2015
Annual report
For safe, effective, innovative and accessible health products
The French National Agency for Medicines and Health Products (ANSM) strengthened its operations in 2015 and signed an Objective and Performance Contract with the French government for 2015 to 2018, thereby entering into a multi-year commitment.

The surveillance of medicines and other health products was the agency's prime focus in 2015. To that end, 630 site inspections were carried out during the year; 7% of these reviews were conducted outside of the European Union (EU), and 11% were conducted randomly. There were also over 4,500 laboratory product quality audits conducted throughout 2015. Pharmacovigilance as well as reagent and medical device vigilance networks were strengthened, and new epidemiological studies were conducted. These activities played a role in the reassessment of the risk/benefit ratio of 52 substances and combinations and led to 21 referrals in Europe. The agency's actions also resulted in several decisions that guaranteed the marketing of safe and high-quality products in France and Europe. Some of these decisions include: 20 health policy rulings, 41 injunctions, several batch withdrawals and recalls, numerous suspended or modified marketing authorisations (MA), and even site closures. Numerous educational interventions with patients and health professionals were conducted to reduce the risks associated with health products.

At the same time, the agency endeavoured to support innovation and make new developments quickly accessible under safe and controlled conditions. These goals were addressed by granting clinical trial authorisations (928 for medicines and 653 for non-health products in 2015), 22 cohort temporary authorisations for use (TAU), 7 new temporary recommendations for use (TRU), and marketing authorisations for over 500 medicines in France and Europe.

The agency's efforts to remain open to the outside world and strengthen its relations with stakeholders were evidenced by its many discussions within technical interface committees, topical meetings, educational day-long events, and breakfasts with the press. The purpose of these outreach efforts is to inform target audiences of the regulatory and legislative changes regarding health products, explain ANSM's actions, and learn more about the public's expectations.

The agency also consolidated its internal processes and improved its activity management procedures in 2015 in order to make case processing more secure. In 2015, ANSM launched a series of structuring projects in an effort to both secure health product processing procedures and reduce investigation times. These projects were also designed to lay the groundwork for future success despite capacity constraints. As stipulated by the health system modernisation law passed in January 2016, the agency made provisions to fulfil new assignments and adapt to operational simplifications and transfers.

ANSM renewed the mandates of its Scientific Board and Board of Administration. The members of the agency's advisory bodies, including working groups and commissions whose mandates ended in early 2016, were renewed. The agency made these decisions while taking care to maintain a high level of expertise and comply with ethical standards.

Once again this year, all of the agency's teams were deeply involved in maintaining business momentum, improving steering capacity, and making processes more secure in order to guarantee the safety of health products.

Agnès Jeannet, Chair of the ANSM Board of Administration in 2015
Catherine de Salins, Chair of the Board of Administration since 11 May 2016
Dominique Martin, Director General of ANSM
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ANSM in brief

The French National Agency for Medicines and Health Products (ANSM) was created on 1 May 2012 as a result of the French law of 29 December 2011 concerning the increased safety of medicines and health products. The agency ensures the safety of medicines and other health products throughout their life cycle. Its decision-making process is fully transparent, enabling all health stakeholders, manufacturers, and the public to understand and take ownership of the agency's actions. To achieve this goal, ANSM relies on its in-house expertise, its Board of Administration, its Scientific Board, advisory bodies, and working groups; these fully independent entities act in accordance with established ethical standards to ensure that the agency's decisions remain impartial.

The agency pursues its public service missions in the sole interest of patients.

Objective: To combine rapid access to innovative developments with the continued surveillance of health products, by adjusting their risk/benefit ratio to match therapeutic progress and real-life usage by patients.

Strategic priorities

- To guarantee a high level of safety for all health products throughout their life cycle
- To promote rapid, closely monitored, and broad access to all health products
- To consolidate ANSM's relationships with stakeholders and enhance their involvement
- To reinforce ANSM's efficiency and pursue its modernisation.

Missions

- To evaluate and monitor the risks and benefits of health products throughout their life cycle
- To promote proper use by monitoring health product advertising
- To inspect operators involved in introducing health products to the French and European markets
- To conduct quality checks in laboratories
- To encourage independent academic research
- To provide legal and regulatory expertise
- To inform patients and health professionals of its actions and decisions in a transparent manner
- To take an active role in work conducted in Europe and abroad.
Health products under the responsibility of ANSM

**Medicines**
- All medicines (pre- and post-MA) and pharmaceutical starting materials
- Blood-derived medicines
- Narcotic and psychotropic substances
- Vaccines
- Homoeopathic and herbal medicines
- Compounded pharmacy and hospital preparations

**Biological products**
- Labile blood products
- Cell and gene therapy products
- Organs, tissues, and cells used for therapeutic purposes
- Microorganisms and toxins
- Ancillary therapeutic products
- Breast milk collected, tested, processed, and preserved by breast milk banks

**Medical devices and in vitro diagnostic medical devices**
- Therapeutics, diagnostics, in vitro diagnostics, technical platforms, and medical software

**Other products**
- Cosmetics and products used for tattooing
- Biocides
ANSM's OPC establishes the agency's priority actions for 2015 to 2018. Signed on 17 July by Marisol Touraine, French Health and Social Affairs Minister, and Dominique Martin, Director General of ANSM, the contract is based on four strategic priorities:

- To guarantee a high level of safety for all health products throughout their life cycle
- To promote rapid, closely monitored, and broad access to all health products
- To consolidate ANSM's relationships with stakeholders and enhance their involvement
- To reinforce ANSM's efficiency and pursue its modernisation.

To meet these priorities, the OPC lists 12 objectives encompassing 22 concrete actions and 28 indicators designed to track the progress of these actions.

These actions and objectives were based on a collective diagnosis. Notable contributors to this effort included the Inspectorate General of Social Affairs (IGAS), which carried out a mission in 2014 to assess the organisation of ANSM upon the Health Minister’s request, and the French Public Audit Office, which inspected the conditions of the agency’s establishment and first year of operations, i.e. 2013. The French government's commitments for the next four years in regard to ANSM's commitments are also specified in the contract.

ANSM, which was created by the law of 29 December 2011, is currently in a stabilisation phase after having undergone profound transformations in terms of governance, internal organisation, and methods of operation when it took over from AFSSAPS and assumed the former agency's set of skills and responsibilities. The OPC was drafted to help consolidate the agency and bring a perspective to its missions. An assessment of the OPC's implementation will be carried out every year by an OPC monitoring committee, and a final evaluation will be conducted in 2018.

Every year, a work programme based on the same objectives supports the OPC by setting goals for the coming year.
Key figures in 2015

GUARANTEEING the safety of health products

Medicines

- **2,800 active substances** are marketed in France, 30% of which are generic medicines
- **115 active substances** are included in the systematic review programme of medicines authorised before 2008
  - 52 have already been re-evaluated, including 21 substances that were subject to a European referral
  - 22 medicines were suspended or withdrawn from the market
  - 25 medicines were subject to a decision to restrict their use or increase their surveillance conditions
- **47,089 adverse effects** were reported to ANSM via regional pharmacovigilance centres, among which 2338 were notified by patients; pharmaceutical laboratories reported 29,469 such cases
- **11 medical and pharmaco-epidemiological studies** were conducted
- **2,741 medication errors** were recorded in 2015 along with 1,702 quality defects
- **ANSM managed 391 supply shortages** and looked for therapeutic alternatives for essential medicines.

Blood products and biological products derived from the human body

- **7,301 adverse effects** related to haemovigilance were reported among recipients of labile blood products
- **527 adverse effects** related to biovigilance (which covers organs, tissues, cells, breast milk, and related therapeutic products) were reported.

Medical devices and in vitro diagnostic medical devices

- **16,194 adverse effects** related to materiovigilance (medical devices) were reported by the network (including 685 reports about PIP breast implants) and 34 were reported by patients
- **1,355 adverse effects** related to reagent vigilance (in vitro diagnostic medical devices) were reported.

ENCOURAGING laboratory controls and inspections

- **630 inspections** were conducted in 2015; 11% of these inspections were random and 7% took place outside of the European Union (starting materials 14%; clinical trials 7%; pharmaceutical laboratories 35%; medical device manufacturers 18%)
- **4,524 test reports** were produced through laboratory work, including 4,150 reports that focused on medicines, starting materials, and biological products.
REINFORCING ANSM's efficiency and pursuing its modernisation

- 70% of MA variation applications are digitised
- 95% of SUSARs are submitted electronically
- 8 internal audits for inspection activities
- 1 internal investigative report on managing conflicts of interest
- 2 European audits (pharmacovigilance and laboratory controls)
- 988 FTE as of 31 December 2014
- 3,317 days of training
- 45 years old—average age of agents
- 72% female workforce
- €137 million: implemented budget.

PROMOTING patients' rapid access to innovative developments

- 10,216 patients are covered by the cohort temporary authorisation for use (TAU) system for medicines
- 12,175 patients have initiated treatment under a named-patient TAU
- 1,799 clinical trials, including 928 trials for medicines and 236 for medical devices, were conducted
- 93 new medicines were authorised through the European centralised procedure, including 10 for which France was the rapporteur (innovative medicines containing a new active substance therapeutically indicated to treat diseases such as AIDS, cancer, neurodegenerative diseases, diabetes, auto-immune diseases, and viral diseases; medicines developed through biotechnology and innovative therapies; and orphan medicines indicated in the treatment of rare and serious diseases)
- 502 MAs were delivered, including authorisations for 339 generic medicines, through decentralised European procedures, mutual recognition arrangements, and France's own authorisation procedure (A MA corresponds to one proprietary product and one pharmaceutical form)
- France (by way of ANSM control laboratories) releases more vaccines than any other member state to the French and European markets
- ANSM is financing 2 academic research projects
- 30 meetings were held with innovative project leaders.

CONSOLIDATING connections with stakeholders

- 110 information updates
- 23 expert reports
- 2.5 million visitors to the website
- Over 1,200 journalist requests were used to write over 5,000 news articles
- 129 CADA (Administrative Document Access Commission) requests were addressed to ANSM
- 2,142 opinions were delivered by the Service of the Ethics of Expertise
- 11 research projects were financed regarding the safe use of health products
- 6 projects piloted by patient associations, focused on using medicines correctly and reducing risks related to the use of health products, have received 149,110 euros in funding
- **5 new partnership agreements** were signed in 2015 (DGCCRF, InVS, Université Paris-Est Créteil and DASS of New Caledonia, and Chamber of Commerce and Industry of the Paris – Ile de France region)
- ANSM participated in **23 steering committees** for national public health plans
- ANSM participated in drafting **23 European and 91 national published regulatory texts**.
Highlights in 2015

**JANUARY**
- Vaccination against invasive serogroup C meningococcal disease: ANSM follows the recommendations of the French High Council for Public Health when these vaccines are in short supply
- Published a description of the clinical evaluation of medical devices as part of the CE marking regulatory process
- Solvent/detergent-treated therapeutic plasma: change of legal status from LBP to medicine
- Call for research proposals issued

**FEBRUARY**
- Call for proposals issued for patient associations
- Bromocriptine indicated to suppress breast milk production: results of the re-evaluation of the risk/benefit ratio

**MARCH**
- TRU for baclofen: initial data collected and reminder of prescription guidelines
- Avastin 25 mg/ml: the risk/benefit commission grants a temporary recommendation for use (TRU)
- Rotavirus vaccine: reminder of the risk of acute intussusception in infants and how to treat the condition
- Breast implants: creation of an expert group to examine the possible risk of anaplastic large cell lymphoma (ALCL)
- TRU for Velcade for the treatment of non-IgM AL amyloidosis and Randall disease
- Third Information and Exchange Day with patient associations

**APRIL**
- Pain management with high-dose ibuprofen: European recommendations regarding cardiovascular risk
- Hydroxyzine (Atarax® and generics) for minor anxiety treatment, as preparation for general anaesthesia, and symptomatic treatment of urticaria: new use restrictions to reduce the risk of Q-T interval prolongation
- Previscan (fluindione): new tablet colour to limit the risk of medication errors
- Vaccination against invasive serogroup C meningococcal disease: end of supply pressure
- Inspection of the Caen University Hospital breast milk bank following several deaths of newborns hospitalised in the neonatal unit (report from the Basse Normandie Regional Health Agency). Suspension of breast milk bank operation authorisation until compliance is assured. Operations resume in June 2015

**MAY**
- Electrocoagulation systems in arthroscopy: communication with healthcare professionals on how to prevent the risk of skin burns
- Publication of the results from the 2007–2013 oral isotretinoin prescription study in France and from the study on compliance with recommendations regarding pregnancy tests as part of the oral isotretinoin pregnancy prevention programme in France. Simultaneous restriction of the initial oral isotretinoin prescription to dermatologists
- Treatment of cholesterol with statins: warnings and stronger precautions due to the risk of immune-mediated necrotising myopathy (musculoskeletal disorders)
- Valproate and derivatives (Depakine®, Depakote®, Depamide®, Micropakine®, and generics) for the treatment of epilepsy and bipolar disorder: announcement of tighter prescription and dispensing criteria due to the serious risk of congenital birth defects and increased risk of neurodevelopmental disorders
- Addition of new synthetic cannabinoids to the list of narcotics
- Mercury in dental amalgams: data update (publication of a report)
- Health software and mobile applications: information on regulatory requirements regarding CE marking
- TRU for Thalidomide Celgene for several indications
- Launch of new ANSM intranet

**JUNE**
- Saxagliptin (Onglyza® and Komboglyze®) for the treatment of type II diabetes: launch of a re-evaluation of all data due to risk of fatal infections
- Mycophenolic acid: new contraindications and prevention measures due to teratogenic risks associated with the medicine
- Humalog: provision of a new 200 ul/ml concentration to prevent risk of errors
- Breast reconstruction: decision to prohibit the marketing, distribution, importation, and use of the Strattice™ device
- In vitro medical devices and diagnostic medical devices: regulatory reminder to manufacturers
- Implantable devices and metal particles: creation of a temporary specialised scientific committee on the toxicity of metal particles shed by implantable medical devices
Breast implants: creation of a temporary specialised scientific committee on "breast implants and large-cell lymphomas"

Informational meeting on the new European regulation concerning clinical trials on medicines

TRU for Avastin for the treatment of the neovascular form of age-related macular degeneration (AMD)

Launch at ANSM of the European Centralised Procedure Electronic Submission Portal (Common Repository)

JULY

Publication of a report on the risks related to the use of health products designed to assist weight loss

Use of chloral hydrate to sedate children for diagnostic exams: use strictly reserved to the performance of certain diagnostic exams (MRI and FRE exams) on children affected by severe pathologies

Olmesartan for the treatment of essential hypertension alone or in combination with other high blood pressure treatments: reminder of risk of severe enteropathy

Human papillomavirus (HPV) vaccinations: assessment of the risk of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) following the administration of an HPV vaccine

Disinfection of endoscopes: assessment of medical device vigilance reports from 2010 to 2013

ANSM supports faecal microbiota transplantation and its monitoring through clinical trials

Signature of ANSM's Objective and Performance Contract (OPC)

TRU for Circadin

Signature of the agreement regarding the transfer of exportation certificate management to the Paris—Ile de France Chamber of Commerce

AUGUST

Total hip replacement: first study conducted on the safety of hip prostheses using data from the French health insurance system

TRU for Verapamil for the prophylactic treatment of cluster headaches

SEPTEMBER

HPV vaccination and autoimmune disease risk: publication of a reassuring ANSM-CNAMTS study

Warning about using PAPP-A IMMULITE to test for Down syndrome during pregnancy: use of test on frozen samples stopped

Launch of a pilot phase to prepare for new European regulations regarding clinical trials

Call for candidates issued to recruit new members to advisory committees

OCTOBER

Systemic quinolone antibiotics: reminder of the safety profile

Announcement of a gradual return to normal supply conditions of proprietary BCG-based medicines for intravesical instillations (Immucyst, Oncolice, and BCG Medac)

Assistance during the shortage of proprietary benzathine-benzylpenicillin medicines indicated for the treatment of syphilis and the prevention of acute articular rheumatism

Warning about the increase in reports of cannabis poisoning in children due to accidental ingestion

Ethylene oxide-sterilised medical devices used in neonatology and paediatrics: implementation of standard NF EN ISO 10993-7

NOVEMBER

Second Information and Exchange Day with Regional Pharmacovigilance Centres

Human papillomavirus (HPV) vaccine: European authorities find no link between the HPV vaccine and complex regional pain syndrome (CRPS) or postural orthostatic tachycardia syndrome (POTS)

Patient lifts: communication about proper procedure to ensure patient safety

Results of a market monitoring operation regarding urinary strip tests designed to check for urinary infections

TRU for Stelara for the treatment of Crohn's disease

Call for candidates issued to recruit new members for the agency's working groups

Publication of the report entitled "Antibiotic consumption and resistance in France: the need for strong, long-term action"

DECEMBER

Temporary suspension of Stallergenes company operations in December 2015 following an inspection by the agency in November 2015

Scientific day-long event to present the results of the sixteen projects selected as part of the call for proposals issued in 2012

TRU granted to Truvada for HIV pre-exposure prophylaxis for high-risk patients

Adoption of the ANSM ethics charter by the Administration Board

Completion of a study to measure the expectations and perceptions of ANSM's various target populations
For safe, effective, innovative and accessible health products

Organisation chart for 2016

Communication and Information Division
N.

Director General
Dominique Martin

Steering and Internal Control Unit
Evelyne Duplessis

Ethics of Expertise Department
Elisabeth Héral

Project Manager
Gaëlle GUYADER

Deputy Director General for Resources
Eric Délás

Deputy Director General for Operations
François Hébert

Budget Controller
Dominique Arbelet

Accounting Officer
Sandrine Gaborel

Human Resources Division
Marie Balland

Finance and Administration Division
David Trivié

Information Technology Division
Raphaël Martin

Division for Data Flows and Repositories
Wenceslas Bubenicek

Division of Medicines used in Oncology, Haematology, Transplantation, Nephrology, Cell Therapy Products, Tissues, and Labile Blood Products
Alexandre Moreau

Division of Medicines used in Cardiology, Rheumatology, Stomatology, Endocrinology, Gynaecology, Urology, Pulmonology, ENT, and Allergology
Jean-Michel Race

Division of Medicines used for Neurology, Psychiatry, Anaesthesiology, Pain Control, Ophthalmology, Narcotics, Psychotropics, and Addictions
Philippe VELLA

Division of Vaccines, Anti-Infective Medicines, Hepatogastroenterology, Dermatology, Gene Therapy and Rare Metabolic Diseases
Caroline Semaille

Operating Divisions

Legal and Regulatory Affairs Division
Carole le Saulnier

Evaluation Division
N.

Surveillance Division
Patrick Maison

Inspection Division
Gaëtan Rudant

Laboratory Controls Division
Laurent Lempierre

Product Divisions

Division for Science and European Strategy
Mahmoud Zureik

Division for Data Flows and Repositories
Wenceslas Bubenicek

July 2016
Part 1.

Guaranteeing the safety of health products throughout their life cycle
1. Monitoring of medicines

ANSM is responsible for evaluating and monitoring medicines. Specifically, the agency ensures that the pharmaceutical quality, the use safety profile, and the efficacy of the medicines that each treated patient receives are proven and validated.

Even though medicines are subjected to in-depth testing through clinical trials before receiving authorisation, some adverse effects that are rare or specific to certain populations or conditions can only be identified when the medicine is used by many people under real-life conditions and sometimes over a long period of time.

For this reason, once a medicine receives marketing authorisation, its risk/benefit ratio is constantly re-evaluated to account for new knowledge concerning its use in real life.

Fulfilling this mission means ANSM must constantly recalculate the risk/benefit ratio for as long as a medicine is sold on the market. The agency relies on its in-house evaluation capacities, but also on external experts organised into working groups, committees, and commissions and on its laboratory control and inspection force.

ANSM’s mission involves: monitoring consumer data; regularly re-evaluating the risk/benefit ratio of medicines; assessing the adverse effects and medication errors reported by its vigilance networks, health professionals, patients, and manufacturers; and regulating medicinal product advertising prior to being publicised. The agency also monitors the market and liaises with manufacturers to manage supply pressures involving medicines of major therapeutic value and quality defects that occur during a medicine’s manufacture.

Monitoring the use of medication and preventing misuse

The purpose of monitoring medicinal use is to understand how medicines are being used in real life and to detect, with the goal of preventing, any anomalous or non-compliant use that could expose the user to excessive risk not justified by the demonstrated health benefits.

Most notably, this surveillance relies on:
- monitoring of medicine sales in their entirety
- monitoring of use and specific, targeted studies of a class or medicine
- non-compliant use reports.

Sales data make it possible to track changes in the French pharmaceutical market. They also reveal information about the market's primary characteristics and point to longer-term trends, in addition to one-off events, that mark its transformation. These data make it possible to segment the market according to criteria that help pinpoint factors creating change. There is no one pharmaceutical market that can be understood as a single unit. Instead, there are several pharmaceutical markets, each of which has its own dynamic. This is because the medicines included in each market contribute in very different ways to the treatment of patients.

ANSM uses medicine consumption data to adopt its monitoring strategy in accordance with a medicine's importance to treatment strategy.

A therapeutic class, pharmaceutical therapeutic class, or medicine comes under targeted surveillance particularly when a risk of non-compliant use has been identified or in order to quantify the impact of a health safety measure. Monitoring can be based on sales data, which includes comparisons between international sales figures or between the target population and the population that is receiving the treatment. Prescription data and health insurance reimbursement data are also helpful. Specific studies were created to aid surveillance (see pharmaco-epidemiological study programme). As part of this surveillance, updated reports are published to provide the public and health professionals with better information about consumption practices and changes.
In 2015, ANSM partnered with InVS to conduct a specific study on antibiotic consumption data. A brochure devoted to the analysis of antibiotic consumption and resistance was published in November for the European Antibiotic Awareness Day.

Finally, reports regarding the non-compliant use of medicines often come from incidents flagged by the pharmacovigilance network, ANSM institutional partners, health professionals, health system users, and manufacturers. Given this, ANSM created a service to centralise all reports of non-compliant use. In September 2015, it published a notice designed to help operators of proprietary medicines report non-compliant medication prescriptions that come to their attention. The purpose is to identify cases of non-compliant use and collect the information needed to evaluate the public health impact of these practices in order to put in place, as necessary, appropriate measures to prevent or reduce non-compliant use.

For example, a pharmacovigilance report concerning oral isotretinoin in France prompted ANSM to analyse how this medicine is used. Following these analyses, prescription and delivery conditions were tightened, and an informational campaign was created to reduce the risks related to the use of oral isotretinoin.

**Surveillance of risks associated with medicines**

Although all medicines are naturally intended to alleviate pain or disease, they all carry a risk of adverse effects; using medication is never an inconsequential act. ANSM therefore performs systematic surveillance at all levels for all medicines in partnership with its European colleagues and network of pharmacovigilance centres.

**Highlights**

- An oral isotretinoin prescription study in France from 2007 to 2013 and a study on compliance with recommendations regarding pregnancy tests as part of the oral isotretinoin pregnancy prevention programme in France (May 2015)
- Every month, ANSM publishes feedback on its website concerning the opinions and recommendations issued by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC)
- On 18 November, ANSM organised an Information and Exchange Day with the Regional Pharmacovigilance Centres to take stock of vigilance reform, the role of the network, and the methods of collaboration between ANSM and the Regional Pharmacovigilance Centres
- Bromocriptine indicated to suppress breast milk production: results of the re-evaluation of the risk/benefit ratio: the risk/benefit ratio remains unchanged as long as prescribers take into account recommendations for safe use and the medicine’s contraindications, especially in terms of cardiovascular, neurological, and psychiatric risk (February 2015)
- Pain management with high-dose ibuprofen: European recommendations regarding cardiovascular risk (April 2015)
- Hydroxyzine (Atarax® and generics) for minor anxiety treatment, as a preparation for general anaesthesia, and for symptomatic treatment of urticaria: new use restrictions to reduce the risk of Q-T interval prolongation (April 2015)
- Treatment of cholesterol with statins: warnings and stronger precautions due to the risk of immune-mediated necrotising myopathy (musculoskeletal disorders) (May 2015)
- Oral isotretinoin for the second-line treatment of severe acne: prescription restricted to dermatologists and strengthened risk reduction programme due to the medicine’s teratogenic effect (May and November 2015)
- Saxagliptin (Onglyza® and Komboglyze®) for the treatment of type II diabetes: re-evaluation of all available data due to the results of the FDA’s SAVOR study and especially the 27% increase in the...
risk of hospitalisation for heart failure among patients treated with these medicines compared to the placebo (June 2015)

- Mycophenolic acid in combination with cyclosporine and corticosteroids to prevent acute organ rejection in patients who have received a renal allograft (MYFORTIC®) and also in the case of heart or liver allografts (CELLCEPT® and generics): new contraindications and pregnancy prevention measures due to the medicine's teratogenic risk (June and November 2015)

- Use of health products designed to assist weight loss: warning issued by ANSM about the risks associated with the use of these products (July 2015)

- Use of chloral hydrate to sedate children for diagnostic exams: use strictly reserved to the performance of certain diagnostic exams (MRI and FRE exams) on children affected by severe pathologies (July 2015)

- Olmesartan for the treatment of essential hypertension alone or in combination with other high blood pressure treatments: reminder of risk of severe enteropathy (July 2015)

- Quinolone antibiotics: reminder of risks requiring a restriction of their use and special surveillance (October 2015)

- Valproate and derivatives (Depakine®, Depakote®, Depamide®, Micropakine®, and generics) for the treatment of epilepsy and bipolar disorder: restriction of prescription and dispensing criteria due to the serious risk of congenital birth defects and increased risk of developmental disorders (between May and December 2015).

Reassessment of the risk/benefit ratio of medicines

Reassessment of the risk/benefit ratio of marketed medicines is a recurrent process throughout their life cycle. It is essential to verify that the efficacy data presented at the time the marketing authorisation (MA) was granted and the safety data reported during clinical trials are still valid given large-scale use of the medicines "in real life". This guarantees that the treatment options available to health professionals and the public are appropriate in regard to efficacy and safety of use.

A reassessment of the risk/benefit ratio procedure is conducted for four reasons:

- a reassessment based on a risk report. For some medicines, the seriousness or number of adverse effects can cast doubt on their conditions for use.
- a reassessment due to a lesser beneficial effect
- a reassessment during the five-year marketing authorisation renewal
- an overall and systematic review/reassessment of medicines. In addition to safety data, this programme also examines therapeutic class and consumption data. This procedure includes the programme for reviewing older medications authorised through the national procedure before 2008. The procedure was created by the agency in 2011.

Between 2011 and 2015, 115 substances or combinations of substances were included in the review/reassessment of the risk/benefit ratio programme, including 52 that were reassessed in 2015. In the latter group, these reassessments resulted in a total of:

- 22 market suspensions or withdrawals or indication restrictions
- 25 modifications/tightened safety of use conditions/harmonisations of summary of product characteristics (SPC) aimed at health professionals.

Of these 52 substances or substance combinations, 21 were the subject of a European referral.
Pharmacovigilance: surveillance of the adverse effects of medicines

The objective of pharmacovigilance is to monitor, evaluate, prevent, and manage the risk of adverse effects resulting from the use of medicines. It applies to all medicines with a marketing authorisation (MA), as well as medicines undergoing clinical trials or those granted a temporary authorisation for use (TAU) or a temporary recommendation for use (TRU).

In July 2012, the definition of adverse effect was extended to include all conditions of use; it now includes adverse effects that occur due to medication errors, abuse, misuse, overdose, and professional exposure.

In France, doctors, dentists and dental surgeons, pharmacists, and midwives are required to report any adverse effect suspected of being due to a medicine or other product to their local Regional Pharmacovigilance Centre (RPC). The 31 Regional Pharmacovigilance Centres (RPCs) enter the adverse effect (AE) reports they receive from healthcare professionals and patients in the national pharmacovigilance database. Information about adverse effects can change over time. These updates are monitored by the Regional Pharmacovigilance Centres. Updates may concern, for example, the patient's medical history or evolution of his/her health status.

Any health professional learning about an adverse effect that might be due to a medicine or another product may also report this to their local RPC. In addition, any person qualified to prescribe, supply, or administer blood-derived medicines must immediately report the occurrence of an adverse effect that may potentially be due to a blood-derived product, even if he/she has not directly prescribed, supplied, or administered the medicine in question.

Since June 2011, patients and patient associations have been able to directly report an adverse effect related to a medicine without going through a healthcare professional. The national pharmacovigilance system opened itself up to patients following a number of experiments carried out by ANSM in partnership with associations over a period of around ten years.

Any company or organisation developing a medicine or product for human use must set up a pharmacovigilance department with the objective of ensuring the collection, recording, and scientific assessment of information regarding adverse effects potentially due to medicines, with a view to preventing and reducing risks and taking appropriate measures, if necessary. This department must be under the permanent responsibility of a qualified person with experience in the field of pharmacovigilance. The pharmacovigilance manager must ensure compliance with obligations concerning pharmacovigilance reporting to ANSM.

The French national pharmacovigilance system is naturally incorporated within a European pharmacovigilance system through France’s participation in the European Pharmacovigilance Risk Assessment Committee (PRAC) and its contribution to the European Medicines Agency (EMA) EudraVigilance database.

<table>
<thead>
<tr>
<th>National pharmacovigilance</th>
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<tr>
<td><strong>Adverse effect reports submitted to ANSM</strong></td>
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<tr>
<td>Total number of adverse effect reports¹ from Regional Pharmacovigilance Centres</td>
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<tr>
<td>- Including serious adverse effect reports</td>
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<td>- Including adverse effect reports submitted by patients</td>
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<tr>
<td>Number of adverse effect reports from pharmaceutical companies</td>
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¹ The number of adverse effect reports includes initial cases and follow-up
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- **Adverse effect reports to the national pharmacovigilance system - Comparison between cumulative data in 2014 and 2015**

- **Adverse effect pharmacovigilance reports received from patients – comparison between cumulative data in 2014 and 2015**
France’s contribution to European pharmacovigilance

The EudraVigilance database is the single collection point for all serious adverse effects reported by competent national authorities or MA holders in Europe. France makes a significant contribution to this database via:

- data collected by the Regional Pharmacovigilance Centres and recorded in the National Pharmacovigilance Database;
- data collected directly by pharmaceutical companies in France.

In 2015, over 1.2 million adverse effect reports, including more than 48,000 reports submitted by patients, were received by EudraVigilance, the European database, i.e. an increase of 10%. The total number of notifications from RPCs accounts for around 17% (47,089) of notifications from member states (283,520) in the EU, whereas the French population represents 13% of the EU population.

<table>
<thead>
<tr>
<th>Pharmacovigilance-related risk assessment work</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases recorded in PRAC agendas</td>
<td>1,565</td>
<td>1,648</td>
<td>1,932</td>
</tr>
<tr>
<td>- for which France is the rapporteur</td>
<td>200</td>
<td>163</td>
<td>224</td>
</tr>
<tr>
<td>Number of national pharmacovigilance investigations opened and monitored</td>
<td>9</td>
<td>24</td>
<td>14</td>
</tr>
</tbody>
</table>
Assessment of referral procedures

Referral procedures address concerns regarding a medicine's safety or risk/benefit ratio. They can also be used to settle a disagreement between member states concerning a medicine's use. During a referral, the agency is asked to carry out a scientific assessment on behalf of the European Union on a specific medicine or class of medicines in order to formulate a single recommendation for the entire EU. The recommendation then becomes a legally binding decision throughout the EU that is issued by the European Commission, or, more rarely and only if the medicines in question have been authorised by a national procedure, the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

- 21 referral procedures were launched in 2015,
- including 5 that were related to pharmacovigilance (according to articles 31, 20, or 107i of pharmacovigilance-related legislation).

The 16 other referral procedures were initiated to address concerns regarding the effectiveness or quality of certain medicines, to harmonise medicines' legal notices on a European level, and to resolve inconsistencies between different member states during decentralised mutual recognition procedures.

<table>
<thead>
<tr>
<th>Medicines examined by European authorities</th>
<th>Main recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine for the treatment of colds and coughs in children</td>
<td>Restricted use to reduce the risk of serious adverse effects in children: contraindication in children under 12, warning for children and adolescents between 12 and 18 with abnormal respiratory function, contraindication during breast feeding, and contraindication in patients known to be ultra-rapid metabolisers of the cytochrome substrate CYP2D</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Restricted use to reduce the risk of Q-T interval prolongation: stronger contraindications, warnings, and precautions for use</td>
</tr>
<tr>
<td>Oral ibuprofen</td>
<td>New warnings issued to reduce the cardiovascular risk associated with high doses of medicines containing ibuprofen</td>
</tr>
<tr>
<td>Epinephrine auto-injectors</td>
<td>Clarification and tightening of instructions for patients to follow during an emergency to maximise their chance of successfully administering epinephrine</td>
</tr>
<tr>
<td>GVK biosciences</td>
<td>MA suspension of proprietary medicines whose bioequivalence trials were administered by the company GVK</td>
</tr>
<tr>
<td>Inductos</td>
<td>MA suspension until the manufacturing system used to make the medicine has been brought up to standard</td>
</tr>
</tbody>
</table>

Since 2015, ANSM has been involved in deliberations to strengthen its position within the European pharmacovigilance system, especially in regard to PRAC. The agency is working to increase communication and forge closer bonds between French PRAC representatives and the agency’s health product divisions in regard to regulatory, organisational, and scientific issues.

Ongoing deliberations are also being conducted concerning how to manage PRAC cases so that French stances carry more weight. To that end, the agency created a dedicated department within the Division for Science and European Strategy that includes the representatives of PRAC, CHMP, and CMDh. Their mission involves monitoring the evolution of French stances and contributions, within the various European committees dedicated to medicines, using indicators that track the impact of these opinions, especially in "major interest" cases. These representatives also work to strengthen the coordination and management of all the agency's European activities.
For safe, effective, innovative and accessible health products

France's contribution to International pharmacovigilance

VigiBase is an international pharmacovigilance database. It is the biggest and most complete database in the world. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) under a World Health Organisation (WHO) mandate. More than 110 countries help collect pharmacovigilance data. France contributes to around 4% of the total number of adverse effect reports.

- Top contributors to VigiBase

Managing medication errors

<table>
<thead>
<tr>
<th>Evolution of medication error reports</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,734</td>
<td>1,589</td>
<td>2,248</td>
<td>2,525</td>
<td>2,741</td>
</tr>
</tbody>
</table>

ANSM also examines medication errors that do not cause an adverse effect. The Medication Errors Service, set up in 2005 to meet a strong demand from health professionals, collects and processes all reports of errors or risks of errors directly related to a medicine, whether these reports concern how the medicine is presented (labelling, packaging), its name, or any other relevant information (package leaflet, SPC, accompanying document, etc.). In ten years, the number of reports has increased by a factor of five.

This activity is coordinated with the pharmacovigilance system (which collects medication errors leading to adverse effects) and performs a complementary role since it concerns the collection of errors without any adverse effects, potential errors, and risks of medication error (latent errors).

In 2015, 2,741 reports were submitted to ANSM, including 2,169 known errors, 322 potential errors, and 250 risks of medication error (or latent errors). Among the reports of known errors, 43% did not lead to an adverse effect. In 3% of cases, the description did not make it possible to specify whether the error led to an adverse effect or not, and 54% led to an adverse effect (half of which were considered to be serious in view of pharmacovigilance criteria).

ANSM can take several actions in response to these errors:

- an immediate action regarding the product on a national or European level: request for modification of the MA; modification of the package leaflet, immediate or outer packaging (medicine box); communication to healthcare professionals or the public; etc.
- an action in the context of an overall reflection on medicines (for example: improved and harmonised labelling for small volumes of injectable solutions, recommendations and informational campaigns regarding administration devices for drinkable solutions, etc.).
Highlights
- Previscan (fluindione): new tablet colour to limit the risk of medicinal errors (April 2015)
- Humalog: provision of a new 200 ul/ml concentration and reminder about risk of error (June 2015).

Monitoring medicine availability on the market

Challenges related to managing quality defects
ANSM records and assesses any quality defects that may occur during the manufacture of medicines and/or active substances.

The number of medicine quality defect reports is constantly rising; this figure rose from 624 in 2004 to 1,702 in 2015. 668 of these reports were the subject of in-depth investigations coordinated by the agency.

When necessary, ANSM works with pharmaceutical companies to organise the recall of already marketed batches via the pharmaceutical dossier management system (run by the French National Board of Pharmacists), which monitors the medicine distribution and supply circuit from end to end. In this way, the information is passed on to all pharmacies in France and its overseas territories and regions, which are linked up to the system. The pharmacists receive the information in real time via a message that is directly displayed on all of the pharmacy's computer screens. 56 batch recalls were performed using this method in 2015.

The agency performs on-site inspections if necessary when the extent, severity, or complexity of the defects warrant such a measure.

The number of reports related to cases of non-compliance with Good Manufacturing Practices (GMP) on active substance production sites has increased sharply since 2012. In 2015, 41 reports (representing 88 active substances) were managed by ANSM.

Highlights
- Market withdrawal of the proprietary products manufactured by Catalent France Laboratories (Blenheim), after their operations were suspended (November 2015).

Change in the number of medicine quality defect reports
Challenges related to managing stock and supply shortages

The medicine stock shortages or risks of stock shortages managed by ANSM concern medicines of major therapeutic value, i.e. medicines for which a temporary, total, or partial unavailability is liable to cause a public health problem (meaning a situation that is life threatening or one that represents a significant loss of opportunity for patients).

Medication stock shortages have a range of causes, including: inadequate production capacity; difficulties during the manufacturing of starting materials or finished products; medication quality defects; decisions taken by ANSM to suspend a site’s, manufacturer’s or operator's activities following inspections that cast doubt on the quality of the medicines; etc.

ANSM’s task is to secure patient access, on a national level, to medicines that do not have therapeutic alternatives or whose lack of availability could represent a public health risk. Assisting on a case-by-case basis, ANSM works with the laboratory in question to implement various stop-gap measures such as: monitoring stocks, helping to introduce a restriction on residual supplies, using a comparable product initially intended for another market, and communicating with health professionals and/or patients.

**Highlights**

- Announcement of a gradual return to normal supply conditions of proprietary BCG-based medicines for intravesical instillations following significant market pressure in 2014 (October 2015)
- Support during supply pressure regarding the BCG SSI vaccine
- Monthly summary of the state of national available quantities of intravenous and sub-cutaneous (IV and SC) polyvalent human immunoglobulin.
- Assistance during supply pressure and stock shortages of combination vaccines containing the pertussis valency (December 2015)
Evolution of supply shortage reports (2008 to 2015)

Monitoring advertisements for medicines: an additional surveillance tool

Monitoring advertising is an integral component of health product surveillance. ANSM’s role is to ensure the safety of the promotional message, which must not lead to poor prescribing habits and which must be consistent with the assessment and communication of the health authorities.

Prior to their release, the agency controls all promotional documents written for the public and for health professionals.

Regulations on the matter set three main objectives: presenting the medicine in an objective manner; promoting its correct use; and ensuring compliance with the standards in force, primarily the marketing authorisation (MA), but also the treatment strategies recommended by the French National Authority for Health.

As regards advertising written for health professionals, the recipient of the advertisement must be able to clearly identify the medicine’s target population and understand the expected risk/benefit ratio of the product.

Approximately 8% of the advertisements submitted to ANSM are rejected because they do not meet these criteria.

Professional advertising 2015
Professional advertising must be sent to the agency during a specific submission window (four per year). Applications are processed within a two-month (statutory) deadline.

As regards advertising written for the general public (self-medication products and certain vaccines), the goal is for the patient to understand the situations in which he or she can use the treatment. Patients should understand the need to follow a pharmacist's advice and to take into account certain safety messages regarding medicines or therapeutic classes that require special attention (for example: paracetamol and medicines contraindicated for pregnant women).

Out of the 1,579 applications submitted in 2015, 99 (6%) were refused.

- **General public advertising - Cumulated number of dossiers submitted - 2015 vs. 2014**

Advertising for the general public must be sent to the agency during a specific submission window (eight per year). Applications are processed within a two-month (statutory) deadline.

**Conducting independent pharmaco-epidemiological studies**

Following the creation in 2012 of a Health Product Epidemiology Department attached to the Division for Science and European Strategy, ANSM now has access to necessary expertise enabling it to autonomously conduct pharmaco-epidemiological studies. It is able to independently develop study protocols, conduct critical analyses, and communicate results. These studies are conducted using the various databases available. They help to reinforce the surveillance of health products in real-life conditions.

Within this framework, ANSM is reinforcing its ties to the French national health insurance system in order to conduct joint studies drawing on data from the French National Health Insurance Information System (SNIIRAM). Since the end of 2013, ANSM has been able to access individual data in the SNIIRAM (see page 106, "Promoting independent research to support the agency's missions").
FOCUS on vaccine surveillance

Vaccines are medicines. As such, they must meet the same requirements as chemical medicines in terms of marketing authorisations, safety of use guidelines, and surveillance conditions. As a health authority, ANSM ensures that each patient receives medicines whose pharmaceutical quality, safety of use profile, and efficacy have been proven and validated. The agency fulfils this role when the medicine is first marketed and then afterward, through the surveillance of consumer data, during the review process of the medicine's risk/benefit ratio throughout its life cycle, and through the analysis of adverse effects reported to the agency by manufacturers and the pharmacovigilance network. ANSM controls authorised advertising directed at the public for some of these medications. ANSM also monitors the market and manages supply pressure in cooperation with manufacturers.

Vaccines are sensitive biological medicines since their production uses starting materials of human or animal origin as well as a complex process that is subject to variability. That is why they are subject to stricter conditions before they are marketed; vaccines are released on a batch-by-batch basis by a national authority. This system, which is governed by European directive 2001/83/EC, stipulates that 100% of vaccine and blood-derived medicine batches must be controlled before they are marketed. Batches released in this way by an independent national authority may circulate freely within the European area. This release, conducted by ANSM in its capacity as the official national control laboratory, involves controls carried out in independent laboratories relating to the identity, efficacy, and safety of vaccine and blood-derived medicine batches. An exhaustive assessment of the manufacturer’s production and control data is also performed. For each batch, the critical parameters to be controlled are defined jointly by all the European laboratories within the European Directorate for the Quality of Medicines and HealthCare in Strasbourg (EDQM—Council of Europe). Such harmonisation also enables mutual recognition between the member states and avoids the unnecessary duplication of tests. France is the country most solicited in Europe by vaccine manufacturers for batch releases. This dominant role can be explained by its expertise, which is recognised throughout Europe and abroad, and the speed with which it operates. Depending on the year, it releases 35% to 40% of all vaccine doses used in Europe and around 50% of the vaccine doses used in France. In 2015, 2,246 batches of vaccines were released by ANSM laboratories, i.e. a 9% increase compared to 2014.

<table>
<thead>
<tr>
<th>MAs granted to vaccines</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of proprietary medicines</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Highlights

✦ Vaccination against invasive serogroup C meningococcal disease
  o ANSM supports the recommendations of the French High Council for Public Health when these vaccines are in short supply (January 2015)
  o ANSM issues communications about the end of supply pressure (April 2015)
  o ANSM updates its information about quality defects observed in 2014 (December 2015).

✦ Rotavirus vaccine
  o ANSM reminds health providers about the treatment of acute intussusception in infants and issues a briefing on the condition (March 2015).

✦ Human papillomavirus (HPV) vaccine
  o The European authorities launch an evaluation of the risk of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) following the administration of an HPV vaccine (July 2015)
  o HPV vaccine and risk of autoimmune disease: A CNAMTS/ANSM study offers reassuring results (September 2015)
  o European authorities find no link between the HPV vaccine and complex regional pain syndrome (CRPS) or postural orthostatic tachycardia syndrome (POTS) (November 2015)

✦ Seasonal flu vaccine
  o ANSM works to release vaccine batches and helps fund the effort (October 2015).
Release of vaccine batches to the European market

France is the leading provider of vaccine doses in circulation in France.

Distribution of vaccine doses in circulation in France and released by OMCLs

France is the leading provider
Involvement of member states in the release of vaccine batches in Europe

- France: 44%
- Belgium: 17%
- Germany: 14%
- United Kingdom: 10%
- Netherlands: 8%
- Austria: 4%
- Italy: 1.7%
- Norway: 1%
- Switzerland: 0.34%
- Denmark: 0.17%
FOCUS on ANSM’s role in the prevention of addictive behaviours and its interactions with other organisations

ANSM is the designated national authority for monitoring the use of narcotic and psychotropic products, regardless of whether or not they are medicines.

ANSM’s mission complies with France’s obligations under the UN 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. The objective of these conventions is to limit the use of narcotics and psychotropic substances to medical and scientific purposes only, in order to prevent any illicit trafficking and any harmful effect on public health. Under the terms of these conventions, each signatory state is required to name an administrative body responsible for applying the conventions.

France is the second biggest legal opioid-producing country. ANSM controls the legal trade and movement of narcotics and psychotropic substances in France. In regard to regulatory matters, ANSM monitors the production, manufacture, import, export, distribution, and consumption of narcotics and psychotropic substances and draws up reports, which it sends each year to the International Narcotics Control Board (INCB). To do so, the agency uses the National Drug Control System (NDS), the IT application developed by the UNODC (United Nations Office on Drugs and Crime).

ANSM monitors and assesses the potential for abuse, dependence, and public health risks related to the use of psychoactive substances, whether legal or illegal, contained in medicines or not (except alcohol and tobacco) in an effort to ensure the correct use of medicines and, if needed, to add substances to the list of narcotics. The agency monitors and authorises the marketing of medicines containing psychoactive substances, including those indicated in opioid substitution treatments (OST). ANSM leads the national addiction vigilance system with assistance from the network of Drug Dependence Evaluation and Information Centres (CEIPs in French) located throughout the country’s regions within a total of thirteen University Hospital Centres.

To detect and assess abuse, drug dependence, and misuse of medicines or psychoactive substances, ANSM and the CEIPs established specific data collection and assessment studies. Hence, alongside the collection of spontaneous notifications concerning cases of abuse, drug dependence, and misuse passed on by healthcare professionals (article R.5132-114 of the French Code of Public Health stipulates that health professionals must report severe cases of abuse and dependence), annual surveys are conducted with entities specialising in the care of drug addicts [OPPIDUM (1)], general practitioners [OPEMA(2)], community pharmacists [OSIAP(3) and ASOS(4)] and toxicology experts [DRAMES(5), DTA2, and the French national survey on chemical dependence]. ANSM also makes sure it keeps healthcare professionals informed of any changes in the safety profile of these medicines and substances.

In addition, the agency participates in the implementation of a drug and addictive behaviour control policy, which is coordinated by MILDECA (the French Inter-Ministerial Mission for Drug and Addictive Behaviour Control), and works in close partnership with the OFDT (Observatoire Français des Drogues et des Toxicomanies—French Monitoring Centre for Drug and Drug Addiction). ANSM studies are passed on to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), especially data concerning deaths from fatal overdoses.

(1) OPPIDUM (Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse—French programme to monitor illicit psychotropic products or misuse of psychotropic medicines)
(2) OPEMA (Observation des Pharmacodépendances en Médecine Ambulatoire—French programme to monitor dependence on pharmacological drugs in out-patient medicine)
(3) OSIAP (Ordonnances Suspectes, Indicateur d’Abus Possible—Suspect prescriptions, an indicator of possible abuse)
(4) ASOS (Analgesiques stupéfiants et ordonnances sécurisées—Narcotic analgesics and secure prescriptions)
(5) DRAMES (Décès en Relation avec l’Abus de Médicaments et de Substances—Deaths related to medicine and substance abuse)

2 DTA (Décès toxiques par antalgiques—drug-poisoning deaths involving analgesics)
Highlights

- Inclusion of new synthetic cannabinoids on the list of narcotics (May 2015)
- Warning about the increase in reports of cannabis poisoning in children due to accidental ingestion (October 2015)
- Withdrawal of diphenhydramine- and dimenhydrinate-based proprietary medicines, which are used as antiemetics, from the list of medicines that can be purchased directly from a pharmacy (October 2015)
- Cohort temporary authorisation for use for a nasal naloxone spray for the emergency treatment of opioid overdoses (November 2015).

Expert assessments

ANSM calls upon the services of an expert commission, the Narcotics and Psychotropics Commission, whose goals are to:

- assess the risk of drug dependence, abuse, and misuse of substances, plants, medicines, or other products indicated in article R. 5132-98 and their consequences on public health
- propose surveys and studies, that it believes would be useful to fulfil its missions, to ANSM's Director General
- provide the Director General with advice concerning measures to be taken to protect public health in terms of controlling drug dependence, abuse and misuse, and to address any issues concerning the application of provisions regarding poisonous substances and preparations.

This commission may be consulted on dossiers pertaining to psychoactive substances and medicines with regard to:

- classifying these substances on a list of narcotic or psychotropic agents
- determining (at the time of MA application submission) or modifying prescribing and supply conditions (after being placed on the market)
- reassessing the risk/benefit ratio of psychoactive medicines
- participating in the implementation or modification of risk management plans for psychoactive medicines
- proposing general measures designed to promote proper use, reduce the misuse and abuse of psychotropic medicines, or to prevent or reduce the risks or manage the consequences of using non-medicinal psychoactive substances.

In 2015, the commission met four times. It issued an opinion in favour of classifying several substances as narcotics due to their potential for abuse and dependence:

- generic classification of NBOMe
- MT-45
- 4,4’-DMAR.

The commission also ruled on:

- the creation of a naloxone distribution programme in France
- the withdrawal of diphenhydramine- and dimenhydrinate-based proprietary medicines, which are used as antiemetic medicines, from the list of medicines that can be purchased directly from a pharmacy as well as the addition of warnings about the risk for abuse to the summary of
product characteristics (SPC) of these proprietary medicines and an information bulletin for pharmacists

- information for health professionals concerning the risk of abuse of pregabalin (Lyrica®)
- the potential psychoactive effects of cannabidiol.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Post-MA survey of dependence on pharmaceutical products</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>9</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Evaluation of abuse and dependence potential as part of the MA application</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Evaluation of abuse and dependence potential of psychoactive substances (plants, synthetic drugs, etc.)</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>National addiction vigilance monitoring</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>
2. Surveillance of blood products and biological products derived from the human body

Haemovigilance: surveillance of the transfusion chain

ANSM is involved in the surveillance of: adverse events that may occur either in blood donors or in the recipients of labile blood products (LBPs), transfusion chain incidents, and post-donation information.

The agency's haemovigilance efforts are supported by the network of haemovigilance correspondents in healthcare or blood transfusion establishments and the national e-FIT online notification system, a database for reporting serious transfusion chain incidents, serious adverse effects occurring in blood donors, and adverse effects occurring in the recipients of labile blood products (LBPs). This database also allows members of the network (regional Haemovigilance Coordinators, Vigilance Division of the Etablissement français du Sang [EFS - French National Blood Service], Haemovigilance Department of the Military Blood Transfusion Centre, and ANSM) to intervene rapidly and share information on any potentially significant event.

In addition, ANSM manages the consequences of epidemiological alerts involving arboviruses (West Nile virus, dengue, and chikungunya) via an inter-institutional structure (Cellule d’aide à la décision, or CAD - decision-making assistance unit) by proposing that exposed travellers returning from epidemic zones be temporarily excluded from donating blood or other products derived from the human body. It also intervenes by proposing preventive measures in response to the risk of transmission via blood transfusions or transplants of other infectious agents responsible for epidemics. In 2015, 55 reports of epidemic situations were received, leading to seventeen consultations with CAD.

- Serious adverse effect reports in haemovigilance (donor) - comparison of cumulated data 2014 vs. 2015

![Graph showing cumulated severe cases and serious adverse effects in blood donors over time]

- Cumulated severe cases - 2015
- Cumulated serious adverse effects in a blood donor - 2015
- Cumulated serious adverse effects in a blood donor - Cumulative 2014
For safe, effective, innovative and accessible health products

- Serious adverse effect reports in haemovigilance (recipient) - comparison of cumulated data 2014 vs. 2015

The number of serious adverse effects among blood donors continues to rise. However, 80% of reported adverse effects are of moderate severity. The most common adverse effects are vasovagal episodes at the blood donating centre and haematomas at the puncture site. The increase in serious adverse effect reports is therefore partially due to the change in the report content.

Biovigilance: surveillance of the organ, tissue, cell, breast milk, and ancillary therapeutic product collection chain

Biovigilance includes monitoring and preventing risks related to the use of elements and products derived from the human body and used for therapeutic purposes. Biovigilance acts retroactively in response to any adverse events occurring throughout the organ, tissue, cell, and breast milk collection chain in the donor upon administration or in the patient upon transplant.

In 2016, these responsibilities will be transferred to the Biomedicine Agency in accordance with law no. 2016-41 of 26 January 2016 regarding the modernisation of our health system (OJ 27/01/16).

<table>
<thead>
<tr>
<th>Biovigilance</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events declared</td>
<td>186</td>
<td>296</td>
<td>387</td>
<td>461</td>
<td>518</td>
<td>540</td>
</tr>
</tbody>
</table>
Breakdown of adverse effects by product category in 2015

FOCUS on breast milk for therapeutic use

Breast milk for therapeutic use is supplied by breast milk banks. The order of 1 September 2005 made the agency the competent authority in charge of breast milk collected and treated by breast milk establishments and prescribed by a physician as a healthcare product to care for extremely premature infants.

The collection, preparation, qualification, treatment, storage, distribution, and supply of medically prescribed breast milk is strictly regulated by best practice rules defined by the agency (September 2007).

To properly monitor the issue, ANSM oversees the technical examination of breast milk bank authorisation applications, which are issued by Regional Health Agencies. It also carries out on-site inspections to assess practices and ensure that proper surveillance conditions are being observed. These inspections rely on biovigilance and adverse incidents and events that could be related to the use of breast milk for therapeutic purposes. The main risk is microbiological contamination.

Highlights:

- April 2015: inspection of the Caen University Hospital breast milk bank following several deaths of newborns hospitalised in the neonatal unit (report from the Basse Normandie Regional Health Agency). Upon investigation, inspectors reported 45 observations, six of which were critical, and identified an uncontrolled risk of breast milk contamination after pasteurisation, a risk of viral contamination, a lack of verification and control over practices and equipment, and a risk of mixing up milk samples. ANSM issued an unfavourable opinion regarding the continued production of pasteurised breast milk. The Regional Health Agency immediately suspended the breast milk bank's authorisation to operate until compliance was assured. Operations resumed in June 2015.

### Surveillance of breast milk banks

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dossiers examined</td>
<td>41</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total number of inspections</td>
<td>11</td>
<td>15</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Number of adverse events reported</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>
ANSM's authorisation regime regarding microorganisms and toxins (MOTs) that are highly pathogenic to humans

The storage, use, import, intra-site transfer, export, purchase, and transport of certain agents responsible for infectious diseases and pathogenic microorganisms and toxins (MOTs) require an authorisation from ANSM. This mission involves two levels of intervention: the evaluation of applications before an authorisation is granted and an on-site inspection of operations involving these microorganisms and toxins.

The granting and renewal of authorisations depends on ANSM's assessment of the risks inherent to such handling in terms of both biological safety and security. In addition, the inspections seek to verify that the operations carried out within laboratories comply with authorisations granted by ANSM and that the facilities operate in full compliance with biological safety and security control requirements given the risks affiliated with MOTs. ANSM also collects administrative reports, which provide additional information about operators and help track any change in their activities. These reports concern the loss or theft of MOTs, incidents, accidents, and more generally, any event that might result in the spread of MOTs.

<table>
<thead>
<tr>
<th>Microorganisms and toxins</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination of authorisation applications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of MOT authorisations granted per year</td>
<td>928</td>
<td>1,259</td>
<td>1,311</td>
<td>899</td>
<td>1,286</td>
</tr>
<tr>
<td>Authorisation suspensions</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Health policy rulings</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site and laboratory inspections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sites</td>
<td>266</td>
<td>122</td>
<td>116</td>
<td>138*</td>
<td>164</td>
</tr>
<tr>
<td>Number of MOT authorisation holders</td>
<td>473</td>
<td>138</td>
<td>143</td>
<td>153</td>
<td>226</td>
</tr>
<tr>
<td>Total number of inspections performed per year</td>
<td>24</td>
<td>24</td>
<td>20</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Number of dossiers passed on to the judicial authorities</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*entities grouped within 102 establishments
3. Surveillance of medical devices and *in vitro* diagnostic medical devices

A medical device corresponds to any instrument, apparatus, device, material, or product (with the exception of products of human origin), including accessories and software, used alone or in combination for medical purposes in humans, that do not achieve their principal intended action by pharmacological, immunological, or metabolic means.

The medical device market is extremely vast, and the sector is highly innovative. It contains over 10,000 product types according to international GMDN nomenclature, including: single-use or reusable consumables; passive or active implants; and devices, reagents, and automated equipment derived from medical biology. The industrial network is comprehensive and highly varied; it includes both large multinational groups and SMEs.

ANSM does not authorise the marketing of medical devices or *in vitro* diagnostic medical devices. Instead, they are marketed by a European regulatory framework, which is governed by three “new approach” directives that require manufacturers to earn the CE marking before their products can be sold on the market. This marking indicates that the medical device complies with the essential health and product safety requirements stipulated in these directives. These essential requirements set the objectives to be met in order to ensure that the medical device is designed in such a way that its use does not compromise either the clinical condition of patients or the safety and health of patients and users. The medical device must achieve the performance objectives assigned to it by the manufacturer, and the potential risks must be acceptable in view of the benefits provided to the patient. The device’s conformity must be demonstrated in accordance with the procedures described in the directives.

**Medical devices** are categorised according to their potential public health risks (class I to III according to an increasing risk of use). With the exception of devices belonging to the lowest risk category (non-sterile class I devices without a measuring function), a manufacturer demonstrates the conformity of its medical devices before marketing by obtaining the CE marking, which is evaluated by an accredited (or notified) body chosen from a list of bodies designated by the competent authorities in the European Union. This notified body assesses the manufacturer’s quality system in all cases. For class III devices (category corresponding to the highest risk) or for active implantable medical devices, the design application is also systematically examined. Upon completion of this process, the notified body issues a certificate of conformity, allowing the manufacturer to place the CE marking on its device and sell it on the European market. All other marketed products must comply with the product that obtained the certificate of conformity allowing it to use the CE marking. For *in vitro* diagnostic medical devices, the marketing conditions follow the same principle.

Once on the market, the medical device is the responsibility of the manufacturer marketing it. Periodic audits are performed by the notified body.

The very principle of CE marking therefore implies an effective and active market surveillance. Each country’s competent authorities, including ANSM in France, performs this task. Within the scope of ANSM control, the agency intervenes on five levels by:

- assessing vigilance incidents (medical device and reagent vigilance) based on incident reports or risk of incident reports as well as market surveillance, by registering the devices with the greatest risk and carrying out topical assessment campaigns per product range
- monitoring advertising since the French law of 29 December 2011 reinforcing the safety of medicines and healthcare products came into force
- inspecting manufacturing sites to verify that activities comply with essential health and product safety requirements as well as with the technical product application supporting the product’s CE marking and to verify that the vigilance system is reliable
- controlling the operation of the French notified body by conducting several inspections. ANSM may also act through joint audits with its European counterparts in foreign notified body audits
- conducting laboratory quality control audits when additional tests are required.

The provisions surrounding market surveillance will be markedly strengthened through two regulations on medical devices and *in vitro* diagnostic medical devices that are being finalised on a European level.
Surveillance of incidents and risks of incidents related to medical devices

Medical device vigilance

Medical device vigilance evaluates incidents and risks of incidents involving a medical device. The medical device vigilance system is structured around a national tier led by ANSM and a local tier managed by local medical device correspondents working in public or private healthcare institutions, healthcare professionals, and manufacturers, who are required to report any incidents or risks of incidents that come to their attention.

Almost 51% of reports come from healthcare institutions, 41% from manufacturers, and 8% from other stakeholders (associations delivering devices to patients’ homes, private individuals, non-hospital healthcare professionals, and French and European institutions).

**Highlights**

- Lasik laser: segment on complications and adverse effects (February 2015)
- Breast implants: communication concerning the risk of anaplastic large cell lymphoma (ALCL) and meeting of a panel of experts (March/April/June 2015)
- Electrocoagulation systems in arthroscopy: best practices to prevent the risk of skin burns (April 2015)
- Tissue fusion surgical forceps: assessment of medical device vigilance reports (April 2015)
- Breast reconstruction: decision to prohibit the marketing, distribution, importation, and use of the Strattice™ device and withdrawal of this product (June 2015)
- Disinfection of endoscopes: assessment of medical device vigilance reports (July 2015)
- Use of health products designed to assist weight loss: warning issued by ANSM about the risks associated with the use of these products (July 2015)
- VARIAN and BRAINLAB linear accelerators for radiation therapy: recommendations regarding pre-treatment verifications and decision on conditions of use (September 2015)
- The ophthalmic product ALA OCTA: market withdrawal due to serious accidents (loss of function in one eye) following retinal surgeries (November 2015)
- Patient lifts: best practices to follow to ensure patient safety (November 2015).
For safe, effective, innovative and accessible health products

- **Origin of medical device vigilance reports**
  - Health establishments: 51%
  - Manufacturers: 41%
  - Other: 8%

- **Declaration of adverse effects in medical device vigilance - Comparison of cumulative data 2014 vs. 2015**

- **Medical device vigilance adverse effect reports received from patients - Comparison of cumulated data 2014 vs. 2015**
Reagent vigilance

Reagent vigilance evaluates incidents and risks of incidents related to the use of in vitro diagnostic medical devices. The reagent vigilance system is based on interventions on a national (ANSM) and local level (local reagent vigilance correspondents, healthcare professionals, and manufacturers or their representatives).

**Highlights**

- Warning about using PAPP-A IMMULITE to test for Down syndrome during pregnancy: the test can no longer be used on frozen samples (September 2015).

<table>
<thead>
<tr>
<th>Reagent vigilance reports</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,359</td>
<td>1,409</td>
<td>1,059</td>
<td>980</td>
<td>1,355</td>
</tr>
</tbody>
</table>

**Origin of reagent vigilance reports**

- Health establishments 14.5%
- Manufacturers 71.3%
- Other 14.3%

**Breakdown in reports by type of in vitro diagnostic medical device (2015)**

- Automated devices 15%
- Equipment (excluding automated devices) 1%
- Non-IVDMD 3%
- Reagents 56%
- Sample collection devices 3%
- Unitary tests 17%
- Other (software, systems, dedicated experts, etc.) 5%
Market control activities

ANSM may also proactively conduct a reassessment of the regulatory conformity and risk/benefit ratio at any point in the life cycle of a medical device as part of its market monitoring activities alongside its vigilance report management activities. To this end, it monitors products after they have been put on the market, carrying out product range audits aimed at demonstrating: compliance with essential requirements, the quality of the procedure followed by the manufacturer and, if applicable, the quality of the procedure followed by the notified body.

Highlights

- Infocament software and the CIRA image compression module: suspended marketing authorisation (January 2015)
- Description of the clinical evaluation of medical devices as part of the CE marking regulatory process (January 2015)
- Condoms: decision to suspend the marketing authorisation, export, and distribution of STAR and STAR VIP condoms manufactured by the company Demapharm and the withdrawal of these products (April 2015)
- Mercury in dental amalgams: data update (May 2015)
- Health software and mobile applications: information on regulatory requirements regarding the CE marking (May 2015)
- Medical devices and in vitro diagnostic medical devices: reminder to manufacturers regarding regulations about the elements that must be included in a device's technical documentation (June 2015)
- Implantable devices and metal particles: creation of a temporary specialised scientific committee on the toxicity of metal particles shed by implantable medical devices (June 2015)
- Breast implants: creation of a temporary specialised scientific committee on "breast implants and large-cell lymphomas" (June 2015)
- Wrinkle filler devices: decision to suspend the marketing authorisation, export, distribution, and use of injectable medical devices from the Evolution range manufactured by the company Renne Biomed as well as the withdrawal of these products (June 2015)
- Total hip replacement implants
  - Study on factors associated with total hip replacement implant revisions: method of fixation and prosthetic components (May 2015)
  - The first study on the safety of hip replacement implants using data from the French health insurance system was carried out by the Institut Curie in partnership with the Institut Gustave Roussy on cancer and breast implants (August 2015).
- Implants: temporary suspension of the CE marking of devices manufactured by the company SILIMED (breast, testicular, buttock, calf, pectoral, and facial implants) due to the presence of particles (September 2015)
- Ocular tamponade devices: following incidents in Spain and France involving an ocular tamponade device used to treat ocular pathologies such as retinal detachment, ANSM has been monitoring this category of devices especially closely. This surveillance, which targets medical device vigilance data and demonstrations of the biocompatibility of these devices, has resulted in safety bulletins and product recalls. The same level of surveillance will continue into 2016 (December 2015)
- PAPP-A Immulite-Siemens reagents: decision stipulating the conditions for use and marketing (September 2015)
- Ethylene oxide-sterilised medical devices used in neonatology and paediatrics: decision to issue a communication to purchasers about residual levels of ethylene oxide (September 2015)
Results of a market inspection regarding urinary test strips designed to check for urinary infections (November 2015)

Results of the market inspection of rapid diagnostic tests for tetanus immunity (December 2015).

Identification of medical devices and in vitro diagnostic medical devices on the market

Each year, ANSM monitors the introduction of medical devices to the market. In addition to French manufacturers of class I devices and custom-made devices, who are required to submit a compulsory declaration of their activity, manufacturers, agents, and distributors of devices from other classes must also notify ANSM. This notification, prior to marketing in France, provides information about market stakeholders as well as the devices used in the country.

<table>
<thead>
<tr>
<th>Registration of medical devices</th>
<th>2011</th>
<th>2012</th>
<th>2013*</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I medical devices</td>
<td>1,307</td>
<td>978</td>
<td>3,142</td>
<td>3,573</td>
<td>4,251</td>
</tr>
<tr>
<td>Class IIa, IIB, III medical devices and active implantable medical devices</td>
<td>4,341</td>
<td>3,527</td>
<td>5,196</td>
<td>5,255</td>
<td>5,583</td>
</tr>
<tr>
<td>Custom-made medical devices</td>
<td>151</td>
<td>441</td>
<td>174</td>
<td>941</td>
<td>693</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices</td>
<td>844</td>
<td>422</td>
<td>394</td>
<td>569</td>
<td>531</td>
</tr>
</tbody>
</table>

* the differences compared to previous years are due to the new method for assessing applications in use since 2013

Main topical campaigns by product range launched and/or continued in 2015

- TAVI-type cardiac valves
- Defibrillation leads
- Total hip replacement implants/total knee replacement implants
- Breast implants: rupture and biocompatibility
- Definitive contraception devices
- Phthalates and teeth whitening products
- Haemodialysis, nutrition, and infusion devices
- Flow diverter stents for brain aneurysms
- Nasal sprays containing essential oils
- Control of leaflets for mammary tomosynthesis systems
- Performance of a survey of thawing systems for LBPs and especially fresh frozen plasma
- Market inspection of glucose meters and risk of interference with maltose
- Market inspection of rapid tetanus tests.
FOCUS on medical devices used in neonatology and paediatrics: application of the NF EN ISO 10993-7 standard to ethylene oxide sterilisation

Ethylene oxide (EO) is a very widely used sterilising agent, especially for single-use medical devices. In France, nearly 85% of single-use sterile devices are sterilised with ethylene oxide. These devices are mostly made from heat-sensitive materials or materials that will not support irradiation or steam treatment. The technique has proven itself in terms of microbiological efficacy. However, as ethylene oxide is a category 1B carcinogen and category 1B mutagen according to CLP regulation3, the technique clearly has constraints, notably the need to control the residues of ethylene oxide and its derivatives that remain in the devices after the sterilisation process and the potential for the patient to be exposed to these residues during use.

The requirements relating to EO sterilisation residue in medical devices are covered by standard NF EN ISO 10993-7. This standard specifies the admissible levels of EO residue following sterilisation. ANSM decided to study how this standard was being implemented in France by conducting a survey-based market surveillance operation4 on EO-sterilised enteral feeding tubes used in neonatology and paediatrics.

The results of this market surveillance operation, which was conducted between 2013 and 2014, revealed gaps in the application of the NF EN ISO 10993-7 standard; the majority of tube manufacturers did not account for the low weight of newborns or the possible concomitant use of other devices sterilised with EO when calculating the admissible levels of EO residue. ANSM therefore issued a reminder of current legislation to manufacturers and sterilisation companies (July 2014).

In 2015, ANSM worked with the International Organization for Standardization to revise ISO standard 10993-7 to clarify some of its requirements, especially in regard to sterilised devices used in neonatology. To the extent that the application of this standard, in its current form, was found to be insufficient to demonstrate compliance with the essential requirements of directive 93/42/CEE, ANSM submitted a formal objection to the European Commission regarding this standard. ANSM also drafted a health policy ruling requiring manufacturers of these devices to provide purchasers in healthcare facilities with information regarding residue levels in order to release these products. This ruling came into effect in April 2016. It was investigated by the French Directorate General of Health/Directorate General of Healthcare, which specified that this information must be one of the criteria used to select products in purchasing procedures for devices used in neonatology, with the goal of allowing the purchaser to compare products and select, whenever possible, devices that limit newborns' exposure to ethylene oxide residues.

FOCUS on Down syndrome testing during pregnancy

In France, foetal screening for Down syndrome is regulated by a decree that specifies best practices in terms of prenatal screening and diagnosis and the use of CE-marked reagents and software to calculate risk during the first and second trimesters of pregnancy. There are currently four reagent/software systems in use in the French market.

As part of its mission to control and monitor, ANSM pays special attention to these types of medical devices by conducting: national quality control operations, surveillance activities through reagent vigilance, and market surveillance.

Through coordinated actions targeting these devices, ANSM identified concentration discrepancies with one of the testing systems (Siemens' PAPP-A Immulite system). Following investigations and consultations with experts, ANSM decided to restrict the conditions of use for this product for one year and instructed the manufacturer to identify the causes of these discrepancies and fix them within this time period (September 2015).

In 2015, ANSM also evaluated new, non-invasive devices for Down syndrome testing. These technologies use high-volume sequencing, or microarray analysis, to look for a potential overrepresentation of chromosome 21 in a sample of the mother's blood. ANSM is working with other health institutions to complete an overall assessment of this new technique in preparation for the next update to the best practices decree.

3 EC regulation no. 1272/2008, called the “CLP” regulation, concerning the classification, labelling, and packaging of substances and mixtures. This regulation repeals directive 67/548/EEC, which targeted substances belonging to categories 1 and 2.
4 This market surveillance operation consisted of a survey of manufacturers and two successive test runs.
Quality control of radiation-emitting medical devices

Quality control of medical devices, instituted by decree 2001-1154 relative to quality maintenance and control, is designed to ensure that medical devices maintain their performance throughout the duration of their use. This control may be applied to all medical devices as soon as they are included on a list approved by the Minister for Health.

Initially, it was decided to conduct this control on medical devices emitting ionising radiation. Around 60,000 devices currently in operation in France are concerned. The quality control methods have been gradually set by ANSM, following consultation with accredited independent bodies tasked with verifying on-site compliance with the control standards drawn up by ANSM itself. In case of doubt during the assessment or at a later date, ANSM may also perform an inspection. Sixty-three certifications are currently in force.

In addition, supervisory bodies and users must report any non-conformities observed during quality controls to ANSM. In the event of a serious non-conformity, ANSM notifies device operators of the need to cease operating until they are brought into compliance.

Since 2003, when external quality control of radiation-emitting medical devices was introduced, over 14,000 non-conformity reports have been received and processed by ANSM.

### Quality control of medical devices

<table>
<thead>
<tr>
<th>Year</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new standards</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Number of certifications granted</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Number of non-conformities reported</td>
<td>1,973</td>
<td>1,516</td>
<td>1,593</td>
<td>1,255</td>
<td>1,335</td>
</tr>
</tbody>
</table>

### Highlights

- ANSM created a medical device quality control committee made up of experts, manufacturers, and supervisory bodies (October 2015)
- Interventional radiology: publication of a quality control standard (December 2015).

### National quality control of medical biology analyses

National quality control of medical biology analyses is an external assessment of the quality of the tests performed by each of the 1,550 medical biology laboratories operating in France. This quality control operation makes it possible to assess the individual performance of each laboratory and the overall performance of the laboratories surveyed upon implementation of a test. It also makes it possible to monitor *in vitro* diagnostic medical devices used in laboratories. In 2015, the agency conducted 22 topical control operations, including 65 tests performed by medical biology laboratories. The activity led to the production of more than 13,428 individual reports.

<table>
<thead>
<tr>
<th>Laboratories participating in national quality control</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private or equivalent laboratories</td>
<td>2,375*</td>
<td>2,243*</td>
<td>1,322</td>
<td>869</td>
<td>805</td>
</tr>
<tr>
<td>Hospital laboratories</td>
<td>820</td>
<td>819</td>
<td>781</td>
<td>723</td>
<td>677</td>
</tr>
<tr>
<td>EFS (French National Blood Service) laboratories</td>
<td>163</td>
<td>160</td>
<td>164</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>Cancer centre laboratories</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Military laboratories</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>3,398</td>
<td>3,262</td>
<td>2,308</td>
<td>1,684</td>
<td>1,550</td>
</tr>
<tr>
<td>&quot;DNA profiling&quot; expert laboratories</td>
<td>70</td>
<td>76</td>
<td>79</td>
<td>84</td>
<td>83</td>
</tr>
</tbody>
</table>

* The reduction in the number of laboratories participating in the national quality control operation since 2011 corresponds to the introduction of order no. 2010-49 dated 13 January 2010 relative to medical biology, which now allows medical biology laboratories to be grouped together.
Control over advertising

Control over advertising is an additional tool used to regulate the safety of use of health products. The law reinforcing the safety of medicines and health products of 29 December 2011 extended the scope of advertising control to medical devices and in vitro diagnostic medical devices as well as objects, devices, and methods. The advertisement must present the MD/IVDMD in an objective manner, particularly in terms of performance or compliance with essential safety requirements. It must also promote its correct use. In addition, advertising aimed at the general public is prohibited for reimbursable class IIb and III MDs. Prior control of advertisements applies for certain categories of medical devices presenting a high risk to human health, the list of which was defined by the ministerial decree of 24 September 2012. Advertising for other MDs/IVDMDs is controlled after dissemination; systematic submissions to ANSM are not required.

<table>
<thead>
<tr>
<th>Control of advertising for medical devices and in vitro diagnostic devices</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of applications submitted</td>
<td>1,187</td>
<td>414</td>
<td>405</td>
</tr>
<tr>
<td>Number of refused applications</td>
<td>26</td>
<td>28</td>
<td>63</td>
</tr>
</tbody>
</table>

FOCUS on heightened medical device surveillance

In 2012, ANSM launched a specific action programme for closer surveillance of some of the highest-risk medical devices, incorporating the three approaches of assessment, inspection, and laboratory control.

Six categories of implantable medical devices were selected:
- breast implants pre-filled with silicone gel
- metal-on-metal hip joint replacement implants
- total knee joint replacement implants
- defibrillation leads
- heart valves
- external defibrillators.

The criteria governing this choice were:
- a large target population
- or, conversely, a limited target population and the life-threatening or innovative nature of the medical device.

<table>
<thead>
<tr>
<th>Surveillance of medical devices considered to pose risks</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast implants</td>
<td>2,738</td>
</tr>
<tr>
<td>Metal hip joint replacement implants</td>
<td>38</td>
</tr>
<tr>
<td>Knee replacement implants</td>
<td>2</td>
</tr>
<tr>
<td>Endovascular and transapical heart valves</td>
<td>71</td>
</tr>
<tr>
<td>Defibrillation leads</td>
<td>257</td>
</tr>
</tbody>
</table>

All of the actions performed in these six medical device categories were continued in 2015. Some actions were adjusted to account for new reports. Finally, new medical device categories were targeted by heightened surveillance operations:

Pre-filled silicone gel breast implants

In addition to the May 2014 report on the assessment of silicone breast implant use (excluding PIP implants) in France between 2010 and 2013, ANSM continued to closely monitor breast implants.

Studies in 2015 focused on the link between breast implants and ALCL in the breast as well as the analysis of cases of rupture reported to ANSM through the medical device vigilance system. A temporary specialised
scientific committee of clinician experts, toxicologists, chemists, and other specialists was created for this purpose. At the end of three meetings, the experts concluded that there was a link between ALCL and the textured surface of the breast implants. Supplementary studies are currently being conducted on texture and the immunological mechanisms triggered by breast implants.

Breast implant rupture was also closely studied and listed in the medical device vigilance database.

Additional work focusing on regulations was conducted as well, especially through the review of data submitted by manufacturers in their technical documentation to demonstrate the biocompatibility of implants marketed in France.

Finally, breast implants produced by the company SILIMED were the subject of a special investigation when the device lost its CE marking in 2015. This surveillance is coordinated on a European level and continues into 2016.

All of these investigations emphasise ANSM’s dedication to strengthening the medical device vigilance system. The agency produces a periodic safety update, which it sends to manufacturers, and is in constant contact with victim service associations.

Metal-on-metal hip joint replacement implants

ANSM continued to investigate any potential toxicity associated with the release of metal particles from metal-on-metal hip joint replacement implants with the help of a multidisciplinary working group. The goal was to identify the systemic risks (effects on health) related to the release of metal particles from implants and to draft treatment guidelines for patients with metal implants. The recommendations for the follow-up of patients fitted with metal-on-metal hip joint replacement implants are liable to change based on the results of this group’s work.

Total knee joint replacement implants

The reassessment work carried out by ANSM on total knee replacement implants began with a status report on data resulting from market surveillance. An inspection campaign was also conducted, and an epidemiological study of patients with knee joint replacement implants was completed. The study report was published in 2015 following an analysis of all study data, and the inspection summary was drafted in January 2016.

Defibrillation leads

ANSM continued its work on defibrillation leads in 2015. Following a situational analysis of the French market, a status report on market surveillance data was conducted that paid special attention to medical device vigilance data. A summary report taking into account these data, as well as the conclusions of the inspection campaign, will be finalised in 2016.

Heart valves for new endovascular and transapical implantation methods

ANSM launched a surveillance programme focusing on heart valves for new endovascular and transapical implantation methods. A situational analysis has been performed, along with a status report on market surveillance data. An inspection campaign aimed at manufacturers of this type of medical device is ongoing.

External cardiac defibrillators

ANSM’s action plan for monitoring external cardiac defibrillators is based on three lines of investigation. The first is centred on vigilance and includes the implementation of a new overall method of processing medical device vigilance reports by publishing periodic six-month safety update reports (PSURs) and conducting an inspection campaign (aimed at manufacturers and distributors) that will conclude during the first quarter of 2016. The second line of investigation involves enforcing obligatory quality control among operators (feasibility study); this work is being carried out in conjunction with the French Directorate General of Health. The third line of investigation focuses on ways to improve the traceability of defibrillators designed for the general public (geolocation database and recommendations to manufacturers). These actions will continue into 2016 with the publication of a summary report of all the actions taken.
4. **Surveillance of other health products**

**Surveillance of risks associated with cosmetic products**

Since 11 July 2013, cosmetic products have been governed by (EC) regulation no. 1223/2009, which specifies the conditions under which these products can be marketed:

- under the responsibility of the manufacturer or its representative
- without prior authorisation
- on the condition that they are safe for human health when used under normal or reasonably foreseeable conditions of use and that they indicate their composition for the purposes of providing information to consumers.

Under these conditions, operators - particularly manufacturers and those responsible for marketing the products - are required to compile a dossier including, in particular, an assessment of the finished product's safety for human health, taking into account the toxicological profile of the substances used in their composition and their level of exposure. This dossier must be permanently accessible to the authorities, ANSM and the French Department for Fair Trade, Consumer Affairs and Fraud Control (DGCCRF in French).

Regulations also stipulate the drafting of lists of substances either prohibited or authorised under certain conditions, defined with a view to guaranteeing the safety of use of cosmetic products and protecting consumer health. These lists are regularly reviewed by the European authorities in the presence of national agencies. They then become enforceable in all European Union countries. Since December 2010, new rules have been in force relative to substances classed as carcinogenic, mutagenic, or toxic for reproduction and liable to be used in the composition of cosmetic substances. The general principle is a ban on their use without any European regulatory adaptation measures. However, exemptions are possible on the basis of defined criteria depending on the substance’s classification.

Cosmetic product surveillance is carried out by both ANSM and the DGCCRF, which pool their activities in the field of inspection and laboratory control. In addition, ANSM performs assessments on the toxicity of substances used in the composition of cosmetic products and on the potential adverse effects that may occur following the use of cosmetic products in the context of the cosmetic products vigilance system. The agency drafts recommendations and may implement health policy measures in the event of any danger to human health. It also carries out assessment studies destined for use by European authorities in order to update European regulations.

**Cosmetic product vigilance**

ANSM is responsible for monitoring adverse effects occurring with the use of cosmetic products and takes measures to better control the use of these products and the substances included in their composition.

The cosmetic product vigilance system, introduced by the law of 9 August 2004 regarding public health policy, is based on notification by health professionals, manufacturers, or users of adverse effects related to the use of a cosmetic product; the collection, recording, assessment, and analysis of these incidents by ANSM; and the implementation of any corrective measures.

Since 11 July 2013, the date on which European regulation 1223/2009/EC relative to cosmetic products came into force requiring the reporting and transmission of serious adverse effects, ANSM has also served as a liaison between the competent European authorities, manufacturers, and end-users concerning these effects.

In 2015, the agency handled 227 cosmetic product vigilance reports (compared to 193 in 2014 and 157 in 2013). Eighty-six of these reports involved serious cases.

**Controlling the cosmetics products market**

ANSM also conducts assessments of the toxicological profile of substances used in the composition of cosmetic products. Usually, these assessment studies lead to active cooperation with other bodies, in particular with the DGCCRF and ANSES (French Agency for Food, Environmental and Occupational Health & Safety).
Several substance families are the subject of in-depth expert assessments, in particular lead and endocrine disruptors.

**Tattooing products**

Tattooing products are colouring substances or mixtures designed to mark the surface of the human body by breaking the skin. They are examined by the Council of Europe's Committee of Experts on Cosmetic Products.

In the field of vigilance event surveillance involving tattooing products, ANSM coordinates its operations with the DGCCRF.

In 2015, ANSM continued its involvement in the European work carried out by the Council of Europe, in particular by leading the risk assessment study relative to tattooing products in collaboration with all member states. This work resulted in a published report.
5. Inspection to ensure compliance of the quality of practices and health products

By law, ANSM is responsible for ensuring the quality of the practices that culminate in the marketing of health products. To this end, the agency:

- helps define enforceable regulatory frameworks (especially best practices aimed at operators)
- manages corresponding sites (authorisations, accreditations, declarations, sanctions, etc.)
- ensures, via on-site inspections, that the enforceable regulatory provisions are implemented in the context of scheduled inspection programmes or random inspections (11% of inspections in 2015).

Inspection makes it possible to establish a degree of confidence in the quality of practices employed by the relevant parties (manufacturers, operators, importers, distributors, trial sponsors, investigators, etc.), who are primarily responsible for their practices and the quality and safety of the health products they place on the market, including the starting materials used in the composition of such products.

The inspection programme is dictated by five criteria:

- inspections required by regulations
- inspections related to the intrinsic risks associated with the activities carried out
- inspections related to the site’s history
- inspections related to reports received by ANSM
- inspections related to a theme.

In 2015, the total number of inspections totalled 630 (compared to 699 in 2014) with a random inspection rate of 11% and an inspection rate outside the European Union of 7%.

The year 2015 was marked by a confirmation in the number of health policy decisions resulting from inspection observations (20 in 2015 compared to 15 in 2014 and 12 in 2013). In addition, ANSM issued 41 injunctions, i.e. slightly more than 7% of all inspections.

Highlights

- ANSM inspection of the CATALENT FRANCE-BEINHEIM (67) pharmaceutical production facilities following a suspected malicious act (judicial inquiry ongoing). The inspection was conducted after a report concerning cross contamination risk at the site was submitted. The inspection revealed numerous problems, particularly in the management of anomalies and, more specifically, cases of cross contamination between soft capsules of different medications. On 13 November 2015, ANSM suspended the facility's operations and issued a recall for the batches of medication potentially affected by this quality defect. In order to ensure the supply of certain necessary medications, ANSM granted exemptions to allow for the manufacture or distribution of certain medicines on a case-by-case basis. These decisions were based on an analysis of the risk management measures proposed by the facility and its directors.
Inspection of the CARGILL FRANCE – LANNILIS (29) starting material manufacturing facility. The inspection of this manufacturer of texturising agents used in various health products (including medicines, cosmetic products, and medical devices) identified unacceptable manufacturing conditions that did not fulfil regulatory requirements. ANSM made an administrative policy decision that included the suspension of operations at the site and the withdrawal of its health products from the market. This incident led ANSM to conduct a wider investigation into the qualification of starting material providers in the field of medicines (finalised in 2016) to raise awareness among manufacturers about better provider management practices.

**Inspection summaries published in 2015**

- Total hip replacement implants and constituent parts (May 2015)
- Transport and storage media (May 2015).

**Facilities - authorisations and modifications - 2014 & 2015 data**

**Number of inspections - comparison of cumulated data in 2015 and the 2015 goal values**
Inspection of medicines and their starting materials

Laboratories that conduct activities contributing to the marketing of medicines in France or Europe must first be authorised by ANSM in order to operate as a pharmaceutical facility.

At the end of 2015, ANSM listed 949 pharmaceutical sites in France, including 427 manufacturers and/or importers, 291 operators, and 471 wholesale distributors (some sites having several statuses). Three hundred and thirty-three sites with the sole status of wholesale distributor are inspected on behalf of ANSM by regional health agencies, while the other sites are inspected by ANSM inspectors. ANSM also lists 750 pharmaceutical starting material manufacturing, distribution, and import sites in France.

Medicine inspection activities concern verification of manufacturing and distribution activities, as well as pharmacovigilance systems targeting operators. In 2015, ANSM performed 201 medicine-related inspections in France and abroad, i.e. 32% of the total number of inspections. ANSM inspected 186 pharmaceutical sites located in France in 2015. On the basis of these inspections and those conducted by regional health authorities, 21 sites received a letter prior to an injunction and 10 were the subject of an injunction. In addition, six pharmaceutical sites were the subject of a decision to totally or partially suspend their opening authorisations.

Pharmaceutical starting material inspection activities concern the verification of manufacturing, distribution activities, and import conditions. In 2015, ANSM performed 87 inspections in this field in France and abroad, i.e. 14% of the total number of inspections.

ANSM also helps prevent the marketing of falsified products and provides information to consumers about this issue. The year 2015 was also marked by the agency’s participation in joint initiatives with the Office central de lutte contre les atteintes à l’environnement et à la santé publique (OCLAESP—Central Office for the Prevention of Damage to the Environment and Public Health). ANSM also took part in Operation PANGEA, working alongside other investigation services in order to combat the illegal sale of medicines online.

<table>
<thead>
<tr>
<th>Inspection of starting materials</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>105</td>
<td>75</td>
<td>75</td>
<td>104</td>
<td>87</td>
</tr>
<tr>
<td>- In France</td>
<td>77</td>
<td>55</td>
<td>59</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>- Outside of France</td>
<td>28</td>
<td>20</td>
<td>16</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Administrative follow-up actions (formal notices, injunctions, health policy decisions, and non-compliance with Good Manufacturing Practice reports)</td>
<td>2</td>
<td>7</td>
<td>11</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Dossiers passed on to the judicial authorities</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection of pharmaceutical sites (operators, manufacturers, importers, and distributors)</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>321</td>
<td>276</td>
<td>204</td>
<td>245</td>
<td>201</td>
</tr>
<tr>
<td>- in France</td>
<td>236</td>
<td>244</td>
<td>188</td>
<td>227</td>
<td>186</td>
</tr>
<tr>
<td>- outside of France</td>
<td>85</td>
<td>32</td>
<td>16</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Injunctions (and formal notices for inspections prior to 1 February 2014)</td>
<td>18</td>
<td>26</td>
<td>16</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Health policy decisions/ suspensions</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dossiers passed on to the judicial authorities</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Inspection of blood products and other biological products

The preparation, import, and storage of products derived from the human body (tissue, cells, and breast milk) are strictly regulated by a set of best practices and a prior authorisation regime that all sites handling these products must follow.

These sites are inspected to ensure they correctly apply the best practices that are relevant to their operations.
For safe, effective, innovative and accessible health products

<table>
<thead>
<tr>
<th>Management of sites producing or distributing blood products and other biological products</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene/cell therapy units, tissue banks, and sites producing advanced therapy medicinal products prepared on a non-routine basis (MTI-PP in French)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authorisations and renewals</td>
<td>19</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Modifications</td>
<td>10</td>
<td>25</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Closures</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Labile blood products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authorisations and renewals</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Modifications</td>
<td>21</td>
<td>33</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>Closures</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast milk banks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dossiers processed</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

### Inspection of medical devices and *in vitro* diagnostic medical devices

Companies involved in introducing medical devices (MD) or *in vitro* diagnostic medical devices (IVD-MD) to the market must first report to ANSM. The companies are inspected to verify that they have taken the proper steps before marketing their MD or IVD-MD; the manufacturing and distribution conditions for these products and the vigilance systems put in place by these operators are likewise inspected.

ANSM conducts topical control and inspection campaigns, which most often focus on the families of medical devices carrying the highest risk (classes IIb and III) and/or those in development. In 2015, inspections targeted heart valves, dental prostheses, external automatic defibrillators, and home pregnancy tests.

ANSM performed 116 inspections in the field of medical devices and *in vitro* diagnostic medical devices, i.e. 18% of the total number of inspections. Seven MD sites and seven IVD-MD sites received an injunction, and ten health policy decisions were issued to suspend or withdraw a product from the market.

In addition to its operator inspection programme, the agency also carries out specific inspections of the organisation France appointed to certify medical devices. To this end, four inspections of LNE/G-MED (medical certification body) were conducted in 2015, including one joint assessment conducted with experts from other competent European authorities as part of LNE/G-MED’s authorisation renewal. Additional joint assessments were carried out by authorised inspectors at the site of other appointed bodies in Europe. The agency also handled authorisation retractions for appointed bodies in 2015. Such retractions may be the result of findings identified through these joint assessments or through a considered decision requiring certain bodies to cease their activities.

<table>
<thead>
<tr>
<th>Inspection of manufacturers</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical devices (excluding medical device vigilance)</td>
<td>92</td>
<td>83</td>
<td>92</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>- inspections outside France</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Number of injunctions</td>
<td>14</td>
<td>21</td>
<td>22</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Number of health policy decisions</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Number of dossiers passed on to the judicial authorities</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>In vitro</em> diagnostic medical devices</td>
<td>41</td>
<td>36</td>
<td>30</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>- inspections outside France</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Number of formal notices/injunctions</td>
<td>12</td>
<td>0</td>
<td>11</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Number of health policy decisions</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Number of dossiers passed on to the judicial authorities</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Inspection of cosmetic products

There are around 3,300 companies (marketing representatives, manufacturers, distributors, etc.) involved in the field of cosmetics, including 600 manufacturers. Cosmetic product manufacturers must submit a report to ANSM.

ANSM inspects cosmetic product manufacturers and marketing representatives, in particular, in order to verify that:

- applications justify the products’ marketing (product information application)
- product manufacturing, distribution, import, and export practices comply with current regulations.

As in previous years, the yearly inspection programme for 2015 focused on verifying the application of Good Manufacturing Practices. It also included a topical campaign on products with cosmetic claims. Among the inspection’s findings, several cases of non-compliance were identified with respect to the format that cosmetic regulations require for safety assessment updates; these regulations now require stricter rules regarding the product information application’s composition.

In 2015, ANSM carried out 32 cosmetic product inspections. Nine manufacturers received an injunction requiring them to bring their product studies or manufacturing conditions into compliance.

As regards cosmetics, ANSM works in conjunction with the DGCCRF under a cooperation protocol, which was renewed on 7 January 2015, stipulating the coordination of yearly cosmetic product control programmes and, in particular, the sharing of information.

---

**Administrative management of MD and IVD-MD manufacturers**

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical devices: number of declared sites</td>
<td>3,000</td>
<td>1,500</td>
<td>1,500</td>
<td>1,500</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices: number of declared sites</td>
<td>450</td>
<td>450</td>
<td>450</td>
<td>450</td>
</tr>
</tbody>
</table>

**Inspection of medical device vigilance systems**

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>- in France</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>- outside of France (EU)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Injunctions</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dossiers passed on to the judicial authorities</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Inspection of cosmetic product sites**

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of inspections</td>
<td>55</td>
<td>48</td>
<td>26</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Number of injunctions</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Number of dossiers passed on to the judicial authorities</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
FOCUS on trial surveillance prior to marketing a health product

Inspection of preclinical trials

ANSM conducts regular inspections of testing facilities in charge of safety trials for cosmetic products and medicines for human use in order to verify their level of compliance with Good Laboratory Practices (GLPs). The OECD’s (Organisation for Economic Co-operation and Development) GLP principles are the only standard followed by all testing facilities of member countries to ensure the quality and mutual acceptance of data from non-clinical safety tests.

ANSM can conduct inspections outside of the regular programme to verify compliance with GLPs upon the request of the competent French authorities, the European Medicines Agency, or the OECD’s GLP working group.

Inspection of clinical trials

ANSM inspects the sites where clinical trials are conducted as well as certain sponsors of these trials. These inspections focus mainly on monitoring the facilities and verifying data regarding the protection of trial subjects and the quality as well as the credibility of test results.

ANSM inspections combine a programme designed to evaluate marketing authorisation requests for medicines in France with a programme created to protect individuals. The latter applies to all clinical trials (medicines, biological products, medical devices, and “non-health product” trials).

A specific component of the inspections to evaluate MA requests focuses on bioequivalence studies for generic medicines. The other inspections under this programme are carried out for French or European MAs, especially upon request of the EMA.

<table>
<thead>
<tr>
<th>Inspection of preclinical trials</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>26</td>
<td>30</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection of clinical medicine trials</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>54</td>
<td>50</td>
<td>47</td>
<td>33</td>
</tr>
<tr>
<td>- in France</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>- outside of France</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Formal notices</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dossiers passed on to the judicial authorities</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
FOCUS on inspections outside of France

ANSM is becoming more invested in countries outside of France due to the increasingly global nature of trade. Today, the majority of starting materials for pharmaceutical usage come from countries outside of the European Union. This development also concerns the harvesting of human tissues and cells from living donors or donors whose heart has stopped, the manufacture of finished products and medical devices, and the implementation of preclinical, clinical, and, in particular, clinical bioequivalence trials. To intervene where the risk(s) is/are greatest, ANSM makes choices and prioritises its international activities based on a risk analysis, in regard to a given country or product, and on the pooling of resources between countries, which is fuelled by active cooperation and mutual recognition.

This is particularly true in the domain of inspections, where ANSM’s involvement is increasingly international. In 2015, 7% of the year’s 630 inspections were conducted outside of France. These inspections guarantee the conditions for implementing clinical trials or manufacturing starting materials and finished products (medicines and medical devices) made outside of France and marketed in France. The inspections ensure that the requirement criteria stipulated by French regulations are also met. To carry out its work, ANSM relies on its own team of inspectors as well as on the skills of the European and international counterparts with whom it has concluded mutual recognition agreements in terms of inspections.

The agency also participates in the work of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), particularly as regards good manufacturing practices for medicines; good wholesale distribution practices for medicines, active substances, blood, tissue, and cells; and risk management through quality assurance. 48 national regulatory authorities participate in the PIC/S alongside observers such as the WHO, UNICEF, and EMA. The agency also takes part in a European project called VISTART (Vigilance and Inspection for Safe Transfusions, Assisted Reproduction, and Transplants) by drafting inspection rules.

FOCUS on injunctions and financial sanctions: an expansive power in health policy

The statute of 19 December 2013 and its application decree of 30 January 2014, which entered into force on 1 February 2014, introduced various administrative measures allowing the managing director of ANSM to penalise operators who violate laws and regulations applying to activities and products mentioned in article L. 5311-1 of the French Code of Public Health (CPH) through the use of:

- injunctions
- financial sanctions.

These measures are not mutually exclusive and supplement health policy decisions already prescribed by the French Code of Public Health in regard to products and facilities subject to authorisation. The penalties are intended be applied uniformly and in an appropriate and proportionate manner regardless of the activity or health product involved; they should reflect the failings and problems observed by ANSM and should not detract from the equity, effectiveness, and transparency of ANSM’s actions.

Injunctions are provided for under article L. 5312-4-3 of the French Code of Public Health.

When an ANSM inspection reveals that a law or regulation is being violated, ANSM may issue an injunction against the operator under inspection requiring the situation to be remedied within a set time frame. Before the injunction is applied, an adversarial process is conducted with the injunction recipient to identify the corrective measures that need to be taken and establish their lead-time. These injunctions are published on the ANSM website until every corrective action has been taken and the problem resolved.

Injunctions are provided for under articles L. 5312-4-1, L. 5471-1, R. 5312-2, and R. 5471-1 of the French Code of Public Health.

Within the scope of its intervention, ANSM can issue financial sanctions against operators if the provisions of the French Code of Public Health are breached. The amount of the fine depends on the operator’s turnover.
and the nature of the infraction uncovered or observed, especially during the course of inspections. An adversarial process is conducted with the operator to identify the corrective measures that need to be taken and establish the lead-time needed to resolve the situation. If the problem remains unresolved after the deadline set by ANSM, daily fines can be issued.

The amount of the financial sanction and daily fines are set by the statute and decree and are payable to the French Public Treasury.

These financial sanctions may be published on the ANSM website until they have been paid to the French Public Treasury and the situation resolved.
6. Quality control of health products in the laboratory

Laboratory control conducted by ANSM teams supplements ongoing assessments of the risk/benefit ratio and provides an independent technical and scientific expert assessment of the quality of medicines, their safety of use, and their effects (pharmacological, biological, toxic, etc.).

In this area, ANSM’s main missions are:

- to release batches of vaccines and medicines derived from blood before they are marketed (see also Releasing batches of vaccines and blood-derived medicines on page 83)
- to perform laboratory tests for all health products, within the framework of scheduled market surveillance or one-off, "emergency" requests
- to contribute to the drafting of French and European Pharmacopoeias. Pharmacopoeia is a regulatory text that publishes monographs and general chapters to define quality and purity criteria for pharmaceutical starting materials along with the analytical methods to be used to test them in the laboratory. Pharmacopoeia monographs must be taken into account in all medicine marketing authorisation applications.

Highlights

- Malaysian intern: received training for the control and release of the dengue fever vaccine
- Inspectors were trained to release vaccine and blood-derived medicine batches and provide cell/microbiological therapy
- Organised a centralised training session (16 interns from 9 countries) with the Division for Science and European Strategy as part of the activities of the French-African network in partnership with the EDQM and WHO (June 2015)
- Published a booklet on health and safety at work (September 2015)
- An audit of the ANSM Control Division took place as part of the European audit programme conducted by EDQM: a “zero fault” rating was awarded indicating the absence of any significant deviations and highlighting its highly satisfactory level of quality and management (December 2015).

Highlights

- Involvement in the control of proprietary chemical medicines authorised according to the centralised European procedure: control of 21 products, including 18 proprietary generic medicines, on behalf of the EMA. Scientific advisor for two series (pramipexole/temozolomide).
- Participation in two collaborative European studies focusing on the quality control of multi-source starting materials (pramipexole/temozolomide)
- Parallel import license (PIL): implementation of a tailored and targeted analytic methodology for the control of medicines operating under a parallel import license. Control of 19 proprietary medicines sampled by the Inspection Division.
- Breast milk banks:
  - Following resumed production at the Marmande site (freeze-dried milk) at the end of 2014, microbiology trials were conducted at the start of 2015. All of the results were compliant with current standards.
  - Caen breast milk bank: laboratory controls in conjunction with the resumption of activity at the Caen breast milk bank. The results of these controls were compliant with best practices.
For safe, effective, innovative and accessible health products

- Analysis reports - 2015

- Analysis reports - comparison of cumulated data 2014 vs. 2015

Quality control of medicines and biological products

Laboratory controls performed in the context of medicinal and biological product market surveillance take two forms:

- scheduled investigations resulting from choices based on a prior risk analysis. This analysis is conducted qualitatively and/or quantitatively on the basis of a scoring model developed by the European network of Official Medicines Control Laboratories (OMCLs). The criteria are based on the probability of the occurrence of a quality defect, the nature of the potential harmful effects, and the level of exposure for the population. The investigations concern both medicines authorised on a European level and medicines authorised in France. The samples come directly from pharmaceutical companies at the request of ANSM or are taken by ANSM inspectors at the premises of a finished product or starting material manufacturer (in France or outside of France). A large number of generic medicines are controlled, irrespective of their MA procedure. Each investigation leads to detailed reports.
controls conducted on an emergency basis following a suspected quality defect reported following inspections, referrals from judicial authorities, and reports by health professionals or users.

In 2015, the total non-conformity rate detected with chemical medicines was around 7% for controls conducted as part of the scheduled programme (mostly minor cases of non-conformity) and around 6% for controls conducted on an emergency basis. This rate reached 53% for products suspected of being falsified (mostly upon the request of judicial authorities). Every case of non-conformity is systematically monitored by way of appropriate follow-up measures.

### Laboratory control in a European context

<table>
<thead>
<tr>
<th></th>
<th>European centralised procedure medicines</th>
<th>European decentralised or mutual recognition procedure medicines</th>
<th>Controls performed by the European Directorate for the Quality of Medicines</th>
<th>Emergency controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical medicines</td>
<td>24</td>
<td>88</td>
<td>21*</td>
<td>1</td>
<td>113</td>
</tr>
<tr>
<td>(including food supplements)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three products derived from biotechnologies were tested as part of the work of BIO joint administrative committees: ATryn, Nivestim, and Synagis.

### Detection of non-compliance

<table>
<thead>
<tr>
<th></th>
<th>Scheduled controls</th>
<th>Emergency controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical medicines</td>
<td>18/267</td>
<td>2/36</td>
</tr>
<tr>
<td>(including food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supplements)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*These concern batches of products similar to growth hormones, seized by customs authorities and that do not have the status of medicines in France.

### Pharmacopoeia

<table>
<thead>
<tr>
<th>Pharmacopoeia</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monograph studies for the French Pharmacopoeia</td>
<td>123</td>
<td>114</td>
<td>73</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Monograph studies for the European Pharmacopoeia</td>
<td>224</td>
<td>126</td>
<td>181</td>
<td>528*</td>
<td>554</td>
</tr>
</tbody>
</table>

*This number includes not only monographs studied during Pharmeuropa surveys, but also the monographs that were studied before being sent to the European Commission for approval (data not included in previous years).

### Laboratory control campaigns for medical devices

Laboratory controls conducted by ANSM teams supplement ongoing assessments of the risk/benefit ratio and provide an independent technical and scientific expert assessment relating to the quality of medicines and their safety of use. These activities are conducted in close collaboration with ANSM's Product Divisions. The Control Division also helps develop alternative methods and participates in European and international collaborative studies.

### Highlights
- Following claims about surgical masks, microbiological controls were carried out on 23 samples from various origins
- Control on single-use, two-part syringes following reports from health professionals, leading to a decision to withdraw these products.
Laboratory control campaigns for cosmetic products and tattooing products

Laboratory control conducted by ANSM teams supplements ongoing assessments of the risk/benefit ratio and provides an independent technical and scientific expert assessment relating to the quality and safety of use of cosmetic products and the substances included in their composition. In this field, laboratory controls concern either targeted surveys at the request of the divisions concerned (Inspection Division and Therapeutic Medical Devices and Cosmetics Division), or suspected quality defect cases (especially following an inspection). ANSM also contributes to the development of joint studies and alternative control methods in the context of its research/development activities. Finally, it contributes to the development of references and standards relative to cosmetic products.

<table>
<thead>
<tr>
<th>Laboratory control of medical devices</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medical devices controlled</td>
<td>129</td>
<td>145</td>
<td>73</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Number of non-conformities detected</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory control of cosmetic and tattooing products</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cosmetic products controlled</td>
<td>217</td>
<td>135</td>
<td>72</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>Number of non-conformities detected</td>
<td>18</td>
<td>39</td>
<td>31</td>
<td>24</td>
<td>4</td>
</tr>
</tbody>
</table>
Part 2.

Promoting patients' rapid access to innovative developments
1. Early access to medicines, medical devices, blood products, and other biological products

ANSM exploits a variety of regulatory mechanisms to enable fair, increasingly rapid, closely monitored, and safe access to health products, particularly in the field of medicines and biological products. The law of 29 December 2011 expanded and strengthened these levers by creating Temporary Recommendations for Use (TRUs) and modifying the rules for named-patient and cohort Temporary Authorisations for Use (TAUn and TAUc), etc.

These levers support:

- innovative medicines that have not yet received a MA by encouraging: the implementation of clinical trials (CTs) in France, the development of cohort TAUs, and the continued consideration of named-patient TAUs
- treatments that could be used outside their current indications under conditions ensuring fair access and safe use via the implementation of TRUs
- sustainable access to medicines via marketing authorisations (MAs) resulting from either European Medicines Agency (EMA) centralised procedures concerning all innovative products, which the Agency actively participates in as a rapporteur or co-rapporteur, or from certain authorisations granted directly by ANSM (national MAs, mutual recognition, and decentralised MAs), as well as via the very numerous MA modifications that it examines
- batch release authorisation activities for vaccines and blood-derived medicines via the involvement of its own laboratories.

Highlights

- On 29 June 2015, ANSM hosted a meeting with clinical medicine testing professionals, academic researchers, and industry stakeholders to inform them of changes in European regulations regarding clinical trials and, especially, of the pilot phase it launched on 28 September 2015
- On 9 December 2015, ANSM organised a day-long scientific event to present the results of the sixteen projects selected as part of the call for proposals issued in 2012.

Supporting the leaders of innovative projects

In order to provide more effective guidance for innovative project leaders from the academic, hospital, and industrial sectors (start-ups, micro-companies, SMEs, incubators, competitiveness clusters, and companies accelerating technology transfer), ANSM set up an "innovation" service in 2008 to support them in the development of their health products. This service was designed to promote patients' rapid access to medical innovations by providing scientific and/or regulatory assistance to project leaders in their innovation processes. However, this service does not have any impact on decisions that ANSM may subsequently make in accordance with the procedures that all new health product applications are required to undergo.

The project leader remains in full control of the development of his/her health product. In concrete terms, this activity takes the form of:

- meetings with innovative project leaders, be they academic or industrial (start-ups, micro-companies, and SMEs)
- an annual meeting with innovative SMEs/micro-companies and academic structures operating in the health field
- the agency's participation in trade fairs, exhibitions, symposia, and debates related to health innovation
- the dissemination of information via ANSM's website
the distribution of the "ANSM innovation" newsletter (three issues in 2015).

The innovation service was consulted 92 times in 2015 and organised 19 cross-functional meetings with concerned project leaders and ANSM divisions. Numerous direct responses were also given to project leaders by telephone or email.

- **Types of projects for which the innovation service was consulted**

<table>
<thead>
<tr>
<th>Type of Project</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD/active implantable medical devices/ IVD-MD</td>
<td>41%</td>
</tr>
<tr>
<td>Innovative medicines</td>
<td>17%</td>
</tr>
<tr>
<td>Chemical medicines</td>
<td>11%</td>
</tr>
<tr>
<td>Other (non-health product, non-qualified product)</td>
<td>13%</td>
</tr>
<tr>
<td>Biological medicines</td>
<td>10%</td>
</tr>
</tbody>
</table>

*(other = products not qualified by the requesting party when the service was contacted, health products excluded)*

- **Profile of the structure that issued the request**

<table>
<thead>
<tr>
<th>Structure Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start-ups/micro business/SME</td>
<td>36</td>
</tr>
<tr>
<td>Academic laboratories</td>
<td>12</td>
</tr>
<tr>
<td>Health facilities</td>
<td>12</td>
</tr>
<tr>
<td>Large groups/consultants</td>
<td>10</td>
</tr>
<tr>
<td>Individuals</td>
<td>10</td>
</tr>
<tr>
<td>Incubators, SATT, competitiveness clusters</td>
<td>12</td>
</tr>
</tbody>
</table>

The innovation service also conducts monitoring and proactive awareness-raising activities related to the regulatory frameworks governing health product development. In 2015, the service continued to work with innovation support and technology transfer players, in particular the Aviesan Alliance and companies accelerating technology transfer. The innovation service took part in numerous conferences, seminars, and round table discussions related to innovation in health and participated in several working groups in France and Europe, particularly as part of the European network of innovation services of the various competent authorities (Germany, Austria, Spain, Finland, France, Italy, Malta, UK, Sweden, and the EMA Innovation Task Force) and the working group on emerging new technologies under the authority of the European Commission.
Access to innovation via scientific opinions

ANSM supports the development of new medicines by formulating national and European scientific opinions. The objective of these opinions is to aid and support the development of new health products based on the specific characteristics of the product and the most recent knowledge in terms of diseases, target populations, and existing treatments.

In 2015, the agency issued 8 national opinions and 66 European opinions.

- The national opinions included 3 related to oncology, 2 related to neurology (including 1 that focused on Alzheimer’s), 2 related to infectious disease, and 1 related to a rare metabolic disease and paediatric indications. Among the European opinions issued, 14 concerned rare diseases, 13 concerned paediatric use, and 38 related to the field of onco-haematology.

<table>
<thead>
<tr>
<th>National scientific opinions issued for medicines</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>National opinions</td>
<td>27</td>
<td>35</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>European scientific opinions issued for medicines</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>European opinions issued by the EMA</td>
<td>433</td>
<td>420</td>
<td>473</td>
<td>551</td>
<td>510</td>
</tr>
<tr>
<td>French opinions</td>
<td>68</td>
<td>54</td>
<td>69</td>
<td>71</td>
<td>66</td>
</tr>
</tbody>
</table>

Access to innovation via clinical trials

ANSM is the authority that authorises clinical trials in France. Irrespective of the health product in question, ANSM’s evaluation of clinical trial authorisation applications covers the safety and quality of the products used during the clinical trial as well as the safety of the individuals taking part in these studies.

ANSM inspects some clinical trial sites. These inspections mainly concern trial implementation practices, including the protection of participating patients and the verification of the reliability of data produced by these trials.

A third of the sponsors are academic and two-thirds are industrial. This distribution has remained stable for the past five years.

Highlights

- ANSM supported the transplantation of faecal microbiota and the monitoring of this practice through clinical trials (July 2015).

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5 It should be noted that a medicine can fall into several categories simultaneously, such as unmet needs and paediatric needs.
Number of authorised clinical trials - total of all health products

Cumulated number of authorised clinical trials - 2015 vs. 2014

Clinical medicine trials

<table>
<thead>
<tr>
<th>Authorisation of clinical medicine trials</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of authorisations granted</td>
<td>704</td>
<td>705</td>
<td>899</td>
<td>821</td>
<td>928</td>
</tr>
</tbody>
</table>

Breakdown of authorised clinical trials by therapeutic field

<table>
<thead>
<tr>
<th>Medicines in oncology, haematology, immunology, and nephrology</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>379</td>
<td>345</td>
<td>426</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicines in cardiology, endocrinology, gynaecology, and urology</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>110</td>
<td>85</td>
<td>224</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicines in neurology, psychiatry, pain management, rheumatology, pulmonology, ENT, ophthalmology, and narcotics</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>262</td>
<td>217</td>
<td>542</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-infectives and medicines in hepatogastroenterology, dermatology, and rare disease treatment</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125</td>
<td>149</td>
<td>229</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccines and biological products</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24</td>
<td>25</td>
<td>68</td>
</tr>
</tbody>
</table>

Inspection of clinical medicine trials

<table>
<thead>
<tr>
<th>Inspection of clinical medicine trials</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>48</td>
<td>54</td>
<td>50</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td>- in France</td>
<td>32</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>- outside of France</td>
<td>16</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Formal notices</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dossiers passed on to the judicial authorities</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
On a European level, ANSM is closely involved in the Voluntary Harmonisation Procedure (VHP), a procedure that enables joint evaluation of clinical trial authorisation applications by all member states. The objective is to harmonise and facilitate biomedical research in Europe.

<table>
<thead>
<tr>
<th>Clinical trials authorised by the European procedure called the Voluntary Harmonisation Procedure</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dossiers with French involvement out of the total number of dossiers received</td>
<td>66/83</td>
<td>91/116</td>
<td>112/143</td>
<td>114/159</td>
<td>92/134</td>
</tr>
<tr>
<td>Number of French reference dossiers out of the total number of dossiers with French involvement</td>
<td>7/66</td>
<td>10/91</td>
<td>5/112</td>
<td>3/114</td>
<td>6/92</td>
</tr>
</tbody>
</table>

Clinical trials in the specific field of "non-health products"

Since June 2008, the agency has had jurisdiction over biomedical research that does not involve health products. These clinical trials mainly concern biomedical research carried out in the fields of physiology, pathophysiology, epidemiology, genetics, nutrition, behavioural sciences, and preventive or diagnostic treatment strategies.

Almost half of these trials concern the areas of neurology, psychiatry, pain management, rheumatology, pulmonology, ENT, ophthalmology, and narcotics. 90% of the sponsors are academics.

<table>
<thead>
<tr>
<th>Clinical trials for &quot;non-health&quot; products</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of authorised clinical trials</td>
<td>641</td>
<td>640</td>
<td>724</td>
<td>690</td>
<td>653</td>
</tr>
</tbody>
</table>

Clinical trials in the field of biological products

As with all health products, clinical trials on biological products (blood products, organs, tissues, multi-tissue transplants, cell therapy, gene therapy) are subject to explicit authorisation by ANSM. Research in this area is particularly promising in terms of its numerous future applications: gene therapy, cell therapy, and organ or multi-tissue transplants are developing fields that are being driven by highly innovative medical and surgical advances. ANSM therefore provides support to "surgical first" projects before authorising them in the context of biomedical research studies. The indications concerned by gene or cell therapy clinical trials are primarily in the fields of onco-haematology and cell engineering.

In 2015, 28 trials were authorised, including 15 in the field of cell therapy, 9 for gene therapy, 3 for tissues, and 1 for labile blood products.

Clinical trials for medical devices

Clinical trials on medical devices (MDs) and in vitro diagnostic medical devices (IVD-MDs) are primarily subject to authorisation by ANSM when they concern medical devices that do not yet have the CE marking or medical devices that already have this marking but are employed for off-label use. They may also concern clinical trials that require investigations involving a significant risk.

ANSM inspects some operators involved in clinical trials in order to control the activities of a trial or trial system, irrespective of the site inspected, either at the sponsor's premises or at study centres.

In 2015, ANSM granted 236 authorisations, including 9 for IVD-MDs. 35% are industrial sponsors and 65% are institutional sponsors. Three applications were declined.

<table>
<thead>
<tr>
<th>MD and IVD-MD clinical trial authorisations</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of authorisations granted</td>
<td>306</td>
<td>296</td>
<td>301</td>
<td>276</td>
<td>236</td>
</tr>
</tbody>
</table>
Breakdown of clinical trials for medical devices by therapeutic field

FOCUS on software and mobile applications

Health software, mobile applications, and connected objects refer to a large range of products, some of which are within ANSM's purview, especially those classified as medical devices.

The rapid changes within the e-health sector and the increasing number of initiatives from public powers in this field have led to a jump in the number of requests to ANSM. The agency's activities in this field address four main themes:

- the increase in European and international regulations
- participation in national e-health coordination projects
- management of vigilance reports concerning medical device software, medical biology laboratory management software, prescription assistance software, and delivery assistance software
- product qualification.
FOCUS on the launch of a pilot phase in anticipation of the new European regulation on clinical trials

A European regulation concerning clinical trials for medicines for human use was published in the Official Journal of the European Union on 27 May 2014. It will come into force as soon as the single European portal is open and will apply to all parties involved in clinical trials.

This new regulation is intended to:

- enhance the innovation capacity and appeal of Europe as regards biomedical research
- facilitate patient access to innovative treatments in Europe while simultaneously guaranteeing their safety
- enhance transparency and access to the data produced by clinical trials, from their authorisation to the publication of their results.

It provides for:

- the implementation of a rapid, centralised, and coordinated review of applications for clinical trial authorisation, as well as their modifications, whenever the trial is conducted in at least one European Union member state. This regulation introduces a single submission process for authorisation applications made by the clinical trial sponsor on a European portal that will group together all of the information and data relating to this trial and be partially accessible to the public.
- a two-part scientific and ethical examination completed within a set period of time:
  - part I: a coordinated review between the member states concerned, leading to a single conclusion
  - part II: a review by each member state concerned, leading to a national conclusion
- the principle of tacit authorisation.

Application of this regulation demands new working methods for the competent authorities and member state Ethics Committees. To prepare for the new regulation, ANSM implemented a "pilot phase" on 28 September 2015 in liaison with representatives of relevant stakeholders (academic and industrial sponsors as well as committees for the protection of individuals).

France was the first European country to launch a pilot phase in 2015. Six months out, a preliminary assessment shows that progress has been made by all stakeholders and that the entire community is working hard to increase the appeal of the biomedical research industry in Europe. During the pilot phase, out of the 51 clinical trial authorisation requests submitted to ANSM, 26 were closed in March and 21 received authorisation from the agency and a favourable opinion from the relevant comities for the protection of individuals.

As of 31 December 2015, 17 applications had been received.

<table>
<thead>
<tr>
<th>Breakdown of received clinical trials by therapeutic field</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines in oncology, haematology, immunology, and nephrology</td>
<td>8</td>
</tr>
<tr>
<td>Medicines in cardiology, endocrinology, gynaecology, and urology</td>
<td>1</td>
</tr>
<tr>
<td>Medicines in neurology, psychiatry, pain management, rheumatology, pulmonology, ENT, ophthalmology, and narcotics</td>
<td>6</td>
</tr>
<tr>
<td>Anti-infectives and medicines in hepatogastroenterology, dermatology, and rare disease treatment</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>

Among these 17 applications:

- 9 were submitted by academic sponsors and eight were submitted by industrial sponsors
- 3 were phase I trials; three were phase I/II trials; six were phase II trials; one was a phase III trial; one was a phase III/IV trial; and three were phase IV studies.
Access to innovation via Temporary Authorisations for Use (TAUs)

A Temporary Authorisation for Use is an exceptional, special procedure, which, since 1994, has given numerous patients, for whom there is no available alternative treatment, access to medicines that do not have a MA in France. They may be named-patient Temporary Authorisations for Use (TAUn), i.e. granted for a specific named patient, or concern a group of patients (cohort Temporary Authorisation for Use, TAUc).

Since 2012, ANSM has been developing a new policy aimed at expanding the use of cohort TAUs in order to foster fair, closely monitored access to innovative treatments for patients whose treatment options have been exhausted.

In 2015, 22 proprietary medicines were authorised as part of these efforts, including 13 proprietary medicines in the field of haematology and oncology.

The number of patients covered by cohort TAUs rose to 10,216.

<table>
<thead>
<tr>
<th>Summary of cohort TAUs</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granted</td>
<td>7</td>
<td>15</td>
<td>9</td>
<td>33*</td>
<td>22</td>
</tr>
<tr>
<td>Number of medicines under cohort TAUs that have received a MA</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td>26*</td>
<td>25</td>
</tr>
</tbody>
</table>

*number of proprietary medicines

<table>
<thead>
<tr>
<th>Number of patients included</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort TAU</td>
<td>21,238*</td>
<td>6,136</td>
<td>12,111</td>
<td>10,216</td>
</tr>
</tbody>
</table>

*The number of patients included in 2012 is very high and is due to the cohort TAU for APROKAM, a product indicated for antibiotic prophylaxis of postoperative endophthalmitis following cataract surgery; 17,000 such patients were treated in 2012.

Cohort TAU - 2015 vs. 2014 comparisons

![Cohort TAU requests comparison chart]

- Cumulative cohort TAU requests – 2015
- Cumulated number of granted cohort TAUs - 2015
- Cumulated number of granted cohort TAUs - 2014
List of pharmaceutical proprietary medicines under a cohort TAU. March 2016

<table>
<thead>
<tr>
<th>Pharmaceutical proprietary medicine</th>
<th>Active substance</th>
<th>Holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD9291 40 and 80 mg, film-coated tablet</td>
<td>AZD9291</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>BLINCYTO 38.5 micrograms, powder for solution for infusion</td>
<td>Blinatumomab</td>
<td>AMGEN SAS</td>
</tr>
<tr>
<td>End of the TAUc: 01/03/2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COBIMETINIB 20 mg, film-coated tablets</td>
<td>Cobimetinib</td>
<td>Roche SAS</td>
</tr>
<tr>
<td>End of the TAUc: 04/01/2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUSTODIOL, cardioplegic solution</td>
<td></td>
<td>Eusa Pharma (France) SAS</td>
</tr>
<tr>
<td>CYSTADROPS 0.55%, eye drops, solution</td>
<td>Cysteamine hydrochloride</td>
<td>Orphan Europe S.A.R.L</td>
</tr>
<tr>
<td>GALAFOLD 123 mg, capsule</td>
<td>Migalastat</td>
<td>Amicus Therapeutics UK Ltd</td>
</tr>
<tr>
<td>IDARUCIZUMAB 2.5 g/50 mL, solution for injection/infusion</td>
<td>Idarucizumab</td>
<td>BOEHRINGER INGELHEIM FRANCE</td>
</tr>
<tr>
<td>End of the TAUc: 20/02/2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCZ696 50 mg, 100 mg and 200 mg, film-coated tablet</td>
<td>Sacubitril/Valsartan</td>
<td>Novartis Pharma SAS</td>
</tr>
<tr>
<td>End of the TAUc: 14/03/2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIKOZAM 1 mg/ml, oral suspension</td>
<td>Clobazam</td>
<td>Laboratoire Advicenne</td>
</tr>
<tr>
<td>LUMACAFTOR/IVACAFTOR VERTEX 200 mg/125 mg, film-coated tablet</td>
<td>Lumacaftor/IVacaftor</td>
<td>Vertex Pharmaceuticals (France)</td>
</tr>
<tr>
<td>LUTATHERA 370 MBq/mL, solution for infusion</td>
<td>[177Lu]-DOTA0-Tyr3-octreotate</td>
<td>Advance Accelerator Applications SA</td>
</tr>
<tr>
<td>MYLOTARG 5 mg, lyophilisate for solution for infusion</td>
<td>Gemtuzumab ozogamicin</td>
<td>Pfizer</td>
</tr>
<tr>
<td>NEODEX 40 mg, scored tablet</td>
<td>Dexamethasone</td>
<td>Laboratoires CTRS</td>
</tr>
<tr>
<td>NOYADA 5 mg/5 ml, oral solution</td>
<td>Captopril</td>
<td>Martindale Pharmaceuticals Limited</td>
</tr>
<tr>
<td>NOYADA 25 mg/5 ml, oral solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSPALOT 50 mg, film-coated tablet and 200 mg, scored film-coated tablet</td>
<td>Sultiame</td>
<td>Inresa</td>
</tr>
<tr>
<td>PALBOCICLIB 75 mg, 100 mg and 125 mg, capsules</td>
<td>Palbociclib</td>
<td>Pfizer</td>
</tr>
<tr>
<td>SIRDALUD 4 mg, scored tablet</td>
<td>Tizanidine</td>
<td>Novartis Pharma</td>
</tr>
<tr>
<td>TMC 207 100 mg, tablets</td>
<td>Bedaquiline</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>End of the TAUc: 18/02/2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPTRAVI (selexipag) 200 µg, 400 µg, 600 µg, 800 µg, 1,000 µg, 1,200 µg, 1,400 µg, 1,600 µg, film-coated tablets TAUc granted on 21/03/2016</td>
<td>Selexipag</td>
<td>Actelion Pharmaceuticals France</td>
</tr>
<tr>
<td>WAKIX 20 mg, quarter-scored film-coated tablet</td>
<td>Pitolisant</td>
<td>Bioprojet Pharma</td>
</tr>
</tbody>
</table>
In addition, nearly 25,000 named-patient TAUs were granted in 2015, corresponding to an average of 2,000 patients treated each month.

<table>
<thead>
<tr>
<th>Summary of named-patient TAUs</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medicines made available per year</td>
<td>227</td>
<td>221</td>
<td>241</td>
<td>208</td>
<td>219</td>
</tr>
<tr>
<td>Number of TAUs granted</td>
<td>25,384</td>
<td>26,326</td>
<td>27,550</td>
<td>25,521</td>
<td>24,791</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients included</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Named-patient TAUs, including 12,713 treatment initiations</td>
<td>19,982</td>
<td>18,831</td>
<td>Including 12,175 treatment initiations</td>
</tr>
<tr>
<td>Named-patient TAUs, including 12,822 treatment initiations</td>
<td>17,829</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Access to innovation via the new Temporary Recommendations for Use (TRU) framework

The Temporary Recommendations for Use (TRU) system is based on French law no. 2011-2012 of 29 December 2011 reinforcing the safety of medicines and health products and modified by French law no. 2014-892 of 8 August 2014 relating to the amendment of the French social security budget for 2014. This law stipulates the monitoring of prescriptions of a proprietary pharmaceutical product outside its indications or conditions of use defined in the MA.

A medicine can be prescribed in a way that does not comply with its MA in the absence of a proprietary medicine with the same active ingredient, same strength, and same pharmaceutical form with a MA or TAU, provided that:

- the indication or conditions of use are covered by a Temporary Recommendation for Use issued by ANSM and that the prescriber deems it essential to use this pharmaceutical product to improve or stabilise a patient's clinical condition
- or, in the absence of a TRU, the prescriber deems it essential, given scientific data, to use this pharmaceutical product to improve or stabilise a patient's clinical condition in the absence of an appropriate alternative medication.

The objective of Temporary Recommendations for Use is to monitor off-label use of medicines outside their MAs. The TRU is granted if ANSM has enough data to assume a favourable risk/benefit ratio of the medicine for the indications or the conditions of use requested.

TRUs are issued for a three-year renewable term. They require follow-up of patients along with the collection of efficacy and safety data relevant to the medicine for indications or conditions of use that fall outside of the MA. The pharmaceutical company must therefore set up and fund surveillance of the medicine covered by the TRU and periodically submit summary reports with an analysis of the risk/benefit ratio.

TRUs are an important incentive encouraging pharmaceutical companies to set up clinical trials with the aim of extending the indications of their medicine.

Since the mechanism was created, 10 TRUs had been granted as of 31 December 2015:

- Baclofen for the treatment of alcohol addiction (March 2014)
- Roactemra for the treatment of inflammatory Castleman's disease (with elevated CRP) not associated with the HHV8 virus (April 2014)
- Remicade for Takayasu's arteritis (October 2014)
- Velcade for the treatment of non-IgM AL amyloidosis and Randall disease (March 2015)
- Thalidomide Celgene for the following indications:
  - treatment of severe aphthosis, including those of HIV-positive patients and patients with Behcet's disease, when first-line treatments have failed (local treatments and colchicine),
second-line treatment of the cutaneous forms of lupus erythematosus, including Jessner-Kanof disease, when synthetic antimalarials (hydroxychloroquine and chloroquine) have failed,

- treatment of severe acute forms of erythema nodosum leprosum (type II lepra reaction),
- treatment of patients with active Crohn’s disease and children over six with the severe form of the disease who have not responded to an appropriate and correctly administered treatment of corticosteroids, immunosuppressants, or anti-TNF agents or for whom these treatments are contraindicated or poorly tolerated (May 2015).

- Avastin for the treatment of neovascular age-related macular degeneration (AMD) (June 2015)
- Circadin for the treatment of sleep-wake disorders related to Rett syndrome, Smith-Magenis syndrome, Angelman syndrome, tuberous sclerosis, or autism spectrum disorder in children over six (July 2015)
- Verapamil for the prophylactic treatment of cluster headaches (August 2015)
- Stelara for the treatment of moderate to severe Crohn’s disease in adult patients when infliximab, adalimumab, and vedolizumab have failed or due to intolerance or contraindication of these treatments (November 2015)
- Truvada as an HIV pre-exposure prophylaxis for high-risk patients (December 2015).
2. Marketing authorisations for medicines (MAs)

Medicines authorised by ANSM

There are four medicine authorisation procedures. One is a national procedure and the other three are European procedures.

On a European level, the centralised procedure is compulsory for advanced therapy medicinal products, medicines derived from biotechnologies, innovative medicines containing a new active substance and for which the therapeutic indication is the treatment of certain diseases (AIDS, cancer, neurodegenerative disease, diabetes, auto-immune diseases, and viral diseases), as well as orphan medicines indicated in the treatment of rare diseases. For other diseases, it remains optional. This procedure may also be considered if the medicine presents a major benefit to European Union patients.

The decentralised procedure applies to medicines that are not yet authorised in the European Union and that are intended to be marketed in at least two member states. In this case, the pharmaceutical company asks one of the member states to act as the reference state. The reference state that it chooses must be a member state where authorisation of the medicine is being sought.

The mutual recognition procedure is based on the recognition of a MA that has already been granted in one of the member states of the European Union, known as the "reference state", by other member states designated by the pharmaceutical company holding the MA. For these two procedures, the competent national authorities who grant the MA are responsible for harmonising the MA appendices (summary of product characteristics, package leaflet, and labelling).

Within France, the national procedure concerns medicines authorised only in France. This is the case for generic medicines, in particular.

ANSM thus grants MAs for medicines authorised using the national procedure, as well as for medicines authorised using the European "decentralised" and "mutual recognition" procedures, since the prescribing and supply conditions for these medicines on French soil are subject to its authorisation.

In 2015, the number of MAs granted by ANSM (national procedure and European decentralised and mutual recognition procedures) dropped slightly compared to 2014 (502 vs. 573). The number of modifications has increased sharply, rising from 6,419 in 2014 to 8,507 in 2015.

Highlights

- Every month on its website, ANSM publishes feedback relative to the opinions and recommendations issued by the CHMP, the European Committee for Medicinal Products for Human Use, under the European Medicines Agency
- It also publishes feedback concerning meetings held by the CMDh, the group for Coordination of European Mutual Recognition and Decentralised Procedures, which is responsible for examining questions about marketing authorisations, pharmacovigilance, and modifications for medicines authorised via the mutual recognition or decentralised procedure
- In addition, it publishes feedback on COMP (Committee for Orphan Medicinal Products) meetings.

Medicines authorised on a European level

<table>
<thead>
<tr>
<th>Medicines authorised through the European centralised procedure</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of applications</td>
<td>99</td>
<td>95</td>
<td>90</td>
<td>74</td>
<td>93</td>
</tr>
<tr>
<td>Applications for which France is the rapporteur or co-rapporteur</td>
<td>14</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Source: EMA
Cumulated number of MAs authorised in NL Centralised procedures - 2014 vs. 2015

* data given in number of applications (NL)
One NL corresponds to one MA application submitted to ANSM. An active substance has several applications and therefore several NLs.

<table>
<thead>
<tr>
<th>Year</th>
<th>Applications managed by France</th>
<th>Applications for which France was the reference country</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>380</td>
<td>34</td>
</tr>
<tr>
<td>2012</td>
<td>316</td>
<td>36</td>
</tr>
<tr>
<td>2013</td>
<td>260</td>
<td>18</td>
</tr>
<tr>
<td>2014</td>
<td>307</td>
<td>18</td>
</tr>
<tr>
<td>2015</td>
<td>334</td>
<td>13</td>
</tr>
</tbody>
</table>

Source: EMA

Cumulated number of MAs authorised in NL Outside of centralised procedures - 2014 vs. 2015

*data given in number of applications (NL)
One NL corresponds to one MA application submitted to ANSM. An active substance has several applications and therefore several NLs.
Medicines authorised by ANSM

<table>
<thead>
<tr>
<th>Summary of MAs authorised in France</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decisions regarding MAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- granted MAs*</td>
<td>1,447*</td>
<td>1,091*</td>
<td>600*</td>
<td>576*</td>
<td>502*</td>
</tr>
<tr>
<td>- national MAs</td>
<td>550</td>
<td>464</td>
<td>340*</td>
<td>269*</td>
<td>168*</td>
</tr>
<tr>
<td>- MAs granted through the European mutual recognition procedure</td>
<td>107</td>
<td>43</td>
<td>36*</td>
<td>36*</td>
<td>334</td>
</tr>
<tr>
<td>- MAs granted through the European decentralised procedure</td>
<td>576</td>
<td>437</td>
<td>224*</td>
<td>271*</td>
<td></td>
</tr>
<tr>
<td>- generic medicines</td>
<td>1,027</td>
<td>816</td>
<td>503*</td>
<td>467*</td>
<td>339*</td>
</tr>
<tr>
<td>Modifications**</td>
<td>7,752**</td>
<td>7,756**</td>
<td>8,169**</td>
<td>6,363**</td>
<td>8,507**</td>
</tr>
</tbody>
</table>

*Data given in number of proprietary medicines - **Data given in number of decisions

MA - modifications - cumulated number of decisions - 2014 vs. 2015

- **Number of modifications - mixed - 2015
- **Number of modifications - non-generic - 2015
- **Number of modifications - generics - 2015
- **Number of modifications - 2014 - TOTAL
Access to orphan and paediatric medicines

Orphan medicines concern medicines developed to treat rare (prevalence < 5/10,000 in the European Union) and serious diseases.

The second National Plan for Rare Diseases for 2011–2014, which was extended until the end of December 2016, is a key contextual component for the stimulation, development, and marketing of orphan medicines in France. This plan is based on three priorities: to improve the quality of patient care, to develop research into rare diseases, and to boost European and international cooperation. ANSM participates in this plan by promoting early access to medicines with respect to their approval and monitoring in off-label situations.

In 2015, 15 orphan medicines were approved, i.e. 16% of medicines approved as part of the European centralised procedure.

<table>
<thead>
<tr>
<th>Orphan medicines</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAs granted to orphan medicines out of the total number of MAs granted through the centralised procedure</td>
<td>5/99</td>
<td>10/95</td>
<td>7/90</td>
<td>15/74</td>
<td>15/93</td>
</tr>
</tbody>
</table>

Orphan medicines: breakdown by therapeutic field

- 10% Digestive tract and metabolism
- 38% Antineoplastics and immune-modulating treatments
- 0% Antiparasitics and insecticides
- 6% Blood and haematopoietic organs
- 1% Cardiovascular system
- 3% Dermatological medicines
- 6% General, systemic anti-infectious medicines
- 1% Sex hormones and urogenital system medicines
- 4% Musculoskeletal medicines
- 12% Nervous system
- 7% Respiratory system
- 7% Sensory organs
- 2% Systemic hormones (excluding sex hormones)
- 3% Miscellaneous

In the area of paediatrics, France and ANSM continue to play an important role in the evaluation of paediatric investigation plan (PIP) applications; this assessment provides details on both the medicine's preclinical and clinical development as well as its formulation depending on the age of the children. PIPs can result in an authorisation for paediatric medicines in Europe (new MA requests and extensions of pre-existing MAs).

The applications are evaluated within the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). In 2015, France was a rapporteur or peer-reviewer (i.e. a co-rapporteur) for 52 PIPs (including 17 new applications). It is ranked fifth in Europe and third for its ten-year history of following European paediatric regulations. ANSM also participates in the development of general or topical recommendations in the field of paediatrics and participates in the preclinical, formulation, medical needs, extrapolation, newborn, and paediatric regulation working sub-groups.
For safe, effective, innovative and accessible health products

<table>
<thead>
<tr>
<th>Paediatric medicines</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PIP applications for which France was the rapporteur or peer reviewer</td>
<td>50</td>
<td>58</td>
<td>59</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Percentage of total number of PIPs</td>
<td>7.6%</td>
<td>7.2%</td>
<td>6.6%</td>
<td>6.4%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

**FOCUS on the European centralised procedure for medicines: a showcase for innovation** [source European Medicines Agency 2015 annual report]

- 93 medicines for human use were granted marketing authorisations in 2015, including 39 new active substances
- A third of the medicines that featured a new active substance were developed to treat cancer
- The CHMP refused 4 medicines; 5 authorisations were withdrawn as directed by the CHMP
- Nearly one out of every two authorisation requesters that received a positive opinion from the CHMP in 2015 also received a scientific opinion during the medicine's development phase. This figure rose to 85% for medicines that contained a new active substance. 50% of the medicines that received a negative opinion were given a scientific opinion.
- 92% of positive opinions issued in 2015 were the product of a consensus among the members of the CHMP.

**New medicines that received a positive opinion from the CHMP in 2015: highlights**

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Indications for use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blincyto</strong> (blinatumomab)</td>
<td>Treatment of Philadelphia chromosome-negative acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td><strong>Entresto</strong> (sacubitril/valsartan)</td>
<td>Treatment of chronic heart failure</td>
</tr>
<tr>
<td><strong>Farydak</strong> (panobinostat)</td>
<td>Treatment of multiple myeloma</td>
</tr>
<tr>
<td><strong>Gardasil 9</strong> (Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, and 58] [recombinant, adsorbed])</td>
<td>Vaccine to prevent certain diseases caused by nine types of HPV (types 6, 11, 16, 18, 31, 33, 45, 52, and 58)</td>
</tr>
<tr>
<td><strong>Hetlioz</strong> (tasimelteon)</td>
<td>Treatment of non-24-hour sleep-wake disorder in completely blind adult patients</td>
</tr>
<tr>
<td><strong>Imlygic</strong> (talimogene laherparepvec)</td>
<td>Treatment of melanoma (type of skin cancer). Imlygic is the first advanced therapy medicinal product (ATMP) derived from a genetically modified virus that infects and kills cancer cells.</td>
</tr>
<tr>
<td><strong>Intuniv</strong> (guanfacine)</td>
<td>Treatment of attention deficit hyperactivity disorder (ADHD)</td>
</tr>
<tr>
<td><strong>Jinarc</strong> (tolvaptan)</td>
<td>Treatment of autosomal dominant polycystic kidney disease (ADPKD)</td>
</tr>
<tr>
<td><strong>Kanuma</strong> (sebelipase alfa)</td>
<td>Treatment of lysosomal acid lipase deficiency</td>
</tr>
<tr>
<td><strong>Keytruda</strong> (pembrolizumab)</td>
<td>Treatment of melanoma</td>
</tr>
<tr>
<td>Name of medicine (medicine name)</td>
<td>Indications for use</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>Treatment of multiple myeloma</td>
</tr>
<tr>
<td>Lenvima (lenvatinib)</td>
<td>Treatment of thyroid cancer</td>
</tr>
<tr>
<td>Mosquix (Vaccine against Plasmodium falciparum and hepatitis B [recombinant, with adjuvant])</td>
<td>Indicated for active immunisation against malaria. Mosquix is the first malaria vaccine assessed by a regulatory agency for use outside of the EU.</td>
</tr>
<tr>
<td>Nivolumab BMS (nivolumab)</td>
<td>Cancer immunotherapy indicated for non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td>Opdivo (nivolumab)</td>
<td>Treatment of advanced melanoma (inoperable or metastatic)</td>
</tr>
<tr>
<td>Praluent (alirocumab)</td>
<td>Treatment to lower very high cholesterol blood levels in patients who cannot control their cholesterol levels despite taking an optimal dose of statins or who cannot take statins</td>
</tr>
<tr>
<td>Praxbind (idarucizumab)</td>
<td>A specific antidote for the anticoagulant Pradaxa (dabigatran etexilate) when this medicine's effects need to be reversed quickly</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>Treatment to lower very high cholesterol blood levels in patients who cannot control their cholesterol levels despite taking an optimal dose of statins or who cannot take statins. Also indicated in the treatment of homozygous familial hypercholesterolaemia.</td>
</tr>
<tr>
<td>Saxenda (liraglutide)</td>
<td>Weight control in overweight patients and obese adult patients</td>
</tr>
<tr>
<td>Stremsiq (asfotase alfa)</td>
<td>Treatment of hypophosphatasia appearing during childhood</td>
</tr>
<tr>
<td>Tagrisso (osimertinib)</td>
<td>Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with a specific mutation (T790M) of the endothelial growth factor receptor (EGFR)</td>
</tr>
<tr>
<td>Unituxin (dinutuximab)</td>
<td>Cancer immunotherapy to treat high-risk neuroblastomas</td>
</tr>
<tr>
<td>Wakix (pitolisant)</td>
<td>Treatment of narcolepsy</td>
</tr>
<tr>
<td>Zykadia (ceritinib)</td>
<td>Treatment of non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK)-positive gene rearrangement</td>
</tr>
</tbody>
</table>

O = orphan designation; A = accelerated assessment; C = conditional approval; E = exceptional circumstances
FOCUS on the summary of France's activities as a rapporteur

ANSM's activities on a European level have been stable since 2013, particularly as a rapporteur or co-rapporteur for MA applications examined through the centralised procedure. Of the 93 medicines that received a positive opinion from the CHMP, France was the rapporteur or co-rapporteur for ten applications:

- AKYNZEO (netupitant/palonosetron)
- LUMARK (Lutetium (177 Lu) chloride)
- PREGABALIN MYLAN (pregabalin)
- PREGABALIN MYLAN PHARMA (pregabalin)
- UNITUXIN (dinutuximab)
- KYPROLIS (carfilzomib)
- BLINCYTO (blinatumomab)
- GENVOYA (elvitegravir/cobicistat/entecavir/tenofovir alafenamide)
- WAKIX (pitolisant)
- ONCASPAR (pegaspargase)

FOCUS on generic medicines

A generic medicine is created using the same molecule as a medicine that has already been authorised (referred to as an "originator medicine" or a "brand name") and is now in the public domain. It has the same qualitative and quantitative active ingredient composition, the same pharmaceutical form, and must have demonstrated its bioequivalence with the reference brand name medicine, i.e. have the same bioavailability in the body.

It can differ in some respects compared to the reference product, but cannot modify the amount of active ingredient released into the body or the rate at which it is released, so that the same therapeutic efficacy is guaranteed. Differences typically concern form, appearance, or excipient composition. Excipients, which are present in all brand name and generic medicines, play a role in the absorption and stability of the medicine and determine its appearance, colour, and taste. They do not have any pharmacological activity.

ANSM evaluates generics to ensure that every patient treated receives products whose pharmaceutical quality, safety profile, and efficacy have been demonstrated and validated.

A generic medicine is governed by the same rules as the reference brand name medicine, including the same procedures for obtaining a marketing authorisation (national or European MAs) and the same requirements in terms of quality, reproducibility from one batch to another, stability of physicochemical characteristics, etc. The obligations of generic medicine manufacturers and operators in terms of pharmacovigilance, notification of adverse reactions, risk management, and information are identical to those of reference medicine operators.


The list of generic medicines is also available in ANSM's generic groups "catalogue", which is updated automatically by the marketing authorisation.

Highlight

- Launch of a national plan to promote generics piloted by the IGAS and implementation by ANSM of a set of actions to improve generic access, information, and safety of use.
MAs for generic medicines

In 2015, 430 generic pharmaceutical products were listed in the catalogue of generic medicines, representing more than 57 reference pharmaceutical products (i.e. 32 active ingredients and 81 new groups).

<table>
<thead>
<tr>
<th>Summary of authorisations for generic medicines</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAs for generic medicines</td>
<td>1,027</td>
<td>816</td>
<td>503</td>
<td>468*</td>
<td>339</td>
</tr>
<tr>
<td>Number of generic groups in the catalogue</td>
<td>1,087</td>
<td>1,139</td>
<td>1,005</td>
<td>1,044</td>
<td>1,077</td>
</tr>
</tbody>
</table>

*including one medicine approved through the centralised procedure

Generic medicines and inspection

Inspections are carried out in the field to ensure the reliability of the bioequivalence data provided by laboratories in their generic medicine MA applications. Nine inspections were conducted in 2015, all of which were outside of France. Two of these inspections were part of a MA request authorised through the European centralised procedure. In addition, some applications were followed especially closely, such as the GVK Bio request. Following a 2014 inspection of the clinical site in Hyderabad, this application led to the suspension of 700 generic medicine MAs throughout Europe. Upon request of the CHMP and following the commission’s decision under article 31 of directive 2001/83/EC of the Parliament and Council, these suspensions were gradually lifted in 2015 in every country concerned. Against this backdrop, ANSM and participating laboratories established a working group, dedicated to bioequivalence studies, within the agency. Created in 2014, the group’s goal was to draft a national action plan, which would serve as a complement to the European action plan (EMA), to improve the quality of bioequivalence studies.

Bioequivalence inspections

<table>
<thead>
<tr>
<th>Bioequivalence inspections</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of inspections</td>
<td>20</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Outside of France</td>
<td>17</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Number of sites inspected</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Number of trials inspected</td>
<td>17</td>
<td>10</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Critical deviations</td>
<td>6 trials</td>
<td>1 trial</td>
<td>15 trials</td>
<td>2 trials</td>
</tr>
</tbody>
</table>

Inspection regions

<table>
<thead>
<tr>
<th>Inspection regions</th>
<th>2012 Number of inspections</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>India</td>
<td>15</td>
<td>10</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Other countries outside of the EU</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Generic medicines and laboratory control

The purpose of laboratory control is to verify the purity of the active ingredient, the quality of the finished product, and compliance with specifications up until expiry. Since 1999, the agency has been organising annual testing of generic medicines in its laboratories. In 2007, these tests switched from an almost systematic approach to an approach founded on risk analysis, in liaison with the European Coordinated Control Programme for Generics with a European MA (mutual recognition or decentralised procedures).

This programme, based on the sharing of resources between official control laboratories and led by the European Directorate for the Quality of Medicines and Health Care (EDQM) and other European bodies (EMA,
and Heads of Medicine Agencies network), relies on sample sharing and recognition of the results obtained by national laboratories. Tests on starting materials (active ingredients) are also performed.

In 2015, the average rate of non-compliance was 8%, which was comparable to the rate for non-generic medicines (7%). All cases of non-compliance are followed up by ANSM in liaison with the pharmaceutical companies concerned.

ANSM is also involved in the European programme developed by the EMA in collaboration with EDQM concerning the control of generics with a centralised MA. In 2013, ANSM was the scientific reference for the first study on Clopidogrel. Since then, two molecules are controlled each year according to the same protocol that ANSM uses as a scientific advisor and in its product controls (Pramipexole and Temozolomide in 2015).

<table>
<thead>
<tr>
<th>Scheduled controls</th>
<th>2015 summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Batches controlled</td>
</tr>
<tr>
<td>Non-generic proprietary medicines</td>
<td>124</td>
</tr>
<tr>
<td>Generic proprietary medicines</td>
<td>122</td>
</tr>
<tr>
<td>Generic starting materials</td>
<td>74</td>
</tr>
</tbody>
</table>

**Generic groups controlled in 2015**

- Amisulpride
- Atorvastatin
- Bromazepam
- Capecitabine
- Tramadol (chlorhydrate)
- Chlormadinone
- Flecainide
- Ketoprofen
- Lamivudine/Zidovudine
- Levetiracetam
- Montelukast
- Pramipexole
- Ropinirole
- Telmisartan
- Temozolomide

**FOCUS on biosimilar medicines**

A biological medicinal product is a substance produced or derived from a living cell or organism. The production of biological medicines is complex since it is based on living cells or organisms. Due to the biological variability of these production sources, manufacturing differences, which may affect the clinical properties of the products, are inevitable.

A biosimilar medicine is similar to a "reference" biological medicine that has already obtained a marketing authorisation. Any off-patent biological medicine may be copied. This copy is called a biosimilar product. Since biosimilar products cannot be strictly identical to the reference product, they cannot be used in the same way as chemical generics.
The development of medicinal products resulting from biotechnology (biomedicines) is a product of the recent explosion in biological knowledge. These medicines are particularly sophisticated in terms of their structure, production, and mechanisms of action. These proprietary pharmaceutical products are mainly developed for the prevention and treatment of diseases, and their indications are often limited and targeted. However, they already represent a substantial and rapidly growing share of the pharmaceutical market. Their cost is much greater than that of medicines produced using chemical synthesis methods.

MA authorisation is granted on the basis of pharmacokinetic bioequivalence and data on quality, safety, and clinical efficacy. Comparison criteria are selected based on their ability to discern differences between the tested product and the reference medicine.

The marketing of biological medicines is accompanied by a monitoring system set up by the manufacturer at the request of health authorities and in accordance with recommendations tailored to each medicine. This system must include the same specific measures as for the reference biological medicine. The immunological profile of the biosimilar product must also be monitored.

Although prescribers are free to choose between the reference product and the biosimilar medicine in the absence of an identified prior treatment, ANSM advises against changing the original prescription (by replacing one proprietary medicine with another) for reasons of safety and traceability, which are not guaranteed. Nevertheless, in light of new knowledge and the constant analysis of the safety and efficacy data for biosimilar medicines in the European Union, a medicine may be substituted with a biosimilar product during treatment as long as the following conditions are met:

- a patient being treated with a biological medicine must be informed that the two biological medicines (the reference medicine and/or a biosimilar medicine) may be interchanged and must give his or her consent
- the patient must receive proper clinical monitoring during treatment
- the traceability of the products must be guaranteed.

Around twenty biosimilar proprietary medicines are authorised and/or marketed in Europe. The quality, safety, and efficacy profile was considered to be comparable to that of the reference medicines for each of these, and, as with the reference products, it was concluded that the risk/benefit ratio for these biosimilar medicines was favourable.

### Biosimilar medicines authorised in 2015 under the European centralised procedure

<table>
<thead>
<tr>
<th>Class</th>
<th>Biosimilar medicine</th>
<th>Reference medicine</th>
<th>Therapeutic area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Omnitrope</td>
<td>Genotropin</td>
<td>Pituitary dwarfism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Epoetin</td>
<td>Epoetin alfa hexal</td>
<td>Eprex</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Binocrit (epoetin alfa)</td>
<td></td>
<td>Autologous blood transfusion</td>
</tr>
<tr>
<td></td>
<td>Silapo (epoetin zeta)</td>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Retacrit (epoetin zeta)</td>
<td>Eprex</td>
<td>Chronic kidney failure</td>
</tr>
<tr>
<td></td>
<td>Abseamed (epoetin alfa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Tevagrasstim</td>
<td>Neupogen</td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Ratiograsstil</td>
<td></td>
<td>Transplant of haematopoietic stem cells</td>
</tr>
<tr>
<td></td>
<td>Biograsstil</td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Zarzio</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filgrastim Hexal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nivestim</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accolfil</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grastofil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follitropin alfa</td>
<td>Bemfola</td>
<td>GONAL-f</td>
<td>Anovulation</td>
</tr>
<tr>
<td></td>
<td>Ovaleap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Abasaglar</td>
<td>Lantus</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Benepali</td>
<td>Enbrel</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, psoriasis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remsima</td>
<td>Remicade</td>
<td>Rheumatoid arthritis, Crohn's disease, ankylosing spondylitis</td>
</tr>
<tr>
<td></td>
<td>Inflectra</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flixabi</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Releasing batches of vaccines and blood-derived medicines

Vaccines and medicines derived from human blood are sensitive biological products since their production uses starting materials of human or animal origin and a complex process that is subject to variability. While they meet the same requirements as other medicines in terms of safety of use and monitoring, their marketing conditions are reinforced via a national authority release process.

This system, which is governed by European directive 2001/83/EC, stipulates that 100% of vaccine and blood-derived medicine batches must be controlled before they are marketed. Batches released by an independent national authority in this manner may circulate freely within the European area.

This release, conducted by ANSM in its capacity as the official national control laboratory, involves controls carried out in independent laboratories relating to the identity, efficacy, and safety of vaccine and blood-derived medicine batches. An exhaustive assessment of the manufacturer’s production and control data is also performed. For each batch, the critical parameters to be controlled are defined jointly by all of the European laboratories within the European Directorate for the Quality of Medicines and Health Care in Strasbourg (EDQM- Council of Europe). This harmonisation work also enables mutual recognition between the member states and avoids the unnecessary duplication of tests.

France is the country most solicited in Europe by vaccine manufacturers for batch releases. This dominant role can be explained by European and international recognition of its expertise and the speed with which it operates. Depending on the year, it releases 35% to 40% of all vaccine doses used in Europe and around 50% of the vaccine doses used in France.

For blood-derived medicines, ANSM is extensively involved in control of the national market since the agency is responsible for releasing the products of the country’s main manufacturer (LFB).

In 2015, the Control Department released 100% of the batches of medicines derived from blood. Regarding vaccines, an important event during the year was the release of a significant quantity of the Prevenar® vaccine (500 batches). ANSM laboratories were also closely involved in managing supply shortages of vaccines containing the pertussis valency. At the end of 2015, ANSM published the first analysis reports for the release of Dengvaxia batches. This dengue fever vaccine is to be sent to Mexico. The vaccine should receive a European MA in 2017. This will allow the agency to quickly release the first batches in the French departments of the Antilles.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>December 2015 total</th>
<th>Change compared to 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certified batches</td>
<td>3,958</td>
<td>+9%</td>
</tr>
<tr>
<td>- Including vaccines</td>
<td>2,246</td>
<td>+9%</td>
</tr>
<tr>
<td>- Including blood-derived medicines and plasma pools</td>
<td>1,712</td>
<td>+8%</td>
</tr>
</tbody>
</table>
4. **Authorisation of blood products and other biological products**

Products derived from the human body cover a multitude of health products: the labile blood products used in blood transfusions; organs, tissues, and cells used for transplants; and breast milk for therapeutic use. They also include ancillary therapeutic products (ATPs) that come into contact with biological products during storage, preparation, processing, packaging, or transport prior to any therapeutic use in humans.

All of these products (with the exception of breast milk and routinely transplanted organs) are subject to authorisation by ANSM or inclusion on a list stipulated by decision of the Director General (labile blood products). Their assessment is based on the same essential benefit and risk criteria that are applied to medicines, namely therapeutic value, efficacy, safety of use, and quality.

Due to the origin of these products, the risk of viral or microbiological contamination or contamination by other infectious biological agents is monitored particularly closely. ANSM therefore assesses viral safety with respect to the transmission of conventional viruses and unconventional transmissible agents (prions). This evaluation combines three aspects:

- the quality of the initial material and the other starting materials used in product composition
- virological controls conducted during production
- the efficacy of virus elimination and inactivation processes when possible.

**Labile blood products** (LBPs) are products derived from the blood of a donor, intended for transfusion into a patient. In particular, these concern red blood cells, platelets, and plasma. These products include autologous products, destined for the donor him or herself, and homologous products, destined for a person other than the donor. ANSM is involved in evaluating labile blood products and in monitoring adverse reactions that may occur either in blood donors or in the recipients of labile blood products. It also monitors post-donation information and transfusion chain incidents (see page 32).

<table>
<thead>
<tr>
<th>Opinions delivered regarding labile blood products</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>New requests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive opinions</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Modifications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive opinions</td>
<td>11</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Update of the list and characteristics of LBPs</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Tissues are functional groups of cells and refer to elements harvested from the human body (corneas, bones, locomotor system components, valves, etc.). Tissues and cell therapy preparations are authorised by ANSM following evaluation of their indications as well as their preparation and storage processes. ANSM also authorises the import and export of stem cells and lymphocytes for transplants.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell therapy preparations</td>
<td>52</td>
<td>44</td>
<td>30</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Tissues</td>
<td>17</td>
<td>29</td>
<td>23</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

**Highlight**

- Solvent/detergent-treated therapeutic plasma: change of legal status from LBP to medicine (January 2015).
Part 3.
Consolidating ANSM's relationships with stakeholders and enhancing their involvement
1. Transparency of the decision-making process and principles governing the use of experts

ANSM’s four commissions, technical committees, and 28 working groups, which were first set up in 2013, continued their work in 2015.

These groups are consulted whenever a question is raised requiring the opinion of external experts. They issue advisory opinions, which serve as additional tools to inform and aid ANSM’s Director General in the decision-making process.

For example, when a multidisciplinary opinion complementary to that of internal experts is required, the relevant dossiers are submitted to the commissions. These generally concern dossiers that are extremely significant in terms of public health, health safety, or information for patients and health professionals.

The duties of the Commission for the Prevention of Risks related to the Use of Categories of Health Products were combined with those of the Committee for Monitoring the Risk/Benefit Ratio of Healthcare Products following an advisory commission activity report. The ANSM Board of Administration approved this reform during its session on 25 June 2015. Beginning in March 2016, ANSM will rely on the expertise of three advisory commissions. The composition and missions of these groups have been adjusted accordingly:

- Commission for initial assessment of the risk/benefit ratio of healthcare products (16 members)
- Commission for monitoring the risk/benefit ratio of healthcare products (18 members)
- Commission for narcotics and psychotropics (14 members).

Working groups are tasked with providing answers to precise questions that emerge following a prior internal assessment of dossiers.

The technical committees serve as an interface with vigilance networks operating in the field. These networks include regional pharmacovigilance centres, drug dependence evaluation and information centres, as well as haemovigilance and medical device vigilance/reagent vigilance correspondents. These expert assessment bodies issue opinions relative to studies conducted by the networks as well as dossiers handled by the agency.

Since the establishment of these advisory bodies in 2013, ANSM has worked to introduce stricter standards in terms of member neutrality and independence in order to limit and manage conflicts of interest. The agency therefore introduced incompatibility criteria that were taken into consideration when selecting experts and that apply throughout the duration of their mandate. In addition, any potential interests that may exist are analysed on the basis of each meeting’s agenda. Public declarations of interest for all external experts, participating in the various bodies, as well as for 600 of the agency’s employees, are available for consultation on ANSM’s website.

Commission sessions were recorded and filmed in their entirety, and the full agendas and reports, as well as video extracts, are also published on the agency’s website.

More than 32 hours of filmed debates from the 12 commission sessions held in 2015 are available on the site: i.e. a total of 41 videos on 32 different topics.

In addition, the agendas and reports of technical committees, working groups, and interface committees are regularly published online.

In 2014, a few changes, which mainly concerned the working groups, were made to the list of bodies initially created in 2012 so that they adapted to ANSM’s needs. At the end of 2015, there were a total of four advisory commissions, four technical committees, five pharmacopoeia committees, 28 working groups, five interface committees, and nine temporary specialised scientific committees.

Finally, ANSM occasionally calls on the services of external experts if a question requires additional expertise. In this event, the experts consulted are appointed by the Director General, and the appointment decisions are published on the agency’s website.
2. The advisory bodies and preparations for their renewal

The work of the four Advisory Commissions

<table>
<thead>
<tr>
<th>Commission</th>
<th>Chairman</th>
<th>Vice-Chairman</th>
<th>Date of appointment</th>
<th>Number of meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commission for initial assessment of the risk/benefit ratio of healthcare products</td>
<td>W. Rozenbaum</td>
<td>M. Biour</td>
<td>26 March 2013</td>
<td>8</td>
</tr>
<tr>
<td>Commission for monitoring the risk/benefit ratio of healthcare products</td>
<td>P. Ambrosi</td>
<td>L. De Calan</td>
<td>19 March 2013</td>
<td>3</td>
</tr>
<tr>
<td>Commission for narcotics and psychotropics</td>
<td>M. Mallaret</td>
<td>N. Authier</td>
<td>21 March 2013</td>
<td>4</td>
</tr>
<tr>
<td>Commission for the prevention of risks related to the use of categories of products</td>
<td>J. Ancellin</td>
<td>D. Cugy</td>
<td>25 April 2013</td>
<td>3</td>
</tr>
</tbody>
</table>

The Initial Assessment Commission issued opinions on the following in 2015:

- 18 cohort Temporary Authorisations for Use
- 8 Temporary Authorisations for Use.

Major events that took place in 2015 include the issuing of TRUs for Avastin® (bevacizumab) for the treatment of exudative age-related macular degeneration (AMD) and Truvada® (emtricitabine/tenofovir disoproxil fumarate) as an HIV pre-exposure prophylaxis for patients presenting a high risk of acquiring HIV through sexual transmission; the latter product is used as an additional tool within a diversified prevention strategy. In addition, the commission was systematically informed of dossiers examined during sessions held by the European Committee for Medicines for Human Use (CHMP).

The Commission for Monitoring the Risk/Benefit Ratio of Health Products issued 24 opinions relating to 18 dossiers in 2015:

- 12 dossiers concerning reassessment/revaluation of the risk/benefit ratio
- 10 opinions issued regarding the risk/benefit ratio of medicines
- 3 opinions regarding medicine reassessment requests
- 10 opinions regarding modifications to marketing authorisations (modifications to the summary of product characteristics)
- 1 opinion regarding modifications to prescribing and dispensing conditions
- 4 market suspension dossiers.

In addition, the commission was systematically informed of the latest developments as well as of the dossiers examined during the sessions of the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC).

The commission for narcotics and psychotropics issued 17 opinions on 12 dossiers presented in 2015, the majority of which concerned measures designed to promote proper use, reduce the misuse and abuse of psychotropic medicines, and prevent or reduce risks or manage the consequences of the use of non-medicinal psychoactive substances.

Some of the noteworthy dossiers discussed during the commission’s sessions include:

- creation of a naloxone distribution programme in France to reduce the risk of fatal opiate overdoses among drug users and the procedures surrounding its provision
- assessment of the risks of misuse and abuse of cough suppressants and antihistamines (“purple drank”) among adolescents and young adults
• assessment of the potential for abuse and dependence and the therapeutic potential of cannabidiol (CBD) as well as the assessment of risks linked to the use of electronic cigarettes containing hemp-derived CBD.

The Commission for the Prevention of Risks related to the Use of Categories of Health Products issued two opinions in 2015. The first opinion concerns an informational document for the general public about the risks of refractive laser surgery, while the second focuses on medical devices, used in neonatology and paediatrics that have been sterilised with ethylene oxide.

Technical interface committees working with vigilance networks

The agency is supported in its work by vigilance networks that play a crucial health product surveillance role on a regional level. Four technical committees were created in 2013 with a six-year mandate.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Date created</th>
<th>Number of meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Committee for Pharmacovigilance</td>
<td>15 March 2013</td>
<td>11</td>
</tr>
<tr>
<td>Technical Committee for Drug Dependence Evaluation and Information Centres (CEIPs)</td>
<td>27 March 2013</td>
<td>5</td>
</tr>
<tr>
<td>Technical Committee for Haemovigilance</td>
<td>21 May 2013</td>
<td>5</td>
</tr>
<tr>
<td>Technical Committee for Medical Device Vigilance and Reagent Vigilance</td>
<td>1 August 2013</td>
<td>3</td>
</tr>
</tbody>
</table>

The committees’ agendas and meeting reports are published on the agency's website.

Twenty-eight working groups in 2015

Working groups are expert assessment bodies composed of, at most, twenty or so external experts from the field(s) concerned. They may be specific to certain diseases or cross-functional and are tasked with providing answers to precise questions raised following the prior internal assessment of dossiers. They were created in February 2013 with a three-year mandate.

The Board of Administration meeting of 11 December 2014 included a discussion about updating the list of working groups. The board decided to cancel certain groups that never met and readjust the scope of other groups to better meet ANSM’s needs. At the end of 2014, there were 28 working groups: nine groups were focused on pathologies (compared to 13 previously) and 19 groups were cross-disciplinary in nature (down from 23).

There were a few changes in 2015, following a call for applicants at the end of 2014, that led to the recruitment of additional experts.

A call for applicants was issued on 3 November 2015 to renew working groups whose mandate ended in February of 2016.
List of working groups in 2015

<table>
<thead>
<tr>
<th>Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>WG for medicines used in oncology and haematology</td>
</tr>
<tr>
<td>WG for medicines used in diagnostics and nuclear medicine</td>
</tr>
<tr>
<td>WG for medicines targeting the cardiovascular system and medicines indicated in thrombosis</td>
</tr>
<tr>
<td>WG for medicines used in diabetology, endocrinology, urology, and gynaecology</td>
</tr>
<tr>
<td>WG for medicines used in neurology, psychiatry, and anaesthesia</td>
</tr>
<tr>
<td>WG for medicines used in infectious diseases</td>
</tr>
<tr>
<td>WG for vaccines</td>
</tr>
<tr>
<td>WG for medicines used in hepatogastroenterology and rare metabolic diseases</td>
</tr>
<tr>
<td>WG for medicines used in dermatology</td>
</tr>
<tr>
<td>WG for conditions involving the prescribing and dispensing of medicines</td>
</tr>
<tr>
<td>WG for generic medicines and the pharmaceutical quality of chemical medicines</td>
</tr>
<tr>
<td>WG for the viral safety and microbiological safety of health products</td>
</tr>
<tr>
<td>WG for herbal medicines and homeopathic medicines</td>
</tr>
<tr>
<td>WG for advanced therapies</td>
</tr>
<tr>
<td>WG for prescription-optional medicines</td>
</tr>
<tr>
<td>WG for medicine interactions</td>
</tr>
<tr>
<td>WG for reproduction, lactation, and pregnancy</td>
</tr>
<tr>
<td>WG for medication errors</td>
</tr>
<tr>
<td>WG for paediatrics</td>
</tr>
<tr>
<td>WG for epidemiological studies on health products</td>
</tr>
<tr>
<td>WG for non-clinical safety</td>
</tr>
<tr>
<td>WG for diagnostic medical devices and technical platforms</td>
</tr>
<tr>
<td>WG for gases intended for medical use</td>
</tr>
<tr>
<td>WG for biomedical research</td>
</tr>
<tr>
<td>WG for cosmetic products, biocidal substances and products, and tattooing products</td>
</tr>
<tr>
<td>WG for the toxicovigilance of medicines</td>
</tr>
<tr>
<td>WG for labile blood products and blood donors</td>
</tr>
<tr>
<td>WG for labile blood product recipients</td>
</tr>
</tbody>
</table>

The agendas and meeting reports for the working groups are published on the agency’s website.
5 French Pharmacopoeia Committees

The Pharmacopoeia Committees participate in the preparation of monographs accurately detailing the control methods to be applied to pharmaceutical starting materials and preparations. Five committees were created on 14 August 2013; they include industry representatives.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Number of meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological products and advanced therapies</td>
<td>4</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>4</td>
</tr>
<tr>
<td>Medicinal plants and essential oils</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical preparations/pharmaceutical technology</td>
<td>2</td>
</tr>
<tr>
<td>Chemical substances</td>
<td>4</td>
</tr>
</tbody>
</table>

The agendas and meeting reports are available on the agency’s website.

14 Temporary Specialised Scientific Committees (TSSC)

These external expert groups, formed expressly to address a given issue (ad hoc), only meet a limited number of times over a determined period. These committees are formed if a permanent working group is unable to answer a question posed to it.

In 2015, 12 TSSCs met. In December 2015, 14 TSSCs were active, even if they had not all yet met.

<table>
<thead>
<tr>
<th>Temporary Specialised Scientific Committee</th>
<th>Date created</th>
<th>Number of meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation on automated labile blood product transport systems</td>
<td>16 October 2013</td>
<td>2</td>
</tr>
<tr>
<td>Transplantation of faecal microbota – Feedback</td>
<td>09 September 2014</td>
<td>1</td>
</tr>
<tr>
<td>Curares and anaphylactic reactions</td>
<td>23 July 2014</td>
<td>1</td>
</tr>
<tr>
<td>Paediatric sedation during diagnostic exams</td>
<td>23 July 2014</td>
<td>1</td>
</tr>
<tr>
<td>HPV vaccines and autoimmune diseases</td>
<td>17 June 2014</td>
<td>2</td>
</tr>
<tr>
<td>Allergens</td>
<td>23 July 2014</td>
<td>1</td>
</tr>
<tr>
<td>Electron accelerators for radiotherapy</td>
<td>17 November 2015</td>
<td>0</td>
</tr>
<tr>
<td>TRU for baclofen for the treatment of alcohol dependence</td>
<td>07 October 2015</td>
<td>1</td>
</tr>
<tr>
<td>TRU for nifedipine for the treatment of preterm labour</td>
<td>24 September 2015</td>
<td>0</td>
</tr>
<tr>
<td>Breast implants and large-cell lymphomas</td>
<td>10 March 2015</td>
<td>3</td>
</tr>
<tr>
<td>Toxicity of metal particles shed by implantable medical devices</td>
<td>05 March 2015</td>
<td>1</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices used to calculate the risk of foetal Down's syndrome</td>
<td>23 February 2015</td>
<td>2</td>
</tr>
<tr>
<td>Assessment of antibiotic treatment of urinary infections</td>
<td>04 December 2014</td>
<td>1</td>
</tr>
<tr>
<td>TRU for Truvada for pre-exposure prophylaxis</td>
<td>19 December 2014</td>
<td>3</td>
</tr>
</tbody>
</table>

The agendas from each session and meeting reports are published on the agency’s website.

A Medical Device Quality Control Committee was created on 8 July 2015 to play a role in changing and standardising quality control practices in France. The ten members of this committee were appointed for a renewable three-year period. They met once in 2015.

Preparing for the renewal of advisory bodies

Because the mandate for advisory body members lasts three years, ANSM laid the groundwork for renewing these groups, which were set up in 2012 and 2013, in 2015. On 24 September 2015, the agency issued a call for applicants to renew three advisory bodies and, on 3 November 2011, it issued a call to renew its working groups and expand its pool of experts who are consulted on an occasional basis. Applications were received until the start of December 2015.
3. Independence and impartiality: ethical obligations

Given the public health issues involved in the use of health products, the impartiality and independence of individuals participating in the work of ANSM bodies are crucial to ensuring the quality, legitimacy, and credibility of the agency's scientific assessment system, as are the plurality and free expression of viewpoints, compliance with adversarial proceedings, and the collegial nature of discussions.

The French law of 29 December 2011 reinforcing the safety of medicines and health products, in particular title 1 relative to the transparency of interests, includes important provisions relating to ethics and reinforces transparency measures concerning interests.

To meet the new requirements, the agency set up a Service of the Ethics of Expertise in April 2012. It is supported by an Ethics Committee, and both entities report to the Director General.

Continued efforts to raise awareness of ethical concerns among ANSM personnel and partners

The effective application of ethics rules remained a priority for ANSM in 2015.

- An ANSM ethics charter was drafted based on prior experience in the matter; it lists the rules and behaviours agency personnel and collaborators must follow when performing their duties. This charter was presented to the ANSM Ethics Committee on 15 December 2015 so it could be adopted and published during the first half of 2016.

- Prior risk analysis regarding ethics was continued, both in terms of internal and external expertise.
  - Concerning ANSM personnel
    As part of the agency's recruitment and nomination process, any possible connections involving candidates are systematically analysed. If necessary, measures are put in place to prevent any and all conflicts of interest. Thirty-two applications during the pre-recruitment phase and 31 applications from pharmacy residents and interns led to an ethical risk analysis in 2015.

    In addition, in the case of employees leaving the agency for the private sector, an ethical risk analysis related to the employee's new position is performed; if applicable, the agency expresses its reservations with respect to pursuing the desired position. This analysis is passed on to the Public Service Ethics Commission following referral by the agency; in 2015, the Ethics Service examined 16 cases of employees leaving ANSM, with 14 of these leading to an opinion being issued by this commission.

  - Concerning the use of external collegial expertise
    Any appointment to an ANSM collegial body (commission, working group, or TSSC) is first examined by the Ethics Service, which studies the connections reported by each member on their CV and public declaration of interests form as well as those contained in the Health Transparency Database. The service works to identify any activity that might be incompatible with the group's mandate and to determine the risks of creating conflicts of interest. As part of ANSM's efforts to renew its advisory bodies in 2016, the Ethics Service had carried out 373 ethics analyses as of 31 December 2015.

Internal control programme to verify the application of ethics rules

The Service of the Ethics of Expertise performs internal audits and controls to guarantee the application of ethics rules. In 2015, it conducted:

- four audits concerning ethics risks in the agency's various decision-making processes pertaining to: medical devices, ANSM's appointment of experts to the EMA, and the operation of the agency's advisory bodies (working groups, TSSCs, and technical committees)
For safe, effective, innovative and accessible health products

- seven compliance controls concerning public declarations of interests involving members of the Board of Administration, Scientific Council, ANSM advisory bodies, experts appointed to the EMA by ANSM, experts consulted occasionally by ANSM, and ANSM personnel (including managerial staff), for a total of 1,039 controlled declarations.

These controls focused on the following:

- declaration compliance in accordance with the requirement to have a published, up-to-date declaration of interests that is no older than one year
- the content consistency of these declarations in terms of the information made publicly available (example: Health Transparency Database [Transparence-Santé])

The Service of the Ethics of Expertise was assigned to conduct an administrative investigation. The goal of this investigation was to draw up a summary of the role played by experts, cited in the Mediapart articles from 24 and 25 March 2015, within ANSM’s advisory bodies. This assignment resulted in three reports, which were submitted to the Director General; the summary was published on the agency’s website.

Overall, in 2015, ANSM’s Service of the Ethics of Expertise performed 2,142 analyses, which can be broken down as follows:

- Number of analysis on external expertise 54%
- Number of analysis on internal expertise 41%
- Number of contributions further to institutional requests 2%
- Number of analysis further to requests from ANSM Divisions (Communication, Human Resources, IT, Science & European Strategy) 3%

Cumulated breakdown of analyses – 2015

The activities of the Ethics Committee

Created by a decision issued by the Director General on 4 May 2012 (Journal Officiel [French Official Gazette] of 1 July 2012), the Ethics Committee is an advisory body that reports to the Director General and may be consulted for any issue related to ethics.

It met twice in 2015 and examined external recruitment dossiers (2) and internal repositioning (1). It also helped draft the ethics charter that was presented in December 2015.

After three years of operation, the committee met to discuss expanding its scope of intervention to include writing general recommendations and propositions regarding measures that could prevent breaches in independence among experts. The committee also considered strengthening its own independence by opening itself up to external participants.

These changes to the Ethics Committee should come into effect during the first half of 2016.
4. Exchanging and sharing information with stakeholders

ANSM produces reference information on the safety of health products aimed at patients and health professionals and regularly circulates it via various information vectors tailored to these audiences. The agency provides industry stakeholders with the tools and information they need to work with ANSM. ANSM also responds to numerous requests for information made by the press, parliamentary representatives, and patient and health system consumer associations; these groups help keep civilian society informed.

Information for healthcare professionals

In 2015, ANSM released 110 information updates; 31 scientific reports, topical assessments or status reports; and 11 bulletins (vigilance reports, news updates, and innovation reports). The information updates that garnered the most attention were those concerning: the MA suspensions of 25 medicines marketed in France (335,500 visits), new oral anticoagulants (76,000 visits), the temporary suspension of the activity of a company that markets allergen extract products (30,000 visits), and the tightening of prescription and delivery conditions for valproate-based proprietary medicines (23,000 visits).

Reports published in 2015

ANSM’s work on various health products (pharmaco-epidemiological studies, evaluations, investigations, controls, inspections, etc.) has resulted in several reports for patients, the scientific community, and health professionals. Around twenty reports, studies, and summaries were published in 2015 concerning biocides, medicines, and medical devices.
FOCUS on reports on medicines

Antibiotics

HPV vaccines
- HPV vaccines and the risk of autoimmune disease: a pharmaco-epidemiological study - Final report (14/09/2015).

Health products and weight loss
- Assessment of the risks related to the use of medicines designed to assist weight loss - Report (07/07/2015)
- Risks related to weight loss practices that use health products - Messages for the general public (07/07/2015)
- Risks related to weight loss practices that use health products - Messages for health professionals (07/07/2015).

Isotretinoin
- Study on the observance of recommendations for pregnancy tests from the oral isotretinoin pregnancy prevention programme in France (13/05/2015)
- Study on oral isotretinoin prescriptions in France - 2007/2013 (13/05/2015).

Other
FOCUS on reports and recommendations concerning medical devices

Diagnostic tests
- Market inspection of rapid tetanus immunity diagnostic tests - Report (09/12/2015)
- Market inspection of urinary test strips used to check for urinary infections - Report (05/11/2015)

Prostheses
- Total hip replacement implants and constituent parts - Inspection summary (28/05/2015)
- Study on factors associated with total hip replacement implant revisions: method of fixation (cementing) and prosthetic components (frictional torque) in surgical revisions - Report (28/05/2015)

Patient lifts

Dental amalgams

Surgical equipment
- Tissue fusion surgical forceps: assessment of medical device vigilance reports (2011–2014) and recommendations (16/04/2015)
- Electrocoagulation systems in arthroscopy: proper use reminder to prevent the risk of skin burns (14/04/2015)

Other
- Medical devices sterilised with ethylene oxide for use in neonatology and paediatrics - Report (13/10/2015)
- Quality control of medical devices that expose people to ionising radiation - 2014 annual report (09/10/2015)
- Assessment of instruction leaflets for mammary tomosynthesis systems - Recommendations (03/04/2015)
- Clinical evaluation of medical devices as part of the CE marking process (22/01/2015)
- Investigation regarding the cellular transport and storage mediums for pathological anatomy and cytology analyses concerning cervical pathologies (HPV virus) - Inspection report (06/05/2015).

Biocides
- Review of market surveillance operations for biocide products since regulation 528/2012 came into force (07/04/2015).
Bolstering discussion with health professionals

In 2015, the agency enhanced its outreach to health professionals. This is one of ANSM’s priorities. Topic-specific consultations were held with the health professionals concerned, especially regarding sodium valproate and benzodiazepines. Regular meetings with boards during conventions and with learned societies or representative professional organisations on specific issues made it possible to take into account practices in the field to better support the agency’s actions and facilitate potential modifications to prescriptions and medicinal use.

Information for patients

ANSM produces reference information on health products aimed at patients in order to respond to the legitimate questions that they ask, given the vast amount of sometimes contradictory and alarmist information to which they are exposed. Suddenly stopping a treatment without seeking medical advice constitutes a serious risk for some patients. In 2015, ANSM focused on developing methods for providing patients with easily accessible, exhaustive, and transparent information that can be understood by all. For complex subjects, "FAQs" specifically aimed at patients are published on the website. In addition, when warranted by the situation, information updates propose recommendations for patients and health professionals.

This information is regularly discussed with patient and user representatives, especially through the Interface Committee with Patient Associations and during the annual Information and Exchange Day.

Annual Information Day with patient associations

On 12 March, 2015, the third Information and Exchange Day with patient associations was held. This event, which took place at the Cercle national des Armées in Paris, brought together over one hundred participants, including 85 association representatives. Among the topics discussed were: a review of the call for proposals that ANSM issued to associations, medicine supply shortages, the reporting of adverse effects due to medicines, the new European regulation on clinical trials, and the agency’s work in the field of paediatrics.

Interface Committee with patient associations

The Interface Committee with accredited patient or health system consumer associations involved in the health products sector was created on 5 June 2013 and has 14 members, with 7 full members representing patient or health system consumer associations and 7 full members representing the agency. 14 deputies were likewise appointed. The committee met three times in 2015 to discuss issues such as ANSM’s measures to boost the safety of certain medicines (isotretinoin, valproate, etc.), the surveillance of medical devices, clinical trials, and biosimilar medicines, etc.

A new working group was created in November 2015 dedicated to medicines used in paediatrics. It is a venue for regular discussions regarding subjects of concern with respect to medicines used to treat newborns, young children, and adolescents. It met for a second time in December 2015 and will continue its work. The agendas and meeting reports are published on ANSM’s website.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Number of Committee meetings in 2015</th>
<th>List of working groups</th>
<th>Total number of working group meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interface committee with accredited patient or health system consumer associations involved in the health products sector</td>
<td>4</td>
<td>Medicines used in paediatrics</td>
<td>2</td>
</tr>
</tbody>
</table>

In addition, ANSM divisions met with associations a dozen times in 2015 to share and listen to various points of view on specific topics.
Support for association projects

In 2015, ANSM launched its fourth competitive call for proposals aimed at patient associations. The objective of this call was to promote initiatives encouraging the proper and safe use of medicines and other health products. Of the 15 eligible projects, six were chosen as a result of the selection process; these projects covered a variety of subjects and corresponded to the agency’s main priorities, which include:

- optimising information for patients
- collecting data on the practical difficulties encountered by patients when using certain categories of health products
- facilitating the transmission of adverse effect reports by patients.

A total of €149,110 was allocated in subsidies.

Patient FAQs published in 2015 by ANSM

- Temporary suspension of the activity of the company Stallergenes - FAQs (21/12/2015)
- Oral isotretinoin - FAQs (05/11/2015)
- Safety profile for systemic quinolone antibiotics - FAQs (15/10/2015)
- Congenital malformations and neuro-developmental disorders in children whose mothers were treated with valproate and its derivatives (Depakine® and generics, Micropakine®, Depakote®, and Depamide®) during pregnancy - FAQs (26/05/2015)
- Oral anticoagulant treatment with a vitamin K antagonist (VKA) - FAQs (05/05/2015)
- Temporary Recommendation for Use (TRU) for baclofen for the treatment of alcohol dependence - Information for the general public - FAQs (20/03/2015).
FOCUS on the Public Medicine Database: users are satisfied, but the tool is not well known

www.medicaments.gouv.fr

More than a year after the Public Medicine Database was launched in October 2013, ANSM contacted Viavoice to request that a survey be conducted measuring the database’s popularity and user satisfaction.

This survey included three phases:

- an awareness survey conducted by telephone, with a sample size of 2,001 people
- a database user satisfaction survey conducted via an online questionnaire that was directly accessible from the database (531 responses submitted).
- a series of individual interviews with 20 people (health professionals and members of the general public).

The main findings of this survey:

- **Awareness of the database is still non-existent.** Out of the 2,001 people questioned over the phone, no one spontaneously mentioned the Public Medicine Database as a source for information. Upon mention of the database, 7% of respondents said they had heard of it before. Twenty-five percent of this 7% segment reported using the tool.6

- **Users are highly satisfied.** The survey shows that the users of the database, whether they are health professionals or members of the general public, are very satisfied with the tool. Eighty-five percent reported that the formatting is understandable; 82% felt that the information is easy to find; 88% said that the information is easy to understand; 83% found the information to be reliable; and 81% reported that they believed the information to be comprehensive. Eighty-five percent of respondents said that they found the information they had been looking for.

- The database is most commonly used by health professionals (58% of users), including a significant portion of pharmacists (54% of all health professionals). Health professionals are more likely to use the database on a regular basis, whereas members of the general public use it from time to time.

- Over 90% of health professionals report using the database for professional reasons outside of patient consultations. Only 15% of health professionals report using it with the patient. This figure rose to 55% for general practitioners.

The results of this survey help inform the debate, currently being held within various institutions, on subsequent database improvements; these improvements will be included in the 2016 working programme.

As of the end of December 2015, 22.7 million Public Medicine Database pages had been consulted (compared to 12 million at the end of 2014).

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6 Equivalent user decrease for all medicine databases (Vidal, Thésorimed, and Eureka Santé). However, 60% of people familiar with Doctissimo report that they use it.
FOCUS on participation in general practitioner professional congresses

The presence of ANSM at professional congresses fosters direct exchange and helps raise awareness among health professionals about the topics examined by the agency and the means used to keep them informed. In 2015, ANSM concentrated its presence on three events aimed at general practitioners, who are the main prescribers of health products.

- 16th General Medicine Resident Congress (ISNAR), 30 and 31 January 2015
- 9th French General Medicine Congress (CMGF), 26 and 28 March 2015
- 15th Congress of the National College of Teaching GPs (CNGE), 26 and 27 November 2015.

FOCUS on topical meetings for patients and users, health professionals, and industry stakeholders

ANSM organised two day-long events and a topical meeting aimed at specific audiences:

- 3rd Information and Exchange Day with Patient Associations, 12 March 2015 (see page 96)
- 2nd Information and Exchange Day with RPCs, 18 November 2015
- Informational meeting on the new European regulation concerning clinical trials on medicines, 29 June 2015.

FOCUS on Second Information and Exchange Day with Regional Pharmacovigilance Centres

On Wednesday, 18 November 2015, at the Health and Social Affairs Ministry, ANSM met with 90 representatives of the 31 Regional Pharmacovigilance Centres (RPCs) and around fifty representatives of the agency and ministry to discuss the changing relationship between ANSM and the RPCs as well as the role of the RPCs in the surveillance of medicines with respect to current reforms, including the vigilance reform and the new region map.

This day of discussion was opened by Benoît Vallet, the General Director for Health, who stressed the RPCs’ duties to not only report cases of pharmacovigilance, but also inform, train, research, and provide expert opinions. He pointed out the importance of the RPC network to the work of ANSM and the Ministry of Health. Dominique Martin, the Director General of ANSM, spoke about how surveillance is the agency’s first priority and major strategic area of focus. He pointed out that a pharmacovigilance system is not possible without the involvement of the RPC network. This network must be maintained and expanded.

Their speeches were followed by three round table discussions:

- The first provided an overall look at the relationship between ANSM and the RPCs. Two RPC representatives and two ANSM representatives shared their viewpoints using concrete examples.
- The second round table focused on the governance of the RPCs and also included two RPC and two ANSM representatives. New methods for governing the RPCs were created; these strategies included the establishment of tools and organisations that will help the network work together to better fulfil its shared missions.
- Finally, during the third round table, Benoît Vallet (Director General for Health), Christian Thuillez (Research Teaching Advisor with DGOS), Dominique de Wilde (representative from the University Teaching Hospital Conference of Directors General — Reims University Teaching Hospital), and Dominique Martin (ANSM Director General) debated the role of the RPC network in medicine surveillance.
Information for manufacturers

The ANSM website provides manufacturers with information, formulas, and procedures related to their interactions with ANSM. These resources cover authorisations and facility management, best practices, the provision of health products, product surveillance, advertising controls, etc. These documents are regularly updated to account for legislative and regulatory changes. The ANSM website also provides manufacturers with various applications, directories, and notices to applicants. An information bulletin containing news from the Co-ordination group for Mutual Recognition and Decentralised Procedures (CMDh) is distributed to manufacturers on a monthly basis. This document contains information regarding CMDh decisions and procedural changes.

Interface Committees and Manufacturer Representatives

These committees serve as a direct interface between ANSM and manufacturers and promote regular and constructive debate concerning questions of general interest in accordance with the agency’s transparency rules. They were created and composed in 2013, with equal numbers of manufacturer representatives and agency representatives.

In addition to reciprocal information-sharing, these committees have led, for example, to the proposal of measures aimed at improving the safety and availability of health products and at implementing the secure and computerised exchange of certain dossiers with industry stakeholders.

Three Interface Committees have been set up with manufacturers along with associated working groups. The results of their work are presented to the Administrative Board each year.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Number of committee meetings in 2015</th>
<th>List of working groups</th>
<th>Total number of working group meetings in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interface committee with representatives from medical industries</td>
<td>3</td>
<td>Information/communication/advertising, Early access to innovation, Surveillance, Industrial practices, Process improvement/MA modification, request process optimisation</td>
<td>12</td>
</tr>
<tr>
<td>Interface committee with representatives from the medical device and <em>in vitro</em> diagnostic medical device industries</td>
<td>2</td>
<td>Industrial practices, Vigilance, Access to innovation</td>
<td>9</td>
</tr>
<tr>
<td>Interface committee with professional organisations representing the cosmetic product industries</td>
<td>0</td>
<td>Industrial practices, Methods for interaction between professional organisations and ANSM outside the scope of inspections, Recommendations for the correct use of cosmetic products</td>
<td>3</td>
</tr>
</tbody>
</table>

The agendas and meeting reports are published on ANSM's website.
Press relations: foresight and support

In 2015, ANSM responded to an average of 95 individual requests from journalists every month, i.e. nearly 1,200 over the course of the entire year. Press requests concerned health products, the agency's activities, and its operating and decision-making methods. Childhood vaccine supply shortages, the reassuring results of the CNAMTS/ANSM study on HPV vaccines and the risk of auto-immune disease, the TRU granted for the use of Truvada as an HIV pre-exposure prophylaxis, and the TRU given to Avastin for the treatment of age-related macular degeneration were among the topics most often reported on by the media. With over 5,000 news articles and/or radio and television stories, ANSM was highly present in the media. The written press accounted for 40% of all media coverage, with the medical press playing a predominant role.

84% of press coverage concerned health products, while institutional information (ethics, expert assessments, transparency, disputes, etc.) accounted for 16%. The media coverage was factual or positive in 90% of cases.

ANSM also continued meeting regularly with the press. The agency participated in five press conferences and held four regular and informal meetings with the press to discuss current dossiers and inform listeners about ANSM's missions and activities.

Requests from citizens to access the agency's documents

Under the provisions of the code governing relations between the public and the administration, 129 administrative document requests were made to ANSM in 2015. The requested documents mostly (over 80%) concern medicines, specifically the assessment of these medicines and pharmacovigilance data. The agency responded to these requests within the one-month period stipulated by the regulation. The documents are sent after confidential information protected by law—in particular industrial or trade secrets or confidential medical information—is concealed.

Information for parliamentary representatives

Three senators and three deputies sit on ANSM's Administrative Board. The Board is responsible for setting the agency's policy directions, budget, and working programme. The agency also contributes to discussions with parliamentary representatives via the responses it provides to letters and written questions submitted to the Health Minister or directly to the agency. In 2015, the agency responded to 52 written questions and 33 letters from parliamentary representatives. The main questions submitted by parliamentary representatives related to:

- the presence of aluminium in vaccines
- the quality of generic medicines
- the review period for MA requests/clinical trials/authorisation to open a facility
- supply shortages of certain medicines and supply issues, especially with regard to the diphtheria and tetanus, polio and BCG vaccines.
5. Developing information dissemination tools

Complementary information vectors

ANSM produces a wealth of information that is published daily on its website. To ensure this information reaches its target audiences, especially health professionals, the agency uses several vectors:

- A **digital monthly letter called "ANSM Actu"** that is sent to 16,503 recipients, including health professionals, patient associations, and industry and institutional stakeholders. The newsletter outlines the agency's news highlights, European information, and new legislation and regulations relating to health products published in the past month. The readership rate is around 40% depending on the month.

- A **website circulation list**, which sends an email to subscribers every six hours, seven days a week, giving them access to the latest information published on the agency's website. Over 19,500 professionals have subscribed to the circulation list; more than a third of these are hospital and community pharmacists.

- ANSM opened its **Twitter account** in April 2014. At the end of 2015, the agency had 4,234 followers. The agency had published 275 tweets and been retweeted 1,195 times. The tweets and retweets generated 4,037 clicks on the ANSM website. This additional communication channel allows the agency to reach out to new audiences. Over 60% of subscribers are individuals, 11% are scientists and health professionals, and 4% are students.

- The **"ANSM Innovation" newsletter** and the **Vigilance Bulletin** are written for specific audiences, including researchers, pharmacovigilance professionals, manufacturers, etc.

Multiplication of information relays

In addition to its own information dissemination methods, ANSM has also set up partnerships and liaises regularly with professional bodies to ensure that information is passed on to relevant professionals; these partners and professional bodies pass on health product information to specific audiences.

Partnerships with the national boards of pharmacists, physicians and midwives; learned societies; other professional bodies; institutions; and patient and healthcare consumer associations serve as targeted information relays for the agency. In particular, ANSM's partnership with the French National Board of Pharmacists makes it possible to pass on safety messages and messages concerning essential drug shortages via pharmaceutical dossiers. Thanks to this tool, all pharmacists are kept informed in real time and can immediately implement safety measures to protect patients.
Changes to the website

ANSM’s website is constantly evolving to adapt to the agency’s missions and to new Internet user behaviours, such as accessing the site via a search engine. ANSM’s website received 2,571,708 individual visitors in 2015 (a 16% increase from 2014), and 31 million pages were read. The great majority of visitors to the site are French. However, 25% of the pages read were accessed from IP addresses in the USA, 2.7% from Germany, 2.5% from the United Kingdom, 2.4% from Russia, 2.3% from Norway, and 2% from Belgium.

The pages most often consulted concerned the latest news, public assessment reports, adverse effect reports, the generic medicine directory, batch and product withdrawals, and the Pharmacopoeia.

Impact of decisions and messages

An image survey was conducted between September and December 2015 with the Institut Viavoice to measure the expectations and perceptions of ANSM’s various target audiences.

The survey found that members of the general public report being well informed about medicines (86%) and that they trust in the agency more and more; 73% of this population reports knowing of the existence of an organisation that oversees the safety of health products.

Only 69% of health professionals report knowing about ANSM, and perceptions vary greatly depending on the type of professional; hospital pharmacists have the most positive perception and feel the most informed, which contrasts with the perceptions of private-practice general practitioners. For 71% of respondents, the level of overall confidence in the agency has increased, and the level of satisfaction regarding information provided by ANSM has remained stable (66%).

This survey, which has been conducted every two years since 2009, allows the agency to tailor its communication activities to match the expectations of each of its target audiences. ANSM also conducted impact surveys on a one-off basis regarding specific subjects to assess whether or not the agency’s measures have been properly understood and applied. The survey of pharmacists concerning valproate is one such example.
6. National integration of health and medical research professionals

Governance bodies

Administrative Board renewed

ANSM’s Administrative Board met three times in 2015 (March, June, and December). The three-year mandate of Administrative Board members ended in October 2015. New members were appointed by order in November 2015. Agnès Jeannet was appointed Acting Chair of the Administrative Board by the decree of 19 October 2015. Parliamentary representation also changed.

Members of ANSM’s Administrative Board as of 31 December 2015

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acting Chairwoman</td>
<td>JEANNET Agnès</td>
</tr>
<tr>
<td>Vice-Chairman</td>
<td>PIGEMEAU Claude</td>
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<tr>
<td>Acting Chairwoman</td>
<td>JEANNET Agnès</td>
</tr>
<tr>
<td>Vice-Chairman</td>
<td>PIGEMEAU Claude</td>
</tr>
<tr>
<td>Representatives of the State</td>
<td></td>
</tr>
<tr>
<td>Director General of Health or his representative</td>
<td>VALLET Benoit</td>
</tr>
<tr>
<td>POIRET Christian - CHOMA Catherine - WEBER Françoise - Assisted by JEAN Emmanuelle</td>
<td></td>
</tr>
<tr>
<td>Secretary General of the Ministries for Social Affairs or his representative</td>
<td>RICORDEAU Pierre</td>
</tr>
<tr>
<td>QUIOT Agnès - BETEMPS Jean-Marc</td>
<td></td>
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<tr>
<td>Director for Social Security or his representative</td>
<td>FATOME Thomas</td>
</tr>
<tr>
<td>EPIS de FLEURIAN Anne-Aurélie - CASANOVA Sophie</td>
<td></td>
</tr>
<tr>
<td>Director General for Health Services or his representative</td>
<td>DEBEAUPUIS Jean</td>
</tr>
<tr>
<td>DEBORD Thierry</td>
<td></td>
</tr>
<tr>
<td>Director General for Fair Trade, Consumer Affairs and Fraud Control or her representative</td>
<td>HOMOBOINO Nathalie</td>
</tr>
<tr>
<td>BOVE Raphaëlle</td>
<td></td>
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<tr>
<td>Director General for Enterprise or his representative</td>
<td>FAURE Pascal</td>
</tr>
<tr>
<td>LEPERCHY Benjamin – BREGENT Alain-Yves</td>
<td></td>
</tr>
<tr>
<td>Director General for Research and Innovation or his representative</td>
<td>GENET Roger</td>
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<tr>
<td>DEMOTES-MAINARD Jacques - CHAPEL Catherine</td>
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<tr>
<td>Budget Director or his representative</td>
<td>MORIN Denis</td>
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<tr>
<td>MANTZ Thimotée - DUMONT Damien</td>
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<tr>
<td>Director of the European Union, represented by the Directorate General of Globalisation, Development and Partnerships</td>
<td>DESCÔTES Anne-Marie</td>
</tr>
<tr>
<td>DAPHIN-LLORENS Catherine</td>
<td></td>
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<tr>
<td>Deputies (members of parliament)</td>
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<tr>
<td>BAPT Gérard</td>
<td></td>
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<tr>
<td>ROBINET Arnaud</td>
<td></td>
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<tr>
<td>Nomination pending</td>
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<tr>
<td>Senators</td>
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<tr>
<td>COHEN Laurence</td>
<td></td>
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<tr>
<td>BARBIER Gilbert</td>
<td></td>
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<tr>
<td>DÉRIOT Gérard</td>
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<tr>
<td>Health Insurance Representatives</td>
<td></td>
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<tr>
<td>BARRET Luc (senior member)</td>
<td></td>
</tr>
<tr>
<td>ALLA François (CNAMTS) - (deputy member)</td>
<td></td>
</tr>
<tr>
<td>FEUILLEUX Bénédicte (MSA) - (senior member)</td>
<td></td>
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<tr>
<td>MASCLAUX Alain (RSI) - (deputy member)</td>
<td></td>
</tr>
<tr>
<td>Representative of the National Board of Physicians</td>
<td></td>
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<tr>
<td>MORALI Jacques (senior member)</td>
<td></td>
</tr>
<tr>
<td>KAHN-BENSAUDEIrène (deputy member)</td>
<td></td>
</tr>
<tr>
<td>Representative of the National Board of Pharmacists</td>
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</tbody>
</table>
The 2015 Scientific Board:

The Scientific Board monitors the consistency of ANSM’s scientific strategy by taking into account evolving knowledge concerning the efficacy and safety of health products. It issues opinions on research strategies and the agency's partnership and scientific programming policy. It helps ANSM's Director General develop calls for research proposals and can also formulate recommendations concerning all scientific and technical issues falling within the scope of the agency's expertise.

The ANSM Scientific Board was created in July 2012 and renewed in 2015 for a three-year period. Annick Alpérovitch is the Chairwoman. As of 31 December 2015 (article R. 5322-18 of the French Code of Public Health), the Scientific Board includes 12 members:

- Subsequent to a call for applicants issued by the agency, 8 members proposed by ANSM’s General Director were appointed by order of the Health Minister for a renewable three-year period; these members were chosen based on their scientific expertise in the field of health products:
  - Annick Alpérovitch
  - Éric Bellissant
  - Alexis Elbaz
  - Éric Ezan
  - Carine Giovannangeli
  - Franck Lethimonnier
  - Maria-Émilia Monteiro
  - Jean-Paul Vernant

- 4 scientific experts proposed by the Research Minister were appointed by decree of the Health Minister for a renewable, three-year period, based on their expertise in health products:
  - Robert Barouki
  - Christiane Druml
  - Christine Kubiak
  - Josep Torrent-Farnell

The February 2015 audit report regarding ANSM’S organisation, written by the Inspectorate General of Social Affairs (IGAS), recommended expanding the board's membership to include medical device and pharmaco-epidemiology specialists. A call for applicants was issued in December 2015 to fill the Scientific Board's current positions.
The Scientific Board met three times in 2015, on 11 March, 24 June, and 26 November. Main topics of discussion dealt with: ANSM's involvement in the fight against the Ebola epidemic, the reform of ANSM's advisory commissions (their mission and constitution), pharmaco-epidemiology platform working programmes, and the LUCIE feasibility study presentation (national cohort of women who have or who have once had breast implants). In addition, the Scientific Board issued an opinion on studies not covered by the call for proposals; this concerned targeted topics and the direction of the 2016 call for research proposals.

**Promoting independent research to support the agency’s missions**

**Funding research projects related to the safe use of health products**

In 2015, the ANSM launched its fourth call for research proposals. Aimed at researchers from non-profit public research bodies, the goal is to provide funding, independent of industry stakeholders, for research projects that concern the safety of health products for human use.

For this fourth call for proposals, 88 applications were submitted, 76 of which were eligible. Each project was sent to at least two independent experts. This initial assessment phase involved 92 experts. Guided by a panel made up of eight scientific experts, the Director General of ANSM awarded funding to seven projects and to four projects on the supplemental list. In the end, ten projects were funded, and coordinators were notified of the funding conventions at the end of 2015 so that all projects could begin in January 2016.

At the same time, the agency followed up with selected projects from 2012 to 2014. While the general principle is to allow coordinators to conduct their studies, ANSM ensures that the studies are correctly implemented and that grant funding is properly used. The funding conventions specify the regular submission of scientific reports, budget reports, and a presentation of interim results halfway through the project's term. Around sixty projects are thus regularly monitored with the help of the Scientific Board and the cooperation of the ANSM employees involved in these research topics. On 9 December, the Scientific Board organised a topical event dedicated to presenting the interim results of the projects funded by ANSM as part of its first call for research proposals in 2012 and 2013.

The close ties between research teams that are unaffiliated with industry stakeholders and ANSM's scientific teams make it possible to forge relationships and build a valuable expertise network. They also help raise ANSM's profile among the scientific community.

Through a procedure known as “HAP,” certain necessary health studies, whose principles or methods fall outside those necessitated by the call for research proposals, may be funded independently of these calls. These independent studies focus on specific themes and address emerging concerns or public debates relating to the safety of products or categories of health products.

In 2015, ANSM thus signed a number of research subsidy conventions, including several with academic bodies (INSERM, AP-HP, university hospital centres, etc.). The call for applicants focused on six topics targeted by the agency. Out of the 48 eligible projects received, nine conventions were signed with select teams.

**Development of epidemiological research activities relating to the safe use of health products**

The development of epidemiological studies on the safety of health products, in addition to the work of vigilance systems and the active search for warning signs, provides a comprehensive view of the safety profile of health products in real-life conditions, thereby increasing the surveillance of these products. To this end, ANSM has set up an Epidemiology of Health Products Department to independently conduct epidemiological studies pertaining to the safety of health products, mostly through the use of data from the SNIIIRAM database, which ANSM has had access to since September 2013.
ANSM conducted 11 pharmaco-epidemiological studies in 2015. Reports and/or scientific articles were written on five of the eleven studies:

- Study on the risk of auto-immune disease associated with exposure to the human papillomavirus (HPV) vaccine. This study, which was carried out in collaboration with CNAMTS, was the subject of an ANSM-CNAMTS report published in September 2015.
- Study on the risk of retinal detachment related to the use of oral fluoroquinolones
- Study on the link between exposure to benzodiazepines and hip replacement prosthesis survivorship.
- Study on the risk of bleeding and arterial thromboembolism due to switching from heparin to a vitamin K antagonist in cases of uncomplicated atrial fibrillation
- Use study on oral nitrofurantoin prescriptions in France (ANSM report — February 2016).

Six of the eleven studies were not completed in 2015. Their results are expected in 2016. These studies include:

- Study on the risk of congenital malformations and mental and neuro-developmental disorders following in utero exposure to Valproate (in collaboration with CNAMTS)
- Study on the risk of pancreatic cancer associated with exposure to incretin mimetics
- Study on muscular and musculoskeletal damage associated with statins
- Study on the risk of cancer and infection associated with the use of biotherapies in patients suffering from inflammatory bowel disease (IBD) in France
- Study on the ischaemic and bleeding risk associated with dual antiplatelet therapy after coronary stenting
- Study of use and factors related to knee replacement prosthesis survivorship.

First year of the two pharmaco-epidemiology platforms’ activity

In order to maintain the independent research efforts initiated by ANSM and improve the ability to carry out studies on the usage and safety of health products under real-life conditions in France, two pharmaco-epidemiology platforms were created in 2014:

- the DRUGS SAFE platform, which is coordinated by the University of Bordeaux. INSERM U657 Bordeaux, INSERM U897 Bordeaux, and INSERM UMR912 Marseille also participate in this platform.
- the PEPS platform coordinated by Rennes University Hospital Centre and also involving the Institut de recherche en informatique et systèmes aléatoires (IRISA—Research Institute of Computer Science and Random Systems), the Laboratoire du traitement du signal et de l’image (LTSI—Signal and Image Processing Laboratory), the Ecole des hautes études en santé publique (EHESP—School for Public Health Studies), INSERM UMR1018, and the Institut de Recherche Technologique B-Com (B-Com Technological Research Institute).

During this first year of activity, the DRUGS SAFE platform began several studies on the use of psychotropic and antidiabetic medicines and the risk of accidents and injuries associated with these substances. The PEPS platform worked on designing the protocols for several studies investigating the use and risk of various medicines and medical devices (valproate, isotretinoin, high blood pressure treatments, and breast implants).
FOCUS on the study regarding the risk of auto-immune disease associated with exposure to the human papillomavirus (HPV) vaccine

This study, which was conducted as part of the convention between CNAMTS and ANSM, was set up and monitored by an independent scientific committee made up of epidemiologists and clinicians from various fields. This observational cohort study sought to evaluate the association between exposure to HPV vaccines and the occurrence of auto-immune disease. It was conducted using the French health insurance database.

The study focused on young girls enrolled in the French social security system who were 13 to 16 years old between January 2008 and December 2012. Among this group of 2.2 million people; 840,000 had received the HPV vaccine (Gardasil® or Cervarix®), and 1.4 million had not.

Analyses compared the frequency of auto-immune disease between vaccinated and unvaccinated young girls, focusing on 14 types of pathologies. These pathologies included demyelinating diseases of the central nervous system: i.e. multiple sclerosis, Guillain-Barré syndrome, lupus, scleroderma, vasculitis, rheumatoid arthritis/juvenile arthritis, Sjögren's syndrome, inflammatory bowel disease, coeliac disease, immune thrombocytopenic purpura, type I diabetes, thyroiditis, and pancreatitis.

Exposure to the HPV vaccine did not appear to be associated with the occurrence of these 14 pathologies taken as a whole, nor did it appear to be associated with 12 of these auto-immune diseases analysed separately. However, the study did find a statistically relevant association between exposure to HPV vaccines and two of the pathologies studied, i.e. inflammatory bowel disease and Guillain-Barré syndrome.

The results of several other additional analyses did not suggest that HPV vaccine exposure was related to an excessive risk of inflammatory bowel disease. However, an increase in the risk of Guillain-Barré syndrome after HPV vaccination appears likely in light of the results of various analyses that have demonstrated a strong and consistent association between the two. This adverse effect is a known risk and is listed in Gardasil's MA.

The results of this study make it possible to specify the syndrome's risk of occurrence, which, in view of the rarity of the disease, is limited; there are approximately one to two additional cases of Guillain-Barré syndrome per 100,000 young girls receiving the vaccine.

As a reminder, Guillain-Barré syndrome, or acute inflammatory polyradiculoneuritis, describes damage to the peripheral nervous system characterised by progressive weakness, or even paralysis, that most often starts in the legs and sometimes spreads upwards to the respiratory nerves or even the nerves of the head and neck. This syndrome is often preceded by an infection and has been reported in connection with other vaccines. The vast majority of patients (90% to 100% of cases in children) recover without neurological sequelae.

Overall, the results of the joint ANSM-CNAMTS study, based on a large-scale population-based cohort, were reassuring with respect to the risk of the occurrence of auto-immune disease associated with HPV vaccines. The benefits that this vaccination provides in terms of public health remain much greater than the possible risks it may present to young girls.

FOCUS on 11 scientific publications in 2015

Scientific publications of the Health Product Epidemiology Department:


Scientific publications of the Laboratory Controls Division

- Rebiere H, Ghyseinlck C, Lempereur L and Brenier C; Investigation of the composition of anabolic tablets using near infrared spectroscopy and Raman chemical imaging. Drug Testing and Analysis, June 2015

Relations with other health system operators

Partnership and conventions

ANSM develops numerous action plans in partnership with other public operators, universities, and professional bodies. These collaborative actions and exchanges are usually conducted in the context of conventions and framework agreements. On an international level, numerous collaborative projects and exchanges are organised by conventions with other medicines agencies or governments.

In 2015, ANSM signed five new conventions. These included conventions regarding collaboration and the exchange of information, for example, with the DGCCRF, INVS, or Université Paris-Est Créteil (UPEC) or with the New Caledonian DASS, in support of pharmaceutical facility inspections.

Finally, a convention for transferring the management of medicine exportation certificates for MDs and IVD-MDs was signed with the Chamber of Commerce and Industry in the Paris - Ile de France Region (CCIP Paris). Other conventions were under implementation in 2015 with public operators (ABM, ANSES, ASN, CNBAE, CNAMTS, CNOP, DGCCRF, DGDDI, EPRUS, INCa INPS, INSERM, MILDT, SOFCOT), countries (French Polynesia, FRENCH-SPEAKING AFRICA, ALGERIA, BRAZIL, CANADA, CROATIA, JAPAN, LEBANON, MEXICO, SERBIA, USA), and other bodies (WHO).

Participation in public health plans

ANSM supports public health policy by participating in various national plans and programmes led by the Ministry of Health and Social Affairs. The Directorate General for Health has been setting up a number of public health plans for several years now, the aim being to improve health prevention and safety. The agency is particularly involved in plans relating to chronic diseases, including cancer and rare diseases, and infectious risks such as HIV and antibiotic resistance. It is also involved in a wide range of other topics such as nutrition and obesity and helps with health alert preparations (heat wave plan). ANSM participates in plan steering and monitoring committees and provides its expertise in terms of health products (chemical medicines, vaccines, diagnostic tests, etc.) and the methods and conditions for their use. In total, for the year 2015, the agency took part in 12 steering or monitoring committees for various public health plans.
Participation in managing health threats

In the context of the law of 5 March 2007, ANSM helps prepare the health system for large-scale health threats, whether these are accidental, deliberate, or epidemic. This activity includes risks related to terrorism, which are the subject of an intergovernmental plan led by the French Department of Defence and National Security (SGDSN). The agency is involved in the Biotox (biological risk), Piratox (chemical risk) and Piratome (radiological risk) parts of the plan. As part of its role, the agency notably helped update the Smallpox Plan, led by the SGDSN, and participated in several working groups examining biological threats.

In addition, the agency is a member of the Scientific Board of the Network of Biotox-Piratox Laboratories (RNLBP), which brings together laboratories responsible for analysing human, animal, or environmental samples in the event of a biological or chemical threat.

The agency helped organise and implement the annual RNLBP exercise in December 2015 concerning the detection and identification of various highly pathogenic microorganisms.

Finally, as part of a tripartite agreement with the French Directorate General for Health (DGS) and EPRUS (responsible body for preparing for and responding to health emergencies), ANSM contributes its expertise in monitoring the quality of certain medicines that form part of the French government’s strategic stocks (antiviral drugs, vaccines, antibiotics, etc.) and participates in the EPRUS “Control and Operational Health Resources” Consultative Commission with respect to topics related to health emergency preparation.

Legal and regulatory activities

ANSM participates in the development of legislation and regulations on both a national and European level. In 2015, the agency helped draft 23 European texts (relative to medicines, substances contained in medical devices, cosmetic products, and biological products).

On a national level, the agency was involved in the drafting of 130 texts: 91 were published in 2015, and 39 are still being prepared in 2016.

In addition, in 2015, ANSM issued 31 health policy decisions. The great majority of these related to medical devices and in vitro diagnostic medical devices marketed in a way that violated the relevant regulations in force.

Litigation and rulings

In 2015, ANSM received 88 new requests related to its decisions. The number of cases heard by the administrative judge has decreased slightly. Forty-eight decisions were issued in 2015, whereas 62 were issued in 2014. The great majority of disputes submitted to the courts of law were rejected (46 rejections or withdrawals or dismissals).

<table>
<thead>
<tr>
<th>Year</th>
<th>Rejection/withdrawal/dismissal</th>
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<tr>
<td>2006</td>
<td>17</td>
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</table>
FOCUS on the ANSM's involvement in the third French Cancer Plan

The third French Cancer Plan is a presidential programme that includes 17 goals to better combat this disease. The plan aims to cure more cancer patients, maintain continuity and quality of life, develop prevention and research and, finally, optimise steering and relevant organisations. In this context, ANSM is the national leader of two actions:

- defining priorities in cancer drug development
- improving the mechanisms for assessing cancer drugs.

The year 2015 was dedicated to starting a two-part thought process to define the indications or clinical situations that should be the primary subject of development in oncology, taking into account the most unmet medical needs, especially in paediatric oncology, and revising the criteria used to evaluate and judge the innovative nature and added value of a molecule so as to potentially reduce a medicine's development time and help patients access real innovations faster.

FOCUS on the ANSM's involvement in the third French National Antibiotic Alert Plan

The third French National Antibiotic Alert Plan was created to combat the development of antibiotic resistance, and the growing number of cases in which treatment options have been exhausted, by reducing antibiotic use by 25%. As part of the plan, ANSM identified and listed all antibiotics associated with high selection pressure and kept this list up to date.

In 2015, ANSM continued its work on antibiotic resistance by participating in the Special Working Group for Safeguarding Antibiotics, which was created in January 2015 upon the request of the French Health Minister. The agency participated in the plenary group as well as in the following sub-groups: "Cost of Antibiotic Resistance", "Proper Use of Antibiotics", "Communication, Information, and Education", and "Research, Innovation, and New Medical Economic Models". This work resulted in proposed innovations in June 2015. In 2015, ANSM also updated the list of critical antibiotics it published in December 2013.

FOCUS on the ANSM's involvement in the French National Generic Medicines Promotion Plan

The French National Generic Medicines Promotion Plan was launched in March 2015. It includes nearly 80 actions divided into seven key areas. ANSM was involved in steps aiming to improve the access of prescribers, pharmacists, and patients to the generic medicines directory. The agency also helped expand the catalogue of plants, minerals substances, and inhaled medicines. ANSM heads up measures to optimise MA delivery times for generic medicines and to draft medicine packaging label recommendations. ANSM is writing prescription guidelines in International Common Denomination (ICD) for database editors. Finally, ANSM is participating in preparing a national communication campaign about generic medicines aimed at the general public and piloted by CNAMTS. It is set to launch in 2016.
7. **European work**

**Creation of a European strategy department**

ANSM's actions within Europe are among the priorities listed in the agency's Objectives and Performance Contract, which was signed in 2015. To strengthen its European strategy and concentrate its investment on issues to which France can most contribute in terms of innovation and product safety, ANSM created a European Unit in 2015 that reports to the Science and European Strategy Director. The majority of agency representatives from the various EMA committees are included in the unit. This group ensures ANSM’s consistency when formulating its positions internally. It also oversees European and international activities, both within committees to make sure France’s representation is consistent and structured, and between committees to address sensitive and strategic topics and develop inter-agency strategies.

**Representation of ANSM within European bodies**

**European Medicines Agency (EMA)**

ANSM represented France on the Administrative Board of the European Medicines Agency (EMA). This authority supervises and exercises overall responsibility for all issues related to budgeting, planning, appointing an executive director, and monitoring the agency’s performance. It also formulates the strategic areas of focus for the scientific networks, adopts procedural rules, and supervises the use of European Union (EU) funds in the agency's activities.

The EMA’s Board of Administration includes:

- a representative of each of the 28 EU member states
- representatives of the European Commission and Parliament
- representatives of European patient organisations and professional healthcare organisations
- observers from the European Economic Area (competent national authorities in Iceland, Norway, and Liechtenstein).

Highlights from its work in 2015:

- The board adopted the strategic areas of focus for the European regulatory network for 2020. For the first time, the common areas of focus for the EMA and the competent national authorities were included in the same document. The document will be specified in multi-annual working plans for the EMA and the Heads of Medicines Agencies (HMA).
- The board approved the creation of a centralised repository for periodic safety update reports (PSURs). This repository will become the single platform for sharing safety information between pharmaceutical laboratories and European regulatory authorities regarding medicines authorised in the European Union.
- The board acknowledged the delay in implementing a management system for information regarding European clinical trials (single portal and database), which is a prerequisite for applying EU regulation no. 536/2014 concerning clinical trials. Postponing this step will give national authorities time to set up essential functions that will allow them to manage the system. The regulation is now scheduled to take effect in October 2018 at the latest.

**Heads of Medicines Agencies (HMA)**

ANSM actively participated in the European Heads of Medicines Agencies network (HMA), which continued to work on a variety of projects aimed at facilitating the application of legislation and supporting joint strategies: The HMA validated the following:

- the drafting of a multi-annual plan for the network of national authorities based on four priorities. These priorities include contributing to the public health network, contributing to animal health and the impact of veterinary medicines on human health, optimising the network’s operation, and contributing to the international regulatory environment.
For safe, effective, innovative and accessible health products

- the adoption of a European strategy regarding information systems and a roadmap for implementing it between 2015 and 2017.

Participation in the work of European committees

ANSM is a stakeholder in the various European committees of the European Medicines Agency for the assessment and surveillance of medicines.

The Committee for Medicinal Products for Human Use (CHMP) is the European body responsible for assessing medicines entering the market and medicines that are subject to modifications in their use (restriction, extension of indications) or their prescribing and supply conditions, with a view to authorising them under the centralised procedure. The CHMP, which is made up of representatives from the different member states, meets every month in London over a period of four days and issues opinions that represent the basis of the European Commission's decisions (granting of MAs, etc.). The assessment studies are conducted by national agencies. Since October 2013, ANSM has been the vice-chair of the CHMP (Dr Pierre Demolis, Deputy Director of the Scientific and European Strategy Directorate, ANSM). In 2015, the CHMP issued 93 positive opinions for new MAs and 54 positive opinions for expanding therapeutic indications.

The European Pharmacovigilance Risk Assessment Committee (PRAC), set up in July 2012 as part of the new European pharmacovigilance law, has reinforced the pharmacovigilance system in the European Union and makes it possible to implement effective and rapid management measures in response to health product safety risks. In 2015, 1,932 dossiers were included in the PRAC’s agenda, with France serving as the rapporteur country for 224 of these cases.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) reports to the Heads of Medicines Agencies. Though it is not an EMA committee, it meets once a month in London for three days because its secretariat is run by the EMA. The CMDh is a multidisciplinary regulatory and scientific group responsible for addressing any question about the marketing authorisation for a medicine authorised in two or more member states. It drafts and updates its recommendations to match changes in the law and provides opinions on regulatory issues. When member states disagree on a matter of public health at the end of the authorisation procedure, the CMDh is consulted to try to find a consensus (through the 60-day CMDh referral procedure). If a solution has not been found at the end of the CMDh referral, the procedure is submitted to the CHMP for a final ruling, which is issued along with a binding decision from the European Commission.

As part of the new pharmacovigilance law, the CMDh is also in charge of adopting the PRAC’s recommendations regarding medicines authorised under a mutual recognition or decentralised procedure and issues opinions on the referrals assessed by the PRAC excluding all medicines evaluated under the centralised procedure.

In 2015, the CMDh met 11 times in London and twice for informal CMDh meetings organised during the rotating presidency of the European Union (Latvia and Luxembourg). In 2015, 12 referrals to the CMDh were resolved and six were referred up to the CHMP.

In 2015, the CMDh issued opinions on four PRAC recommendations as part of a referral under article 31 that began with PRAC, following a request to re-examine a PRAC recommendation. The CMDh also issued opinions on 37 PSUSA procedures (assessment of pharmacovigilance data by active substance) and adopted 89 PSUR worksharing procedures.

Inspection coordination

Coordinating inspections on a national and European level is particularly important. Coordination efforts help optimise the use of inspection resources among the various member states and harmonise their practices.

In the field of medicines, this work is primarily carried out through the "Inspectors Working Group" (IWG) created by the EMA. In the particular case of starting materials for pharmaceutical use, the Council of Europe oversees significant coordination efforts through the Directorate for the Quality of Medicines and Health Care (EDQM).
Due to its size, the medical device and in vitro diagnostic medical device sector requires the creation of coordinating bodies within the competent authorities of the European Union. Given the key role of notified organisations in compliance certification procedures regarding these products, it is critical to maintain exacting and harmonised standards among member states during the appointing process. The European Commission’s Notified Body Operations Group (NBOG) works to ensure these standards. It includes notified body appointment experts, as well as an ANSM representative, and monitors the notified bodies.

In the field of cosmetic products, ANSM participates in the work of the Platform of European Market Surveillance Authorities (PEMSAC). The goal of this European network, which was created by the European Commission, is to facilitate cooperation among the authorities in charge of monitoring the cosmetic product market.

**FOCUS on negotiating European draft regulations and preparing for their implementation**

**Draft regulations on medical devices**

In 2015, the agency continued to work alongside the French Directorate General of Health (DGS), taking an active part in negotiations within the European Council concerning regulations relative to medical devices (MD) and in vitro diagnostic medical devices (IV-DMD). Work relating to these two draft regulations represented a total of 20 working sessions (1 or 2 days) in Brussels. These draft regulations also required significant internal coordination. Negotiations continued during the Latvian presidency, and documents detailing a general approach were submitted to the EPSCO Council in June 2015. During the Luxembourg presidency, the negotiators finalised their examination of the document, allowing the EPSCO Council to adopt general approaches for the two propositions (DMs and IV-DMDs) on 5 October 2015.

Drawing from these two general approaches, the Luxembourg presidency launched the first informal three-way discussions with the European Parliament and the Commission.

These regulations will significantly improve the safety of health products. One of the main challenges is to improve the assessment of the risk/benefit ratio prior to marketing and surveillance during the product’s lifetime, particularly for implantable MDs or, more generally, those with a therapeutic purpose.

**FOCUS on implementing a pilot phase to prepare for the European regulation on clinical trials**

The European regulation concerning clinical trials for medicines for human use was published on 27 May 2014. It will come into force as soon as the single European portal is open and will apply to all parties involved in clinical trials. In the meantime, ANSM launched a pilot phase in September 2015 to prepare for the implementation of this regulation in cooperation with academic and industry sponsors and ethics committees (CPP). An information meeting regarding this project was held on 29 June 2015. The regulation requires the implementation of a rapid, centralised and coordinated review of applications for clinical trial authorisation, as well as their modifications, whenever the trial is conducted in at least one European Union member state. It calls for new working methods for the competent authorities and Ethics Committees of member states (CPP in France).

France was the first country to launch a pilot phase to prepare for the new European regulation’s implementation.
8. International cooperation activities

Multilateral cooperation activities

Cooperation between international agencies

The strategic goal of the ICMRA (International Coalition of Medicines Regulatory Authorities) is to develop effective cooperation between agencies, on an international level, without overlapping with other international initiatives (ICH, PIC/S, etc.). As a part of its work, the agency participates in two groups focusing on generics and another dedicated to GMP inspections (including the use of reports to better target necessary inspections). In the field of medical devices, Japan presided over the International Medical Device Regulators Forum (IMDRF) in 2015. ANSM is part of the European delegation alongside the European Commission, Germany, and Ireland and, as such, participated in the seventh meeting of the steering committee. The main work items discussed concern the sharing of vigilance information, medical device software, recognition between regulators of manufacturer audits, standardisation of the electronic marketing authorisation application dossier, and patient registers.

Cooperation with WHO

Activities related to the prequalification of medicines, vaccines, and reagents continued in 2015. The agency participated in an evaluation of the Vietnamese authority regarding vaccines as well as two joint assessments concerning the prequalification of the national control laboratories of Armenia and Madagascar. The agency also released 451 vaccines batches. ANSM helps strengthen competent authorities and took part in a meeting about the polio vaccine and efforts to eradicate the disease along with manufacturers and national regulatory authorities. As is the case every year, the agency participated in the “Expert Committee for Biological Standardisation” to share its expertise in blood-derived medicines and vaccines with primary global stakeholders.

In the context of the convention signed with the World Health Organisation (WHO), ANSM participated in several inspections, on behalf of WHO, concerning both clinical trials and starting materials or medicine manufacturers in India, China, and Germany.

ANSM continued to participate in the BRN network (Blood Regulators Network), which was created in 2006 at the request of WHO. This network brings together countries (Australia, Canada, Germany, Japan, Switzerland, France, and the United States) that have a leading role at the international level in blood product regulation (labile blood products and blood-derived medicines). The goals of this network include sharing information regarding risks (especially emergent risks related to blood products), new technologies in this field, and the standardisation of relevant regulatory requirements as soon as possible. To this end, the BRN group published several recommendations and positions on the WHO website.

Cooperation with the US FDA

ANSM participates actively in efforts intended to solidify mutual recognition of medicine inspections between the United States and the European Union (EU). These negotiations are part of a trade and investment agreement with the United States called the Transatlantic Trade and Investment Partnership (T-TIP). ANSM was one of the member states to audit the US FDA, an American regulatory authority, in 2015 to assess the equivalence between inspection systems in the US and Europe.

ANSM and the US are already working together on many pharmaceutical product projects. Finalising the agreement would boost cooperation and, by extension, facilitate inspections conducted by ANSM’s counterparts. The agreement would help to better prioritise resources allocated to inspections in a medicine supply chain that is often global.

In addition, in the field of clinical trials, France is one of six countries in the European Union that contributes to the joint EMA-FDA initiative launched at the end of 2013 with the goal of promoting joint inspections and information sharing with regard to bioequivalence inspections.
Cooperation with French-speaking Africa

The French-African network of national medicine control laboratories includes fifteen countries as well as institutional representatives (WHO, EDQM, AFD, Ministry of Foreign Affairs, OCEAC, and UEMOA). The 2015 action programme was written to reflect decisions made during the annual directors’ meeting in April 2014. ANSM organised a centralised, five-day training session in its Vendargues laboratories pertaining to the management and qualification of reference and secondary standards. Fifteen trainees from eight countries were in attendance. ANSM also coordinated a collaborative study to help the network's members assess their technical skills. The theme chosen for the study was rifampin dosages. In addition, under the coordination of the Tunisian National Control Laboratory, a feasibility study was put into place at the same time in order to study oral contraception. An interactive platform managed by ANSM and designed to promote exchange is available to all members of the network.

Technical and scientific multilateral cooperation

The agency participated in the work of the International Conference on Harmonisation (ICH) on the electronic common technical document for MA applications (regulated products submission/eCTD).

ANSM continued to participate in the work of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Specifically, this work dealt with good manufacturing and distribution practices for medicines (including biologic medicines), active substances, blood, tissue and cells, and risk management through quality assurance. In 2015, ANSM participated in the assessment of two national agencies (Philippines and Hong Kong SAR). At the end of 2015, the PIC/S included 48 national agencies.

As is the case every year, the agency was involved in the work of the Council of Europe’s European Directorate for the Quality of Medicines (EDQM), bringing together 37 member states and 26 observer countries. ANSM contributes to the work of the Official Medicines Control Laboratories (OMCL) network, the European Pharmacopoeia, and European Certification. In 2015, ANSM’s laboratories participated in 18 collaborative studies, including 11 performance studies. ANSM also participated in five joint quality audits of other OMCLs in Switzerland, Poland, Slovenia, Finland, and the United Kingdom on behalf of the EDQM.

Finally, ANSM was itself audited in December 2015 by the EDQM. The inspection focused on the agency's release of blood-derived medicine batches and vaccine controls in its Saint-Denis laboratories. The audit did not result in any major findings and underscored the competence of the agency's teams as well as the effectiveness of its quality management system.

In the blood sector, ANSM assesses the EDQM's work and coordinates various reports and surveys. As the national authority designated to supervise the use of narcotic and psychotropic products, ANSM participates in the United Nation's Commission for narcotics and psychotropics and draws up an annual report for the International Narcotics Control Board (INCB).

Bilateral cooperation activities

Bilateral activities with the national competent authorities of countries outside of the EU continued in the context of previously signed bilateral agreements, in particular, with:

- **The United States:** via numerous exchanges concerning medicines, medical devices, and cosmetic products (inspection reports, medical device batch recalls, compassionate use of medicines, medical device system benchmarks, vaccine evaluations, etc.) as part of a confidentiality agreement.

- **Japan:** in the context of the confidentiality agreement signed at the end of 2012, ANSM regularly receives medicine safety profile information leading to SPC modifications by its counterparts in the Japanese agency (PMDA) and the Japanese Ministry of Health (MHLW). The agency also responds regularly to questions from the Japanese embassy in France regarding specific technical concerns such as compassionate use and medicine imports.
• **Brazil**: the renewal of the convention between ANSM and its Brazilian counterpart, ANVISA, in April 2015 prepared the way for the exchange of confidential information such as inspection reports. ANSM met with ANVISA in Brazil regarding the surveillance of the medical device market.

• **Canada**: under the confidentiality agreement signed with Santé Canada, it became possible to share information about medical abortions.

• **South Korea**: as part of an agreement between the South Korean Ministry of Food and Drug Safety (MFDS) and ANSM, two delegations visited the Lyon and Saint-Denis facilities; one focused on the release of vaccine and blood-derived medicine batches, while the other studied cosmetic claims.

• **Lebanon**: under a cooperation protocol signed in November 2011 between the French Ministry for Labour, Employment and Health and the Lebanese Public Health Minister, and a bilateral agreement between ANSM and the Ministry of Public Health of the Republic of Lebanon, exchanges relating to generic medicines and medical devices continued. In particular, Lebanese procedures and draft regulations were reviewed, and a training session was held in Beirut.

• **Malaysia**: a one-off agreement was signed to host a trainee in Lyon for five days during which the trainee studied the release of dengue fever vaccine batches.

• **Mexico**: following the conclusion of a collaboration protocol in July 2015, regarding the exchange of information between ANSM and the Mexican Health Ministry, via the Federal Commission for the Protection against Sanitary Risk (COFEPRIS), the two institutions worked together to facilitate administrative processes and promote access to French medicines in Mexico.

• **Tunisia**: ANSM agreed to participate in a twinning arrangement, the goal of which was to provide “institutional support regarding the control of health and environmental risks to the Tunisian National Health and Environmental Control of Products Agency (ANCSEP)”. The agreement will be put into practice in 2016 with the arrival of trainees.

Other exchanges that were not the subject of an agreement took place with:

• **Algeria**: ANSM general management participated in the first health meetings between France and Algeria.

Finally, concerning French overseas departments and territories:

• there were almost 120 exchanges in 2015 with **French Polynesia** concerning TAUs; stock shortages; and the qualification of health products, tissue banks, and breast implants. ANSM laboratories inspected several products (complementary export declaration, coconut oil) at the request of the local Polynesian authority.

• negotiations with **New Caledonia** culminated in early 2015 with the signing of a cooperation convention concerning the authorisation and control of pharmaceutical sites that manufacture medicinal gases.

**Highlights**

• 13 declarations were submitted by 7 countries (Brazil, China, South Korea, India, Japan, Lebanon, and Mexico).

• 16 trainees were accepted from 9 countries (Malaysia and 8 African countries).
Part 4.

Reinforcing ANSM's efficiency and pursuing its modernisation
1. **Optimising internal processes and the integrated management system**

In 2015, ANSM continued to improve its steering activities and optimise its processes in order to consolidate and fully benefit from the internal organisation it enacted in 2012. In particular, these improvements concerned the efficiency and security of the application processing chain.

In order to fulfil additional missions assigned to it by the 2011 law and by new European directives, ANSM continued to modernize its tools and processes. To this end, it worked to mobilise a wide variety of skill sets and did so against a backdrop of resource allocation scarcity and public employment cutbacks (20 full-time positions below authorized strength).

The Objective and Performance Contract, which enables the agency to envision its future priorities, has already produced concrete results, especially in terms of human resource policy and information system strategy.

**Strengthening steering activities and internal oversight**

After its creation at the end of 2014, the Steering and Internal Control Unit (MPCI) became operational in early 2015 with the addition of quality implementation, risk management, and performance management activities.

It monitored and supported the creation of a project portfolio, which included a dozen priority projects whose aim was to optimise the facility’s processes to better serve the public.

5 projects were finalised in 2015, and the other projects will continue into 2016.

As of early 2016, the project portfolio was made up of 9 priority projects, including the launch of two new projects.

**Optimising MA modification processing**

One of the internal structuring projects launched in 2015 concerned the processing of market authorisation (MA) modifications. A multi-disciplinary project team was formed to optimise the processing of MA modification requests. The goal of their work was to meet regulatory guidelines regarding decision notification while also ensuring that requests are processed in a consistent and high-quality manner.

The project consisted of classifying all MA modifications described in the European regulation guidelines (EC no. 1234/2008) into four processing categories ranging from the simplest to the most complex cases.

The modification categorisation process was drafted and optimised, and the processing of categories 1 and 2 was assigned to the Division for Data Flows and Repositories (DMFR) to ensure cases would be examined quickly and to avoid internal referrals, which waste time and create a larger work load.

After an initial pilot phase and promising results, this arrangement for processing the first two modification categories was made permanent.

The processing and notification lead times for these two categories are currently between five and fifteen days on average.

**Improving workflow management**

Another priority project in 2015 was the improvement of workflow management, which began with a comprehensive steering and traceability programme for workflows received and processed by the agency. ANSM is focusing on steering and monitoring the entire “life cycle” of workflows and applications submitted to the agency.
This exhaustive and comprehensive traceability will make it possible to better manage cases that are in the process of being examined by the departments through the implementation of stable and reliable activity and performance indicators.

The agency’s enhanced steering efforts will focus on meeting deadlines in order to benefit patients and fulfill its public service obligations.

**Accrediting inspection and internal audit activities**

The ANSM Inspection Division was accredited by COFRAC on 1 July 2014 in accordance with the ISO/CEI 17020 standard. This accreditation constitutes recognition of the quality of the agency's inspection activities, as well as its compliance with ethics and international rules related to impartiality, independence, and competence.

The purpose of COFRAC accreditation, which is granted by a recognised external auditor, is to certify that the Inspection Department follows a structured approach and that it is working in accordance with internationally accepted rules and ethics (impartiality, independence, and competence).

Accreditation also helps further increase the level of confidence that various interested parties (governments, operators, etc.) have in ANSM’s ability to:

- draw on recognised inspection expertise that has the requisite high level of reliability and is regularly verified and controlled via accreditation
- mobilise its teams around a unifying company project
- maintain its technical expertise.

The fields of inspection currently covered by the accreditation include the following:

- on-site inspections to verify regulatory compliance as part of monitoring efforts involving the medical device and *in vitro* diagnostic medical device (MD and IV-DMD) market
- inspections of facilities that manufacture, import, or distribute pharmaceutical starting materials to verify compliance with good manufacturing practices and other regulatory requirements
- inspections as part of surveillance efforts involving operations authorised to be carried out by certified individuals in facilities that work with microorganisms and toxins (MOT), or in order to grant the authorisations required for these operations, to verify that regulatory requirements in terms of biological safety and security are being followed
- on-site facility inspections as part of surveillance efforts involving the cosmetic product market to verify that regulatory requirements and good manufacturing practices are being followed.

A surveillance audit took place on 9 and 10 June 2015.

Following the audit, the team of auditors expressed their confidence in the implementation and durability of the management system and in the technical performance of inspections.

This external audit complements internal surveillance measures, including, for example, technical and organisational provisions and their application within the Inspection Division. These provisions were audited internally eight times in 2015. After each internal audit, a written report and a correction or preventative action plan are produced; the application and effectiveness of these measures are continually verified.

**European audits of control activities**

ANSM’s laboratory control activities were audited from 8 to 10 December 2015 as part of the programme of European audits conducted by EDQM, the European Directorate for the Quality of Medicines and Healthcare. The four European auditors verified the application of the ISO 17025 standard in the Saint-Denis laboratories, specifically as regards the release of vaccine and blood-derived medicine batches.
The auditor's report presented during the closing meeting on 10 December did not include any problematic findings and underscored the quality of the work conducted in the ANSM laboratories.

This audit, which is part of the division's efforts to ensure quality, also highlighted the highly satisfactory level of quality management.

It should be noted that the Control Division's quality management system relies on the participation of the entire division in issuing quality documents (procedures, operating instructions, etc.) and internal and external audits as part of an ongoing drive to improve.

**Finalising the Objective and Performance Contract (OPC) with supervisory bodies**

ANSM's OPC, which sets the agency's priorities for 2015 to 2018, was signed on 17 July 2015 by Marisol Touraine, the French Health and Social Affairs Minister, and by Dominique Martin, the Director General of ANSM. It had already been adopted by the ANSM Administrative Board on 25 June 2015.

The OPC is based on four strategic areas of focus:
- Guaranteeing a high level of safety for all health products throughout their life cycle
- Promoting rapid, closely monitored, and broad access to all health products
- Consolidating ANSM's relationships with stakeholders and enhancing their involvement
- Reinforcing ANSM's efficiency and pursuing its modernisation.

To meet these priorities, 12 objectives and 22 concrete actions were put in place along with 28 indicators designed to track the progress of these actions.

The OPC was created to help consolidate the agency and formulate a more long-term view of its missions. An assessment of the OPC's implementation will be carried out every year by an OPC monitoring committee, and a final evaluation will be conducted in 2018.
2. Modernisation of processes and tools

Simplified administrative processes

In 2015, ANSM pursued its various efforts to simplify administrative processes and refocus its strategic missions. This work was part of the agency’s preparation for the health system modernisation law that was definitively adopted in December 2015 and passed in January 2016. This law simplifies a certain number of processes, particularly those related to specific authorisation systems, including procedures that concern:

- the import of medicines by individuals through the mail,
- the import of medicines by team physicians treating athletes during competitions in France,
- the elimination of the framework governing auxiliary therapeutic products.

In addition, the draft of the 2016 financial law is set to eliminate the tax on cosmetic products. As a result, it is no longer required to submit a declaration of sale of cosmetic products to the agency after 2016.

As of October 2015, the management of export certificates was transferred to the Chamber of Commerce and Industry in the Paris – Ile de France Region (CCI Paris - Ile de France). Prior to this date, Certificates of Free Sale (CFS), which facilitate the export of medicines for human use, medical devices (MDs), and in vitro diagnostic medical devices (IVD-MDs), were granted by ANSM. The agency granted 12,000 Certificates of Free Sale per year. An agreement regarding the transfer of export certificate management was signed on 17 July 2015 between the CCI Paris – Ile de France and ANSM to give the chamber all the information it needs to take over this responsibility. ANSM created a dedicated support plan to help companies during this transition.

Paperless communication

The purpose of the Common European Submission Platform (CESP) is to replace paper/CD/DVD applications by a completely paperless format to improve processing time and the efficiency of actors along the chain (industry stakeholders and ANSM).

Step III of the pilot phase, which started at the end of 2013, concluded on 12 January 2015. All procedures regarding eCTD- and NeeS-format MAs can now be submitted to the CESP (excluding ASMF).

Another highlight at ANSM in 2015 was the opening of the Common Repository on 3 June. This resource contains all electronic submissions of MA applications handed into the EMA through the centralised procedure. The Common Repository makes it possible to search, navigate, and download centralised-procedure applications in eCTD format. By implementing this solution in all member states, the time needed to receive and approve requests and provide continuous, up-to-date access to applications is significantly reduced. ANSM gained access to this system on 3 June 2015.

Finally, ANSM participated in all steps of the PSUR Repository pilot phase, which took place from February to December 2015 under the direction of the EMA. This resource functions as a shared storage space for PSURs, PSUR assessment reports, and any final comments and results. Competent authorities and the European Commission have secured access to this information. The repository contains both PSUSAs and simple, strictly national procedures regarding active substances that are only authorised in one specific member state.
Change in CESP submissions
3. Implementation of the Information System Master Plan (ISMP)

The information system (IS) is an integral part of the agency's modernisation efforts. Its purpose is to help make ANSM's activities more secure and to enable vital gains in productivity.

The 2014–2018 Information System Master Plan (ISMP) was approved by the Administrative Board on 27 March 2014 and implementation began immediately, focusing on the first structuring projects.

As planned, the ISMP was modified in early 2015 to account for regulatory changes and strategy adjustments within the agency.

In accordance with the ISMP schedule, the agency:

- brought LIMS in-house. This management tool for the agency's laboratory activities represents a complex technical operation. This software product was previously housed outside of the agency. This shift led to a better mastery of the tool.
- launched KUSURI, the agency's new intranet. KUSURI was quickly adopted by all personnel and is now the agency's main internal communication tool.
- continued the switch to paperless communication with external partners through the roll-out of online inspection registration tools (Jade, VDG, and Saphir)
- launched the new GBCP accounting management tool, which is used by several health security agencies (see page 136)
- launched a better performing version of the human resources management application, CIRIL V5.

In accordance with the ISMP schedule, the agency worked on 19 projects in a variety of fields, including health product authorisations, vigilance, European activities, clinical trials, health product standards, inspection management tools, and expert management.

The agency also selected and tested an analysis and steering tool called QlikView, with a gradual roll-out planned for 2016. This powerful tool should significantly facilitate the work of managers and internal evaluators.

Modernising and securing the IS and strengthening the agency’s methodological approach

The agency's approach to its information system was revised to increase its effectiveness and to account for the creation of an autonomous project manager network. The network is made up of 15 representatives from the operating divisions. These individuals are in charge of making sure a project meets the agency's needs. The representatives are involved in every step of a project as soon as these needs are formulated. They are the main point of contact for users and project owners. Training sessions, which included the representatives of both project owners and project managers, further strengthened the close collaboration between these two parties, which is essential for a project's success.

These efforts to professionalise project ownership supports general management’s choice to undertake the creation of an IS using a process-based approach while focusing on priority projects in each operating division. Each project is the subject of a strategic IS memo that promotes the implementation of an urbanisation plan and facilitates the ISMP's annual revision process. This process creates a framework for the creation of the information system.

Moreover, following an audit from the French National Information System Security Agency (ANSSI), the process of securing the information system was made stronger with the recruitment of a data and information system security manager (RSSI) in 2015. An action plan was written and will be rolled out in 2016 and 2017.
Increasing the agency's structuring and modernisation efforts

The agency continued its efforts to structure and strengthen its information system teams through external resources and gradual outsourcing of in-house production activities.

In accordance with the ISMP, the agency implemented several projects designed to increase the efficiency and control of its processes.

One of these projects led to the agency purchasing a project portfolio management tool (NQI). The year 2015 was dedicated to training personnel and configuring and rolling out the tool on 1 June 2015 in accordance with the schedule. A new phase to extend the tool to other profiles within the agency is set to begin in 2016.

A structuring urbanisation process was implemented. A cartography tool was purchased and shared with the agency’s quality network (Mega). Target architecture plans for five priority projects were drafted.

Finally, efforts to modernise infrastructure continued with the roll-out of a new technical platform. The agency started to create its service catalogue; this project will continue into 2016. A ticket management system (ITSM) was selected and is currently being rolled out in accordance with the schedule; this is also the case for the project to set up the VCenter (VMware for machine virtualisation).

Continuing to modernise workstations

The migration of 1,500 workstations to recent operating system versions and office software suites was finalised in 2015. This large-scale operation, which was completed without any service interruption and accompanied by the required training, has improved the reliability of the security mechanisms associated with the workstations.

Throughout 2015, around 300 personnel changes (new arrivals, internal transfers, moves) also took place.

Preliminary studies, prior to the implementation of a professional virtualisation system and a change-over from the Storage Area Network (SAN) in response to the exponential growth in requirements, have been initiated and will lead to the roll-out of new technical solutions in 2016.
4. Human resources

Optimising human resources

To fulfil its health product safety missions, ANSM is supported by a workforce corresponding to 983 full-time equivalents (FTEs) as of 31 December 2015. The agency also had six temporary positions not included in the cap in 2015.

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<tbody>
<tr>
<td>Below cap</td>
<td>978</td>
<td>1003 (1)</td>
<td>1003 (2)</td>
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<td>983 (4)</td>
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<tr>
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<td>16</td>
<td>6 (3)</td>
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<td>-10</td>
<td>=</td>
<td></td>
<td>-20</td>
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(1) New resources, specifying that the creation of 40 posts in 2012 fell within the context of the 2012 Finance Law, and 15 were filled via internal redeployment within the Agency. The 2012 Finance Law also identified 40 posts for 2013. The cap of 1,003 FTEs was decreased to 998 FTEs by a management measure in 2012.

(2) Reintegration into the ceiling of 10 posts dedicated to long-term missions, filled by personnel on permanent contracts or by civil servants, and previously outside the ceiling. The cap of 1,003 FTEs was decreased to 1,009 FTEs by a management measure in 2013.

(3) Posts outside the cap for 2013, which include CAE contracts (state-subsidised part-time contracts designed to help vulnerable people integrate into the job market) and agreed fixed-term contracts, were supplemented by seven temporary-contract WFTEs (13 WFTEs in 2013) on a one-off basis; these employees participated in a task force mission to clear the backlog relating to old MA applications.

(4) Cutting twenty positions from the FTE cap for 2015 (983 instead of 1,003 in 2014) would have required a major adjustment on the part of ANSM, which must employ experts in a variety of fields to process the constant flow of applications coming in from France and other European countries as well as to process public health alerts. Due to this, ANSM was allowed to have secondary cap of 993 WFTEs so it could plan for the reduction in its personnel by the end of 2015.

![Implementation of positions under the cap 2009-2015](image)
Permanent personnel account for 98% of employees (88% contracted and 12% civil servants).
The average age of employees is 45 years (44.5 in 2014).
Women make up 72% of employees (same as in 2014).
The average retirement age (11 employees in 2015) is 62.8 for contracted employees (7) and 64 for civil servants (4).

Non-permanent personnel (2% of employees in 2015) comprise contracted employees on fixed-term contracts (due to an increase in work or to replace an employee on maternity leave), temporary employees, and employees on work support contracts (above cap).
Personnel expenditure

The allocation for personnel expenditure within ANSM’s initial 2015 budget was €80.3 million, including 79 million dedicated to payroll and 1.3 million for social actions.

The allocation for personnel expenditure was ultimately set at €79.7 million, or 99.2% (99.5% for payroll and 78.9% for social actions) of the initial budget.

<table>
<thead>
<tr>
<th>Payroll budget in K€</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tr>
<td>Budget for personnel expenditure</td>
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<td>78,550</td>
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<td>78,983</td>
</tr>
<tr>
<td>Implementation of personnel spending (account 64-63*)</td>
<td>72,526</td>
<td>74,260</td>
<td>78,224</td>
<td>77,657</td>
<td>78,625</td>
</tr>
<tr>
<td>Implementation/budget ratio</td>
<td>99%</td>
<td>95%</td>
<td>99%</td>
<td>98%</td>
<td>99.5%</td>
</tr>
</tbody>
</table>

* (excluding social actions)

Promoting individual and collective professionalism

In 2015, the agency drafted a Human Resources Master Plan (HRMP), which should bridge the gap between major strategic areas of focus, especially those listed in the Objective and Performance Contract (OPC), and ANSM’s human resource policy, which must make the agency more efficient as a whole to meet the challenges of providing high quality public service and keeping users of the health system safe.

The HRMP will help implement a certain number of baseline tools, such as the business line map and the employment reference base, which will serve as a reference for the roll out of the agency's recruitment plans, professionalisation programme, and training standards created to meet Strategic Workforce Planning (GPEC) goals. Efforts to design these tools began in 2014 and continued into 2015.

Integrating training within a professionalisation-based approach

The purpose of ANSM's training policy is to help adapt and consolidate employees’ business skills and to help them fully adopt application handling and examination methods in order to ensure that the decision-making process is secure.

In coordination with the operating divisions, the human resource division devises the agency's professional training programme. These programmes must include the baseline training and support policies offered in real-life conditions when an employee joins a new division and when an employee is undergoing professional development. In this way, each employee can have a training programme customised to meet his or her needs.

In 2015, the agency started designing a training programme for non-clinical and vigilance evaluators. This training offer will be fully available in 2016.

Regarding the budget, special attention was paid to controlling training costs by focusing on two strategies, namely bulk purchases of training programmes and procurement contracts. An agreement was signed with UGAP, and procurement contracts cover various training areas that are specific to the agency, such as scientific, quality, legal, and regulatory training programmes.

In particular, the 2015 training plan was marked by the design and implementation of scientific training programmes, support for internal mobility, and the implementation of new procedures.

In 2015, 32 training projects were designed and implemented, including 23 training sessions conducted internally by ANSM employees. In addition to efforts centred on the standard training offer, which leads the HR division to coordinate with the scientific divisions to request services from specialised providers, ANSM also started diversifying its training methods to better meet the agency's professional requirements. Some of these strategies include asking temporary employees who are experts in their fields to lead training sessions or in-house conferences, organising practical training programmes in real-life conditions, providing access to EMA webinars, and purchasing a Learning Management System platform to expand online training (e-learning modules, forums, quizzes).
**The main themes of the 2015 training plan**

- 1. Supporting employees by offering professionalisation programmes (scientific/technical/regulatory/linguistic) 56%
- 2. Facilitating the implementation of working processes and tools 17%
- 3. Developing managerial skills 1%
- 4. Grounding collaboration in professional practices 2%
- 5. Helping improve the quality of life at work 4%
- 6. Supporting internal mobility and professional development 20%

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training expenditure</td>
<td>€812,128</td>
<td>€1,107,093</td>
<td>€1,513,715</td>
<td>€1,277,947</td>
<td>€1,219,873</td>
</tr>
<tr>
<td>% of payroll spent</td>
<td>1.2%</td>
<td>1.5%</td>
<td>1.6%</td>
<td>1.65%</td>
<td>1.55%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of training days per employee trained</td>
<td>4</td>
<td>4.39</td>
<td>4.36</td>
<td>3.87</td>
<td>4.3</td>
</tr>
<tr>
<td>Average number of in-service training days per ANSM employee</td>
<td>3.02</td>
<td>3</td>
<td>3.97</td>
<td>3.67</td>
<td>3.2</td>
</tr>
<tr>
<td>Number of training days</td>
<td>3,132</td>
<td>3,267</td>
<td>4,258</td>
<td>3,870</td>
<td>3,317</td>
</tr>
</tbody>
</table>

**Dialogue between management and employees**

Given the agency's return to stability and employees' high expectations, especially in terms of the quality of work life as expressed by management and labour representatives, the agency started a process to improve the dialogue between management and employees in 2015.

In this context, ANSM called on the French National Agency for the Improvement of Working Conditions (ANACT) in May 2015 to help it strengthen its dialogue with employees. The proposed methodology focused on the following themes:

- definition of the dialogue between management and employees
- role of the various stakeholders
- means and time dedicated to the dialogue.
Participants in the labour relations support programme, which was jointly created and piloted by ANACT and the French Ministry of Labour, had separate exploratory meetings with unions and ANSM management in June 2015, then suggested holding a meeting between all parties in September. These efforts continued in early 2016 and included the Human Resource Department and four representative union organisations.

It should also be noted that 2015 was marked by an increase in the number of meetings between labour and management. 71 meetings were held in 2015 (compared to 51 in 2014) including 32 group meetings and 39 working, discussion, and/or coordination meetings with labour.

**Improving the quality of life at work**

**Preventing psychosocial risks**

As a follow-up to a diagnostic study, conducted by an external service provider in 2014, to identify psychosocial risks within the agency, an action plan was formulated in 2015 and the first measures were implemented. The action plan was created with help from five working groups comprising more than 50 agents in total. Approved during an exceptional meeting of the Health and Safety Committee on 4 May 2015, the action plan is centred on five main themes:

- workload management
- work organisation
- professional support
- environment
- monitoring and alert processes.

A monitoring committee tasked with following up on the implementation of the action plan was created; it met four times between June and November 2015.

**Continued renovation of facilities**

In 2015, the agency continued its ambitious renovation work, especially at the main site at Saint-Denis and more specifically within Buildings A and B. Relaxation areas were established to the extent possible.

The renovation of the site’s company restaurant, made necessary due to its outdated technical equipment and deteriorated reception area, began in 2015 and is set to finish in 2016. The new restaurant will be ready in December 2016.

This ambitious project is covered through a selection-based procurement procedure enabling the agency to select an architectural firm that will help ANSM manage the project's technical, regulatory, and financial aspects. The restaurant's renovation is estimated to cost €2.5 million.

**Internal communication: uniting personnel and building a corporate mindset**

Internal communication is based on several complementary tools:

- A **new intranet site** as of May 2015. This tool is based on a cross-cutting approach and information sharing. The new website presents content in a harmonious manner. Navigation is simplified, and a search engine enables users to easily access information and documents that are practical and useful to daily tasks. The homepage functions as a command centre and opens automatically when the computer is turned on. It highlights, among other things, the agency’s latest internal and external news.
L’Hebdo, a newsletter published at the start of each week, covers the external communication operations of the previous week.

Les Echos de l’ANSM, a monthly newsletter, gives a voice to employees and supports various projects.

Mots du directeur général (Memos from the Director General) provides information regarding strategic issues and topics prominently featured in the media involving ANSM.

In 2015, ANSM’s editorial policy regarding the publication of information for personnel changed with the creation of the new intranet, which has now become the main tool for in-house communication. Between May and December, 264 news updates were published on the homepage. In addition, a total of 167 internal communication messages were circulated (compared to in 246 in 2014, 239 in 2013, and 158 in 2012).

ANSM filmed its first videos showcasing its various professions. The first four professions selected to participate in this new mode of communication were laboratory technicians, inspection technicians, pharmacovigilance assessment technicians, and administrative management technicians. The purpose of these videos is two-fold: internally, the agency seeks to explain and showcase its professions and to forge ties in support of internal mobility; externally, the videos increase the visibility of ANSM’s professions to restore the public’s confidence and increase the agency’s attractiveness in terms of recruitment.

Internal communication is also focused on supporting the agency’s priority projects launched in April 2015 (see page 119) with the goal of sharing this new structuring procedure with personnel and encouraging them to support it. The purpose of the procedure is to secure and optimise the agency’s method of examining and processing applications by looking for opportunities for improvement at every level: simplification, harmonisation, prioritisation, and traceability.
5. The agency’s budget

Following three budget revisions, ANSM final budget for 2015 rose to €143 million (including the investment budget); it was implemented at 96% with €137 million.

Expenditure by type

Change in ANSM spending since 2011 (in thousands of euros)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel</td>
<td>73,557</td>
<td>75,630</td>
<td>80,635</td>
<td>79,089</td>
<td>79,713</td>
</tr>
<tr>
<td>Operation</td>
<td>39,159</td>
<td>35,852</td>
<td>31,965</td>
<td>34,134</td>
<td>33,698</td>
</tr>
<tr>
<td>Intervention</td>
<td>0</td>
<td>18,760</td>
<td>17,285</td>
<td>16,576</td>
<td>12,672</td>
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<tr>
<td>Investment</td>
<td>6,933</td>
<td>13,014</td>
<td>9,434</td>
<td>9,259</td>
<td>10,901</td>
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<tr>
<td>Total</td>
<td>119,649</td>
<td>143,256</td>
<td>139,319</td>
<td>139,058</td>
<td>136,984</td>
</tr>
</tbody>
</table>

Change in ANSM spending since 2011

Income

Change in ANSM income since 2012 (in thousands of euros)

<table>
<thead>
<tr>
<th>Operating income</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government subsidies</td>
<td>129,544</td>
<td>116,359</td>
<td>103,176</td>
<td>113,160</td>
</tr>
<tr>
<td>EMA</td>
<td>7,053</td>
<td>7,286</td>
<td>8,597</td>
<td>8,198</td>
</tr>
<tr>
<td>Reconciled taxes and fees</td>
<td>7,226</td>
<td>595</td>
<td>4,937</td>
<td>849</td>
</tr>
<tr>
<td>Other income from ongoing operations</td>
<td>1,589</td>
<td>4,161</td>
<td>5,640</td>
<td>3,750</td>
</tr>
<tr>
<td>Total operating income</td>
<td>145,412</td>
<td>128,401</td>
<td>122,351</td>
<td>125,957</td>
</tr>
</tbody>
</table>
The subsidy for public service costs is paid by the French government and represented 90% of ANSM's operating income in 2015. This amounted to €113.2 million in 2015, i.e. an increase of over 9% from 2014 (€103.2 million) and nearly a 3% decrease compared to 2013 (€116.4 million).

Revenue from the EMA (European Medicines Agency) consisted of payment for ANSM's work in the following areas:
- study of marketing authorisation application procedures (69%)
- issuing of scientific opinions (10%),
- inspections conducted upon request (10%)
- translations (1%)
- studies of pharmacovigilance dossiers (11%).

### Change in income since 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Other income from ongoing operations</th>
<th>Reconciled taxes and fees</th>
<th>EMA</th>
<th>Government subsidies</th>
<th>Total operating income</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>145,412</td>
<td></td>
<td></td>
<td></td>
<td>145,412</td>
</tr>
<tr>
<td>2013</td>
<td>128,401</td>
<td></td>
<td></td>
<td></td>
<td>128,401</td>
</tr>
<tr>
<td>2014</td>
<td>122,350</td>
<td></td>
<td></td>
<td></td>
<td>122,350</td>
</tr>
<tr>
<td>2015</td>
<td>125,957</td>
<td></td>
<td></td>
<td></td>
<td>125,957</td>
</tr>
</tbody>
</table>
Expenditure by envelope

Personnel: €79.7 million

The personnel budget was implemented to the tune of €79.7 million, i.e. 99% of the initial budget provision. Authorisation for positions under the cap rose to 993 and was implemented at 99.8%.

The budget includes expenditures for the following:
- payroll: €71.7 M (€70.9 M in 2014)
- income taxes and payroll taxes: €6.9 million (1.5% increase compared to 2014)
- social actions: €1 million (slight decrease compared to 2014)
- provisions: €0.05 million

Operation: €33.7 million

The operating budget includes the following:
- amortisation and depreciation: €8.3 million
- the IT budget, which equalled €5.6 million in 2015
- property rentals: €3.4 million
- national quality control of medical biology and laboratory control activities: €3.3 million
- travel costs (inspections, committees and commissions, European projects): €1.7 million

Intervention: €12.6 million

The intervention envelope is divided into several components:
- 11 new projects were selected following a call for research proposals in 2015, raising the number of research projects funded by the agency since 2012 to 72. The eleven agreements were written up before the end of 2015, allowing the agency to make a first payment of nearly one million euros to fund these projects. The subsidy balance received a provisions allocation. The total amount of payments in 2015 for agreements in the current fiscal year and previous years was nearly €2.4 million.
- call for proposals (AAP) — associations: expenditures related to this AAP were posted in 2015 and equalled €293,000, including €149,000 spent in 2015
- funding of the Regional Pharmacovigilance Centre (CRPV) network, the Drug Dependence Evaluation and Information Centre (CEIP) network, and the Reference Centre for Teratogenic Substances (CRAT): €7.2 million and €0.3 million for the funding of six medical device vigilance centres (CRMRV)
- 18 new research agreements were signed in 2015, which represents an initial payment of €1.6 million. A payment of €169,000 for projects from previous years brought the total 2015 payment amount for research projects outside of calls for proposals to €1,769,000.
- allocation to intervention provisions (non-cash credits) for €1 million.

Investment: €10.9 million

The main investment expenditures in 2015 are as follows:
- the laboratory equipment plan accounted for €0.3 K
- IT investments reflected the gradual ramp-up of the IS Master Plan: €4.5 million
- property investments: €3.8 million.
The 2015 financial accounts and 2016 initial budget

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Personnel</td>
<td>80,3</td>
<td>79,7</td>
<td>80,2</td>
<td>State subsidies</td>
<td>115,1</td>
<td>113,2</td>
<td>113,2</td>
</tr>
<tr>
<td>Operation</td>
<td>34</td>
<td>33,7</td>
<td>34,1</td>
<td>Other resources</td>
<td>11</td>
<td>12,8</td>
<td>9,3</td>
</tr>
<tr>
<td>Intervention</td>
<td>14,3</td>
<td>12,7</td>
<td>12,9</td>
<td>EMA</td>
<td>7,5</td>
<td>8,2</td>
<td>8,3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other resources</td>
<td>3,5</td>
<td>4,6</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL EXPENSES</td>
<td>128,6</td>
<td>126,1</td>
<td>127,2</td>
<td>TOTAL PRODUCTS</td>
<td>126,1</td>
<td>126</td>
<td>122,5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TOTAL BALANCE of income statement</td>
<td>128,6</td>
<td>126,1</td>
<td>127,2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMPLOYMENT</th>
<th>IB 2015</th>
<th>FA 2015</th>
<th>IB 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investments</td>
<td>8,4</td>
<td>10,9</td>
<td>11,2</td>
</tr>
</tbody>
</table>

155 notified contracts in 2015

The total number of ANSM's active contracts is 371, including 155 notified contracts for 2015.

The number of notifications is up 10% compared to 2014.

There are more construction and service contracts due to the agency's renovation works and the increase in the number of training contracts is related, in particular, to support and management issues.

> Breakdown of active contracts by nature – Total: 371 contracts

- Construction 29 contracts 8%
- Services 264 contracts 71%
- Supplies 78 contracts 21%
Strengthening purchasing procedures

ANSM is pursuing its purchasing performance goals, which primarily aim to reduce the use of amendments (29 in 2015 compared to 36 in 2014, i.e. a 20% decrease) and negotiation in the case of purchasing procedures whenever possible (12 procedures in 2015).

Moreover, the agency is continuing its work with the Department of Government Procurement (formerly the SAE) in an effort to pool needs, especially with the production of a Procurement Action Plan, which will allow the agency to review past contracts and publish a 2016 forecast and multi-annual schedule for 2017–2019.

In 2015, ANSM entered into framework agreements with the Department of Government Procurement for the provision of gas and electricity.

Implementing the GBCP project

As of 1 January 2016, health employees must have an information system compatible with Budget Management and Public Accounting (GBCP). Under the initiative of the Directorate General of Health, five agencies (ANSM, INCa, InVS, EPRUS, and INPES) worked together throughout 2015 to implement a shared IT solution. The Finance IS for Health Agencies (SIFAS) was rolled out and launched in January 2016.
## Appendices

**OVERVIEW OF MAIN FRENCH AND EUROPEAN TEXTS PUBLISHED IN 2015**  
(excluding health policy decisions and the agency's organisation)

### MEDICINES

**EUROPEAN TEXTS**

<table>
<thead>
<tr>
<th>Text Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Council implementing Decision (EU) 2015/1873 of 8 October 2015 subjecting 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR) and 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) to control measures</td>
<td></td>
</tr>
<tr>
<td>Council implementing decision (EU) 2015/1874 of 8 October 2015 subjecting 4-methylamphetamine to control measures.</td>
<td></td>
</tr>
<tr>
<td>Council Implementing Decision (EU) 2015/1875 of 08 October 2015 subjecting 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe), 3,4-dichloro-N-[1-(dimethylamino)cyclohexyl]methyl]benzamid (AH-7921), 3,4-methylenedioxyxypyrovalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) to control measures</td>
<td></td>
</tr>
<tr>
<td>Commission implementing decision (EU) 2015/1057 of 1 July 2015 modifying the implementation decision 2012/715/EU establishing a list of countries outside of the EU whose regulatory framework for active substances destined for medicines for human use and control and implementation activities ensure a level of public health security equal to that provided by the European Union.</td>
<td></td>
</tr>
<tr>
<td>19 March 2015 guidelines regarding the best practice principles of distributing active substances of medicines for human use</td>
<td></td>
</tr>
<tr>
<td>19 March 2015 guidelines regarding the formal assessment of risk with the goal of determining the appropriate good manufacturing practices for excipients used in medicines for human use.</td>
<td></td>
</tr>
</tbody>
</table>
FRENCH TEXTS

| Decree no. 2015-709 of 22 June 2015 regarding modifications to a marketing authorisation and a registry of medicines for human use and a marketing authorisation for veterinary medicine |
| Orders supplementing the Pharmacopoeia (several texts) |
| Order of 14 November 2015 authorising the use of atropine sulphate, 40 mg/20 ml PCA injectable solution and antidote for organophosphorus neurotoxins |
| Orders establishing the list of poisonous substances (several texts) |
| Orders establishing the list of substances classified as narcotics (several texts) |
| Orders granting exemptions to the regulation on poisonous substances for use in human medicines (several texts) |
| Order of 5 August 2015 regarding the approval procedure and operation conditions for eco-organisations involved in unused medicines for human use brought back to the pharmacy in application of article R. 4211-28 of the French Code of Public Health |
| Order of 20 April 2015 acknowledging the entry into force of the provisions of articles R. 5125-70 and R. 5125-74 of the French Code of Public Health regarding the shared logo that must be displayed on websites selling medicines. |
| Order of 20 March 2015 modifying the order of 14 April 2014 stipulating the form, content, and methods for reporting adverse effects and new events in the context of a biomedical study concerning a medicine for human use |
| Order of 20 March 2015 modifying the order of 14 April 2014 stipulating the reporting methods, form, and content of the safety report for a biomedical study concerning a medicine for human use |
| Decision of 25 September 2015 regarding good manufacturing practices for active substances used as starting materials for medicines for human and veterinary use and modifying the decision of 04 December 2013 (OJFR no. 0240 of 16 October 2015) |
| Good distribution practices of active substances for medicines for human use |
| Decision of 25 September 2015 regarding good manufacturing practice for active substances used as starting materials for medicines for human and veterinary use and modifying the decision of 4 December 2013 |
| Decision of 25 September 2015 regarding the best practice principles of distributing active substances of medicines for human use. |
| Decisions modifying the generic medicine directory (several texts) |
| Decision modifying the list of medicines available in pharmacies mentioned in article R 5121-202 of the French Code of Public Health (several texts) |
| DG decision of 26 February 2015 taken to apply article R. 5124-46 of the French Code of Public Health and establishing the form and content of the state of pharmaceutical facilities mentioned in 1o to 15o of article R. 5124-2 of the same code (OJFR no. 0087 of 14 April 2015) |
| Decision of 24 February 2015 regarding good manufacturing practices and modifying the decision of 4 December 2013 (OJFR no. 0070 of 24 March 2015) |
| DG decision of 26 February 2015 taken to apply article R. 5124-46 of the French Code of Public Health and establishing the form and content of the state of pharmaceutical facilities mentioned in no. 1 to no. 15 of article R. 5124-2 of the same code |
| Decision of 24 February 2015 regarding good manufacturing practices and modifying the decision of 4 December 2013 |
| Decision of 24 February 2015 establishing the form and content of authorisation requests for the manufacturing, import, and distribution of active substances and the declaration of manufacturing, import and distribution activities involving excipients stipulated in article L. 51381 of the French Code of Public Health. |
**BIOLOGICAL PRODUCTS**

**EUROPEAN TEXTS**

<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commission directive (EU) 2015/566 of 08 April 2015 applying directive 2004/23/EC regarding verification procedures of equivalent standards for quality and security of imported tissues and cells</td>
</tr>
<tr>
<td>Commission directive (EU) 2015/565 of 08 April 2015 modifying directive 2006/86/EC regarding certain technical requirements concerning the codification of cells and tissues of human origin.</td>
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</table>

**FRENCH TEXTS**

<table>
<thead>
<tr>
<th>Decree no. 2015-1747 of 23 December 2015 regarding granting derogations for transplants in the event of hepatitis C infection markers in the donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decree no. 2015-1281 of 13 October 2015 regarding gamete donation (managed by ABM)</td>
</tr>
<tr>
<td>Decree no. 2015-509 of 06 May 2015 regarding the simplification of authorisation schemes for the preparation, storage, distribution, transfer, import, or export of tissues, their derivatives, cells and cellular therapy preparations from the human body and used for therapeutic purposes.</td>
</tr>
<tr>
<td>Decree no. 2015-155 of 11 February 2015 regarding research involving embryos and embryonic stem cells and biomedical research into medically assisted reproduction</td>
</tr>
<tr>
<td>Decree no. 2015-100 of 02 February 2015 regarding plasma produced through an industrial process</td>
</tr>
<tr>
<td>Order of 23 December 2015 regarding the conditions of use of organs or cells from donors with hepatitis C markers</td>
</tr>
<tr>
<td>Order of 29 October 2015 standardising the best practices regarding organ harvesting from human cadavers for therapeutic purposes</td>
</tr>
<tr>
<td>Order of 04 November 2015 establishing the doses and maximum concentrations of microorganisms and toxins included in the list from article L. 5139-1 and applying article R. 5139-20 of the French Code of Public Health</td>
</tr>
<tr>
<td>Decree of 02 October 2015 modifying the decree of 30 April 2012 setting the list of microorganisms and toxins stipulated in article L. 5139-1 of the French Public Health Code</td>
</tr>
<tr>
<td>Order of 22 June 2015 defining the best practices for ovarian stimulation, including when this technique is used for reasons other than medically assisted reproduction</td>
</tr>
<tr>
<td>Order of 03 February 2015 regarding storage methods for the delivery and traceability of plasmas meant for transfusions and produced through an industrial process covered by an import authorisation</td>
</tr>
<tr>
<td>Decisions establishing the list and characteristics of labile blood products (several texts).</td>
</tr>
</tbody>
</table>
MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

EUROPEAN TEXTS

| Commission statement as part of the implementation of directive 2006/95/EC of the European Parliament and Council regarding the merger of member state legislation concerning electric equipment designed to be used within certain voltage limits (Publication of titles and references of harmonised standards as part of European Union harmonisation legislation) and provisions regarding medical devices |
| Commission delegate directive (EU) 2015/573 of 30 January 2015 modifying, for the purpose of adapting the directive to account for technical progress, Appendix IV of European Parliament and Council directive 2011/65/EU regarding an exemption for lead in polyvinyl chloride used in in vitro diagnostic medical devices |
| Commission delegate directive (EU) 2015/574 of 30 January 2015 modifying, for the purpose of adapting the directive to account for technical progress, Appendix IV of European Parliament and Council directive 2011/65/EU regarding an exemption for mercury in intravascular ultrasound imaging systems |

FRENCH TEXTS

| Decree no. 2015-1223 of 02 October 2015 applying article L. 4362-10-1 of the French Code of Public Health regarding the online sale of corrective lenses and contacts |
| Decree no. 2015-1171 of 22 September 2015 regarding the information that must be presented to a patient prior to undergoing a cosmetic surgery procedure and after the implantation of a medical device |
| Decree no. 2015-888 of 21 July 2015 regarding the delivery conditions for corrective contact lenses for first-time users |
| Decree no. 2015-374 of 31 March 2015 applying Commission regulation (EU) no. 722/2012 of 08 August 2012 regarding medical devices manufactured with animal tissue |
| Order of 14 April 2015 appealing order of 13 September 2005 regarding detailed specifications setting out the essential requirements to which medical devices manufactured with animal tissue must conform |
| Decisions renewing the accreditation of bodies responsible for the quality control of medical devices (several texts) |
| Best practices for home delivery of oxygen for medical use |
| DG decision of 12 August 2015 establishing the quality control methods of certain radiodiagnostic facilities |
| DG decision of 12 August 2015 establishing the quality control methods of radiodiagnostic facilities used for radio-guided interventional procedures |
| Opinion of the Director General of the French National Agency for Medicines and Health Products Safety regarding the status of sterilisation indicators. |

For safe, effective, innovative and accessible health products
**COSMETIC AND TATTOOING PRODUCTS**

**EUROPEAN TEXTS**

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**FRENCH TEXTS**

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<th>Decree no. 2015-1417 of 04 November 2015 regarding cosmetic products and tattooing products</th>
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<th>Memorandum of 16 December 2014 presenting the provisions of ordinance no. 2013-1183 of 19 December 2013 regarding the standardisation of financial and penal sanctions for health products and the adaptation of the scope of authorities and agents in charge of reporting infractions and texts written to apply the decision (applies to all health products)</th>
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<td>Decree no. 2015-373 of 31 March 2015 regarding the methods for issuing payment requests for financial sanctions related to health products</td>
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<td>Guidelines for determining financial sanctions and the &quot;medicine pricing chart&quot; and &quot;medical device pricing chart&quot; appendices (October 2015).</td>
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