In order to better fulfil its mission to the public, ANSM has worked collectively to overhaul the agency. Several priority projects have spearheaded these efforts. Throughout 2016, the agency's activities have been marked by heightened steering efforts, the implementation of a quality control process, and the use of modernised tools.

The objectives and performance contract (COP) was implemented for the first time in 2016. During the year, the agency also saw preliminary results from its tool and process adaptation project.

Improvement in the agency's ability to serve the public is especially evident in its continuing efforts to strengthen health product surveillance and provide innovative products that patients can access safely, quickly, and fairly.

In 2016, ANSM launched a new programme to track risk/benefit ratios based on risk management as it pertains to the use of medicines. By the end of the year, fourteen active substances were added to the programme. Pharmacovigilance network management was augmented: twenty-one new pharmacovigilance investigations were opened in 2016, and the results from twenty-eight other investigations were reported by the regional pharmacovigilance centres. With respect to medical device surveillance, four new regional medical device and reagent surveillance representatives were put in place. The agency handled some 1,790 quality defect reports, seventy-six of which required a batch recall, and helped manage 405 reports of shortages or potential shortages.

As part of its surveillance policy, the agency initiated fifteen pharmacoepidemiology studies in 2016 to attain an overall view of the safety profile for medications (or categories of medications) and medical devices.

The agency's control (4,996 test reports produced) and inspection activities (a total of 692 inspections, 8% of which were conducted abroad) led to many administrative decisions, including fifty-nine authorisations to open a pharmaceutical site, 180 authorisations to change a site, three decisions to completely or partially suspend an opening authorisation, fifty-eight injunctions, seven health policy rulings, and one financial sanction.

France’s contribution to European projects, in terms of medication surveillance, risk assessment, new medication evaluation, and the evaluation of new indications for medications that already have MAs, was maintained in 2016. ANSM acted as the rapporteur for 190 out of the 2,164 cases on the agenda of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). The agency also helped prepare two European regulations regarding medical devices. These laws will change how these products are monitored and released on the market.
In 2016, the agency renewed its advisory bodies, which help clarify the decisions of the director general. The agency hired an ethics officer and improved its organisation to better apply its rigorous ethics policy, thereby guaranteeing the independence and impartiality of its experts.

The agency pursued its educational and informative programmes regarding health product safety in 2016. It also continued to foster discussions and information sharing between various relevant stakeholders. It strengthened its partnerships with other health system operators and took part in eleven public health plans. ANSM helped change legislation and regulations on both a national (114 texts) and European level (37 texts).

In order to better adapt to today's health safety challenges, fulfil its public health missions to the best of its ability, and provide the level of public service expected by patients and external stakeholders, the agency implemented a quality control programme with a view to managing risk through a process-centred approach. This strategy will become a central part of each of its missions by 2017.

To continue fulfilling its missions despite fewer personnel and a limited budget, the agency examined the structure of its activities in 2016 so as to more clearly identify its priority actions and decisions. It continued to help employees adapt and consolidate their professional skills by implementing a training policy that supports employees throughout their career, beginning their very first day on the job. It also designed a business line reference base to meet projected management goals for jobs and skill sets.

In addition to its efforts to improve performance, the agency worked to ameliorate its employees' quality of life at work by pursuing a psycho-social risk prevention plan and a pro-active policy to hire and retain disabled personnel. It also experimented with remote work.

All of ANSM's teams worked tirelessly throughout the year to promote public health and help transform the agency. We would like to commend them for their efforts.

Catherine de Salins,  
Chairwoman of the ANSM Board of Administration

Dominique Martin  
Director General of ANSM
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The French National Agency for the Safety of Medicines and Health Products (ANSM) was created on 1 May 2012 as a result of the French law of 29 December 2011 reinforcing the safety of medicines and health products. The agency ensures the safety of medicines and other health products throughout their life cycle. It transparently shares its decisions and actions regarding health products with all healthcare stakeholders, manufacturers, and members of the public, to enable them to understand and take ownership of said actions. The agency pursues its public service missions in the sole interest of patients.

ANSM has an administrative board, a scientific board, and 3 advisory commissions. It also relies on an Ethics of Expertise Committee and Department which help guarantee the independence and impartiality of the agency’s decisions.

ANSM’s goal: to combine rapid access to innovative developments with the continued adjustment of health products’ risk/benefit ratio to match therapeutic progress.
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 promote 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 monitor advertising that promotes health products
- To inspect manufacturing and distribution sites
- 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
- Related therapeutic products
- Breast milk collected, tested, processed, and preserved by breast milk banks.

Medical devices and in vitro diagnostic medical devices

- Diagnostic and in vitro diagnostics therapeutics, technical platforms, and medical software.

Biocides, cosmetics and tattoos
KEY FIGURES IN 2016

Guaranteeing the safety of health products

In France, 2,800 active substances are marketed; 30% of these products are generic medicines. As of 31 December 2016, the risk/benefit ratio of 14 active ingredients was being revised or reassessed.

55,761 adverse effect reports were registered by regional pharmacovigilance centres, 3,061 of which were submitted by patients; 29,963 cases of serious adverse effects were reported by pharmaceutical laboratories.

21 national pharmacovigilance investigations were opened by ANSM.

2,414 medication error or risk of medication error reports were reported by ANSM and 1,790 quality defects were reported.

ANSM managed 405 supply shortages and sought therapeutic alternatives for essential medicines.

Blood products and biological products derived from the human body

7,618 adverse effects related to haemovigilance were reported among recipients of labile blood products.

544 adverse effects related to biovigilance (organs, tissues, cells, breast milk, and related therapeutic products) were reported.

Medical devices and in vitro diagnostic medical devices

15,961 adverse effects related to medical device vigilance were reported, 129 of which were received from patients and patient associations.

1,474 adverse effects related to reagent vigilance (in vitro diagnostic medical devices) were reported.
Promoting patients' rapid access to innovative developments

11,909 patients are covered by the cohort temporary authorisation for use (TAU) system for medicines

14,029 patients have initiated treatment under a named-patient TAU

1,033 clinical trials have been authorised including 756 trials for medications and 227 for medical devices and in vitro diagnostic medical devices

114 new medications have been authorised under the centralised European procedure including thirteen medications for which France was the rapporteur

ANSM is financing 10 new academic research projects

565 MAs, including 406 generic medication authorisations, have been issued under the French national procedure, the European decentralised procedure, and the mutual recognition procedure

France, by way of ANSM control laboratories, releases more vaccines to French and European markets than any other member state
Consolidating ANSM's relationships with stakeholders and promoting their involvement

Bodies
- 3 advisory commissions
- 4 technical interface committees working with vigilance networks
- 5 French pharmacovigilance committees
- 23 working groups
- 14 active TSSCs (Temporary Specialised Scientific Committees).

Ethics
- 3,411 Public Declarations of Interest [DPIs] examined
- 4,155 ethics analyses conducted by the Ethics Department.

Information/exchanges
- 100 information updates added to the ANSM website
- 4 vigilance reports
- 2,622,296 visitors to ANSM's website
- 22,400 subscribers to the "ANSM Actu" newsletter
- 7,571 Twitter followers as of the end of 2016
- 6,500 press articles and/or radio or television segments on topics related to ANSM
- 106 ADAC (Administrative Document Access Commission) requests were addressed to ANSM
- 4 projects piloted by patient associations were supported (€80,000 in total)
- 3 Interface Committee and patient association working group meetings on paediatric medications were held.

Scientific research
- 15 pharmacoepidemiology studies were launched
- The results of 6 pharmacoepidemiology studies were published
- 13 articles from ANSM teams were published in international scientific journals
Performing laboratory controls and inspections

692 inspections were conducted in 2016, 16% of which were random and 8% of which were conducted abroad (starting materials: 14%, pharmaceutical laboratories: 30%)

4,729 analysis reports were produced by laboratories.

Reinforcing ANSM's efficiency and pursuing its modernisation

949 FTE (full-time equivalents) as of 31 December 2016
45 years old—average age of employees
72% female workforce
4 days of training on average per every ANSM employee

Budget of €128.7 million in terms of commitment authorisation and €132.3 million in payment appropriations.
HIGHLIGHTS IN 2016

January
- The TRU for Truvada, established by ANSM as a pre-exposure prophylaxis (PrEP) to prevent HIV, is in effect while the indication extension for this condition, which was granted by the European Commission in August 2016, is pending
- Emergency inspection of the BIOTRIAL company in Rennes due to serious adverse effects in healthy volunteers during a biomedical research trial involving experimental medication developed by the BIAL company
- Investigation report and recommendations on automated labile blood product transport systems
- Launch of fifth call for scientific research proposals aiming to improve current knowledge concerning the misuse of medications and medical devices
- Launch of fifth call for proposals aimed at patient associations to promote initiatives encouraging the proper and safe use of health products
- Publication of the results of an ANSM study on the Haemorrhagic and thromboembolic risks associated with dual anticoagulation treatment using VKA and heparinotherapy (LMWH) during the initiation of VKA in uncomplicated auricular fibrillation
- Investigation of the rapid syphilis diagnostic screening market: assessment of sensitivity and specificity of testing options
- Operational implementation of the accounting and budgetary information system SIFAS, which is also used by five other health agencies.

February
- Bioequivalence Study Quality Day
- Publication of the study on the use of nitrofurantoin in France between March 2012 and February 2015
- Twenty-two working groups renewed or created.

March
- Organisation of two informational meetings for pharmaceutical companies to review recent regulatory changes and best manufacturing and distribution practices
- Implementation of safety measures for phase 1 clinical trials involving healthy volunteers
- Misuse of cough suppressants and antihistamines among adolescents and young adults: warning issued by ANSM to all relevant stakeholders
- Establishment of the Commission for the Initial Assessment of the Risk/Benefit Ratio of Healthcare Products
- Participation in the tenth conference of General Medicine (Paris, France).
April

- Establishment of the Commission for Monitoring the Risk/Benefit Ratio of Healthcare Products
- Establishment of the Commission on Narcotics and Psychotropic Drugs
- Publication of a report on a medical device vigilance investigation concerning the risk of allergic reactions caused by dialysers
- Publication of the 2015-2016 heightened surveillance report on external automatic defibrillators
- Suspension of the marketing authorisation for skin whitening injections
- Cosmetic regulations - Publication of a question/answer document.

May

- ANSM hosted the twenty-first annual meeting of the network of Official Medicines Control Laboratories (OMCLs)
- Publication of a summary report on biosimilar medicines
- Pipettes and other oral solution administration devices: seventeen recommendations to manufacturers to limit medication errors
- Reminder of recent and previous data on the risks of neural-developmental disorders in children exposed to certain antidepressants in utero
- Implantable defibrillation leads: summary and surveillance report
- Phthalate labelling for medical devices - Recommendations to manufacturers
- Market surveillance of DEHP-free PVC medical devices - Report
- Director general’s decision to reconvene the Ethics Committee
- Distribution of the ANSM Ethics Charter

June

- Fourth Information and Exchange Day with patient associations
- Catherine de Salins appointed Chair of the Board of Administration.
- Information meeting on updates to the Standard Prion Protocol (PSP)
- Tramadol oral solution for children: warning about medication errors
- Pregabalin (Lyrica and generics): warning issued by ANSM on the risks of abuse, misuse, and drug dependency
- Participation in the Benchmarking of European Medicines Agencies (BEMA IV).

July

- Provision of a naloxone nasal spray as an emergency treatment for opioid overdose as part of a cohort TAU
- Meningitec: the results of the supplementary analyses conducted by ANSM and the opinions of experts questioned by the Temporary Specialised Scientific Committee (TSSC) confirm that people who received the Meningitec vaccine are under no risk due to a quality defect
- Biocompatibility of textured breast implants: investigation results
- Quality control of medical devices that expose people to ionising radiation - 2015 annual report
- Appointment of the head of the ANSM Ethics of Expertise Department: Elisabeth Hérail.

August

- Publication of the ANSM/HAS report Use of coronary endoprosthesis (stents) in France in 2014: study based on SNIIRAM data
Use of artificial nails: ANSM informs consumers about the risks and precautions they should take

Publication of the study Exposure to valproic acid and its derivatives during pregnancy in France from 2007 to 2014: observational study of SNIIRAM data.

September

Baclofen: ANSM simplified the TRU and thoroughly examined all efficacy and safety data for baclofen with a view to analysing the risk/benefit ratio for this medication so as to determine its conditions of use to treat alcohol addiction

Risk of serious colchicine overdose: reminder of the guidelines governing proper use

Results of calls for proposals issued to researchers and patient associations

De-notification or cessation of activities of notified bodies: implementation by ANSM of a procedure to manage the consequences faced by manufacturers who use their services; these management principles were approved through a consensus between the relevant European authorities

Participation in the sixth Euripa Rural Health Forum in Marseille

Creation of a new Interface Committee with the Collège de la médecine générale

Renewal of the Interface Committee with patient associations.

October

Participation in the institutional information campaign regarding generic medications.

November

Publication of a report on antibiotic consumption in France between 2000 and 2015

Publication of a brochure on the analysis of consumption and resistance in partnership with ANSES [The French Agency for Food, Environmental, and Occupational Health Safety] and Santé publique France [The French Public Health Agency]

New interventional radiodiagnostic and radiology decisions to clarify the scope of these two decisions

Publication of the results of an ANSM study on the treatment of patients suffering from IBD in France

Participation in the annual Collège National des Généralistes Enseignants [National College of Generalists in Medical Education] conference in Grenoble.

December

Durogesic (fentanyl): new patch colour to limit the risk of medication errors

Following serious complications in four patients at the Nantes University Hospital (use of the BEAC protocol), an investigation was immediately conducted on the quality of the relevant batches of proprietary medicines: it was determined that these medications were not the cause of the aforementioned complications

Update of best manufacturing practices in accordance with a decision made by the director general of ANSM

Publication of the study Exposure to incretin mimetics and risk of pancreatic cancer among type 2 diabetics.
Part 1

Guaranteeing the safety of health products throughout their life cycle

1. Monitoring medicines
   - Monitoring medication use data
   - Conducting independent pharmacoepidemiology studies
   - Monitoring and managing risks
   - Monitoring market supply
   - Control over advertising.

2. Surveillance of blood products and biological products derived from the human body
   - Haemovigilance: surveillance of the transfusion chain
   - Biovigilance: surveillance of the collection chain for organs, tissues, and cells.

3. Surveillance of medical devices and in vitro diagnostic medical devices
   - Surveillance of incidents and risks of incidents
   - Market control activities
   - Control over advertising.

4. Surveillance of other health products
   - Surveillance of cosmetic products
   - Surveillance of tattoo products.

5. Inspection to ensure practice and health product quality compliance
   - Inspection of clinical and non-clinical trials
   - Inspection of medicines and their starting materials
   - Inspection of blood products and other biological products
   - Inspection of medical and IVD devices
   - Inspection of cosmetic products.

6. Quality of health products in the laboratory
   - Quality control of medicines and biological products
   - Laboratory control campaigns for medical devices
   - Laboratory control campaigns for other health products.
1- Monitoring medicines

Medicine surveillance covers all activities that occur after a medicine receives marketing authorisation. These actions include:

- monitoring medicine use and reducing misuse, medication errors, and overexposure,
- the detection, characterisation, and management of risks related to medication exposure,
- the implementation of measures intended to increase a given medicine’s safe use and the surveillance of the impact of these measures as needed,
- securing patient access to medicines of major therapeutic interest when no therapeutic alternatives are available or when the supply of these medications is inadequate in France,
- securing the market by working with manufacturers to manage medication quality defects,
- ex-ante oversight of medication advertisements.

Monitoring medication use data

The surveillance of sales, prescription, and reimbursement data makes it possible to track changes in the French pharmaceutical market. It also reveals information about the market’s main characteristics, particularly in comparison to other countries in and outside of Europe, and points to longer-term trends, in addition to one-off events, that shape the way the market is changing, thereby allowing ANSM to adapt its surveillance strategy.

Regarding a specific medicine or class of medicines, the monitoring of its use makes it possible to assess the population's level of exposure and evaluate the impact of a measure or recommendation on consumption, which in turn tells authorities how to best adjust a medication's prescription recommendations and conditions of use.

In light of this, up-to-date reports on the consumption of specific products, or on the pharmaceutical market as a whole, are written and published to keep health professionals and the public informed about medication consumption practices and how they are changing.

Highlights in 2016

- In 2016, ANSM published an updated report on antibiotic use in France from 2000 to 2015
- Moreover, a special brochure on antibiotic surveillance, devoted to the analysis of antibiotic consumption and resistance, was published in November for European Antibiotic Awareness Day in partnership with ANSES and Santé publique France.

FOCUS ON: Detecting medicine misuse through surveillance

The purpose of medicine use surveillance is to understand how medicines are used under real-life conditions and detect, quantify, and assess the potential consequences of any type of use that does not comply with the terms of a medicine's authorisation or TRU. The aim is to prevent any practice that could expose the user to an excessive risk which is not offset by a proven benefit.

Reports of medicine use that is not in compliance with the terms of its TRU or authorisation can come from a range of sources:

- They most often come from reports and information collected by the regional pharmacovigilance centre network, which receives information about actual practices from patients and health professionals.
- Patient associations and health system users, as well as organisations that represent health professionals (learned societies, organisations, etc.), are also special sources of information about real-life practices.
Similarly, the interactions between ANSM, its partners, and the French health insurance system are essential for detecting and preventing misuse.

Moreover, some uses that are not in compliant with the terms of a medicine’s TRU or authorisation are identified through ANSM’s surveillance and assessment activities. For example, the quantitative or qualitative detection of “abnormal” consumption may be based on the surveillance of changes in consumption patterns over time, on the measurement of the gap between the target population and the user population, and on a comparison of international data for the pharmaco-therapeutic classes at risk for non-compliant use.

Finally, manufacturers must monitor and collect usage information for the medicines they are responsible for, especially through educational and pharmacovigilance activities, and pass this information on to ANSM. The legislation stipulates that a company that manufacturers a proprietary medicine must help ensure that it is used properly and take every educational measure it deems necessary to inform health professionals when it observes prescriptions that are non-compliant with the proper use of the medication. Moreover, the company must inform ANSM of these practices. It must also provide ANSM with any information that can help assess the medicine’s risks and benefits. This includes the results of efficacy and safety studies for all indications and populations, whether or not they are included in the MA, as well as data concerning any use of the medicine that is not in compliance with the terms of its MA and any sales and prescription volume data for the medicine or product in question. Given this, ANSM created a service to centralise all non-compliant use reports. In September 2015, it published a guide designed to help manufacturers of proprietary medicines report non-compliant medication prescriptions that come to their attention. The purpose of this measure is to identify cases of non-compliant use and collect the information needed to evaluate the public health impact of these practices so as to put in place, as necessary, appropriate measures to prevent or reduce non-compliant use.

Highlights in 2016

- Topiramate (Epitomax® and generics): warning about conditions of use that fall outside of the MA and potential impact on mood (October 2016)
- Risk of serious colchicine overdose: reminder concerning the proper use of this medication (September 2016)
- ANSM issued a warning about the non-MA combination of growth hormone with GnRH analogues or aromatase inhibitors in children and adolescents (September 2016)
- Equimolar mixture of nitrous oxide and oxygen (Antasol®, Entonox®, Kalinox®, Oxynox®): reminder concerning proper use and safety of use (September 2016)
- Nitrofurantoin: reminder about proper use and observance of indications (May 2016)
- Warning about the non-MA use of aripiprazole (Abilify® and generics) and the risk of suicide (February and April 2016).

In 2016, these surveillance efforts and aforementioned sources of reporting resulted in the discovery of thirty-nine cases of medication use that were not in compliance with the terms of the medicine’s authorisation and that exposed users to a potential or proven risk. During the course of 2016, risk reduction measures were implemented for 49% of these cases. The remaining cases were still being evaluated as of 31 December 2016.

Conducting independent pharmacoepidemiology studies (see Chapter 3)

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 pharmacoepidemiology studies. It is able to independently develop study
protocols, conduct critical analyses, and communicate results. These studies are conducted using various available databases, including the National Health Insurance Inter-Scheme Information System (Système national interrégimes de l’assurance maladie [SNIIRAM]). They help to reinforce the surveillance of health products under real-life conditions.

⇒ See page 107, “Promoting independent research to support the agency’s missions”.

Monitoring and managing risks

While the purpose of every medicine is to reduce or prevent suffering and disease, care should be taken when using medicinal products. Indeed, all medicines carry the risk of adverse effects. Therefore, ANSM works with its European partners and pharmacovigilance centre network to monitor each stage in the life cycle of all medicines.

Annual risk/benefit ratio revision and reassessment programme for medications

Reassessment of the risk/benefit ratio of marketed medicines is a recurrent process that occurs throughout their life cycles. It is essential to verify that the efficacy data presented at the time the marketing authorisation (MA) was granted and the safety data initially reported during clinical trials are still valid under real-life conditions when the medicine is subject to large-scale use. This guarantees that the treatment options available to health professionals and the public are tailored to efficacy and safety of use data.

A medicine’s risk/benefit ratio can be reassessed for a number of reasons related to various risk management scenarios:

- following an adverse effect report,
- following a decreased benefit report,
- after an assessment of the latest data, especially during the MA renewal process which occurs every five years.

The risk/benefit ratio monitoring programme for thirty-one active substances, which the agency launched in 2011, was concluded in 2015. This programme was based on the revision (using immediately available data) and reassessment (using all available data regarding the medication’s benefits and safety of use, including the data available to laboratories) of expired marketing authorisations.

In 2016, a new risk/benefit ratio monitoring programme was launched to manage the risk associated with medication use. Following the opinion of the Commission for Monitoring the Risk/Benefit Ratio of Health Products, this programme resulted in restricted indications, modified MA information, and changes to the prescription and delivery conditions for medications1.

As of 31 December 2016, the risk/benefit ratio of fourteen active ingredients was being revised or reassessed.

Focus on: List of the active substances and proprietary medicines whose risk/benefit ratio is currently under revision or reassessment as of 31 December 2016

Paracetamol / opium powder / caffeine (Lamaline®), dexamethasone / salicylamide / hydroxyethyl salicylate (Percutalgine®), isothipendyl chlorhydrate (Apaisyl®), almitrine bimesylate (Vectorion®), promethazine (Phenergan®), alimemazine (Théralène®), porfimer sodium (Photofrin®), mephenesin (Decontractyl®), omega-3 triglycerides (Ysomega®), troxerutin / heptaminol chlorhydrate / ginkgo extract (Ginkor®), cicletanine chlorhydrate (Tenstaten®), tenoxicam (Tilcotil®), chlorambucil (Chloraminophène®), and niaouli.

1 Summary table of the opinions rendered in 2016 by the Commission for Monitoring the Risk/Benefit Ratio of Health Products can be found in Appendix 1, p. 140.
Pharmacovigilance

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). Pharmacovigilance examines adverse effects that occur under normal conditions of use as well as those that arise due to medication errors, abuse, misuse, overdose, or 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 to their local Regional Pharmacovigilance Centre (RPC). The thirty-one RPCs record the adverse effect (AE) reports they receive in the national pharmacovigilance database. When information regarding an adverse effect changes over time (for example due to a change in a patient's health status), they are recorded as case follow-up data.

Any health professional who is aware of an adverse effect, which may have been caused by a medicine, 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, which may have been caused by a blood-derived product, even if he/she has not directly prescribed, supplied, or administered the medicine in question.

Since June 2011, patients and authorised patient associations have also been able to directly report an adverse effect related to a medicine without going through a healthcare professional.

Any company or organisation developing a medicine 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 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 and the European Medicines Agency (EMA).

On a national and European scale, ANSM has worked to continuously improve the quality of its organisation with respect to vigilance, particularly pharmacovigilance.

In 2016, the agency focused on the following matters:

- closer management of the pharmacovigilance network in an effort to affirm the role of RPCs by improving the organisation’s efficiency, including the gradual implementation of activity and performance indicators for each centre under a new 2016-2018 ANSM-CHU-ARS agreement and a plan to monitor them through an activity report written jointly with the French Directorate General of Healthcare starting in 2016. The agreement is centred around a follow-up committee created in 2015 and must account for vigilance and regional reforms;
- implementation and application of the recommendations of the pharmacovigilance audit conducted in 2015 in accordance with the action plan written for this purpose, along with the implementation of revised processes to secure and simplify internal pharmacovigilance (processing, timing, scientific quality, traceability, and workload);
- continuation of the improvement and modernisation process for existing information systems as well as the development of new databases, especially with regard to vigilance. This programme is designed to meet European requirements;
- continued active participation in the creation of a future report portal under the initiative of the Directorate General of Health (scheduled for March 2017).
Adverse effect reports submitted to ANSM

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<td>Total number of cases received and recorded by RPCs*</td>
<td>38 296</td>
<td>46 843</td>
<td>46 497</td>
<td>47 089</td>
<td>55 761</td>
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<tr>
<td>• including serious adverse effect reports</td>
<td>25 331</td>
<td>31 089</td>
<td>30 156</td>
<td>30 412</td>
<td>35 622</td>
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<td>• including adverse effect reports submitted by patients</td>
<td>1 446</td>
<td>2 151</td>
<td>1 983</td>
<td>2 331</td>
<td>3 061</td>
</tr>
<tr>
<td>Number of adverse effect reports from pharmaceutical companies*</td>
<td>23 975</td>
<td>28 180</td>
<td>26 478</td>
<td>29 469</td>
<td>29 963</td>
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*The number of adverse effect reports includes initial cases and follow-up.

Adverse effect reports reported to the national pharmacovigilance system – comparison between cumulated data in 2016 and 2015
Adverse effect pharmacovigilance reports received from patients – comparison between cumulated data in 2016 and 2015

Profile of declarants reporting adverse effects recorded in the national pharmacovigilance base in 2016

National pharmacovigilance investigations

Pharmacovigilance investigations analyse all available pharmacovigilance data (reports, literature, statistical detection, etc.) to characterise the risks associated with medicine exposure. For example, these investigations can confirm a new report, identify a risk related to misuse, or monitor how a risk...
that has already been identified is changing. In 2016, 105 pharmacovigilance investigations were in progress.

Number of national pharmacovigilance investigations decided upon by ANSM through the Technical Pharmacovigilance Committee

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In 2016, ANSM opened twenty-one new pharmacovigilance investigations. In addition, twenty-eight national pharmacovigilance investigations conducted by RPCs were presented during ten meetings of the Technical Pharmacovigilance Committee in 2016. In response, the Technical Pharmacovigilance Committee issued the following opinions:

- revision/reassessment of the risk/benefit ratio for three active substances (two additional requests to revise/reassess the risk/benefit ratio were made following exceptional cases);
- modification of the prescription and delivery conditions for an active substance;
- modification of the MA information for six active substances.

Since September 2016, an automated report detection system for the national pharmacovigilance database has been in use. The results are systematically sent on to the RPCs in charge of investigations.

France's contribution to European pharmacovigilance

The French national pharmacovigilance system is seamlessly integrated into the European pharmacovigilance system as a whole. France participates in the Pharmacovigilance Risk Assessment Committee (PRAC) and contributes to the European Medicines Agency’s (EMA) EudraVigi database.

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 2016, over 1.2 million adverse effect reports, including slightly more than 47,000 reports submitted by patients, were received by EudraVigilance, the European database, i.e. a similar number to last year. The total number of notifications from RPCs accounts for approximately 16% (55,761) of notifications from member states (339,544) in the EU, whereas the French population represents 13% of the EU population.

Number of cases recorded in PRAC agendas

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<tr>
<td>Number of cases recorded in PRAC agendas</td>
<td>1 565</td>
<td>1 648</td>
<td>1 932</td>
<td>2 164</td>
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<tr>
<td>- for which France is the rapporteur</td>
<td>200</td>
<td>163</td>
<td>224</td>
<td>187</td>
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</table>
PRAC France rapporteur – Procedure type

<table>
<thead>
<tr>
<th></th>
<th>Referral</th>
<th>Report</th>
<th>RMP*</th>
<th>PSUR**</th>
<th>PASS***</th>
<th>Renewal of MA****</th>
<th>Other</th>
<th>Total</th>
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<td>3</td>
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<tr>
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<td>6</td>
<td>0</td>
<td>4</td>
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<tr>
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<tr>
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<td>6</td>
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<tr>
<td>Dec.</td>
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<td>6</td>
<td>7</td>
<td>3</td>
<td>4</td>
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<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td>54</td>
<td>68</td>
<td>36</td>
<td>17</td>
<td>9</td>
<td>187</td>
</tr>
</tbody>
</table>

*Risk Management Plan  
**Periodic Safety Update Report  
*** Post-Authorisation Safety Studies  
**** Marketing Authorisation

Highlights in 2016

- 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)
- Within PRAC, France is the rapporteur for the assessment of the periodic reports on the risks and benefits (PBRER) of 115 substances included on the European list of active substances and combinations of active substances covered by MAs in more than one member state
- With respect to collective assessments of the safety of use data for all proprietary medicines containing the same active substance (PSUSA), ANSM completed the assessments and wrote the reports for sixty-one active substances in 2016. The agency also relayed comments to European authorities concerning ninety-two assessment reports about active substances (for which France was not the rapporteur) that were singled out as priority applications on the basis of pre-defined criteria.

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 European Union (EU). The recommendation then becomes a legally binding decision throughout the EU. It is issued by the European Commission, or, if the medicines in question have been authorised by
a national procedure but are available in additional member states, the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

- Nineteen referral procedures were finalised in 2016²
- Six of these referral procedures were related to pharmacovigilance (according to articles 31, 20, or 107i of pharmacovigilance-related legislation).

The thirteen 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.

In 2016, ANSM continued deliberations to strengthen its position within the European pharmacovigilance system, especially within PRAC. The agency is working to forge closer bonds between French PRAC representatives and the agency's health product divisions and foster communication pertaining to regulatory, organisational, and scientific issues.

Since 2015, the Scientific and European Strategy Division has included a dedicated department made up of PRAC, CHMP, and CMDh members. The department’s mission is to monitor the evolution of French positions and contributions within various European committees working in the field of medications. To do this, the department uses indicators that help it evaluate the impact of French positions, especially in terms of “high-stakes” issues. The department is also tasked with helping to better coordinate and manage the agency's European activities.

**Highlights in 2016**

- Apremilast (Otezla®): new, important recommendations regarding suicidal thoughts and behaviour (24/11/2016)
- Lenalidomide (Revlimid®): new, important recommendations regarding viral reactivation (09/11/2016)
- Blinatumomab (Blincyto®): risk of pancreatitis (28/10/2016)
- Thalidomide (Celgene®): important recommendations regarding viral reactivation and pulmonary hypertension (22/06/2016)
- Pomalidomide (Imnovid®): new, important recommendation regarding hepatitis B screening prior to initiating treatment (25/04/2016)
- Bcr-Abl tyrosine-kinase inhibitor (Glivec®, Sprycel®, Tasigna®, Bosulif®, Iclusig®): hepatitis B screening must be done prior to initiating treatment due to a risk of reactivating the hepatitis B virus (07/04/2016)
- Idelalisib (Zydelig®): restrictions regarding the use of this medication to treat chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL) relapses after new clinical trial results (24/03/16)
- Aflibercept (Zaltrap®): information regarding osteonecrosis of the jaw (17/03/2016)
- Erlotinib (Tarceva®): restricted indication for maintenance treatment of non-small cell lung cancer, exclusive to patients with tumours that have a mutation that activates the epidermal growth factor receptor (EGFR) (15/01/2016)
- Combination of ombitasvir/paritaprevir/ritonavir (Viekirax®) with or without dasabuvir (Exviera®): treatment contraindicated in patients with moderate liver failure (Child-Pugh class B) (06/01/2016).

**France’s contribution to international pharmacovigilance**

VigiBase is an international pharmacovigilance database that was created in 1978. It is the largest and most complete database in the world. VigiBase is maintained by the Uppsala Monitoring Centre (UMC)

² Complete table of referral procedures can be found in Appendix 2, p. 142.
under a World Health Organisation (WHO) mandate. More than 110 countries participate in the collection of pharmacovigilance data. France is the fourth largest contributor, providing approximately 4% of the total number of adverse effect reports received. As of 31 December 2016, it had transmitted a total of 560,880 cases from the French National Pharmacovigilance Database.

Countries contributing to ICSR (Individual Case Safety Report) VigiBase

<table>
<thead>
<tr>
<th>Countries</th>
<th>ICSR as of 31/12/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>6 784 199</td>
</tr>
<tr>
<td>South Korea</td>
<td>790 069</td>
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<tr>
<td>UK</td>
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<td>France</td>
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<td>China</td>
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<td>Italy</td>
<td>333 265</td>
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<tr>
<td>Thailand</td>
<td>330 016</td>
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<tr>
<td>Other</td>
<td>9 658 240</td>
</tr>
<tr>
<td>Total</td>
<td>14 018 926</td>
</tr>
</tbody>
</table>

Risk reduction measures

Medicines are regulated by routine measures (Summary of Product Characteristics for medical professionals, patient leaflets, prescription status, etc.) that rationalise their use. When these measures are insufficient to ensure safe and effective use, other steps may be taken to prevent or reduce the probability of adverse effects, their severity, and/or their impact on patients. These measures include:

- letters to health professionals: thirty-nine such letters were sent in 2016 regarding risk management, including thirty-four that were sent for product safety reasons

- additional risk reduction measures: various types of informational tools or documents for patients and/or health professionals, including letters, guides, checklists, brochures, patient cards, and training programmes:
  - 23 active substances were subjected to new additional measures in 2016 (leading to 48 documents distributed), including nineteen substances covered by an MA (new active substances or substances with extended indications) and four substances that were targeted by surveillance efforts involving active substances already on the market
  - additional measures were approved for five generic active substances, which must apply the same measures as the corresponding proprietary medicines
  - thirty-four additional measures were updated (59 documents)

- a restricted access programme: product access is restricted by specific measures pertaining to prescription conditions, delivery, and use.

These measures can be combined, as in the case of a pregnancy prevention plan. 13 teratogenic active substances are subject to a pregnancy prevention plan that requires, among other measures, a signed consent to treatment form.

The application of these measures is the responsibility of the MA holder and is overseen by ANSM. The latter ensures that all documents are tailored to a given product’s safety concerns and conditions of use. Such documents cannot be used for promotional purposes and their presentation must be
distinguishable from that of pharmaceutical advertisements.

The content of these documents must be clear, adapted for public use, and targeted to address any identified safety issues. Prescription advice (patient selection, follow-up, etc.) should be included, as should information pertaining to the treatment of adverse effects. The reporting of adverse effects should also be encouraged.

**Highlights in 2016**

**Pregnancy prevention plan:**

- Mycophenolic acid (CellCept® and generics, Myfortic®): mycophenolic acid is a major teratogen that results in an increased risk of miscarriage and birth defects if used during pregnancy. Three documents were created in order to limit this risk:
  - a guide for health professionals outlining the risks associated with exposure to mycophenolic acid during pregnancy and the measures that must be taken to reduce these risks;
  - a guide that every patient should receive from their prescribing physician informing them of the foetal risks associated with mycophenolic acid. The guide should also explain how to best reduce these risks and stress the importance of planning a pregnancy so that an alternative treatment method may be chosen;
  - a treatment consent and contraception form for women of child-bearing age to ensure that the patient is fully informed and understands the risks associated with taking mycophenolic acid during pregnancy. The patient's treatment is safeguarded in that the form must be signed by the specialised prescribing physician and the patient every six months. The pharmacist cannot dispense the medication unless the prescription is accompanied by the signed form.
- In addition, work has been implemented to strengthen the overall medication risk prevention strategy with respect to exposure during pregnancy.

**FOCUS ON: Risk reduction measures related to the use of medications containing valproate or its derivatives during pregnancy**

*In utero* exposure to medications containing valproate or its derivatives results in an increased risk of birth defects and neurodevelopmental disorders in the foetus. In light of these risks, these medications were reassessed throughout Europe in 2013.

After this reassessment, a series of risk reduction measures were put in place in France. These measures concern both patients and health professionals:

- Creation of educational materials, including a guide for the prescribing physician, an informational brochure for patients, and a treatment consent form.

- New prescription and delivery conditions, which went into effect in May 2015, were created for treatment initiation. These conditions were also applied to ongoing treatments as of 1 January 2016:
  - These medications cannot be prescribed to girls, female adolescents, pregnant women, or women of child-bearing age unless alternative medicines are not tolerated or are not effective;
  - A year prescription by a specialised physician is required (neurologist, psychiatrist, or paediatrician depending on the indication);
  - These medicines cannot be dispensed to patients without an initial yearly prescription from a specialist and a treatment consent form.

- A warning label must be added to the exterior packaging of these medications beginning in the first quarter of 2016. This measure applies only in France.

These measures will be completed in 2017 following the creation of a patient card. The purpose of this card is to remind patients of the foetal risks associated with *in utero* exposure to medications containing
valproate or its derivatives as well as the need to use effective contraception during treatment. An icon will also be added to the packaging box of these medications in 2017. In addition, ANSM has launched a reassessment of the risks associated with *in utero* exposure to all anticonvulsants, not just valproate. This study will be completed in 2017.

**Managing medication errors**

Monitoring medication errors is an integral part of the medicine surveillance policy. This work, which is coordinated with pharmacovigilance activities, focuses on non-adverse-effect errors, potential errors, risks of medication errors (latent errors), and medication errors resulting in adverse effects.

The Medication Errors Service, created 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 documentation, etc.). Since 2005, the number of reports has increased by a factor of five.

In 2016, 2,414 reports were submitted to ANSM, including 1,982 known errors, 179 potential errors, and 253 risks of medication error (or latent errors). Out of the substantiated error reports, 60% resulted in an adverse effect (half of which were considered serious by pharmacovigilance standards) and 36% did not. For the remaining 4% of cases, the incident's description made it impossible to determine whether or not the error resulted in an adverse effect.

ANSM can take the following risk reduction measures:

- 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.
- action in the context of a more overarching discussion about medicines (for example: improved and harmonised labelling for small volumes of injectable solutions, recommendations and informational campaigns regarding administration devices for oral solutions, etc.).

In 2016, new medication error prevention measures regarding oral solution administration devices in multi-dose bottles (pipettes, droppers, measuring spoons, etc.) were implemented as part of this process.

**Change in medication error reports**

<table>
<thead>
<tr>
<th>Change in medication error reports</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<tr>
<td></td>
<td>1,734</td>
<td>1,589</td>
<td>2,248</td>
<td>2,525</td>
<td>2,741</td>
<td>2,414</td>
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</table>

**Highlights in 2016**

- Pipettes and other oral solution administrative devices: seventeen recommendations to manufacturers to limit medication errors (May 2016). ANSM regularly receives error risk and medication error reports regarding oral solution administration devices in multi-dose bottles (pipettes, droppers, measuring spoons, etc.) that can result in serious consequences for the patient. In response, ANSM continues to take actions to prevent medication errors related to these administration devices. In 2016, the agency published a document for manufacturers detailing its recommendations for these devices.
- Tramadol oral solution for children: warning about medication errors (June 2016).
- Eligard®, powder and solvent for injectable solution: (leuprolide acetate): medication errors, reassessment of prescription and delivery conditions/completion of a serum testosterone test (September 2016)
- Colour change of Duloxetine Mylan 30 mg and 60 mg gel capsules (September 2016)
Monitoring market supply

Securing the supply of medicines of major therapeutic value when manufacturers report a limited supply or a stock shortage

ANSM manages stock shortages and risks of stock shortages for medications of major therapeutic value, i.e. medications or classes of medication for which a break in supply would endanger the lives of patients in the short or medium term or represent a significant loss for patients regarding the progression of their disease, or for which there is no appropriate treatment alternative available in sufficient quantities in France.

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. To this end, ANSM requests and coordinates measures to be implemented by pharmaceutical laboratories. Such measures promote:

- the optimisation of stock distribution (stock tracking, quantitative and/or qualitative quotas)
- reporting on proprietary medicines, along with any corresponding recommendations as needed, and input from the relevant laboratories to increase the production of substitute medicines
- the import of medicines available abroad that are not covered by an MA in France, after verifying that they meet national standards
- communication with patients and/or health professionals.

The year 2016 was marked by the publication of new texts containing the legislative and regulatory measures established by the health system modernisation law. These texts consolidated and itemised the measures to be taken to manage supply shortages for medicines of major therapeutic value, especially those that should be carried out by pharmaceutical distribution laboratories and wholesaler distributors, in order to prevent supply interruptions.

Highlights in 2016

- Support during periods of limited supplies or supply shortages for certain vaccines, such as the hepatitis A vaccine or vaccines containing the pertussis valency, due to an insufficient supply of vaccine production facilities
- Oversight of measures implemented during instances of limited supply or supply shortages of several injectable antibiotics due to problems with the supply of starting materials
- Management of the secure supply of essential medicines (oncology, anaesthesia, etc.) during supply shortages caused by the closure of production sites located outside of France.
Change in reports of stock shortages and limited supplies (2012-2016): the number of reports of stock shortages or risks of stock shortages has stabilised over the past few years

Managing quality defects

ANSM processes and assesses all medication quality defect reports that it receives. These defects can occur during the manufacture of medications and/or active substances.

The number of medication quality defect reports is constantly rising; this figure rose from 624 in 2004 to 1,790 in 2016. Depending on various criteria and the associated patient risk, a solution is formulated based on each report. In 2016, 685 reports resulted in in-depth investigations.

If necessary, batches can be recalled by the laboratory in cooperation with ANSM. In most cases, the pharmaceutical dossier management system (the PD portal managed by CNOP) is used to issue the recall. Seventy-six batch recalls were performed using this method in 2016. The main reasons for these recalls were stability defects, cross-contamination, and non-compliance with product specifications. In some cases, other risk reduction measures related to quality defects may be put in place based on an evaluation of the risk/benefit ratio, for example when a batch recall would lead to a supply shortage for a medication of major therapeutic value.

ANSM can also issue "Rapid Alerts" for the quality defect reports it receives. This informs the relevant authorities in other countries of the assessments and decisions made with respect to a report that concerns several countries. The agency also participates in working groups with EU member countries to harmonise quality defect management practices. It is in close contact with the EMA when these reports affect medications with European MAs.

Highlights in 2016

- Batch recalls for several proprietary medications following the MA suspensions of Sandoz and Teva Sante (decision dated 08/07/2016, effective 19/07/2016) due to serious reservations regarding the medications' bioequivalence data
- Recall of the proprietary medications Kogenate Bayer 1000 UI, powder and solvent for solution for injection; Kogenate Bayer 3000 UI, powder and solvent for solution for injection; and Bayer Healthcare and Helixate Nexgen 2000 UI, powder and solvent for solution for injection/Helixate Nexgen 3000 UI, powder and solvent for solution for injection from CSL Behring SA following stability monitoring tests that demonstrated non-compliant results over time (July 2016)
- Following serious complications in four patients at Nantes University Hospital (use of BEAC protocol), an investigation was immediately conducted on the quality of the relevant batches of proprietary medicines: it was determined that these medications were not the cause of the aforementioned complications (December 2016).
Change in the number of quality defect reports

Number of recalls due to a quality defect - comparison of the cumulated data from 2015 and 2016
Control over advertising

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

Advertisements for health professionals. Number of dossiers submitted in 2016

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 conditions under which he or she should 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).

Of 1,607 dossiers examined in 2016, 6% were refused and 57% were sent back for corrections.
General public advertising – Cumulated number of dossiers submitted – 2016 vs. 2015

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.

**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.

This mission is defined by two international agreements adopted by the UN, the 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. In France, this authority is ANSM.

France is the second largest legal opioid-producing country in the world. 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 to the International Narcotics Control Board (INCB) each year. 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 (with the exception of 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 procedures. 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 Public Health Code 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), DTA, and the French national survey on chemical dependence]. ANSM also 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** (Antalgiques 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)
6. **DTA** (Décès toxiques par antalgiques - Drug-poisoning deaths involving analgesics)

**Highlights in 2016**

- Creation of a naloxone nasal spray for narcotic drug users for the emergency treatment of opioid overdoses (July 2016) as part of a cohort temporary authorisation of use
- Pregabalin (Lyrica and generics): warning issued by ANSM on the risks of abuse, misuse, and drug dependency (June 2016)
- Mercalm, Nausicalm (dimenhydrinate), Nautamine (diphenhydramine): warning issued by ANSM about the risk of abuse and misuse (March 2016)
- Misuse of cough suppressants and antihistamines among adolescents and young adults: warning issued by ANSM to all stakeholders involved in the healthcare or social treatment of young people about the misuse of these medications delivered with or without a prescription (March 2016).

**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.
The French National Agency for the Safety of Medicines and Health Products

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

- classifying these substances on the 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 prevent or reduce the risks or manage the consequences of using non-medicinal psychoactive substances.

In 2016, the commission met three times. It issued an opinion in favour of classifying several substances as narcotics due to their potential for abuse and dependence:

- 10 new synthetic cannabinoids and twelve synthetic cannabinoid families.

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<tbody>
<tr>
<td>Post-MA survey of dependence on pharmaceutical products</td>
<td>12</td>
<td>9</td>
<td>14</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Evaluation of abuse and dependence potential as part of the MA application</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Evaluation of abuse and dependence potential of psychoactive substances (plants, synthetic drugs, etc.)</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>National addiction vigilance monitoring</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

The commission also ruled on:

- The availability of naloxone (Nalscue) in a nasal spray (cTAU) for narcotic drug users for the emergency treatment of opioid overdoses
- Continued national addiction vigilance monitoring of methadone, high-dose buprenorphine, and sodium oxybate
- The modification of the distribution circuit for the proprietary medicine Xyrem with the possibility of deliveries through non-hospital-based pharmacies.
2 - Surveillance of blood products and biological products derived from the human body

Haemovigilance: transfusion chain surveillance

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, post-blood donation information, and adverse effects occurring in recipients. This database also enables 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 that could impact the safety of the blood transfusion chain and the safety of blood donors.

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. The agency 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 2016 87 reports of epidemics were received, leading to seventeen consultations with CAD. These reports involved (in descending order): Zika virus, West Nile virus, dengue fever, Crimean-Congo haemorrhagic fever (Nairovirus), and Plasmodium vivax (malaria)

Serious adverse effect reports in haemovigilance (donor) – comparison of cumulated data 2015 vs. 2016
Adverse effect reports in haemovigilance (recipient) – comparison of cumulated data 2015 vs 2016

These reports concern blood vigilance events with possible, probable, and certain accountability. 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 changes in the report content.

Highlights in 2016

- Recommendations regarding automated transport devices for labile blood products - Report (January 2016)
Biovigilance: surveillance of the collection chain for organs, tissues, and cells

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, or breast milk collection chain and affecting the donor upon administration or the patient upon transplant.

This activity was transferred to the Biomedicine Agency on 1 December 2016 in accordance with law no. 2016-41 of 26 January 2016 regarding the modernisation of our health system (OJ 27/01/16). ATP biovigilance is still overseen by ANSM and will remain under its purview until such products become compliant with the latest regulations, no later than 26 January 2019 (Article 3 of Decree no. 2016-1622).

It should be noted that clinical trial vigilance regarding organs, tissues, cells, and breast milk remains the responsibility of ANSM.

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</thead>
<tbody>
<tr>
<td>Number of events declared</td>
<td>387</td>
<td>461</td>
<td>518</td>
<td>540</td>
<td>544*</td>
</tr>
</tbody>
</table>

* data from 01/01/2016 to 30/11/2016, excluding ATPs (01/01/2016 to 31/12/2016)

Breakdown of adverse effects by product category in 2016 (from 01/01/2016 to 11/30/2016)

<table>
<thead>
<tr>
<th></th>
<th>Organs</th>
<th>Tissues</th>
<th>Cells</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
<td>145</td>
<td>5</td>
<td>37</td>
<td>187</td>
</tr>
<tr>
<td>Incidents</td>
<td>165</td>
<td>17</td>
<td>110</td>
<td>292</td>
</tr>
<tr>
<td>Adverse effect and incident</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
<td>30</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>Events</td>
<td>311</td>
<td>52</td>
<td>167</td>
<td>530</td>
</tr>
</tbody>
</table>

Highlights in 2016

- Suspension of the delivery of breast milk from the Paris region breast milk bank run by Necker on 2 September 2016. This suspension took place after two extremely premature infants died from a *Bacillus cereus* infection after consuming breast milk from this breast milk bank. Analyses did not reveal a common source for the strains identified in the newborns, breast milk, and environment. The Paris region breast milk bank resumed its activities on 3 October 2016.
3 - Surveillance of medical devices and in vitro diagnostic medical devices

A medical device is 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 20,000 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, these products are marketed under 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 any 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 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) and for active implantable medical devices, the design dossier 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 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 performing market surveillance by registering the devices with the greatest risk and carrying out one-off or topical assessment campaigns per product range
- inspecting the market to verify the compliance of medical devices after they are released on the French market
- 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

- monitoring the French notified body’s operations by conducting several inspections. ANSM may participate in joint audits with its European counterparts in order to conduct foreign notified body audits
- conducting laboratory quality control audits when additional tests are required.

In September 2016, the Council of the European Union reached a political agreement on two compromises, regarding regulations on medical devices and in vitro diagnostic medical devices, that strengthened the market surveillance measures detailed in current directives. The European Council and Parliament are expected to adopt and publish the new texts in 2017.

Highlights in 2016

- In 2016, ANSM continued to experiment with regional reagent and medical device vigilance correspondents, a project it began in 2015, while adding four new regions. In addition to running the local network of reagent and medical device correspondents, the six regional correspondents are now tasked with their first assessment of medical device vigilance incidents that occurred in a healthcare establishment in their region as well as the management of a range of regional and national investigations.
- ANSM held an informational meeting on updates to the Standard Prion Protocol (PSP) on 29 June 2016. Following the appearance of transmissible spongiform encephalopathies (TSEs) and the identification of unconventional transmissible agents (UTAs or prions), special measures for treating reusable medical devices were implemented in French health establishments to limit the risk of transmitting these agents. To assess the performance of products and procedures claiming to target prions, a benchmark method called the Standard Prion Protocol (PSP) was developed and published in November 2011 under the direction of ANSM and the French Directorate General of Health. Given increasing scientific knowledge on the subject, ANSM decided to review the PSP so it could be adapted to the latest techniques and newly available "strain/animal" models. This initial meeting consisted of a presentation and discussion with participants regarding the pre-project preparation measures to be taken before the public consultation phase.
- De-notification or termination of notified bodies’ activities (September 2016): Several notified bodies have ceased their operations over the past few years, either voluntarily or following a de-notification decision made by a competent authority. In the past three years, the number of notified bodies has decreased from eighty-three to fifty-seven. Due to this situation, ANSM has implemented a procedure to manage the consequences of the de-notification of a notified body on manufacturers that depended on their services. These management principles were detailed in a text published in September 2016 and were agreed upon by the competent European authorities.
- Clay-based medical devices for oral use: ANSM has launched an investigation into these medical devices, which are designed to be ingested in order to treat bloating and digestive discomfort. This investigation involves verifying the lead content of these devices. Consequently, the decision was made to suspend the manufacture, marketing, exportation, and distribution of the TERRAFOR and DEFILIGNE devices. ANSM will continue to investigate this market in 2017.

Reports

- Use of coronary endoprosthesis (stents) in France in 2014: Study based on SNIIRAM data—Report (August 2016)
- Medical software security - Study conducted by Serma Ingenierie at the request of ANSM (July 2016)
- Implantable defibrillation leads: Summary and surveillance report (May 2016)
- Phthalate labelling for medical devices - Recommendations to manufacturers (May 2016)
- Market surveillance of DEHP-free PVC medical devices - Report (May 2016)
- Investigation of the rapid syphilis diagnostic screening market: assessment of sensitivity and specificity of testing options (January 2016).
Surveillance of incidents and risks of incidents

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.

Nearly 44% of reports come from healthcare institutions, 47% from manufacturers, and 9% from other stakeholders (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, and French and European institutions).

<table>
<thead>
<tr>
<th>Medical device vigilance</th>
<th>2012*</th>
<th>2013*</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of reports</td>
<td>13 168</td>
<td>13 822</td>
<td>16 194</td>
<td>15 783</td>
<td>15 961</td>
</tr>
<tr>
<td>- Serious</td>
<td>807</td>
<td>989</td>
<td>972</td>
<td>825</td>
<td>749</td>
</tr>
<tr>
<td>- Submitted by patients and patient associations</td>
<td>56</td>
<td>43</td>
<td>38</td>
<td>34</td>
<td>129</td>
</tr>
</tbody>
</table>

*Data from 2012 and 2013, excludes PIP silicone breast implants.

Highlights in 2016

- Publication of a report on a medical device vigilance investigation concerning the risk of allergic reactions caused by dialysers (April 2016)
- Batch withdrawal for Cell Saver, consumables used during autotransfusion procedures (April 2016)
- Investigation into the use of iodoform gauze: decision to suspend the manufacture, marketing, distribution, and exportation of the product Ercemeche due to its non-compliance with regulatory requirements needed for the marketing of this type of medical device (May 2016)
- Biocompatibility of textured breast implants: Results from investigations (July 2016)
- Study of the premature degradation of biological heart valves; recommendation to monitor patients with Mitroflow heart valves from the company LivaNova (September 2016)
- ANSM message with recommendations to monitor patients fitted with Unify Fortify defibrillators (October 2016)
- Recommendation establishing the conditions of use for Clinac 6 VARIAN + DPS radiation therapy systems prohibiting the use of a Clinac radiation therapy accelerating torque system and a Brainlab target positioner (November 2016)
- Continued heightened surveillance of breast implants, particularly reports of anaplastic large cell lymphoma associated with breast implants
- Investigation and heightened surveillance of vigilance cases involving the permanent birth control device Essure.
FOCUS ON: Breast implants, Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL). Ongoing investigation update

Since 2015, as part of heightened surveillance efforts regarding breast implants, ANSM has pursued specific actions in response to the regular occurrence of BIA-ALCL. Each medical device vigilance report is thoroughly reviewed. By the end of 2016, thirty-one cases had been identified and confirmed in France. In addition, studies were launched to determine the immunological mechanisms involved once tissues are brought into contact with the surface of breast implants.

The major areas of focus in 2016 included:

- Continued investigations into the link between ALCL in the breast and breast implants. The topic of ALCL had been addressed in 2015 through the creation of a temporary specialised scientific committee that included clinic experts, toxicologists, chemists, and other specialties. Supplementary studies launched in 2015 were continued in 2016. This work focused on texture and the immunological mechanisms triggered by breast implants.

- A review of biocompatibility data from manufacturers that sell textured breast implants in France was finalised. In 2016, this review led to the creation of a Temporary Specialised Scientific Committee (TSSC) to study the development of an assessment strategy for breast implant biocompatibility. The committee found that the majority of textured breast implant manufacturers were unable to prove the biocompatibility of their marketed products, despite such proof being required by law. Each manufacturer was asked to provide biocompatibility data within one year. Action plans for each manufacturer were sent out, and they should be completed by July 2017. An update on the subject was published on ANSM’s website on 6 July 2016. The press release was accompanied by an official line document instructing manufacturers to demonstrate the biocompatibility of textured breast implants.

- In 2015, SILIMED breast implants lost their CE marking. A dedicated task force was set up to monitor this incident, in collaboration with other European competent authorities. The medical devices that had already been released on the French market were held in quarantine in 2016.

FOCUS ON: Essure, Information on the tubal sterilisation implant Essure (April 2016)

The medical device Essure has been under heightened surveillance by ANSM since July 2015 following a rise in the number of incident reports occurring during clinical studies. This surveillance is based on several methods, including:

- a systematic review of all medical device vigilance incidents reported to ANSM
- an analysis of epidemiological data using data from the National Health Insurance Inter-Scheme Information System (Système national interrégimes de l’assurance maladie [SNIIRAM])
- an assessment of the clinical and pre-clinical data available for this device
- on-site inspections.

The medical device ESSURE is a permanent hysteroscopic contraceptive device for women. It has been sold in France since 2002 and is under heightened surveillance due to an increased number of reports involving the device. ESSURE is most commonly used in France and in the United States.

In light of this situation, ANSM took the following measures:

- the agency asked the manufacturer to publish a leaflet to be given to patients prior to each placement procedure in order to keep them better informed, emphasize the need for a three-month placement check, and explain the risks associated with this sterilisation method
- a decree was published in February 2016 regulating the placement procedure for this device: only obstetrician-gynaecologists with significant experience in operative hysteroscopy, who practise in designated healthcare establishments, can place this device. In April 2016, ANSM published an article reviewing the precautions that should be taken when placing the ESSURE device and the methods for monitoring patients after the procedure. Women who experienced
complications after the placement procedure were encouraged to submit a medical device report.

- The agency launched an epidemiological study, based on data from the French healthcare system, to describe the use of the ESSURE device and assess its safety by comparing it to the benchmark method, laparoscopic tubal ligation. The study is scheduled to be completed in the first quarter of 2017.

Investigations continued throughout 2016 and led to the creation of a Temporary Specialised Scientific Committee to obtain an expert opinion on the risk/benefit ratio of this device.

The agency was in constant contact with patient associations, and information was distributed through the press, ANSM's website, and social networks.

Other countries also became interested in the topic, especially the United States, where a working group was created to investigate the device's risk/benefit ratio. Measures were taken to better assess the device's safety and inform patients about the potential risks associated with using it.

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).

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<td></td>
<td>1409</td>
<td>1 059</td>
<td>980</td>
<td>1 355</td>
<td>1474</td>
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Origin of reagent vigilance reports (2016)

- Health establishments - 13%
- Manufacturers - 74%
- Other - 13%
Market control activities

ANSM may also proactively conduct a reassessment of the regulatory conformity and risk/benefit ratio of a medical device, at any point in its life cycle, as part of its market monitoring and vigilance report management activities. To this end, the agency monitors products after they have been released 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 in 2016**

- De-notification or termination of the activities of notified bodies: monitoring of French manufacturers faced with the de-notification of their notified bodies and permission, under certain conditions, to continue marketing their products (September 2016)
- Decision to suspend the manufacture, exportation, distribution, marketing, and advertising of the product Olioseptil Inhalation, which was incorrectly classified as a medical device instead of a medication (February 2016)
- Zika virus testing and diagnosis.

**Identificiation 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), manufacturers of devices belonging to other classes must also notify ANSM. This notification, which must be received prior to the device’s release in France, provides information about market stakeholders as well as devices in use within the country.

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<tbody>
<tr>
<td>Class I medical devices</td>
<td>978</td>
<td>3 142</td>
<td>3 573</td>
<td>4 251</td>
<td>3 591</td>
</tr>
<tr>
<td>Class IIa, IIb, &amp; III medical devices and active implantable medical devices</td>
<td>3 527</td>
<td>5 196</td>
<td>5 255</td>
<td>5 583</td>
<td>8 094</td>
</tr>
<tr>
<td>Custom-made medical devices</td>
<td>441</td>
<td>174</td>
<td>941</td>
<td>693</td>
<td>536</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices</td>
<td>422</td>
<td>394</td>
<td>569</td>
<td>531</td>
<td>863</td>
</tr>
</tbody>
</table>

* Any data discrepancies, as compared to previous years, are due to the new method for assessing applications (which has been in use since 2013).
Main target-specific campaigns by product range launched and/or continued in 2016

- Heart valves for new endovascular and transapical implantation methods (TAVI)
- Implantable defibrillation leads: summary and surveillance report
- Total hip replacement implants and constituent parts—Study
- Breast implants: BIA-ALCL, rupture and biocompatibility
- Definitive contraception devices
- Oral clay-based medical devices
- Evaluation of the toxicity of metal particles shed by medical devices
- Phthalate labelling for medical devices—Recommendations to manufacturers
- Market surveillance of DEHP-free PVC medical devices—Report
- Flow diverter stents for brain aneurysms
- Nasal sprays containing essential oils
- Investigation of Lyme disease reagent market
- Investigation of *Chlamydia trachomatis* diagnostic reagent market
- Continued studies regarding automatic external defibrillators (traceability, QC, vigilance reports).

**FOCUS ON: Market investigation following leaflets on Lyme disease serological reagents**

As part of the French High Council for Public Health's (HCSP) work on Lyme disease, including the publishing of a report in 2014, ANSM conducted an assessment on the reagents used to diagnose Lyme disease in blood samples. The agency noted some problems in the instruction leaflets for these reagents, including a deficiency of information regarding their composition and performance (evaluation data).

To address these problems, the HCSP report issued manufacturer recommendations that took into account the essential requirements of European Directive 98/79/EC and the European recommendations based on the scientific consensus of the European Union Concerted Action on Lyme borreliosis (EUCALB).

Following these assessments and based on the HCSP recommendations, ANSM investigated the leaflets for reagents available on the French market. The report was finalised in November 2016 following a series of discussions between ANSM and manufacturers. It includes the modifications, leaflet information, and performance data provided by manufacturers.

Notable reagents marketed in France include:

- ELISA and equivalent reagents, the majority of which offer performance in line with HCSP recommendations. Except for two of these reagents, they are made up of antigens from the various pathogenic species in Europe or antigens that are shared between these different species;
- Western blot analysis reagents, which also offer performance that corresponds to HCSP recommendations, with the exception of one reagent involving cerebrospinal fluid. These reagents are made up of antigens from the various pathogenic species in Europe or antigens that are shared between these different species;
- rapid diagnostic tests and a self-diagnostic test. These reagents show inadequacies and use assessment methods that still require additional studies. ANSM has already taken action against the manufacturers of these tests. These steps could lead to administrative measures if the manufacturers do not comply.

The ANSM report maintained existing manufacturer recommendations and added recommendations for users. ANSM has intervened and will continue to work with manufacturers to ensure that their reagents comply with the essential requirements of European Directive 98/79/EC regarding *in vitro* diagnostic medical devices. ANSM’s commitment concerning reagents is now a part of the French National Plan to Combat Lyme Disease and Other Tick-Borne Illnesses. This plan was announced in 2016 by the French Health Ministry.
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. Approximately 60,000 devices, currently in service in France, are concerned. Quality control methods have gradually been set by ANSM, which relies on accredited independent bodies responsible for verifying on-site compliance with the control standards drawn up by the agency itself. If compliance is doubt, either during the assessment or at a later date, ANSM may also perform an inspection. Sixty-two certifications are currently in force.

Furthermore, 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 plant operators of the need to cease activities until they are brought into compliance.

Since 2003, when external quality control of radiation-emitting medical devices was introduced, over 1,493 non-conformity reports have been received and processed by ANSM.

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<tbody>
<tr>
<td>Number of new standards</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Number of certifications granted</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Number of non-conformities reported</td>
<td>1 516</td>
<td>1593</td>
<td>1255</td>
<td>1 335</td>
<td>1176</td>
</tr>
</tbody>
</table>

Highlights in 2016

- Quality control of medical devices that expose people to ionising radiation—2015 Annual Report (July 2016)
- New interventional radiodiagnostic and radiology decisions issued in November 2016 to clarify the scope of these two decisions
- Development of a quality control protocol for breast tomosynthesis devices included in ANSM’s working agenda.

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 test implementation. It also makes it possible to monitor in vitro diagnostic medical devices used in laboratories. In 2016, the agency conducted 20 target-specific control operations, including 64 tests performed by medical biology laboratories. The activity led to the production of more than 8,724 individual reports.
Laboratories participating in national quality control | 2012 | 2013 | 2014 | 2015 | 2016
--- | --- | --- | --- | --- | ---
Private or equivalent laboratories | 2,243 | 1,322 | 869 | 805 | 756
Hospital laboratories | 819 | 781 | 723 | 677 | 670
EFS (French National Blood Service) laboratories | 160 | 164 | 53 | 37 | 36
Cancer centre laboratories | 27 | 27 | 26 | 18 | 18
Military laboratories | 13 | 14 | 13 | 13 | 13
Total | 3,262 | 2,308 | 1,684 | 1,550 | 1,493
"DNA profiling" expert laboratories | 76 | 79 | 84 | 83 | 84

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

### Control over advertising

Advertising control is an additional tool used to regulate the safety of use of health products. The law of 29 December 2011, reinforcing the safety of medicines and health products, extended the scope of advertising control to medical devices and in vitro diagnostic medical devices as well as objects, instruments, and methods.

Advertisements must present the MD/IVDMD in an objective manner, particularly in terms of performance or compliance with essential safety requirements. It must also promote correct use. In addition, advertising aimed at the general public is prohibited for reimbursable class II b 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.

| Control of advertising for medical devices and in vitro diagnostic devices | 2013 | 2014 | 2015 | 2016 |
--- | --- | --- | --- | ---
Number of applications submitted | 1,187 | 414 | 405 | 506 |
Number of applications denied | 26 | 28 | 63 | 49 |

### Highlights in 2016

- Two operators were fined following the dissemination of advertisements promoting an intraocular lens and a hip prosthesis. These operators did not comply with regulations pertaining to medical device advertisements and did not receive prior approval from ANSM.
FOCUS ON: Zika virus testing and diagnosis

The Zika virus is a flavivirus transmitted by mosquitoes from the genus *Aedes* that caused a significant epidemic in French Polynesia in 2013 and again in Brazil in 2015. The epidemic quickly spread throughout the Caribbean as well as Central and South America, including the French overseas departments in the region, resulting in cases of microcephaly and Guillain-Barré syndrome.

In 2016, the scientific community and the WHO decided that the Zika virus represented “a potentially global public health emergency”.

In this context, ANSM was approached about existing *in vitro* diagnostic medical devices involved in screening for and diagnosing a Zika virus infection.

There are several types of tests that detect a Zika virus infection. The RNA test by PCR directly detects the presence of the virus in a sample. Immunological tests (ELISA) look for Zika antibodies. These antibodies appear a few days to a few weeks after infection.

In the beginning of 2016, all Zika detection devices were in the process of receiving the CE marking. ANSM assessed these tests and helped several manufacturers complete the CE marking process. By the end of 2016, eight reagents (five PCR and three ELISA reagents) received the CE marking necessary for diagnosing patients and potential donors.

The epidemic ended in the French departments in the Americas at the end of 2016.

FOCUS ON: Surveillance programme for high-risk medical devices

Total knee replacement implants

Knee replacements are one of the five categories of medical devices included in the heightened surveillance plan established by the French Law of 29 December 2011. After an analysis of data from the market, vigilance network, and registers, the agency concluded there were no major problems with these devices.

An investigation was conducted among thirty-one manufacturers. It focused on the current state of the market and a study of all patient leaflets provided by manufacturers. The study did not find any cases of regulatory non-compliance. However, the leaflet study did indicate that the standardisation of patient materials would make them easier to read and therefore improve the safety of these devices. In addition, recent regulations, which require manufacturers to submit all medical device advertisements to ANSM, led to a reassessment of the relevance of brochure claims as compared to available data, clinical data in particular.

Finally, the analysis of medical device vigilance data enabled authorities to identify problematic issues: the breakage of hinged replacements and the detachment of non-constrained replacements. In addition, risk factors such as obesity and arthrosis should be taken into account during the procedure. Indeed, the increasing percentage of obese patients affects the revision rate. Therefore, this factor needs to be monitored just like any other pathology. This increase also indicates that measures to combat this pathology are a crucial part of public health policy and need to be implemented.

Hip replacements

Following the patient follow-up recommendations published in 2014 regarding metal-on-metal hip replacement implants, the agency continued to study the issue, particularly the potential precipitation of metallic particles, with a view to further adapting patient follow-up. The agency also continues to monitor these devices by tracking medical device vigilance reports. Special surveillance and analysis studies were also launched in 2016 on modular femoral necks.
Cardiac defibrillation leads

An overview of surveillance activities regarding cardiac defibrillation leads was published in May 2016. Due to the number of patients fitted with implantable defibrillation leads in France, the inherent risk associated with their use (permanent cardiac implantation), and the various safety measures associated with various models, cardiac defibrillation leads were added to the heightened medical device surveillance plan created by the French Law of 29 December 2011.

To this effect, an assessment of endocavitary defibrillation leads sold in France and a summary of the surveillance activities aimed at these devices were written, including a summary of the medical device vigilance data and an inspection campaign targeting the relevant manufacturers.

Five endocavitary defibrillation lead manufacturers (of devices that are marketed in France or could still be used by patients) were questioned by ANSM. In addition, a detailed analysis of the incident reports involving defibrillation leads was conducted. This work showed that the majority of the reports submitted to ANSM concerning defibrillation leads during this period came from manufacturers. Meanwhile, ANSM studied all advertising materials provided by manufacturers. ANSM requested that a large portion of them be changed. However, data analysis did not reveal any specific problems requiring additional measures at this stage. Careful monitoring of these devices remains necessary given their inherent therapeutic risk and the various safety measures implemented over the past few years for several lead models.

Heart valve surveillance for new endovascular and transapical access is currently being finalised

Heart valves for new endovascular and transapical access are included on the heightened medical device surveillance plan created by the French Law of 29 December 2011 because:

- their placement can be life threatening for the patients receiving these devices,
- their use is associated with an inherent level of risk (cardiac implantation, permanent use).

An assessment of transcatheter implantation procedures for aortic and pulmonary bioprostheses was conducted as was a technical and regulatory evaluation of the use leaflets, CE certificates, and all other documents accompanying the introduction of these devices on the market. The investigation is ongoing and includes:

- a clinical data study from each manufacturer,
- active bibliographic surveillance,
- an assessment of the medical device data,
- a study of the available data in French registries.

Finally, an inspection campaign was carried out on these medical devices.
4 - Surveillance of other health products

Surveillance of 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, i.e.:

- 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
- on the condition that they indicate their composition for the purposes of providing information to consumers.

Operators—particularly manufacturers and those responsible for marketing the products—are required to compile a dossier including, most importantly, 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 exposure levels. 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, established 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 to ban 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.

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 that occur 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.

On 11 July 2013, European regulation 1223/2009/EC relative to cosmetic products entered into force and stipulated that serious adverse effects (SAEs) must be reported and transmitted. Since that date, ANSM has served as a liaison between the competent European authorities, manufacturers, and end-users concerning these effects.
Since 2013, ANSM has received a growing number of cosmetic product vigilance reports. In 2016, the agency handled 238 cosmetic product vigilance reports (compared to 227 in 2015, 193 in 2014, and 157 in 2013). One hundred and five of these reports involved serious cases.

**Controlling the cosmetic 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. Several substance families are the subject of in-depth expert assessments, lead and endocrine disruptors in particular.

**Highlights in 2016**

- Use of artificial nails: ANSM informed consumers about the risks and precautions they should take (August 2016)
- Suspension of the market authorisation for skin whitening injections (April 2016)
- Regulation on cosmetic products—Question/response (April 2016)
- Decision to suspend the manufacture, exportation, distribution, marketing, and advertising for the product Baume Secours, which was incorrectly classified as a cosmetic product instead of as a medication (February 2016).

**Surveillance of tattoo 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 2016, ANSM continued its involvement in the European work carried out by the Council of Europe. This included 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 practice and health product quality compliance

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 enforceable regulatory provisions are implemented in the context of scheduled inspection programmes or random inspections (12% of inspections in 2016).

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 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 2016, the total number of inspections totalled 692 (compared to 630 in 2015) with a random inspection rate of 12% and an inspection rate outside the European Union of 8%.

The year was marked by a confirmation of the number of administrative decisions resulting from observations made during inspections. ANSM issued fifty-eight injunctions (forty-one in 2015), meaning that slightly over 8% of inspections led to this type of measure. ANSM also issued seven health policy decisions (twenty in 2015 and fifteen in 2014) as well as one financial sanction.

Highlights in 2016

- All of the division’s inspection activities were accredited by COFRAC [the French accreditation body] in accordance with ISO norm 17020
- The first financial sanction to be implemented following an inspection was adopted by ANSM.

Inspection summaries

- Total knee replacement—Inspection summary (01/14/2016)
- Best Manufacturing Practices for Cosmetic Products—Inspection summary (02/03/2016)
- Implantable defibrillation leads—Inspection summary (05/19/2016)
- Assessment of the active substance amoxicillin—Inspection summary (08/11/2016)
- Automated external defibrillators (AEDs) - (11/24/2016)
Inspection of clinical and non-clinical trials

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 the sponsors of these trials. These inspections mainly focus on the safety of the individuals participating in the trials and on the verification of the quality and credibility of the data obtained from the trials.

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.

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Highlights in 2016

- Emergency inspection on 15 and 16 January of the company BIOTRIAL in Rennes in light of the serious adverse effects experienced by healthy volunteers that occurred during biomedical research to test an experimental medication developed by the company BIAL.
- On 9 February 2016, ANSM organised a Bioequivalence study quality day. The event provided participants with an opportunity to discuss the quality of bioequivalence studies and lay the foundations for an action plan involving manufacturer requests for generic medicine marketing authorisations.
Medicine and starting material inspection

In order to operate as pharmaceutical facilities, laboratories conducting activities related to the marketing of medicines in France or Europe must first be authorised by ANSM.

At the end of 2016, ANSM listed 978 pharmaceutical sites in France, including 438 manufacturers and/or importers, 287 operators, and 442 wholesale distributors (some sites having several statuses). Regional health agencies inspect 355 sites with the sole status of wholesale distributor on behalf of ANSM, while the other sites are monitored by ANSM inspectors. ANSM also lists 750 pharmaceutical starting material manufacturing, distribution, and import sites in France. These facilities are inspected by ANSM. In 2016, 59 authorisations to open a pharmaceutical site were issued (56 in 2015), and 180 authorisations to modify a pharmaceutical site were granted (164 in 2015).

Medicine inspection activities cover verification of manufacturing and distribution conditions, as well as operators' pharmacovigilance systems. In 2016, ANSM performed 209 medicine-related inspections in France and abroad, i.e. 30% of the total number of inspections. ANSM inspected 191 pharmaceutical sites located in France in 2016. On the basis of these inspections and those conducted by regional health authorities, twenty-six sites received a letter prior to an injunction and eighteen were the subject of an injunction. In addition, three 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, and import conditions. In 2016, ANSM performed eighty-one of these inspections in France and fifteen abroad, i.e. 14% of the total number of inspections.

ANSM also works to prevent the marketing of falsified products and provides information to consumers about this issue. The year 2016 was 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 on the Internet.

### Starting material inspections

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### Pharmaceutical site inspections (operators, manufacturers, importers, and distributors)

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The French National Agency for the Safety of Medicines and Health Products

### Administrative site management

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### Pharmacovigilance system inspection

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### Highlights in 2016

- Authorisation for the CATALENT pharmaceutical site in Beinheim to reopen once its business was brought up to standard (April 2016)
- Authorisation for the Stallergènes pharmaceutical site in Antony to gradually resume its activities once its business was brought up to standard (March 2016)
- ANSM organised two educational day events for pharmaceutical sites on 23 and 24 March 2016. These meetings allowed participants to review recent regulatory developments and analyse the main inconsistencies found during inspections with respect to best manufacturing and distribution practices. They also provided the opportunity to discuss ongoing organisational changes in the management of application files (opening, modification, annual statement, etc.)
- Decision to update best manufacturing practices made by the Director General of ANSM (30 December 2016).

### Inspection of blood products and other biological products

The preparation, import, and storage of products derived from the human body (blood, tissue, cells, and breast milk) are strictly regulated by a set of best practices and a prior authorisation scheme that all sites handling these products must follow. The sites are inspected to ensure they correctly apply the best practices that are relevant to their operations.

### Inspection activities for blood products and other biological products

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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 conduct its monitoring activities, ANSM oversees the technical appraisal of breast milk bank operating authorisation applications, which are issued by Regional Health Agencies. The agency also carries out site inspections to evaluate operational practices and ensure that the breast milk delivered by breast milk banks is handled safely.

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Authorisation scheme for highly pathogenic human toxins and micro-organisms

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

The granting and renewal of authorisations depend on ANSM’s assessment of the risks inherent to such handling in terms of both biological safety and security. Inspections aim to verify that the operations carried out within laboratories comply with authorisations granted by ANSM and that these facilities operate in full compliance with the biological safety and security control requirements put in place due to the risks associated with MOTs. In addition, ANSM monitors licensed representatives who are authorised to hold and handle MOTs. The agency also collects administrative reports, which provide additional information about operators and help track any changes in their activities. These reports

3 Number of adverse events reported between 1 January and 30 November 2016. On 1 December, biovigilance was transferred to the Biomedicines Agency (See page 37).
concern the loss or theft of MOTs, incidents, accidents, and more generally, any event that could potentially result in the spread of MOTs.

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</tr>
<tr>
<td>Laboratories and sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of entities (teams able to work at the same site)</td>
<td>122</td>
<td>116</td>
<td>138*</td>
<td>Not available</td>
<td>138***</td>
</tr>
<tr>
<td>Number of MOT authorisation holders</td>
<td>138</td>
<td>143</td>
<td>153</td>
<td>161‡</td>
<td>152</td>
</tr>
<tr>
<td>Total number of inspections performed per year</td>
<td>24</td>
<td>20</td>
<td>21</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Number of dossiers forwarded to the judicial authorities</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Entities grouped within 102 sites
** The issuance of multiple authorisations, sanctioning several types of operations, was systematised in 2016, notably for MOT transfers (handovers, imports, and exports)
*** Entities grouped within 110 sites

Surveillance 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. These companies are inspected to verify that they have followed 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 also inspected.

ANSM conducts target-specific control and inspection campaigns, which most often focus on the groups of medical devices that carry the highest risk (classes IIb and III) and/or developing groups. In 2016, inspections targeted heart valves, dental implants, external automatic defibrillators, and immunohaematology tests. An inspection campaign involving the activity of representatives was also finalised in 2016.

ANSM performed 140 inspections of medical devices and in vitro diagnostic medical devices, i.e. 18% of the total number of inspections. Eleven MD sites and eight IVD-MD sites received an injunction, and two 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 notified body appointed by France to certify medical devices. To this end, three inspections of LNE/G-MED (medical certification body) were conducted in 2016. Two joint assessments were conducted by ANSM inspectors at the site of other notified European bodies. The agency also handled authorisation retractions for notified bodies in 2016. Such retractions may result from findings identified through these joint assessments or through a considered decision requiring certain bodies to cease their activities.

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* The 2015 annual report contained an error: the total number of MOT authorisations issued during the year 2015 was 1,236.
‡ The 2015 annual report contained an error: the number of MOT authorisation holders during the year 2015 was 161.
Cosmetic product inspection

There are approximately 3,300 companies (marketing representatives, manufacturers, distributors, etc.) involved in the field of cosmetics, 600 of which are involved in the manufacturing process. Cosmetic product manufacturers are required to register with ANSM.

ANSM inspects cosmetic product manufacturers and marketing representatives to verify that:

- the product application justifies its marketing (product information application)
- product manufacturing, distribution, import, and export practices comply with current regulations.

As in previous years, the 2016 annual inspection programme focused on validating compliance with the Cosmetic Products Regulation, including conformance with Best Manufacturing Practices. Among the inspection programme’s key findings, several cases of non-compliance were identified. These cases involved the formatting of safety assessment updates. Formatting requirements were modified by the Cosmetic Products Regulation, making evaluation standards for product information records more rigorous.

In 2016, ANSM carried out thirty-six cosmetic product inspections. Eight manufacturers received an injunction, requiring them to bring their product studies or manufacturing conditions into compliance, and one health policy decision was made.

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 annual cosmetic product control programmes and, in particular, the sharing of information.
The French National Agency for the Safety of Medicines and Health Products

### Highlights in 2016

- In 2016, the inspection programme incorporated a target-specific campaign regarding customisable cosmetics. This sector is growing and constantly changing. The marketing of these products must comply with cosmetic regulations, especially those governing safety assessments.

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of inspections</td>
<td>48</td>
<td>26</td>
<td>32</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Number of injunctions</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Number of health policy decisions</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of dossiers forwarded to the judicial authorities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
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 prior to marketing (see also “Releasing batches of vaccines and blood-derived medicines” on page 82)
- To perform laboratory tests for all health products, within the framework of scheduled market surveillance or one-off, “emergency”, requests
- To contribute to the work of the European Pharmacopoeia in developing new monographs by conducting laboratory analyses and participating in different strategic working groups
- Moreover, the Control Division (Direction des Contrôles) regularly takes part in numerous collaborative studies, both on a national and, more often, European and international level.

Highlights in 2016

- ANSM hosted the twenty-first annual meeting of the network of Official Medicines Control Laboratories (OMCLs) from 23 to 27 May 2016. This meeting, which is presided over by the EDQM (European Directorate for the Quality of Medicines) and organised each year in a host European country, provides all network members with the opportunity to discuss a variety of common themes. In 2016, France, and therefore ANSM, was the organising country. During the meeting, Dominique Martin opened the general session with an ANSM presentation, and the Control Division addressed several topical concerns related to medicines and medical devices, both in terms of market surveillance and batch releases.
- Following the presentation of pharmacovigilance reports, an investigation was conducted to ensure the quality of cancer treatments used in the pre-autotransplant protocol. As part of this process, five proprietary medicines used to treat cancer were analysed. The results were compliant with stated specifications.
- BIOTRIAL clinical trial (BIA 10-2474, sponsored by BIAL): inspection of products used during a trial involving serious adverse events.
- Meningitec: no risk to individuals receiving this vaccine. The results of supplementary analyses conducted by ANSM in its control laboratories, as well as the opinions of experts contacted by the Temporary Specialised Scientific Committee (TSSC), confirmed that people who received the Meningitec vaccine are not at-risk due to a quality defect (July 2017).
- A study was also launched to research particles and elements in vaccines and other injectable health products—Comparative study (07/18/2016).
- BCG vaccine shortage/import of the BIOMED BCG vaccine: launch of a stability study to adapt storage conditions for this vaccine once it is reconstituted in syringes (stored for four hours at +4°C).
- Yellow fever: control of a falsified vaccine batch circulating in Africa.
- Participation in a feasibility study to control all filgrastim biosimilar products in accordance with a standardised technique.
- Hosting of foreign delegations: Thailand/training in the release and control of a dengue fever vaccine. Northwest Africa (Morocco, Tunisia, Algeria)/training in batch releases.
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 based on a tool 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 in Europe (in which case the results are shared with other European countries) and medicines authorised only 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. All investigations are followed by detailed reports that are shared with all relevant ANSM divisions. Following the introduction of prior risk analyses, these investigations are now moving towards optimising the selection of controlled products (to avoid controlling identical products with different forms or names) and towards a two-step analytical practice designed to quickly control the selected products and concentrate exclusively on those whose results were flagged during the first stage.

ANSM has positioned itself to control medicines derived from biotechnologies as part of the annual programme organised by the EMA and EDQM. Various criteria have guided its choices, especially analytical feasibility and the acquisition of new techniques for the control of new products, especially biosimilar products or biosimilar products still under development. The Control Division tested the following three products:

- Avastin, in keeping with the work ANSM had already conducted in 2015 as part of the TRU
- NovoThirteen, the recombinant coagulation factor XIII, in accordance with the heightened appraisal of blood-derived medicines and the latest biotechnological innovations with respect to these product lines
- The monoclonal antibody Erbitux, which is indicated to treat metastatic colon cancer.

ANSM was also involved in numerous collaborative studies at the European and international levels (WHO):

- work on the general monograph for Infliximab and method verification for the European Pharmacopoeia
- participation in the implementation of the first international standard for the proprietary medicine Infliximab
- collaborative study on Filgastrim, the reference medicine Neupogen®, and all biosimilar products.

- **Controls conducted on an emergency basis following a suspected quality defect reported** through inspections, referrals from judicial authorities, and reports from health professionals or users.

In 2016, the total chemical medicine non-conformity rate was approximately 8% for controls conducted as part of the scheduled programme (mostly minor cases of non-conformity) and approximately 10% for controls conducted on an emergency basis. This rate climbed to 60% for products suspected of being falsified (these controls were mostly conducted at the request of judicial authorities). Every case of non-conformity is systematically monitored using appropriate follow-up measures.
Highlights in 2016

- Many cancer medicines were controlled in response to pharmacovigilance reports in collaboration with the Division of Medicines used in Oncology, Haematology, Transplantation, Nephrology, Cell Therapy Products, Tissues, and Labile Blood Products:
  - an investigation was conducted to ensure the quality of cancer treatments used in the pre-autotransplant protocol. As part of this investigation, several proprietary medicines were analysed.
  - a large study on the quality of Docetaxel was also launched in 2016.
  - The quality of proprietary medicines based on the cancer medicine Ifosfamide was investigated due to the occurrence of serious adverse effects.

- In association with the Division for Generic, Homeopathic, Herbal Medicines and Preparations, a comprehensive investigation on Latanoprost-based eye drops was conducted. The results were made available outside of ANSM.

- Many psychotropic medicines (SSRI antidepressants, anxiolytics, antipsychotics) were the subject of controls in collaboration with the Division of Medicines used for Neurology, Psychiatry, Anaesthesiology, Pain Control, Ophthalmology, Narcotics, Psychotropics, and Addictions as part of an investigation launched in 2015.

### 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 medications</td>
<td>10</td>
<td>83</td>
<td>9</td>
<td>6</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(medicines approved through the centralised procedure)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Non-compliance detection

<table>
<thead>
<tr>
<th></th>
<th>Scheduled controls</th>
<th>Emergency controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical medications</td>
<td>25/318, i.e. 8%</td>
<td>6/58, i.e. 10%</td>
</tr>
</tbody>
</table>

### Pharmacopoeia

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monograph studies for the French Pharmacopoeia</td>
<td>114</td>
<td>73</td>
<td>57</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Monograph studies for the European Pharmacopoeia</td>
<td>126</td>
<td>181</td>
<td>528*</td>
<td>554</td>
<td>402</td>
</tr>
</tbody>
</table>

*This number includes not only monographs studied during Pharmeuropa surveys, but also those 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 independent technical and scientific expert assessments 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.

<table>
<thead>
<tr>
<th>Laboratory control of medical devices</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medical devices controlled</td>
<td>145</td>
<td>73</td>
<td>91</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>Number of non-conformities detected</td>
<td>7</td>
<td>0</td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Highlights in 2016

- Approximately sixty hyaluronic acid dermal filler medical devices were controlled as part of a collaborative European study. No major anomaly was observed with respect to the parameters tested.
- In collaboration with the Division for Therapeutic Medical Devices and Cosmetics (DMTCOS), the analysis of a clay-based product (an oral gel capsule) showed lead levels that were higher than the permitted value in medications. A follow-up programme was put in place and other comparable products were analysed.

Laboratory control campaigns for cosmetic products and tattooing products

Laboratory control conducted by ANSM teams provides technical and scientific expert assessments 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, conducted at the request of the divisions concerned (Inspection Division and Products Division), or suspected quality defect cases (especially following an inspection). ANSM also participates in the development of joint studies and alternative control methods in the context of its research/development activities. Finally, the agency contributes to the development of references and standards relative to cosmetic products.

<table>
<thead>
<tr>
<th>Laboratory control of cosmetic and tattooing products</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cosmetic products controlled</td>
<td>135</td>
<td>72</td>
<td>42</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>Number of non-conformities detected</td>
<td>39</td>
<td>31</td>
<td>24</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Highlights in 2016

- In collaboration with the Inspection Division and DMTCOS, an investigation of high-protection sunscreens for children was conducted over a three-month period under controlled conditions to ensure that the products maintained their effectiveness over time. Two products were found to be non-compliant. These products are being monitored by both divisions.
PART 2

PROMOTING PATIENTS’ RAPID ACCESS TO INNOVATIVE DEVELOPMENTS

ANSM utilises 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).

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) ensuing 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 numerous quantity of MA modifications that it examines

- batch release authorisation activities for vaccines and blood-derived medicines via the involvement of its own laboratories.

1. Early access to innovation ............................................................. 65

2. Marketing authorisations (MAs) for medicines ................................. 74

3. Releasing batches of vaccines and blood-derived medicines .............. 82

4. Authorisation of blood products and other biological products .......... 85
1 - Early access to medicines, medical devices, blood products, and other biological products

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 new health product development based on specific product characteristics and the most recent knowledge pertaining to diseases, target populations, and existing treatments.

In 2016, the agency issued nine national opinions and 78 European opinions.

Of the national opinions, three concerned oncology (including two targeted therapies), three involved innovative medicines (one gene therapy, two cell therapies), five concerned rare diseases, and six dealt with unmet medical needs (one significant therapeutic advance and one biosimilar of Actilyse).

Among the European opinions issued, 16 concerned rare diseases, 11 concerned paediatric use, and 38 related to the field of onco-haematology.

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</tr>
</thead>
<tbody>
<tr>
<td>National opinions</td>
<td>27</td>
<td>35</td>
<td>13</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>European scientific opinions issued for medicines</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>European opinions issued by the EMA</td>
<td>420</td>
<td>473</td>
<td>551</td>
<td>510</td>
<td>578</td>
</tr>
<tr>
<td>French opinions</td>
<td>54</td>
<td>69</td>
<td>71</td>
<td>66</td>
<td>76</td>
</tr>
</tbody>
</table>

France represents 6% of the members of the Scientific Advice Working Party (SAWP), i.e. 3/50. These representatives produce 13.2% of European opinions.

FOCUS ON: Supporting innovative project leaders in the field of medical devices

The innovation service was created to assist project leaders, whether from the academic, hospital, or industrial (start-ups, micro-companies, SMBs) sector, who are working on innovative medical devices and who do not often interact with regulatory agencies.

It aims to provide project leaders with specific scientific and/or regulatory guidance as they create their innovative products, without this influencing the decisions that ANSM might take at a later date as part of normal procedures that apply to all new health product applications. The project leader remains in full control of the development of his/her health product.

In addition to organising meetings with project leaders and holding discussions with public stakeholders interested in promoting innovation and technology transfers, the innovation service also monitors innovation and proactively raises awareness about regulatory frameworks that apply to the development of health products. The innovation service coordinated internal studies on the 3D printing of medical...

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6 It should be noted that a medicine may fall under several categories simultaneously, such as unmet needs and paediatric needs.
devices and the use of these devices within health facilities. Interviews with sector professionals and an analysis of the new European regulatory framework regarding medical devices resulted in discussions with the French Ministry of Social Affairs and Health.

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 certain 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 six years.

Highlights in 2016

- Safety measures for phase I clinical trials involving healthy volunteers (March and June 2016)

Cumulated number of authorised clinical trials – 2016 vs. 2015
Clinical medicine trials

<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of authorisations granted</td>
<td>705</td>
<td>899</td>
<td>821</td>
<td>928</td>
<td>756</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>On-site inspections</td>
<td>54</td>
<td>50</td>
<td>47</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>- in France</td>
<td>30</td>
<td>31</td>
<td>32</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>- outside of France</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>15</td>
<td>10</td>
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<tr>
<td>Injunctions/Formal notices</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dossiers forwarded to the judicial authorities</td>
<td>2</td>
<td>0</td>
<td>1</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 known as the Voluntary Harmonisation Procedure – VHP</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dossiers involving France (out of the total number of dossiers received)</td>
<td>91/116</td>
<td>112/143</td>
<td>114/159</td>
<td>92/134</td>
<td>107/194</td>
</tr>
<tr>
<td>Number of French reference dossiers (out of the total number of dossiers involving France)</td>
<td>10/91</td>
<td>5/112</td>
<td>3/114</td>
<td>6/92</td>
<td>8/107</td>
</tr>
</tbody>
</table>

FOCUS ON: Premature termination of a phase I clinical study following serious adverse effects in healthy volunteers, leading to one death

On 14 January 2016, ANSM was informed of serious adverse effects in healthy volunteers participating in a clinical trial. These events led to the hospitalisation of six volunteers, one of whom died a few days following admission. This phase I clinical trial, conducted by the company Biotrial on behalf of Bial Laboratory, administered the molecule BIA-10-2474 to humans for the first time. The trial was immediately terminated.

In order to investigate the causes of this accident and fulfill its mission to monitor clinical trials, ANSM ordered an inspection of the Biotrial site that very same day so as to evaluate the trial’s adherence to best clinical practices.

ANSM went on to create two Temporary Specialised Scientific Committees (TSSC) composed of independent experts. Their purpose was to develop hypotheses to explain the toxicity that occurred during the study and provide recommendations to further protect the safety of volunteers. The committees also analysed clinical and imaging data to determine if there were neurological signs and/or neuro-radiological abnormalities in the volunteers that could explain the hospitalised participants’ symptoms.

ANSM strengthened the rule regarding vigilance data reporting (adverse effects, new safety developments) for clinical medicine trials conducted on healthy volunteers. The agency also put additional precautionary measures in place to strengthen the safety conditions of first-in-human (i.e. “first-in-man”) clinical trials conducted on healthy volunteers. Henceforth, in order to decide whether to move from one dose step to the next, clinical trial promoters must have the pharmacokinetic (PK) data of the current dose analysed in connection with the trial vigilance data, if applicable. This is a
requirement for both single ascending dose (SAD) and multiple ascending dose (MAD) studies involving an experimental medicine, or when shifting from a SAD to a MAD protocol.

Finally, at the European level, ANSM participated in the reassessment of the European Medicines Agency (EMA) recommendation regarding first-in-human clinical medicine trials. The EMA launched this work in May 2016. Two groups, comprised of experts chosen by the member states, were created. The revised recommendation will no longer apply to SAD trials exclusively; it will now include MAD trials and address issues related to transitioning from one step to another in the case of combined protocols (e.g. switching from SAD to MAD trials).

Clinical trials in the special 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 essentially concern biomedical research carried out in the fields of physiology, pathophysiology, epidemiology, genetics, nutrition, behavioural sciences, and preventive or diagnostic treatment strategies.

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.

Clinical trials for "non-health" products

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</thead>
<tbody>
<tr>
<td>Number of authorised clinical trials</td>
<td>640</td>
<td>724</td>
<td>690</td>
<td>653</td>
<td>681</td>
</tr>
</tbody>
</table>

Clinical trials in the field of biological products

In 2016, 30 trials were authorised, including 15 in the field of cell therapy, 11 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 being employed for an off-label use. They may also concern clinical trials that require investigations pertaining to a significant risk.

ANSM inspects certain 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.

Clinical trials for medical devices

In 2016, ANSM granted 227 authorisations, including eight for IVD-MDs. 44% are industrial I sponsors and 56% are institutional sponsors. Four applications were declined.

<table>
<thead>
<tr>
<th>MD and IVD-MD clinical trial authorisations</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of authorisations granted</td>
<td>296</td>
<td>301</td>
<td>276</td>
<td>236</td>
<td>227</td>
</tr>
</tbody>
</table>
Breakdown of clinical trials for medical devices by therapeutic field

- Anaesthesiology/intensive care - 4%
- Cardiology - 18%
- Dermatology - 5%
- Endocrinology/diabetology - 1%
- ENT - 4%
- Gastroenterology - 6%
- Gynaecology - 4%
- Imaging/diagnostics - 7%
- Neurosurgery - 2%
- Ophthalmology - 6%
- Orthopaedics - 6%
- Pulmonology - 4%
- Urology/nephrology - 4%
- Other - 14%
- Oncology - 11%

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 2016, 12 proprietary medicines were authorised as part of these efforts, including six proprietary medicines in the field of haematology and oncology. The number of patients covered by cohort TAUs rose to 11,909 (excluding Nalscue\(^7\)).

<table>
<thead>
<tr>
<th>Summary of cohort TAUs</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granted</td>
<td>15</td>
<td>9</td>
<td>33*</td>
<td>22</td>
<td>23*</td>
</tr>
<tr>
<td>Number of medicines under cohort TAUs that have received a MA</td>
<td>11</td>
<td>7</td>
<td>26*</td>
<td>25</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>
<th>2016</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>
<td>11 909</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.

List of pharmaceutical proprietary medicines under a cohort TAU granted in 2016

<table>
<thead>
<tr>
<th>Pharmaceutical proprietary medicine</th>
<th>Active substance</th>
<th>Holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABOMETIX, film-coated tablet</td>
<td>cabozantinib</td>
<td>IPSEN</td>
</tr>
<tr>
<td>DARATUMUMAB 20 mg/mL solution for dilution for infusion</td>
<td>daratumumab</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>GALAFOLD 123 mg, capsules</td>
<td>migalastat</td>
<td>AMICUS THERAPEUTICS UK Ltd</td>
</tr>
<tr>
<td>LEDAGA 160 microgrammes/g gel (formerly VALCHLOR®, gel for cutaneous application)</td>
<td>Chlormethine</td>
<td>Actelion Pharmaceuticals France</td>
</tr>
<tr>
<td>MIDOSTAURINE 25 mg, soft capsule</td>
<td>Midostaurin</td>
<td>NOVARTIS PHARMA S.A.S.</td>
</tr>
<tr>
<td>NALSUCUE 0.9 mg/0.1 ml solution for nasal spray in a unidose receptacle</td>
<td>Anhydrous naloxone hydrochloride</td>
<td>Indivior UK Limited</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>OCALIVA 5 mg, film-coated tablets</td>
<td>Obeticholic acid</td>
<td>Intercept Pharma</td>
</tr>
<tr>
<td>QIZENDAY 100 mg, capsule</td>
<td>Biotin</td>
<td>Holder: Medday Pharmaceuticals SA - Owner: Pharma Blue</td>
</tr>
<tr>
<td>UPTRAVI 200 µg; 400 µg; 600 µg; 800 µg; 1000 µg; 1200 µg; 1400 µg; 1600 µg film-coated tablet</td>
<td>selexipag</td>
<td>Actelion</td>
</tr>
<tr>
<td>VENETOCLAX AbbVie 10 mg, 50 mg, and 100 mg, film-coated tablets</td>
<td>Venetoclax</td>
<td>Laboratoire Abbvie</td>
</tr>
</tbody>
</table>

\(^7\) Nalscue: on 24 March 2017, 218 doctors were affiliated with the cohort TAU as well as 547 patients, and 383 kits were dispensed. To our knowledge: Five overdoses were successfully treated (used by patients, including third parties).
In addition, nearly 27,000 named-patient TAUs were granted in 2016 for an average of 1,600 patients treated each month.

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</tr>
</thead>
<tbody>
<tr>
<td>Number of medicines made available per year</td>
<td>221</td>
<td>241</td>
<td>208</td>
<td>219</td>
<td>205</td>
</tr>
<tr>
<td>Number of TAUs granted</td>
<td>26,326</td>
<td>27,550</td>
<td>25,521</td>
<td>24,791</td>
<td>27,095</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients included</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Named-patient TAUs</td>
<td>19,982</td>
<td>18,831</td>
<td>17,829</td>
<td>19,625</td>
</tr>
<tr>
<td>including 12,713 treatment initiations</td>
<td>included 12,822 treatment initiations</td>
<td>included 12,175 treatment initiations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14,029 treatment initiations</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Access to innovation via Temporary Recommendations for Use (TAUs)

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 manner 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 an 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 a Temporary Recommendation for Use is to monitor the 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 period. They require patient follow-up 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. It must also 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 medicines.

Since the mechanism was created, twelve TRUs had been granted as of 31 December 2016:

- 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 HHV-8 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 (May 2015) for the following indications:
- treatment of severe aphthosis, including that 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 syndrome, 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

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)

Xalkori for the treatment of metastatic or locally advanced ROS1-rearranged non-small cell lung cancer in patients with no other treatment options (February 2016)

Hemangiol for the treatment of children with high blood pressure, heart failure and cardiomyopathy, a heart rhythm disorder, tetralogy of Fallot, or congenital long QT syndrome and Marfan's syndrome justifying treatment with betablockers (February 2016)

Methotrexate for the medical treatment of extra-uterine pregnancy (March 2016).

Highlights in 2016

- Baclofen: ANSM simplified the TRU and thoroughly studied the efficacy and safety data for baclofen to analyse the risk/benefit ratio of this medicine and determine its conditions of use with respect to treating alcoholism (September 2016)
- The TRU that ANSM issued for Truvada as an HIV pre-exposure prophylaxis (PrEP) is effective (January 2016) until August 2016, when the European Commission will extend the indication for this medicine to include this use.

FOCUS ON: New provisions governing clinical trials

In 2016, specific measures were introduced in France to strengthen protection for individuals, especially healthy volunteers participating in trials in which a medicine or health product is being administered to humans for the first time.

Strengthening trial vigilance

As of March 2017, ANSM has implemented a high-priority circuit for receiving and analysing vigilance data regarding interventional medicine research carried out on healthy volunteers, thereby creating a system to process such vigilance data during and outside of working hours and days.
In November 2016, new legislative provisions and regulations under Ordinance no. 2016-800 of 16 June 2016 regarding research involving humans (modifying Law no. 2012-300 of 5 March 2012, known as the Jardé Law) and Decree no. 2016-1537 of 16 November 2016 strengthened all rules applying to vigilance over interventional research subject to ANSM authorisation. As a result:

- any fatal or life-threatening unexpected serious adverse event that occurs during these studies must now be reported to ANSM immediately (NOT after a seven-day period);
- additionally, any serious adverse event or serious adverse effect (expected or not) that occurs during medical research and involves healthy volunteers must now be reported to ANSM without delay;
- the definition of new developments was expanded to specify that any serious adverse effect, reported in the context of research involving the first administration or use of a health product in healthy volunteers, constitutes a new development;
- additionally, the occurrence of a new development during research, involving the first administration or use of a health product in healthy volunteers, must result in the project leader suspending the product’s administration or use in individuals participating in the research. This suspension must remain in effect pending definitive action, and appropriate urgent safety measures must be taken. ANSM, the CPP, and the director general of the Regional Health Agency (ARS), of the region in which each research site is located, must be informed immediately.

**Additional safety measures must be taken by project leaders who are conducting phase I clinical medicine trials involving healthy volunteers**

With respect to phase I clinical medicine trials involving healthy volunteers and a single ascending dose (SAD) protocol, multiple ascending dose (MAD) protocol, or both, ANSM requires project leaders to have the pharmacokinetic data for each medicine dose administered. ANSM also requires that project leaders analyse these data in connection with data regarding clinical and biological tolerance, the safety margin, and trial vigilance data when deciding to move up to the next dose in SAD and MAD studies or when deciding to switch from a SAD to a MAD study.

**Strengthening the independence of Ethics Committees**

As of November 2016, the Ethics Committee in charge of submitting research project opinions is no longer chosen by the project leader but randomly selected by the French Ministry of Health. The selections are currently made through VRB applications (https://vrb.sante.gouv.fr/vrb/). In the future, committees will be assigned through the information system of the National Commission for Research on Humans.

In addition, trials involving a health product’s first administration or use in humans will require the Ethics Committee to call on an expert in the field (if the committee does not have such a specialist internally).

**Research site authorisations**

As of November 2016, site authorisations delivered by Regional Health Agencies will remain valid for three years for sites conducting first-in-human clinical medicine trials (seven years for other cases).

Finally, a detailed guideline pertaining to first-in-human clinical medicine trials (“Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products”) is currently being revised on a European level.
2 - Marketing authorisations (MAs) for medicines

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

- **At the European level, the centralised procedure** is compulsory for advanced therapy medicinal products, medicines derived from biotechnologies, innovative medicines containing a new active substance 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 exclusively 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 2016, the number of MAs granted by ANSM (national procedure and European decentralised and mutual recognition procedures) increased slightly compared to 2015 (565 vs. 502).

**Highlights in 2016**

- Each month, ANSM publishes feedback on its website relative to the opinions and recommendations issued by the CHMP, the European Committee for Medicinal Products for Human Use, under the European Medicines Agency
- The agency 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, ANSM publishes feedback pertaining to COMP (European Committee for Orphan Medicinal Products) meetings.
FOCUS ON. Access to orphan and paediatric medicines

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

France’s second national rare disease plan (2011-2015) was extended to the end of December 2016. It plays an important role in promoting, developing, and marketing medicines designed to treat rare diseases. The launch of a third rare disease plan was announced in June 2016. ANSM contributes to these plans, especially as regards early access to medicines, research, and innovation. In 2016, 14 orphan medicines were approved, i.e. 12% of medicines approved as part of the European centralised procedure.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>MAs granted to orphan medicines (out of the total number of MAs granted through the centralised procedure)</td>
<td>10/95</td>
<td>7/90</td>
<td>15/74</td>
<td>15/93</td>
<td>14/114</td>
</tr>
</tbody>
</table>

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 children. PIPs can result in authorisations 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 2016, France was a rapporteur or peer-reviewer (i.e. a co-rapporteur) for 64 PIPs (including 15 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 and target-specific recommendations in the field of paediatrics and participates in the following working sub-groups: preclinical, formulation, medical needs, extrapolation, newborn, and paediatric regulation.

<table>
<thead>
<tr>
<th>Paediatric medicines</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PIP applications for which France was the rapporteur or peer reviewer</td>
<td>58</td>
<td>59</td>
<td>57</td>
<td>55</td>
<td>64</td>
</tr>
<tr>
<td>Percentage of total PIPs</td>
<td>7.2%</td>
<td>6.6%</td>
<td>6.4%</td>
<td>6.3%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Medicines authorised at the European level

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of applications</td>
<td>95</td>
<td>90</td>
<td>74</td>
<td>93</td>
<td>114</td>
</tr>
<tr>
<td>Applications for which France was the rapporteur or co-rapporteur</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>10</td>
<td>14*</td>
</tr>
</tbody>
</table>

Source: EMA

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Applications managed by France</td>
<td>316</td>
<td>260</td>
<td>307</td>
<td>334</td>
<td>320</td>
</tr>
<tr>
<td>Applications for which France was the reference country</td>
<td>36</td>
<td>18</td>
<td>18</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

Source: EMA

* France was appointed the rapporteur three times, the co-rapporteur seven times, and the co-rapporteur four times as part of a multinational team.
### Medicines authorised by ANSM

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Decisions regarding MAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- granted MAs*</td>
<td>1,091*</td>
<td>600*</td>
<td>576*</td>
<td>502*</td>
<td>565</td>
</tr>
<tr>
<td>- national MAs</td>
<td>464</td>
<td>340*</td>
<td>269*</td>
<td>168*</td>
<td>245</td>
</tr>
<tr>
<td>- MAs granted through the</td>
<td>43</td>
<td>36*</td>
<td>36*</td>
<td>334*</td>
<td>25</td>
</tr>
<tr>
<td>European mutual recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MAs granted through the</td>
<td>437</td>
<td>224*</td>
<td>271*</td>
<td></td>
<td>295</td>
</tr>
<tr>
<td>European decentralised procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- generic medicines</td>
<td>816</td>
<td>503*</td>
<td>467*</td>
<td>339*</td>
<td>406</td>
</tr>
<tr>
<td>Modifications**</td>
<td>7 756**</td>
<td>8 169**</td>
<td>6 363**</td>
<td>8 507**</td>
<td>7239</td>
</tr>
<tr>
<td>including generics</td>
<td>1002</td>
<td>4 591</td>
<td>2 912</td>
<td>3 533</td>
<td>3 289</td>
</tr>
</tbody>
</table>

*Data representing the number of proprietary medicines
*Data representing the number of decisions

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**FOCUS ON: MA modification processing reform**

One of ANSM's priority projects involves optimising the MA modification process. This project was launched in the spring of 2015. Like the agency's other priority projects, this work entails simplifying the process to help patients and health professionals. Another goal of this project is to help us better serve the public while complying with regulatory timetables.

This project applies to national MAs and MAs delivered through decentralised and mutual recognition procedures.

A variety of optimisation measures, including the implementation of a new organisational method and the digitisation of the processing chain, were gradually put in place for the entire process leading up to June 2016.

The one-year review for the totality of the project was positive and resulted in marketing authorisation updates.

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**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") whose patent 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 to the original medicine, i.e. have the same bioavailability in the body.

It can differ in some respects as compared to the reference product, but it 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 affect 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.

The generic medicine follows the same rules as the brand name reference medicine, including the same procedures for obtaining a marketing authorisation (national or European MA) and the same
requirements with respect to quality, reproducibility from one batch to the next, and the stability of its physical and chemical characteristics.

The requirements for generic medicine manufacturers and operators are exactly the same as those for reference medicine operators in terms of pharmacovigilance, adverse effect reporting, risk management, and information.

Generic and reference medicines are subject to the same prescribing and dispensing rules and surveillance conditions. All information about medicines is available on the public medicine database: http://base-donnees-publique.medicaments.gouv.fr/index.php.

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

**Highlights in 2016**

- **Launch of the institutional information campaign regarding generic medications**

  A national campaign entitled "Generic status must be earned", designed to educate the general public, was launched on 27 September 2016. Several institutions worked on the campaign, including the French Ministry of Social Affairs and Health, the French health insurance authority, and the French National Agency for Medicines and Health Products Safety (ANSM). The campaign also involved health professionals through partnership with the Collège de la médecine générale (CMG—College of General Practitioners). This campaign is part of the National Action Plan to Promote Generics, which was launched in March 2015. Its purpose is to remove obstacles preventing the use of these medicines, boost consumer confidence, and offer a new perspective. The campaign used several national communication channels, including TV, radio, posters, the press, the internet, and social networks. It is also promoted locally by the French health insurance network and regional health agencies (ARS) as well as through regional media outlets. In support of the campaign, ANSM published an article about generic medicines on its website: http://ansm.sante.fr/Dossiers/Medicaments-generiques/Qu-est-ce-qu-un-medicament-generique/(offset)/0

- **During its April 2016 meeting, the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) launched a reassessment procedure for the risk/benefit ratio of proprietary medicines whose bioequivalence studies were conducted at the private research centre SEMLER Research located in Bangalore, India. This review was carried out following inspections conducted by the US Food and Drug Administration (FDA) and the World Health Organisation (WHO). In July 2016, ANSM decided to suspend the marketing authorisations (MAs) of nine proprietary medicines on the market due to serious doubts regarding the validity of the data produced by the bioequivalence trials conducted at this centre. New studies were carried out by different laboratories and resulted in the reauthorisation of these medicines.**
**MAs for generic medicines**

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>MAs for generic medicines</td>
<td>816</td>
<td>503</td>
<td>468*</td>
<td>339</td>
<td>406</td>
</tr>
<tr>
<td>Number of generic groups in the catalogue</td>
<td>1139</td>
<td>1005</td>
<td>1044</td>
<td>1077</td>
<td>1130</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. Six inspections were conducted in 2016, all of which took place outside of France. Two of these inspections were part of an MA request authorised through a European procedure.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of inspections</td>
<td>20</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>- outside of France</td>
<td>17</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Number of sites inspected</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Number of trials inspected</td>
<td>17</td>
<td>10</td>
<td>22</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Critical gaps</td>
<td>6 trials</td>
<td>1 trial</td>
<td>15 trials</td>
<td>2 trials</td>
<td>2 trials</td>
</tr>
</tbody>
</table>

### Map of the inspection regions

<table>
<thead>
<tr>
<th>Map of the inspection regions</th>
<th>2012 In number of inspections</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>India</td>
<td>15</td>
<td>10</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other countries outside of the EU</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</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 until expiry. The agency has organised generic medicine annual testing in its laboratories since 1999. 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). More recently, the agency began using an approach based on optimising controls through a more targeted selection of proprietary medicines and a two-step analytical process, including one screening step. All results obtained during the controls were featured in communications issued during the educational campaign on generics launched in 2016.

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 2016, the average non-compliance rate was 6% for generics. This figure was 8% for all medicines controlled in 2016. All cases of non-compliance are monitored 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. Since 2013, two molecules are controlled each year using a shared protocol. ANSM contributes regularly, as both a scientific advisor and product controller.
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 products' clinical properties, 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 biotechnological medicinal products (biomedicines) is a result 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.

The MA is granted based on 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 health authorities’ request in accordance with recommendations tailored to each medicine. This system must include the same specific measures used 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 safety and efficacy data pertaining to 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.

Approximately thirty biosimilar proprietary medicines are authorised and/or marketed in Europe. The quality, safety, and efficacy profiles were found to be comparable to those 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.

**Highlights in 2016**

- Publication of the *Summary Report on Biosimilar Medications* (May 2016, updated version of the original report dated September 2013).
### Biosimilar products authorised in Europe (May 2017)

<table>
<thead>
<tr>
<th>Reference medicine</th>
<th>Biosimilar medicine</th>
<th>Active substance</th>
<th>Laboratory</th>
<th>Authorisation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin</td>
<td>Omnitrope</td>
<td>Somatropin</td>
<td>Sandoz GmbH</td>
<td>04/12/2006</td>
</tr>
<tr>
<td>Eprex</td>
<td>Binocrit</td>
<td>Epoetin alfa</td>
<td>Sandoz GmbH</td>
<td>08/28/2007</td>
</tr>
<tr>
<td></td>
<td>Epoetin alfa hexal</td>
<td>Epoetin alfa</td>
<td>Hexal AG</td>
<td>08/28/2007</td>
</tr>
<tr>
<td></td>
<td>Retacrit</td>
<td>Epoetin zeta</td>
<td>Hospira UK Limited</td>
<td>12/18/2007</td>
</tr>
<tr>
<td></td>
<td>Silapo</td>
<td>Epoetin zeta</td>
<td>Stada Arzneimittel AG</td>
<td>12/18/2007</td>
</tr>
<tr>
<td>Neupogen</td>
<td>Biograstim</td>
<td>Filgrastim</td>
<td>AbZ-Pharma GmbH</td>
<td>09/15/2008</td>
</tr>
<tr>
<td></td>
<td>Tevagrabst</td>
<td>Filgrastim</td>
<td>Teva GmbH</td>
<td>09/15/2008</td>
</tr>
<tr>
<td></td>
<td>Ratiograftim</td>
<td>Filgrastim</td>
<td>Ratiopharm GmbH</td>
<td>09/15/2008</td>
</tr>
<tr>
<td></td>
<td>Filgrastim Hexal</td>
<td>Filgrastim</td>
<td>Hexal AG</td>
<td>02/06/2009</td>
</tr>
<tr>
<td></td>
<td>Zarzio</td>
<td>Filgrastim</td>
<td>Sandoz GmbH</td>
<td>02/06/2009</td>
</tr>
<tr>
<td></td>
<td>Nivestim</td>
<td>Filgrastim</td>
<td>Hospira UK Limited</td>
<td>06/08/2010</td>
</tr>
<tr>
<td></td>
<td>Grastofil</td>
<td>Filgrastim</td>
<td>Apotex Europe BV</td>
<td>10/18/2013</td>
</tr>
<tr>
<td></td>
<td>Accofil</td>
<td>Filgrastim</td>
<td>Accord Healthcare Ltd</td>
<td>09/18/2014</td>
</tr>
<tr>
<td>Remicade</td>
<td>Remsima</td>
<td>Infliximab</td>
<td>Celltrion Healthcare Hungary Kft.</td>
<td>09/10/2013</td>
</tr>
<tr>
<td></td>
<td>Inflectra</td>
<td>Infliximab</td>
<td>Hospira UK Limited</td>
<td>09/10/2013</td>
</tr>
<tr>
<td></td>
<td>Flixabi</td>
<td>Infliximab</td>
<td>Samsung Bioepis UK Limited</td>
<td>04/01/2016</td>
</tr>
<tr>
<td>GONAL-f</td>
<td>Ovaleap</td>
<td>Follitropin alfa</td>
<td>Teva Pharma B.V.</td>
<td>09/27/2013</td>
</tr>
<tr>
<td></td>
<td>Bemfola</td>
<td>Follitropin alfa</td>
<td>Finox Biotech AG</td>
<td>03/27/2014</td>
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<tr>
<td>Lantus</td>
<td>Abasaglar</td>
<td>Insulin glargine</td>
<td>Eli Lilly Regional Operations</td>
<td>09/09/2014</td>
</tr>
<tr>
<td></td>
<td>Lusduna</td>
<td>Insulin glargine</td>
<td>Merck Sharp &amp; Dohme Limited</td>
<td>01/04/2017</td>
</tr>
<tr>
<td>Humira</td>
<td>Amgevita</td>
<td>Adalimumab</td>
<td>Amgen Europe B.V.</td>
<td>03/22/2017</td>
</tr>
<tr>
<td></td>
<td>Solymbic</td>
<td>Adalimumab</td>
<td>Amgen Europe B.V.</td>
<td>03/22/2017</td>
</tr>
<tr>
<td>MabThera</td>
<td>Truxima</td>
<td>Rituximab</td>
<td>Celltrion Healthcare Hungary Kft.</td>
<td>02/17/2017</td>
</tr>
<tr>
<td>Forsteo</td>
<td>Movymia</td>
<td>Teriparatide</td>
<td>Stada Arzneimittel AG</td>
<td>01/11/2017</td>
</tr>
<tr>
<td></td>
<td>Terrosa</td>
<td>Teriparatide</td>
<td>Gedeon Richter Plc.</td>
<td>01/04/2017</td>
</tr>
<tr>
<td>Lovenox</td>
<td>Inhixa</td>
<td>Enoxaparin</td>
<td>Techdow Europe AB</td>
<td>09/15/2016</td>
</tr>
<tr>
<td></td>
<td>Thorinane</td>
<td>Enoxaparin</td>
<td>Pharmathen</td>
<td>09/15/2016</td>
</tr>
<tr>
<td>Embrel</td>
<td>Benepali</td>
<td>Etanercept</td>
<td>Samsung Bioepis UK Limited</td>
<td>01/14/2016</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 territory.

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 Health Care in Strasbourg (EDQM - Council of Europe). This harmonisation work also enables mutual recognition between member states and avoids unnecessary test duplication.

France is the country that is 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, the country releases 35% to 40% of all vaccine doses used in Europe and around 50 % of the vaccine doses used in France.

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

As for vaccines, the number of release requests dropped in 2016. This may be explained by a variety of factors, including increased competition between the various vaccine manufacturers, an increase in the batch sizes being released by manufacturers, and production issues experienced by several manufacturers.

Batch releases of vaccines and blood-derived medicines

<table>
<thead>
<tr>
<th>Indicators</th>
<th>2015 total</th>
<th>2016 total</th>
<th>Change compared to 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certified batches</td>
<td>3 958</td>
<td>3 481</td>
<td>- 12%</td>
</tr>
<tr>
<td>- including vaccines</td>
<td>2 246</td>
<td>1 724</td>
<td>- 23%</td>
</tr>
<tr>
<td>- including blood-derived medicines and plasma pools</td>
<td>1 712</td>
<td>1 758</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Highlights in 2016

- Blood-derived medicines:
  - 2016 saw the release of the first batch of a new polyvalent immunoglobulin (Ig), Panzyga, developed by the company Octapharma.
  - Preparations for controlling and releasing the first batch of Octaplas LG, which is scheduled for 2017, were also made.

- Vaccines:
  - Controls for the new Pfizer vaccine Meningo B (Trumenba), which should be available in 2017
  - Support from the Control Division to manage the BCG vaccine shortage and a stability appraisal for the Biomed BCG vaccine after transfer to syringes. This study demonstrated that the vaccines could be stored for four hours at 4°C after reconstitution.
Batch certification - 2016

Batch certification – change in cumulated data 2016 vs. 2015
Release of vaccine batches to the European market

Member state involvement in vaccine batch releases in Europe. France is the leading provider.

Distribution of vaccine doses circulating in France and released by OMCLs

France is the leading provider of vaccine doses in circulation in France.
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 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 and intended to be transfused into a recipient patient. They primarily consist of 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 monitoring adverse reactions that may occur in either blood donors or recipients of labile blood products. The agency also monitors post-donation information and transfusion chain incidents (see page 32).

<table>
<thead>
<tr>
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<th></th>
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<th></th>
<th></th>
<th></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>2</td>
<td>3</td>
<td>6</td>
<td>4</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>8</td>
<td>15</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Update of the list and characteristics of LBPs</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</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 transplant.

**Highlights in 2016**

- Pursuant to Decree no. 2015-509 of 6 May 2015 on the simplification of authorisation regimes involving the preparation, storage, distribution, transfer, import, and export of human tissues, their derivatives, cells, and cell therapy preparations used for therapeutic purposes: the procedures and products routinely used by authorised tissue and cell banks to prepare tissues and cell therapies are no longer subject to authorisation. Instead, they are evaluated through a single authorisation delivered to the facility by the Inspection Division.
Part 3

Consolidating ANSM's relationships with stakeholders and promoting their involvement

1. Transparency of the decision-making process and principles governing the use of experts

2. Advisory bodies

3. Independence and impartiality: ethical obligations

4. Exchanging and sharing information with stakeholders

5. National integration of health and medical research professionals

6. European work

7. International cooperation activities
1- Transparency of the decision-making process and principles governing the use of experts

Commissions, technical committees, working groups, and other advisory bodies are formed when a response from external experts is required. These bodies issue advisory opinions, which serve as additional tools to inform and aid ANSM's Director General in the decision-making process.

ANSM relies on the expertise of three advisory commissions:

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

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

Working groups are tasked with providing answers to precise questions that emerge following prior internal dossier assessments.

The technical committees 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 so as to limit and manage conflicts of interest. The agency therefore introduced incompatibility criteria that were taken into consideration when selecting experts. These criteria apply throughout the duration of their mandate. In addition, any remaining conflicts of interest that may exist are cross-referenced with 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 minutes, as well as video extracts, are also published on the agency's website.

With respect to the 12 commission meetings held in 2016, 20 videos were posted online.

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

Finally, ANSM periodically calls on the services of external experts, whenever 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 - Advisory bodies

The work of the three Advisory Commissions

The three commissions were formed on 7 March 2016 for a duration of six years. Following a call for applications, their members were appointed for a three-year period, subject to one renewal.

<table>
<thead>
<tr>
<th>Commission</th>
<th>President</th>
<th>Vice-Chairman</th>
<th>Date of appointment</th>
<th>Number of meetings in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commission for initial assessment of the risk/benefit ratio of healthcare products</td>
<td>Marc Bardou</td>
<td>Albert Trinh-Duc</td>
<td>10 March 2016</td>
<td>6</td>
</tr>
<tr>
<td>Commission for monitoring the risk/benefit ratio of healthcare products</td>
<td>Pierre Ambrosi</td>
<td>Joël Ancellin</td>
<td>05 April 2016</td>
<td>3</td>
</tr>
<tr>
<td>Commission for narcotics and psychotropics</td>
<td>Nicolas Authier</td>
<td>Michel Mallaret</td>
<td>14 April 2016</td>
<td>3</td>
</tr>
</tbody>
</table>

The advisory commissions issued opinions on:

- requests for cohort temporary authorisations for use (thirteen applications in 2016)
- temporary recommendations for use (four applications in 2016)
- risk/benefit ratio revision/reassessment applications (five applications in 2016)
- applications regarding modifications to marketing authorisations (modifications to the summary of product characteristics) (four applications in 2016)
- applications regarding modifications to prescription and delivery conditions (two applications in 2016)
- measures designed to promote proper use and 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 addition, the Initial Commission was systematically apprised of dossiers examined during sessions held by the European Committee for Medicines for Human Use (CHMP).

The Monitoring Commission evaluates topical developments as well as the applications examined during sessions held by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC).
Technical interface committees working with vigilance networks

The agency's work is supported by vigilance networks which play a crucial health product surveillance role on a regional level. Four technical committees, with a six-year mandate, were created in 2013. Committee members are appointed for a period of three years. Their term was renewed in 2016 and will end in 2019.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Date created</th>
<th>Number of meetings in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Committee for Pharmacovigilance</td>
<td>15 March 2013</td>
<td>10</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>4</td>
</tr>
</tbody>
</table>

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

Twenty-three working groups formed in 2016

Working groups are expert assessment bodies composed of 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 prior internal dossier assessments.

The mandate for the working groups formed in February 2013 came to an end in February 2016. Following a call for applications in November 2015, 22 working groups were formed for a term duration of three years in February 2016 and one was formed in August 2016. A 24th working group on dermatological medicines and cosmetic products was created in March 2017.

List of working groups created in 2016

- WG for medicines used in oncology and haematology
- WG for medicines used in diagnostics and nuclear medicine
- WG for cardiovascular risk and therapy
- WG for medicines used in diabetology, endocrinology, urology, and gynaecology
- WG for viral infectious diseases
- WG for medicines used in non-viral infectious diseases
- WG for vaccines
- WG for medicines used in hepato-gastroenterology and rare metabolic diseases
- WG for the pharmaceutical quality of chemical medicines
- WG for the viral safety and microbiological safety of health products
- WG for herbal medicines and homeopathic medicines
- WG for prescription-optional medicines
WG for medicine interactions
WG for reproduction, breast feeding, and pregnancy
WG for medication errors
WG for paediatrics
WG for epidemiological studies on health products
WG for non-clinical safety
WG for clinical methodology
WG for gases intended for medical use
WG for interfacing with the toxicovigilance network
WG for labile blood products and blood donors
WG for recipients of labile blood products (created in August 2016)

Working group agendas and meeting minutes are published on the agency’s website.

Five French Pharmacopoeia Committees

The Pharmacopoeia Committees participate in the preparation of monographs, detailing precise 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 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological products and advanced therapies</td>
<td>2</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>1</td>
</tr>
<tr>
<td>Chemical substances</td>
<td>4</td>
</tr>
</tbody>
</table>

The agendas and meeting minutes are available on the agency's website.
The Temporary Specialised Scientific Committees (TSSC)

These external expert groups, formed expressly to address a given (ad hoc) issue, 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 2016, 14 TSSCs were active even if they had not yet all met.

<table>
<thead>
<tr>
<th>Temporary Specialist Scientific Committee</th>
<th>Date created</th>
<th>Number of meetings in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curares and anaphylactic reactions</td>
<td>Extended on 01/05/2016</td>
<td>1</td>
</tr>
<tr>
<td>Toxicological evaluation of metals in vaccines</td>
<td>01/12/2016</td>
<td></td>
</tr>
<tr>
<td>Phagotherapy</td>
<td>01/13/2016</td>
<td>1</td>
</tr>
<tr>
<td>Breast implant biocompatibility evaluation strategy</td>
<td>01/18/2016</td>
<td>2</td>
</tr>
<tr>
<td>FAAH inhibitors</td>
<td>01/21/2016</td>
<td>2</td>
</tr>
<tr>
<td>Revision of best preparation practices</td>
<td>03/15/2016</td>
<td>3</td>
</tr>
<tr>
<td>Mechanical circulatory assistance medical devices</td>
<td>03/25/2016</td>
<td></td>
</tr>
<tr>
<td>Stents, anti-platelet biotherapy, and ischemic and haemorrhagic risk: real-life study</td>
<td>05/23/2016</td>
<td></td>
</tr>
<tr>
<td>Examination of clinical and cerebral imaging data of healthy volunteers who participated in the Rennes trial on BIA 10-2474</td>
<td>06/21/2016</td>
<td>1</td>
</tr>
<tr>
<td>Electron accelerators for radiotherapy</td>
<td>11/17/2015</td>
<td></td>
</tr>
<tr>
<td>TRU for baclofen for the treatment of alcohol dependence</td>
<td>10/07/2015</td>
<td>2</td>
</tr>
<tr>
<td>TRU for nifedipine for the treatment of preterm labour</td>
<td>09/24/2015</td>
<td></td>
</tr>
<tr>
<td>Toxicity of metal particles shed by implantable medical devices</td>
<td>Extended on 03/18/2016</td>
<td>3</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices used to calculate the risk of foetal Down's syndrome</td>
<td>Extended on 01/22/2016</td>
<td></td>
</tr>
</tbody>
</table>

The agendas from each session and meeting minutes are published on the agency's website when the TSSC's work is finished, at the very latest.

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 the committee were appointed for a renewable three-year period. They met three times in 2016.
FOCUS ON: Phase I clinical trials, two TSSCs created following the Rennes incident

Following the accident that took place on 10 January 2016 in Rennes during the first-in-human, phase I, clinical trial for the molecule BIA 1-2474 conducted by the laboratory BIOTRIAL, the Director General of the French National Agency for Medicines and Health Products Safety (ANSM) created a Temporary Specialised Scientific Committee (TSSC) on FAAH (Fatty acid amide hydrolase) inhibitors.

This TSSC, made up of independent experts and attended by European observers, met twice in February and again in March to further explore preferred hypotheses formed during the first meeting.

Data on the molecule in question, the endocannabinoid system on which it is supposed to act, the conduct of the trial and its follow-up, the toxicological and pharmacological analyses, and the physiopathology of the accidents all confirmed that the accident was caused by the molecule.

A second TSSC was created to examine the clinical summaries and brain MRIs of all individuals who participated in the clinical trial. This TSSC met once in September.
3- Independence and impartiality: ethical obligations

Given the public health issues involved in health product usage, 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.

The organisation adopted by ANSM to implement its ethics policy and monitor its application relies on a department especially designed for this purpose. This department is run by the agency's ethics officer. It also relies on an ethics committee, and each of these entities report directly to the director general.

Measures to prevent conflicts of interest and monitor compliance with the duty to report them

In 2016, ANSM focused on applying its ethics rules effectively by analysing the ethics-related risks prior to beginning a project, 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 all conflicts of interest. Twenty-nine candidate applications during the pre-recruitment phase and 29 applications from pharmacy residents and interns led to an ethical risk analysis in 2016. 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 forwarded to the Public Service Ethics Commission following referral by the agency; in 2016, the Ethics of Expertise Department examined 27 cases of employees leaving ANSM, with 14 of these leading to an opinion being issued by this commission.

Concerning the periodic use of external collegial expertise

Appointments to an ANSM collegial body (commission, working group, or TSSC) are first examined by the Ethics Department, 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 determines the risk of creating conflicts of interest. An ethics analysis was conducted during the appointment renewal process for experts who serve on an occasional basis and whose term ended on 31 December 2016. The Ethics Department conducted 399 ethics analyses in 2016.

Finally, with respect to disclosing conflicts of interest, a section designed to archive public declarations of interests from former experts and personnel who have changed jobs was added to ANSM's website. The public can now access these declarations for a period of five years following the individual's departure from the agency.
Internal control programme to verify the application of ethics rules

The Ethics of Expertise Department performs internal audits and controls to guarantee the application of ethics rules. In 2016, it conducted:

- two process audits regarding ethical risk considerations in the agency’s decision-making process with respect to:
  - an authorisation request for a medical device clinical trial
  - a request to include a product on the list of labile blood products.
- Eleven compliance controls related to 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 periodically by ANSM, and ANSM personnel (including managerial staff), for a total of 3,411 controlled declarations. These controls focused on:
  - declaration compliance in accordance with the requirement to have a published, up-to-date declaration of interests that is no more than one year old
  - the content consistency of these declarations with respect to publicly available information (example: Health Transparency Database [Transparence-Santé]).

We should note that these operations were strengthened in 2016 and are now conducted twice per year for all external experts (members of advisory bodies and periodic experts) as well as for all personnel subject to these obligations. Corrective measures will be monitored in the future by the relevant directorates.

Overall, in 2016, ANSM’s Ethics of Expertise Department performed 4,155 analyses, which can be broken down as follows:

- Contributions following institutional requests: 59 - 1%
- Contributions following requests from ANSM divisions (especially DIRCOM, DRH, DSI, DSSE): 102 - 3%
- Opinions submitted on internal expertise (internal agency personnel consultations): 1,764 - 42%
- Opinions submitted on external expertise: 2,230 - 54%
Ethics Committee reform

The Ethics Committee was formed following the decision of the director general on 4 May 2012 (OJ of 1 July 2012) in the wake of Administrative Board discussions dated 28 March 2012. This committee is an advisory body that reports to the director general and provides opinions on all issues regarding the ethics of expertise, specifically as it relates to preventing conflict of interest risks and handling the more sensitive and complex cases.

The Ethics Committee underwent reform by decision of the director general on 11 May 2016 and 29 December 2016. These reforms bolstered the committee’s independence, opened it to external participants, and made the appointment of its members by the director general contingent on Administrative Board agreement.

The committee is comprised of the chairpersons of the Administrative Board and the Scientific Board (or their representatives), the members of the Administrative Board, an external participant, and the representatives of health profession organisations and associations advocating the causes of health system users.

In addition, a new member was added to this committee, namely an ethics reference representative having ANSM's supervisory authority.

Lastly, ANSM's ethics officer attends committee meetings in an advisory capacity. The annual report written by the ethics officer must take the opinions and recommendations of this committee into account.

Following these reforms, the committee met on 10 October 2016 and examined the controls carried out by the Ethics Division since 1 January 2016. During this meeting, the committee made a number of recommendations concerning provisions to be put in place so as to ensure compliance with the legal obligation to have an up-to-date public statement of interests report for all ANSM experts and agents subject to this requirement. These recommendations will be definitively adopted in March 2017.

The committee also considered the ethics rules that should apply to associations that represent health system users.
FOCUS ON: Appointment of ANSM’s ethics officer

After receiving the opinion of the Ethics Committee and in accordance with Decree no. 2016-779 of 10 June 2016, pursuant to Article 179 of the Law of 29 January 2016 regarding the modernisation of the French health system, ANSM’s director general made the decision (1 July 2016) to appoint the current director of the agency’s Ethics of Expertise Department.

The ethics officer oversees conflict of interest reporting and prevention, verifying that such reports are submitted at least once a year and are up to date. This officer ensures that the authority or body, to which he/she has been appointed, takes appropriate measures to guarantee that all individuals required to declare conflicts of interest do so. He or she also analyses reported conflicts of interest and submits recommendations to the individual responsible for his/her appointment. These recommendations outline appropriate measures that should be taken by the organisation so as to ensure that conflicts of interest are reported and prevented. The ethics officer then verifies the implementation of these measures.

In addition, to guarantee independence and impartiality, the ethics officer cannot solicit or receive instructions from ANSM’s director general.

Elisabeth Herail, ANSM’s ethics officer, submitted her 2016 Public Report on the actions taken by ANSM to prevent and manage conflicts of interest. This report is available online and can be found on ANSM’s website.

FOCUS ON: The creation of ANSM’s Ethics Charter

An ethics charter, specific to ANSM, was distributed in May 2016 after it was presented to the Ethics Committee, the agency’s Technical Committee, and the Administrative Board.

Based on acquired experience, it lists the rules and behaviours to be followed by agency personnel and collaborators in the performance of their duties.

The charter presents a concrete synopsis of requirements pertaining to impartiality, integrity, and transparency as well as discretion and confidentiality.

The charter outlines the principles behind each ethical concern and then refers to related informational documents and detailed procedures, which are distributed through ANSM’s internal IT network and grouped under a section specifically dedicated to ethics.

Consequently, ANSM employees benefit from the educational content in the ethics charter, which includes behavioural guidelines based on various situations that may be encountered during the performance of day-to-day activities.
4- Exchanging and sharing information with stakeholders

Informational and educational measures regarding the safety of health products

ANSM's various activities (including evaluations, decisions, studies, actions to protect patient safety, etc.) facilitate its production of reference documentation pertaining to health product safety. Such documentation may be intended for patients, the general public, health professionals, the scientific community, and/or manufacturers. The goal of this work is to share knowledge and support the implementation of decisions.

This information is distributed through a variety of formats specific to each audience. In addition to our website, it is communicated through various channels including newsletters, a circulation list, the agency's Twitter account, etc.

In 2016, ANSM added 100 information updates to its website, offering patient recommendations whenever a situation warranted such action. The agency also published seven Q&As (questions and answers) on technical or practical issues, a pamphlet entitled You and...your dopamine medications (to help patients better understand their treatments), and four vigilance reports. A dozen summaries on inspections, surveys, and market controls as well as assessments and activity summaries for most surveillance investigations into medical devices, biosimilar medicines, and cosmetic products have been published and distributed to the relevant audiences. The results of five pharmaco-epidemiology studies conducted by ANSM have been shared with health professionals and the general public.

ANSM's website was consulted by 2,622,296 different visitors in 2016, i.e. nearly 2% more than in 2015. The website's mailing list sent a message to its 22,500 subscribers, every 6 hours/7 days a week, mentioning the latest information posted online.

A dozen issues of the ANSM Actu newsletter were sent to nearly 22,400 subscribers.

The number of users subscribing to ANSM's Twitter account, which was created in April 2014, reached 7,571 by the end of December 2016.

Number of unique visitors* (1 January 2016 – 31 December 2016)

*One unique visitor = one IP address
The number of visitors to ANSM's website is constantly increasing:

- from 01/01/2015 to 12/31/2015: 2,571,708 unique visitors
- from 01/01/2016 to 12/31/2016: 2,622,296 unique visitors.

**FOCUS ON: The public medicine database, highlights in 2016**

A new audience measuring tool was incorporated into the public medicine database. This tagging system, which is used on all the Health Ministry's websites, makes it possible to track usage statistics on a day-to-day basis, including number of visits, source of visits, unique visitors, time spent on the website, etc.

During the last seven months of 2016, over **6,000,000 visitors** and more than **700,000 unique visitors per month** used the database. 81.8% of users accessed the database using a search engine.

An audit of the database’s listings on search engines, which represent users' main method of accessing the site, was conducted in 2016. This audit revealed points that can and must be improved. These improvements will be implemented in 2017.

As part of a national campaign on generics, supplementary information was also added to the webpages pertaining to generic groups (excipients with known effects).

**Information distributed to health professionals, patients, and the public**

In addition to its own distribution channels, ANSM has regular interactions and established partnerships with professional organisations. The latter share the agency’s information with specific audiences, especially health professionals. As a result, ANSM’s information is distributed by boards of pharmacists, doctors, midwives, nurses, masseur-physiotherapists, and learned societies. Consumer and patient groups also distribute information to specific audiences regarding the safe use of health products.

A partnership with the French National Board of Pharmacists keeps pharmacists informed of safety measures and information meant to protect patients in real time (e.g. batch withdrawals, stock shortages affecting essential medicines, etc.) so that they can take immediate action.

In order to promote exchanges with general practitioners regarding the use of health products, ANSM took part in three conferences in 2016:

- The 10th French General Medicine Conference in Paris from 31 March to 2 April
- The 6th European Rural Physician Forum in Marseille on 23 and 24 September
- The 16th annual conference of the French National College of Generalists in Medical Education in Grenoble from 23 to 25 November.

The agency also organised:

- A Bioequivalence Study Quality Day on 9 February
- Two informational days for pharmaceutical sites on 23 and 24 March 2016 to review recent regulatory changes and present principal shortcomings with respect to best manufacturing and distribution practices noted during inspections
- An informational meeting on updates to the Standard Prion Protocol (PSP, in French) on 29 June 2016.
Press relations: foresight and support

Professional and general press outlets are another important channel for publicising safety information and educating a variety of audiences about the risk/benefit ratio associated with health products.

In 2016, ANSM responded to an average of 110 individual requests from journalists each month, i.e. nearly 1,300 over the course of the entire year. Press requests concerned health products, the agency’s activities, and its operating and decision-making methods. The topic of clinical trials (in light of the Rennes accident) and risks related to the use of valproate during pregnancy were among the topics most often discussed in the media. With nearly 6,500 news articles and/or radio and television stories, ANSM was highly present in the media. The written press accounted for nearly 40% of all media coverage.

ANSM also continued to conduct regular meetings with the press. The agency participated in four press conferences and held four meetings with the press to discuss current topics and provide information about ANSM's missions and activities.

Information for parliamentary representatives

In 2016, the agency responded to 12 written questions and 26 letters from parliamentary representatives. The main questions submitted by parliamentary representatives related to:

- stock shortages for certain medicines and supply problems,
- the substitution of biosimilar medicines,
- the strengthening of the pharmacovigilance system,
- Depakine,
- the permanent birth control method Essure,
- the names of medicines and the use of umbrella brands,
- access to rare disease treatments or innovative therapies,
- the impact of antidepressants on pregnant women and their babies,
- the timing of the examination of applications regarding human research.

Under the provisions of the code governing relations between the public and the administration, 106 administrative document requests were made to ANSM in 2016.

Patient information and patient involvement in the agency's work

The relevance and effectiveness of the agency's decisions rely on keeping patients informed and involving patient representatives in ANSM's work.

Annual Information Day with patient associations

On 18 May 2016, the fourth Information and Exchange Day with patient associations was held at the French Ministry of Social Affairs and Health. Topics discussed during the event included the agency’s inspection activities and the sharing of information with the public as well as the misuse of medicines. A discussion on treatment adherence factors and patients' confidence in their medicine, as seen from both a national and international perspective, was also organised with the participation of the Collège de la médecine générale, UFC-Que Choisir, and the French National Board of Pharmacists. Finally, recent studies were presented to give the audience an overview of adverse effect reporting by patients.
Association interviews within ANSM's advisory commissions and working groups

During a meeting of the Temporary Specialised Scientific Committee (CSST) on phagotherapy, one association expressed its concerns and expectations regarding the identification of situations of need, the conditions surrounding availability, the problems created by “doctor-shopping”, and regulatory issues.

In 2015, six patient groups spoke during TSSC meetings pertaining to the temporary recommendation for use of a proprietary medicine as an HIV pre-exposure prophylaxis. In early 2016, as part of the agreement on TRU implementation, ANSM and these patient groups continued to work together to support the measure, provide regular patient follow-up, share feedback about problems encountered in the field, and promote communication with patients.

Support for association projects

In 2016, 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 16 eligible projects, four were chosen as a result of the selection process; these projects corresponded to the agency’s main priorities, which include:

- optimising patient information
- collecting data on practical difficulties encountered by patients using certain categories of health products
- facilitating adverse effect reporting by patients.

A total of €80,000 was allocated in subsidies.

Regular and constructive exchanges within the interface committees

Interface committees work with patient groups, the Collège de la médecine générale, and manufacturing representatives. These committees were formed to ensure regular and constructive discussions between parties in the interest of continuously improving patient safety. They include equal numbers of stakeholder representatives and agency representatives.

The Collège de la médecine générale Interface Committee

The Collège de la Médecine Générale and ANSM share a common objective, that of ensuring patient safety. In order to achieve this objective, it is necessary to collaborate with the field of general medicine as closely as possible. This is because general practitioners are the main, centralised point of contact in the patient-doctor relationship when it comes to the safe use of health products.

To this end, a new interface committee was created to link ANSM with the Collège de la Médecine Générale.

This interface committee meets four times per year. Its goal is to create a space for discussion in order to best anticipate actions and decisions that could impact general practitioners. The Collège de la Médecine Générale will also be asked to present specific topics throughout the year.

The objectives of ANSM’s new partnership with the Collège de la Médecine Générale are as follows:

- To better understand and take into account the expectations of general practitioners: to discuss the health product difficulties that general practitioners encounter in their practice and learn about their expectations vis-à-vis ANSM
To increase the transparency and scope of ANSM's activities

To work with general practitioners to promote their involvement in ANSM's activities and missions (e.g. serving as experts in working groups, helping to draft and distribute information, etc.)

To optimise the collection and assessment of information to detect and monitor risks.

Renewal of the Patient Association Interface Committee

The interface committee that works with accredited patient and health system consumer associations involved in the health products sector was created on 5 June 2013 and consists of 14 members, with seven full members representing patient or health system consumer associations and seven full members representing the agency. It also has 14 deputies. Following a call for applicants launched in the second quarter of 2016, the composition of the interface committee was renewed.

In 2016, the committee met once with its first-term members in attendance and once, during the second quarter, with its new members in attendance.

A working group dedicated to paediatric medicines was created in November 2015. It is a venue for regular discussions on issues of concern involving medicines used to treat newborns, young children, and adolescents. This working group met three times in 2016. Following a series of meetings devoted to European paediatric medicine regulations, the group shared the position of patient associations with the General Directorate for Health, which is a ruling body within the European Commission.

The agendas and meeting minutes are published on ANSM's website.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Number of committee meetings in 2016</th>
<th>List of working groups</th>
<th>Total number of working group meetings in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interface committee working with accredited patient or health system consumer associations involved in the health products sector</td>
<td>2</td>
<td>Medicines used in paediatrics</td>
<td>3</td>
</tr>
</tbody>
</table>

Manufacturing Representative Interface Committees

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 manufacturing representatives and agency representatives.

In addition to reciprocal information-sharing, these committees have led 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 and 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 2016</th>
<th>List of working groups</th>
</tr>
</thead>
</table>
| Interface committee working with representatives from medical industries | 3                                    | - Information/communication/advertising  
- Early access to innovation  
- Surveillance  
- Industrial practices  
- Process improvement/Optimisation of the MA modification request process |
| Interface committee working with representatives from the medical device and in vitro diagnostic medical device industries | 2                                    | - Industrial practices  
- Vigilance  
- Access to innovation |
| Interface committee working with professional organisations representing the cosmetic product industries | 1                                    |                                                                                       |

The composition of these committees as well as their agendas and meeting minutes are published on ANSM’s website.

**FOCUS ON: ANSM’s main publications in 2016**

**Brochures published in 2016**
- Antibiotic consumption and resistance in France: the need for strong, long-term action (key figures)—Brochure (11/18/2016)
- Dopamine medicines: understanding certain adverse effects to facilitate their discussion—The proper use of health products (04/04/2016).

**Question/answer documents published in 2016 to inform patients and manufacturers**
- GlucaGen Kit: information on the batch withdrawal
- Information on medical treatments in the event of heat waves
- Cosmetic product regulations
- De-notification/cessation of activities performed by notified bodies (NB)
- Conditions for reporting hospital preparations to ANSM
- Best manufacturing and distribution practices for starting materials for pharmaceutical use—Additional information on regulatory requirements
- The principles of best laboratory practices.

**Inspection summaries, activity reports, assessments, market controls, and inquiry reports published in 2016**

**Medical devices**
- Automated external defibrillators (AED)—Inspection summary (11/24/2016)
- Quality control of medical devices that expose people to ionising radiation—2015 annual report (07/21/2016)
- Implantable defibrillation leads: Summary and surveillance report (05/19/2016)
- Implantable defibrillation leads—Inspection summary (05/19/2016)
- Market surveillance of DEHP-free PVC medical devices—Report (05/11/2016)
Summary of a medical device vigilance investigation concerning the risk of allergic reactions caused by dialysers (04/05/2016)
Total hip replacement implants and constituent parts—Study (01/14/2016)
Total hip replacement implants and constituent parts—Inspection summary (01/14/2016)
Investigation of the rapid syphilis diagnostic screening market: Assessment of sensitivity and specificity of testing options—Report (01/12/2016).

Medicines
- Assessment of the active substance amoxicillin—Inspection summary (08/11/2016)
- Assessment of biosimilar medicines—Report (05/03/2016)
- Analysis of adverse effects reported with Benfluorex—excluding effects associated with valvulopathies, pulmonary hypertension, and pleural fibrosis—ANSM pharmacovigilance report (05/09/2016).

Cosmetics
- Best Manufacturing Practices for Cosmetic Products—Inspection summary (02/03/2016)

Vaccines
- Research on particles and elements in vaccines and other injectable health products—Comparative study (07/18/2016).

Pharmacoepidemiology studies published in 2016 (see page 110)
5 - National integration of health and medical research professionals

Governance bodies

Administrative Board renewed

ANSM’s Administrative Board met four times in 2016 (February, May, June, and November).

The three-year mandate of Administrative Board members ended in October 2015. New members were appointed by order in November 2015.

The new Chairwoman, Mrs. Catherine de Salins, was appointed by decree on 10 May 2016.

Members of ANSM’s Administrative Board as of 31 December 2016

Chairwoman: Catherine de Salins
Vice-Chairman: Claude Pigement

State Representatives
Director General of Health or his representative: Benoît Vallet
  ◆ Anne-Claire Amprou
  ◆ Catherine Choma
  ◆ assisted by Emmanuelle Jean

Secretary General of the Ministries for Social Affairs or his representative: Pierre Ricordeau
  ◆ Agnès Quoit
  ◆ Jean-Marc Betemps

Director for Social Security or his representative: Thomas Fatome
  ◆ Edouard Hatton
  ◆ Thomas Filleur
  ◆ Sophie Casanova

Director General for Health Services or her representative: Katia Julienne
  ◆ Thierry Debord

Director General for Fair Trade, Consumer Affairs, and Fraud Control or her representative: Nathalie Homobono
  ◆ Raphaëlle Bove

Director General for Enterprise or his representative: Pascal Faure
  ◆ Benjamin Leperchey
  ◆ Alain-Yves Bregent

Director General for Research and Innovation or his representative: Alain Beretz
  ◆ Jacques Demotes-Mainard
Budget Director or her representative: Amélie Verdier
  - Claire Vincenti
  - Thimotée Mantz

Director of the European Union, represented by the Directorate General of Globalisation, Development, and Partnerships:
Anne-Marie Descôtes
Catherine Dauphin-Llorens

Deputies (members of parliament)
  - Gérard Bapt
  - Arnaud Robinet
  - Nomination pending

Senators
  - Laurence Cohen
  - Gilbert Barbier
  - Gérard Deriot

Health Insurance Representatives
  - Luc Barret (senior member)
  - François Alla (CNAMTS) - (deputy member)
  - Bénédicte Feuilleux (MSA) - (senior member)
  - Alain Masclaux (RSI) - (deputy member)

Representative of the National Board of Physicians
  - Jacques Morali (senior member)
  - Françoise Stoven - (deputy member)

Representative of the National Board of Pharmacists
  - Isabelle Adenot - (senior member)
  - Carine Wolf-Thal - (deputy member)

Representatives of Health System Consumer Associations
  - Alain-Michel Ceretti (Le Lien) - (senior member)
  - Philippe Schneider (CLCV) - (deputy member)
  - Hélène Berrue-Gaillard (Alliance maladies rares) - (senior member)
  - Gisèle Kesler (UFC Que Choisir) - (deputy member)

Qualified Experts
  - Claude Pigement, Vice-Chairman
  - Bernadette Devictor

Representatives of the Agency’s Personnel
  - Corinne Civade
  - Lilian Berruyer
  - Renaud Kiesgen De Richter
The 2016 Scientific Board

The ANSM Scientific Board was created in 2012 and renewed in 2015 for a three-year period. It is made up of 16 members chosen for their fields of expertise and also includes foreign scientists. Annick Alpérovitch is the chairwoman. The Scientific Boards meets three times per year.

The Scientific Board currently includes (modified article R. 5322-18 of the French Public Health Code) 16 members:

Subsequent to a call for applicants issued by the agency, ten 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-Emilia Monteiro
- Marc Vasse
- Jean-Paul Vernant
- Nadia Younes

Six 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
- Greet Musch
- Victoria Rollason
- Josep Torrent-Farnell

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 projects and may also formulate recommendations concerning all scientific and technical issues falling within the scope of the agency’s expertise.

The Scientific Board met three times in 2016, on 3 February, 8 June, and 9 November. Main topics discussed include ANSM’s action plan on breast implants, the ANSM Ethics Committee’s missions, the working programme for the pharmacoepidemiological platforms, ANSM’s European strategy, and the agency’s participation in the national study programme on diabetes, ENTRED. It also looked at risks and issues related to biosimilar medicines, bacteriophages, and social network surveillance. 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 2017 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 2016, ANSM launched its **fifth 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. This fifth call for proposals was dedicated exclusively to projects designed to shed light on the proper use and misuse of medicines and medical devices. 52 applications, 38 of which were eligible, were received. Each project was sent to at least two independent experts. This initial assessment phase involved 49 experts. Guided by a panel made up of four scientific experts, the Director General of ANSM awarded funding to ten projects. All coordinators were notified of the funding agreements at the end of 2016 so that the projects could begin in January 2017.

At the same time, the agency **followed up with selected projects from 2012 to 2015**. 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 also regularly tracked. On 30 November, 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 2013 and 2014.

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” (hors appel à projets - studies outside of the call for proposals)**, certain necessary health studies, whose principles or methods fall outside the call for research proposals, may be funded independently of these calls. These studies, which are independent of the industry, address emerging concerns or public debates relating to the safety of products or categories of health products.

In 2016, ANSM thus signed a number of research subsidy conventions, including several with academic bodies (INSERM, AP-HP, university hospital centres, etc.). The call for proposals focused on seven topics targeted by the agency. Of the 36 eligible projects received, eight agreements were signed with selected 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 SNIIRAM database, to which ANSM has had access since September 2013.

A total of 15 pharmacoepidemiological studies were launched through ANSM's health product Epidemiology Department in 2016.
Of these 15 studies, the results of six were shared with the public (report, scientific article and/or oral presentation during a scientific conference) in 2016:

- Exposure to valproic acid and its derivatives during pregnancy in France from 2007 to 2014 (study conducted in collaboration with CNAMTS)
- Use of coronary stents in France in 2014 (study conducted in collaboration with HAS)
- Exposure to incretin mimetics and risk of pancreatic cancer among type-2 diabetics
- Determining factors of prosthesis survivorship in modular femoral neck hip replacements
- Risk of lymphoma associated with biotherapies in individuals receiving treatment for chronic inflammatory bowel disease (IBD)
- Infectious risk associated with biotherapies in individuals receiving treatment for chronic inflammatory bowel disease (IBD).

Nine studies were not completed in 2016. Their results are expected in 2017. These studies include:

- Risk of congenital malformations and mental and neuro-developmental disorders following in utero exposure to valproate (in collaboration with CNAMTS)
- Study on the safety of the permanent birth control device ESSURE
- Study on ischemic and haemorrhagic risk with respect to coronary stent type
- Study on the ischemic and haemorrhagic risk with respect to the duration of dual antiplatelet therapy after coronary stenting
- Liver toxicity of agomelatine (Valdoxan®) and other antidepressants
- Risk of lymphoma associated with metal hip replacements
- Risk of cardiomyopathy associated with metal hip replacements
- Exposure to mycophenolic acid in women of childbearing age
- Use of Truvada as an HIV pre-exposure prophylaxis.

FOCUS ON: Exposure study on valproic acid and its derivatives during pregnancy in France from 2007 to 2014

Valproic acid, which was first marketed in France in 1967, is a major anti-epileptic drug. In the form of sodium valproate and valpromide, it was subsequently used as a second-line treatment for bipolar disorders. The teratogenic effects of valproic acid have been recognised since the early 1980s and include neural tube closure defects (spina bifida). More recently, an increased risk of developmental delays and autism spectrum disorders were found in children who were exposed to valproic acid in utero. This new evidence on the effects of in utero exposure to valproic acid led the European Medicines Agency (EMA) to re-evaluate the risk-benefit ratio. It implemented risk reduction measures at the end of 2014. Nevertheless, the EMA reaffirmed the need to make these medicines available to girls, pregnant women, and women of childbearing age, but specified that they should only be used in this population if other therapies prove ineffective or lead to intolerance. The EMA also emphasised the need for women of childbearing age to use contraception when taking these medicines. In France, valproic acid prescription and dispensing conditions for this population were strengthened as of May 2015. As a result, an initial annual prescription must be obtained from a specialist (neurologist, psychiatrist, or paediatrician), and pharmacy dispensation is subject to the presentation of a treatment agreement (signed by both the prescribing physician and the patient). These measures were accompanied by an information campaign targeting prescribers and patients. Additionally, a warning label must be affixed to the outer packaging of valproic acid-based specialities.

In this context, a joint pharmacoepidemiologic study programme was initiated in 2015 by the French medicines and health products safety agency (Agence Nationale de Sécurité du Médicament et des produits de santé—ANSM) and the French salaried workers health insurance fund (Caisse Nationale de l’Assurance Maladie des Travailleurs Salariés—CNAMTS) in order to evaluate, on the basis of data
The French National Agency for the Safety of Medicines and Health Products

from the national health insurance inter-scheme information system (Système national interrégimes de l’assurance maladie—SNIIRAM), the health situation arising from this issue in France.

The first part of this programme had the primary goals of estimating the frequency of pregnant women’s exposure to valproic acid and its derivatives and analysing any changes in this frequency between 2007 and 2014, both generally and with respect to the pathology underlying the prescription (epilepsy or bipolar disorder). The study also aimed to describe the characteristics of women exposed to valproic acid during pregnancy, as well as those of their prescribers, during this same time period. In addition, it evaluated pregnancy outcomes after exposure and investigated the details surrounding valproic acid prescription (duration, dose) during pregnancy. Finally, exposure to valproic acid in women of childbearing age, outside of pregnancy, was described up until the end of the first quarter of 2016.

The assessment of pregnant women’s exposure to valproic acid and its derivatives from 2007 to 2014 showed that 14,322 pregnancies, with conception occurring between 1 January 2007 and 31 December 2014, involved valproic acid exposure, representing nearly two out of every 1,000 pregnancies in France. Of these pregnancies, 61% (i.e. 8,701 pregnancies) resulted in one (or several) live birth(s). Thirty percent of pregnancies involving valproic acid exposure resulted in an elective or therapeutic abortion, 8% resulted in a miscarriage or ectopic pregnancy, and 1% resulted in one (or several) stillbirth(s).

Since 2007, the annual number of pregnancies involving valproic acid exposure is steadily declining, dropping from 2,316 in 2007 to 1,333 in 2014. This 42% decrease over eight years is due more to epilepsy treatment (56% decline) than bipolar disorder treatment (18% decline). Along with this decrease, the study showed an increase in the number of pregnant women using other treatments for epilepsy and bipolar disorder.

The assessment of exposure levels in women of childbearing age (15-49 years) also shows a significant drop in exposure levels from 2007 to 2015. The annual number of women of childbearing age (15-49 years) exposed to valproic acid decreased from 122,382 in 2007 to 83,712 in 2015 (a 32% decrease), and the decline was especially apparent in the last year with respect to bipolar disorder (a 12% drop between 2014 and 2015). The analysis carried out using quarterly data, which provides the latest information (incorporating data from the first quarter of 2013 through the first quarter of 2016), also suggested a more significant decline in the first quarter of 2016. This analysis will continue to assess the impact of the risk reduction measures implemented at the end of 2014.

The results of this study demonstrate a persistently high level of valproic acid exposure in pregnant women and women of childbearing age in France. With respect to pregnancies occurring in 2014, 1,333 still involved valproic acid exposure. Furthermore, 51,512 women of childbearing age were exposed to this drug in the first quarter 2016. Such levels remain troublesome, in spite of a marked reduction in the rate of exposure in pregnant women (a 42% decrease) and women of childbearing age (a 32% decrease) since 2007 (a reduction which is most likely due to the prescription of alternative treatments: a phenomenon that appears to have escalated in 2015 and early 2016). The results also show contrasting scenarios according to the disorder for which valproic acid was prescribed.

These results suggest that the application of risk reduction measures should be strengthened, taking into account the specific pathologies for which prescriptions are issued. Valproic acid exposure monitoring should be continued in order to determine the impact of these measures. It is also essential to extend exposure monitoring to other epilepsy and bipolar disorder treatments.

Second year of the two pharmacoepidemiology platforms’ activity

In order to maintain the independent research efforts initiated by ANSM and improve its 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
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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 its second year of activity, the DRUGS SAFE platform pursued its programme of use and risk studies on psychotropic drugs, oral anti-diabetics, opioid substitution treatments, and statins and on the risk of accidents and injuries associated with these substances. It also launched new studies by expanding its scope to include other classes of medicines: NSAIDS, antibiotics, migraine medicines, and targeted cancer treatments.

The PEPS platform pursued its programme of use and risk studies on various medicines and medical devices, including isotretinoin, high blood pressure treatments, breast implants, the trans-aortic valve implantation device, and sodium valproate. It also launched new studies by expanding its scope to include new medicine classes, including immunotherapy cancer treatments, biotherapies, multiple sclerosis treatments, and antiplatelet therapies.

ANSM's pharmacoepidemiology studies published in 2016

  Division of Vaccines, Anti-Infective Medicines, Hepatogastroenterology, Dermatology, Gene Therapy and Rare Metabolic Diseases (Ingrid Chau, Isabelle Pellanne, Nathalie Morgensztejn, Caroline Semaille)
  Publication on the ANSM website in May 2016

- Metal-on-metal hip replacements and risk of non-Hodgkin's lymphoma
  Master 2 report (Anne Moulin, Sandrine Colas, Mahmoud Zureik, Rosemary Dray-Spira) - June 2016

- Use of coronary endoprosthesis (stents) in France in 2014: Study based on SNIIARAM data
  ANSM-HAS report (Emmanuelle Schapiro-Dufour, Aurore Tricotel, Rosemary Dray-Spira, Mahmoud Zureik) - June 2016

- Exposure to valproic acid and its derivatives during pregnancy in France from 2007 to 2014: observational study of SNIIARAM data
  ANSM-CNAMTS report (Fanny Raguideau, Carole Ehrhardt, Rosemary Dray-Spira, Mahmoud Zureik, Pierre-Olivier Blotière, Alain Weill, Joël Coste) - August 2016

- Valproate and related substances in women of childbearing age: health outcomes in France and impact of new prescribing and dispensing recommendations
  Master Eu2P report (Bordeaux) (Carole Ehrhardt, Fanny Raguideau, Rosemary Dray-Spira) - September 2016

- Exposure to incretin mimetics and risk of pancreatic cancer among type-2 diabetics ANSM report - December 2016

Focus on: ANSM’s scientific publications in 2016

Scientific publications of the Health Product Epidemiology Department:


The Health Product Epidemiological Department also gave 13 presentations during conferences in 2016 in France, Ireland, and Austria.

Scientific publications of the Laboratory Control Division


Relations with other health system operators

Partnership and agreements

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.

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 implementing various 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 issues such as nutrition and obesity as well as health alert preparations (heat wave plan). ANSM participates in plan monitoring and steering 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 2016, the agency took part in 11 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 helped update the new 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 2016 concerning the detection and identification of various highly pathogenic microorganisms.

Finally, under a tripartite agreement with the French Directorate General of Health and Santé Publique France, the agency uses its expertise to monitor the quality of certain medicines included in the government's strategic stocks (antivirals, vaccines, antibiotics, etc.).

Legal and regulatory activities

ANSM participates in the development of legislation and regulations on both a national and European level. In 2016, the agency contributed to the preparation of 37 European texts (all manner of texts relative to medicines, medical devices, cosmetic products, and biological products).

On a national level, the agency was involved in drafting 114 texts: 74 were published in 2016 (laws, decrees, and orders, excluding decisions).

In addition, in 2016, ANSM issued 15 health policy decisions. The great majority of these related to medical devices and in vitro diagnostic medical devices marketed in a manner that violated relevant regulations in force.
Litigation and rulings

In 2016, ANSM received 67 new requests related to its decisions.

The number of cases heard by the administrative judge has decreased slightly. Forty decisions were issued in 2016, whereas 48 were issued in 2015. The vast majority of disputes submitted to the courts of law were rejected (37 rejections, withdrawals, or dismissals).

History of all disputes combined

<table>
<thead>
<tr>
<th>All disputes combined</th>
<th>Rejection / withdrawal / dismissal</th>
<th>Cancellation / conviction</th>
</tr>
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<tbody>
<tr>
<td>2016</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>2015</td>
<td>46</td>
<td>2</td>
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<tr>
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<td>12</td>
<td>5</td>
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<tr>
<td>2006</td>
<td>17</td>
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6 - European work

ANSM representation within European bodies

European Medicines Agency (EMA)

ANSM ensured French representation 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 Administrative Board includes:
- a representative from each of the 28 EU member states,
- representatives from the European Commission and Parliament,
- representatives from 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 2016 include:
- the development of the multi-country MA evaluation concept, which refers to a multinational team approach to MA assessment, based on the expertise that is available in the European network of competent national authorities (versus in the country itself), thereby optimising the use of scientific resources. In 2016, this concept was expanded to include post-MA evaluations as well
- efforts to centralise the management of standardised terminology, used by all national authorities to link medicinal information available in member states to the IT system operated by the EMA, especially that used to support continued vigilance efforts
- preparatory work to face challenges created by the British referendum of June 2016, which cast doubt over the agency’s future due to the loss of expertise and the agency’s location, given the likely exit of the United Kingdom from the European Union.

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 its strategy.

Following the adoption of the Joint Strategic Guidelines for 2020 (for the EMA network and national agency heads), the HMA adopted the Multi-year plan for 2020 for the HMA network, which includes 11 strategic areas of focus during the five-year period.

In 2016, the Dutch and Slovakian presidencies concentrated their efforts on four of these areas:
- antimicrobial resistance,
- access to legally authorised, high-quality medicines,
- access to innovation,
- regulatory operation optimisation.

Inspection coordination

Coordinating inspections on a national and European level is particularly important. Such coordination helps standardise practices, promotes information sharing with respect to topics of common interest, and optimises the use of inspection resources between the various member states.
The Inspection Division oversees all of ANSM's products and activities. As such, it is authorised to intervene, depending on the field, in the activities of various authorities that report to the EMA, the European Commission, the Council of Europe, and the OECD (Organisation for Economic Co-operation and Development).

In the field of medicines (manufacturing, pharmacovigilance, and clinical trials), this work is primarily carried out through the "Inspectors Working Groups" (IWG) created by the EMA.

Given their long history of involvement in bioequivalence studies for generics, French inspectors are very active within the EMA groups working on this topic. This participation extends to the bioequivalence trials conducted by the EMA and US FDA. As concerns the particular area 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).

The appointment and surveillance procedures for notified bodies involved in compliance certification protocols for medical devices and in vitro diagnostic medical devices are overseen by the competent national authorities. A representative of ANSM serves on the European Commission's Notified Body Operations Group (NBOG). The latter is comprised of experts involved in appointing and monitoring notified bodies.

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

Safety trials for medicines, tattoos, and cosmetic products are conducted in accordance with the OECD’s best laboratory practices. Therefore, inspectors are highly involved in the European and international bodies (i.e. the EMA, the European Commission, and the OECD, among others) that formulate rules pertaining to how laboratories carrying out these trials should be inspected.

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. A description of two of these is provided below:

- The Committee for Medicinal Products for Human Use (CHMP) is the European body responsible for assessing medicines released on the market and medicines that are subject to modifications pertaining to their use (restrictions, indication extensions) or their prescribing and supply conditions, with a view to authorising them under the centralised procedure. The CHMP, which is comprised 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. Between 2013 and 2016, France served as the CHMP vice president. In 2016, the CHMP issued 81 positive opinions for new MAs and 59 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 2016, 2,164 dossiers were included in the PRAC’s agenda, with France serving as the rapporteur country for 190 of these cases.
Negotiating European draft regulations and preparing for their implementation

Draft regulations on medical devices

Building on the two general approaches adopted in 2015, the start of 2016, which was overseen by the Dutch presidency, was marked by the pursuit of informal three-way talks with the European Union Council, the European Parliament, and the Commission. ANSM continued its active collaboration within the Council's expert group alongside the Directorate General of Health and the Directorate General of Companies (11 working sessions). During the tenth informal three-way dialogue in May 2016, the respective representatives of the European Council and Parliament agreed on compromises regarding two medical device (MD) and in vitro diagnostic medical device (IVDMD) regulations, followed by the Commission on 15 June 2016. On 20 September 2016, the Council arrived at a political agreement regarding the two compromise texts.

The European Council and Parliament are expected to adopt and publish the new texts in 2017.

These regulations, which will be shared pieces of legislation, will significantly increase health safety by introducing stricter procedures, especially with respect to compliance evaluations. One of the main challenges is to improve the risk/benefit ratio assessment prior to marketing and surveillance activities conducted over the product's lifetime, particularly for implantable MDs or, more generally, those with a therapeutic purpose. The rules that apply to notified bodies have also been modified. They are now more closely overseen by the competent authorities in each member state, and they have greater authority over economic operators. The implementation of the new EUDAMED database should increase the traceability of devices and operators and facilitate the exchange of information between authorities.

The implementation of 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). 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. The one-year assessment of the trials accepted during the pilot phase was conducted at the end of September 2016. Of the 89 authorisation requests processed by 30 September 2016, 73 were granted an authorisation by ANSM and a favourable opinion from the relevant CPP. The average time it took to issue the final notification and initiate the trial was 64.3 days. Overall, the deadlines were respected along each step of the process.

FOCUS ON. ANSM’s commitment to joint market surveillance

In order to implement future regulations on medical devices and in vitro diagnostic medical devices, ANSM took part in a joint effort regarding the surveillance of the medical device market (Joint Action Market Surveillance). This joint effort will be conducted for a three-year period, beginning in 2016, and is under the direction of the European Commission. The action includes two working programmes, a manufacturer inspection involving the Inspection Division, and the clinical evaluation of medical devices as part of market surveillance involving the Cosmetic and Therapeutic Medical Device Divisions. The goal is to lay the foundation for greater cooperation between member states, including the exchange of practices, the development of joint methodologies and tools, training sessions, and joint inspections.
7- 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.). To this end, ANSM participated in a group working on GMP inspections. This group concluded a pilot phase in 2016 to potentially share inspection reports between coalition members. The coalition decided to extend the pilot phase in order to widen the experience base to include other authorities. PIC/S, on the condition of a clear mandate from the heads of the ICMRA agencies, accepted to oversee the group's activity in its working programme.

In the field of medical devices, Brazil presided over the International Medical Device Regulators Forum (IMDRF) in 2016. ANSM is part of the European delegation alongside the European Commission, Germany, and Ireland and, as such, participated in the meeting of the steering committee. The main work items discussed concern the sharing of confidential vigilance information, medical device software, standardisation of the electronic marketing authorisation application dossier, and patient registers. Work began to explore a new cooperative approach between international regulators and international standardisation bodies (ISO, IEC). Finally, preliminary documents regarding the naming of medical device incidents were adopted.

Cooperation with WHO

Activities related to the prequalification of medicines, vaccines, and reagents continued in 2016. The agency participated in a joint inspection for the prequalification of Cameroon's national control laboratories. ANSM is participating in a project to 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 starting material or medicine manufacturers in India, China, and Korea.

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) and new technologies in the field. It also works on standardising relevant regulatory requirements as quickly as possible. To this end, the BRN group published several recommendations and positions on the WHO website.

Cooperation with the US FDA

ANSM actively pursues its efforts to solidify mutual recognition of medicine inspections between the United States and the European Union (EU). This work began in 2015. Negotiations are now being conducted within the mutual recognition agreement concluded with the United States in 1997. ANSM was one of the member states to audit the US FDA to assess the equivalence between inspection
systems in the US and Europe. The agency also participated in audits in member states within the European Union to facilitate the application of this agreement.

ANSM and the US are already working together on many projects involving pharmaceutical products. The conclusion of an agreement would make it possible to deepen this cooperation so as to rely on inspections conducted by counterparts, better prioritise inspection resources in a medicine supply chain that is often global, and rationalise operators’ efforts in the field of surveillance with respect to countries importing products made in France.

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 to promote 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 2016 action programme was developed in accordance with the decisions made during the yearly directors’ meeting in January 2016. ANSM organised a collaborative study to help the network's members assess their technical skills. The theme chosen for the study was the dosage for the fixed combination of irbesartan and hydrochlorothiazide. An interactive platform managed by ANSM and designed to promote exchange is available to all members of the network.

**Technical and scientific multilateral cooperation**

ANSM stepped up its participation in the work of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), specifically with respect to best manufacturing and distribution practices for medicines (especially innovative medicines), active substances, blood, tissue and cells, and the management of data integrity. In 2016, ANSM evaluated a national agency (that of Thailand). By the end of 2016, the PIC/S included 51 national agencies certified in inspections.

As is the case every year, the agency was closely involved in the work of the Council of Europe’s European Directorate for the Quality of Medicines (EDQM), bringing together 38 member states and 29 observer countries. ANSM contributes to the work of the Official Medicines Control Laboratories (OMCL) network, the European Pharmacopoeia, and European Certification. In 2016, ANSM's laboratories participated in 28 collaborative studies, including 12 performance studies. ANSM also participated in six joint quality audits with other OMCLs in Italy, Slovakia, Bosnia, Hungary, Germany, and Lithuania on behalf of the EDQM.

As the national authority designated to supervise the use of narcotic and psychotropic products, ANSM participates annually 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 action with the competent national authorities of third countries continued under previously signed bilateral agreements and often resulted in the sharing of information on medicines and medical devices (inspection reports, batch withdrawals, compassionate use of medicines, imports, regulatory information, etc.) with the US, Japan, Brazil, Canada, South Korea, Mexico, and Lebanon. ANSM continues to provide monitoring and technical assistance to the latter, with respect to generics and medical devices.

One-off agreements have been signed with Thailand to organise the five-day reception of a delegation of Thai authorities in Lyon. The delegates plan to work on the quality assurance, production, and control of a tetravalent dengue vaccine as well as on the release of batches and a policy for controlling the vaccines.
Other discussions, not governed by an agreement, took place, particularly with Algeria, and ANSM participated in the second French-Algerian Meeting on Health in Paris.

Finally, with respect to France’s overseas departments and territories, nearly 40 technical opinion exchanges took place in 2016 with French Polynesia regarding TAU, supply shortages, the qualification of health products, the safety of cosmetic products, and the transmission of information on Polynesian analysis laboratories that participated in the National Quality Control List. The latter pertains to French tissue banks authorised to import, export, and store tissues and concerns pharmacovigilance and medical device vigilance data as well.

<table>
<thead>
<tr>
<th>French-African meetings:</th>
<th>foreign delegations received from Myanmar, Thailand, South Korea, and Lebanon.</th>
<th>trainees received (Inspection Division and Laboratory Controls Division) from China, Mexico, and Tunisia.</th>
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<tbody>
<tr>
<td>6 countries and WHO</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Reinforcing ANSM's efficiency and pursuing its modernisation

In 2016, ANSM continued to improve its steering activities, optimise and deploy its processes, and modernise its tools to consolidate and fully benefit from the internal organisation it established in 2012. In particular, these improvements concerned the efficiency and security of the application-processing chain.

1. **Optimising internal processes and the integrated management system**
   - The integrated management system
   - The agency's transformation policy
   - Information system security
   - Optimisation of MA modification processing
   - Optimisation of non-health-product clinical trial processing
   - Improvements to workflow management
   - Paperless communication
   - Accreditation of inspection and internal audit activities
   - European audits of control activities

2. **Implementing the Information System Master Plan (ISMP)**
   - Reinforcement of the agency's methodological approach and measures to modernise and safeguard the IS
   - Infrastructure modernisation plan

3. **Human resources**
   - The HR policy is based on the master plan for jobs and skill sets
   - Job changes
   - Business line changes
   - ANSM's training policy is designed to modernise the agency and increase its efficiency
   - Measures to improve the quality of life at work
   - Dialogue between management and employees
   - Internal communication: strategic project support

4. **The agency's budget**
   - A context of significant budgetary constraints
   - Expenditure by type
   - Revenue
   - Expenditure by envelope
   - 116 notified contracts in 2016
   - Application of the GBCP decree—Implementation of SIFAS—QUALIAC
1- Optimising internal processes and the integrated management system

The integrated management system

The Integrated Management System (IMS) achieved full capacity in 2016. This system relies on the following:

♦ adjustments and operational monitoring of the 2015-2018 COP [Objectives and Performance Contract]
  ✓ 19 of the 28 indicators were reached in 2016, and nine are close to being reached,
  ✓ continued development of the Qlikview application to effectively equip COP steering efforts as of 2017

♦ mapping of the agency's major risks and overhaul of macroprocess and process mapping as approved by the Management Committee in March 2016

♦ the launch of a quality programme integrating risk coverage to earn ISO 9001 certification by the end of 2018 (initially with respect to the “Managing risk” macroprocess)
  ✓ ISO 9001 certification will provide a guarantee to internal and external stakeholders that the organisation and working methods of the agency are able to provide a constant level of service quality. It will also make the agency's work visible to external partners and regulatory authorities
  ✓ As part of this effort, in 2016, the agency structured its plan to gradually implement processes and process-based risk management plans throughout 2017 (with priority given to high risk processes in keeping with the scope of certification). It also developed a new quality governance method to support this deployment in the future

♦ Finally, following the recruitment of an internal auditor in 2016, an initial internal audit on the "MA modification" process was launched at the end of the year. This effort will continue into 2017 with the development of an annual auditing programme and the implementation of a governance structure and internal auditor network.

The agency's transformation policy

The agency continued to focus on priority projects which began in 2015: 8 projects launched in 2015 were implemented in 2016, and teams continued to receive support during the transformation. In addition, a new project was launched at the end of 2016 and involves the initial marketing authorisation process. It will first focus on MAs for generics.

A strategic project owner programme was created to assist each priority project and ensure that the information system meets the needs of the changing business lines in accordance with the Information System Master Plan (ISMP).

Activity structuring: throughout 2016, each division also examined the structuring of agency activities so as to ensure that they were complementary and consistent with its priority projects.

The aim of this approach was to question the agency's activities, and their priority levels, and to modify process management methods that do not pertain to priority projects, thereby giving the agency greater flexibility to conduct its missions in the context of a limited budget.

Between May and October 2016, the divisions were tasked with identifying the scope of their activities, based on joint guidelines and in presence of all agents, during plenary sessions and workshops.
The summary results of this work were studied and discussed during the management seminar of 8 and 9 December 2016. This work was referred to the General Directorate in early 2017 so as to create a “2017 transformation programme”.

Information system security (ISS)

The information system security policy was developed and approved in March 2016. Employees will receive a message once the new IT Security Charter is distributed and an action plan is put in place to ensure its enforcement and surveillance. An assessment of the information system security policy's implementation was written at the end of the year and will be updated annually.

FOCUS ON: BEMA IV (Benchmarking of European Medicines Agencies)

In June 2016, the agency took part in a European benchmarking exercise for the organisations of medicines agencies overseen by the HMA network (heads of medicines agencies) and managed by the HMA Steering Group. This exercise is carried out at every European agency and uses a shared survey to identify strengths and areas for improvement to help develop a medicine regulatory system that is based on the best possible practices. ANSM passed this test with an average score of 3.9/5.

Optimisation of MA modification processing

In 2016, efforts to optimise MA modifications continued and were heightened. In order to comply with regulatory deadlines and take charge of its new responsibilities, the agency invested heavily in improving the proficiency of its agents and recruiting technical and scientific advisors. In the pursuit of continuous improvement, processes were revised to handle any encountered difficulties. The agency also increased its steering efforts by implementing standard “Cross-Cutting Dossier Tracking”. In addition, collaboration between the agency’s various divisions was strengthened, resulting in the efficient handling of dossiers.

Over 2,000 dossiers from all categories were processed prior to regulatory deadlines.

Optimisation of non-health-related clinical trial processing

An optimised processing method for non-health-product clinical trials was implemented in 2016. The method used was similar to that established for MA modifications (working groups, process redefinition and optimisation, training, and implementation).

The centralised processing approach made it possible to notify all non-health-product clinical trials in compliance with regulatory deadlines. This is because the product divisions were relieved of a task having no relation to the agency's core business.

Improvements to workflow management

Another priority project in 2016 was the improvement of workflow management; this goal was pursued through a comprehensive steering and traceability programme for workflows received and processed by the agency. The implementation of the "Cross-Cutting Dossier Tracking" application makes it possible to monitor and manage the "life cycle" of each dossier. The "Cross-Cutting Dossier Tracking" application was deployed to all divisions in 2016, starting with those involved in MA modifications. It will be applied to other workflows in 2017.
This exhaustive and comprehensive traceability system makes it possible to better manage cases that are being examined by the divisions thanks to the implementation of stable and reliable activity and performance indicators.

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

Paperless communication

In 2016, the agency continued its efforts to switch to paperless communications; over 80% of all dossier transmissions and discussions are now electronic.

As part of this pursuit, the reception and traceability of electronic dossiers sent to the Common European Submission Platform (CESP) were optimised through a semi-automatic entry registration system using the OTES (Input-Output Traceability Tool) application.

FOCUS ON: Urbanisation

Urbanisation: In keeping with work conducted in 2015, the IS urbanisation system made it possible to incorporate the needs of business lines into the existing IS and work towards reaching the functional target.

In late 2016, the agency also deployed this system to the business lines. The goal is to identify the best processing method for a given activity. This target, which serves as a guideline, will help the agency continue to improve as it implements its quality policy.

Accreditation of inspection and internal audit activities

The ANSM Inspection Division was accredited by COFRAC [the French Accreditation Committee] 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 regulations 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 Division 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.

In 2016, the agency obtained accreditation for all its inspection and evaluation activities through COFRAC (for more detailed information, please refer to accreditation certificate no. 3-1094 ver. 2 published on the COFRAC website).
European audits of control activities

Following the audit carried out on ANSM laboratory control activities in December 2015, as part of the European audit programme conducted by EDQM (European Directorate for the Quality of Medicines and Healthcare), the agency formulated a response to deviations in 2016. This response was found to be satisfactory by the four European auditors, who 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.

This audit, which is part of the department's efforts to ensure quality, also highlighted a 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 department in issuing quality documents (procedures, operating instructions, etc.) and internal and external audits as part of an ongoing drive to improve.
2- Implementing the Information System Master Plan (ISMP)

The information system is an important component of ANSM’s modernisation efforts. It must contribute to securing the agency’s activities and increasing its productivity.

The 2014-2018 Information System Master Plan (ISMP), which was approved by the Administrative Board on 27 March 2014, was updated in 2016 in order to adapt it to the agency’s new business lines and steering needs.

In accordance with the updated ISMP schedule, the agency effectuated:

- The upgrading of the Marketing Authorisation management tool
- The launch of the standard version of the Cross-Cutting Dossier Tracking (STD) tool to facilitate the agency’s steering activity
- The commissioning of a reporting tool (Qlikview) that will produce steering indicators and process demands for all agency activities
- A new version of the electronic MA request registration software package (EURS).

Changes to the IT system were made in a variety of fields, including health product authorisation, vigilance, European activities, clinical trials, health product standards, inspection management tools, and expert management.

Reinforcement of the agency's methodological approach and measures to modernise and safeguard the IS

The assessment of the information system project demonstrated that the network, which is made up of 15 representatives from the business line divisions, improves the visibility of IS projects within the divisions, supports implementation lead time for tools, and helps ensure that needs are met.

In addition, the data and information system security manager (ISSM) recruited in 2015 created an action plan that will be implemented up until 2019. The purpose of this plan is to meet the requirements of the French National Information System Security Agency (ANSSI) as well as those of the Military Programming Law (LPM), with which the agency must comply.

Infrastructure modernisation plan

In order to account for technological advances, comply with safety requirements, and increase its agility and reliability, the agency launched a plan to modernise its infrastructure.

These modifications will take place over the next three years and include changes in methodology, automated implementation and surveillance activities, and a significant investment in equipment in order to enforce the Continuity Plan for the agency’s activities.
3- Human resources

The HR policy is based on the master plan for jobs and skill sets

In 2015, the agency initiated its Human Resources Master Plan (HRMP), which was designed to bridge the gap between major strategic areas of focus, especially those listed in the Goal and Performance Contract (COP) and ANSM’s human resource policy. The goal is to allow each employee to take part in the agency’s collective environment to better serve health and health safety consumers.

Voted on by the Administrative Board on 26 May 2017, it includes four strategic areas of focus:

**Area 1:**
Make collaborative work one of the agency’s strengths

**Area 2:**
Consolidate managerial practices and orient them towards helping to promote individual and collective professional effectiveness

**Area 3:**
Support individual and collective professional development and anticipate business line changes, both in terms of quality and number

**Area 4:**
Promote the development of a respectful working environment that fosters individual and collective professionalism

Job changes

To fulfil its health product safety missions, ANSM is supported by a workforce corresponding to 949 full-time equivalents (FTEs) as of 31 December 2016. It also has 16 non-permanent FTEs that are covered by work support and internship contracts and not included in the cap.

Evolution of jobs authorised between 2011 and 2016

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Below cap</td>
<td>978</td>
<td>1,003 (1)</td>
<td>1,003 (2)</td>
<td>1,003</td>
<td>983 (4)</td>
<td>969.5</td>
</tr>
<tr>
<td>Beyond cap</td>
<td>16</td>
<td>16</td>
<td>6 (3)</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>994</td>
<td>1,019</td>
<td>1,009</td>
<td>1,009</td>
<td>989</td>
<td>985.5</td>
</tr>
<tr>
<td>+/-</td>
<td>+25</td>
<td>-10</td>
<td>=</td>
<td>-20</td>
<td>-3.5</td>
<td></td>
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</table>

(1) New resources, specifying that the creation of 40 jobs 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 jobs 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 changed 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 granted a secondary cap of 993 WFTEs so it could plan for the reduction in its personnel by the end of 2015.

Evolution of job implementation

<table>
<thead>
<tr>
<th>FTEs as of 31 December</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent</td>
<td>942</td>
<td>933</td>
<td>987</td>
<td>954</td>
<td>959</td>
<td>926</td>
</tr>
<tr>
<td>Temporary</td>
<td>30</td>
<td>33</td>
<td>21</td>
<td>49</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>FTE under cap</td>
<td>972</td>
<td>996</td>
<td>1,008</td>
<td>1,003</td>
<td>983</td>
<td>949</td>
</tr>
<tr>
<td>FTE above cap</td>
<td>13.7</td>
<td>12.7</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Total FTE below and above cap</td>
<td>985.7</td>
<td>1,008.7</td>
<td>1,013</td>
<td>1,005</td>
<td>988</td>
<td>965</td>
</tr>
</tbody>
</table>

Implementation of jobs under the cap 2011-2016
Permanent personnel account for 98% of employees (88% contracted employees and 12% civil servants).

The average employee age is 45 years (same as in 2015).

Women make up 72% of employees (same as in 2015).

The average retirement age (9 employees in 2016) is 64.8 for contracted employees (6) and 61.3 for civil servants (3).

The permanent personnel age pyramid
Non-permanent staff (2% of personnel in 2016) are temporary employees hired to absorb increased workload or to replace employees on maternity leave.

An internship programme was launched in September 2016 and is overseen by trained tutorship teams (10 recruits with various qualification levels and business line profiles).

**Business line changes**

The structuring of an updated business line reference base, which began in 2014, continued through 2016. This reference base will help guide the implementation of recruitment plans, professional development pathways, and training resources so as to meet the anticipated management goals for skills and employment.

**ANSM's training policy is designed to modernise the agency and increase its efficiency**

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

**Main themes of the 2016 training plan**

- Designing professionalisation/business line training programmes - 56%
- Assisting in the implementation of tools and working processes - 28%
- Strengthening management practices during change - 4%
- Improving the quality of life at work - 2%
- Excluding reports and orientations - 10%

Between 2015 and 2016, the agency designed seven training programmes organised by business line (pharmacovigilance, pre-clinical, clinical, administrative and financial management, management control, auditing, and project management). The agency continued to use its training programme for inspection and secretariat-related business lines.

The training programme should allow the agency to systematise the support it offers its employees as they take up their duties and develop their skills.
Steps taken by ANSM in 2016 to improve its training plan include:

- the development of an e-learning (i.e. distance learning) programme within the agency and the EMA
- a training course conducted with the "Ethics of Expertise Division" to strengthen the ethics framework surrounding the purchase of HR services
- the reestablishment of a university partnership in late 2016 to offer a degree in health product surveillance, which had been suspended due to internal issues within the university.

The agency’s training budget was maintained at 1,382,000 euros (same as the 2015 budget).

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<tbody>
<tr>
<td>€812 128</td>
<td>€1 107 093</td>
<td>€1 513 715</td>
<td>€1 277 947</td>
<td>€1 219 873</td>
<td>€1 178 832 (€1 448 902 invested)</td>
<td></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>
<td>1.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average number of training days per employee trained</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4.39</td>
<td>4.36</td>
<td>3.87</td>
<td>4.3</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average number of in-service training days per ANSM employee</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.02</td>
<td>3</td>
<td>3.97</td>
<td>3.67</td>
<td>3.2</td>
<td>4.0</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Number of training days</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 132</td>
<td>3 267</td>
<td>4 258</td>
<td>3 870</td>
<td>3 317</td>
<td>4 067</td>
<td></td>
</tr>
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</table>

Measures to improve the quality of life at work

Continuation of the psycho-social risk prevention plan

In 2016, the agency continued to implement the actions set forth in the psycho-social risk prevention plan developed in 2015. This action plan aims to improve the collective functioning of the agency, the quality of life at work, and the organisation of work to better fulfil ANSM's public service mission.

Among the priority topics identified, several actions were implemented, including:

- the provision of more information on the intranet regarding health and safety at work (new sections on the quality of life at work, "Disability and health at work", "Remote work", etc.),
- the appointment in early 2016 of a Prevention Advisor along with four prevention assistants who will be trained and operational as of 2017,
- the development of an Activity Continuity Plan in the summer of 2016 that will be further defined by action plans.

Remote work experiment

In March 2016, the agency experimented with remote work in collaboration with the inspection division. Thirty-one inspectors and 13 employees from "sedentary" business lines within the division took part.

This experiment made it possible to:

- test new methods of working within a division
- develop a framework that was compatible with the agency's service requirements (continuity and quality of service)
identify potential limits, risks, and constraints associated with remote work
• gather feedback from employees and managers after the experiment.

A pro-active policy to employ and retain disabled personnel

In 2016, as part of its policy to improve working conditions and in accordance with its regulatory obligations, the agency initiated a programme to develop and implement a pro-active policy to employ and retain employees with a disability or significant health problem. The ultimate goal is to improve the working conditions of employees most affected by this policy and raise disability awareness among ANSM staff and managers to better identify people living with disabilities or significant health problems.

The agency supports its staff members who are living with disabilities by adapting work stations, purchasing adapted equipment, offering temporary at-home work arrangements, proposing adapted work hours, and providing a taxi service to help transport such employees. All stakeholders within the prevention chain are involved in this effort.

To improve the support that it provides to employees living with disabilities or suffering from serious health problems, and to keep these individuals in the workforce, the agency analysed its practices, developed an action plan, and implemented a communications plan in 2016.

Continued renovation of the agency’s facilities

In 2016, the agency continued its ambitious renovation work, particularly at the Saint Denis site, and more particularly on the main building. The fifth floor was completely renovated (500 m²) as was one wing on the fourth floor (337 m²).

The cafeteria was completed at the Saint Denis site, and it reopened on 2 January 2017. This large-scale operation increased the cafeteria’s guest capacity from 200 to 250, replaced 98% of the kitchen equipment, and provided employees with a dining space featuring improved acoustics and temperature control.

Heightened security and safety at ANSM

In 2016, the agency worked to improve safety through substantial investments. ANSM initiated work on two major projects. First, it brought its safety work station up to standard by creating an entirely new video-surveillance circuit that complies with the requirements of the French National Information System Security Agency. It also completely overhauled the agency’s safety architecture to make its intruder detection, entry protection, and video surveillance systems interoperable.

In the short term, the agency plans on migrating its current MIFARE-type badge numbering system to the more robust DESFIRE EV1-type numbering solution.

Dialogue between management and employees

The annual schedule of working topics regarding unions was created and followed. Fifty-six meetings were held in 2016, including 29 group meetings and 27 working, discussion, and/or coordination meetings with labour.

Management and employee survey

The agency conducted its first management and employee survey with a 65.6% response rate. The results were shared with governing bodies and employees.
Fifteen general indicators provide an overview of the management-employee relationship, the perception of staff regarding current strategic changes, the agency's internal organisation, and the impact recent changes have had.

The analysis of identified trends will make it possible to adapt, if necessary, the implementation methods of strategic orientations and certain action plans in progress (HRMP, ISMP, etc.), as well as to adapt, adjust, or better communicate about HR services and identify areas for improvement regarding employee satisfaction.

Internal communication: strategic project support

Internal communication relies on several complementary tools including an Intranet, launched in May 2015, that serves as a central tool for adopting a cross-cutting approach and sharing information. The intranet provides access to all practical and useful information and documents for day-to-day work. New content was added in 2016 to support the agency's strategic projects (priority projects, activity structuring, quality policy, risk management, and management seminars) as well as projects regarding quality of life, health, and safety at work (disability, management and employee survey, remote work, new office cafeteria, single professional risk assessment document, and information security).

In 2016, staff were invited to attend two philosophy conferences on the topic of responsibility. Due to their popularity, the agency decided to offer philosophy workshops in 2017.
4- The agency’s budget

Following two budget revisions, ANSM’s 2016 budget amounted to €128.7 million in terms of commitment authorisation and €132.3 million in payment appropriations (including the savings plan). The budget was implemented at 98% in commitment authorisation (€126.2 million) and 93% in payment appropriations (€123.4 million).

A context of significant budgetary constraints

The initial draft budget for 2016, like those of the two previous financial years, was developed against a backdrop of significant financial constraints.

Since 2013, the agency has had to balance its budget by drawing from its working capital fund. The goal of this approach is to reduce it in accordance with the COP and decrease the subsidy for public service expenses commensurately. However, the scheduled decrease of the working capital fund was magnified by regulation measures. As a result, it decreased faster than was planned in the COP, leaving the agency no leeway.

The initial pre-notification for the funds allocated to the agency for 2017 did not take these more difficult circumstances into account, leading ANSM to immediately implement a savings plan in 2016 to limit the deterioration of its anticipated working capital fund and cash flow.

These efforts led to either direct savings or deferments in the scheduling of certain operations, but nevertheless sought to preserve the agency’s same level of operation and ability to fulfil its health safety missions.

Expenditure by type

Change in ANSM spending since 2012 – K€

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<tr>
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</tr>
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<tbody>
<tr>
<td>Personnel</td>
<td>75 630</td>
<td>80 635</td>
<td>79 089</td>
<td>79 713</td>
<td>79 622</td>
</tr>
<tr>
<td>Operations</td>
<td>35 852</td>
<td>31 965</td>
<td>34 134</td>
<td>33 698</td>
<td>23 011</td>
</tr>
<tr>
<td>Interventions</td>
<td>18 760</td>
<td>17 285</td>
<td>16 576</td>
<td>12 672</td>
<td>12 678</td>
</tr>
<tr>
<td>Investment</td>
<td>13 014</td>
<td>9 434</td>
<td>9 259</td>
<td>10 901</td>
<td>8 131</td>
</tr>
<tr>
<td>Total</td>
<td>143 256</td>
<td>139 319</td>
<td>139 058</td>
<td>136 984</td>
<td>123 442</td>
</tr>
</tbody>
</table>

In payment appropriations
Change in spending since 2012

Revenue

Change in ANSM revenue since 2012 – K€

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>State subsidy</td>
<td>129 544</td>
<td>116 359</td>
<td>103 176</td>
<td>113 160</td>
<td>111 786</td>
</tr>
<tr>
<td>EMA</td>
<td>7 053</td>
<td>7 286</td>
<td>8 597</td>
<td>8 198</td>
<td>4 270</td>
</tr>
<tr>
<td>Tax and fee settlement</td>
<td>7 226</td>
<td>595</td>
<td>4 937</td>
<td>849</td>
<td></td>
</tr>
<tr>
<td>Other income from regular operations</td>
<td>1 589</td>
<td>4 161</td>
<td>5 640</td>
<td>3 750</td>
<td>319</td>
</tr>
<tr>
<td>Operating revenue total</td>
<td>145 412</td>
<td>128 401</td>
<td>122 351</td>
<td>125 957</td>
<td>116 375</td>
</tr>
</tbody>
</table>

In payment appropriations

Type of revenue for the 2016 financial accounts

- State subsidy - K€111 786
- EMA - K€4 270
- Other income from regular operations - K€319
The subsidy for public service costs is paid by the French government and represented 96% of ANSM's operating income in 2016. This amounted to €111.8 million in 2016, i.e. a decrease of 1.2% compared to 2015 (€113.2 million) and nearly a 13.5% decrease compared to 2012.

With respect to EMA revenue, it should be noted that only around €4.3 million could be entered into the budgetary and accounting tool prior to 31 December 2016; this applies to the €8.082 million for which a revenue order was indeed issued.

Revenue from the EMA consisted of payment for ANSM's work in the following areas:
- study of marketing authorisation application procedures (70%),
- issuing of scientific opinions (13%),
- inspections conducted upon request (5%),
- translations (1%),
- studies of pharmacovigilance dossiers (11%).

Change in revenue since 2012

![Graph showing change in revenue since 2012]

**Expenditure by envelope**

**Personnel: €79.6 million**

The personnel budget was implemented to the tune of €79.6 million, i.e. 99% of the initial budget.

The budget includes expenditures for the following:
- payroll: €78.4 M (€78.7 M in 2015)
- social actions: €1.2 million.
Employment authorisations are implemented as follows:

<table>
<thead>
<tr>
<th>Posts</th>
<th>2016 authorisations</th>
<th>2016 Implementations</th>
<th>Implementation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>WFTE</td>
<td>FTE</td>
</tr>
<tr>
<td>Below cap</td>
<td>969.5</td>
<td>969.5</td>
<td>948.9</td>
</tr>
<tr>
<td>Beyond cap</td>
<td>16.0</td>
<td>9.3</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>985.5</td>
<td>978.8</td>
<td>964.9</td>
</tr>
</tbody>
</table>

**Operation: €23 million**

The operating budget includes the following:

- the IT budget, which amounted to €4 million in 2016 (assigned budget was €5.7 million);
- property rentals: €3.3 million;
- national quality control of medical biology and laboratory control activities: €2.3 million;
- travel costs (inspections, committees and commissions, European projects): €1.4 million
- Training: €1.2 million (assigned budget was €1.4 million);
- Spending on internal and external communication: €1.2 million;
- Security-related expenses: €1.2 million.

**Intervention: €12.7 million**

The intervention envelope is divided into several components:

- ten new projects were selected following a call for research proposals in 2016, raising the number of research projects funded by the agency since 2012 to 82. The total amount of payments in 2016 for agreements in the current fiscal year and previous years was nearly €2 million;
- call for proposals (AAP) – associations: expenditures were posted in 2016 and came to €94,000, including €22,000 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);
- 13 new research agreements were signed in 2016, which represents an initial payment of €1.2 million;
- the funding of pharmaco-epidemiology platforms (PEPS from Rennes University Hospital and DRUGS SAFE from Bordeaux University) in late 2014 with a €1.8 million payment in 2016 to conduct studies on the safety of health products in France.

**Investment: €8.1 million**

The main investment expenditures in 2016 concern:

- the laboratory equipment plan representing €0.4 K (purchase of a mass spectrometer);
- nearly €4.5 million in IT investments under the Information System Master Plan: €2.5 million;
- property investments for an overall total of €4.7 million, including the continued renovations of the agency office and the complete renovation of the company cafeteria;
- work related to security, primarily the modernisation of the general security system for the checkpoint and security station: €0.2 million.
Financial accounts for 2016 – K€

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel</td>
<td>80 200</td>
<td>79 622</td>
<td>80 895</td>
<td>Subsidy for</td>
<td>113 209</td>
<td>111 786</td>
<td>109 795</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>public service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operations</td>
<td>28 100</td>
<td>23 011</td>
<td>26 349</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>12 902</td>
<td>12 678</td>
<td>11 176</td>
<td>EMA revenue</td>
<td>8 300</td>
<td>4 270</td>
<td>8 200</td>
</tr>
<tr>
<td>Investment</td>
<td>11 200</td>
<td>8 131</td>
<td>6 956</td>
<td>Other</td>
<td>1 100</td>
<td>319</td>
<td>1 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>resources</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total expenses</td>
<td>132 402</td>
<td>123 442</td>
<td>125 376</td>
<td>Total</td>
<td>122 609</td>
<td>116 375</td>
<td>119 095</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budget surplus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Budget deficit</td>
<td>9 893</td>
<td>7 066</td>
<td>6 281</td>
</tr>
</tbody>
</table>

116 notified contracts in 2016

The total number of active ANSM contracts is 404.

Breakdown of active contracts by type

- **Supply**: 80 contracts - 19.8%
- **Construction**: 33 contracts - 8.2%
- **Services**: 291 contracts - 72%

Of the 404 active contracts, 116 were notified in 2016.

The number of notified contracts decreased significantly (25% fewer than in 2015) due to the fact that the work contracts were concluded in previous years (contracts related to the renovation of the offices and working spaces of the Saint-Denis site as well as the contracts for the Lyon and Vendargues sites).

The same applies to service contracts, which were also concluded at an earlier time (training contracts to meet new needs related to management and support) and are still ongoing. Finally, many contracts for the supply of laboratory animals, materials, and equipment were concluded in previous years and are still ongoing.
Breakdown of contracts by type

- Supply: 11 contracts (9.5%)
- Construction: 23 contracts (19.8%)
- Services: 82 contracts (70.7%)

Strengthening purchasing procedures

ANSM is pursuing its purchasing performance goals, which primarily aim to reduce the use of amendments (18 in 2016 compared to 29 in 2015, i.e. a 38% decrease) and instead rely on negotiation procedures with respect to purchasing procedures whenever possible (50 procedures in 2016 compared to 12 procedures in 2015).

Two other goals were included in 2016:
- to ensure the traceability and economic efficiency (by mandating competition) of all purchases costing between €5,000 and €25,000, excluding tax. Thirty-one contracts were concluded in 2016 using this procedure, which came into effect in February 2016;
- to maximise savings on purchases: the financial gains achieved in 2016 amounted to €850,000 including tax.

ANSM is continuing its work with the Department of Government Procurement (formerly the SAE) in an effort to pool needs. In 2016, ANSM entered into framework agreements with the Department of Government Procurement for the provision of electricity and optimisation of property lease agreements.

Purchasing strategy formalisation and approval

Following the first Purchasing Action Plan (PAP) developed by ANSM between the end of 2015 and early 2016, at the request of the Department of Government Procurement, another PAP was written for the 2017-2020 period.

This PAP is based on ANSM’s purchasing strategy, which was specifically addressed and approved by the Administrative Board on 28 February 2017.
Implementation of the GBCP decree—Deployment of the SIFAS tool—QUALIAC

It's important to note that the management context in 2016 was unusual due to the implementation of the GBCP decree and the launch of the budgetary and accounting information system SIFAS at the start of the year. This system was developed as part of an ambitious mutualisation project involving five health agencies and became operational on 2 January 2016. However, it had to be significantly adjusted, modified, and corrected throughout the year, delaying the divisions' management operation entries and resulting in significant technical difficulties for the accounting and financial departments as part of the end management work.

At the same time, the agency structured its budget by allocations in line with the strategic priorities of the COP.
### Appendix 1

**Summary table of opinions issued by the Risk/Benefit Ratio Monitoring Commission in 2016**

<table>
<thead>
<tr>
<th>Medicine(s)</th>
<th>Opinion of the Risk/Benefit Ratio Monitoring Commission</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)ilretinoin (Toctino® 10 and 30 mg, soft capsule)</td>
<td>Restriction of initial half-year prescription to dermatologists.</td>
</tr>
<tr>
<td>trimebutine (Débridat®, Débricalm®, Transacalm®, and Trimébutine®)</td>
<td>Unfavourable risk/benefit ratio in children under two years of age.</td>
</tr>
<tr>
<td>trimebutine/ruscogenin (Proctolog®)</td>
<td>Unfavourable risk/benefit ratio for the indication “Symptomatic treatment of rectal pain, itching, and fissures, particularly in association with haemorrhoids”.</td>
</tr>
<tr>
<td>Abstention for the risk/benefit ratio for the indications &quot;symptomatic treatment of acute pain associated with functional disorders of the gastrointestinal tract&quot; and &quot;adjunct therapy for post-operative paralytic ileus&quot;; Unfavourable risk/benefit ratio for the indications &quot;symptomatic treatment of acute pain associated with functional disorders of the bile ducts&quot; and &quot;in preparation for radiological and endoscopic exams&quot;; A majority opinion was not obtained regarding the merits of asking the marketing authorisation laboratory to conduct efficacy studies concerning the symptomatic treatment of acute pain associated with functional disorders of the gastrointestinal tract. Nor was it obtained for efficacy studies concerning its use as an adjunct therapy for post-operative paralytic ileus.</td>
<td></td>
</tr>
</tbody>
</table>
| Oral trimebutine (Débridat® and generics), excluding proprietary medicines for which prescription is optional | Favourable risk/benefit ratio for the "symptomatic treatment of pain, constipation, and intestinal discomfort associated with functional intestinal disorders" on the condition of modifying the SPC and the leaflet for granulated forms in order to account for the unfavourable risk/benefit ratio in children under 2 years of age:  
- Section 4.2 (Dosage): deletion of dosages and administration modes in children under 24 months of age;  
- Section 4.3 (Contraindications): addition of a contraindication in children under 24 months of age.  
Unfavourable risk/benefit ratio for the "symptomatic treatment of pain associated with functional disorders of the bile ducts". |                                                                                                                                  |
| optional prescription for trimebutine (Débricalm® 100 mg and Trimebutine Biogaran Conseil® 100 mg) | Unfavourable risk/benefit ratio for the "symptomatic treatment of pain associated with functional disorders of the gastrointestinal tract in adults".                                                                                                       |
| pinaverium bromide (Dicétel® and Pinavérium®)                               | Favourable risk/benefit ratio with the following additions to section 4.4 (Special precautions and precautions for use) of the SPC and equivalent sections in the leaflet: "The tablets must be swallowed while sitting. Do not suck or chew them. Take with a large glass of water in the middle of a meal. Do not lie down for 30 minutes after taking the medicine";  
Favourable risk/benefit ratio for the indication "Symptomatic treatment of pain, constipation, and intestinal discomfort associated with functional intestinal disorders" on the condition of specifying the typology of immediate hypersensitivity reactions (Quincke’s oedema) in section 4.8 (Adverse effects) of the SPC and equivalent sections in the leaflet;                                                                 |

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**The French National Agency for the Safety of Medicines and Health Products**

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2016 Annual Report
A majority opinion was not obtained regarding the proposition to eliminate the maximum dosage of 300 mg/day from section 4.2 (Dosage and method of administration) of the SPC and equivalent sections in the leaflet with respect to the symptomatic treatment of pain, constipation, and intestinal discomfort associated with functional intestinal disorders;

Unfavourable risk/benefit ratio for the indications "Symptomatic treatment of pain associated with functional disorders of the bile ducts" and "Preparation for a barium enema".

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk/Benefit Ratio</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferoxamine (Desféral® 100mg/ml, powder and solvent for injectable solution):</td>
<td>Favourable risk/benefit ratio</td>
<td>A majority opinion was not obtained regarding the proposition to add to section 4.4 (Special warnings and precautions for use) of the SPC and equivalent section in the leaflet the following warning: &quot;Transaminase elevation has been reported with deferoxamine&quot;.</td>
</tr>
</tbody>
</table>
| Iproniazide (Marsilid® 50mg, scored tablet) | Favourable risk/benefit ratio | Favourable opinion regarding the modification of the SPC and equivalent sections in the leaflet:  
- Section 4.1 (Therapeutic indications): "Major (i.e. characterised) depressive episodes following the failure of several antidepressants or electroconvulsive therapy. Because of the time frame that must be observed between the failure of the first therapy and the start of another antidepressant, MAOIs are not typically prescribed as first-line treatments";  
- Section 4.3 (Contraindications): "Transaminases three times higher than normal levels";  
- Section 4.4 (Special warnings and precautions for use): "Liver function must be tested in all patients at the start of treatment, monthly for the first three months of treatment, and then every three months for the first two years of treatment and/or if there are signs of hepatitis. If the patient presents with symptoms or signs that indicate hepatitis, iproniazide treatment must be terminated immediately until this diagnosis has been ruled out."  
- Section 4.8 (Adverse effects): "Sometimes serious" cases of cytolytic or icteric hepatitis ("Rare cases of fulminant hepatitis resulting in death or liver transplant have been reported); acute hypertension (pseudopheochromocytoma)";  
Favourable opinion regarding the restriction of the initial or annual prescription to psychiatrists;  
Recommendation that psychiatrists inform general practitioners about treatment initiation and iproniazide’s precautions for use, particularly risks pertaining to medicine interactions. |
| Porfimer sodium (Photofrin® 75mg, powder for injectable solution) | Unfavourable risk/benefit ratio in oncology. | |
| Alverine/simethicone (Météospasmyl® and generics) | Favourable risk/benefit ratio for the indication "Symptomatic treatment of functional intestinal symptoms, especially abdominal distension", on the condition that the SPC (sections 4.2, 4.4, and 4.8) and the corresponding sections in the leaflet are modified. |
### Appendix 2:
Referrals sent to the CHMP and PRAC

**Referrals sent to the CHMP**

<table>
<thead>
<tr>
<th>Name of procedure (International Common Denomination [ICD]) or common name</th>
<th>Start of procedure</th>
<th>End of procedure</th>
<th>Referral type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linxyd and associated names (linezolid)</td>
<td>24/09/2015</td>
<td>Withdrawal of MA(^9)</td>
<td>Article 29(4) of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Linezolide Accord and associated names (linezolid)</td>
<td>24/09/2015</td>
<td>Withdrawal of MA(^10)</td>
<td>Article 29(4) of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Otipax and associated names (lidocaine hydrochloride)</td>
<td>22/10/2015</td>
<td>Withdrawal of MA(^11)</td>
<td>Article 29(4) of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Levonelle, 1,500 μg tablets and associated names (levonorgestrel)</td>
<td>22/10/2015</td>
<td>26/05/2016</td>
<td>Article 13 of Regulation (EC) no. 1234/2008</td>
</tr>
<tr>
<td>Tobramycin VVB and associated names (tobramycin)</td>
<td>22/10/2015</td>
<td>28/01/2016</td>
<td>Article 29(4) of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Lovenox and associated names (enoxaparin sodium)</td>
<td>19/11/2015</td>
<td>15/12/2016</td>
<td>Article 30 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing metformin (metformin)</td>
<td>28/01/2016</td>
<td>13/10/2016</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Diclofenac, 50 mg tablets (diclofenac epolamine)</td>
<td>25/02/2016</td>
<td>21/07/2016</td>
<td>Article 29(4) of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing dienogest/ethinylestradiol (dienogest/ethinylestradiol)</td>
<td>25/02/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Akem (cefuroxime, rifuzole, ibuprofen)</td>
<td>01/04/2016</td>
<td>23/06/2016</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing vancomycin (vancomycin)</td>
<td>01/04/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Symbioflor 2 and associated names (Escherichia coli bacteria [cells and autolysate])</td>
<td>01/04/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Pharmaceuticals International, Inc. (Amnonaps [sodium phenylbutyrate], Lutinos and associated names [progesterone], Dutasteride Actavis and associated names [dutasteride], SoliCol D3 [cholecalciferol])</td>
<td>23/06/2016</td>
<td>13/10/2016(^12)</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Paracetamol/ibuprofen 500 mg/150 mg</td>
<td>10/11/2016</td>
<td>Ongoing</td>
<td>Article 29(4) of</td>
</tr>
</tbody>
</table>

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\(^9\) Withdrawal of MA in January 2016  
\(^10\) Withdrawal of MA in January 2016  
\(^11\) Withdrawal of MA in April 2016  
\(^12\) Date of CHMP opinion after revision
### Referrals sent to the PRAC

<table>
<thead>
<tr>
<th>Name of the procedure (International Common Denomination [ICD])</th>
<th>Start of procedure</th>
<th>End of procedure</th>
<th>Referral type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines containing inhaled corticosteroids indicated in the treatment of chronic obstructive pulmonary disease (beclometasone, budesonide, flunisolide, fluticasone propionate, fluticasone furoate)</td>
<td>07/05/2015</td>
<td>28/04/2016</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Tysabri (natalizumab)</td>
<td>07/05/2015</td>
<td>25/02/2016</td>
<td>Article 20 of Regulation (EC) no. 726/2004</td>
</tr>
<tr>
<td>Medicines containing SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)</td>
<td>11/06/2015</td>
<td>25/02/2016</td>
<td>Article 20 of Regulation (EC) no. 726/2004</td>
</tr>
<tr>
<td>Medicines containing fusafungin for oromucosal and nasal use (fusafungin)</td>
<td>10/09/2015</td>
<td>31/03/2016</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing gadolinium (gadolinium)</td>
<td>17/03/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Direct-acting antivirals (DAA) indicated for the treatment of hepatitis C (without interferon) (daclatasvir, dasabuvir, simeprevir, sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir)</td>
<td>17/03/2016</td>
<td>15/12/2016</td>
<td>Article 20 of Regulation (EC) no. 726/2004</td>
</tr>
<tr>
<td>Zydelig (idelalisib)</td>
<td>17/03/2016</td>
<td>21/07/2016</td>
<td>Article 20 of Regulation (EC) no. 726/2004</td>
</tr>
<tr>
<td>SGLT2 inhibitors and lower limb amputation (canagliflozin, capagliflozin, empagliflozin)</td>
<td>14/04/2016</td>
<td>Ongoing</td>
<td>Article 20 of Regulation (EC) no. 726/2004</td>
</tr>
<tr>
<td>Medicines containing retinoids (acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tretinoin, tazarotene)</td>
<td>07/07/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Paracetamol for modified or prolonged release (paracetamol)</td>
<td>07/07/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing recombinant coagulation factor VIII (coagulation factor VIII, efmoroctocog alfa, moroctocog alfa, octocog alfa, simoctocog alfa, susoctocog alfa, turoctocog alfa)</td>
<td>07/07/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
<tr>
<td>Medicines containing bovine lactose for the IV/IM treatment of acute allergic reactions (methylprednisolone)</td>
<td>01/12/2016</td>
<td>Ongoing</td>
<td>Article 31 of Directive 2001/83/EC</td>
</tr>
</tbody>
</table>
Appendix 3:
Overview of major French and European texts published in 2016 (excluding health policy decisions and agency organisation)

<table>
<thead>
<tr>
<th>MEDICINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUROPEAN TEXTS</td>
</tr>
<tr>
<td>Regulation (EU) 2016/793 of the European Parliament and Council dated 11 May 2016 aiming to prevent the diversion of certain essential medicines to European Union countries</td>
</tr>
<tr>
<td>Agreement in the form of diplomatic messages exchanged with Japan in accordance with Article 15 Paragraph 3 Point b) of the Mutual Recognition Agreement to modify Part B of the sector-specific appendix on best manufacturing practices for medicines</td>
</tr>
<tr>
<td>Council conclusions on strengthening of the balance within pharmaceutical systems of the European Union and its member states (2016/C 269/06)</td>
</tr>
<tr>
<td>Council conclusions on the next steps in the fight against antimicrobial resistance as part of the “One health” concept (2016/C 269/05)</td>
</tr>
<tr>
<td>Council implementation decision (EU) 2016/1070 of 27 June 2016 subjecting 1-phenyl-2-(pyrrolidin-1-yl) pentan-1-one (α-pyrrolidinovalerophenone, α-PVP) to control measures</td>
</tr>
<tr>
<td>Commission implementation decision (EU) 2016/1658 of 13 September 2016 modifying decision 2008/911/EC establishing a list of botanical substances, plant-based preparations, and plant-based combinations with a view to their use in traditional, plant-based medicines [notified under the number C(2016) 5747]</td>
</tr>
<tr>
<td>Commission implementation decision (EU) 2016/1659 of 13 September 2016 modifying decision 2008/911/EC establishing a list of botanical substances, plant-based preparations, and plant-based combinations with a view to their use in traditional, plant-based medicines [notified under the number C(2016) 5748]</td>
</tr>
<tr>
<td>Decisions to grant European MAs</td>
</tr>
<tr>
<td>Opinion of the European Commission regarding the application of Articles 3, 5, and 7 of regulation (EC) no. 141/2000 regarding orphan medicines</td>
</tr>
</tbody>
</table>
### FRENCH TEXTS

<table>
<thead>
<tr>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Law no. 2016-701 of 30 May 2016 authorising the ratification of the</td>
</tr>
<tr>
<td>agreement of the European Council on counterfeited medical products</td>
</tr>
<tr>
<td>and similar infractions that threaten public health</td>
</tr>
<tr>
<td>Decree no. 2016-317 of 16 March 2016 regarding the prescription and</td>
</tr>
<tr>
<td>delivery of medicines, containing one or several critically</td>
</tr>
<tr>
<td>important antibiotic substances, used in veterinary practise</td>
</tr>
<tr>
<td>Decree no. 2016-401 of 5 April 2016 regarding the presentation of</td>
</tr>
<tr>
<td>offers made to benfluorex victims</td>
</tr>
<tr>
<td>Decree no. 2016-469 of 14 April 2016 regarding provisions concerning</td>
</tr>
<tr>
<td>the inclusion of proprietary medicines, whose principle active</td>
</tr>
<tr>
<td>ingredient is plant or mineral based, on the list of generic groups</td>
</tr>
<tr>
<td>Decree no. 2016-960 of 12 July 2016 regarding the inclusion of</td>
</tr>
<tr>
<td>biosimilar medicines on the reference list of biosimilar groups</td>
</tr>
<tr>
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The French National Agency for the Safety of Medicines and Health Products

mentioned in paragraph 1 of article L 1121-1 of the French Public Health Code regarding medicines for human use.

Order of 15 December 2016, modifying the order of 22 August 1990 applying article R. 5132-86 of the French Public Health Code regarding marijuana

Decision of 29 December 2015 regarding best manufacturing practices

Decision modifying the list of generic groups, mentioned in article R 5121-5 of the French Public Health Code

Decision modifying the list of medicines available in pharmacies mentioned in article R 5121-202 of the French Code of Public Health

Decision of 22 December 2015 to apply article R. 5124-46 of the French Public Health Code and establish the form and content of pharmaceutical facility conditions, as mentioned in nos. 1 through 15 of article R. 5124-2 of the aforementioned code

Decisions to grant MAs

Decisions to grant PIAs

Decisions to suspend MAs

Decisions to withdraw MAs

Decisions regarding internship programme authorisations

Decision of 31 October 2016 establishing the schedule and submission periods for 2017 as well as the form and content of advertising authorisation requests for medicines for human use (31/10/2016)

Decision of 12 December 2016 establishing the content, format, and methods for presenting an authorisation application to ANSM for research involving humans and medicines for human use

Best manufacturing practices (active substances and medicines for human use—Decision of 29 December 2015 regarding best manufacturing practices)

Opinion regarding the withdrawal of heavy metal trials from the French Pharmacopoeia, 11th edition

Opinion regarding the examination of French Pharmacopoeia monographs
**BIOLOGICAL PRODUCTS**

**EUROPEAN TEXTS**

European Commission Directive (EU) 2016/1214 of 25 July 2016, modifying directive 2005/62/EC regarding the norms and specifications that apply to the quality system in blood transfusion establishments (text applicable to the EEA)

**FRENCH TEXTS**

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MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

EUROPEAN TEXTS

European Commission delegated directive (EU) 2016/585 of 12 February 2016 modifying, so as to match technical progress, Appendix IV of directive 2011/65/EU of the European Parliament and Council regarding the exemption for lead, cadmium, hexavalent chromium, and polybrominated diphenyl ethers (PBDEs) in recovered spare parts from medical devices and electronic microscopes that are used to repair or renovate this equipment

Commission statement with respect to the implementation of directive 2014/53/EC of the European Parliament and Council regarding the standardisation of member state legislation, concerning the market availability of radio-electric equipment, and appealing directive 1999/5/EC (Publication of titles and references of standardised norms as part of European Union standardisation legislation—MD 1 norms)

Commission statement with respect to the implementation of directive 90/385/EEC of the European Council regarding medical devices (Publication of titles and references of harmonised standards as part of European Union standardisation legislation)

Commission statement with respect to the implementation of directive 93/42/EEC of the European Council regarding medical devices (Publication of titles and references of harmonised standards as part of European Union standardisation legislation)

Commission statement with respect to the implementation of directive 98/79/EC of the European Parliament and Council regarding in vitro diagnostic medical devices (Publication of titles and references of harmonised standards as part of European Union standardisation legislation)

Commission statement with respect to the implementation of directive 2014/30/EC of the European Parliament and Council regarding the standardisation of member state legislation concerning electromagnetic compatibility (Publication of titles and references of harmonised standards as part of European Union standardisation legislation)

Commission statement modification with respect to the implementation of directive 98/79/EC of the European Parliament and Council regarding in vitro diagnostic medical devices (Publication of titles and references of harmonised standards as part of European Union standardisation legislation)

European Social and Economic Committee opinion on the "Proposed regulation of the European Parliament and Council regarding mercury, appealing regulation (EC) no. 1102/2008" (especially with respect to dental amalgams)

FRENCH TEXTS

Decree no. 2016-46 of 26 January 2016 regarding medical biology (ANSM and the Regional Health Agencies)

Decree no. 2016-778 of 10 June 2016 regarding the certification and testing of bodies authorised to assess medical device and in vitro diagnostic medical device compliance

Decree no. 2016-839 of 24 June 2016 regarding the working conditions and procedures of biomedical laboratory employees and the creation of the National Biology Laboratory Commission

Decree no. 2016-1430 of 24 October 2016 regarding the accreditation methods of biomedical laboratories
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<td>Order of 5 February 2016 regarding the extension of validity criteria set forth by the order of 3 July 2012, limiting aortic valvular bioprosthesis procedures using transcutaneous arterial or transapical placement, to certain health establishments in application of the provisions of article L. 1151-1 of the French Public Health Code</td>
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<td>Order of 1 August 2016 determining: the list of tests, collections, and treatments for biological signals that are not a part of biomedical laboratory examinations; the categories of people who can conduct these examinations; and the conditions for implementing certain tests, collections, and treatments pertaining to biological signals</td>
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### Decisions to renew or transfer the accreditation of external bodies in charge of MD quality control

- Decision of 12 December 2016 establishing the content, format, and methods of presenting ANSM authorisation requests involving medical devices and/or \textit{in vitro} diagnostic medical device research.

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### COSMETIC AND TATTOOING PRODUCTS

#### EUROPEAN TEXTS


#### FRENCH TEXTS

- Order of 31 May 2016 establishing the list of information to provide to the poison control centre regarding the substances contained in tattoo products.
- Order of 19 August 2016 regarding the professional qualifications of individuals responsible for the manufacturing, packaging, import, quality control, human safety evaluation, detention, and supply surveillance of starting materials and finished tattoo products.
- Order of 30 November 2016 establishing the list of information contained in the cosmetic product establishment and packaging declaration, as stipulated in article L. 5131-2 of the French Public Health Code.
- Order of 2 December 2016 establishing the research list, stipulated in paragraph 2 of article L. 1121-1 of the French Public Health Code.
- Order of 2 December 2016 establishing the content, format, and procedures for submitting a research proposal opinion request application, to the Ethics Committee, regarding a research.
The French National Agency for the Safety of Medicines and Health Products

### Proposal as stipulated under paragraphs 1 and 2 of article 1121-1 of the French Public Health Code regarding a cosmetic or tattoo product

### Order of 2 December 2016 establishing the content and presentation procedures for substantial research modification requests (as stipulated in paragraphs 1 and 2 of article L. 1121-1 of the French Public Health Code regarding cosmetic and tattoo products) submitted to the French National Agency for Medicines and Health Products Safety and Ethics Committee

### Decision of 12 December 2016 establishing the content, format, and presentation procedures for ANSM authorisation requests regarding tattoos and cosmetic products (14/12/2016)

### OTHER PRODUCTS OVERSEEN BY ANSM

#### EUROPEAN TEXTS

- Commission implementation decision (EU) 2016/586 of 14 April 2016 regarding technical norms pertaining to electronic cigarette filling mechanisms

#### FRENCH TEXTS

- Order no. 2016-800 of 16 June 2016 regarding human research
- Order of 2 December 2016 establishing the research list, as stipulated in paragraph 2 of article L. 1121-1 of the French Public Health Code
- Order of 2 December 2016 establishing the content and procedural methods for requesting a substantial research modification, as stipulated in paragraphs 1 and 2 of article L. 1121-1 of the French Public Health Code (such a request not involving a product mentioned in article L. 5311-1 of the French Public Health Code in association with the French National Agency for Medicines and Health Products Safety and the Ethics Committee)
- Decision of 12 December 2016 establishing the content, format, and procedural methods pertaining to non-health product authorisation request applications, processed by ANSM, that do not involve a product mentioned in article L. 5311-1 of the French Public Health Code

### CROSS-DISCIPLINARY FRENCH TEXTS

- Order no. 2016-966 of 15 July 2016 regarding the simplification of implementation procedures by the French National Agency for Medicines and Health Products Safety
- Order no. 2016-967 of 15 July 2016 regarding the coordination of the national agency systems overseeing health, health safety, and medical accidents
- Decree no. 2016-183 of 23 February 2016 to simplify the administrative procedures of the French National Agency for Medicines and Health Products Safety in the field of health products
- Decree no. 2016-1151 of 24 August 2016 regarding the adverse health event reporting portal
- Decree no. 2016-1537 of 16 November 2016 regarding human research