high, arising from different species at which they are aimed, and the need to prevent various susceptible infectious diseases through vaccination programmes. This requires a major investment in research and development on the part of the pharmaceutical laboratories and efficient, specialised support by the AEMPS, thus contributing to animal health needs.

Access to medicines in exceptional circumstances

In exceptional circumstances, the AEMPS may authorise access to medicines in the clinical trial phase to patients with seriously debilitating or life-threatening diseases and in need of satisfactory alternative therapies.

Three situations are differentiated: use of medicines in investigation, use of medicines in conditions different from those authorised and access to foreign medicines.



In exceptional circumstances, the AEMPS may authorise access to medicines in the clinical trial phase to patients with seriously debilitating or life-threatening diseases and in need of satisfactory alternative therapies.

USE OF MEDICINES IN INVESTIGATION

The AEMPS is able to authorise the use of medicines in investigation before they are marketed in Spain for specific patients with no available satisfactory alternative therapy, who are not participating in a clinical trial or whose clinical situation does not permit them to wait until the investigation concludes and the new treatments are authorised. Access to these medicines may be on an individual basis for one patient or with a temporary authorisation issued by the AEMPS for use in a group of patients.

USE OF MEDICINES IN CONDITIONS DIFFERENT FROM THOSE AUTHORIZED

This includes the use of approved medicines when there is a need to use them in conditions different from those authorised. These situations principally occur in paediatrics or oncology.

The need for prior individual authorisation in each case by the AEMPS is eliminated, and the responsibility of health centres, information to the patients and vigilance of their use is reinforced. The AEMPS is able to issue recommendations, taking into account the therapeutic-healthcare protocols prepared by the health centres.

ACCESS TO FOREIGN MEDICINES

The AEMPS has a procedure for access to medicines that are not authorised in Spain, but are being marketed in other countries, for those cases in which their use is essential. The AEMPS also regulates access to medicines which are authorized in other countries but not in Spain.

Likewise, in an exceptional way, uncertified medical devices can be authorised for health purposes if considered necessary for medical or surgical treatment of patients.

The AEMPS maintains a strategic state deposit of medicines and medical devices for emergencies and disasters or for international cooperation and coordinates the supply of vaccines, medicines and medical devices for health campaigns.

In the case of veterinary medicines, the AEMPS has implemented the Availability of Veterinary Medicines Committee, and more especially, has created a specific working group on regulatory and administrative aspects, so as to permit authorisation, marketing and use of veterinary medicines in special situations.

3.

How are authorised medicines followed up?

Once the medicine has been marketed, the AEMPS continues to guarantee quality, safety, efficacy and accurate medicine information through pharmacovigilance systems, inspections, quality controls and fighting against illegal and falsified medicines, all of which it communicates to the public and healthcare professionals through constantly updated information.

The Pharmacovigilance System

The Pharmacovigilance System is aimed at detecting, coordinating, studying and preventing adverse reactions and any problem related to medicines, including medication errors causing harm to patients.

All medicines can cause adverse reactions. The objective of the AEMPS is to detect them as early as possible, before and after marketing and sale and to arrive at an accurate assessment of the benefits and risks at all times.

Informative actions, updates on the summaries of product characteristics and package leaflets, and, in exceptional circumstances, even withdrawal of the product from the market can be carried out through pharmacovigilance.

Informative actions, updates on the summaries of product characteristics and package leaflets, and, in exceptional circumstances, even withdrawal of the product from the market can be carried out through pharmacovigilance.

MEDICINES FOR HUMAN USE

The new legislation of human pharmacovigilance, which has been in force since 2012, has been a step forward in the guarantees of safety in medicines that are already marketed in Europe. This new legislation is directed towards the promotion and protection of public health, thus strengthening the European monitoring system on the safety and benefit-risk balance of medicines. It is based, on one hand, on already existing systems and structures and, on the other, on the imposition of new tasks, which have been added to those already in place.

The new definition of an adverse reaction includes any harmless and unintentional effect, so that now it is not only when a medicine is used in authorised conditions, but also when it is used outside these indications or whenever an error in administration, incorrect use or abuse occurs.

The current organisation of pharmacovigilance rests on different pillars, namely the spontaneous notification systems under the responsibility of the **Spanish Human Pharmacovigilance System and the Technical Committee of the Spanish Human Pharmacovigilance System** which encompasses the 17 Autonomous Communities, management of the Spanish pharmacovigilance database (FEDRA), integration of the aforementioned database in the resources of the European Medicines Agency (EudraVigilance) and the World Health Organisation and the generation and assessment of signals. The appearance of several similar cases serves to initiate studies to seek the causality between exposures to the medicine and the concurrence of the suspected adverse reaction.

Each year, the Spanish Human Pharmacovigilance System receives and analyses between **13,000 and 15,000 suspected adverse reactions** to medicines.

The new legislation introduces the right of European Union citizens to notify suspected adverse reactions directly to the competent authority of the Member State. This activity did not exist before and all notifications were carried out by healthcare professionals and the pharmaceutical industry. This is all now conducted through the yellow card or on Internet in the website www.notificaram.es.

The assessment of safety, that is responsible for the management and oversight of the periodic safety reports of all medicines, the assessment of risk management plans or safety referrals, is coordinated at a European level. In this respect, the coordination of the work of the AEMPS in the European Pharmacovigilance Risk Assessment Committee (PRAC) is vital. In this way, the list of medicines subject to additional monitoring, which are identified by an inverted black triangle, is established, risk management plans of medicines are generalised and a new referral procedure specifically designed to confront any safety problem arising in the European Union, regardless of the original authorisation procedure, is established.

The implementation of regulatory actions and communications of risks is responsible for the coordination of the evaluation of training/educational materials associated with management risk plans, the management and oversight of the safety variations of medicines authorised by national procedures (national, mutual-recognition and decentralised procedures), management of safety communications to healthcare professionals and patients, and management of external enquiries with regard to pharmacovigilance. The legislation establishes the commitment of the Member States to publish all information related to safety of medicines from a broad perspective. Thus, each Member State has to maintain a website portal on medicines without exclusion.

Pharmacoepidemiology and post authorisation studies are responsible for the management of the work of the Post Authorisation Studies Committee, management and oversight of the classification of post authorisation studies and advice on intra and extramural pharmacovigilance. The legislation establishes a new approach to post authorisation studies on safety and efficacy. A Post Authorisation Safety Study is a



study on an authorised medicine to identify, characterise or quantify a safety risk, confirm a risk profile of a medicine or assess the effectiveness of the risk minimisation measures applied. A Post Authorisation Efficacy Study is directed to clarifying the efficacy of a marketed medicine used in clinical practice conditions. The objective of both studies is to support regulatory decisions on the safety and benefit/risk profile of a medicine.

VETERINARY MEDICINES

The Veterinary Pharmacovigilance Area of the AEMPS is responsible for all the activities aimed at constant knowledge and assessment of the efficacy and safety of veterinary medicines registered in Spain. It identifies and quantifies the efficacy and known and unknown risks of veterinary medicines so as to guarantee their correct benefit risk balance while they are on the market. Moreover, it plans strategies that allow risks associated with their use to be minimised. The principal activities carried out in this area are management and assessment of Individual Notifications of Suspected Adverse Effects, assessment of Periodic Safety Reports and analysis of the Pharmacovigilance Systems the marketing authorisation holder has to present with each registration application and certain variations.

Moreover, the AEMPS also coordinates the **Spanish Veterinary Pharmacovigilance System and Pharmacoeepizootiology** specifically for veterinary medicines, which, apart from assessing possible adverse reactions to animals, also take into account possible effects on people coming into contact with a medicine through the presence of substances in food products or through accidental exposure, as well as assessing side effects on the environment. Information on adverse reactions to veterinary medicines, managed by the AEMPS, arises from notifications from the veterinary pharmaceutical industry as well as from veterinary health professionals to the Spanish Veterinary Pharmacovigilance System through the Green card. The agency also receives information from national authorities, Autonomous Communities and international health organisations.



Quality controls and inspections

Medicines are subjected to strict quality controls from the start of their manufacture to their dispensation. To guarantee monitoring of quality, the AEMPS carries out inspections on manufacturer facilities and medicine control campaigns in the pharmaceutical distribution chain. Moreover, it intervenes immediately when confronted with a problem detected in the quality, even ordering the recall of the medicine when it poses a health risk. These exhaustive controls of the product are aimed at protecting public health.

On the other hand, in coordination with the Autonomous Communities, the AEMPS oversees guaranteed medicine supply, initiating requisite actions as soon as a problem in the medicine supply is detected, so as to re-establish supply as soon as possible.

INSPECTIONS OF GOOD MANUFACTURING PRACTICE

Good Manufacturing Practice (GMP) is defined as that part of quality assurance which ensures that medicines are produced and controlled in accordance with the quality standards appropriate to their intended use.

The AEMPS and the Autonomous Communities with competence in this area confirm that quality standards, as stipulated in the GMP Guidelines for medicines for human and veterinary use, are fulfilled in the manufacturing process through inspections to these manufacturers. Moreover, the AEMPS is responsible for conducting inspections of Good Manufacturing Practice in foreign countries whenever the medicines registered in Spain or their active ingredients are manufactured in foreign countries.

If the result of the inspections is favourable, the corresponding EU certificate of Good Manufacturing Practice is issued and uploaded in European databases, which are public.

INSPECTIONS OF GOOD DISTRIBUTION PRACTICE

Good Distribution Practices are the guidelines which ensure that the distribution of medicines is carried out correctly in order to protect their quality and integrity from their manufacturing or importation to their dispensation, guaranteeing at all times optimal conditions of storage, transportation and supply.

The AEMPS and the Autonomous Communities, in a coordinated way and according to their competences, oversee the fulfilment of Good Distribution Practice in the supply chain of medicines by means of inspections. In the case of a favourable result being obtained in these inspections, a certificate is issued and also remitted to the corresponding European databases, given that exchange of information and transparency are essential for the distribution chain.

INSPECTIONS OF GOOD LABORATORY PRACTICE

Within the scope of the AEMPS, Good Laboratory Practice refers to the quality system and the conditions applied to pre-clinical safety trials, thus ensuring the quality and reliability of the data generated in said trials. These pre-clinical studies form part of the information assessed before a medicine is authorised, in order to know the safety of the products contained in medicines for human and veterinary use and their impact on human health and the environment.

The fulfilment of Good Laboratory Practice is verified through inspections of pre-clinical safety studies conducted in different laboratories, a task carried out by the AEMPS in conjunction with the Autonomous Communities.

In addition to pursuing inspection activities in conjunction with the Autonomous Communities, the AEMPS coordinates actions at a national level and holds representation both in the working groups of the European Medicines Agency (EMA) and the European Commission as well as in the Organisation for Economic Cooperation and Development (OECD).

GOOD CLINICAL PRACTICE AND PHARMACOVIGILANCE INSPECTIONS

These inspections ensure that clinical trials are carried out according to regulations currently in force and following the norms of good clinical practice (GCP). In this way, the safety and wellbeing of clinical trial participants are guaranteed, as well as the reliability of results. Management of responsibilities and obligations, established by the pharmacovigilance regulations, are also checked.

QUALITY CONTROL PROGRAMMES

Every year, AEMPS, in collaboration with Autonomous Communities, develops a quality control programme for medicines on the market in order to check the quality of authorised medicines in the distribution chain. The inclusion of medicines in this programme is made on the basis

of risk criteria. The **Official Medicines Control Laboratories (OMCL)** of the AEMPS carry out specific analytical tests on samples collected, in response to complaints about quality.

The AEMPS also participates in the market control campaign of centralised medicines in collaboration with the European Medicines Agency, the European Directorate for the Quality of Medicines and Healthcare (EDQM) and the different Member States.

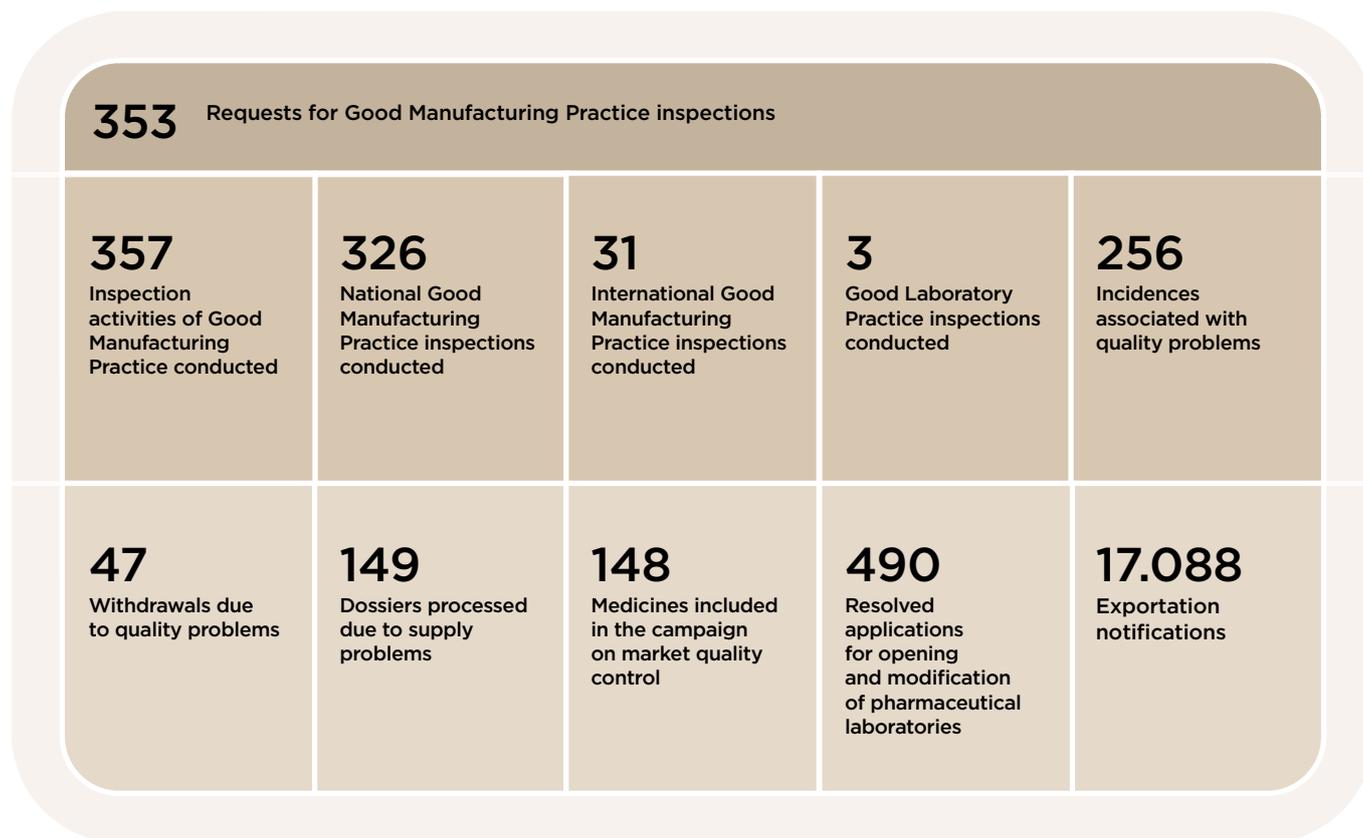
Additionally, and in a continuous manner, the AEMPS follows up the quality of medicines through reception and investigation of possible incidences in quality. Whenever the existence of a quality defect is confirmed, the AEMPS assesses and adopts necessary measures on a case by case basis, in order to control possible associated risks and thus maintain the safety of patients.

Guarantees of supply

Another control activity carried out with significant healthcare repercussions is the implementation of measures to guarantee medicine availability. The AEMPS maintains, in collaboration with the Autonomous Communities, an information system for rapid detection of supply problems and searches for solutions with the market authorisation holders. In addition to informing healthcare professionals of these problems on its website www.aemps.gob.es, as well as foreseen dates of initiation and resolution, possible therapeutic alternatives are studied and shared. Whenever necessary, exportation of affected medicines is blocked and authorisations may be given for medicines to be imported from other countries. All these actions are to reduce negative consequences for patients arising from a medicine shortage.

Follow-up of the activities of INSPECTION AND ENFORCEMENT of medicines

SUMMARY OF ANNUAL ACTIVITY



SOURCE: AEMPS Annual Report of Activities 2012, www.aemps.gob.es



Combating illegal medicines

Illegal medicines are products offered with supposed therapeutic properties but which have not been approved as medicines by the AEMPS as benefits. The AEMPS is the only body with the legal authority in Spain to grant the status of medicine to a product. Any medicine not authorised by the AEMPS is considered an illegal medicine.

Falsified medicines are a special kind of illegal medicine that imitate authentic medicines and misleadingly represent their identity, composition, history or source.

The AEMPS, in collaboration with State police forces, State security bodies and customs develops procedures to avoid the marketing of these illegal medicines, including falsified medicines, and, if existing on the market, orders the withdrawal of these products from the market.

In Spain, there has been no case of medicine falsifying in the legal distribution chain to date. However, the AEMPS has collaborated in different investigations to prevent their entry into the legal market channels. In all these actions, a concerted effort is required by both public and private agents against this public health threat especially in cases detected in the distribution network of other European and South American countries. To join in the efforts of the agencies involved against this new threat to public health, the AEMPS has developed the Strategy against Falsified Medicines 2012 - 2015.

Procedures on medicines sold on the Internet



The AEMPS has developed specific procedures against illegal web pages and works in collaboration with the pharmaceutical border inspection services, Autonomous Communities and State police forces.

Medicines are found among the many products offered on Internet. However, unlike other products sold on Internet, medicines have a direct impact on public health. For their use to be safe, guarantees of quality, safety, efficacy and correct information given by health authorities and the correct action of healthcare professionals in their prescription and dispensation are required.

A medicine sold on an illegal website lacks the aforementioned legal guarantees and puts consumers' health at risk. They are usually illegal, falsified or low-quality medicines which therefore, have no guarantees as regards their quality, safety, efficacy and correct information that permits their correct use.

Measures are included in European and national legislation that allow consumers to easily identify the websites selling medicines legally. These informative measures to consumers include the presence of a logo in the web pages of legal entities and links to the websites of health authorities.

The AEMPS has developed specific procedures against illegal web pages and works in collaboration with the pharmaceutical border inspection services, Autonomous Communities and State police forces.

Given the complexities and difficulties in dealing with the marketing of medicines on Internet, raising public awareness on the risks of acquiring medicines on these illegal websites or by any other means outside the pharmaceutical chain becomes the major weapon for combating this danger. The AEMPS is conscious of the need to increase citizen awareness on the risks of buying on these illegal websites and has therefore carried out specific information campaigns.

4.

How are Medical Devices regulated?

The definition of medical device includes all the products used in healthcare service which are not medicines, but which are of a very different nature and serve different objectives: from instruments to correct deficiencies (such as glasses and hearing aids), diagnostic equipment, active implants (such as pacemakers), or non-active implants (such as cardiac valves), diagnostic reagents, or computer programmes used in healthcare service.

The catalogue of medical devices is classified into 12 different categories:

- 1 **Diagnostic medical devices “in vitro”, which are applied to samples extracted from the body.**
- 2 **Active implant medical devices which are implanted into the human body and function as an energy source, for example, pacemakers, defibrillators, cochlea implants.**
- 3 **Non-active implants, such as cardiac valves, breast implants, hip implants and sutures.**
- 4 **Dental products.**
- 5 **Ophthalmic and optical products.**
- 6 **Products which use radiation for diagnostic and therapeutic purposes.**



7 Products for anaesthesia and respiration.

8 Electro-medical/mechanical products, such as supervision monitors in intensive care units.

9 Reusable instruments, such as surgical instruments.

10 Products of only one use, such as condoms and dialyzers.

11 Technical help for the disabled.

12 Hospital equipment.

These products are governed by EU harmonised health regulations. Any manufacturer, European or otherwise, who wishes to market one of these medical devices in Europe, has to approach an assessment body, so-called Notified Bodies, with all documentation pertaining to the design, manufacturing processes and sterilisation, operational tests, clinical trials, packaging materials, relevant technical norms and information accompanying the product. The Notified Body assesses this documentation, in addition to carrying out an audit on the facilities where the product has been manufactured. If the result of the tests is favourable, it issues a certificate of conformity that allows the distinctive CE marking and the number of notified body to be placed on the product, indicating that it fulfils all the criteria of the regulations. With this mark, the product can be marketed in all member countries of the EU without the need for new assessments.

In Spain, the only body designated by the Ministry of Health, Social Services and Equality is the AEMPS itself, Notified Body number 0318, who carries out assessment functions through the Medical Devices Certification Division (Notified Body).



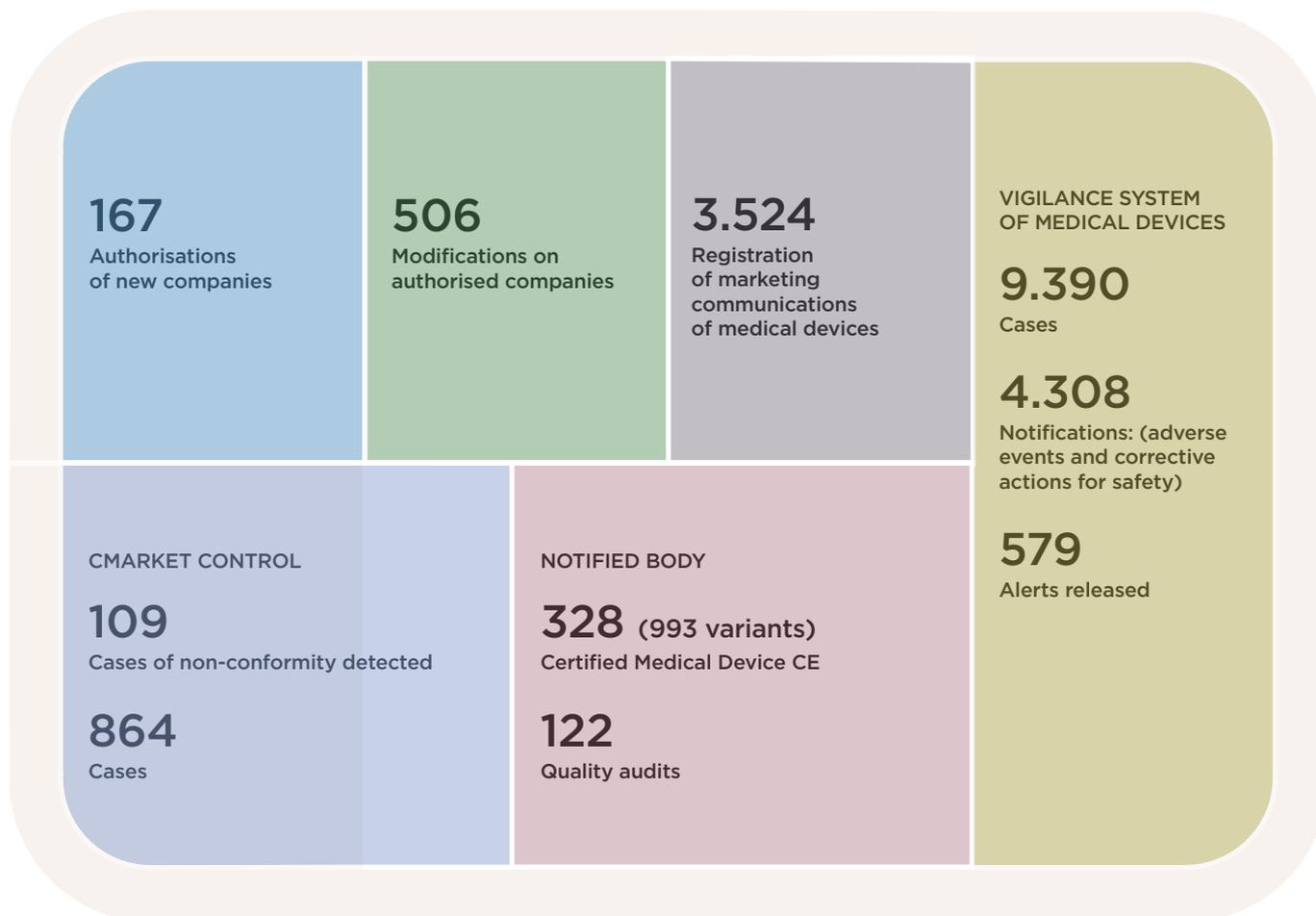
Health authorities exercise actions in order to monitor and track medical devices marketed, including actions on illegal and falsified medical devices. Among these is the management of the **Medical Devices Vigilance System**, which has an international dimension. In addition to the EU, other participating countries include the United States, Canada, Australia and Japan.

At a national level, there is an Alert network, formed by the AEMPS and vigilance points in the Autonomous Communities, which transmits information, recommendations, and measures for adoption by professionals and health centres. The AEMPS oversees the protection of health and safety by preventing the incidence of new adverse incidents through its Vigilance System and exercising actions necessary to stop sales of products or have them withdrawn from the market should they pose a risk. Every year, some 10,000 cases are recorded in the medical devices vigilance system.

Actions performed by the AEMPS on medical devices are completed with the authorisation of the clinical trials, authorisation and inspections of the facilities where they are manufactured, imported or sterilised, the marketed products' record, controls carried out by pharmaceutical inspectors at the border on the entry of products, and coordination of inspection services in the Autonomous Communities for market control. Likewise, and in a similar way to medicines, medical devices that do not have the CE marking are authorised for health reasons in situations where there are no other alternatives for the treatment of patients.

Follow-up of MEDICAL DEVICES

SUMMARY OF ANNUAL ACTIVITY



SOURCE: AEMPS Annual Report of Activities 2012, www.aemps.gob.es

5.

Cosmetics and Personal Care Products

Cosmetics are products which come into contact with the body, albeit externally. They act through the presence, transfer or absorption of components in the skin, hair, teeth or mouth. This contact can give rise to undesirable effects such as toxicity, irritation or sensitivity, which may affect health.

Personal Care Products are all the substances or mixtures which, without being legally considered to be medicines, medical devices, cosmetics or biocides of clinical or personal use, are applied to the skin, teeth or body mucosa for personal care or aesthetics or to neutralise or eliminate ectoparasites.

Both cosmetics and personal care products are subject to pharmaceutical inspection at the border to prevent entry of illegal products.



Cosmetics

Cosmetics are products which come into contact with the body, albeit externally. They act through the presence, transfer or absorption of components in the skin, hair, teeth or mouth. This contact can give rise to undesirable effects such as toxicity, irritation or sensitivity, which may affect health.

With such characteristics, the regulation of cosmetics is based on guarantees of harmlessness and information for the consumer so as to achieve a high level of protection of human health. It is also aimed at achieving other objectives, such as animal protection and the protection of the environment.

European legislation, applied directly in all Member States guarantees that only safe cosmetics can be distributed within the European zone countries, and with accurate information on product composition and properties.

Said legislation establishes that only cosmetic products with a designated physical or judicial person as the **responsible person** in the European Union may be put on the market. This designated responsible person guarantees fulfilment of the relevant requirements laid down in the Regulation for each cosmetic introduced in the European Community market. Before its introduction on the market, the person responsible for the cosmetic product should present information on the cosmetic to the European Commission, such as product category and name, the name and address of the responsible person, country of origin for cosmetics imported from outside the European Union, if there are any nanomaterials, the composition and original labelling. This information permits knowledge of the products being marketed in the European zone.

With regard to the **composition of the products**, there are lists of prohibited substances, those restricted regarding concentration and/or application zone, authorised dyes, authorised preservatives and authorised ultraviolet filters. These lists are prepared following the opinion of the Product Safety Scientific Committee in the European Commission. The use of carcinogen or mutagen substances or those toxic for reproduction are also prohibited.

In addition to submitting to these composition norms, each cosmetic product is subject to a **safety assessment**, which is documented in a **Safety Report**. This assessment must be carried out by persons with specific qualifications and is based on the toxicological data of the ingredients and on product exposure.

Legislation demands that the manufacturing of cosmetic products is in conformity with **good manufacturing practice**. Manufacturing conditions are essential to guarantee the absence of microbial contamination of the products, stability of the formulation, absence of cross-contamination, correct container and packaging and the maintenance of traceability.

With regard to the manufacturing and/or importation of cosmetics, legislation permits each Member State to regulate the establishment of economic operators at a national level. Thus, in Spain, the companies that carry out manufacturing and cosmetic importation activities have been subject to prior authorisation of their activities by the AEMPS until 2013. In the Law 10/30, this authorisation has been substituted by a **responsible declaration**.

In this respect, since 2013, companies who wish to initiate activities of manufacture and/or importation of cosmetics have to previously present a responsible declaration of fulfilment of legal requirements to the AEMPS. This allows them to initiate activities of manufacturing and/or importation without prejudice to subsequent verification by the AEMPS through documental verification and/or inspection.

On the basis of the inspection results, the AEMPS issues certificates of the fulfilment of Good Manufacturing Practice within the framework of market control activities.



Despite all the foreseen guarantees of safety, **undesirable effects** of different degrees of seriousness, acute or chronic, may arise. Legislation foresees the obligation of the responsible persons and distributors to inform health authorities of all serious undesirable effects they may know. Also, professionals need to collaborate in this process and the users themselves can also do so, communicating all those undesirable effects they suffer, as well as those of a non-serious character to the health authority.

To prevent the presence of non-compliant and even dangerous products on the market, different **market control actions** of varying importance are carried out. These include assessment of the technical documentation of the products, acceptance of claims or complaints, coordination of inspections with the health authorities of the Autonomous Communities and management of the cosmetics alerts network.



Personal Care Products

Personal care products are all those substances or mixtures that, although not legally considered to be medicines, medical devices, cosmetics or biocides for clinical or personal use, are applied to the skin, teeth or body mucosa for reasons of personal care or aesthetics, or to neutralise or eliminate ectoparasites.

These products, **not defined as cosmetics**, require authorisation of the AEMPS to be marketed in Spain. Among these are found tattoo and micropigmentation inks, pediculicides, chemical masks, certain types of dental whiteners and special toothpastes, products for xerostomia and dental plaque revealers, vaginal moisturising creams, products for sports massage, etc.

To authorise personal care products, the technical documentation required in legislation, basically related to technical and analytical aspects, as well as the identity and efficacy of the product, has to be presented to the AEMPS. A document of authorisation, whose reference must be visible on labelling, is issued for each product.

Like cosmetics, the authorisation regime of manufacturing and importation activities was substituted by a **Responsible Declaration** in 2013. As from the 26th of July, 2013, companies must present a responsible declaration of activities to the AEMPS.

The AEMPS also issues health certificates on the legal situation of cosmetic and personal care products and their manufacturing installations in Spain so that exporting companies are able to certify them in the countries to which they are being exported.

Follow-up of COSMETICS AND PERSONAL CARE PRODUCTS

SUMMARY OF ANNUAL ACTIVITY



SOURCE: AEMPS Annual Report of Activities 2012, www.aemps.gob.es

6.

AEMPS on the international stage

The AEMPS not only operates as a state authority which oversees the protection of public health in Spain with regard to medicines and medical devices, but also often acts in the name of the European Agencies' network and the European Medicines Agency in medicine authorisation procedures and as the certifying authority of medical devices in the EU.

The European Medicines Agency is a European body in which all the Agencies of Member States are integrated to share decisions and valid authorisations for the entire EU. The AEMPS is one of the European agents, excelling in its performance in assessments and inspections, which it coordinates with the European Medicines Agency. In the last few years the AEMPS has been ranked fifth among the European Agencies Network due to volume of activity.

On the other hand, it also participates actively in technical and specialised meetings at the European Council, in particular in relation to the European Pharmacopoeia and with the European Network of Official Medicines Control Laboratories, as well as in other committees of experts, or in the global fight against falsified medicines. In this way, AEMPS technical personnel, as part of its remit, have developed intense activity and participation in Committees, working groups and European projects.



The European Pharmacopoeia sets out common standards in its texts and monographs which provide a legal and scientific foundation for medicine quality control. These texts are necessary for the regulatory authorities, the responsible medicine quality control personnel and manufacturers of raw materials and medicines. It is a fundamental element in European harmonisation with regard to manufacture and quality control, pursuing the objective of establishing common criteria for all EU member states in any of the appropriate medicine-related activities. The AEMPS participates in drawing up these texts and is the authority responsible for the Spanish version of the European Pharmacopoeia as well as for the publication of the Real Farmacopea Española (Royal Spanish Pharmacopoeia).

The AEMPS maintains special cooperation with the competent medicine authorities in Spanish American countries to share best practice, technical and regulatory expertise, and to maximise guarantees of quality, safety and efficacy of medicines. In this context, periodic meetings of the Competent Authorities on Medicines in Spanish America (under the Spanish acronym EAMI), the online information exchange system, training in cooperation with the Spanish Agency of International Cooperation for Development, and the establishment of bilateral agreements for cooperation with different Spanish American regulatory bodies are all worthy of mention.

7.

Information for the public and professionals

The AEMPS is committed to providing both citizens and professionals with prompt information regarding medicines and medical devices in a comprehensible way, while adhering to criteria of transparency, independence and scientific rigour.

To reach this objective, the AEMPS has developed numerous informative actions, among which those carried out on its web page www.aemps.gob.es, the organisation of events open to personnel from outside the Agency, informative campaigns and constant attention to the numerous questions and requests for information coming from citizens, professionals and the media throughout the year are worthy of mention.

The AEMPS publishes on its website www.aemps.gob.es information on all the products and activities they regulate. On this website, citizens and professionals have a primary source of information on medicines, medical devices and cosmetics prepared with criteria of independence and scientific rigour so as to be sure and reliable.

The facilitated information covers which medicines are authorised, conditions of use, availability, supply problems, suspensions, withdrawals, safety problems, illegal medicines, alerts due to quality problems and the notification of many other regulatory actions as well as any legislation that forms part of the responsibilities entrusted to the AEMPS, so as to ensure guarantees of quality, safety, efficacy and accurate information on medicines and medical devices in order to protect the health of citizens.



Every year, the AEMPS publishes on its website more than 200 informative notes and alerts, as well as press releases, different publications, such as guidelines, recommendations, reports, consensus and question and answer documents, protocols and periodic bulletins with the principal news in each area of activity. All the material prepared for informative training days and courses or information campaigns may also be added to the aforementioned documents.

On the website, the databases, online registers, and catalogues which facilitate constantly updated information have special prominence, among which are the following:

The AEMPS online Human Use Medicine Information Centre (under the Spanish acronym CIMA) and the Centre of Authorised Medicines in Spain for Veterinary Use.

The Registry of Pharmaceutical Laboratories and the Catalogue of Distribution Entities.

The list of Medicines with supply problems.

The Spanish Registry of clinical studies (under the Spanish acronym REec).

All procedures may be carried out telematically from the Electronic Headquarters of the AEMPS sede.aemps.gob.es.

The webpage and the Electronic Headquarters of the AEMPS are valuable tools to achieve its objective of transparency and also to improve agility and proximity to society by implementation of electronic administration, guaranteeing the electronic access of companies and professionals to procedures and administrative steps through the AEMPS Electronic Headquarters.

More information is available on the webpage www.aemps.gob.es.

