



# ANNUAL REPORT 2018

**ansm**

French National Agency for  
Medicines and Health Products Safety

# CONTENTS

- Editorial..... p. 3
- ANSM in brief..... p. 5
- Highlights in 2018..... p. 6
- Key figures in 2018..... p. 7
- Organisation chart..... p. 9
- Governance bodies..... p. 11
- Part 1. Guaranteeing the safety of health products throughout their life cycle..... p. 12
- Part 2. Promoting fast, controlled, and widespread access to innovation..... p. 92
- Part 3. Consolidating ANSM's relationships with stakeholders and increasing their involvement..... p. 124
- Part 4. Reinforcing ANSM's efficiency and pursuing modernisation..... p. 162
- Glossary..... p. 186
- Appendices..... p. 191

## The agency places risk management firmly **at the heart of its missions**



Catherine de Salins  
Chair of the Board of Directors



Dominique Martin  
Director General of ANSM

**“ANSM is determined to fulfil its health product safety missions in order to better protect the safety of the patients using these products”**

The year 2018 was marked by a number of important transformations that improved ANSM's ability to carry out all of its public health missions. These changes are a product of the agency's push to become more open and increase stakeholder involvement in order to make its services more relevant and effective for users.

The year 2018 thus saw the rise of a new internal structure, CASAR, which is designed to increase the agency's ability to respond to emergency situations, health alerts, and risk management needs with help from a team whose sole purpose is to anticipate and coordinate all events that could turn into high-risk situations.

The creation of this body is part of the agency's risk management-centred approach, which underpinned all of its activities in 2018. This step demonstrates that ANSM is determined to fulfil its health product safety missions in order to better protect the safety of the patients using these products. This approach, which includes the analysis of all pharmacological, medical, and social risks, is backed by a more extensive dialogue with stakeholders and a decision to become more open to the rest of society.

It is in this context that the agency hosted several public consultations, including an event dedicated to raising awareness among patients and healthcare professionals about the liver toxicity risk associated with the misuse of paracetamol, and another regarding the implementation of new mandatory vaccines, with a focus on the safety data for vaccines that are mandatory for children under the age of two. It is also with this goal in mind that the agency organised public hearings featuring expert committees that were broadcasted live online.

ANSM also developed a strategy to publicise its data on health products and its processes that will be rolled out in 2019. This is part of a broader governmental policy aimed at the effective use of data.

Among its many interactions with healthcare professionals, the agency worked with general practitioners to reduce private practice medication errors and met with representatives of proprietary medicines to resolve supply shortages.

This push to become more open and increase the involvement of stakeholders was also seen in the agency's reform of its scientific advisory bodies, which began at the end of 2018. ANSM issued a call for applicants to recruit external experts from all fields within its purview as well as human and social science experts. The call was also opened to representatives of regionally and nationally certified user and patient associations that, starting in 2019, will become full members of all the agency's governing bodies.

In order to better meet the needs of stakeholders with respect to providing faster access to innovative treatments, the agency implemented new processing methods for named-patient TAUs and fast-track systems for authorising clinical trials involving medicines to reduce the time to process these applications. A Strategy and European Activity Piloting Centre was created to boost France's participation in the centralised procedure, which serves as the main gateway for pharmaceutical innovation.

In addition, to better meet the growing need for health product epidemiology expertise, ANSM and CNAM pooled their pharmaco-epidemiology teams in a single scientific interest group (SIG) founded in December 2018 known as EPI-PHARE. This structure will result in enhanced epidemiological expertise to help monitor health products in real time.

The agency's Quality Policy, which supports all of these changes, was adopted in March. In December, it helped ANSM earn ISO 9001 certification for its risk management. This certification recognises the agency's ability to secure its processes and enables it to reach the main objectives listed in its 2015-2018 Objectives and Performance Contract. It also provides a powerful boost to the agency's transformation process and will empower it to better protect public health and respond to the needs of civil society.

These significant advancements serve as the foundation for the strategic guidelines included in the next Objectives and Performance Contract for 2019-2023, which the agency has been working on in collaboration with its partners and regulatory authorities throughout the year, and were implemented even as the agency continued to work diligently every day to ensure that health products are safe and that patients can access them under optimum conditions. The agency issued over 84,000 decisions in 2018. This work was possible thanks to the efforts of all of the agency's teams, whose commitment and dedication in the interest of better serving users must be recognised and commended.

# ANSM IN BRIEF

## **ANSM's goal:**

**to combine rapid access to innovative developments with the continued adjustment of health products' risk/benefit ratio to match therapeutic progress for the sole benefit of patients.**

The French National Agency for Medicines and Health Products (ANSM) was created on 1 May 2012 as a result of the French law of 29 December 2011 concerning the increased safety of medicines and health products.

The agency ensures the safety of medicines and other health products throughout their life cycle. 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 a Board of Directors, a Scientific Board, and Advisory Commissions.

It also relies on an Ethics of Expertise Committee and Department which help to guarantee the independence and impartiality of the agency's decisions.

## **MISSIONS**

- Evaluating and monitoring the risks and benefits of health products throughout their life cycle
- Monitoring advertising that promotes health products
- Inspecting manufacturing and distribution sites
- Conducting quality checks in laboratories
- Encouraging independent academic research
- Providing legal and regulatory expertise
- Speaking with patients and healthcare professionals about its actions and decisions in a transparent way
- Taking 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
- 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 softwares

### **Cosmetics and tattoos**

## Highlights in 2018

- **Application of new treatment methods** for named-patient TAUs
- **Creation of two fast-track channels** for authorisations for medicinal clinical trials
- **Paracetamol**: public consultation to raise awareness among patients and healthcare professionals regarding the risk of liver injury due to misuse
- **Issuance of market authorisation** for the use of baclofen in the treatment of alcohol addiction
- **Favourable opinion issued by the TSSC** regarding the use of cannabis for therapeutic purposes in France
- Organisation of an ANSM-College of General Practitioners **discussion day** on medication errors in high-street pharmacies
- **Creation of the scientific interest group (SIG) EPI-PHARE** between ANSM and CNAM's health product epidemiology teams
- **AFNOR certification audit** on “Risk Management”

# KEY FIGURES IN 2018

**84,000 decisions**  
issued by ANSM in 2018

## GUARANTEEING THE SAFETY OF HEALTH PRODUCTS

### Medicines

- **71,130** cases of adverse effects were collected and registered by the RPCs, including **20,192** adverse effects reported by patients
- **59,371** cases of serious adverse effects were reported through pharmaceutical laboratories
- **98** pharmacovigilance studies were in progress in 2018, and **17** new studies were begun
- **17** pharmacoepidemiological studies were implemented by ANSM
- **2,197** medication errors or risks of medication error were reported to ANSM
- **1,987** quality defect reports were submitted
- **871** reports of shortage or risks of shortage were managed by ANSM, as were strategies for finding medicinal alternatives for critical products

### Blood products

- **6,587** adverse effects related to haemovigilance were reported among donors of labile blood products
- **8,611** adverse effects related to haemovigilance were reported among recipients of labile blood products

### Medical devices and *in vitro* diagnostic medical devices

- **18,838** adverse effects related to medical device vigilance were reported, 682 of which were received from patients and patient associations
- **1,344** adverse effects related to reagent vigilance (*in vitro*) diagnostic medical devices

### Laboratory tests and inspections

- **677** inspections were conducted in 2018, including **11%** random and **6%** conducted abroad
- **4,225** test reports based on laboratory studies were completed

## PROMOTING PATIENTS' RAPID ACCESS TO INNOVATION

- **5,642** patients covered by cohort TAUs for medicines
- **15,987** patients covered by named-patient TAUs, of which **11,342** were starting treatment
- **741** clinical trials authorised for medicines and **83** for MDs and IVDMDs
- **16** centralised-procedure MA applications attributed to France
- **18,671** MA updates granted through national procedure and European decentralised and mutual recognition procedures
- **1,162** MAs, including 932 generic medicine authorisations, were issued through 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 INCREASING THEIR INVOLVEMENT

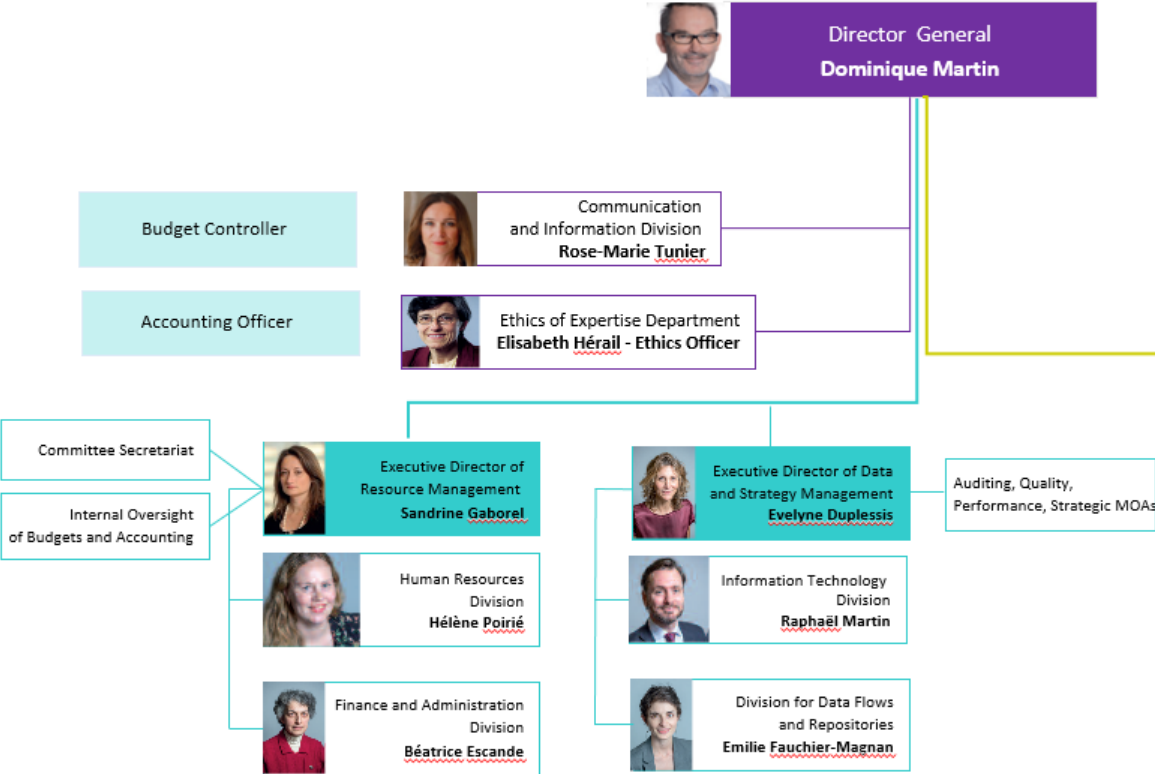
- **1,265** conflicts of interest investigated as part of an internal ethics compliance report
- **1,872** ethics contributions and analyses
- **10** Temporary Specialised Scientific Committees (TSSCs) created
- **32** meetings organised through the interface committees
- **129** information updates added to the ANSM's website
- **2.9** million unique visitors to ANSM's website
- **16,617** followers on ANSM's Twitter account as of the end of 2018 (5,000 more followers gained during 2018)
- **Over 23 million** visits to the Public Medicine Database
- **2** NGO projects funded through a seventh call for proposals
- **2** new research projects funded through a seventh call for proposals

## REINFORCING ANSM'S EFFICIENCY AND PURSUING ITS MODERNISATION

- **927.2** WFTEs
- **€123.5** million budget
- **58** meetings held between management and employees



# ORGANISATION CHART as of July 2019



EPI-PHARE  
Epidemiology Scientific Interest Group

Board of Directors  
Scientific Board



Deputy Director General  
for Operations  
**Christelle Ratignier-Carbonneil**

Emergency Response, Health Warnings  
And Risk-Management Support Centre

European Strategy Support Centre

**Operating Divisions**



Legal and Regulatory  
Affairs Division  
**Carole le Saulnier**



Evaluation Division  
**Elodie Chapel**



Surveillance Division  
**Céline Mounier**



Inspection Division  
**Bernard Celli**



Laboratory Controls Division  
**Françoise Duperray**

**Product Divisions**



Division of Medicines used in Oncology, Haematology,  
Transplantation, Nephrology, Cell Therapy,  
Radiopharmaceuticals and Blood Products  
**Lotfi Boudali**



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



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

Division of Vaccines, Anti-Infective Medicines,  
Hepato-gastroenterology, Dermatology, Gene Therapy and  
Rare Metabolic Diseases



Division for Generic, Homeopathic, Herbal Medicines  
and Preparations  
**Valérie Salomon**



Division for Medical Devices, Cosmetics and *in vitro*  
Diagnostic Devices  
**Thierry Sirdey**

# Governance bodies

## BOARD OF DIRECTORS

The ANSM Board of Directors was renewed in 2018 for a three-year period. Its new composition takes into account the new provisions of the decree regarding equal access between men and women to boards of directors (decree no. 2017-1781 of 27 December 2017).

The chair is Mrs Catherine de Salins.

It comprises 27 members, most of whom are members of Parliament, healthcare professionals, and patient representatives<sup>1</sup>.

Votes are evenly distributed between government representatives (9 members, 18 votes) and the 18 other members, each of whom has one vote.

Outside of the representatives of the Agency's personnel, who are elected, the members of the Board of Directors are appointed by the Health Minister. Aside from the members of Parliament, their mandate lasts for three years and can be renewed once.

The Board of Directors determines the broad focus of the agency's policies and adopts the budget. It met three times in 2018 in March, June, and November.

## SCIENTIFIC BOARD

The ANSM's Scientific Board was created in 2012 and renewed in 2015 for a three-year period. Its mandate ended in September 2018.

The Scientific Board is currently being renewed. A call for applicants was launched in May 2018, and new members will be appointed in 2019.

The Scientific Board comprises 16 members chosen for their fields of expertise and also includes foreign scientists.

- Subsequent to a call for applicants issued by the agency, ten members proposed by ANSM's Director General 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.
- 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.

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.

It met twice in 2018 in March and September.

In 2018, the Scientific Board worked on reforming ANSM's scientific bodies. This reform was presented to the Scientific Board in November 2018 and implemented in 2019<sup>2</sup>.

The Scientific Board also discussed the work it had accomplished since 2012 and how it has evolved. It must now have a more strategic and cross-cutting role in ANSM.

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<sup>1</sup> Full list of members provided in Appendix 1, p. 191.

<sup>2</sup> For more information, read "Reforming ANSM's advisory bodies" on page 128.

## **Part 1**

# **Guaranteeing the safety of health products throughout their life cycle**



<b>Risk management</b>	<b>p. 15</b>
<b>Surveillance of medicines</b>	<b>p. 17</b>
• Pharmacovigilance	p. 17
• Monitoring the use of medicines	p. 32
• Monitoring medication use data	p. 34
• Conducting independent pharmacoepidemiology studies	p. 35
• Revision of medicine risk/benefit ratio and reassessment programmes	p. 38
• Risk reduction measures	p. 39
• Managing medication error	p. 40
• Monitoring the coverage of patients' health needs	p. 43
• Control over advertising	p. 48
• ANSM's role in the prevention of addictive behaviours and its interactions with other organisations	p. 49
<b>Surveillance of blood products</b>	<b>p. 52</b>
<b>Surveillance of medical devices and <i>in vitro</i> diagnostic medical devices</b>	<b>p. 56</b>
• Surveillance of incidents and risks of incidents	p. 59
• Market control activities	p. 62
• Control over advertising	p. 71
<b>Surveillance of other health products</b>	<b>p. 72</b>
• Surveillance of cosmetic products	p. 72
• Surveillance of tattoo products	p. 73
<b>Quality compliance inspections of practices and health products</b>	<b>p. 74</b>
• Inspection of clinical and non-clinical trials	p. 76
• Medicine and starting material inspection	p. 77
• Inspection of blood products and other biological products	p. 80
• Surveillance of medical devices and <i>in vitro</i> diagnostic medical devices	p. 82
• Inspection of cosmetic products	p. 83
<b>Quality control of health products in the laboratory</b>	<b>p. 84</b>
• Quality control of medicines and biological products	p. 86
• Laboratory control campaigns for medical devices	p. 89
• Laboratory control campaigns for cosmetic products and tattooing products	p. 90

# RISK MANAGEMENT

By incorporating risk management into all of its decision-making processes, ANSM is seeking to reduce the risks faced by any patient who is exposed to health products.

More specifically, this new principle involves the following actions:

- prioritising all surveillance actions based on a process of risk analysis,
- expanding epidemiological studies,
- developing a monitoring and planning strategy in accordance with the agency's openness strategy,
- implementing a heightened risk situation (HRS) coordination plan.

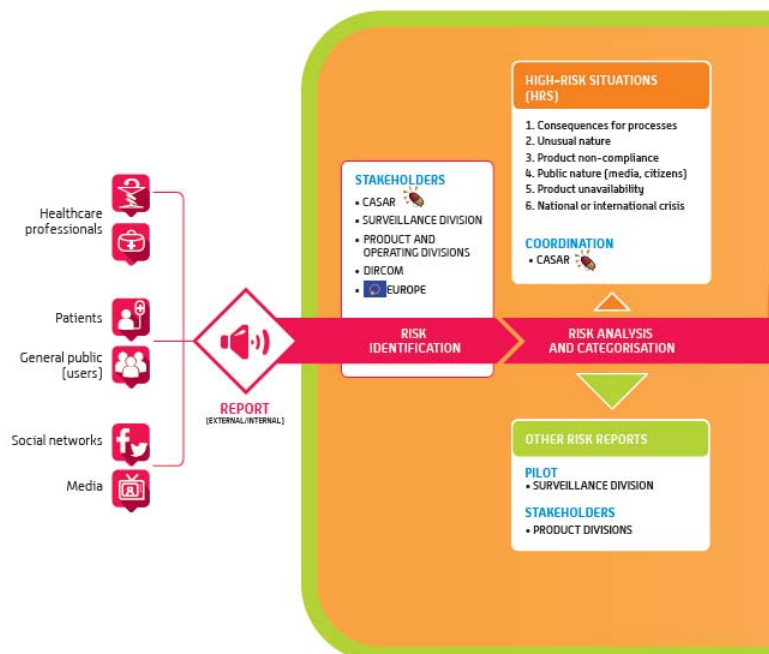
To address this new concern, ANSM created an Emergency Situation Support Centre (ESSC), health alerts, and risk management at the end of 2017 to make it easier to manage the most sensitive alerts and to strengthen ANSM's response capacities both internally and externally, especially given the agency's growing exposure to a national and European health environment that is in the midst of monumental change.

ESSC's team is tasked with planning for and coordinating any event that could become a heightened risk situation (HRS), whether it is the result of reports submitted to the agency or data and information that the agency has gathered itself.

An HRS is defined as an emerging or unusual event that is flagged during the everyday management of incoming alerts and ongoing cases on the basis of its breadth, seriousness, or treatment in the media.

The ESSC evaluates the situations that are reported to it by analysing the risks involved, including social impact, the acceptability of the situation, and internal and external risk management. It then establishes the conditions necessary for internal dialogue to quickly implement immediate risk reduction measures and define an action plan and timeline.

The ESSC works in close collaboration with senior management and the Communication and Surveillance Departments and oversees coordination efforts with all stakeholders.



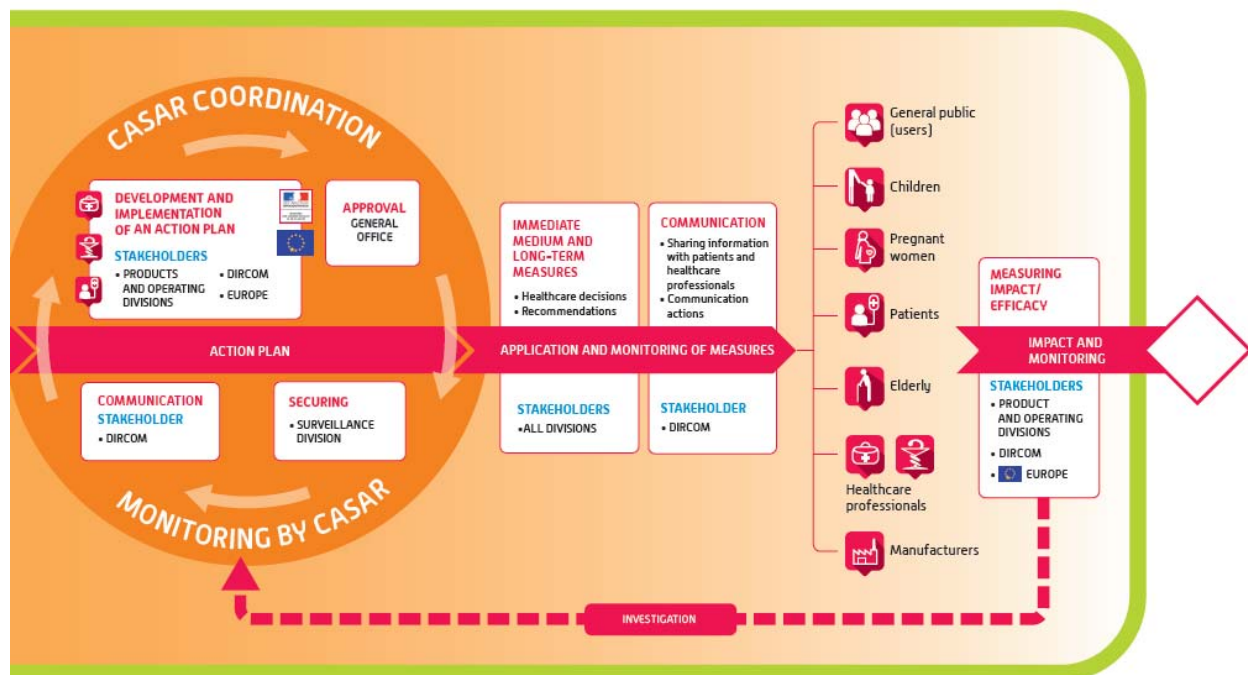
## HIGHLIGHTS IN 2018

- **ISO 9001 certification** of the ESSC regarding the management of health-related risks (audit in December 2018 and certification in January 2019).
- **Implementation with the Ministry of Health/CORRUS of a common operation protocol regarding monitoring and health safety actions (August 2018).**

## 2018 DATA

Management of **77 HRSs**, including a number of especially sensitive events: Levothyrox, Androcur<sup>3</sup>, macrotextured breast implants<sup>4</sup>, Valsartan<sup>5</sup>, and Brexit<sup>6</sup>.

QUALITY **TURNING RISK MANAGEMENT INTO THE BASIS OF ALL OUR DECISIONS**  
**MANAGING A HIGH-RISK SITUATION (HRS)**



<sup>3</sup> See also the focus on “Cyproterone acetate (Androcur and its generics) and risk of meningiomas”, page 24.

<sup>4</sup> See also the focus on “Breast implants: ANSM's investigations into the risk of ALCL”, page 64.

<sup>5</sup> See also the focus on “Quality defects in sartan-based medicines”, page 45.

<sup>6</sup> See also the focus on “Preparing for Brexit”, page 155.



# SURVEILLANCE OF MEDICINES

ANSM monitors every stage in a medicine's life cycle in partnership with the pharmacovigilance centre network and its European counterparts to guarantee patient safety.

Medicine surveillance covers all steps taken to ensure:

- monitoring medicine use and reducing misuse, medication errors, and overexposure,
- detecting, characterising, ranking, and managing risks related to medication exposure,
- implementing measures intended to increase a given medication's safe use and monitoring the impact of these measures as needed,
- working with manufacturers to secure patient access to medications 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,
- overseeing medication advertisements before they are published.

## Pharmacovigilance

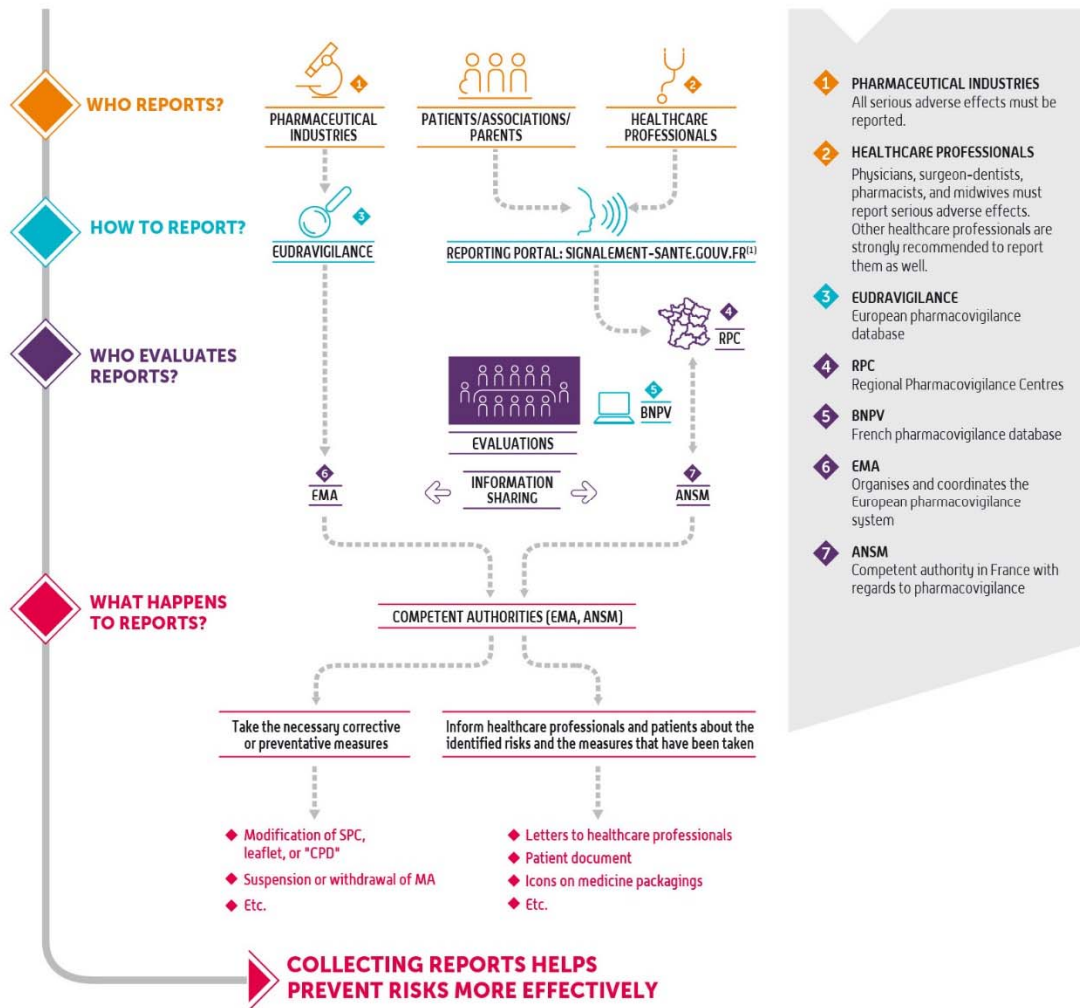
The objective of pharmacovigilance is to monitor, evaluate, prevent, and manage the risk of adverse effects resulting from the use of medicines.

It applies to all medicines with a marketing authorisation (MA) as well as medicines that have been granted a temporary authorisation for use (TAU) or a temporary recommendation for use (TRU).

Pharmacovigilance studies adverse effects that occur under normal conditions of use as well as those that arise due to medication errors, abuse, misuse, overdose, and professional exposure.

Pharmacovigilance is active on a regional level through France's 31 regional pharmacovigilance centres, on a national level through ANSM, and on a European level through the European Medicines Agency and member states.

## Reporting and monitoring the adverse effects of a medicine (pharmacovigilance)



(1) Reporting can also be made by telephone, mail or e-mail to the Regional Pharmacovigilance Centres

## FRENCH PHARMACOVIGILANCE

**Healthcare professionals, health system users, and pharmaceutical manufacturers report any adverse effects that come to their attention.**

- **Health professionals**

In France, doctors, dentists and dental surgeons, pharmacists, and midwives are required to report any adverse effect they suspect is due to a medicine to their local Regional Pharmacovigilance Centre (CPRV). Any health professional who is aware of an adverse effect that may have been caused by a medicine may also report it.

- **Health system users**

Since June 2011, patients, their representatives, and authorised patient associations have also been able to directly report an adverse effect they suspect might be caused by a medicine without going through a healthcare professional.

An online reporting portal for [sante.gouv.fr](http://sante.gouv.fr), has been available the French Minister of Health and This portal is designed to increase the reporting process. It is healthcare professionals and

**ANSM centralises and processes information on the benefits, risks, and uses of medicines**

adverse health events, [www.signalement-sante.gouv.fr](http://www.signalement-sante.gouv.fr) since 2017 thanks to a partnership between healthcare agencies, including ANSM. health safety vigilance while also simplifying accessible to everyone, including both users.

- **Pharmaceutical manufacturers**

Moreover, any company or body distributing a medicine must implement a pharmacovigilance system that is permanently overseen by a contact person who has demonstrated their experience in the field. It is the responsibility of this person to implement and manage the operator's pharmacovigilance system and ensure all its pharmacovigilance obligations are upheld.

Distributors submit the medicine-related adverse effect reports they collect directly to the European pharmacovigilance base (EudraVigilance).

The goal of this system is to ensure the monitoring, collection, recording, and scientific evaluation of information about adverse effects that could be due to a medicine, to inform ANSM and the EMA, and, if needed, to take the necessary measures.

**The Regional Pharmacovigilance Centres (RPCs) collect, record, and analyse reports and conduct expert assessments.**

The 31 RPCs located throughout France collect adverse effect reports from healthcare professionals and patients or their representatives. They then carry out a clinical, biological, and pharmacological analysis and submit the reports to a national pharmacovigilance base (BNPV).

When information regarding an adverse effect changes over time (for example due to a change in a patient's health status), this information is recorded as case follow-up data.

The RPCs are also charged with raising awareness and providing training with respect to pharmacovigilance, adverse effects, and the proper use of medicine. The RPCs fulfil their obligation of providing information and advice by answering questions submitted by healthcare professionals and health system users regarding a medicine's adverse effects, their diagnosis and treatment, and the prescription and use of medicines. RPCs play a critical role by drawing ANSM's attention to potential reports in the form of noteworthy cases and by performing expert assessments. These assessments make it possible to confirm, dismiss, and characterise reports and risks.

## **ANSM centralises and processes information on the benefits, risks, and uses of medicines**

ANSM does so by sharing all pertinent information and cooperating with the EMA and other member states.

The agency forwards adverse effect reports that have been submitted by the RPC to the BNPV to the European EudraVigilance database and monitors the information submitted to both of these databases.

More broadly, it monitors, collects, and centralises all information about the risks and uses of a medicine that could affect its risk/benefit ratio. It analyses them to identify any new risks or changes to known risks.

ANSM can initiate pharmaco-epidemiological studies to obtain an overall view of a health product's profile of use in real life, confirm a report, or quantify a risk<sup>7</sup>.

It also encourages and promotes academic authorities to carry out safety studies after a medicine has received its marketing authorisation.

ANSM studies and takes measures aimed at preventing or reducing risks to ensure medicines' safe use.

### **HIGHLIGHTS IN 2018**

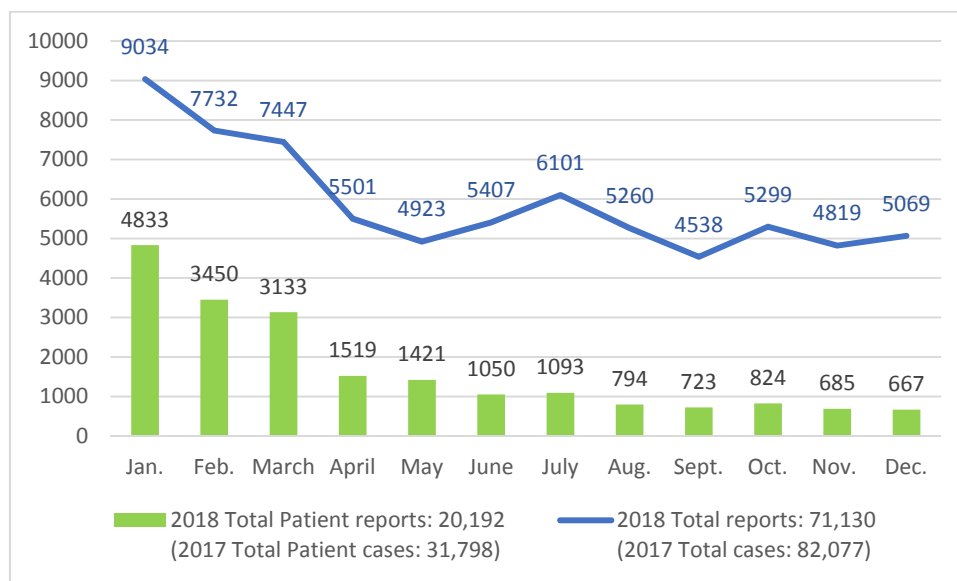
- Prevention of serious adverse effects caused by dihydropyrimidine dehydrogenase (DPD) deficiency during treatment by fluoropyrimidines (5-fluorouracil and capecitabine) (February and December 2018).
- Discontinuation of the anti-lice lotion Prioderm following the issuance of stricter prescription guidelines (December 2018).
- Suspension of initiation of treatment with fluidione (Previscan) (November 2018).
- Reminder of the risks of using laxative prep treatments (November 2018).
- Reminder regarding propofol infusion syndrome (September 2018).
- Reminder of proper use of diclofenac following the publication of a new study regarding cardiovascular risk (September 2018).
- Reduction of risks associated with mycophenolate exposure during pregnancy: publication of updated guides and treatment consent form (July 2018).
- Reminder of usage warnings for Lariam (mefloquine) (May 2018).
- Esmya (ulipristal acetate): suspension of treatment initiations and monitoring of liver function of patients undergoing treatment (February 2018).
- Reminder regarding the proper use of injectable amoxicillin to reduce the risk of urine crystals (February 2018).  
Update of "Pharmacovigilance Best Practices" (February 2018).
- Reminder regarding the proper use of nicotine patches (January 2018).

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<sup>7</sup> See also "Conducting independent pharmaco-epidemiological studies", page 35.

## 2018 DATA

### Adverse effect reports submitted to the national pharmacovigilance system



### Changes to the number of adverse effect reports submitted to the national pharmacovigilance system

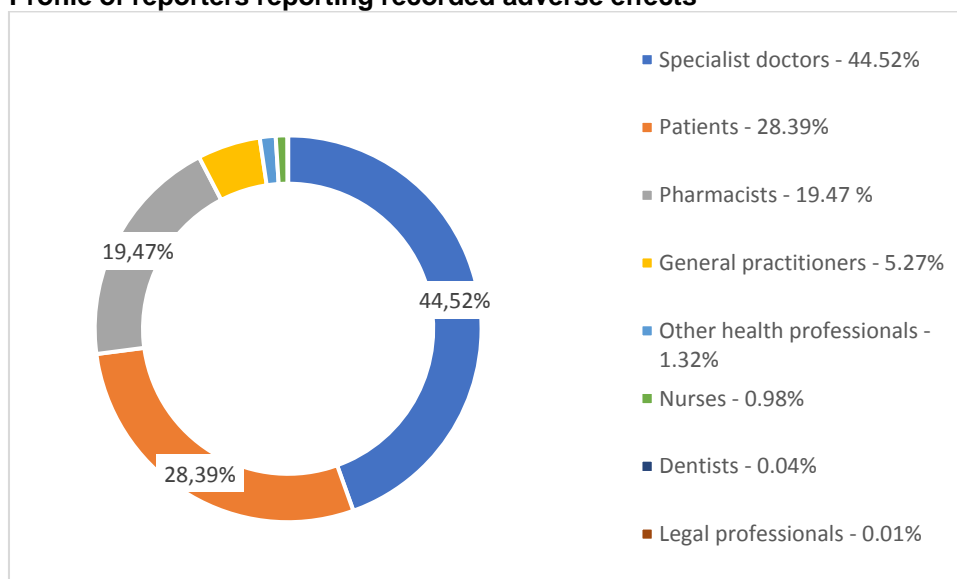
Adverse effect reports submitted to ANSM	2014	2015	2016	2017	2018
Total number of cases received and recorded by RPCs <sup>(1)</sup>	46,497	47,089	55,761	82,077 <sup>(2)</sup>	71,130
• of which serious adverse effect reports	30,156	30,412	35,622	42,715	34,387
• of which adverse effect reports submitted by patients	1,983	2,331	3,061	31,798	20,192
Number of adverse effect reports from pharmaceutical companies <sup>(3)</sup>	-	-	-	-	59,371
• of which serious adverse effect reports	14,101	15,411	17,109	23,433	18,436

(1) The number of adverse effect reports includes initial and follow-up cases

(2) The number of adverse effect reports has risen steadily from 2014 to 2018. The significant rise that occurred in 2017 is primarily due to the many reports submitted following the Levothyrox formula change.

(3) The number of adverse effect reports includes initial cases

### Profile of reporters reporting recorded adverse effects



## NATIONAL PHARMACOVIGILANCE SURVEYS

### GOALS

Through the analysis of all pharmacovigilance data (reports, literature, statistical studies, etc.) national pharmacovigilance studies make it possible to confirm a potential signal, characterise a proven signal, and classify the overall safety profile of a given medicine. They can also be included in a broader, European-wide survey.

### METHODS AND STAKEHOLDERS

The decision to launch a national survey is made by ANSM's Director General. The Director General appoints one or several expert rapporteurs and an editor within the RPCs in accordance with general ethics rules and any conflicts of interest and depending on the relevant field of expertise.

The pharmaceutical manufacturer(s) involved in the survey are informed by ANSM when they have to provide their data in accordance with the deadlines and communication methods set by the agency.

The expert rapporteur collects, approves, and quantitatively and qualitatively analyses all the available data and writes a report. The editor ensures the conclusions made using the available data are consistent and relevant.

The conclusions of the survey can be presented upon ANSM's request to one of its advisory bodies for either informational purposes or to formulate recommendations.

Based on the conclusions of the survey, the Director General of ANSM can decide to end or continue the survey. The director takes the necessary measures to prevent and reduce any identified risks.

## HIGHLIGHTS IN 2018

- As part of the law that added eight new mandatory vaccines for children under the age of two that were previously only recommended and in addition to the three previous mandatory valences, ANSM committed to pursue the implementation of the new vaccine policy in partnership with the Health Ministry. To this end, in 2018, the agency created a national pharmacovigilance plan for each vaccine covered by this law.
- Launch of a pharmacovigilance survey on cyproterone acetate and the risk of meningioma<sup>8</sup> following a growing number of patients suffering from meningiomas and taking cyproterone acetate reported in France in 2018.
- Launch of a national pharmacovigilance survey regarding medicines that include 5 Fluorouracile (5 FU) and capecitabine as part of an overall approach to strengthen the surveillance of these medicines in addition to other pharmacovigilance efforts on the subject. The goal of this survey is to assess the impact of the GPCO's recommendations that were published on 24 February 2018 regarding the risk of toxicity related to DPD deficiency.
- Creation of a national pharmacovigilance monitoring plan regarding the treatments used by patients exposed to the Ebola virus and defined by the decree dated 18 September 2014 and modified by the decree dated 31 October 2014.

## 2018 DATA

- **98** pharmacovigilance surveys were underway in 2018
- **17** new surveys were opened
- **9** Technical Pharmacovigilance Committee (TPC) meetings with collective expertise from 42 national pharmacovigilance investigations

### Number of new national pharmacovigilance surveys

2014	2015	2016	2017	2018
24	14	21	8	17

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<sup>8</sup> See also the focus on "Cyproterone acetate (Androcur and its generics) and risk of meningioma", page 24.

## Focus on: Cyproterone acetate (Androcur and its generics) and risk of meningioma

**In order to secure the use of medicines containing cyproterone acetate (CA), ANSM launched an educational campaign to encourage discussion between doctors and patients. All of the tools included in the campaign were created in partnership with representatives of users and relevant healthcare professionals.**

Cyproterone acetate (CA) is a medicine used in the following situations:

- ✓ in women, in the treatment of certain hormonal disorders that cause excessive hair growth (hirsutism),
- ✓ in men, to reduce the symptoms of prostate cancer,
- ✓ in the treatment of certain types of paraphilia (sexually deviant behaviour) in combination with psychotherapy.

Off-label indications such as acne, seborrhoea, and moderate hirsutism should be avoided, and use in children and post-menopausal women is not recommended.

### **Studies dating back to 2009**

In 2009, a study<sup>9</sup> showed an association between CA and meningioma. The case was studied and evaluated on a European level by France and Germany. In 2011, following a European-wide reassessment, the SPC and leaflet for CA medicines in tablet form with a dosage of 50 to 100 mg were changed to include that meningioma was a contra-indication for taking CA and that patients should stop taking it if they develop meningioma.

Since then, a special monitoring system for these medicines has been in place. A pharmacovigilance investigation presented in 2014 on the risk of meningioma associated with CA and other progestogens could not quantify this risk or draw a conclusion on a possible class-wide effect applicable to all progestogens.

### **An epidemiological study to measure/objectify the risk**

To quantify the link between taking cyproterone acetate and the risk of meningioma, CNAM launched a pharmaco-epidemiological study based on SNDS data in 2016<sup>10</sup>.

The preliminary results were presented to ANSM's epidemiology team in April 2018. It has now been established that cyproterone acetate promotes the development of meningioma, especially if it is prescribed in high doses and over a long period of time. In fact, the CNAM study showed that this risk increased by seven for all patients who took the medication for over six months at an average dose that was more than or equal to 25 mg per day. This risk increases by a factor of 20 beyond a cumulative dose of 60 g, or around five years of treatment with a dosage of 50 mg per day, or 10 years at 25 mg per day.

### **ANSM's actions aimed at professionals and patients**

Following the results of this investigation, ANSM created a multidisciplinary team of independent experts to discuss the usage and prescription conditions for these medicines with the aim of limiting the risk of meningioma. This Temporary Specialist Scientific Committee (TSSC) included endocrinologists, paediatric endocrinologists, gynaecologists, neurosurgeons, and dermatologists.

After its **first meeting in June 2018**, the committee proposed that recommendations be written with healthcare professionals. The relevant learned societies were then mobilised to inform their members regarding the main results of the CNAM study and to establish temporary usage recommendations for CA pending the writing of more specialised recommendations during the second TSSC.

- ✓ On 20 September 2018, ANSM sent the temporary recommendations to all relevant healthcare professionals.
- ✓ ANSM also created a freephone number to answer questions from patients and those close to them.

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<sup>9</sup> Froelich S et al. Endocrine Abstracts 2008;16 P158 (European Congress of Endocrinology Berlin 2008).

<sup>10</sup> CNAM study: "Exposure to high doses of cyproterone acetate and the risk of meningioma in women: a French cohort study from 2006 to 2015".



Based on these temporary recommendations, the experts of the TSSC were **consulted for a second time in October 2018** to establish the general conditions of use for CA (indications, dosage, duration of treatment, warnings, and risk monitoring measures, including brain imaging).

- ✓ These consolidated recommendations, which were written to limit the risk of meningioma, were sent to healthcare professionals on 8 October 2018.

ANSM also wanted to launch an **educational campaign** to encourage discussion between doctors and patients and guarantee that patients were being fully informed.

To ensure the campaign would meet the needs of both professionals and patients, the agency asked all stakeholders to help create it. A working group comprising representatives of CA users, representatives of healthcare professionals, and the French healthcare system met on 16 November and again on 19 December 2018 to discuss the type of educational tools needed to improve treatment and prevention.

The proposed actions included:

- ✓ designing a yearly consent form signed by both the patient and prescriber that is a prerequisite for dispensing the medication by the pharmacy (as per the medication prescription and dispensing guidelines),
- ✓ creating an educational pamphlet for users,
- ✓ sending individual letters to everyone who uses or prescribes CA in partnership with CNAM.

This campaign will start in June 2019.

To date, the sales of CA have dropped by around 50% in France, which shows the effectiveness of the preliminary measures taken nationally. Given the over-prescription and misuse of CA that was especially prevalent in France, the measures that are set to be rolled out in 2019 are expected to lead to a drastic decrease in the amount of cyproterone acetate that is dispensed.

ANSM will continue to pursue its actions, including the launch of another similar epidemiological methodology study to quantify the risk of meningioma associated with the use of other progestones (especially Luteryl and Luteran).

## FRANCE'S CONTRIBUTION TO EUROPEAN PHARMACOVIGILANCE

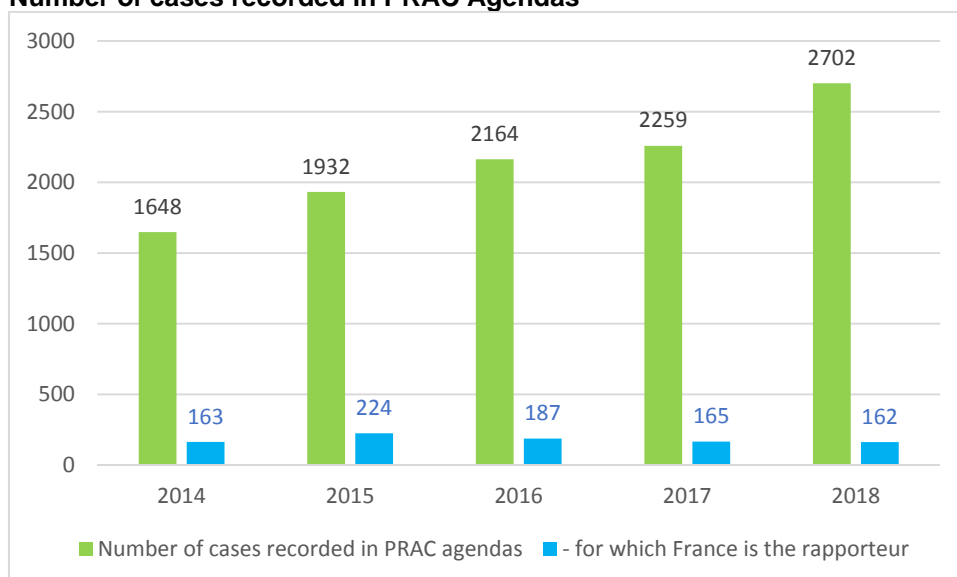
The French national pharmacovigilance system is part of the European pharmacovigilance system. France provides data to the European Medicines Agency (EMA) database, EudraVigilance. This database is the sole collection site in Europe for all serious adverse effects, as well all non-serious adverse effects (as of 22 November 2017) that have occurred in Europe since and been reported by the relevant national authorities or by pharmaceutical laboratories.

France makes a significant contribution to this database through the data it collects via:

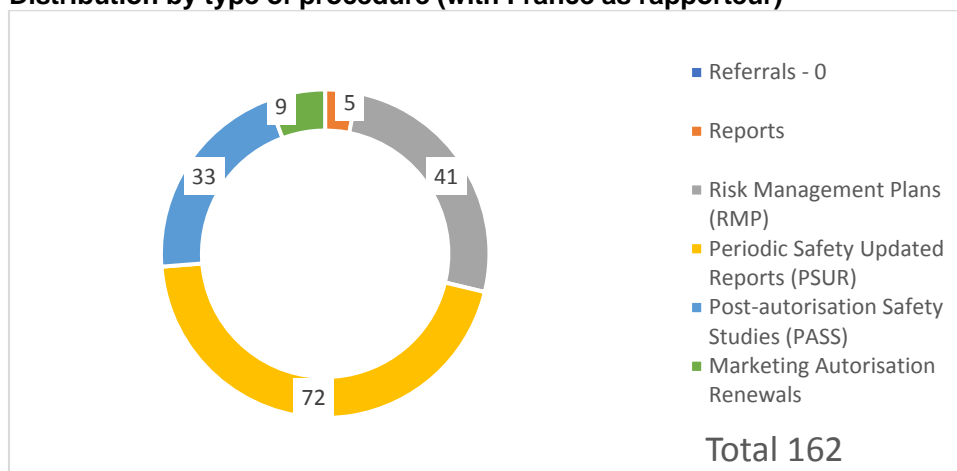
- Regional Pharmacovigilance Centres; this data is recorded in the National Pharmacovigilance Database, which ANSM forwards to EudraVigilance daily,
- pharmaceutical laboratories; this data is forwarded directly to EudraVigilance.

In addition, France works closely with the EMA and the competent authorities of member states to monitor and ensure the safe use of medicines in France and the rest of the European Union. ANSM actively participates in European pharmacovigilance working groups and advisory bodies, especially the Pharmacovigilance Risk Assessment Committee (PRAC<sup>(11)</sup>). It assists with common European evaluation procedures that track medicines' risk-benefit ratio. These procedures monitor reports, PSUSA, PGR, referrals, and more.

### Number of cases recorded in PRAC Agendas



### Distribution by type of procedure (with France as rapporteur)



<sup>11</sup> See also "Representation of ANSM within European bodies", page 157.

## HIGHLIGHTS IN 2018

- **European re-evaluation of the risk-benefit ratio:**  
Esmya (ulipristal)  
Hydroxyethyl starch (HES) solutions for infusion: MA maintained under the condition that usage guidelines are strictly followed (August 2018).
- **Re-evaluation of usage data for:**  
Valproate and derivatives during pregnancy and in women of reproductive age (February 2018).  
Retinoids (all indications): teratogenic and neuro-psychiatric risks (February 2018).
- Recommendations for healthcare professionals regarding medicines containing hydrochlorothiazide and the associated risk of skin cancer (November 2018).
- Finalisation of the European evaluation (referral procedure in accordance with article 31) on fluoroquinolone and quinolone antibiotics and the risk of disabling, long-lasting, and potentially irreversible side effects primarily effecting the muscles, joints, and nervous system (October 2018).
- Launch of a re-evaluation regarding the data on the risk of medication errors with methotrexate-containing medications.

## 2018 DATA

In 2018, **over 2 million** adverse effect reports, including just over **172,000** reports submitted by patients, were received by EudraVigilance, the European database, that's a **37% increase** compared to last year. This substantial increase is due to the new rule put in place in late 2017 requiring non-serious cases to be reported to EudraVigilance as well.

The total number of reports from French CRPVs accounts for around **7% (71,130)** of reports from member states (1,028,386) in the EU; the French population represents 13% of the EU population.

## ASSESSMENT OF REFERRAL PROCEDURES

### GOALS

Referral procedures address major 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.

### METHODS AND STAKEHOLDERS

During a referral, ANSM and other competent authorities are asked to carry out a scientific assessment on behalf of the European Union on a specific medicine or class of medicines in order to formulate a single recommendation for the entire EU. The recommendation then becomes a legally binding decision throughout the EU. 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).

## 2018 DATA

- **Seventeen** referral procedures were finalised in 2018<sup>(12)</sup>
- **Eight of these** referral procedures **were related to pharmacovigilance** (according to articles 31, 20, or 107i of pharmacovigilance-related legislation).

**The nine 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.

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<sup>12</sup> See also the complete table of referral procedures, which can be found in Appendix 2, p. 193.

## FRANCE'S CONTRIBUTION TO INTERNATIONAL PHARMACOVIGILANCE

VigiBase is an international pharmacovigilance database created in 1968 by the World Health Organization (WHO).

It is the largest and most complete database in the world. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) under the WHO's mandate.

More than 150 countries help collect pharmacovigilance data. France has participated in the programme since 1986.

France is the fifth largest contributor, providing approximately 4% of the total number of adverse effect reports received.

### 2018 DATA

**754,531 cases taken from the National Pharmacovigilance Database** and submitted by France as of 31 December 2018.

Countries contributing to the VigiBase	ICSR <sup>(1)</sup> : cumulative data as of 31/12/2018
USA	8,721,109
South Korea	1,320,707
United Kingdom	888,933
China	846,540
<b>France</b>	<b>754,531</b>
Germany	725,686
Canada	634,450
Italy	463,887
Thailand	354,209
Other	3,734,349
<b>Total</b>	<b>18,444,401</b>

(1) ICSR: individual case safety report

## Focus on: Medicines and pregnancy

Activities aimed at monitoring and evaluating the risks of exposure to medicines during pregnancy and breastfeeding as well as on reproduction are carried out by ANSM's "Pregnancy" unit in partnership with the agency's product divisions.

The goal of this multidisciplinary body, which was created in 2017 as part of the monitoring division, is to provide specific expertise during preclinical, clinical, and pharmaco-epidemiological work.

### 2018 DATA

- **80 evaluations regarding section 4.6** (pregnancy, breastfeeding, fertility) and/or **section 5.3** (non-clinical–reproductive toxicity) of SPCs and leaflets
- **42 reports submitted by Regional Pharmacovigilance Centres**, three-quarters of which had an action in progress or led to new measures
- **42 reports from the literature were received and processed, 21% of which** led to actions from the Pregnancy Unit (variations, European report initiations, etc.) and **29% of which** involved reports with actions that were already in progress
- **2 European reports triggered (Carbimazole and Olanzapine)**
- **16 analyses of paediatric investigation plans**
- **8 MA applications studied**
- **12 ICH S5** (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Safety Reproductive toxicology) **meetings attended** as a participant
- **5 meetings of the "Pregnancy-Breastfeeding-Reproduction" working group organised**

### HIGHLIGHTS IN 2018

- **Publication of an educational brochure entitled "Medicines and pregnancy"** aimed at patients in addition to the brochure published in 2017 in partnership with the College of General Practitioners that was aimed at healthcare professionals (November 2018)



These brochures were developed to summarise the general approach to continuing or starting drug treatment in patients who are pregnant, could be pregnant, or are of reproductive age.

- **VKAs: contra-indication for all pregnant women except those with heart valves** (November 2018)  
The Pregnancy Unit coordinated a collaborative project through the "Reproduction-Pregnancy-Breastfeeding" working group that evaluated the benefit of using VKAs during pregnancy given its known teratogenic risk. These discussions resulted in stricter recommendations that contra-indicated VKAs for all pregnant women except those with heart valves. A general educational document was distributed to healthcare professionals and patients regarding the proper use of VKAs and the suspension of the initiation of fluindione treatment entitled "What's new with vitamin K antagonists? ".

- **Topical retinoids: new contraindication during pregnancy** (October 2018)

ANSM published an alert on its website on the European decision to contraindicate topical retinoids for patients who are pregnant or planning on becoming pregnant. This decision was issued after the European Medicines Agency (EMA) re-evaluated the risk-benefit ratio of oral retinoids and concluded that the teratogenic risk of topical retinoids could not be excluded, even though the transfer of retinoids from the skin to the bloodstream appears negligible.

- **Acetazolamide: contraindication and mandatory contraception** (October 2018)

Following a report regarding acetazolamide issued by Pharmacovigilance Regional Centres, the Pregnancy Unit analysed the data on the risk of in-utero exposure to this substance. The conclusions were discussed during meetings of the “Reproduction-Pregnancy-Breastfeeding” working group and with learned societies specialising in ophthalmology and glaucoma. Due to the risk of birth defects and foetotoxic effects in fetuses and newborns exposed to acetazolamide during pregnancy, ANSM decided to issue stricter risk reduction measures by contraindicating the medication during pregnancy and requiring women of reproductive age to use contraception.

A letter was sent to healthcare professionals, and an alert was published on ANSM's website.

- **Update to the summary of product characteristics for general anaesthesia medicines used in pregnant women and young children, EMA working group** (August 2018)

France took part in the EMA's non-clinical working group (NcWG) on the use of general anaesthesia medicines used in pregnant women and young children. This evaluation resulted in an update to the summary of product characteristics for these products and the inclusion of a reference to data from animal models in the pregnancy section.

- **Mycophenolate: changes to recommendations regarding contraception and the treatment agreement** (June-July 2018)

The pregnancy prevention measures for women taking mycophenolate were increased in 2015 and 2016 in France and throughout Europe. However, consultations with patient associations and healthcare professionals revealed these measures needed to be changed to improve observance and effectiveness. The changes involved the recommendations regarding contraception and the timing of the treatment agreement, which is now annual.

These risk reduction measures were communicated to patients and healthcare professionals and the guide for patients, the guide for healthcare professionals, and the treatment agreement form were updated.

- **Dolutegravir: reports of abnormalities in neural tube closure among children who were exposed *in utero*** (May 2018)

ANSM, in collaboration with the EMA, WHO, and FDA, informed healthcare professionals about the existence of a new report on the potential risk of neural tube closure defects due to the use of dolutegravir, an antiretroviral indicated for the treatment of HIV, early on in pregnancy.

In addition, and even though the evaluation of this new report is still in progress and results are pending, ANSM, in partnership with the EMA and according to French treatment guidelines, decided to apply the principle of precaution and recommend the following in May 2018:

- to quickly replace dolutegravir with another antiretroviral for all women being treated by dolutegravir during the first stage of pregnancy as long as appropriate treatment alternatives are available,
- to implement effective contraception methods among women of reproductive age who are being treated with dolutegravir,
- to not prescribe this medication to patients wishing to become pregnant,
- to not advise women who are currently taking dolutegravir to stop their treatment without first consulting their doctor.

- **Valproate: European referral procedure broadening the scope of risk reduction measures** (May 2018)

On 31 May 2018, following a European re-evaluation initiated by ANSM, the European Commission approved the risk reduction measures that were already in place in France and expanded them further.

Now, to avoid any exposure during pregnancy to this teratogenic (10.7% of birth defects) and foetotoxic (up to 30-40% of neuro-developmental disorders) medication:

- For epilepsy, valproate is contraindicated:
  - during pregnancy, except when no suitable treatment alternative exists,

-for women of reproductive age, except when other treatments are ineffective or not tolerated and if all conditions of the pregnancy prevention programme are met.

As a reminder, since July 2017 in France:

- For manic episodes associated with bipolar disorder, valproate is contraindicated:
  - during pregnancy,
  - for women of reproductive age, except when other treatments are ineffective or not tolerated and if all conditions of the pregnancy prevention programme are met.

Further information is available on ANSM's website: [https://www.ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/\(offset\)/0](https://www.ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/(offset)/0)

**Further information about “Medicines and pregnancy” is also available  
on ANSM's website:**

**[https://www.ansm.sante.fr/Dossiers/Medicaments-et-grossesse/Medicaments-et-grossesse/\(offset\)/0](https://www.ansm.sante.fr/Dossiers/Medicaments-et-grossesse/Medicaments-et-grossesse/(offset)/0)**

## Monitoring the use of medicines

The purpose of medicine use surveillance is to understand how medications are used in 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 medication's MA 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. The surveillance of non-compliant medicine use, which includes off-label uses, is a key concern for the agency because misuse occurs frequently, represents a major source of side effects, and the methods for controlling the practice are complex and often difficult to put in place.

Reports of non-compliant medicine use come from a wide range of sources:

- the **RPC network**, which collects information on practices in the field from patients and healthcare professionals,
- **patient associations and organisations that represent societies, organisations, etc.**, about real-life practices,
- discussions ANSM has with its French health insurance **ANSM's monitoring and quantitative or qualitative** can be based on monitoring 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.
- **manufacturers**, who 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 surveillance of non-compliant medicine use is a key concern for the agency**

**healthcare system users, as well as healthcare professionals** (learned and special sources of information

**institutional partners**, especially the system,

**evaluation activities**, for example, the detection of "abnormal" consumption

For manufacturers, the legislation stipulates that a company that manufactures a proprietary medicine must help ensure that it is used properly and take every educational measure it deems necessary to inform healthcare 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 the 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 is to identify cases of non-compliant use and collect the information needed to evaluate the public health impact of these practices in order to put in place appropriate measures to prevent or reduce non-compliant use, as necessary.

To prevent risks associated with non-compliant use, ANSM can implement or require informational actions aimed at patients and healthcare professionals (emails, information bulletins, reports, etc.), provide educational material (prescribing guide, patient logbooks, etc.), advertisement measures, changes to the MA, or a risk management plan. Article L.5421-8 8 also authorises ANSM to enact financial sanctions.

### HIGHLIGHTS IN 2018

- **Discontinuation of the anti-lice lotion Prioderm** following the issuance of stricter prescription guidelines (December 2018).
- **Antipsychotics**: reminder of cardio-metabolic monitoring measures (October 2018).
- **Metformin and risk of lactic acidosis** in the event of kidney failure: reminder of proper usage (January 2018).
- **Ibuprofen**: reminder of proper usage after the publication of a study that suggests it can disrupt testicular physiology (January 2018).



## 2018 DATA

**45 cases of use that did not comply** with the medicine's marketing authorisation and exposed patients to a potential or proven risk were identified.

During the year, **risk reduction measures** were implemented for **69%** of these cases.

The remaining cases were still being evaluated as of 31 December 2018.

## Monitoring medication use data

The surveillance of medicinal sales, prescription, and reimbursement data makes it possible to track changes in the French pharmaceutical market. It also helps the agency understand the main characteristics of this market, especially in comparison to other countries in Europe and in the rest of the world. Through monitoring, ANSM can detect short-term and long-term trends that change the market, thereby allowing the agency to adapt its monitoring 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 healthcare professionals and the public informed about medication consumption practices and how they are changing.

### HIGHLIGHTS IN 2018

- Publication of a study regarding the **use of proton pump inhibitors** (PPIs) (December 2018).
- **For the fourth consecutive year**, in celebration of European Antibiotic Awareness Day, a **brochure dedicated to the analysis of antibiotics consumption** and antibiotic resistance in France was published in partnership with the French Health Insurance System (Assurance Maladie), ANSES, and Santé publique France (November 2018).
- Publication of a study regarding **changes in the consumption of analgesic** in France and Europe (March 2018).

## Conducting independent pharmaco-epidemiological studies

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 Team to independently conduct epidemiological studies pertaining to the safety of health products, mostly through the use of data from the National System of Health Data database (SNDS, formerly SNIIRAM), which ANSM has been able to access since September 2013.

In addition, in order to improve the ability to carry out studies on the usage and safety of health products under real-life conditions in France, two pharmacoepidemiology platforms were created in 2014:

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

### 2018 DATA

In 2018, ANSM launched a total of **17 pharmacoepidemiological studies**.

Of these 17 studies, **the results of seven were shared** with the public (report, scientific article and/or oral presentation during a scientific conference):

- Risk of mental and neuro-developmental disorders following in utero exposure to valproate (in collaboration with CNAM)
- Monitoring the use of levothyroxine-containing products since October 2017
- Ischaemic and haemorrhagic risk after coronary stenting (in collaboration with the HAS)
- Use of proton pump inhibitors in France
- Incidence of malignant haemopathies due to breast cancer in France
- Use of Truvada as an HIV pre-exposure prophylaxis
- Lumbar arthrodesis and thromboembolic risk

**Ten studies that were not completed in 2018** will be continued in 2019:

- Exposure to mycophenolic acid in women of childbearing age and during pregnancy
- Risk of pancreatic cancer associated with incretin mimetics
- Risks associated with exposure to valproate in children - Exploratory study
- Risks associated with the long-term use of proton pump inhibitors
- Monitoring adverse effect indicators for vaccines and expanding the mandatory vaccine expansion programme
- Risk of malignant haemopathies after breast cancer treatment
- Determining factors of prosthesis survivorship in knee replacements
- Knee replacement fixation method and thromboembolic risk
- Consequences of suspending the permanent sterilisation device ESSURE
- Levothyrox: use of the new formula and associated risks

### Activity of the two pharmacoepidemiology platforms

During its fourth year of operation, the DRUGS SAFE platform continued its risk and use study programme and launched new studies on DPP-4 inhibitors, statins, and costly and advanced therapy medicinal

products. It also launched new methodological projects such as the monitoring of medicine use based on reimbursement data.

The PEPS platform continued its use and risk study programme for various medicines and medical devices and began new studies on alitretinoin, abiraterone, and enzalutamide.

In 2018, the two platforms were the target of a financial audit and an external and independent scientific review. This provided ANSM with a precise and comprehensive view over the platforms' structure, their ability to carry out studies, and the scientific quality of their work in the four years they have been operating. After these evaluations and based on the results, ANSM decided to extend the mandate for the two platforms for another year pending the implementation of a new system associated with the EPI-Phare scientific interest group.

## HIGHLIGHTS IN 2018

- **Creation of the scientific interest group (SIG) EPI-PHARE** between the health product epidemiology teams at ANSM and CNAM (December 2018)<sup>13</sup>.

- **ANSM pharmaco-epidemiological studies published in peer-reviewed scientific journals in 2018**

Bouillon K, Bertrand M, Bader G, Lucot JP, Dray-Spira R, Zureik M. Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes. *JAMA* 2018;319(4):375-387. doi:10.1001/jama.2017.21269.

Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel MF, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018;155(2):337-346.e10. doi: 10.1053/j.gastro.2018.04.012.

Lassalle M, Colas S, Rudnichi A, Zureik M, Dray-Spira R. Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res* 2018 doi: 10.1097/01.blo.0000533617.64678.69. [Epub ahead of print].

Blotière PO, Weill A, Dalichampt M, Billionnet C, Mezzarobba M, Raguideau F, Dray-Spira R, Zureik M, Coste J, Alla F. Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: An application to antiepileptic drug use in 4.9 million pregnant women in France. *Pharmacoepidemiol Drug Saf* 2018. DOI: 10.1002/pds.4556.

Coste J, Billionnet C, Rudnichi A, Pouchot J, Dray-Spira R, Giral P, Zureik M. Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France. *Eur J Prev Cardio*. 2018. doi: 10.1177/2047487318776831. [Epub ahead of print].

Bouyer B, Rudnichi A, Dray-Spira R, Zureik M, Coste J. Thromboembolic risk after lumbar spine surgery: a cohort study of 325,000 French patients. *J Thromb Haemost* 2018 Jun 12. doi: 10.1111/jth.14205. [Epub ahead of print].

Billioti de Gage S, Collin C, Le-Tri T, Pariente A, Bégaud B, Verdoux H, Dray-Spira R, Zureik M. Antidepressants and Hepatotoxicity: A Cohort Study among 5 Million Individuals Registered in the French National Health Insurance Database. *CNS Drugs* 2018; 32(7):673-684. doi: 10.1007/s40263-018-0537-1. Chaignot C, Zureik M, Rey G, Dray-Spira R, Coste J, Weill A. Risk of hospitalisation and death related to baclofen for alcohol use disorders: comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165,334 patients between 2009 and 2015 in France. *Pharmacoepidemiol Drug Saf* 2018; 27:1239-1248. DOI: 10.1002/pds.4635.

Lassalle M, Colas S, Zureik M, Dray-Spira R. Reply to the Letter to the Editor: Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res* 2018;476(12):2462-2463. doi: 10.1097/CORR.0000000000000525.

<sup>13</sup> See also the focus entitled "ANSM and CNAM join forces to create EPI-PHARE, a public expertise body specialising in health product epidemiology", page 37.

## Focus on: ANSM and CNAM join forces to create EPI-PHARE, a public expertise body specialising in health product epidemiology

In late December 2018, Dominique Martin, ANSM's Director General, and Nicolas Revel, the Director General of CNAM, signed an agreement to create a scientific interest group (SIG) made up of the health product epidemiology teams at the two institutions.

Known as EPI-PHARE, this SIG is a public expertise body specialising in health product epidemiology. Its goal is to address the growing demand for studies based on the analysis of the vast and complex data available through the National System of Health Data (SNDS) in a responsive manner.

Epidemiological studies on health products make it possible to identify the risks associated with health products more quickly and accurately and help public authorities make decisions to ensure health safety. The SIG provided such assistance through its work on *in utero* exposure to valproic acid (Depakine and Depakote) and other treatments for epilepsy and bipolar disorders and the associated risks to children, the occurrence of meningioma among women treated with cyproterone acetate (Androcur), the safety of HPV vaccines, the occurrence of venous thromboembolic events related to combined oral contraceptive pills, the haemorrhagic risk associated with new oral anticoagulants, the risks associated with the permanent sterilisation device for women called Essure, and the new Levothyrox formula.

The SIG will conduct, manage, and coordinate epidemiological studies in real-life conditions on health products in accordance with a structured programme. The goal of this programme will be to carry out usage studies on health products with special attention given to misuse, vulnerable populations (the elderly, infants and children, pregnant women, etc.), and new medications, as well as studies on the safety of medications and medical devices. It will be approved by the SIG Scientific Board, which comprises eight independent and internationally known scientists and chaired by Professor Bernard Bégaud.

The SIG will also use its expertise to evaluate studies conducted by other bodies (academic teams or pharmaceutical companies).

It will also provide methodological support regarding the use of SNDS data and develop scientific guidelines for the academic scientific community. The SIG will draw from pharmaco-epidemiological platforms that include independent university teams. Finally, it will also provide funding to the independent academic teams of private interests for the purposes of conducting studies.

In an environment in which health data is now broadly available, this public expertise body, which is supported by the French Ministry of Health and Solidarity, will be expanded, strengthened, and opened up to include other institutions that are active in the health product sector.



## Revision of medicine risk/benefit ratio and reassessment programmes

Reassessment of the risk/benefit ratio of marketed medicines is a recurrent process that takes place 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 safe 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.

### HIGHLIGHTS IN 2018

- **Curaspotaqua 5%, gel (benzoyl peroxide)**: withdrawal from the list of over-the-counter medicines and the publication of stricter guidelines regarding methods of administration due to adverse effects and misuse (December 2018).

### 2018 DATA

**In 2018, a risk/benefit ratio monitoring procedure was kept in place to manage the risk associated with medication use.**

Following the opinion of the Commission for Monitoring the Risk/Benefit Ratio of Health Products<sup>14</sup>, this programme resulted in restricted indications, modified MA information, and changes to the prescription and dispensing conditions for medications<sup>15</sup>.

Over the course of 2018, the risk/benefit ratio of seven active substances was revised as part of a revision or reassessment procedure<sup>16</sup>.

**Reassessment of the risk/benefit ratio guarantees that the treatment options are tailored to efficacy and safe use data**

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<sup>14</sup> See the chapter entitled "The work of advisory bodies", p. 129.

<sup>15</sup> See the summary table of the opinions issued in 2018 by the Commission for Monitoring the Risk/Benefit Ratio of Health Products in Appendix 3, p. 195.

<sup>16</sup> See the full list provided in Appendix 4, p. 198.

## Risk reduction measures

Systemic measures regarding the proper use of medication: this includes the Summary of Product Characteristics (SPC), which are aimed at professionals, and the package leaflet, which is written for patients as well as the medication's packaging and the prescription and dispensing conditions. When these guidelines are found to be insufficient to ensure safe and effective use, additional risk reduction measures can be put in place.

Additional risk reduction measures are created to prevent or reduce the probability of adverse effects, their seriousness, and/or their impact on the patient. These measures include:

- letters to healthcare professionals,
- educational documents for healthcare professionals and/or patients through a variety of media, including letters, guides, checklists, brochures, patient cards, and training slides,
- restricted-access programmes: product access is restricted by specific measures pertaining to prescription conditions, dispensation, and use (controlled distribution, pregnancy-prevention programme).

These measures can be combined as well.

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 2018

- **Creation of the “Additional risk reduction measures” section**, which provides users access to documents that have been approved by ANSM: [https://ansm.sante.fr/Activites/Surveillance-des-medicaments/Mesures-additionnelles-de-reduction-du-risque/\(offset\)/1](https://ansm.sante.fr/Activites/Surveillance-des-medicaments/Mesures-additionnelles-de-reduction-du-risque/(offset)/1)
- **Recommendations regarding the names of medicines** (February 2018).

### 2018 DATA

- **50** letters to healthcare professionals sent out in 2018

#### **Additional risk reduction measures:**

- New measures put in place for **24** active substances (48 documents)
- Updates: **31** active substances (60 documents)

## Managing medication errors

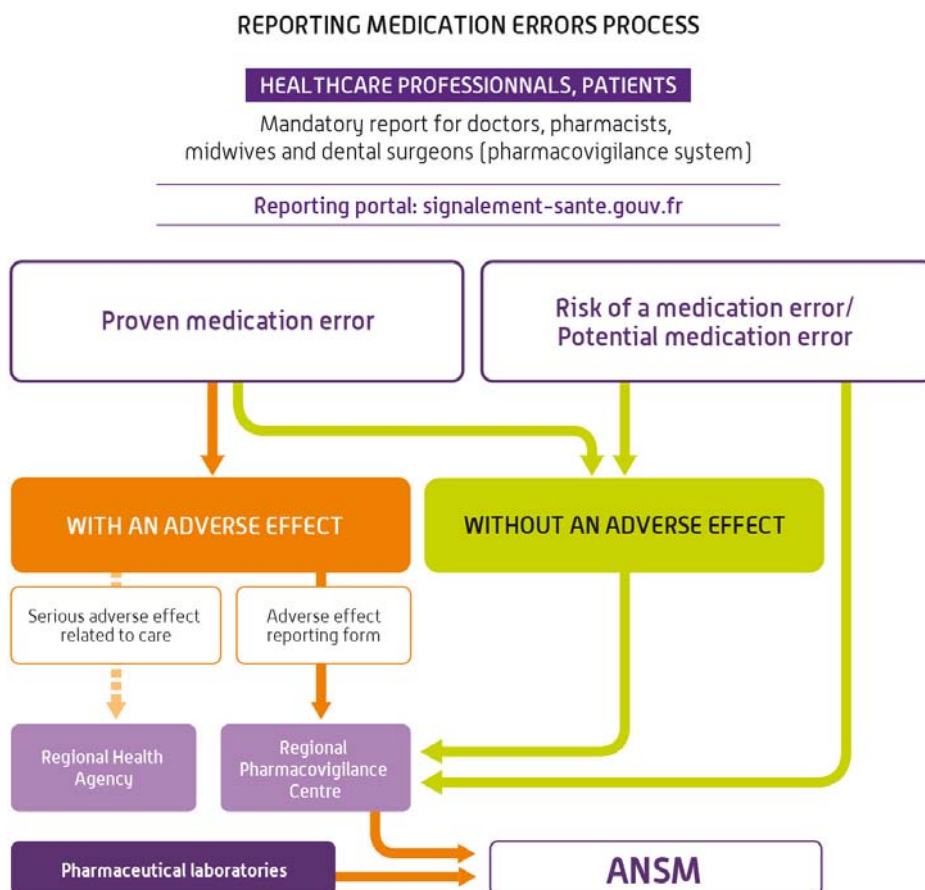
Monitoring medication errors is an integral part of the medicine surveillance policy. This work, which is coordinated with pharmacovigilance activities, focuses on non-adverse-effect errors (potential errors, risks of medication errors, and latent errors), and medication errors resulting in adverse effects.

The “Medication Errors Service” was created in 2005. It 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.

ANSM evaluates any priority reports as well as any pharmacovigilance cases that include an especially troubling number of errors so risk reduction measures can be put in place if necessary. These measures can include the following:

- an immediate action regarding the product on a national or European level: request for modification of the MA; modification of the package leaflet, immediate or outer packaging (medicine box); communication to healthcare professionals or the public; etc.
- an action in the context of a more overarching discussion about medicines (for example: improved and harmonised labelling for small volumes of solution for injections, recommendations and informational campaigns regarding administration devices for oral solutions, etc.).

### Medication error report channel



[For more information about medication errors: watch our infographic video  
What are medication errors? \(in French\)](#)



## 2018 DATA

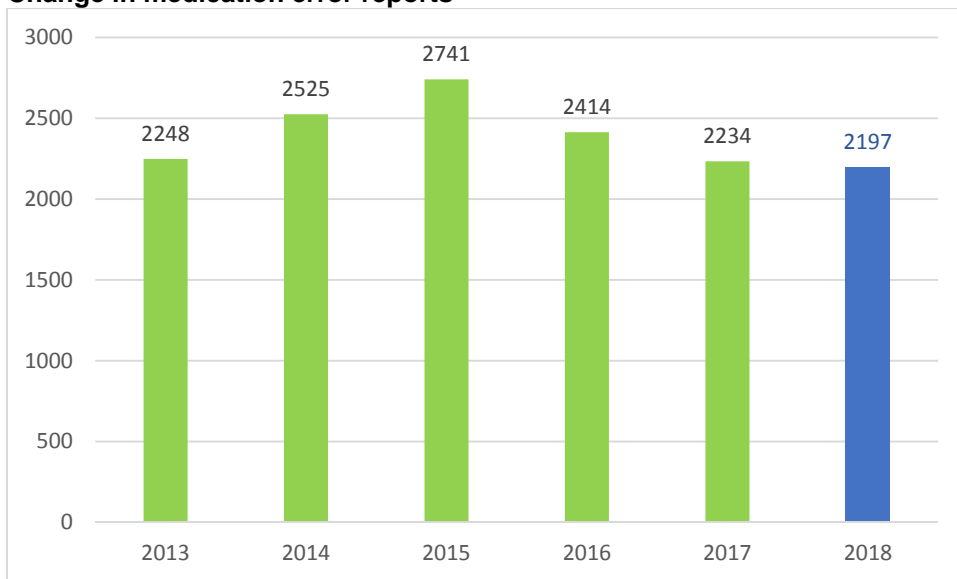
**2,197** reports were submitted to ANSM, including 1,940 known errors, 119 potential errors, and 138 risks of medication error (or latent errors)

**58%** of reports of proven errors resulted in an adverse event (half of these reports were considered serious based on pharmacovigilance criteria)

**38%** of proven error reports did not result in an adverse effect

The description did not make it possible to determine if the error led to an adverse event for the remaining 4% of reports

**Change in medication error reports**



## HIGHLIGHTS IN 2018

- Organisation of an **ANSM-College of General Practitioners discussion day** on *Medication errors in high-street pharmacies* (November 2018)<sup>17</sup>.
- **Phosphoneuros**: changes to the dosage and graduated pipette used for oral administration were made to the medication Phosphoneuros, oral solution in drops (120 ml bottle). These changes were applied in response to medication error reports among newborns that led to overdoses that were sometimes serious and even fatal (December 2018).
- **Theralene**: restricted indications and updated safety profile information. These medications are now available by prescription only, and the appearance and colours of the exterior packaging of Theralene 0.05% syrup and Theralene 4% oral suspension were changed to prevent any confusion between the two forms (September 2018).
- **Starting materials used to manufacture a pharmaceutical preparation containing vitamin D and risks of confusion regarding dosages**: reminder of recommendations following a medication error that occurred in the manufacturing process for a compound containing vitamin D that led to an overdose with a favourable evolution (August 2018).
- **Viperfab-Viperatab**: end of a shortage of the medication Viperfav that led to the importing of another medication, Viperatab, from the United Kingdom. Possible temporary co-existence of Viperfav and Viperatab: ANSM issued a reminder about the differences (indications, composition, presentation, and dosage) between the two medications to limit the risk of medication errors (July and August 2018).
- **Ceritinib (Zykadia 150 mg-gel capsule)**: new dosage recommended for treatment initiation. The package leaflet that is included in boxes already on the market did not have this change. As a result, pending the update and in order to prevent any risk of medication error, ANSM recommended that prescribing doctors talk to patients about the correct dose while instructing them on how to take Zykadia and that pharmacists include a patient information sheet about the dosage change (July 2018).
- **Exjade** (deferasirox): the medications Exjade 90 mg and 360 mg, film-covered tablets that have been marketed in France since January 2018, will permanently replace the medications Exjade 125 mg and 500 mg, dispersible tablets, beginning on 26 July 2018. To limit the risk of any medication errors, information on the main differences between the film-covered tablet and dispersive tablet was provided in a “prescriber” guide and in a “patient” educational booklet (July 2018).
- **Fluconazole, powder for oral suspension (Triflucan and generics)**: change to the administration system and description of the dosage following a European harmonisation procedure. To avoid any medication errors, a communication campaign was conducted (letter to healthcare professionals, educational update, patient information sheet, pharmaceutical dossier message, and a message from prescription assistance software) (June 2018).
- **Cefepime (Axepim and its generics)**: reminder about the risk of serious adverse neurological effects if dosage recommendations are not followed, especially in the case of kidney failure. Dosage errors in patients with kidney failure have led to serious side effects (neurotoxicity) that have sometimes resulted in the patient's death (April 2018).
- **Fiasp (insulin aspart), solution for injection with 100 units/ml**: change in packaging colour. In Europe, cases of wrongly administering Fiasp, a rapid-acting insulin with yellow packaging, instead of Tresiba, 100 units/ml, a basal insulin with light green packaging, or vice versa, have been reported. This type of confusion can result in serious medical consequences, including hyperglycaemia or hypoglycaemia. (April 2018).
- **Recommendations regarding the package labelling of solid oral medicines**. The goal of these recommendations is to reduce the risk of medication errors and promote the proper use of medications by making it easier to identify them and by improving the visibility, readability, and understanding of medication packaging (February 2018).
- **Metformin and the risk of lactic acidosis in the case of kidney failure**: as part of the expansion of the use of anti-diabetic medications containing metformin to include patients with moderate kidney failure, ANSM issued a reminder about the importance of adjusting the dose in the case of moderate kidney failure to prevent the risk of lactic acidosis. Cases of metformin overdose leading to lactic acidosis due to kidney failure have been reported, some of which have been fatal (January 2018).

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<sup>17</sup> See also the chapter entitled “The College of General Practitioners Interface Committee”, page 142.

## Monitoring the coverage of patients' health needs

### SECURING THE SUPPLY OF MEDICINES OF MAJOR THERAPEUTIC VALUE WHEN MANUFACTURERS REPORT A LIMITED SUPPLY OR A STOCK SHORTAGE

When a stock shortage for a medicine is imminent, ANSM concentrates its efforts on securing the supply of 'essential' medicines, which are referred to as medicines of major therapeutic value. The unavailability of these medicines would constitute a public health risk.

ANSM's goals include evaluating, approving, and, if necessary, coordinating the actions that pharmaceutical companies must take to secure patients' access to these medicines. Pharmaceutical companies are responsible for ensuring the availability of the medicines they bring to market.

In 2016, new texts containing the legislative and regulatory measures established by the health system modernisation law consolidated the measures to be taken to manage supply shortages for medicines of major therapeutic value, especially the actions that should be taken by pharmaceutical distribution laboratories and wholesaler distributors, in order to prevent supply interruptions. Since January 2017, manufacturers have created shortage management plans for certain categories of products.

In addition, ANSM would like to encourage the participation of patients and healthcare professionals early on in the event of stock shortages and limited supplies by doing the following:

- communicating regularly about the supply situation of certain essential proprietary medicines. Since the first quarter of 2018, supply information has been published on the agency's website regarding mandatory vaccines and blood-derived medicines,
- by including patient and healthcare professional representatives in discussions on the risk of supply shortages,
- by organising discussion meetings with healthcare representatives, patients, and manufacturers about certain situations involving limited supplies or shortages (example: Steering committee on human immunoglobulins (IGh) held in May 2018, Steering committee on blood clotting factors (BCF) in October 2018, and European Immunisation Week (EIW) in October 2018).

The agency takes part in European efforts to harmonise each member state's approach when it comes to preventing and managing medication supply shortages.

**For more information on limited medication supplies and supply shortages, view our infographic (in French):**

<https://ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments>



## HIGHLIGHTS IN 2018

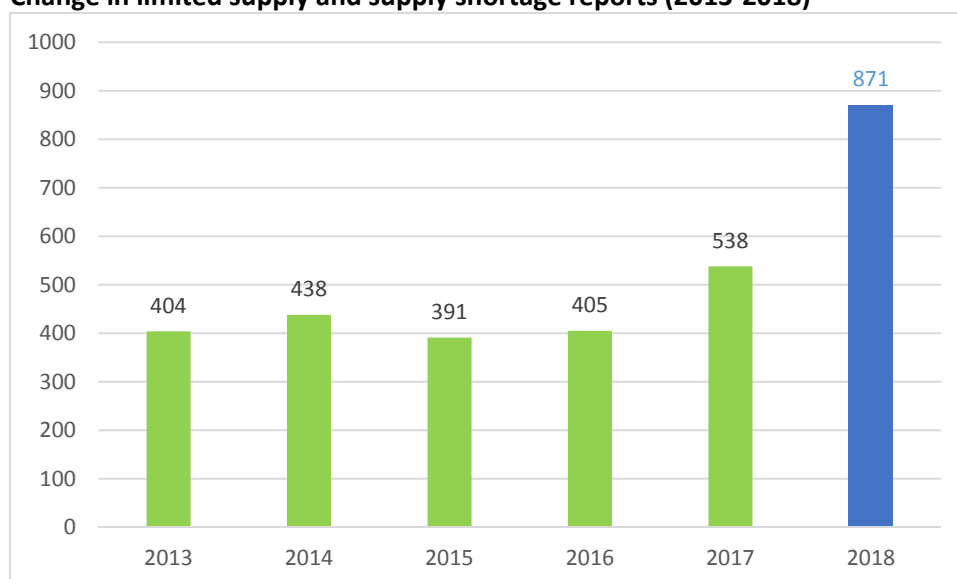
- **Limited supply of medications containing sodium heparin** (December 2018).
- **Extremely limited supply of medications containing 5-Fluorouracil** (September 2018).
- **Long-term supply shortage of Sinemet** (levodopa/carbidopa): creation of an action plan to avoid any interruption in the treatment plans of affected patients (September 2018).
- Recommendations to manage **significant supply challenges for Celestene** 0.05% oral solution drops and its generics (September 2018).
- **Limited supply of sartans** following a quality defect caused by the presence of impurities in the starting material since July 2018<sup>18</sup>.
- **Securing the supply of Extencilline** after the pharmaceutical company Sandoz stopped manufacturing benzathine benzylpenicillin (July 2018).
- **Limited supply of medications containing cytarabine** starting in April 2018.
- **Limited supply of benzathine benzylpenicillin** (February 2018).
- **Limited supply of LFB medications** following the laboratory's non-compliance with manufacturing best practices starting in November 2017<sup>19</sup>.

## 2018 DATA

In 2018, the number of reports increased. This rise was primarily due to cardiovascular and nervous system products, general anti-infection products for systemic use, and blood-derived medicines.

The percentage of reports regarding sartans and LFB products is 11% (99 reports) and 5% (45 reports), respectively.

### Change in limited supply and supply shortage reports (2013-2018)



<sup>18</sup> See also the focus on "Quality defects in sartan-based medicines", page 45.

<sup>19</sup> See also the focus entitled "Extremely limited supply of blood-derived medicines produced by LFB Biomédicaments", page 54.

## FOCUS ON: Quality defects in sartan-based medicines

On 26 June 2018, the European Medicines Agency (EMA) informed ANSM of a quality defect involving certain medications containing valsartan used to treat high blood pressure, heart failure, and following a recent myocardial infarction.

The defect involved the presence of a genotoxic impurity, N-nitrosodimethylamine (NDMA), which the WHO has determined to be a probable human carcinogen. This agent was found in the active ingredient, valsartan, which was manufactured by a Chinese company and sold in Europe and worldwide.

This impurity was not expected and was not detected during the course of routine testing.

Given the link that was established between the occurrence of this impurity and the manufacturing process used, investigations were launched in Europe and internationally to determine if other sartans were affected as well. These investigations, which first focused on valsartan, were expanded to include four other sartans featuring a similar structure, namely irbesartan, candesartan, losartan, and olmesartan. In numerous countries, the work resulted in a recall of batches of medicines that contained levels of impurities (NDMA, NDEA (N-nitroso-diethylamine), NMBA (4-(methyl)(nitroso)amino)butanoic acid), or other impurities from the nitrosamine family that were identified during testing) that were above the thresholds set by the EMA. ANSM took part in these investigations, particularly by opening up its own testing laboratories. Since the summer of 2018, ANSM, in collaboration with the European Union's Official Medicines Control Laboratories (OMCLs), helped develop testing methods. It also analysed medications and starting materials containing sartans that are available in France and that can potentially create these impurities through the synthesis process.

Moreover, in this context, beginning in July 2018, ANSM created educational materials to assist patients and healthcare professionals, including several information updates, letters to healthcare professionals, FAQ documents, pharmacy posters, and various infographics on the best approach to take to treatment for both patients and healthcare professionals. Recommendations for healthcare professionals were also written instructing them to set aside supplies for patients without alternative treatment options during extreme supply shortages caused by large-scale batch recalls.

These actions were taken in close collaboration with the National Board of Pharmacists, the French Medical Board, the College of General Practitioners, learned societies, patient associations, and the National Health Insurance Fund.

A freephone number was also created to answer questions from patients and healthcare professionals.

In addition, in order to ensure a sufficient supply and cover the needs of French patients, ANSM asked all pharmaceutical companies that sell sartans or other alternatives to take all necessary measures, including increasing their production capacities. A regular stock and supply monitoring system was implemented. Up-to-date predictions on the coverage of needs in France for valsartan and other sartans are published every month on the ANSM's website to provide healthcare professionals and members of the public with information on the availability of these medications.

In addition, following the different batch recalls issued in France between July and December 2018 and the investigations conducted at both national and international level, the EMA and ANSM requested that manufacturers take additional measures to fulfil their obligation to ensure the quality and safety of all sartan-based medications currently on the French market and in the future.

As a result, at European level, it was decided that testing for these impurities would be conducted directly on the starting materials, which are the manufacturer's responsibility, before any sartan-based medication could be produced. This new rule took effect on 1 January 2019. Testing before the manufacturing stage is a check aimed at guaranteeing the quality of the medications.

In addition, ANSM asked that all manufacturers marketing these sartans in France to test the levels of these impurities, before 31 March 2019, in any active ingredient included in the composition of medications that are currently available or will soon be sold in French pharmacies and were produced before 1 January 2019.

All information on this subject is available in a subject-specific file featured on ANSM's homepage.

## MANAGING QUALITY DEFECTS

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

Depending on various criteria and the associated patient risk, a solution is formulated based on each report.

After a quality defect has been reported, several measures can be taken:

- **batch recall**: when necessary, the laboratory, in collaboration with ANSM, issues a batch recall by using the pharmaceutical dossier management system (PD, recall managed by CNOP) in most cases.

The main reasons for these recalls are stability defects, cross-contamination, and non-compliance with product specifications.

- In certain cases, such as when a batch recall would lead to a supply shortage for a medication of major therapeutic value, other risk reduction measures related to quality defects can be considered, such as **implementing a quarantine or issuing alerts** to potential users. A risk-benefit assessment is then carried out to determine which measures to take.
- **Quality defect "Rapid Alerts"**: ANSM can also issue quality defect "Rapid Alerts" in response to the reports it receives to inform the competent authorities in other countries of the assessments and decisions made with respect to a report that concerns several countries.

In addition, the agency 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 2018

- **Valsartan**: discovery of potentially carcinogenic impurities (NDMA) in valsartan manufactured by the Chinese company Zhejiang Huahai (June 2018). Expansion of the dossier to include all sartans containing a tetrazole group and NDEA and NMBA impurities (November 2018)<sup>20</sup>.
- **Octapharma Octagam 5% Alburnorm 20% Albumin Gammanorm**: female blood donor with neurological symptoms resembling Creutzfeldt-Jakob disease (MCJ) (October 2018).
- **WFI manufactured by Delpharm Tours (2.5 ml, 5 ml, and 10 ml formats)** and used to reconstitute freeze-dried injectable medications from LFB Biomedicaments: presence of particles (glass delamination) in the WFI bottles used as solvents for LFB's blood-derived medicines. No batch recall was issued. Exchange of WFI bottles in blood-derived medicines on a patient, hospital pharmacy, and laboratory level (June 2018).
- **Serb proinsulin 25%, (I.V.) solution for injection /Inutest 25%**: reminder about serious adverse effects, including death (March 2018).
- **GSK vaccines (Twinrix (adult and paediatric), Boostrix-IPV (=Boostrix Tetra), Infanrix-IPV+Hib (=Infanrix Quinta), Infanrix Hexa, Havrix, Engerix (=Engerix B), Fendrix)**: leak between needle and syringe during the injection process. No recall. Letter to healthcare professionals (February 2018).
- **Santane N9, herbal tea blend in single-serving sachets**: reminder for patients about the presence of salmonella (January 2018).
- **Raspberry Lansoyl, oral gel in a single-dose recipient**: a shard of glass found in a jar of jelly. Patient reminder in the form of mini-posters (January 2018).

<sup>20</sup> See also the focus on "Quality defects in sartan-based medicines", page 45.

## 2018 DATA

The number of medication quality defect reports rises every year; this figure increased from 624 in 2004 to **1,987** in 2018.

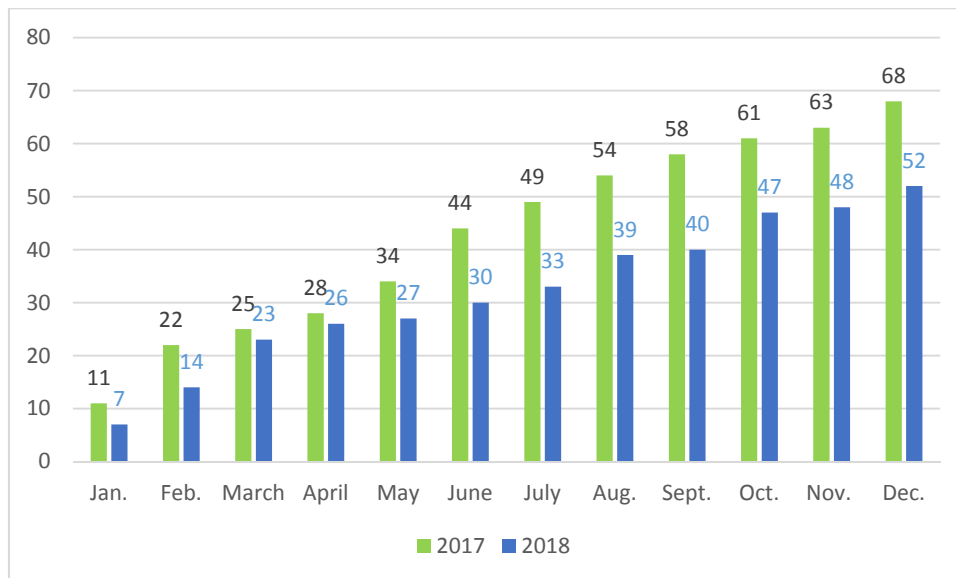
**599** reports were the subject of an in-depth investigation, and **52** batch recalls were issued.

### Change in the number of quality defect reports (2004-2018)

	Number of reports	Number of recalls
2004	624	45
2005	824	61
2006	948	38
2007	930	46
2008	937	57
2009	1,095	37
2010	1,223	49
2011	1,395	129
2012	1,518	87
2013	1,595	76
2017	1,699	76
2015	1,703	56
2016	1,790	76
2017	1,930	68
<b>2018</b>	<b>1,987</b>	<b>52</b>

### Number of recalls following a quality defect

*Comparison of the data from 2017 and 2018*



## Control over advertising

Control over advertising is an integral component of health product monitoring. ANSM's role is to ensure the safety of the promotional message; advertisements must not encourage poor prescribing habits and must be consistent with the assessment and communications of the health authorities. Prior to their release, the agency verifies all promotional documents written for the public (General Public approval) and for healthcare professionals (Medical Professional approval).

The law has three main goals:

- to present the medication objectively,
- to promote its proper use,
- and to ensure current standards are followed, especially the MA, as well as the treatment strategies recommended by the HAS.

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.

Professional advertising is subject to submission periods (4 per year), and applications are processed in less than 2 months (regulatory deadline).

As regards advertising written for products and certain understand the conditions treatment. Patients should pharmacist's advice and to regarding medicines or attention (for example: contraindicated for pregnant

**Ensuring the safety of the promotional message is an integral component of ANSM's role**

for the general public (self-medication vaccines), the goal is for the patient to understand the need to follow a take into account certain safety messages therapeutic classes that require special paracetamol and medicines women, etc.).

General public advertising is subject to submission periods (8 per year), and applications are processed in less than 2 months (regulatory deadline).

## 2018 DATA

### APPROVAL REQUESTS FOR ADVERTISEMENTS FOR HEALTHCARE PROFESSIONALS

- **8,978** approval requests (around 700 more than in 2017)
- **8.8%** of these requests were declined

### APPROVAL REQUESTS FOR ADVERTISEMENTS FOR THE GENERAL PUBLIC

- **1,436** approval requests
- **61%** of these requests were revised
- **10 %** of these requests were declined

ANSM prohibits or restricts advertising to the general public if there is a potential risk to public health, such as product misuse (pseudoephedrine, nifuroxazide), or if, for a given indication, the medication requires the intervention of a physician to diagnose the condition or initiate and monitor treatment.

In 2018, ANSM prohibited advertising to the general public for a medication containing vitamin B1 due to its indications (treatment for B1 deficiency: Berberi. Gayet-Wernicke encephalopathy, following the injectable form), which was not suitable for use without the intervention of a doctor.

Excluding the growing number of general public approval requests, the data is stable compared to previous years.



## 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 psycho-active products, regardless of whether or not they are medicines.

This task 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 one of the largest legal opioid-producing country in the world. ANSM controls the legal trade and movement of narcotics and psychotropic substances in France. With respect 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 evaluates the potential for abuse and addiction and the public health risks related to the use of both legal and illegal psychoactive substances that are present in medicines and non-medicines alike (except for alcohol and tobacco) in order to ensure the medications are being used properly and to add substances to the list of narcotics if necessary. It evaluates marketing authorisation requests and monitors medicines containing psychoactive substances, including those indicated for opioid replacement therapy. ANSM manages the national addiction vigilance system with help from a network of thirteen Centres for evaluation and information on pharmacodependence - addiction vigilance (CEIP-A) located in each region in university hospitals.

To detect and assess abuse, drug dependence, and misuse of medicines or psychoactive substances, ANSM and the CEIP-As established specific data collection and assessment studies. Hence, in addition to collecting 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 healthcare professionals must report severe cases of abuse and dependence), annual surveys are conducted with entities specialising in addiction care [OPPIDUM (1)], general practitioners [OPEMA(2)], community pharmacists [OSIAP(3) and ASOS(4)] and toxicology experts [DRAMES(5), DTA (6), and the French national survey on chemical dependence]. At the same time, ANSM makes sure it keeps patients and 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 with the OFDT (*Observatoire Français des Drogues et des Toxicomanies*—French Monitoring Centre for Drug and Drug Addiction). ANSM sends its studies to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), especially data concerning deaths from fatal overdoses.

### EXPERT ASSESSMENTS

ANSM calls upon the services of an expert commission, the Narcotics and Psychotropics Commission (CSP)<sup>21</sup>, 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 accomplish its tasks 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.

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<sup>21</sup> See the chapter entitled "The work of advisory bodies", p. 129.

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

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

(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 2018

- Informational update on the **increase in the number of cases of cannabis intoxication** among children due to accidental ingestion (August 2018).
- The Commission for Narcotics organised a **partner discussion day on 21 June with the main stakeholders in the addiction sector** (representatives of users and healthcare professionals) and healthcare organisations (DGS, MILDECA, ANSES) to propose a plan aimed at reducing the number of overdoses related to opioid substitutes (primarily methadone) and ensure sufficient access to these medications, which play a key role in treating opioid addiction (June 2018).
- **Informational update on the increase in intoxication reports** related to cocaine and crack consumption (January 2018).
- **Start of the MA for the nasal naloxone spray Nalscue and issuance of an MA for three naloxone-based medications** (Naloxone Adapt, Prenoxad, Ventizolve) for the emergency treatment of opioid overdose.

Topical summary	2013	2014	2015	2016	2017	2018
Post-MA survey of dependence on pharmaceutical products	9	14	6	5	8	12
Evaluation of abuse and dependence potential as part of the MA application	4	2	9	7	3	8
Evaluation of abuse and dependence potential of psychoactive substances (plants, synthetic drugs, etc.)	3	6	5	3	7	4
National addiction vigilance monitoring	6	9	10	10	10	10

## 2018 DATA

In 2018, the **Narcotics and Psychotropics Commission met 5 times**.

### **It approved the addition of:**

- so-called “generic” molecules derived from a benzofurane group in accordance with the decree of 3 May 2018 to the list of **narcotics** due to their potential for abuse and addiction;
- 20 designer benzodiazepines in accordance with the decree of 3 May 2018 to the list of **psychotropic substances** due to the increase in the number of cases reported in France and the harmful effects associated with these substances, which have similar pharmacological properties to “traditional” benzodiazepines.

# SURVEILLANCE OF BLOOD PRODUCTS

ANSM monitors:

- adverse effects that can occur in both blood donors and the recipients of labile blood products (LBP),
- transfusion chain incidents,
- post-blood donation information.

Haemovigilance includes all monitoring and assessment procedures regarding adverse effects among LBP recipients, serious adverse effects in blood donors, serious transfusion chain incidents, and post-donation information that could compromise the quality or safety of blood products derived from these donations or previous donations. It covers the entire blood transfusion chain, ranging from the collection of blood and its components (including the epidemiological monitoring of donors) to the transfusion of LBPs to recipients.

The agency's haemovigilance efforts are supported by the network of haemovigilance correspondents in healthcare and blood transfusion establishments and the national online notification system, e-FIT<sup>22</sup>.

This database 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, chikungunya and Zika) via an inter-institutional structure (*Cellule d'aide à la décision*, or CAD—decision-making assistance unit) by proposing that exposed travellers returning from epidemic zones be temporarily excluded from donating blood or other products derived from the human body. It also intervenes by proposing preventive measures in response to the risk of transmission via blood transfusions or transplants of other infectious agents responsible for epidemics.

## HIGHLIGHTS IN 2018

- **Publication of a decree regarding biological analyses and screening tests** carried out while screening donated blood (December 2018).
- **Publication of the updated decision** on blood transfusion best practices (July 2018).
- **Authorised promotional advertising for therapeutic plasma products** (last update on April 2018).
- **Publication of the updated decision** on the list and characteristics of labile blood products (February 2018).
- **Management of preventative measures for arbovirus epidemics**, particularly given the spread of the WNV epidemic in Europe in 2018.
- **Generalisation of the preparation, distribution/release, and use of platelet concentrates** that have been treated to inactivate pathogenic agents (November 2017).
- **Study on the management of the transfusional risk of hepatitis E virus.**
- **Study on anaemia and iron-deficiency anaemia** among blood donors in France.

## 2018 DATA

- **51 reports received, leading to 33 consultations with CAD.**

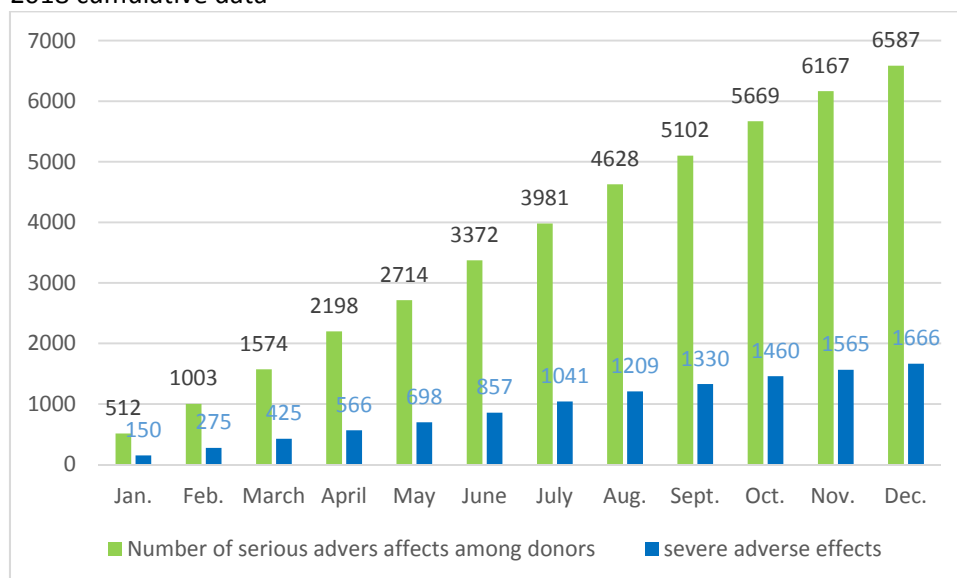
These reports involved, by descending order of frequency, the following pathogens: **West Nile virus, chikungunya, *Plasmodium vivax*, Rift Valley fever, dengue, Zika, and Q fever.**

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<sup>22</sup> E-Fit is 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.

## Haemovigilance reports of serious adverse effects among donors

2018 cumulative data



## Haemovigilance reports of adverse effects among recipients

2018 cumulative data

	Number of adverse effects among recipients	Severe adverse effects
January	775	24
February	1,448	41
March	2,163	51
April	2,854	65
May	3,518	77
June	4,247	97
July	5,024	111
August	5,847	124
September	6,461	132
October	7,232	147
November	7,826	163
December	8,611	168

These reports concern blood vigilance events with possible, probable, and certain accountability.

The number of reports 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.

## FOCUS ON: Extremely limited supply of blood-derived medicines produced by LFB Biomédicaments

LFB Biomédicaments has three pharmaceutical sites in France that work with blood-derived medicines (BDMs). The site in Lille (59) manufactures sterile biological medications produced in a sterile environment from intermediary products sourced from the Ullis site (91). The Carvin site (62) takes in starting materials, except for plasma, and redistributes them to the two other sites.

The Lille site produces a wide variety of medicines derived from plasma intended for human use, including albumin, polyvalent and specific immunoglobulin solutions (hepatitis B, tetanus) and clotting factors (FVIII, FIX, FXI, fibrinogen, Willebrand, protein C, alpha-1-antitrypsin, antithrombin). These medications are of major therapeutic value. For some medications, LFB covers nearly all of the demand in France.

In 2018, several production issues at LFB Biomédicaments resulted in a limited supply of BDMs. It is difficult to find alternatives to these medications. Nevertheless, ANSM did everything in its power to satisfy the demand for these medicines as much as possible and ensure continuity of treatment.

Against this backdrop, various actions were implemented to help protect patients.

### Inspection of LFB Biomédicaments

In January 2018, ANSM carried out a follow-up inspection following the injunction that was issued in January 2017. In May 2018, after finding that previously identified shortfalls were not fully corrected, ANSM issued a second injunction ordering LFB Biomédicaments to complete its required actions. ANSM will monitor the company to ensure every action is corrected in accordance with the set deadline.

Until this time, and given the existence of cases of non-compliance with manufacturing best practice and regulations, ANSM cannot release European-format batches according to the EU's administrative procedure regarding the official release of batches for biological products for human use. However, in order to reduce the risk of shortages within France as much as possible, a special procedure was created to approve an exceptional "release" of batches for the French market alone as long as the head pharmacist ensured the quality of the released products.

### Securing the supply

ANSM authorised the import of equivalent or identical medications that were initially intended for other markets (Europe and outside of Europe) and the remobilisation of batches that were initially meant to be exported. Before making these medications available in France, ANSM evaluated and approved their pharmaceutical quality based on the relevant requirements.

With this approach, ANSM was able to ensure that patients throughout France did not have to interrupt their treatment.

ANSM and the pharmaceutical companies distributing these imported or remobilised medications implemented communication and support measures to ensure patients and healthcare professionals could use these products as safely as possible.

In addition, supply shortage alerts, which are published on the ANSM website and specific to each medication, are updated as the situation changes. These alerts provide information about supply shortages and limited supplies that are either imminent or ongoing. These alerts include the information provided in the various letters to healthcare professionals issued by the distributing pharmaceutical companies, as well as all other documentation found to be necessary and relevant.

To add to its in-depth surveillance efforts regarding the supplies of blood-derived medicines and to help it manage shortages as early and effectively as possible, ANSM developed an internal database using the data from MIFs (marketing information forms) reported by BDM distributors to ANSM's testing division in compliance with the European directive regarding the release of batches of BDMs and vaccines (ANSM's

testing division is the French OMCL (official Medicines Control Laboratory)). This tool provides ANSM with increased visibility over the supply of the French market through the market's various stakeholders and in real time, as reports must be issued seven days before the medication is brought to market. As a result, ANSM is better able to manage existing and future supply shortages and instances of limited supplies and better oversee corrective measures (especially the import of medications and the reorganisation of batches intended for export) and monitor their progress.

Regarding the specific case of immunoglobulins, which are often in short supply throughout Europe and even globally, and in order to redirect the limited available supplies towards clinical situations that require these medications, ANSM updated its recommendations regarding the ranking for human polyvalent immunoglobulins following the opinion issued by an *ad hoc* Temporary Specialist Scientific Committee (TSSC) that met on 4 April 2018 and was attended by healthcare professionals and patient associations concerned by the issue.

Moreover, as part of an enhanced monitoring programme, steering committees dedicated to immunoglobulins and clotting factors were created. These groups include various stakeholders that are involved in the topic, including ANSM, all relevant laboratories in the French market, and the relevant patient associations and healthcare professional representatives.

### **Mobilisation of local and regional stakeholders**

In addition to national efforts to manage the supply of blood-derived medicines during shortages, regional actors (Regional Health Agency with the support of OMEDIT) performed a local assessment in each health establishment.

ANSM continues to closely monitor LFB Biomédicaments to ensure it meets every requirement within the delay set by the injunction.

**For more information, please read the “Blood-derived medicines” file on the ANSM website, which includes a summary table with information about each available product and alternative**

# SURVEILLANCE OF MEDICAL DEVICES AND *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

A medical device is an instrument, material, device, piece of equipment, implant, or software that is used for medical purposes in humans and whose primary desired action is not achieved through pharmacological, immunological, 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<sup>23</sup> 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.

Medical devices are categorised into four classes according to the level of risk associated with their use: class I, class IIa, class IIb, and class III.

## Bringing a medical device to market

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 be awarded 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 the safety or health of patients and users.

The product's compliance is evaluated by an accredited (or notified) body for all devices except those belonging to the lowest risk category (class I: without a measuring function and supplied in a non-sterile condition). The evaluation must be done in accordance with the procedures described in the directives.

The notified body evaluates the manufacturer's quality assurance system. For class III devices (the highest risk category), or for active implantable medical devices, the design application is also systematically examined.

Upon completion of this process, the notified body issues a certificate of conformity, allowing the manufacturer to place the CE marking on its device and sell it on the European market.

All other products that are subsequently put on the market 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. The manufacturer must carry out tests to ensure the use of the product does not create problems and take preventative or corrective measures if it does.

Regular audits are performed by the notified body. The CE marking is renewed periodically. The decisions made by notified bodies have a maximum validity of five years and can be renewed for a maximum period of five years.

## ANSM's role

The principle of CE marking implies effective and active market surveillance. Each country's competent authorities, including ANSM in France, performs this task.

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<sup>23</sup> Global Medical Device Nomenclature

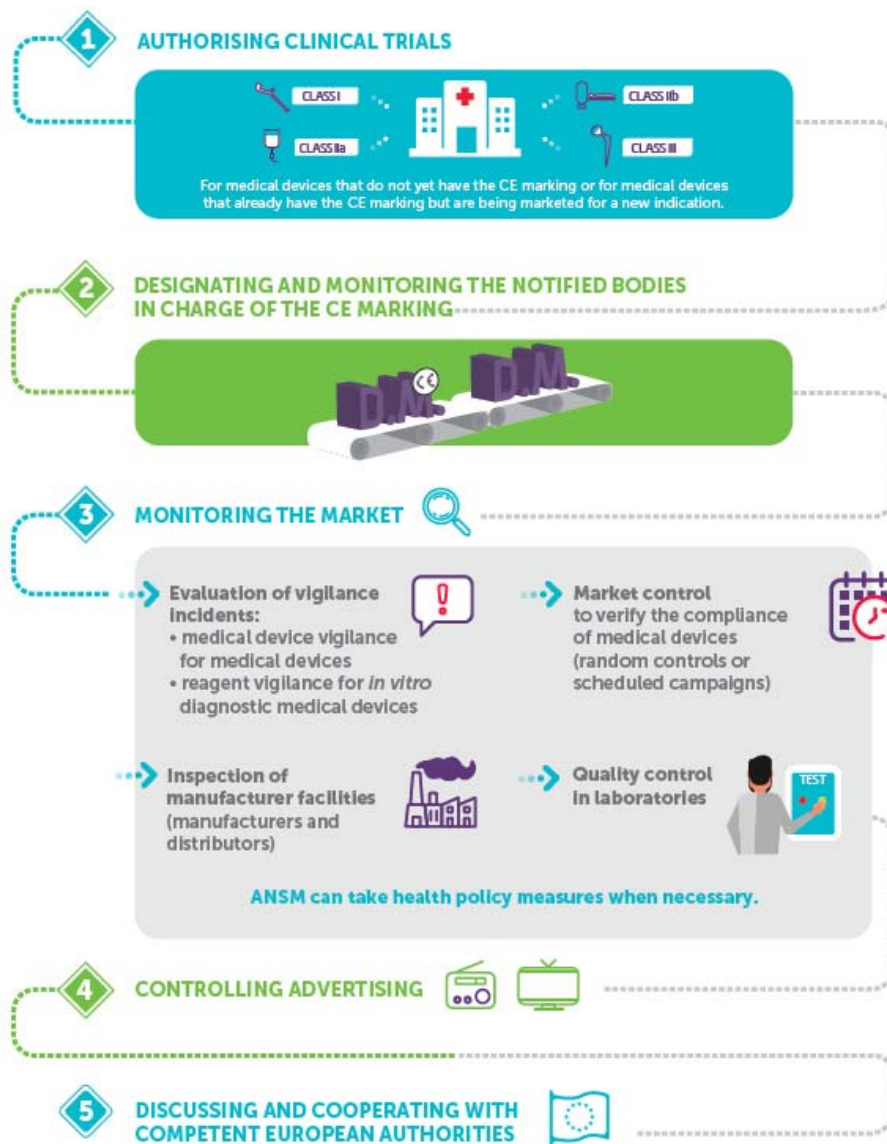


Within the scope of ANSM control, the agency intervenes on several levels by:

- Authorising clinical trials.
- Designating and then monitoring the French notified body by conducting several inspections. The agency may participate in joint audits with its European counterparts in order to conduct foreign notified body audits.
- Market surveillance via:
  - the evaluation of vigilance (medical device and reagent vigilance) incidents based on reports of incidents or risks of incidents,
  - market controls aimed at verifying the compliance of medical devices after they have been placed on the French market, including the registration of the most high-risk devices and the performance of periodic tests and topical evaluation campaigns aimed at specific product ranges,
  - inspections of 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,
  - laboratory quality control of medical devices.

ANSM also monitors the advertising for certain medical devices that present a significant health risk.

### ANSM's role regarding medical devices



For more information about medical devices, see our three video infographics (in French):

- **What is a medical device?**

[https://www.youtube.com/watch?v=mzGm\\_fjYbGc&list=PLWW-ynCS\\_y0vp87LFINIABJUHDwD\\_gDEc&index=2&t=0s](https://www.youtube.com/watch?v=mzGm_fjYbGc&list=PLWW-ynCS_y0vp87LFINIABJUHDwD_gDEc&index=2&t=0s)

- **Bringing a medical device to market**

[https://www.youtube.com/watch?v=PIRII75J53M&list=PLWW-ynCS\\_y0vp87LFINIABJUHDwD\\_gDEc&index=4&t=0s](https://www.youtube.com/watch?v=PIRII75J53M&list=PLWW-ynCS_y0vp87LFINIABJUHDwD_gDEc&index=4&t=0s)

- **ANSM's role in the life cycle of medical devices**

[https://www.youtube.com/watch?v=PIRII75J53M&list=PLWW-ynCS\\_y0vp87LFINIABJUHDwD\\_gDEc&index=4&t=0s](https://www.youtube.com/watch?v=PIRII75J53M&list=PLWW-ynCS_y0vp87LFINIABJUHDwD_gDEc&index=4&t=0s)



## HIGHLIGHTS IN 2018

- **Publication of the new version of the Prion standard protocol** (May 2018).
- **Recommendations for the proper use of self-tests sold in pharmacies** (February 2018).

## 2018 REPORTS

### Vigilance

- Medical devices for apheresis - context (January 2018).
- Ischaemic and haemorrhagic risks associated with coronary endoprosthesis ranges (stents) in France January 2018 - Study report (February 2018).
- Analysis of cases of breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) (July 2018).
- Medical device vigilance investigation regarding complications associated with the use of medical devices designed to treat prolapse and urinary incontinence (from 1 October 2016 to 31 December 2016) (November 2018).

### Market controls

- Mesh implants used to treat urinary incontinence and pelvic organ prolapse - French market review from 2014 to 2017 (November 2018).
- Market inspection of diagnostic devices for chlamydia trachomatis infections - Sensitivity and specificity report (included in leaflets) - Final report (July 2018).
- Enhanced surveillance of Flow Diverter intracranial stents - Report (June 2018).

### National quality control

- Annual national quality control report for 2016-2017 (July 2018).
- Annual reports of external quality evaluation bodies - 2017 summary (May 2018).

### National quality control of medical devices

- Quality control of medical devices that expose people to ionising radiation - 2017 annual report (August 2018).

### Other scientific reports

- Control over the pre-analytic phase of samples meant for the microbiological qualification of organ donors, tissues, and cells - ANSM/ABM report (January 2018).
- Prion Standard Protocol, version 2018 (May 2018).
- Intracranial stents - Flow Diverter - Inspection summary (June 2018).
- Definition of a texturing range for breast implants - IEM report (July 2018).
- Analysis of particles produced by PCS2 plasmapheresis - Summary note 18-A-0403 (December 2018).

## 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 (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 to ANSM that come to their attention.

#### HIGHLIGHTS IN 2018

- **Launch of a medical device investigation on citrate dialysate** (December 2018).
- **Suspension of the use of apheresis devices** produced by Haemonetics (September 2018).
- **Review of cases of breast implant-associated ALCL** (July 2018).
- **Market surveillance:** publication of a TSSC expert opinion and a texturing study (July 2018).
- **Review of medical device vigilance** for the glucose measuring device FreeStyle Libre (June 2018).
- **Health policy decision** establishing special conditions of use following deaths that occurred while using Sécuridrap restraining bed linens (June 2018).
- **Reminder about warnings and precautions for use** regarding alcoholic antiseptics used in conjunction with an electric scalpel during surgery. ANSM has noted that the number of incidents involving burns associated with the simultaneous use of electric scalpels and alcoholic antiseptics in France has remained stable (around nine cases annually) but is not decreasing despite the publication in 2009 and again in 2012 of recommendations regarding the use of electric scalpels in the presence of alcoholic antiseptics (February 2018).
- **Creation of a monthly trend surveillance programme** for all material device incident reports about the medical device Essure. A webpage about this device has been created on the ANSM website that summarises the key moments about this file: [https://www.ansm.sante.fr/Activites/Surveillance-des-dispositifs-medicaux-implantables/Surveillance-des-dispositifs-medicaux-de-sterilisation-definitive/\(offset\)/2](https://www.ansm.sante.fr/Activites/Surveillance-des-dispositifs-medicaux-implantables/Surveillance-des-dispositifs-medicaux-de-sterilisation-definitive/(offset)/2)

ANSM also takes part in the Essure monitoring committee, which is coordinated by the French Ministry of Health.

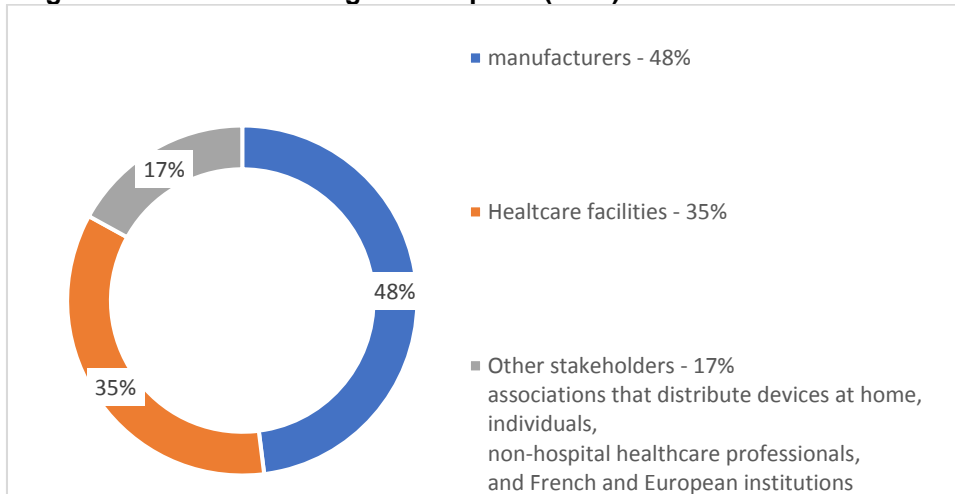
### 2018 DATA

#### Medical device vigilance reports

Medical device vigilance	2014	2015	2016	2017	2018
Number of reports	16,194	15,783	15,961	18,208	<b>18,838</b>
• Serious	972	825	749	1,015 <sup>24</sup>	<b>1,133</b>
• Submitted by patients and patient associations	38	34	129	1,432	<b>682</b>

<sup>24</sup> The 2017 annual report contained an error: the number of serious medical device vigilance reports was 1,015 and not 796.

### Origin of medical device vigilance reports (2018)



### REAGENT VIGILANCE

Reagent vigilance evaluates incidents and risks of incidents related to the use of *in vitro* diagnostic medical devices.

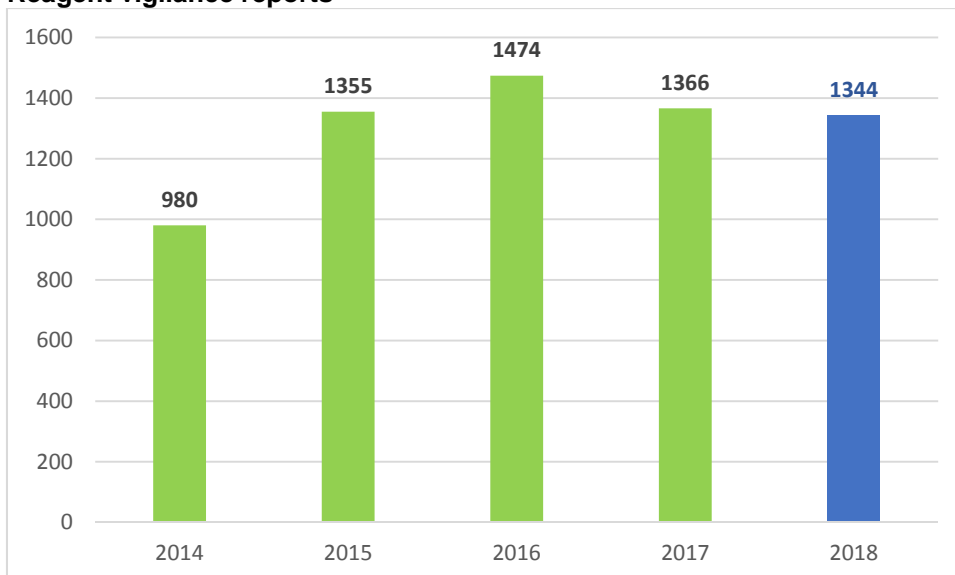
The reagent vigilance system is structured around a national tier led by ANSM and a local tier managed by local reagent correspondents working in public or private healthcare institutions, healthcare professionals, and manufacturers, who are required to report any incidents or risks of incidents that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

### HIGHLIGHTS IN 2018

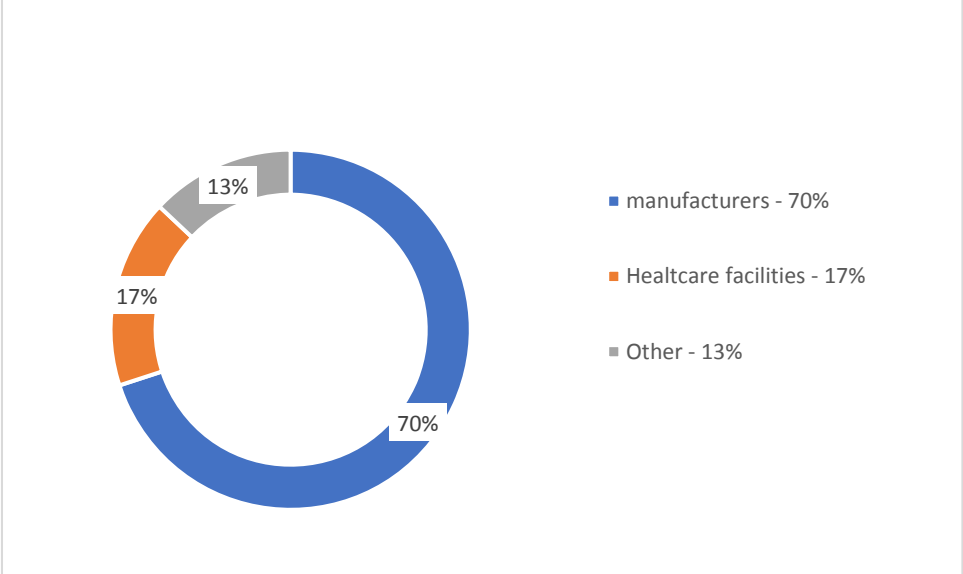
- **Three recommendation letters regarding *in vitro* diagnostic devices:**
  - Alere HIV Combo rapid test (two letters in July 2018),
  - Biotin interference in immunoassays (April 2018).

### 2018 DATA

#### Reagent vigilance reports



**Origin of reagent vigilance reports (2018)**



## Market control activities

### IDENTIFICATION OF MEDICAL DEVICES AND *IN VITRO* DIAGNOSTIC MEDICAL DEVICES ON THE MARKET

Each year, ANSM monitors the introduction of new medical devices to the market.

In addition to French manufacturers of class I devices and custom-made devices (which 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.

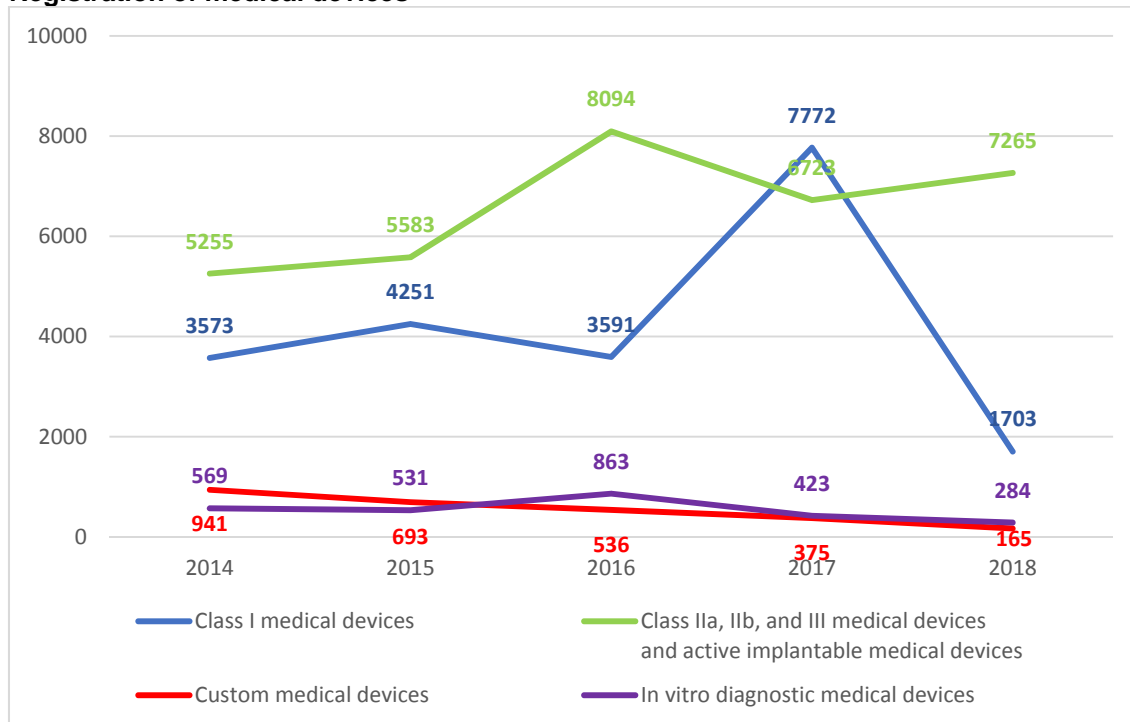
This notification, which must be received prior to the device's release in France, provides information about market stakeholders as well as devices in use within the country.

#### HIGHLIGHTS IN 2018

- **Non-renewal of the CE marking for Allergan brand textured breast implants** (Microcell and Biocell) by the LNE-GMED notified body (December 2018).
- **Update on the ongoing investigations** on Haemonetics apheresis devices (December 2018).
- **Public hearing on the use of breast implants** and recommendation to use smooth implants (November 2018)<sup>25</sup>.
- **Suspension of Market Authorisation and distribution** of the Calvin brand customisable condoms (May 2018).

#### 2018 DATA

##### Registration of medical devices



2017<sup>26</sup>

<sup>25</sup> See also the focus on enhanced surveillance of breast implants, page 64.

<sup>26</sup> A large number of MD reports (4,000) was received in 2017. In these reports, every version of a product within a single range was entered individually, which contributed to the large number of reports. Different product versions within the same range are now registered together and count for a single registration. In 2018, ANSM received and registered fewer reports, and the number of MDs per report was also less.

## MAIN THEMED CAMPAIGNS BY PRODUCT RANGE LAUNCHED AND/OR CONTINUED IN 2018

ANSM may 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 carries 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.

## 2018 DATA

### THEMED CAMPAIGNS BY PRODUCT RANGE LAUNCHED AND/OR CONTINUED IN 2018

- Breast implants: BIA-ALCL, texture and biocompatibility
- Medical devices for apheresis
- Definitive contraception devices
- Evaluation of the toxicity of metal particles shed by medical devices
- Flow diverter stents for brain aneurysms
- 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: Enhanced surveillance of certain categories of medical devices

### Intracranial “flow diverter” stents

“Flow diverter” stents are implantable medical devices that have been on the market since 2008 and are designed to treat intracranial aneurysms. They are technologically more advanced than traditional stents due to their denser mesh.

Due to a lack of clinical data on these stents, ANSM implemented a special surveillance programme for these medical devices in 2010.

As part of this surveillance, ANSM published a summary report in 2018 about these medical devices in France. It also included a medical device vigilance data analysis as well as the results of its regulatory review of manufacturer's design records (regulatory, preclinical, and clinical data). The preliminary results of the *Diversion* registry, which was created by the French Neuro-Radiology Society (SFNR) in 2012 with help from ANSM, are also presented in the report.

Finally, in 2018, ANSM also published a summary of the inspection campaigns carried out for four “flow diverter” stent manufacturers.

At this point, ANSM's analyses have not revealed any problematic evidence that would justify taking special measures aimed at “flow diverter” stents, but it has nevertheless decided to maintain its in-depth medical device vigilance efforts.

### Breast implants: ANSM's investigations into the risk of ALCL

Since 2011, when the first cases of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) were reported, ANSM has been investigating the link between the occurrence of ALCL and the texture of breast implants.

In February 2018, ANSM convened a Temporary Specialist Scientific Committee (TSSC) to issue rulings on all investigations and studies into the occurrence of ALCL and the disease's link to breast implants.

This TSSC included experts in polymer chemistry, material biocompatibility, plastic and reconstructive surgery, immunology, toxicology, anatomical pathology, and tribology. Its work centred around hearings with healthcare professionals and patient associations. It also used data from available studies (study on lymphomagenesis in mice models, LYSA study) and medical device reports.

A study describing the surface of breast implants, which the European Membrane Institute of Montpellier (EMI) conducted at the request of ANSM, was also presented during this TSSC.

Following these investigations, ANSM announced in November 2018 that public hearings would be held in early 2019 on the role of breast implants in cosmetic and reconstructive surgery. To this end, ANSM recommends that healthcare professionals ideally use breast implants with smooth shells.

The hearings took place in February 2019.

On the basis of available information, including the opinion of independent experts, ANSM considers that the texturing of certain macrot textured and polyurethane-covered implants is a risk factor for BIA-ALCL. Therefore, ANSM decided in April 2019, as a precautionary measure, to recall these implants to reduce the risk for patients to develop ALCL, which remains a rare but serious risk. Given the rarity of this risk, the ANSM has not advised women with textured breast implants to have them removed as a preventive measure. A freephone number was also set up to answer patients' questions.

A follow-up report on these actions was presented during the monitoring committee for women with breast implants, which is held under the umbrella of the French Ministry of Health. The committee met in 2018.



## Mesh implants for the treatment of urinary incontinence and pelvic organ prolapse

Medical devices for the treatment of prolapse, a condition in which organs drop down from their original position, and urinary incontinence are shaped like strips and implantable pelvic mesh implants.

ANSM has been monitoring these implantable devices for several years. At this stage, the agency does not have access to many investigations into reports and asks that patients and healthcare professionals submit reports about any adverse effects to the reporting portal.

In 2019, ANSM also decided to consult with patients and healthcare professionals (urologists, gynaecologists, general practitioners, nurses, midwives, etc.) to come up with a consensus about these medical devices and the risks associated with their use. This meeting will be followed by an action plan based specifically on the situation in France.

### Focus on: ANSM's enhanced surveillance includes several areas of focus

- **Market surveillance:**
  - A review of the market in France from 2014 to 2017, published on the ANSM website in 2018, identified implants sold in France and uncovered a clinical evaluation on these implants. Around 50,000 implants from approximately one hundred marketed brands are sold every year in France. During this period, the number of products sold increased. For some devices, the investigation into the quality of the clinical evaluation will continue.
  - ANSM also takes part, along with its European colleagues, in a task force overseeing these devices. The goal of this group is to ensure that manufacturers continue to monitor their product after it has been put on the market.
- **Medical device vigilance:**
  - Medical device vigilance reports are closely monitored. Perioperative and post-implant complications were reported to ANSM in 2018 for around sixty patients in France. Around fifty of these patients were reported in December 2018.
  - The results of ANSM's medical device vigilance investigation were reported in 2018. The level of complications observed from 1 October to 31 December 2016 was 1.43%.
- **Inspection:** an inspection campaign targeting manufacturers that market this type of device in France was launched in 2018 to verify the compliance of their products and manufacturing processes.
- **Clinical study:** following a call for proposals, ANSM funded the VIGIMESH clinical study coordinated by Poitiers University Hospital. The purpose of this monitoring effort is to collect reports from several healthcare facilities of short- and long-term complications after surgery, with or without implants. The final results are expected to be available in late 2019.

A webpage dedicated to mesh implants for the treatment of urinary incontinence and pelvic organ prolapse was published on the ANSM website to provide a summary of the key moments in this dossier.

## Medical devices for apheresis

Following on from the work it began in 2017 to re-evaluate the risk-benefit ratio of apheresis procedures, ANSM recommended a certain number of measures designed to closely monitor medical devices for apheresis and supplement the general information donors receive about apheresis by adding explanations about the risk caused by particles.

ANSM periodically monitors medical device vigilance reports about the presence of particles in apheresis circuits. With respect to actions aimed at apheresis device manufacturers, these companies have worked to improve their machines and have completed their studies in accordance with ANSM's demands. With respect to the diversification of the equipment of EFS and the Army Blood Transfusion Centre (CTSA), ANSM issued a report recommending both organisations diversify their equipment and closely monitor their machines throughout this transition.

Finally, several meetings with stakeholders, including the EFS, CTSA, ANSM, and patient and blood donor associations, took place under the umbrella of the French Ministry of Health to monitor the progress of all the measures recommended by ANSM.

During the course of this in-depth surveillance, several medical device vigilance incidents were reported to ANSM at the end of August 2018 that involved the apheresis machines of the company Haemonetics.

An incident that occurred at the EFS office in Tarbes at the end of August 2018 revealed the presence of a large quantity of particles inside the apheresis separator and the plasma bag for the first time. This incident did not harm the donor because the devices were equipped with single-use filters that filtered the red blood cells before they reached the donor. A preliminary decision to suspend the batch of devices involved in this incident was taken on 30 August 2018 by ANSM, and EFS Occitanie was asked to conduct an inspection.

On 11 September 2018, another incident, this time at the EFS site in Annonay, that was similar to the one in Tarbes and involved the same Haemonetics apheresis devices was reported to ANSM. This incident was followed by another ANSM inspection. It also did not result in consequences for the donor.

In light of these incidents and the lack of any explanation for their occurrence, on 12 September 2018, ANSM decided to suspend the marketing authorisation in France for single-use apheresis medical devices with the reference number 782HS-P-SL manufactured and marketed by the company Haemonetics as well as the use of its MCS + and PCS2 separators.

ANSM continued to investigate devices manufactured by Haemonetics, particularly through additional inspections, and, in collaboration with the Atomic Energy and Alternative Energy Commission, through analyses of apheresis products affected by these incidents in an effort to determine the particles' origin. The goal of the analyses was to identify and characterise the particles that were present and sampled during the incidents.

The commission conducted analyses to determine the size and shape of the particles found during these incidents. Qualitative elementary analyses were also conducted as well as molecular analyses using a mass spectrometer to compare the particles with the sections of a joint of an SMD with the reference number 782HS-P-SL.

All of the analyses conducted by ANSM and the commission indicated that the particles were organic in origin and were most likely related to the various blood elements contained in the device. No particles from a joint in the device or any other part of the equipment were found. These reports are available on ANSM's website.

ANSM also consulted all relevant European authorities to determine if they had received any medical device vigilance reports involving the release of particles from Haemonetics apheresis machines. The responses the agency has received to date have not described any malfunctions of this type.

At this stage in the investigation, there is no proven risk for plasma and platelet donors using an apheresis device in France, either for patients receiving these products or the professionals using the machines.

Nevertheless, ANSM is continuing to investigate the Haemonetics devices to determine the origin of the malfunction. It is likely multi-factorial and related to the machines' maintenance schedule and frequency of use.

ANSM is doing everything in its power to secure patient supply and guarantee donors' safety when apheresis machines are in operation.

Through this series of measures, ANSM is able to meet the needs of the French market and serve patients' interests.

## Focus on: Prion Standard Protocol (PSP)

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 healthcare facilities between 1994 and 2011 to limit the risk of transmitting these agents.

The products used to inactivate UTAs must be tested using a benchmark method known as the Prion Standard Protocol (PSP). ANSM published a new version of the PSP on 15 May 2018. This version will be the only method used starting on 15 May 2021.

The first version of the PSP, which was published in November 2011, was written in compliance with the state of the art in 2011 in the absence of standardised guidelines. From its initial publication, it was understood that this version would be updated as science's understanding of the matter improved.

The goal of this update is to ensure the standard aligns with science's current understanding of the topic. For example, updates to the protocol have included *in vivo* tests on human strains and new *in vitro* techniques. They also ensure the transparency of the scientific data underpinning the PSP's compliance.

The 2018 version of the PSP was written after several hearings with stakeholders, a public consultation, and an opinion issued by ANSM's Commission for monitoring the risk-benefit ratio of healthcare products. The new protocol includes an additional *in vivo* study on a human prion strain using an appropriate animal model, a third strain studied *in vitro*, an increased sensitivity threshold, and a review of the procedure for publication on the ANSM website.

## QUALITY CONTROL OF RADIATION-EMITTING MEDICAL DEVICES

Quality control of medical devices, instituted by decrees 2018-434 and 2018-436, which replaced decree 2001-1154 regarding quality maintenance and control on 01/07/2018, 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 ANSM's Director General.

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. Seventy accreditations were valid at the end of 2018.

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 17,168 non-conformity reports have been received and processed by ANSM.

### HIGHLIGHTS IN 2018

- **Three plenary Medical Device Quality Control Committee meetings.** The Medical Device Quality Control Committee helps update and harmonise the quality control practices used for medical devices in France. It also applies to medical devices that expose people to ionising radiation.
- **5 dedication committee sub-group meetings** (four meetings on digital mammography and one on interventional radiology).
- **Publication of the 2017 annual report for external quality control bodies** (August 2018).
- **Euratom transposition and adaptation of CQDM regulations:** application of two decrees (July 2018 and June 2018).
- **Publication of recommendations regarding medical device installations used for radio-guided interventional procedures** (April 2018).

### 2018 DATA

Quality control of medical devices	2014	2015	2016	2017	2018
Number of new standards	0	2	2	0	0
Number of certifications granted	10	25	12	14	9
Number of non-conformities reported	1,255	1,335	1,176	726	730

## NATIONAL QUALITY CONTROL OF MEDICAL BIOLOGY ANALYSES

National quality control of medical biology tests is an external assessment of the quality of the tests performed by each of the 800 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 with respect to conducting a test. It also makes it possible to monitor the *in vitro* diagnostic medical devices used in laboratories.

### HIGHLIGHTS IN 2018

- **Meeting of the “National quality control relations” working group** as part of the MD/IVDMD manufacturing interface committee (October 2018).
- **Publication of the annual national quality control annual report** (July 2018).
- **Publication of the annual report summary for external quality assessment bodies** (May 2018).

### 2018 DATA

In 2018, ANSM continued its national quality control campaigns as part of decree no. 2016-46 of 26 January 2016.

To this end, **it conducted six national quality control operations**: newborn screening, DNA profiling for legal purposes (2), blood lead measurements, and trisomy 21 (2).

Due to a lack of supply of samples, the operation concerning Epstein-Barr virus (EBV) serology was re-scheduled for the second half of 2019. Under these conditions, medical biology laboratory data is now updated operation-by-operation instead of systematically.

### Number of laboratories participating in each operation

Discipline	Operation	Month	Test controlled	Maximum number of laboratories / experts controlled per operation
Newborn screening	18DNN-1	Dec.	<b>T181 and T182</b> : TSH <b>H181 and H182</b> : 17-OH progesterone <b>P181 and P182</b> : Phenylalanine <b>M181 and M182</b> : Trypsine IR <b>D181 and D182</b> : newborn sickle cell anaemia screening	<b>20</b>
DNA profiling	18IEG-1	April	<b>IEGAQ1, IEGAQ2, IEGAQ3, IEGAQ4</b> : DNA profiling	<b>90</b>
	18IEG-2	Oct.	<b>IEGAR1, IEGAR2, IEGAR3, IEGAR4</b> : DNA profiling	<b>90</b>
Blood lead measurement	18PLO-1	Sept.	<b>PLO18-01, PLO18-02, PLO18-03, PLO18-04, PLO18-05</b> : Lead	<b>26</b>
Trisomy 21	18T21-1	Sept.	<b>18TA: MSM2T screening</b> : AFP, hCG, hCGb, free estriol <b>18TA</b> : sequential screening included during 2nd trimester (MSM2T + CN): AFP, hCG, hCGb, free estriol <b>18TB</b> : first semester combined screening (MSM1T): hCGb, PAPP-A	<b>87</b>
Trisomy 21	18T21-2	Dec.	<b>18TA: MSM2T screening</b> : AFP, hCG, hCGb, free estriol <b>18TB</b> : first semester combined screening (MSM1T): hCGb, PAPP-A	<b>86</b>

As part of the new tasks of the national quality control campaign, a "National Quality Control Relations" working group was created within the interface committee working with representatives from MD/IVDMD medical industries to facilitate discussions with external quality evaluation bodies. Among the various measures it will take with external quality evaluation bodies, ANSM must publish the summary of their

reports. A preliminary summary report was published on the ANSM website in May 2018. In addition, external quality evaluation bodies were asked to submit 2017 activity data. This information was summarised in a report.

As part of this working group, ANSM also worked with the external quality evaluation bodies to lay the foundation for the reagent coding tables described in the decree. ASIP and the French Society of Laboratory Information Technology also took part in these discussions. The first meeting took place in December 2017, and many discussions were held in 2018 on the topic of creating and updating the coding table. A preliminary survey was conducted among these bodies to create a list of the medical biology exams being controlled by these bodies.

Following on from work completed in 2017, the data was updated in 2018 in the following areas: hormonology, tumour markers, and bacterial and parasite serologies.

## Control over advertising

The law of 29 December 2011, which increased the safety of medicines and health products, extended the scope of advertising control to medical devices and *in vitro* diagnostic medical devices. It is an additional tool to help manage their safe use.

The advertisement must present the MD/IVDMD objectively, particularly in terms of performance or compliance with essential safety requirements. It must also promote its correct use. In addition, advertising aimed at the general public is prohibited for reimbursable class 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 publication; systematic submissions to ANSM are not required.

### 2018 DATA

#### Control of advertising for medical devices and in vitro diagnostic devices

	2014	2015	2016	2017	2018
Number of applications submitted	414	405	506	339	396
Number of applications denied	28	63	49	26	43

# SURVEILLANCE OF OTHER HEALTH PRODUCTS

## Surveillance of cosmetic products

Since 11 July 2013, cosmetic products have been governed by (EC) regulation no. 1223/2009. This law governs how they are released to the market, which:

- takes place under the responsibility of the manufacturer or its representative,
- does not require prior authorisation,
- is allowed on the condition that they are safe for human health when used under normal or reasonably foreseeable conditions of use,
- requires the mention of 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 safe 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 relating 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.

ANSM 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.

ANSM, in collaboration with the French Ministry of Health, responds to requests for public consultations on opinions issued by the Scientific Committee on Consumer Safety (SCCS) regarding the safety of substances used in cosmetics. These opinions help change cosmetics regulations and can become a health concern when they involve endocrine disruptors or CMR-type substances<sup>27</sup>.

## COSMETIC PRODUCT VIGILANCE

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

The cosmetic vigilance system, which was created by the law of 9 August 2004 regarding public health policy, is based on:

- the reporting of adverse effects related to the use the cosmetic products by healthcare professionals, manufacturers, and users,
- the collection, recording, assessment, and analysis of these incidents by ANSM and the application of corrective measures when necessary.

In addition, since 11 July 2013, the date on which European regulation no. 1223/2009/EC on cosmetic products came into force requiring the reporting and forwarding of serious adverse effects, ANSM has also

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<sup>27</sup> Chemical substances that are carcinogenic, mutagenic, or reprotoxic.



acted as a liaison between the relevant European authorities, manufacturers, and end-users concerning these effects.

#### **HIGHLIGHTS IN 2018**

- **Nair Cire Divine**: reminder to users about precautions for use (June 2018).
- **Publication of a report by the TSSC** on the use of phenoxyethanol in cosmetics (May 2018).

#### **2018 DATA**

**231 cosmetic product reports processed by ANSM (compared to 234 in 2017), nearly half of which were classified as serious.**

#### **CONTROLLING THE COSMETICS 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.

#### **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.

ANSM is responsible for monitoring adverse effects occurring with the use of these products and takes measures to better control their use and the substances they include. It coordinates its efforts with the DGCCRF.

# QUALITY COMPLIANCE INSPECTIONS: PRACTICES AND HEALTH PRODUCTS

ANSM monitors the quality of the practices that culminate in the marketing and monitoring of health products:

- it helps define enforceable regulatory frameworks (especially relevant best practices and standards),
- it manages corresponding sites (authorisations, accreditations, declarations, sanctions, etc.),
- it conducts field inspections to ensure enforceable regulatory provisions are being followed. These inspections are part of an annual inspection programme and can be conducted at random.

Inspections make it possible to establish a level of confidence in the quality of the practices of stakeholders, including manufacturers, operators, import companies, distributors, trial sponsors, investigators, etc. Stakeholders are responsible for their practices as well as the quality and safety of the health products they put on the market, including the starting materials used to make these products.

The purpose of these inspections is to:

- evaluate the compliance of stakeholders' practices with the best practices or standards that apply for a given activity, product, or clinical or non-clinical trial,
- ensure stakeholders' ability to produce high-quality data and/or healthcare products,
- carry out technical investigations in response to a quality defect report, incident, or especially significant event,
- gather the necessary information for administrative actions such as technical opinions, certificates (issuances, renewals, or withdrawals), injunctions, and health policy rulings on health products or activities that involve risk.

The annual inspection programme is based on a risk-based approach, which combines:

- regulatory requirements,
- the intrinsic risk involved with the activities overseen by the stakeholders,
- the stakeholder's inspection history,
- reports received by ANSM,
- internal referrals (from other departments) or external referrals (other agencies, decentralised departments, etc.),
- topical campaigns,
- administrative action follow-up.

The ANSM Inspection Department was accredited by COFRAC (French Accreditation Committee) in accordance with the ISO/CEI 17020 standard. This accreditation constitutes recognition of the quality of ANSM's inspection activities, as well as its compliance with ethics and international regulations related to impartiality, independence, and competence. The department was audited in April 2018, and its accreditation was renewed.

## 2018 DATA

- **ANSM conducted 677 inspections** (667 in 2017), including:
  - **11% random inspections,**
  - **6% inspections outside of France.**
- **The year confirmed the number of administrative decisions resulting from observations made during inspections:**
  - **65 injunctions issued by ANSM** (53 in 2017). 10% of inspections led to this type of measure,
  - **8 health policy rulings** (six in 2017),
  - **5 financial sanctions,**
  - **1 procedure sent to the public prosecutor.**

## HIGHLIGHTS IN 2018

- **Launch of a platform designed to detect abnormal sales of certain medications** in partnership with the National Board of Pharmacists (November 2018).
- **Renewal of the COFRAC accreditation** based on the ISO 17020 standard of the inspection department (April 2018).

## Inspection summary and other documents 2018

- **Pharmaceutical distribution:** review and issues (November 2018).
- **Flow diverter intracranial stents:** inspection summary (June 2018).
- **Review of inspections aimed at verifying compliance with LBP** from 1994 to 2017 (June 2018).
- **Guidelines on inspection follow-up**—bilingual French/English version (May 2018).

## Inspection of clinical and non-clinical trials

### INSPECTION OF PRECLINICAL TRIALS

The laboratory best practices (LBP) principles are followed by all testing facilities of OECD member countries to ensure the quality and mutual acceptance of data from non-clinical safety tests.

ANSM checks to what extent the trial installations charged with conducting safety trials on medicines for human use, cosmetics, tattoo products, and, subsequent to referrals, medical devices follow LBP principles.

### INSPECTION OF CLINICAL TRIALS

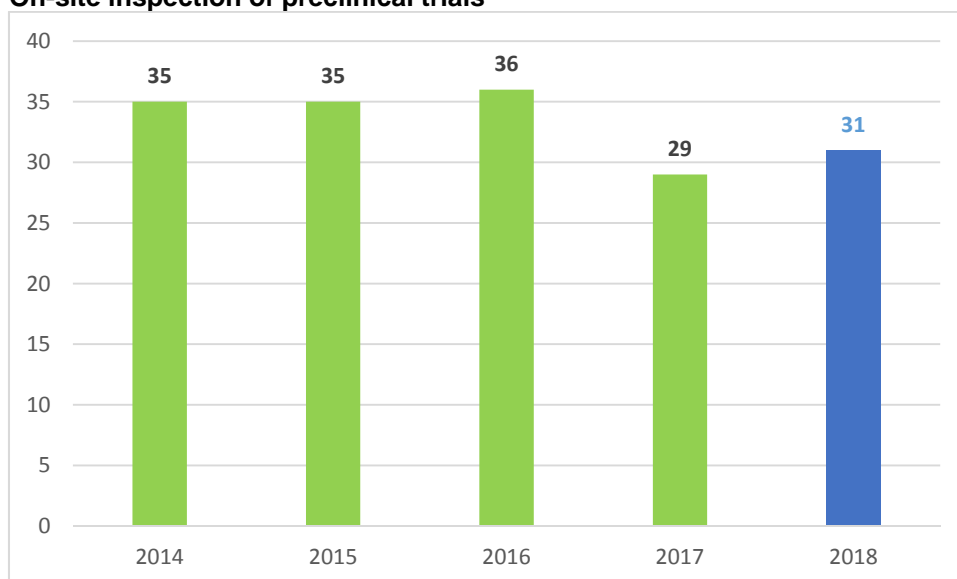
ANSM inspects sites where clinical trials are conducted, including healthcare facilities, authorised research sites, and more. It also inspects the facilities of the sponsors of this research and the subcontractors who work for these sponsors (“CRO”). These inspections focus on the safety and rights of the individuals participating in the trials and on the verification of the quality and credibility of the data obtained from the trials.

Clinical best practice constitutes the primary guidelines for medicine trials.

A special part of the inspections conducted as part of MA request assessments focuses on bioequivalence studies for generic medicines.

### 2018 DATA

#### On-site inspection of preclinical trials



#### Inspection of clinical trials

	2014	2015	2016	2017	2018
On-site inspections	47	33	38	41	37
• in France	32	18	28	32	26
• outside of France	15	15	10	9	11
Injunctions/Formal notices	1	0	0	1	0
Dossiers forwarded to the judicial authorities	1	1	1	2	0

## Medicine and starting material inspection

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

Inspecting pharmaceutical facilities makes it possible to verify their compliance with laboratory best practice, wholesale distribution best practice with respect to medicine manufacturing and distribution conditions, and pharmacovigilance best practice.

ANSM also works to prevent the marketing of falsified products and provides information to consumers about this issue.

Facilities that manufacture, import, and distribute active substances are subject to ANSM's authorisation scheme. Facilities that perform these same activities for excipients are subject to a report-based scheme.

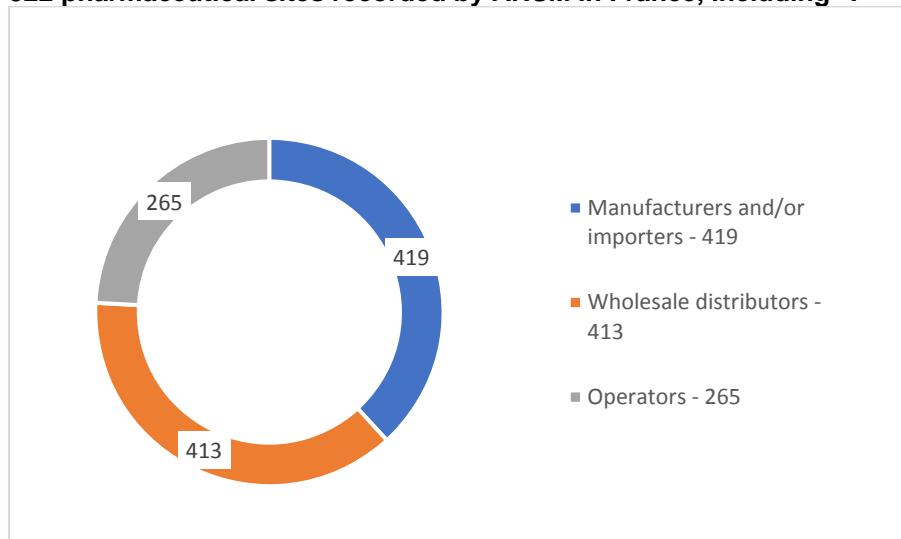
The goal of these inspections is to verify the facility's compliance with manufacturing best practice and distribution best practice.

### HIGHLIGHTS IN 2018

- **ANSM took part in Operation PANGEA**, working alongside other investigation services in order to combat the illegal sale of medicines on the internet (October 2018).
- **Publication of a FAQ document** that provides additional information about chapter four of the new version of pharmacovigilance best practice and the role of the MA holder and owner (June 2018).

### 2018 DATA

922 pharmaceutical sites recorded by ANSM in France, including<sup>28</sup>:



- **328** sites with the exclusive status of wholesale distributor inspected for ANSM by Regional Health Agencies.  
The other sites are inspected by ANSM directly.
- **Over 750** manufacturing, distribution, and import sites specialising in pharmaceutical starting materials recorded by ANSM in France.

<sup>28</sup> Some sites have several statuses.

- **43** authorisations for opening pharmaceutical sites delivered (48 in 2017).
- **110** authorisations for modifying pharmaceutical sites delivered (133 in 2017).
- **238** medicine-related inspections conducted by ANSM in France and abroad (i.e. 35% of the total number of inspections).
- **227** pharmaceutical sites located in France inspected by ANSM.

On the basis of these inspections and those conducted by regional health authorities, 25 sites received a letter warning of an injunction, and 24 were the subject of an injunction. In addition, one pharmaceutical site was the subject of a decision to totally or partially suspend their operating authorisations.

- **90** inspections in France related to starting materials for pharmaceutical use
- **20** abroad, or **18%** of the total number of inspections.

#### Inspection of starting materials facilities

	2014	2015	2016	2017	2018
On-site inspections	104	87	96	98	<b>110</b>
• in France	80	70	81	81	<b>90</b>
• outside of France	24	17	15	17	<b>20</b>
Injunctions	1	3	2	3	<b>3</b>
Health policy decisions or manufacturing best practice non-compliance ruling	4	5	2	0	<b>2</b>
Dossiers forwarded to the judicial authorities	0	0	0	0	<b>0</b>

#### Pharmaceutical site inspections

(Operators, manufacturers, importers, and distributors)

	2014	2015	2016	2017	2018
On-site inspections	245	201	209	231	<b>238</b>
• in France	227	186	191	211	<b>227</b>
• outside of France	18	15	18	20	<b>11</b>
Injunctions	9	10	19	19	<b>24</b>
Health policy decisions/suspensions	6	6	4	1	<b>1</b>
Dossiers forwarded to the judicial authorities	3	2	5	4	<b>1</b>

#### Administrative site management

	2014	2015	2016	2017	2018
<b>Pharmaceutical sites</b>					
Operating authorisations	41	56	59	48	<b>43</b>
Closure decisions	46	72	70	60	<b>44</b>
Certificates of compliance with GMP for medicines issued following inspection	226	168	267	288	<b>197</b>
<b>"Starting material" sites</b>					
Certificates of compliance with manufacturing best practice for pharmaceutical starting materials issued following inspection	118	93	61	111	<b>79</b>

#### Inspection of pharmacovigilance systems

	2014	2015	2016	2017	2018
On-site inspections	18	7	27	29	<b>27</b>
• in France	18	7	27	29	<b>27</b>
• outside of France	0	0	0	0	<b>0</b>
Injunctions	2	3	5	0	<b>3</b>
Dossiers forwarded to the judicial authorities	0	0	0	0	<b>0</b>

## Focus on: ANSM takes steps to curtail “short-liners”

Wholesaler distributors, or pharmaceutical sites that purchase and store medicines for the purpose of distributing them on a wholesale basis, must fulfil public service obligations (PSOs). To this end, they must:

- have an assortment of products that includes at least nine-tenths of the medicines currently marketed in France,
- deliver any order to the pharmacies within their area of distribution within 24 hours,
- have an inventory corresponding to at least two weeks' worth of the products their client base consumes,
- take part in an on-call system on the weekend (Saturday after 2:00 p.m.) and during holidays.

These obligations are underpinned by the fact that these sites must provide retail pharmacies with an appropriate and continuous supply in order to meet the needs of patients in France.

Moreover, wholesale distributors cannot sell their products outside of France or to wholesale distributors that export their products until they have fulfilled their PSOs.

However, despite these obligations, some wholesale pharmaceutical distributors, called “short-liners”, use their operating licenses to purchase an inventory of medicines made up of a very limited assortment of products, then resell these medicines to wholesale distributors within the European Union. In doing so, they restrict the product inventory available to patients in France and increase the risk of shortages in the country. This flow of medications, which is a product of legal and parallel trade within the European Union, has developed over the past few years due to the cheaper cost of medications in France.

Based on observations made during inspections, which are overseen by regional health authorities according to national control guidelines, ANSM implemented stricter measures for these facilities, including:

- increased vigilance over the quality and completeness of dossiers submitted as part of the operating license application process,
- the publication on its website of an opinion concerning head pharmacists of wholesale distributors that details proper operating and start-up procedures for distribution operators,
- the start of systematic site inspections during the first year of operation to verify that commitments the head pharmacist made during the operating licence request process are being fulfilled,
- administrative procedures, including injunctions, health policy rulings, and
- financial sanctions.

## Inspection of blood products and other biological products

The preparation, import, and storage of products derived from the human body (blood products, tissue, cells, and breast milk) and other biological products (microorganisms and toxins) are regulated by an accreditation scheme or 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.

### BREAST MILK FOR THERAPEUTIC USE

Breast milk for therapeutic use is supplied by breast milk banks.

The order of 1 September 2005 made ANSM the competent authority in charge of breast milk collected and treated by breast milk facilities and prescribed by a doctor as a healthcare product to care for extremely premature infants.

ANSM oversees the technical appraisal of breast milk bank operating authorisation applications, which are issued by Regional Health Agencies.

It also carries out inspections to ensure the facilities' compliance with ANSM's best practice guidelines.

### AUTHORISATION SCHEME FOR HIGHLY PATHOGENIC HUMAN TOXINS AND MICRO-ORGANISMS

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 storage, use, interfacility transfer, import, and export of certain agents responsible for infectious diseases and pathogenic microorganisms/toxins (MOTs) require authorisation from ANSM. Authorisation is provided once biological safety and security risks have been evaluated.

The inspections seek to verify that the operations carried out within laboratories comply with authorisations granted by ANSM and that the facilities operate in full compliance with biological safety and security control requirements.

ANSM also monitors licenced 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 concern the loss or theft of MOTs, incidents, accidents, and more generally, any event that could potentially result in the spread of MOTs.

### HIGHLIGHTS IN 2018

- **Revision of the decision establishing the content of the operation authorisation request dossier** (production, manufacturing, transportation, import, export, detention, supply, transfer, acquisition, and use) regarding toxins and microorganisms after consulting with stakeholders from the sector during an informational day hosted at the agency in October 2017 (decision of 10 January 2018).



## 2018 DATA

### Inspection activities for blood products and biological products

	2014	2015	2016	2017	2018
Inspection activities for gene/cell therapy units and tissue banks	26	22	37	28	26
Inspection activities for labile blood products	41	38	26	17	27
Inspection activities for breast milk banks	12	16	15	7	10
Injunctions	2	1	5	5	6
Health policy decisions/suspensions	0	1	0	0	2
Dossiers forwarded to the judicial authorities	0 <sup>29</sup>	0	0	0	0

### Management of sites producing or distributing blood products and other biological products

	2014	2015	2016	2017	2018
<b>Gene/cell therapy units, tissue banks, and sites producing advanced therapy medicinal products prepared on a non-routine basis (MTI-PP in French)</b>					
Authorisations and renewals	8	9	30	38	5
Modifications	17	22	23	50	111
Closures	3	5	2	4	0
<b>Labile blood products</b>					
Authorisations and renewals	0	2	0	3	13
Modifications	43	32	30	36	50
Closures	0	0	0	0	0

### Breast milk bank surveillance

	2014	2015	2016	2017	2018
Number of dossiers examined	4	1	26	3	3

### Toxins and microorganisms

	2014	2015	2016	2017	2018
<b>Authorisation application appraisal</b>					
Total number of MOT authorisations granted during the year	899	1,236	662 <sup>(1)</sup>	827	1,069
Authorisation suspensions	0	0	0	0	0
Health policy rulings	1	1	0	0	0
<b>Laboratories and sites</b>					
Number of entities (teams working within the site)	138	NA	138	141	130
Number of facilities	102	NA	110	109	112
Number of MOT authorisation holders	153	161	152	146	129
Total number of inspections performed per year	21	28	32	30	33
Number of dossiers forwarded to the judicial authorities (excluding consignment)	1	2	1	1	0

(1) The issuance of multiple authorisations sanctioning several types of operations was systematised in 2016, notably for MOT transfers (handovers, imports, and exports).

<sup>29</sup> The 2017 annual report contained an error: the number of dossiers forwarded to the judicial authorities in 2014 was 0 and not 2.

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

ANSM inspects the various stakeholders involved in the medical device (MD) and *in vitro* diagnostic medical device (IVDMD) sector, including notified bodies, manufacturers, agents, and distributors, to ensure they follow all applicable regulatory requirements. There are around 2,500 such companies.

Given the large number of products and stakeholders, an annual or multiyear topical inspection campaign schedule is followed. In 2018, it focused on wrinkle fillers, devices designed to treat prolapse and urinary incontinence, dental implants, and class III MD manufacturers.

### HIGHLIGHTS IN 2018

- **Transfer of LNE/G-MED accreditations as a body in charge of certification procedures** involving the marketing of MDs and IVDMDs to its newly created subsidiary, GMED SAS, by decision of ANSM's Director General (20 July 2018). The organisation was able to keep the same notified body ID number after the transfer process (NB 0459).

### 2018 DATA

- **106 inspections related to MDs, medical device vigilance, and IVDMDs, i.e. 16% of the total number of inspections.**
- **8 sites operating in the MD sector and 3 from the IVDMD sector received an injunction.**
- **3 health policy rulings** involving the suspension or withdrawal of products **were adopted.**

In addition to inspecting industrial operators, ANSM also oversees and monitors the notified body in France. To this end, three inspections of LNE/G-MED (medical certification body) were conducted in 2018. ANSM inspectors participated in the joint evaluation of another European notified body.

### Manufacturers' inspections

	2014	2015	2016	2017	2018
<b>Medical devices (excluding medical device vigilance)</b>					
Inspections	74	77	79	79	<b>73</b>
• in France	63	63	68	69	<b>64</b>
• outside of France	11	14	11	10	<b>9</b>
Injunctions	8	7	9	9	<b>8</b>
Health policy rulings	6	7	2	4	<b>3</b>
Dossiers forwarded to the judicial authorities	2	0	1	0	<b>0</b>
<b><i>In vitro</i> diagnostic medical devices</b>					
Inspections	36	39	44	33	<b>19</b>
• in France	33	37	44	32	<b>18</b>
• outside of France	3	2	0	1	<b>1</b>
Injunctions	5	7	8	7	<b>3</b>
Health policy rulings	2	3	0	0	<b>0</b>
Dossiers forwarded to the judicial authorities	1	2	0	0	<b>0</b>
<b>Medical device vigilance system inspection</b>					
	2014	2015	2016	2017	2018
On-site inspections	9	15	17	20	<b>14</b>
• in France	8	12	17	19	<b>13</b>
• outside of France	1	3	0	1	<b>1</b>
Injunctions	1	3	2	0	<b>2</b>
Dossiers forwarded to the judicial authorities	0	0	0	0	<b>0</b>

## Inspection of cosmetic products

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 representatives in charge of bringing these products to market to verify the following:

- applications justifying the products' marketing (product information application);
- manufacturing, distribution, import, and export practices for products and their compliance with European cosmetics regulations, especially manufacturing best practice.

Given the large number of products and stakeholders, an annual or multiyear topical inspection campaign schedule is followed. The 2018 campaign focused on cosmetic products used by beauty professionals.

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

### 2018 DATA

- **32 inspections involving the cosmetics sector in France.**
- **16 manufacturers received a compliance injunction.**

#### Cosmetic product site inspections

	2014	2015	2016	2017	2018
Inspections	32	32	36	26	<b>32</b>
Injunctions	9	9	8	9	<b>16</b>
Health policy rulings	0	1	1	1	<b>0</b>
Dossiers forwarded to the judicial authorities	0	0	1	0	<b>0</b>

# QUALITY CONTROL OF HEALTH PRODUCTS IN THE LABORATORY

Laboratory testing conducted by ANSM's teams provides an independent technical and scientific evaluation of the quality of health products and their safe use.

In this area, ANSM's main tasks are:

- Releasing batches of vaccines and blood-derived medicines before they are brought to market<sup>30</sup>.
- Conducting laboratory controls for all health products as part of scheduled or “emergency” market surveillance measures, which can be requested by various bodies (internal or external to ANSM) and particularly in the context of an HRS.
- Contributing to the work of the European Pharmacopoeia in developing new monographs by conducting laboratory analyses and participating in different strategic working groups.
- Taking part in numerous collaborative studies on a national scale and, as is most often the case, on a European or even international scale.
- Helping to implement the new European regulation on medical devices.

ANSM plays a key role within the European network of OMCLs, which is headed up by the European Directorate for the Quality of Medicines (EDQM).

## HIGHLIGHTS IN 2018

- Significant involvement by ANSM in the development of methods and **control of starting materials and finished products containing active ingredients from the sartan family** (angiotensin II receptor antagonist) following an alert regarding the contamination of certain sources with nitrosamines<sup>31</sup>. Involvement on a European level in collaboration with the EMA and EDQM.
- **New analyses of the medication Levothyrox** (following the change in its formula that took place in 2017) demonstrating its excellent pharmaceutical quality.
- **An investigation into the quality of mobile diffusers in partnership with the Medical Device, Cosmetics, and *In Vitro* Diagnostic Medical Device Division** in response to claims. Their quality, and especially their flow rate, was generally found to be satisfactory.
- **Organisation of the release of the Mosquirix vaccine** (malaria + hepatitis B) and the Tetravac vaccine.
- **Close involvement in the biotechnology sector**: appointment of the Controls Division as project manager for the study on etanercept biosimilars.

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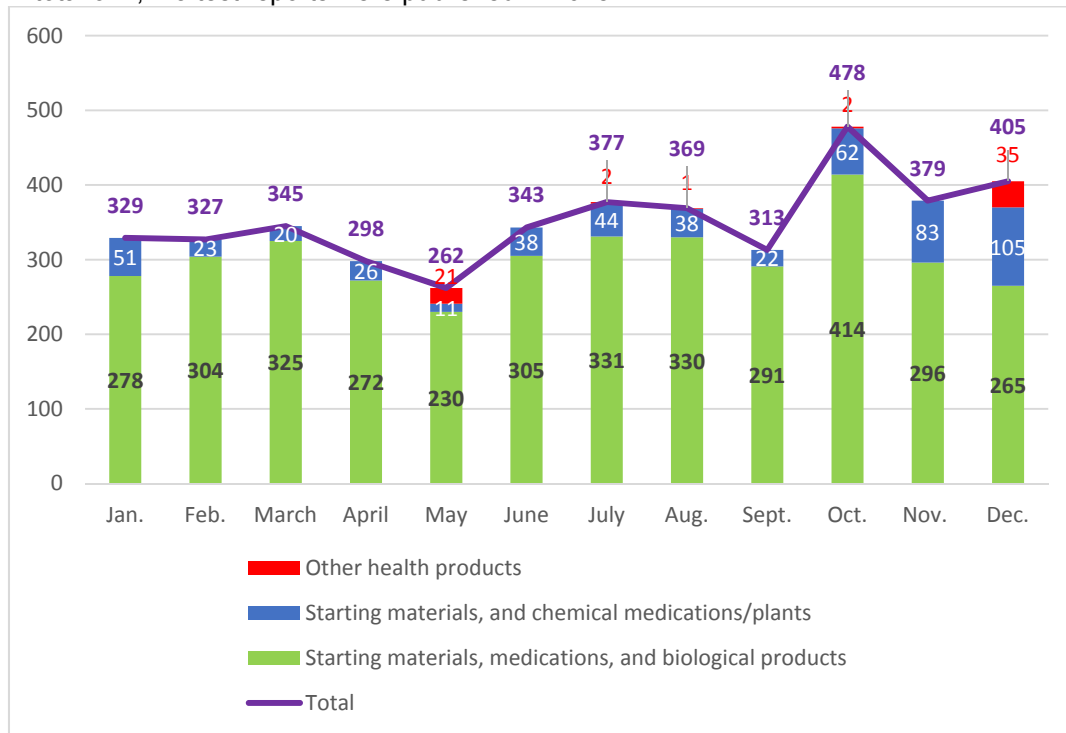
<sup>30</sup> See also “Releasing batches of vaccines and blood-derived medicines”, p. 119.

<sup>31</sup> See also the focus on “Quality defects in sartan-based medicines”, page 45.

## 2018 DATA

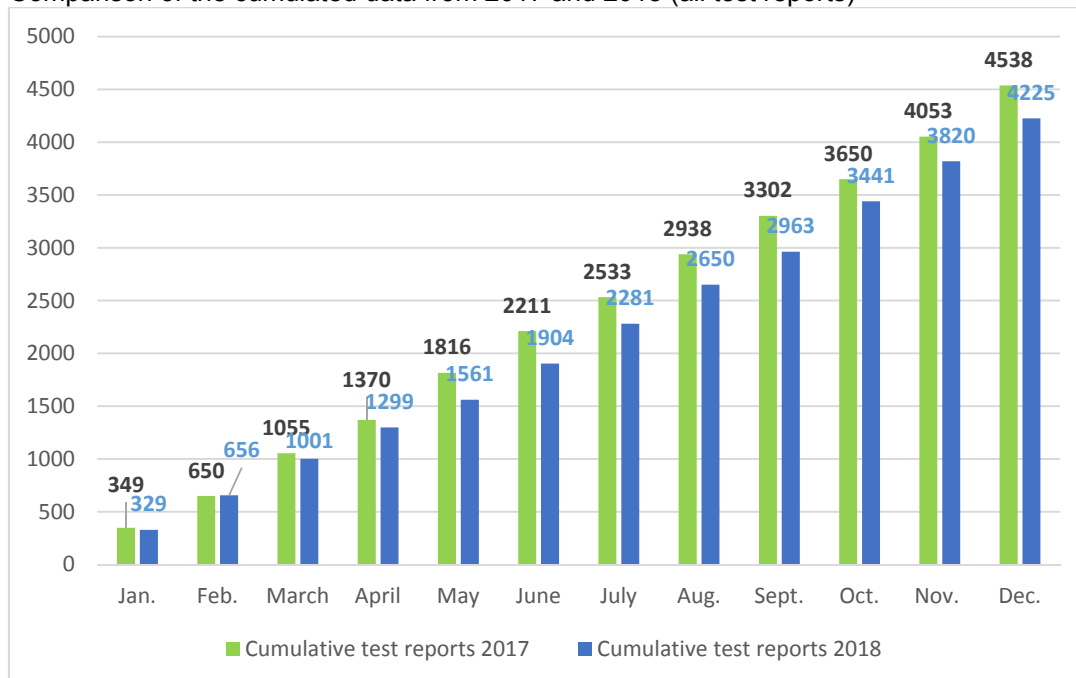
### Test reports – 2018

A total of 4,225 test reports were published in 2018



### Test reports

Comparison of the cumulated data from 2017 and 2018 (all test reports)



The decrease in the number of test reports in 2018 compared to 2017 is related to the significant slowdown in requests for the release of blood-derived medicines<sup>32</sup>.

<sup>32</sup> See also the focus entitled “Extremely limited supply of blood-derived medicines produced by LFB Biomédicaments”, page 54.

## Quality control of medicines and biological products

Laboratory controls conducted as part of market surveillance efforts for biological products and medicines take two forms: scheduled investigations, which are based on a prior risk analysis, and controls that are done on an emergency basis.

### SCHEDULED INVESTIGATIONS

Prior risk analyses are conducted using 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 only authorised in France.

The samples come directly from pharmaceutical companies at the request of ANSM or are taken by ANSM inspectors at the premises of a finished product or starting material manufacturer (in France or outside of France).

A large number of generic medicines are controlled, irrespective of their MA procedure.

All investigations are followed by detailed reports that are shared with all relevant ANSM departments.

It is important to note that these investigations were recently changed. The selection of the products chosen for testing has been optimised to avoid testing identical products that have a different appearance or name, and they now include a more targeted analysis involving specific parameters.

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.

### EMERGENCY CONTROLS

Emergency controls take place in response to a suspected quality defect found during inspections, referrals from judicial authorities, and reports by health professionals or users.

### HIGHLIGHTS IN 2018

- **Significant involvement in the control of European medicines**, including the analysis of 157 medicines as part of the EMA's programme or on a joint basis with the OMCL network.
- **Control of several groups of generics**, especially those including new medicines with indications related to the central nervous system (triptans, antiparkinson agents, antiepileptics, etc.).
- **An exhaustive investigation** into the quality of parenteral solutions with MAs: 83 products were tested for their microbiological quality, which was found to be compliant, and another panel was tested for aluminium.
- **Three biowaver studies conducted as part of the MA application process** at the request of the Generics Division.
- **Comparative study on the stability of medicines containing suxamethonium** (general anaesthesia adjuvant) after a manufacturer found evidence of impurities.
- **Completion of a broad study on 39 raw plant medicines** (powder in gel capsule or herbal tea) demonstrating that their quality was good overall despite the discovery of microbial contamination in one medicine.
- **Study on insulins and EPOs** circulating within the French market: control of a parallel import product, Granocyte.

## 2018 DATA

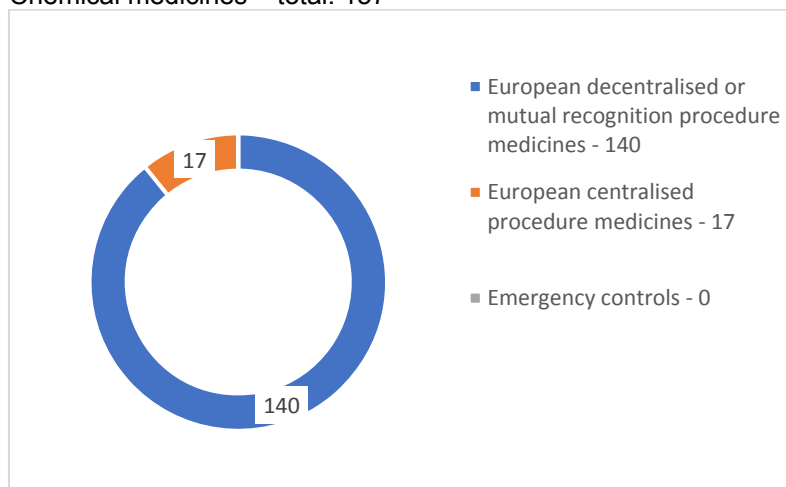
In 2018, the total chemical medicine non-conformity rate was approximately 6% for scheduled controls (including those related to mentions on the label and/or leaflet) and approximately 23% for controls conducted on an emergency basis. Every case of non-conformity is systematically monitored using appropriate follow-up measures.

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

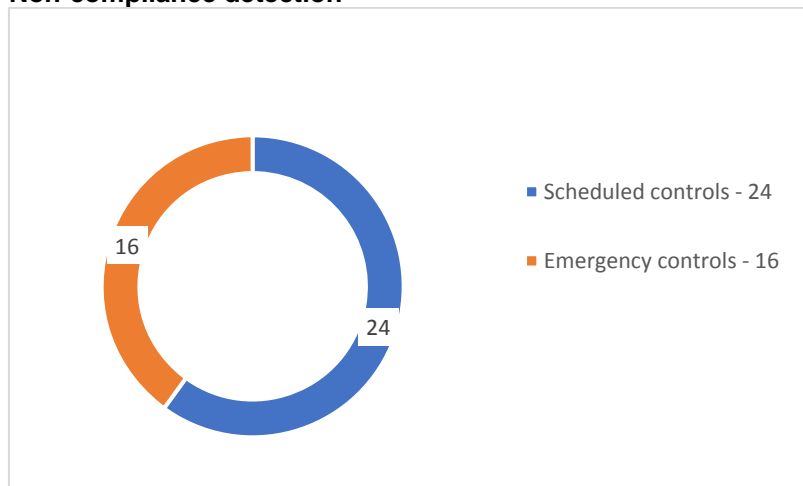
- Participation in European study (MSS) on medicines containing zoledronic acid (following on from the 2017 generic CAP programme).
- Participation in the chemical CAP programme (EMA/EDQM) through the control of three medicines with a centralised marketing authorisation.
- Participation in a collaborative study to implement the first international adalimumab reference (WHO).
- Control of four products from CAP biotechnologies (Repatha, Remsima, Inflectra, and Flixabi).

### Laboratory control in Europe

Chemical medicines – total: 157

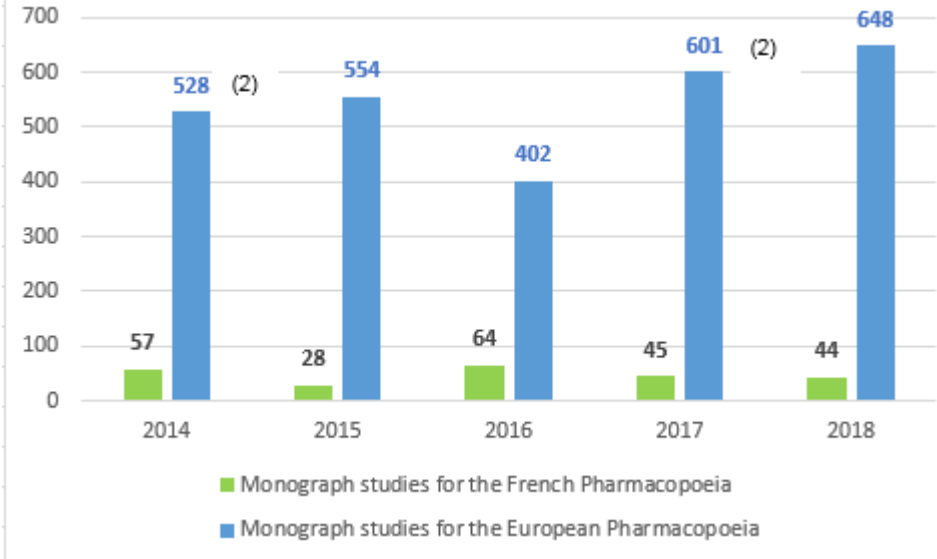


### Non-compliance detection<sup>1</sup>



(1) Including 19 related to package leaflet/labelling problems.

**Pharmacopoeia**



(2) 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 involving medical devices are conducted as part of targeted surveys that are requested by divisions at ANSM (Inspection Division and Products Division) or when there is a suspected quality defect (especially following an inspection).

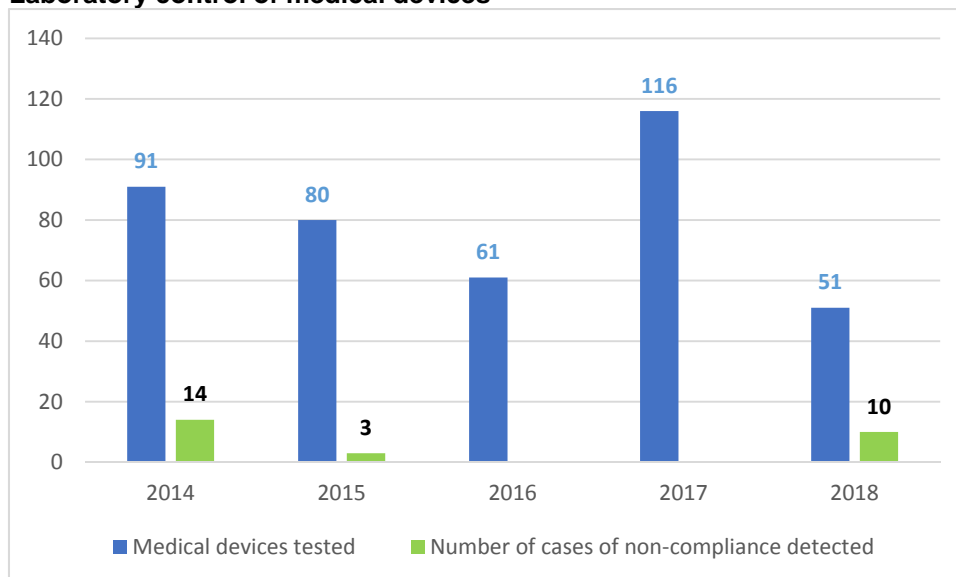
Medical device market surveillance is a key issue at ANSM. The Controls Division would like to improve the agency's ability to conduct controls in close partnership with the *In Vitro* Diagnostic Medical Device Division. An action plan is currently being created.

### HIGHLIGHTS IN 2018

- **In addition to the survey conducted in 2017 on hyaluronic acid-based wrinkle filler products**, analyses were conducted to test for the presence of visible particles in response to a request from the Inspection Division.
- **Investigation into the quality of mobile diffusers**, especially with respect to the advertised flow rate, at the request of the *In Vitro* Diagnostic Medical Device Division.
- **Emergency sterility analysis on 33 liaison tubes** (from two batches) at the request of the *In Vitro* Diagnostic Medical Device Division due to a suspected sterility defect. The results confirmed that some tubes were not sterile, including one that had not yet reached its expiration date.

### 2018 DATA

#### Laboratory control of medical devices



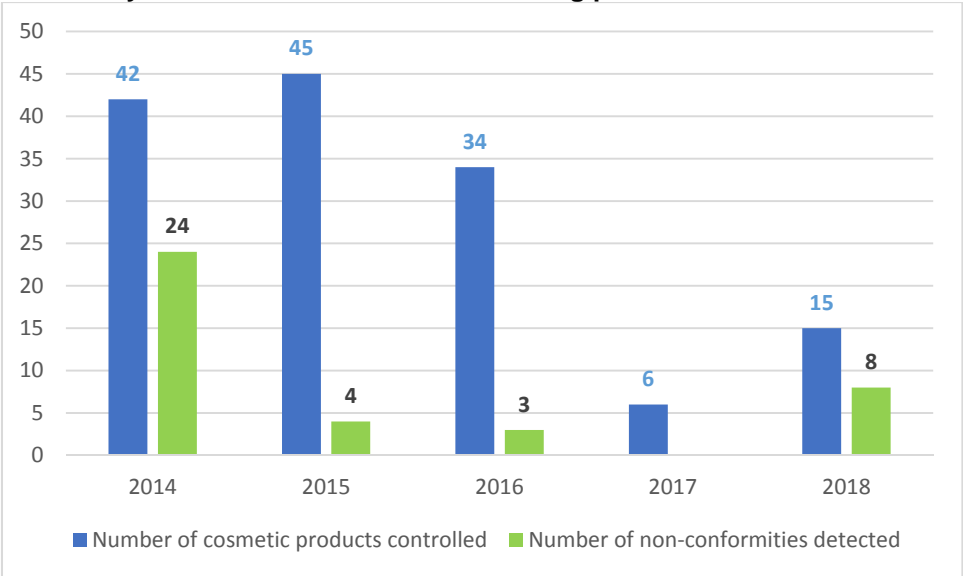
# Laboratory control campaigns for cosmetic products and tattooing products

Laboratory controls involving cosmetic and tattoo products are conducted as part of targeted investigations that are requested by divisions at ANSM (Inspection Division and Products Division) or when there is a suspected quality defect (especially following an inspection).

- HIGHLIGHTS IN 2018**
- **Emergency control of eight batches of Brazilian blowout products at the request of the *In Vitro* Diagnostic Medical Device Division in response to cosmetic product vigilance reports.** The amount of formaldehyde present in these products was found to be compliant with regulations (however, their labelling was found to be non-compliant with these same regulations).

## 2018 DATA

Laboratory controls of cosmetic and tattooing products





## **Part 2**

### **Promoting fast and fair access to innovation for patients**

## Promoting fast and fair access to innovation for patients

<b>Early access to medicines, medical devices, blood products, and other biological products</b>	<b>p. 94</b>
• Scientific opinions	p. 94
• Clinical trials	p. 96
• Temporary authorisations of use	p. 99
• Temporary recommendations for use	p. 103
<b>Marketing authorisations for medicines (MAs)</b>	<b>p. 105</b>
• Procedures for marketing authorisations (MAs)	p. 105
• Access to orphan and paediatric medicines	p. 108
• Generic medicines	p. 110
• Biosimilar medicines	p. 113
• Herbal medicines	p. 117
• Medicine preparations	p. 117
• Authorisation and re-evaluation of homeopathic medicines	p. 118
<b>Releasing batches of vaccines and blood-derived medicines</b>	<b>p. 119</b>
<b>Authorisation of blood products and other biological products</b>	<b>p. 122</b>

# EARLY ACCESS TO MEDICINES, MEDICAL DEVICES, BLOOD PRODUCTS, AND OTHER BIOLOGICAL PRODUCTS

## 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.

The purpose of ANSM's scientific opinions is to facilitate patients' quick access to products that are innovative, represent a major therapeutic advancement, or address a medical need that is not being met, especially with respect to rare diseases or paediatric ailments. This access is free.

In Europe, France represents 5% of the members of the Scientific Advice Working Party (SAWP), i.e. 4/78. These representatives produce 12.4% of European opinions.

**HIGHLIGHTS IN 2018**

- **Appointment of an additional French representative to SAWP, bringing the total number French representatives to four.**

## 2018 DATA

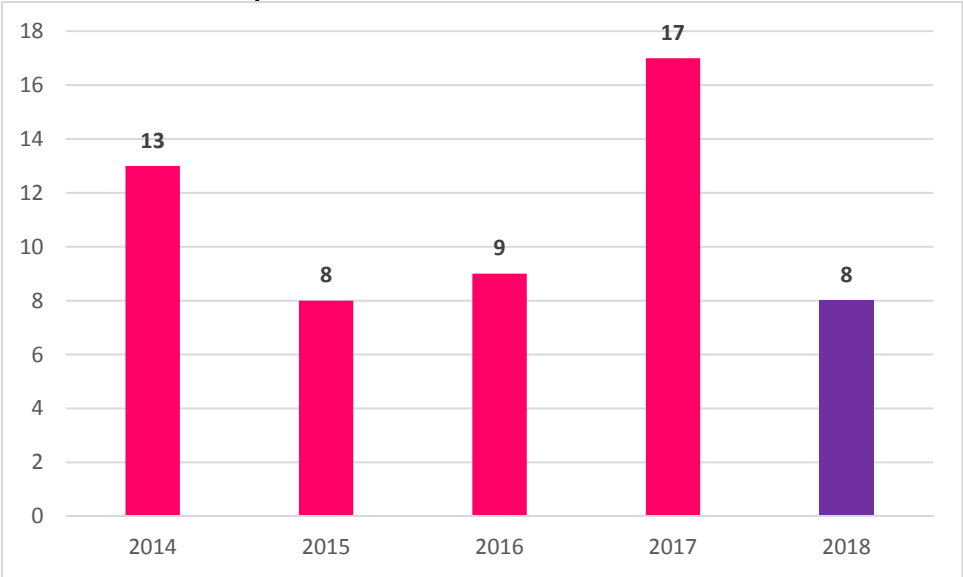
### National opinions

Out of the 8 national opinions issued by ANSM, 3 opinions involved innovative therapies (2 gene therapies, 1 cell therapy), 2 opinions involved rare paediatric diseases, and 3 involved cancer treatment.

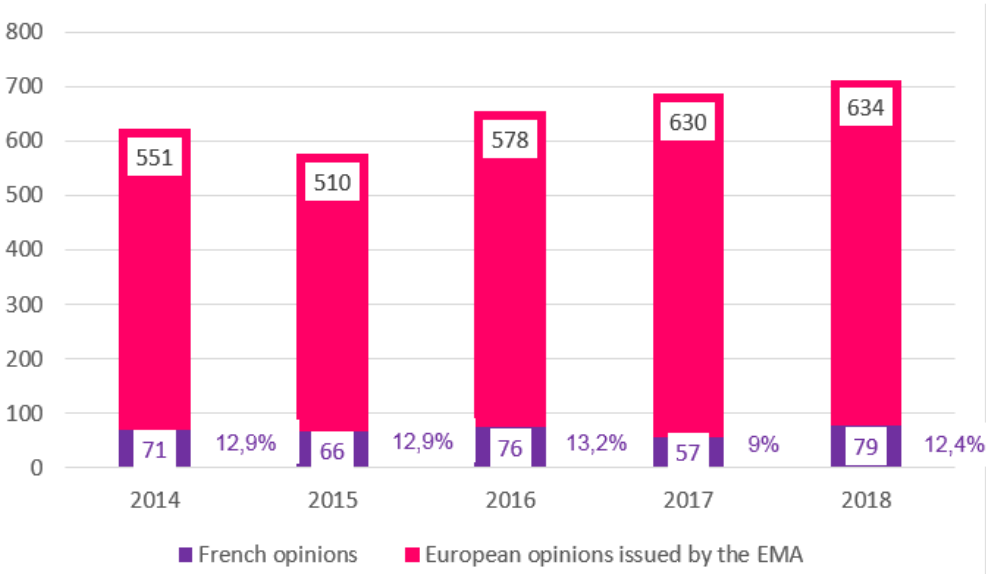
### European opinions

Out of the 79 European opinions in which ANSM participated, 32 opinions involved oncology/haematology, and 25 involved rare genetic diseases (13 neuro-developmental diseases). Out of all the opinions, 25 opinions were related to paediatrics.

### National scientific opinions issued for medicines



**European scientific opinions issued for medicines**



## Clinical trials

ANSM is in charge of authorising clinical trials in France. Regardless 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 trial, as well as the safety of the individuals taking part in these studies.

The agency also 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<sup>33</sup>.

Since 15 October 2018, ANSM has implemented fast track systems, known as Fast Track 1 and Fast Track 2, to shorten clinical trial authorisation processing times and provide patients with access to innovative treatments faster while still guaranteeing their safety<sup>34</sup>.

On a European level, ANSM is involved in the Voluntary Harmonisation Procedure (VHP), a procedure that enables joint evaluation of clinical trial authorisation applications involving medicines by all relevant member states. The objective is to harmonise and facilitate biomedical research in Europe.

### CLINICAL TRIALS IN THE SPECIAL FIELD OF “NON-HEALTH PRODUCTS”

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

### CLINICAL TRIALS FOR 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 human 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 MEDICAL DEVICES AND *IN VITRO* DIAGNOSTIC 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 used for an off-label use. They may also concern clinical trials that require investigations pertaining to a significant risk.

### HIGHLIGHTS IN 2018

- **ANSM implements Fast Track clinical trial authorisation programme** (October 2018).

<sup>33</sup> See also the chapter entitled “Inspection of clinical and non-clinical trials”, page 76.

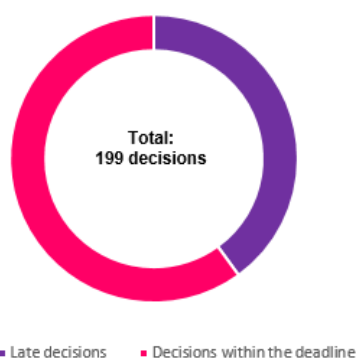
<sup>34</sup> See also the focus entitled “ANSM implements Fast Track clinical trial authorisation programme”, page 101.



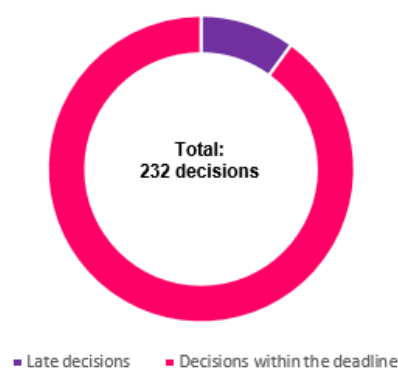
## 2018 DATA

- 14 cell and gene therapy trials authorised (76 substantial amendment requests submitted)
- 83 clinical trial for medical devices authorisations delivered, including six for IVDMD
  - 51% are industrial sponsors
  - 49% are institutional sponsors
- 12 denials issued
- In 2018, 90% of innovative medicine trials and medicines were authorised ahead of the regulatory deadline.  
For medicines:

Last quarter of 2017  
Evaluation average time: 78 days



Last quarter of 2018  
Evaluation average time: 46 days



### Clinical trials for medicines

	2014	2015	2016	2017	2018
Number of authorisations issued (initial applications)	821	928	756	727	741
Number of authorisations issued (substantial amendment applications)	N/A	N/A	N/A	2,682	2,234

### Clinical trials for “non-health products”

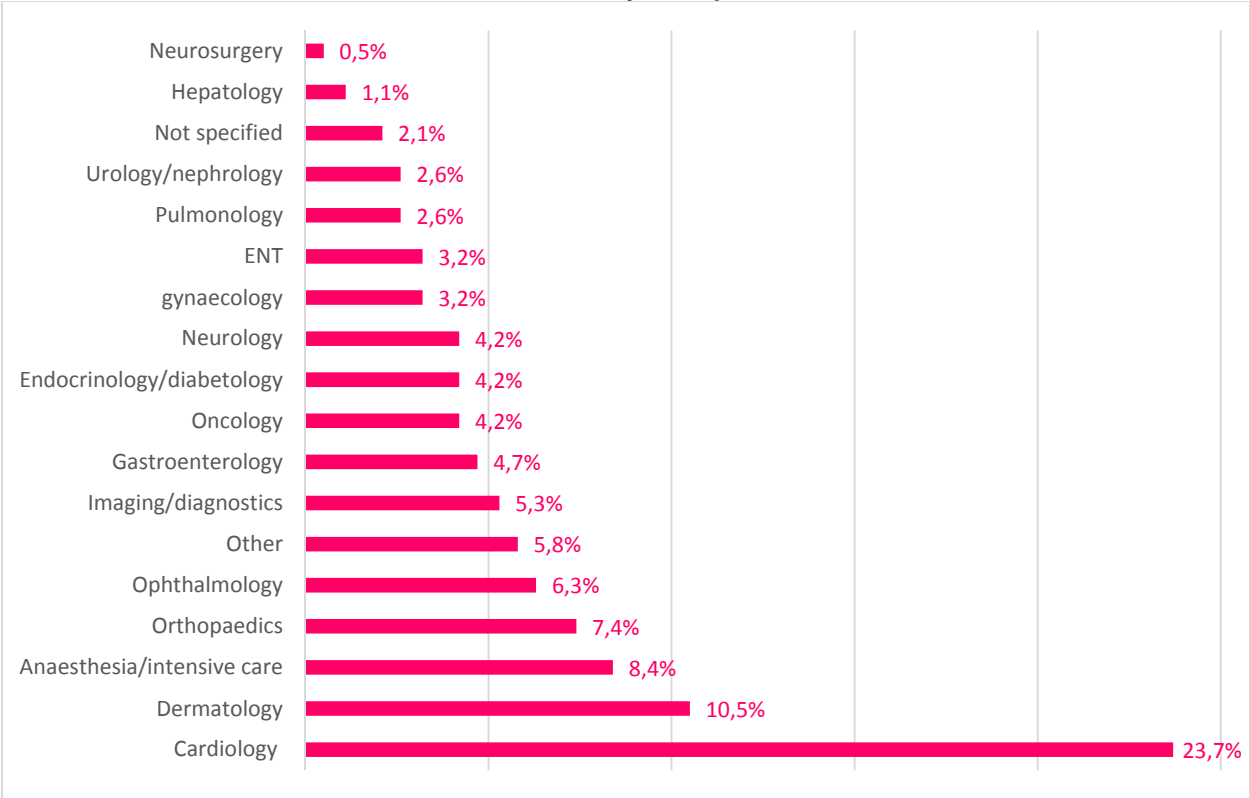
	2014	2015	2016	2017	2018
Number of authorisations issued (initial applications)	690	653	681	165*	190
Number of authorisations issued (substantial amendment applications)	N/A	N/A	N/A	636	485

### MD and IVDMD clinical trial authorisations

	2014	2015	2016	2017	2018
Number of authorisations issued (initial applications)	276	236	227	93	83
Number of authorisations issued (substantial amendment applications)	N/A	N/A	N/A	215	168

\*In 2017, after the introduction of law no. 2012-300 of 5 March 2012 on human research (the Jardé Law), which was amended by order no. 2012-800 of 16 June 2016 and application decree no. 2016-1537 of 16 November 2016 on human research (J.O 17/11/2016), the number of clinical trial authorisation applications for health products and non-health products decreased. In fact, only category 1 application (high-risk interventional research) are now subject to authorisation by ANSM.

**Breakdown of clinical trials for medical devices by therapeutic field**



## Temporary authorisations for use

A Temporary Authorisation for Use (TAU) is an exceptional, special procedure, which, since 1994, has given numerous patients that have no available alternative treatment access to medicines that do not have an MA in France.

ANSM delivers TAUs under the following conditions:

- medicines designed to treat, prevent, or diagnose serious or rare diseases,
- when there is no suitable treatment available on the market,
- the effectiveness and safe use of the medicine are assumed and the start of treatment cannot be delayed.

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).

### HIGHLIGHTS IN 2018

- **Application of new processing methods for named-patient TAUs** (September 2018)<sup>35</sup>.
- **Gene therapy: early access to advanced therapy medicinal products known as “CAR T-cells” for the treatment of certain blood cancers** - issuance of two cohort TAUs (July 2018).

### 2018 DATA

#### Summary of named-patient TAUs

	2014	2015	2016	2017	2018
Named-patient TAUs issued	25,521	24,791	27,095	22,295	<b>21,633</b>
Medicines made available per year	208	219	205	253	<b>217</b>
Patients included	18,831, including 12,822 treatment initiations	17,829, including 12,175 treatment initiations	19,625, including 14,029 treatment initiations	16,621, including 11,390 treatment initiations	<b>15,987, including 11,342 treatment initiations</b>

#### Summary of cohort TAUs

	2014	2015	2016	2017	2018
New substances that have obtained a cohort TAU	25	13	10	11	<b>20</b>
Medicines under cohort TAUs that have received an MA	24	12	9	8	<b>16</b>
Newly included patients	12,111	10,216	11,909	8,250	<b>5,642</b>

<sup>35</sup> See also the focus entitled “ANSM implements new processing methods for named-patient TAUs”, page 101.

## List of proprietary medicines that were granted a cohort TAU in 2018

In 2018, 26 proprietary medicines corresponding to 20 active substances received authorisation through a cohort TAU, including 13 new substances in the field of haematology and oncology

PROPRIETARY MEDICINE	Active substance
APALUTAMIDE 60 mg, film-coated tablet	apalutamide
ATGAM 50 mg/ml, solution for dilution for infusion	equine anti-human thymocyte immunoglobulin
BRIGATINIB 30 mg, film-coated tablet BRIGATINIB 90 mg, film-coated tablet BRIGATINIB 180 mg, film-coated tablet	brigatinib
CAPLACIZUMAB 10 mg, powder and solvent for solution for injection	caplacizumab
CRYSVITA 10 mg, solution for injection CRYSVITA 30 mg, solution for injection	burosumab
DURVALUMAB 50 mg/ml, concentrate solution for infusion	durvalumab
EMICIZUMAB 30 mg/ml, solution for injection EMICIZUMAB 150 mg/ml, solution for injection	emicizumab
KYMRIAH 1.2 x 10 <sup>6</sup> – 6 x 10 <sup>8</sup> cells, dispersion for perfusion	tisagenlecleucel
LORVIQUA 25 mg, film-coated tablet LORVIQUA 100 mg, film-coated tablet	lorlatinib
LUXTURNA 5 x 10 <sup>12</sup> vector genomes/ml, injection solution for dilution	voretigene neparvovec
MYALEPTA 11.3 mg, powder for solution for injection	metreleptin
PATISIRAN 2 mg/ml, solution for dilution for infusion	patisiran
POTELIGEO 4 mg/ml, solution for dilution for infusion	mogamulizumab
TAKHZYRO 300 mg/2 ml, solution for injection	lanadelumab
TEGSEDI 248 mg/1.5 ml, solution for injection for pre-filled syringe	inotersen
URSOFALK 250 mg/5ml, oral suspension	ursodeoxycholic acid
VONVENDI 650 UI, powder and solvent for solution for injection VONVENDI 1300 UI, powder and solvent for solution for injection	vonicog alfa, recombinant human vW factor
VYXEOS 44 mg/100 mg, concentrate powder for solution for infusion	daunorubicine-cytarabine
YESCARTA 1 x 10 <sup>6</sup> - 2 x 10 <sup>6</sup> cells/kg, dispersion for infusion	axicabtagene ciloleucel

## Focus on: ANSM implements Fast Track clinical trial authorisation programme

To offer patients faster access to innovative treatments, the ANSM has set up two Fast Track options that shorten clinical trial authorisation processing times without compromising patient safety.

This new system, which was launched on 15 October 2018, handles clinical trials for innovative treatments (Access to innovation => Fast Track 1) and new trials concerning known molecules (Support for development => Fast Track 2).

Fast Track processing times will not exceed 25 or 40 days, depending on the type of trial, whereas current regulations call for 60 days.

This new system also aims to prepare ANSM for greater responsiveness in view of upcoming European regulations on clinical trials—coming into effect no later than 2020—and improve the quality and safety of the clinical trials proposed in submitted applications.

Starting on 18 February 2019, this system will also be open to clinical trials involving a complex design and trials on advanced therapy medicinal products.

## Focus on: ANSM implements new processing methods for named-patient TAUs

As part of its modernisation and transparency programme, ANSM decided to overhaul its system for processing named-patient temporary authorisations of use (TAUs).

In September 2018, a single service was created for healthcare professionals to make requests and exchanges simpler.

ANSM also published a directory on its website of the medicines that received a named-patient TAU along with, in most cases, the criteria that led to the fast issuance of these named-patient TAUs. These criteria stem from clinical situations that practitioners often encounter.

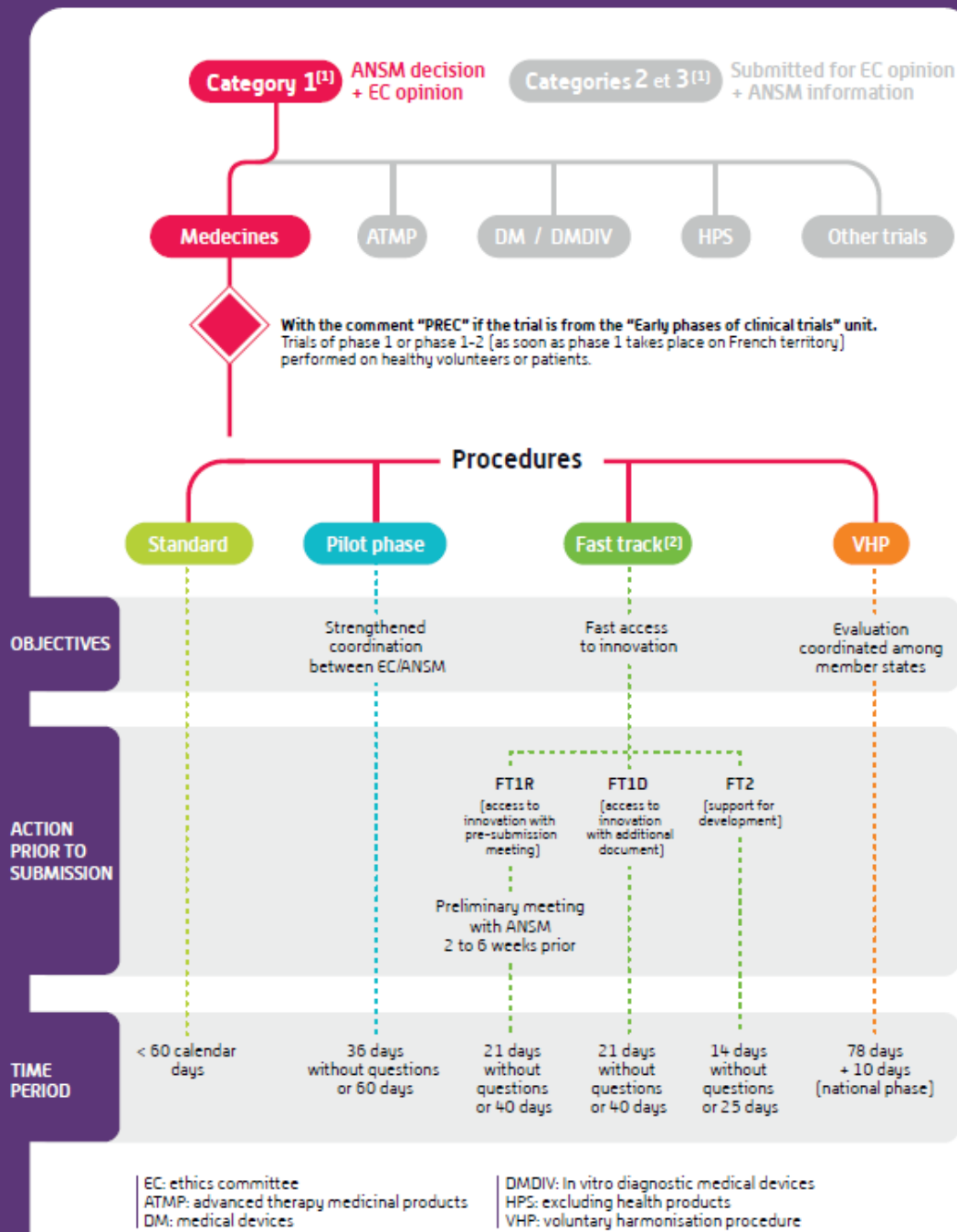
When submitting a request (treatment initiation or renewal), healthcare professionals can now agree to follow the posted granting criteria in accordance with the patient's clinical situation. Requests that include this commitment are processed more quickly.

Finally, in March 2019, an online application, e-Saturne, was created for healthcare professionals to allow them to submit named-patient TAU requests remotely (as opposed to by fax) and further simplify exchanges.

The e-Saturne application allows healthcare professionals to submit a name-patient TAU request and receive authorisation completely electronically. It secures all communications between prescribers, pharmacists, and ANSM, and reduces response time, especially for renewal requests.

The goal of this new system is to simplify communications between the agency and healthcare professionals and to guarantee patients fast, transparent, and fair access to innovative treatment. It will become the only process for granting named-patient TAUs starting in January 2020.

## DIFFERENT MANAGEMENT PROCEDURES FOR CATEGORY 1 CLINICAL TRIALS OF MEDICATIONS



[1] **Category 1** research involving the human person (RIPH) according to the Jardé law (art. L. 1121-1 of the CSP): interventional research involving an intervention not justified within the person's usual care. **Category 2** RIPH: interventional research involving only minimal risks and constraints. **Category 3** RIPH: non-interventional research involving neither risks nor constraints, in which all actions are performed and all products are used in the usual way.

[2] Eligibility based on defined criteria.

## Temporary recommendations for use

Since 2011, the temporary recommendations for use (TRU) procedure has been used to manage prescriptions of proprietary medicines outside of their indications or conditions of use as defined in their MAs.

The TRU is granted to meet a therapeutic need if there is sufficient data for ANSM to presume the medicine would have a favourable risk/benefit ratio for the indication or conditions of use under consideration.

TRUs last for a period of three years. They can be renewed and are paired with a laboratory-organised patient support programme.

Since the programme was created, ANSM has granted 25 TRUs.

### HIGHLIGHTS IN 2018

- **Application of three Temporary Recommendations for Use (TRU) for an adjuvant melanoma therapy (August 2018).**

## FOCUS ON: Evaluation of the relevance and feasibility of making medical cannabis available in France

On 10 September 2018, ANSM created a Temporary Specialist Scientific Committee (TSSC) with a mandate of one year in order to evaluate the relevance and feasibility of making medical cannabis available in France.

This committee comprises experts chosen for their skills in a variety of fields, including pharmacology, neurology, oncology, pain treatment, human sciences, and medical ethics. Healthcare system users were also appointed to the committee.

The three sessions of this TSSC that took place between September and December 2018 allowed the committee to summarise the current state of medical and scientific knowledge regarding the risks and benefits of cannabis, hear from the various stakeholders and collect testimony and perspectives from healthcare professionals and patient representatives, and review the use of medical cannabis in certain European countries like Germany and the Netherlands, where similar policies are already in place. These hearings were filmed and are available on ANSM's YouTube channel.

The TSSC issued the first half of its conclusions in December. It found that it was pertinent to authorise the use of medical cannabis for patients in certain clinical situations and in cases in which other available therapies, whether or not they are medications, do not provide sufficient pain relief or are not tolerated by the patient.

The experts approved the use of medical cannabis for the following treatment scenarios:

- for pain that is not controlled by other therapies (involving medication or not),
- for certain forms of severe epilepsy that is not controlled by medication,
- as a supportive cancer therapy,
- in palliative situations,
- For painful spasticity caused by multiple sclerosis.

The committee immediately ruled against administration through smoking due to the health risks associated with this method.

ANSM agreed with these conclusions.

The TSSC will continue its work in 2019 and will issue an opinion on treatment and follow-up methods. In this part of its conclusions, the committee will define the type of prescriber, administration method, pharmaceutical form, and the dosages and concentrations of the main active ingredients.

Medical cannabis access will first be tested through an exploratory phase in order to fine-tune the framework and, if necessary the methods used for treating and following up patients.



# MARKETING AUTHORISATIONS FOR MEDICINES (MAs)

## Procedures for marketing authorisations (MAs) for medicines

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

### European procedures

- **The centralised procedure** is compulsory for innovative therapies, medicines derived from biotechnologies, advanced therapy medicinal products, containing a new active substance indicated in the treatment of certain diseases (AIDS, cancer, neurodegenerative diseases, 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 patients in the European Union.
  - After the procedure, the MA is issued by the European Commission for all member states.
  
  - **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 the medicine's marketing authorisation is being sought.
  
  - **The mutual recognition procedure** is based on the recognition of an 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 identified by the pharmaceutical company holding the MA.
- ⇒ At the end of the European phase of these last two procedures (decentralised and mutual recognition), the relevant national authorities then issue the MAs in their national language along with the appendices (summary of product characteristics, package leaflet, and labelling).

**The national procedure** applies to medicines that are only authorised within France. Most MA requests submitted through the national procedure are for generic medicines.

ANSM delivers MAs for medicines authorised under the national procedure and medicines authorised under the European procedures, namely the decentralised and mutual recognition procedures. The decisions also specify the prescription and dispensation conditions for the medicine, which are specific to each country.

### HIGHLIGHTS IN 2018

- **Issuance of market authorisation for the use of baclofen in the treatment of alcohol addiction** (October 2018).

## 2018 DATA

**1,162 Mas granted by ANSM in 2018**, (national procedure and European decentralised and mutual recognition procedures) compared to 995 in 2017.

### Medicines authorised at the European level

<b>CENTRALISED PROCEDURES</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>2018</b>
Number of applications submitted	100	111	114	90	<b>84</b>
Applications assigned to France (rapporteur, co-rapporteur, multi-team)	8	10	14	12	<b>16</b>
<b>DECENTRALISED AND MUTUAL RECOGNITION PROCEDURES</b>					
Applications in which France is involved	307	334	320	650	<b>817</b>
Applications for which France was the reference country	18	13	7	7	<b>16</b>

Source: EMA

### Medicines authorised by ANSM

<b>SUMMARY OF MAs AUTHORISED IN FRANCE</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>2018</b>
<b>Decisions regarding MAs<sup>(1)</sup> (MAs granted)</b>	576	507	565	955	<b>1,162</b>
- national MAs	269	168	245	305	<b>345</b>
- MAs granted through the European mutual recognition procedure	36	339	25	44	<b>63</b>
- MAs granted through the European decentralised procedure	271		295	606	<b>754</b>
<b>Modifications<sup>(2)</sup> of MAs (including generics)</b>	6,363	8,507	7,239	4,412	<b>5,470</b>

(1) Data representing the number of proprietary medicines.

(2) French national MAs - Data representing the number of decisions.

## FOCUS ON: Issuance of market authorisation for the use of baclofen in the treatment of alcohol addiction

**In October 2018, ANSM granted a marketing authorisation (MA) for the medication Baclocur (baclofen) for the treatment of alcohol addiction. The evaluation of this MA primarily relied on opinions from independent experts as well as on clinical experience as reported by healthcare professionals and the patients who use this medicine.**

Baclofen is a GABA B receptor agonist and a centrally acting muscle relaxant. Two medications containing baclofen are currently available in France. Lioresal 10 mg and Baclofen Zentiva 10 mg are indicated for the treatment of spastic contractions that are neurological in nature.

In March 2014, based on the results of studies suggesting that baclofen could affect a patient's alcohol addiction and cravings and in response to its growing use among patients, ANSM issued a temporary recommendation for use to better control this treatment method.

In April 2017, the pharmaceutical company Ethypharm submitted an MA request to ANSM for the medication BACLOCUR (baclofen) for the treatment of alcohol addiction. At the time, it was the only MA request ever submitted in Europe for this indication.

In addition to conducting an internal MA evaluation, ANSM contracted an external body to assess the soundness of its decision. ANSM created a Temporary Specialist Scientific Committee (TSSC) to obtain its opinion on the risk-benefit ratio of baclofen in the treatment of alcohol addiction. It also created an *ad hoc* commission. This commission, which comprises the agency's three current consulting commissions, was meant to provide a multi-disciplinary, scientific, and social perspective on the matter, especially through public hearings with healthcare professionals and associations representing patients who use this medicine to treat alcohol addiction.

In October 2018, based on the available data, including clinical experience reported by the various stakeholders involved in the issue, and given the serious public health problem that alcohol represents, ANSM granted an MA to the medicine Baclocur (baclofen) for the treatment of alcohol addiction. ANSM decided to do so to provide an option for patients facing treatment failure and, by extension, help improve public health.

An in-depth monitoring programme will be established as soon as Baclocur is brought to market. Based on this information and the evolution of scientific data, ANSM might revise the conditions of use for baclofen for this indication.

The temporary recommendation of use for baclofen regarding the treatment of alcohol addiction has been extended until Baclocur becomes available on the market.

## 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. They must be registered through the centralised procedure.

Since 2005, in addition to the European policy aimed at developing medicines for the treatment of rare diseases, France has implemented two rare disease plans (2011-2014). Its third plan, which was launched in July 2018, covers the period between 2018 and 2024.

These plans, which ANSM takes part in, play a key role in stimulating, developing, and marketing medicines for rare diseases in France, especially with respect to promoting early access to medicines, research, and innovation.

In the area of paediatrics, France and ANSM 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 and its formulation, depending on the children's age.

Since the implementation of the European Paediatric Regulation in 2007, PIPs have become mandatory, and they must be done before any new MA or MA extension request, regardless of the type of procedure (centralised, decentralised, mutual recognition, or national) except when a PIP exemption has been granted or for certain clinical trial reports with the agreement of the Paediatric Committee (PDCO), before any medication authorisation application is submitted in Europe.

PIP applications and the monitoring process for these applications, as well as other paediatric issues, including scientific opinions, are evaluated by the members of the EMA's Paediatric Committee (PDCO). This committee includes representatives of doctor and patient associations as well as representatives from each member state. France plays a key role in the committee (70 PIPs evaluated in 2018). It actively takes part in several PDCO working groups that directly contribute to evaluating PIPs, including the "Non-clinical working group", which evaluates juvenile pre-clinical studies, the "Formulation Working Group", which focuses on formulation, and the "Modelling and Simulation Working Group".

France takes part in working groups associated with the PDCO and the EMA that focus on neurology, paediatric oncology, and neonatology. It also helps write general recommendations and scientific opinions at European level, both with respect to regulations and specific topics, that play a pivotal role in the development of paediatric medicines. France's contributions in 2018 include the creation of recommendations and scientific opinions related to developments in clinical therapeutic areas (including neuromuscular diseases, epilepsy, and haemophilia) and pharmacovigilance (including recommendations published at the end of 2018 regarding good pharmacovigilance practice in paediatrics).

It also contributed to the European Form.

### HIGHLIGHTS IN 2018

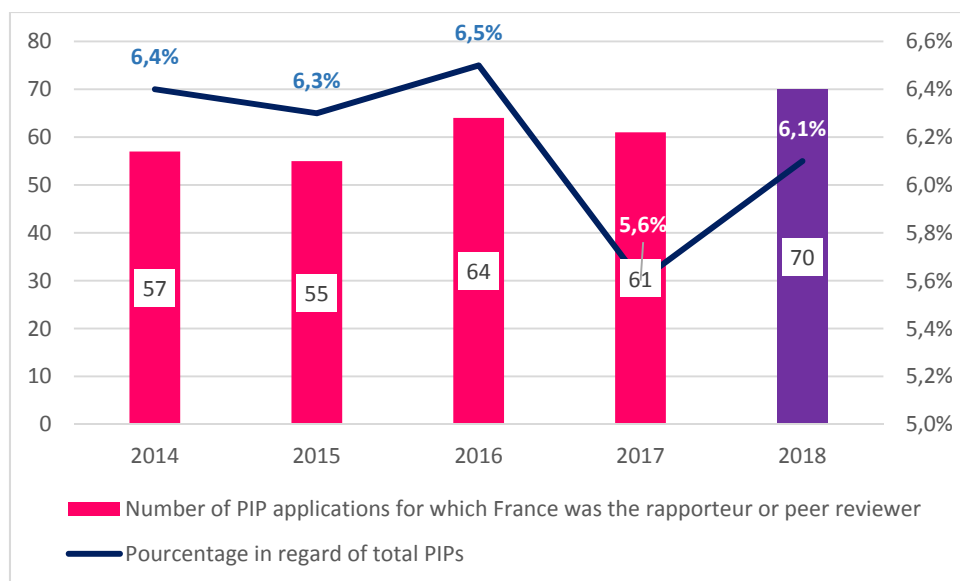
- **Revision of the EMA's guideline for epilepsy, published for consultation in 2018.**
- **Participation in the creation of good pharmacovigilance practice for the paediatric population (EMA GVP IV), finalised in 2018.**

## 2018 DATA

In 2018, in the field of paediatrics, France was the rapporteur or co-rapporteur for **70 PIPs** and PIP modifications, including **21 new applications (up 15% compared to 2017)**, in addition to verifications that the PIPs had been completed prior to the MA or paediatric MA extension request. In Europe, France is **6th** in terms of evaluating paediatric PIP developments.

### Paediatric medicines

Number of Paediatric Investigation Plan (PIP) applications for which France was the rapporteur or peer reviewer



### Orphan medicines authorised

	2014	2015	2016	2017	2018
MAs granted to orphan medicines out of the total number of MAs granted through the centralised procedure	15/74	15/93	14/114	14/92 <sup>(1)</sup>	22/164 <sup>(1)</sup>

(1) Data from the EMA registry.

## 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 original and generic medicines, play a role in the absorption and stability of the medicine and determine its appearance, colour, and taste. They do not have any pharmacological activity.

*Further information about "What is a generic medicine?" is available on the ANSM's website: [https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Qu-est-ce-qu-un-medicament-generique/\(offset\)/0](https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Qu-est-ce-qu-un-medicament-generique/(offset)/0)*

### MARKETING GENERIC MEDICINES

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 original 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 the information about generics that is available on the market is available on the public medicine database: <http://base-donnees-publique.medicaments.gouv.fr/>

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

[https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Le-repertoire-des-generiques/\(offset\)/5](https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Le-repertoire-des-generiques/(offset)/5)

Each group includes the reference medicine (R) and its generics (G). A reference medicine can be substituted with a generic from the same group as well as with any other generic within that group.

### GENERIC MEDICINES AND BIOEQUIVALENCE INSPECTIONS

Inspections can be carried out to field-test the reliability of the bioequivalence data provided by laboratories in their generic medicine MA applications.

### GENERIC MEDICINES AND LABORATORY CONTROLS

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 annual generic medicine 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 an analytical process that was more focused on critical parameters.

This programme is also conducted at European level. It is based on resource sharing between official control laboratories and is 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). It relies on sample sharing and the recognition of the results obtained by national laboratories. Tests on starting materials (active ingredients) are also performed.

In 2018, the average non-compliance rate was 6% for all of non-compliance are followed pharmaceutical companies

**Since 1999, ANSM has organised annual generic medicine testing in its laboratories**

compliance rate was 5% for generics. medicines controlled in 2018. All cases up by ANSM in liaison with the concerned.

ANSM is also involved in the EMA in collaboration with EDQM,

centralised MA. Since 2013, two molecules have been controlled each year in accordance with a joint protocol. ANSM contributes regularly, as both a scientific advisor and a product controller.

European programme, developed by the concerning the control of generics with a

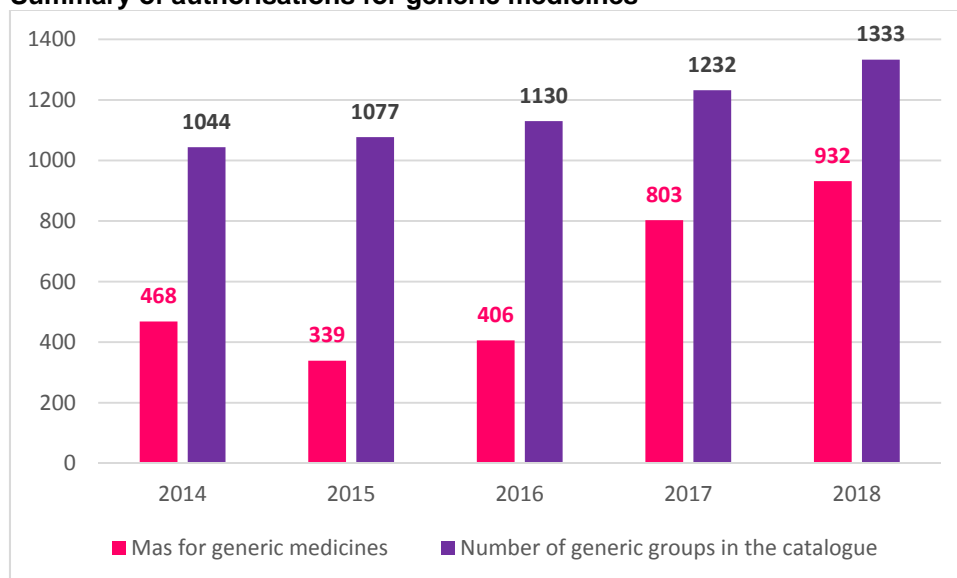
## HIGHLIGHTS IN 2018

- **Controls conducted as part of the pre-MA process for three molecules** as part biowaiver requests.
- Participation in a **collaborative European study on generics containing zoledronic acid**.
- Participation in the **development of methods and in the control of multiple generics containing an active ingredient from the sartan family** (tetrazole group) as part of a national and European process<sup>36</sup>.
- **Control of generic series containing recent proprietary medicines and featuring sensitive indications** (especially those related to the CNS).
- **Control of starting materials** of international origin used to manufacture generics.

<sup>36</sup> See also the focus on "Quality defects in sartan-based medicines", page 45.

## 2018 DATA

### Summary of authorisations for generic medicines



### Scheduled controls

#### 2018 Summary

	Batches controlled	Percentage of non-compliant products detected
Non-generic proprietary medicines	221	16, i.e. 7%
Generic medicines	159	8, i.e. 5%
Generic starting materials	35	0

### Emergency controls related to concerns with sartans

#### 2018 Summary

	Batches controlled	Percentage of non-compliant products detected
Generic starting materials	22	12

### Generic groups controlled in 2018

Zoledronic acid
Almotriptan
Duloxetine
Eletriptan
Exemestane
Levodopa/carbidopa/entacapone
Oxycodone
Quetiapine
Sertraline
Sodium valproate
Voriconazole
Zolmitriptan



## 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 biotechnology-based medicines 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.

### MARKETING AND MONITORING BIOSIMILAR MEDICINES

The MA is granted on the basis of quality, safety, and clinical efficacy and safety. Comparison criteria are selected based on their ability to reveal the slightest 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 measures as for the reference biological medicine. The immunological profile of the biosimilar product must also be monitored.

In principle, biosimilar medicines are authorised to treat the same diseases as the reference medicine. If a clinical similarity between a reference biologic and a biosimilar product can be shown for an indication that is considered to be representative, efficacy and safety data can potentially be extrapolated to other indications approved for the reference biologic under certain conditions. However, a biosimilar medicine can have fewer indications than a reference medicine, most often due to a lack of thorough efficacy and safety studies for the indication in question when the mechanism of action requires such studies. Once the MA is granted, a biosimilar medicine can evolve independently of its reference medicine. If a positive risk-benefit ratio is shown for an indication or route of administration that is different than those approved for the reference medicine, the biosimilar medicine's legal mentions (summary of product characteristics and package leaflet) may be changed.

### INTERCHANGEABILITY OF BIOSIMILAR MEDICINES

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.

As for any medicine, products and medicine batches must be constantly traced to ensure they remain continually monitored. This concept is especially important for biologics due to their greater variability. It is crucial that different products with the same international common name or containing the same active

substance be easily identifiable in order to detect and evaluate any safety or immunogenicity problems associated with the product.

Around fifty biosimilar proprietary medicines are authorised and/or marketed in Europe (April 2019). The quality, safety, and efficacy profiles were considered 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.

## **SURVEILLANCE**

The marketing of biological medicines is accompanied by a surveillance 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.

The pharmacovigilance network has not identified any differences in the nature, seriousness, or frequency of the adverse effects associated with biosimilar medicines and reference medicines in the past twelve years.

## **LIST OF BIOSIMILAR MEDICINES**

The list of biosimilar medicines authorised in Europe is published on ANSM's website. This list makes it possible to clearly match the dose and pharmaceutical form of a reference biologic to a corresponding biosimilar medicine (or the reverse).

The medicines included on this list are categorised by similar biological group. These groups are then organised by active substance. For each medicine, the reference list indicates the name and any information regarding its presentations, dose, pharmaceutical form, the name of the marketing authorisation owner, the name of the company or organisation operating the medicine (if not the MA owner), and its therapeutic indications, links to a website showing all the data from the public medicine database, including the medicine's SPCs and package leaflet.

*Further information about biosimilar medicines is available on the ANSM's website:*

[https://www.ansm.sante.fr/Activites/Medicaments-biosimilaires/Les-medicaments-biosimilaires/\(offset\)/0#paragraph\\_113825](https://www.ansm.sante.fr/Activites/Medicaments-biosimilaires/Les-medicaments-biosimilaires/(offset)/0#paragraph_113825)

## **HIGHLIGHTS IN 2018**

- **Publication of a guide for patients and healthcare professionals (EC).**
- **European MA for the first bevacizumab and pegfilgrastim biosimilars.**

**2018 DATA**
**Biosimilar products authorised in Europe (April 2019)**

Reference medicine	Biosimilar medicine	Active substance	Laboratory	Date of authorisation
<b>Genotropin</b>	Omnitrope	Somatropin	Sandoz GmbH	12/04/2006
<b>Eprex</b>	Binocrit	Epoetin alfa	Sandoz GmbH	28/08/2007
	Epoetin alfa hexal		Hexal AG	28/08/2007
	Abseamed		Medice Arzneimittel Pütter GmbH	28/08/2007
	Retacrit	Epoetin zeta	Hospira UK Limited	18/12/2007
	Silapo	Stada Arzneimittel AG	18/12/2007	
<b>Neupogen</b>	Tevagrastim	Filgrastim	Teva GmbH	15/09/2008
	Ratiograstim		Ratiopharm GmbH	15/09/2008
	Filgrastim Hexal		Hexal AG	06/02/2009
	Zarzio		Sandoz GmbH	06/02/2009
	Nivestim		Hospira UK Limited	08/06/2010
	Grastofil		Apotex Europe BV	18/10/2013
	Accofil		Accord Healthcare Ltd	18/09/2014
<b>Remicade</b>	Remsima	Infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013
	Inflectra		Hospira UK Limited	10/09/2013
	Flixabi		Samsung Bioepis UK Limited	26/05/2016
	Zessly		Sandoz GmbH	17/05/2018
<b>GONAL-f</b>	Ovaleap	Follitropin alfa	Teva Pharma B.V.	27/09/2013
	Bemfola		Finox Biotech AG	27/03/2014
<b>Lantus</b>	Abasaglar	Insulin glargine	Eli Lilly Regional Operations	09/09/2014
	Semglee		Mylan S.A.S	22/03/2018
<b>Enbrel</b>	Benepali	Etanercept	Samsung Bioepis UK Limited	14/01/2016
	Erelzi		Sandoz GmbH	23/06/2017
<b>Humira</b>	Amgevita	Adalimumab	Amgen Europe B.V.	21/03/2017
	Imraldi		Samsung Bioepis UK Limited Amgen Europe B.V.	24/08/2017
	Hulio		Mylan S.A.S.	15/09/2018
	Hefiya		Sandoz GmbH	25/07/2018
	Hyrimoz		Sandoz GmbH	25/07/2018
	Halimatoz		Sandoz GmbH	25/07/2018
<b>Clexane</b>	Inhixa	Enoxaparin	Techdow Europe AB	15/09/2016
	Thorinane		Pharmathen S.A.	15/09/2016
<b>Forsteo</b>	Terrosa	Teriparatide	Gedeon Richter Plc.	04/01/2017
	Movymia		STADA Arzneimittel AG	11/01/2017

<b>Humalog</b>	Insulin lispro Sanofi	insulin lispro	Sanofi-Aventis group	19/07/2017
<b>MabThera</b>	Truxima	Rituximab	Celltrion Healthcare Hungary Kft.	17/02/2017
	Rixathon		Sandoz GmbH	15/06/2017
	Riximyo		Sandoz GmbH	15/06/2017
	Blitzima		Celltrion Healthcare Hungary Kft.	13/07/2017
	Ritemvia		Celltrion Healthcare Hungary Kft.	13/07/2017
	Rituzena		Celltrion Healthcare Hungary Kft.	13/07/2017
<b>Herceptin</b>	Ontruzant	trastuzumab	Samsung Bioepis NL B.V.	14/11/2017
	Kanjinti		Amgen Europe B.V., Breda	15/05/2018
	Herzuma		Celltrion Healthcare Hungary Kft.	07/02/2018
	Ogivri		Mylan S.A.S	11/12/2018
	Trazimera		Pfizer Europe MA EEIG	26/07/2018
<b>Avastin</b>	Mvasi	bevacizumab	Amgen Europe B.V.	14/01/2018
<b>Neulasta</b>	Ziextenzo	pegfilgrastim	Sandoz GmbH	21/11/2018
	Pelgraz		Accord Healthcare Limited	19/09/2018
	Fulphila		Mylan S.A.S	19/11/2018
	Pelmeg		Cinfa Biotech S.L.	20/11/2018
	Udenyca		ERA Consulting GmbH	19/09/2018

## Herbal medicines

ANSM has been publishing a list of groups of generic herbal medicines since 2017. These ten groups are included in the list of generic groups in Appendix II, which is published on ANSM's website.

Herbal medicines within the same group share the same qualitative and quantitative composition in terms of their herbal active substance. They also have the same pharmaceutical form and share an equivalent therapeutic activity. These groups do not have a reference proprietary medicine. Each is identified by its active substance, which is described in accordance with the corresponding plant monograph published by the European Medicines Agency for a well-established medical use.

The ten groups concern seven herbal active substances: ginkgo, ispaghul, common ivy, St. John's Wort, saw palmetto, Alexandrian senna, and the common grape vine.

*More information about "Herbal medicines" is available on ANSM's website.*

[https://www.ansm.sante.fr/Activites/Medicaments-a-base-de-plantes/Les-medicaments-a-base-de-plantes/\(offset\)/0#paragraph\\_15788](https://www.ansm.sante.fr/Activites/Medicaments-a-base-de-plantes/Les-medicaments-a-base-de-plantes/(offset)/0#paragraph_15788)

## Medicine preparations

ANSM is in charge of activities related to pharmaceutical and hospital preparations. As part of this role, it manages an e-filing database for hospital preparations created by pharmacies for internal use and pharmaceutical facilities. This base lets ANSM monitor the state of activity in France and consider alternatives in case of a shortage.

ANSM monitors and helps answer the technical and regulatory questions of the various stakeholders (ARS, PUI, pharmaceutical facilities, patient associations, etc.).

In response to feedback regarding alerts, ANSM can issue warnings about certain preparations. In 2018, ANSM worked on the following:

- reminder of the regulatory framework governing preparations containing melatonin (April 2018)  
[https://www.ansm.sante.fr/content/download/143065/1891015/version/1/file/Recos\\_melatonine\\_avril2018.pdf](https://www.ansm.sante.fr/content/download/143065/1891015/version/1/file/Recos_melatonine_avril2018.pdf)
- Recommendations for starting materials containing vitamin D and the risk of dosage confusion (August 2018)  
[https://www.ansm.sante.fr/content/download/148581/1957643/version/1/file/Reco\\_MP\\_Vitamine-D\\_2018-08-27.pdf](https://www.ansm.sante.fr/content/download/148581/1957643/version/1/file/Reco_MP_Vitamine-D_2018-08-27.pdf)

In 2018, efforts to revise the best practice guidelines for preparing medicines for dispensaries and pharmacies for use in healthcare facilities continued with 18 TSSC meetings since the committee was founded in 2016.

Finally, ANSM continued to participate in the work of the French Health Minister regarding parenteral nutrition. For example, ANSM's Controls Division conducted stability trials on NP binary formulas previously defined by a working group at the Health Ministry specialising in neonatal intensive care.

*More information about, "Compounded pharmacy and hospital preparations" is available on ANSM's website.*

[https://www.ansm.sante.fr/Activites/Preparations-hospitalieres-magistrales-et-officinales/Preparations-hospitalieres-magistrales-et-officinales/\(offset\)/0](https://www.ansm.sante.fr/Activites/Preparations-hospitalieres-magistrales-et-officinales/Preparations-hospitalieres-magistrales-et-officinales/(offset)/0)

## Authorisation and re-evaluation of homoeopathic medicines

Homoeopathic medicines, like other medicines, cannot be marketed without first receiving authorisation, which guarantees their quality and safety and recognises their homoeopathic usage (traditional usage). This authorisation is issued by ANSM.

Since 2001, European Directive 2001/83/EC regarding all medicines for human use has established the marketing conditions for homoeopathic medicines through two authorisation procedures:

- a marketing authorisation procedure (MA) that involves medicines that have a specific indication, dosage, target population, duration of treatment, and method of administration,
- a specific registration procedure for medicines that meet the following criteria: oral or external administration, lack of a specific therapeutic indication on the label or in any of the documentation regarding the product, and a degree of dilution that guarantees the medicine's safety (article L. 5121-13).

ANSM re-evaluates all homoeopathic medicines on the market that received authorisations prior to 18 January 1994 (approvals, market authorisations - provisions under Law no. 94-43 of 18 January 1994).

On 21 June 1984, the French Health Minister approved 1,163 unitary homoeopathic medicines. These 1,163 strains are being re-evaluated by several laboratories.

The re-evaluation pays special attention to issues related to safety and quality and assesses risks based on the composition of the starting material included in each strain. The non-clinical re-evaluation makes it possible to estimate the safety of each strain by identifying a suitable dilution level that does not pose a risk to human health. The recognition of homoeopathic tradition must also be justified. After the evaluation, ANSM decides to register the medicine or grant an MA based on the requirements set by current regulations.

Once the validation process is complete, the medicines that are subject to the MA scheme receive specific labelling information and a package leaflet that is aimed at educating the patient and increasing his or her safety. This is used to guarantee there are no lost opportunities, when applicable.

The decision to register a medicine can include, for each homoeopathic strain, all authorised dilutions and the various authorised pharmaceutical forms (granules, granules in a single-dose container, tablets, oral solutions in an ampoule, oral drop solutions, pomades, and oral powder).

At the same time, ANSM also evaluates all new requests to register strains or receive an MA for a homoeopathic medicine.

As they are granted, ANSM publishes the following:

- registration decisions,
- marketing authorisations for homoeopathic medicines.

These authorisations (registrations and MAs) can be viewed in the list of proprietary medicines or the public database of medicines on the ANSM website.

Between 2017 and 2018: 115 registration applications and 25 MAs for homoeopathic medicines have been authorised.

## 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 safe use and monitoring, their marketing conditions are made more stringent through 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 redundancy.

Over the past few years, France has established itself as one of the most prolific vaccine-releasing countries in Europe. This dominant role can be explained by its expertise, which is recognised throughout Europe and abroad, and its responsiveness. Depending on the year, it releases 35% to 40% of all vaccine doses used in Europe and around 50% of the vaccine doses used in France.

ANSM is extensively involved in the 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). It is also one of the top actors in Europe. However, 2018 was an exception given the situation that occurred with the country's main BDM producer, which supplies a large percentage of the demand<sup>37</sup>.

### HIGHLIGHTS IN 2018

- **Release of the Mosquirix and Tetravac vaccines.**

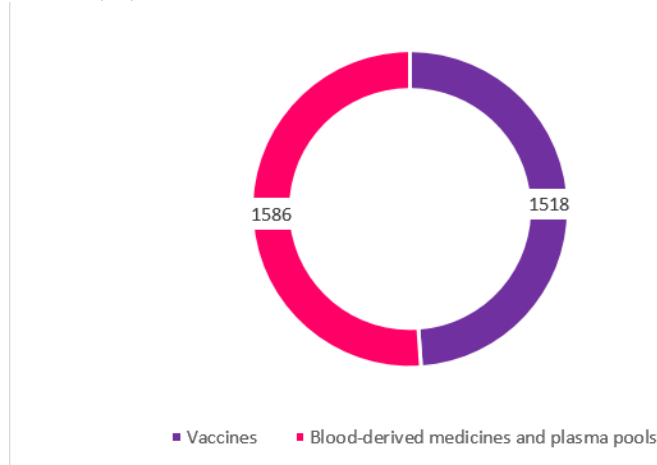
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<sup>37</sup> See also the focus entitled "Extremely limited supply of blood-derived medicines produced by LFB Biomédicaments", page 54.

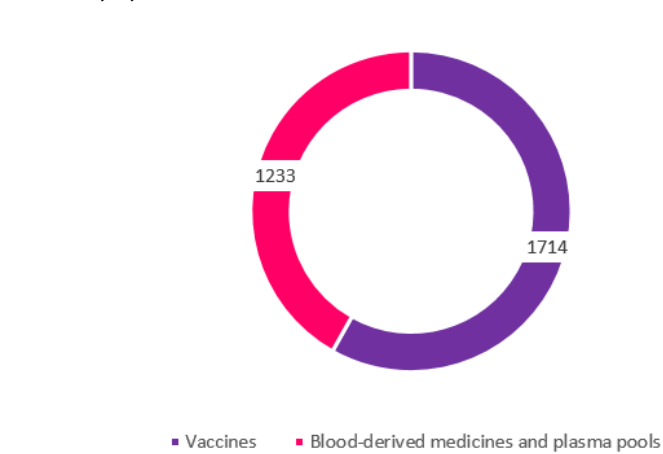
**2018 DATA**

**Batch release of vaccines and blood-derived medicines**

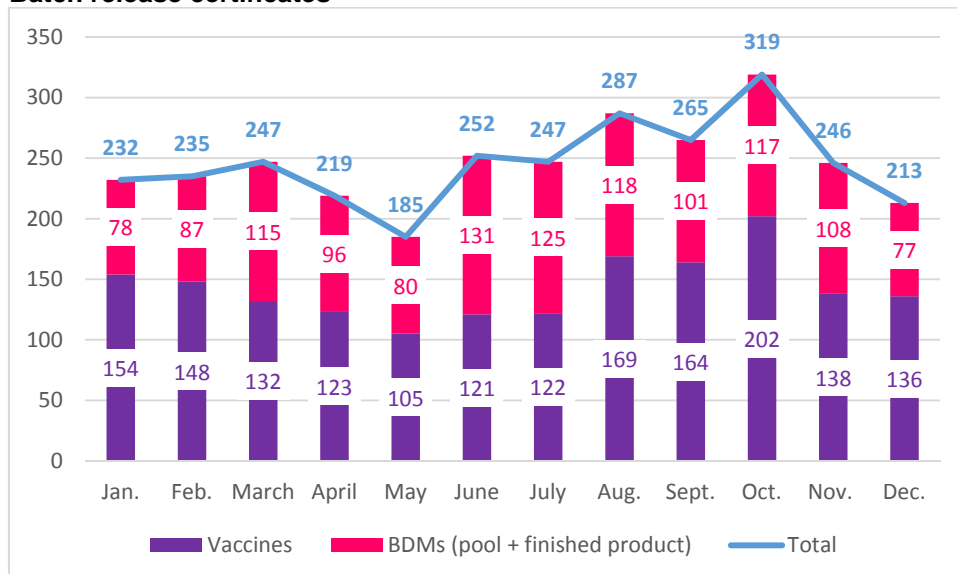
**In 2017, 3,104 certified batches**



**In 2018, 2,947 certified batches**



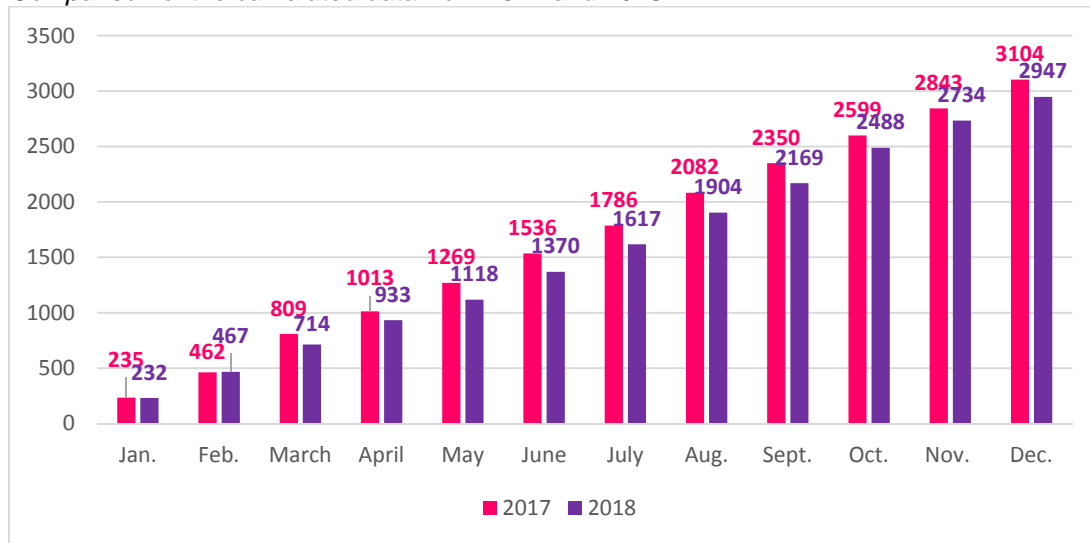
**Batch release certificates**





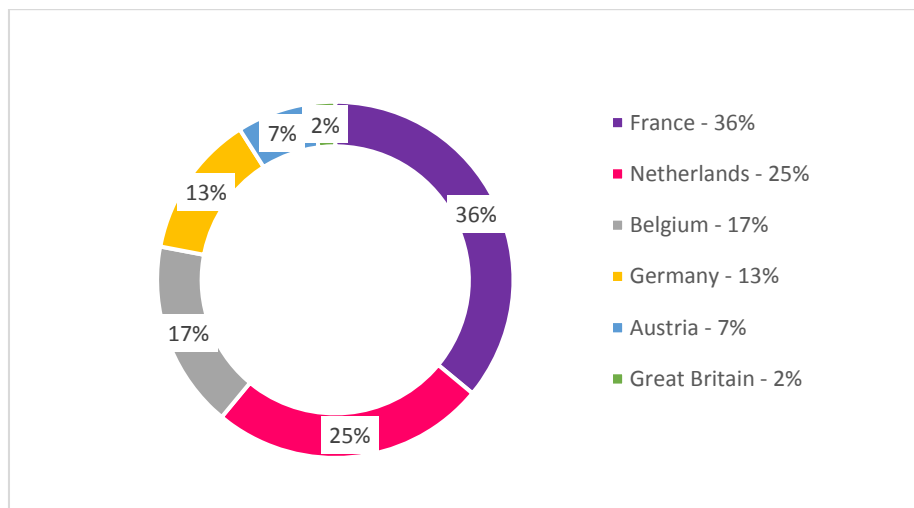
### Batch certifications

Comparison of the cumulated data from 2017 and 2018



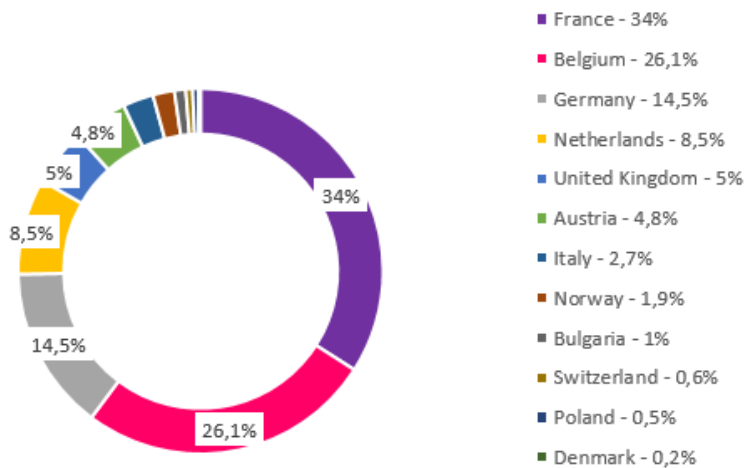
### Distribution of vaccine doses circulating in France and released by OMCLs

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



### Member state involvement in vaccine batch releases in Europe

France is the top provider.



# 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 in 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, safe use, and quality.

Due to the origin of these products, the risk of viral or bacterial 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 for the purpose of being 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<sup>38</sup>.

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 2018

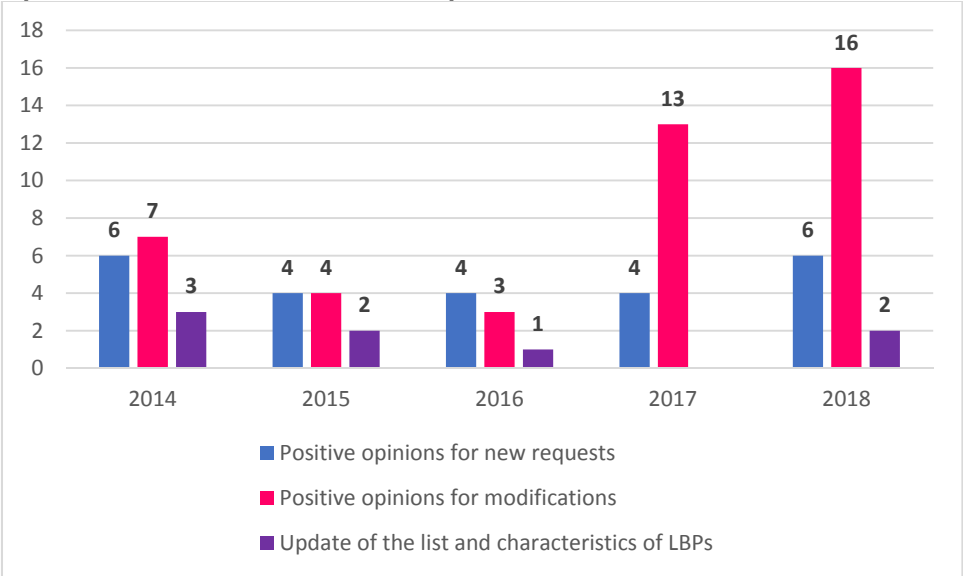
- **Favourable opinion regarding the preparation and release of blends of granulocyte concentrates** derived from units of whole blood (July 2018).
- **Authorisation of the extension by seven days of the maximum storage time for platelet concentrates treated with amotosalen-UVA** to inactivate pathogenic agents (decision of 3 May 2018 modifying the decision of 8 February 2018 establishing the list and characteristics of labile blood products, OJFR of 5 May 2018).
- **Authorisation of the use of frozen fresh plasma** that has been quarantined for up to a maximum of 24 hours after thawing if the thawed plasma is kept in a refrigerator during this time (decision of 8 February 2018 establishing the list and characteristics of labile blood products, OJFR of 13 March 2018).
- **Favourable opinion regarding the preparation and release of platelet concentrates** treated with amotosalen-UVA to inactivate pathogenic agents collected in bags made out of a new type of plastic that does not contain DEHP (phthalates) (February 2018).
- **Favourable opinion regarding the first medical device** to prepare a blend of platelet concentrates from eight leuco-platelet strains (5 July 2018).

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<sup>38</sup> See also the chapter entitled "Surveillance of blood products", page 52.

**2018 DATA**

**Opinions delivered for labile blood products**



## **Part 3**

### **Consolidating ANSM's ties to stakeholders and boosting their involvement**

## **Consolidating ANSM's ties to stakeholders and boosting their involvement**

<b>Transparency of the decision-making process and principles governing the use of experts</b>	<b>p. 126</b>
<b>The work of advisory bodies</b>	<b>p. 129</b>
• Advisory commissions	p. 129
• Technical interface committees working with vigilance networks	p. 130
• Temporary Specialised Scientific Committees	p. 130
• Working groups	p. 131
<b>Independence and impartiality: ethical obligations</b>	<b>p. 133</b>
• Measures to prevent conflicts of interest and monitor compliance with reporting requirements	p. 133
• Internal control programme to verify the application of ethics rules	p. 135
• The Ethics Committee	p. 136
<b>Exchanging and sharing information with stakeholders</b>	<b>p. 137</b>
• Informational and educational measures regarding the safety of health products	p. 137
• Information distributed to health professionals, patients, and the public	p. 139
• Press relations	p. 140
• Information for parliamentary representatives	p. 141
• Patient information and patient involvement in the agency's work	p. 141
• Discussions within the Interface Committees	p. 142
<b>National intergration of health and medical research professionals</b>	<b>p. 148</b>
• Promoting independent research to support the agency's missions	p. 148
• Relations with other health system operators	p. 150
• Legal and regulatory activities	p. 152
<b>European work</b>	<b>p. 154</b>
• European strategy	p. 154
• Representation of ANSM within European bodies	p. 157
<b>International cooperation activities</b>	<b>p. 159</b>
• Multilateral cooperation activities	p. 159
• Cooperation activities with agencies within the European network	p. 160
• Bilateral cooperation activities	p. 160

# 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 collective 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, especially with respect to the "real-life" use of products in the field.

ANSM relies on the expertise of **three advisory commissions**:

- Commission for initial assessment of the risk/benefit ratio of healthcare products,
- Commission for monitoring the risk/benefit ratio of healthcare products,
- Commission for narcotics and psychotropics.

When a multidisciplinary opinion in addition 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.

When these advisory body were created and in order to limit and manage risks related to conflicts of interest, ANSM increased its standards and independence requirements for the members of these bodies in 2013. The agency introduced incompatibility criteria that were taken into consideration when selecting experts. These criteria apply throughout the duration of their term limit.

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 the DPI Santé website.

Commission sessions are 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.

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

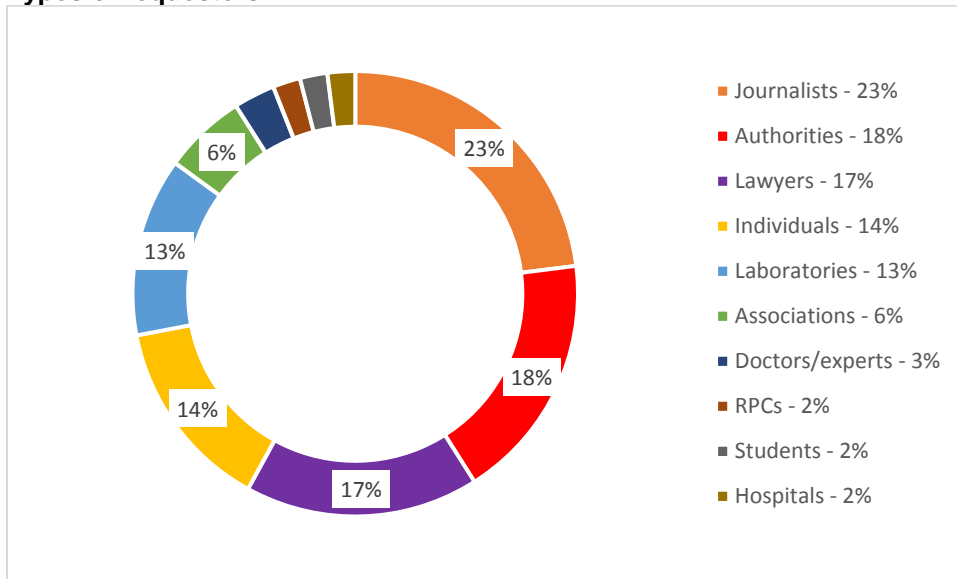
Finally, ANSM periodically calls on the services of **external experts** whenever a question requires additional expertise. In this event, the experts consulted are appointed by the Director General, and the appointment decisions are published on the agency's website. These experts are subject to the same ethics requirements as all other experts.

## RESPONDING TO THE PUBLIC'S REQUESTS

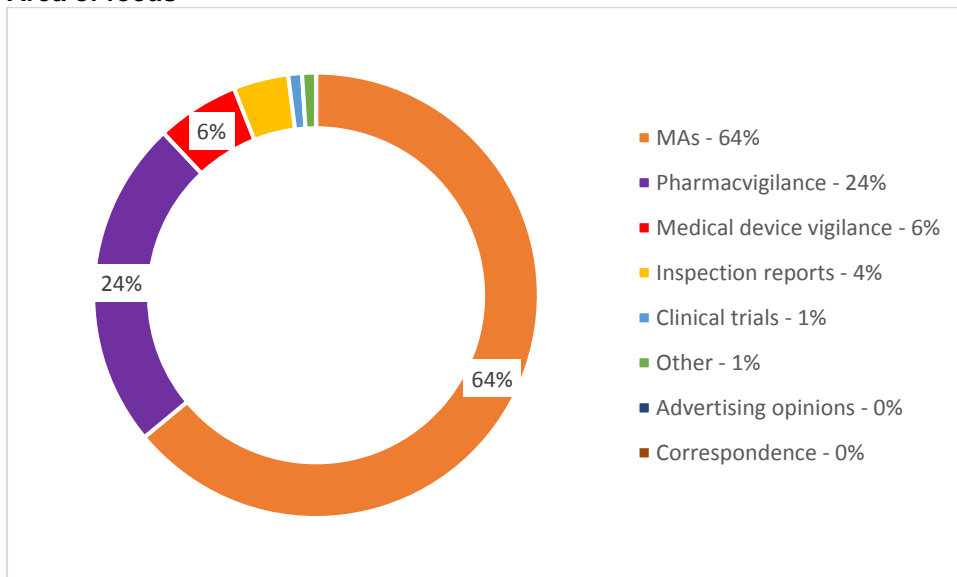
As part of the application of the provisions of the Code of Relations between the public and the administration, the agency responded to 161 requests for administrative documents. The number of requests has increased compared to 2017, when 143 requests were made. A request must be processed within 27 days.

## 2018 DATA

### Types of requesters



### Area of focus



## Focus on: Reforming ANSM's advisory bodies

As part of its efforts to adopt a more open approach and take into account a diverse range of experts, ANSM decided to reform its advisory bodies. The purpose of this reform is to systematise the participation of healthcare system users in all advisory bodies and to better account for every dimension, especially with respect to social concerns, of the dossiers being studied. It is also meant to make the advisory body system more efficient, responsive, and user friendly.

This reform was unanimously approved by the Board of Directors on 29 November 2018.

The new advisory bodies include:

- fifteen permanent committees that will replace the current commissions and working groups and are tasked with issuing an opinion on long-term or recurrent topics;
- temporary scientific committees (the current temporary specialised scientific committees) tasked with addressing one-off or specific subjects;
- interface committees in charge of building relationships with stakeholders and French pharmacopoeia committees.

A health product informational committee will be created to address education- and communication-related topics.

ANSM's decision to open itself up to all of society and allow a variety of viewpoints and areas of expertise to inform the debates within its advisory bodies will also take the form of public hearings on specific themes that will be filmed and shown live on the agency's YouTube and Dailymotion channels.

These bodies will be subject to ANSM's ethics requirements.

The new permanent committees will be created in the summer of 2019. The experts on these committees will be appointed for a term of four years. They can participate in a maximum of three committees.



# THE WORK OF ADVISORY BODIES

## Advisory commissions

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

Commission	Chair	Vice-Chair	Start date	Number of members	Number of meetings in 2018
Commission for initial assessment of the risk/benefit ratio of healthcare products	Marc Bardou	Albert Trinh-Duc	10 March 2016	11 members	6
Commission for monitoring the risk/benefit ratio of healthcare products	Pierre Ambrosi	Joël Ancellin	5 April 2016	17 members (1 resignation in May 2018)	2
Commission for narcotics and psychotropics	Nicolas Authier	Michel Mallaret	14 April 2016	14 members	5

The Monitoring Commission evaluates topical developments as well as the dossiers examined during sessions held by the Pharmacovigilance Risk Assessment Committee (PRAC<sup>39</sup>).

### HIGHLIGHTS IN 2018

- Discussions regarding the MA for methadone, which is indicated for pain management in cancer patients.
- On 21 June 2018, ANSM's Commission for narcotics and psychotropics organised a discussion day with the main stakeholders in the addiction sector to present a plan to reduce the number of overdoses associated with opioid substitution treatments (OSTs) that would also maintain sufficient access to these medications, which play a key role in treating addictions to opioid, including heroine. The debates throughout the day were broadcast live online.
- In 2018, for the first time, ANSM used the work of a mixed *ad hoc* commission to evaluate the MA request for approving baclofen as an alcohol addiction treatment. This commission, which comprises members from ANSM's three advisory bodies, met on 3 and 4 July 2018. During the meeting, the commission heard from experts and representatives of patients and healthcare professionals whose testimony and feedback shed light on the perspectives of all stakeholders. The commission then provided the agency's Director General with its opinion. The *ad hoc* commission also drew from the conclusions of the TSSC in charge of evaluating the risk-benefit ratio of baclofen in the treatment of alcohol addiction. All debates were broadcast live online<sup>40</sup>.

### 2018 DATA

The advisory commissions issued opinions on:

- **requests for cohort temporary authorisations for use** (14 applications in 2018),
- **temporary recommendations for use** (1 applications in 2018: Misoprostol),
- **MA requests and MA extension requests** (3 applications in 2018): Zoryon (methadone), Clinimix (N9 G15 E), Gynophilus (freeze-dried culture *Lactobacillus rhamnosus*),
- **risk-benefit ratio revision/reassessment applications** (6 applications in 2018),

<sup>39</sup> See the chapter entitled "European work", p. 154.

<sup>40</sup> See also the focus entitled "Issuance of MA for the use of baclofen in the treatment of alcohol addiction", page 107.

- **dossiers regarding health product vigilance and surveillance**, including modifications for prescription and dispensation conditions for medicines,
- **measures designed to promote proper use** and reduce the misuse and abuse of psychotropic medicines; to prevent or reduce risks, such as the plan to reduce the number of overdoses caused by opioid substitutes; or manage the consequences of using non-medicinal psychoactive substances.

## Technical 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 basis. Four technical committees, each 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.

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

### 2018 DATA

Committee	Date created	Number of meetings in 2018
Technical Pharmacovigilance Committee <sup>41</sup>	15 March 2013	9
Technical Committee for Drug Dependence Evaluation and Information Centres	27 March 2013	4
Technical Haemovigilance Committee	21 May 2013	4
Technical Committee for Medical Device Vigilance and Reagent Vigilance	1 August 2013	3

## Temporary Specialised Scientific Committees

Temporary Specialised Scientific Committees (TSSCs) are created for the sole purpose of addressing a specific problem (*ad hoc*) if a permanent working group cannot answer a question it is asked. They are made up of external experts and only meet a limited number of times over a specific period.

The agendas from each session and meeting minutes (reports) are published on the agency's website when the TSSC's work is finished, at the very latest. Live broadcasting of committee hearings started in 2017 and became widespread in 2018.

### HIGHLIGHTS IN 2018

- **Following the submission of an MA application by the pharmaceutical company Ethypharm for the use of baclofen in the treatment of alcohol addiction, ANSM created a TSSC to evaluate the risk-benefit ratio of baclofen in the treatment of patients addicted to alcohol<sup>42</sup>.**
- **To help implement the expansion of the mandatory vaccine programme overseen by the French Ministry of Health and Solidarity, ANSM decided to provide healthcare professionals and the general public with regularly updated information on safety data** taken from the pharmacovigilance system regarding the eleven vaccine valences that became mandatory for children under the age of 2 starting on 1 January 2018. To offer information that meets the needs of both patients and healthcare professionals, the agency implemented a public consultation in the form of a temporary specialised scientific committee (CSST) that including public hearings. The goal of this committee was to obtain a collective opinion about the categories of information and communication methods that should be provided to healthcare professionals and the general public. This CSST was created in the wake of preliminary meetings with healthcare professionals, patient associations, and manufacturers. Based on the recommendations of the TSSC, an annual report on safety data for vaccines that are required for children under the age of 2 will be published every year.

<sup>41</sup> See also the chapter entitled "Pharmacovigilance", p. 17.

<sup>42</sup> See also the focus entitled "Issuance of MA for the use of baclofen in the treatment of alcohol addiction", page 107.

- **Because ANSM was asked to evaluate the relevance and feasibility of making medical cannabis available in France**, a TSSC was created for one year to explore the value of allowing access to medical cannabis<sup>43</sup>.

## 2018 DATA

Ten TSSCs were created in 2018, and three TSSCs created in 2017 continued to meet.

Temporary Specialist Scientific Committee	Date created	Number of meetings in 2018
"Assessment of the risk/benefit ratio of baclofen for the treatment of alcohol addiction" TSSC	28/11/2017	2
"Evaluation of the relevance and feasibility of making medical cannabis available in France" TSSC	10/09/2018	3
"Public consultation on the communication of safety data for mandatory vaccines for children under the age of 2" TSSC	29/06/2018	1
"Meningioma and cyproterone acetate" TSSC	12/06/2018	2
"Medical device software cybersecurity" TSSC	08/06/2017 Extended on 22/06/2018	2
"Revision of preparation best practice - continued work" TSSC	10/08/2018	8
"Inclusion in clinical trials of asymptomatic patients at risk of developing Alzheimer's disease" TSSC	16/03/2018	1
"Physical restraint medical devices" TSSC	05/02/2018	2
"Ranking of indications for polyvalent human immunoglobulins during shortages" TSSC	09/01/2018	1
"Anaplastic large-cell lymphoma and breast implants: measure summary and recommendation update" TSSC	12/01/2018	1
"Misoprostol TRU" TSSC	30/01/2018	1
"Exemptions for organ transplants from HIV+ donors" TSSC	23/06/2017	1
"Use of phenoxyethanol in cosmetics" TSSC	06/11/2017	Report published on 28/05/2018

## Working groups

Working groups (WGs) are expert assessment bodies comprising external experts from the field(s) concerned. They may be specific to certain diseases or multidisciplinary and are tasked with providing answers to precise questions raised following prior internal dossier assessments.

The 23 working groups created in 2016 for a duration of three years met regularly in 2018.

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

<sup>43</sup> See also the focus entitled "Evaluation of the relevance and feasibility of making medical cannabis available in France", page 104.

## 2018 DATA

### The 23 Working Groups

			2016	2017	2018
1	2016-29 WG for labile blood products and blood donors	22/02/2016	0	5	4
2	2016-32 WG for vaccines	22/02/2016	0	0	0
3	2016-33 WG for medicines used in diabetology, endocrinology, urology, and gynaecology	22/02/2016	1	0	0
4	2016-34 WG for cardiovascular risk and therapy	22/02/2016	0	5	4
5	2016-35 WG for epidemiological studies on health products	22/02/2016	0	3	4
6	2016-36 WG on clinical methodology	22/02/2016	0	0	0
7	2016-37 WG for paediatrics	22/02/2016	3	4	3
8	2016-38 WG on non-clinical safety	22/02/2016	1	1	0
9	2016-39 WG for the viral safety and microbiological safety of health products	22/02/2016	4	4	2
10	2016-40 WG for the pharmaceutical quality of chemical medicines	22/02/2016	0	8	6
11	2016-41 WG on medication interactions	22/02/2016	4	3	1
12	2016-42 WG for prescription-optional medicines	22/02/2016	0	2	3
13	2016-43 WG for herbal medicines and homoeopathic medicines	22/02/2016	0	3	2
14	2017-184 WG for dermatological medicines and cosmetic products	15/03/2017	0	2	1
15	2016-45 WG for medicines used to treat non-viral infectious diseases	22/02/2016	0	0	0
16	2016-4206 WG for medicines used to treat viral infectious diseases	22/02/2016	0	0	0
17	2016-47 WG for medicines used in hepatogastroenterology and rare metabolic diseases	22/02/2016	2	1	0
18	2016-48 WG for gases intended for medical use	22/02/2016	1	0	0
19	2016-49 WG for medicines used in diagnostics and nuclear medicine	22/02/2016	7	8	7
20	2016-50 WG for medicines used in oncology and haematology	22/02/2016	0	7	6
21	2016-51 WG for reproduction, breast feeding, and pregnancy	22/02/2016	4	5	5
22	2016-52 Interface WG for the medication toxicovigilance network	22/02/2016	0	0	0
23	2016-53 WG on medication errors	22/02/2016	0	0	0
<b>Total annual working group meetings</b>			<b>27</b>	<b>61</b>	<b>48</b>

# 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, and 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 and an ethics committee that is independent from the agency's senior management. The ethics department reports directly to the Director General.

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

In 2018, ANSM continued to focus 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 any and all conflicts of interest.

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 the agency's referral.

### CONCERNING THE USE OF COLLEGIAL EXTERNAL EXPERTISE

Appointments to an ANSM collegial body (commission, working group, or temporary specialised scientific committee) are first examined by the Ethics Division, which studies the connections reported by each member on their CV and public declaration of interests form as well as those contained in the public 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.

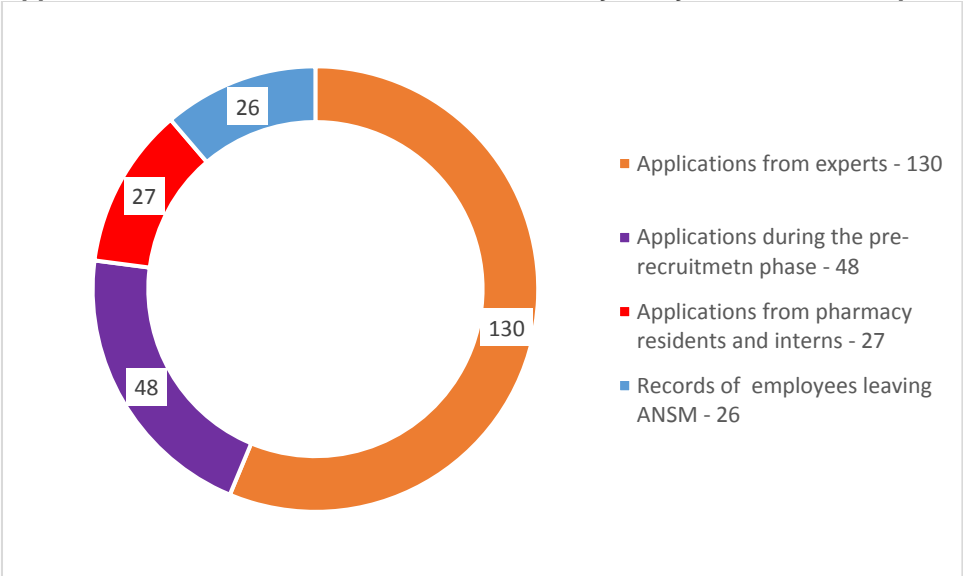
### HIGHLIGHTS IN 2018

- Update of the ANSM Ethics Charter (August 2018)



**2018 DATA**

**Applications that resulted in an ethics risk analysis by the Ethics of Expertise Department**



## Internal control programme to verify the application of ethics rules

Since 2012, ANSM has been developing an internal control programme overseen by the Ethics of Expertise Department designed to verify the application of ethics rules in various decision-making processes as well as the mandatory reporting of conflicts of interest.

This control programme and its findings are presented before the Ethics Committee.

These controls focused on:

- the compliance of the conflicts of interest reports submitted by agency personnel subject to mandatory reporting laws, members of the agency's governing bodies (board of administration and scientific council), advisory board members (commissions, working groups, technical committees, temporary specialised scientific committees), and external experts that are consulted on a one-off basis with respect to the requirement to report and publish conflicts of interest in the past year,
- the consistency of the content of these statements compared to publicly available information (especially via the Health Transparency Database [Transparence-Santé]).

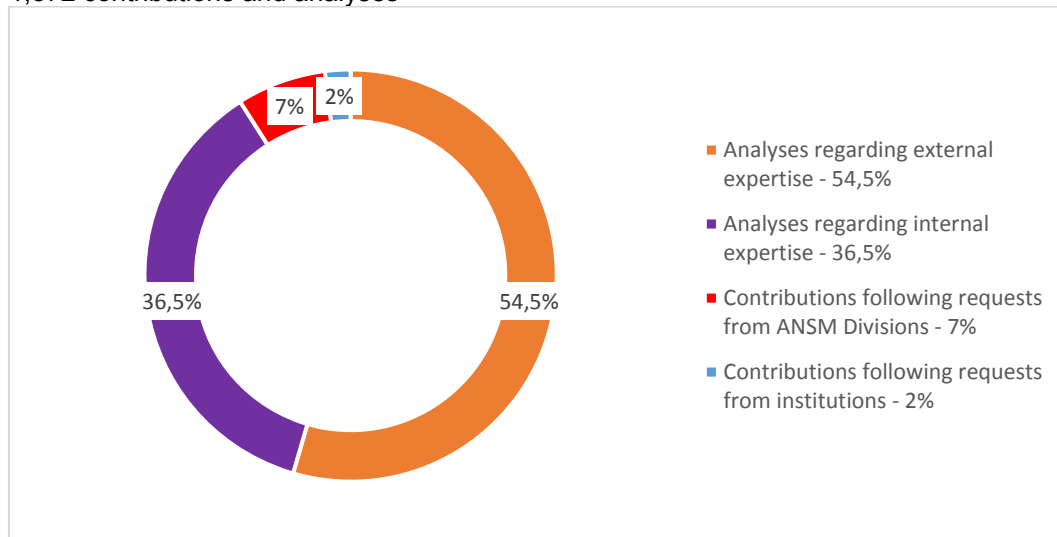
Regarding audits of the agency's decision-making processes, in addition to the areas of control listed above involving the internal and external actors who participate in these processes, the audit also verifies the existence of measures aimed at preventing and managing potential conflicts of interest, their traceability in the file, and their transparency in the reports of any advisory bodies consulted during the process.

### 2018 DATA

- **14 compliance control operations on 1,265 conflicts of interest reports**
- **4 audits regarding the operation of advisory bodies**
- **5 audits on decision-making processes regarding clinical trials on medicines were also conducted**

### Breakdown of total analyses

1,872 contributions and analyses



## Ethics Committee

The Ethics Committee was formed following the decision of the Director General on 4 May 2012 (OJ of 1 July 2012) and modified by the decisions of the Director General dated 11 May 2016 and 29 December 2016. 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 most sensitive and complex cases.

The committee comprises the chairs of the Board of Directors and the Scientific Council (or their representatives), an external participant, and the representatives of health profession organisations and associations advocating the causes of health system users, members of the Board of Directors, and a representative of the ethics committee of the ministries in charge of social affairs. ANSM's Ethics Officer attends committee meetings in an advisory capacity. It is important to note that the annual report written by the Ethics Officer must take the opinions and recommendations of this committee into account.

The Ethics Committee, whose administrative office is overseen by the Ethics of Expertise Department, met twice in 2018. A recommendation and a subsequent opinion were adopted regarding ANSM's new internal ethics control methods. These methods are designed to ensure the ethics rules that all ANSM experts and agents must obey are in fact followed.

- These recommendations, which were written by the Ethics Committee during its session on 28 February 2018, are in addition to those created by the Inspectorate General of Social Affairs (IGAS) during its 2018 audit regarding ANSM's management of health-related risks. These measures have modified the organisation of ANSM's internal control system to ensure the agency's ethics rules are followed.
- As a result of these recommendations, the relevant departments will now have to ensure the traceability of all the control operations they oversee (first-level internal controls). The purpose of this approach is to ensure their experts fulfil their reporting requirements and to verify that any conflicts of interest have been analysed and that appropriate measures to address these conflicts have been put in place before any meetings or one-off expertise assignments have taken place.
- The Ethics Department will conduct second-level controls through a random sampling process. These controls will consist of verifying that the departments conduct their first-level controls, and ensuring the conflict of interest prevention and management system is functioning properly.
- A series of operating procedures and traceability documents applicable to all ANSM departments has been created by the Ethics of Expertise Department and presented to the Ethics Committee during its meeting on 24 October 2018 to lay the groundwork for the application of these new control methods in April 2019.

### HIGHLIGHTS IN 2018

- **Expansion of rules regarding the ownership by ANSM employees of financial assets of companies overseen by the agency**

In an effort to implement ANSM's ethics rules regarding its employees in compliance with the provisions adopted the EMA and based on the recommendations written in November 2017 by the Ethics Committee, a letter to the agency's employees from the Director General was published on 28 August 2018 informing them that they can no longer personally own or purchase financial assets from the companies or bodies that fall within the agency's scope.

It should be noted that this rule has applied to new arrivals since 2012. Employees hired before this date could still own this type of asset. However, if their assets were valued at over €5,000, employees could no longer take part in ANSM's work on any of the relevant company's applications. These new measures regarding the ownership of financial assets by employees were added to the agency's ethics charter.



# 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 and communicated through various channels, including a mailing list, the "ANSM Actu" newsletter, the agency's Twitter account, and more.

The Twitter account was used to live tweet several events, including press briefing breakfasts and Temporary Specialised Scientific Committee sessions.

### HIGHLIGHTS IN 2018

- **Creation of concise educational documents** for patients and healthcare professionals regarding topical issues (new TAU treatment methods, quality defect in certain medicines containing valsartan, long-term shortage of Sinemet, and end of Previscan treatment initiations).
- **Development of infographics to explain the agency's activities** (new clinical trial procedure, pharmacovigilance system, and the reporting channel for medication errors).
- **Creation of three educational videos** on medical devices and one video on medication errors.

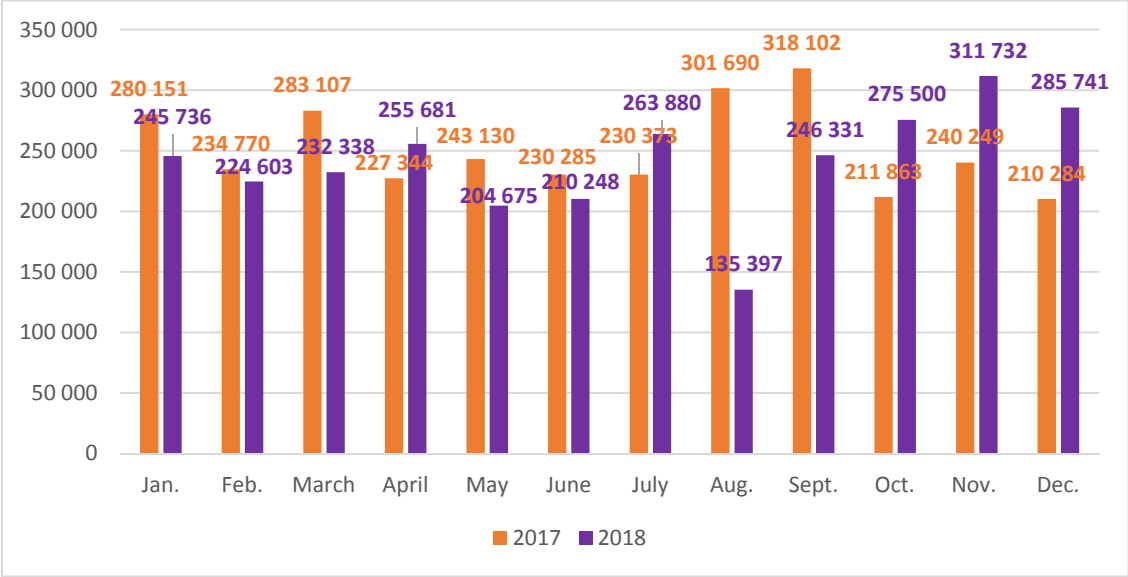
### 2018 DATA

- Publication of **129** updates and **18** press releases
- Publication of **6** "ANSM Actu" newsletters
- **16,617** Twitter followers by the end of December 2018, including around **5,000** new followers<sup>44</sup>
- **2,891,862** unique visitors to [ansm.sante.fr](http://ansm.sante.fr), i.e. nearly **100,000** more than in 2017
- **Over 23 million** visits to the Public Medicine Database were recorded, with an average of **over 1 million** unique visitors per month.

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<sup>44</sup> ANSM created a Twitter account in April 2014.

**Change in the number of unique visitors<sup>45</sup> to ANSM's website**



<sup>45</sup> One unique visitor = one IP address

## Information distributed to healthcare 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.

The agency also partners with the College of General Practitioners (CGP) through an Interface Committee that meets three to four times per year<sup>46</sup>. ANSM also attends the annual CGP conference and has taken part in the group's regional meetings, known as "Les Régionales", since 2018.

### HIGHLIGHTS IN 2018

In order to promote exchanges with general practitioners, ANSM took part in three conferences in 2018:

- **12th French General Medicine Congress (CMGF)** in Paris from 5 to 7 April and participation in the round table discussion entitled "Not one bit: pain patients and medications".
- **18th annual conference of the French National College of Generalists in Medical Education (CNGE)** in Tours from 21-23 November with participation in the round table discussion entitled "Contraception in France in 2018 a few years after the pill crisis".
- **College of General Practitioners Regional Meetings** in Nice (30 June), Toulouse (15 September), and Rennes (8 December) and the co-organisation of a sessions entitled "Pregnancy and medication: always a choice?"

In 2018, the agency also organised meetings for specific audiences:

- informational meeting on **the new European regulation regarding medical devices** on 13 April,
- informational meeting on **the new European regulation on *in vitro* diagnostic medical devices** on 19 June,
- An informational meeting on **the implementation of the e-Saturne application** on 18 October.

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<sup>46</sup> See also "The College of General Practitioners Interface Committee", page 142.

## Press relations

ANSM is in constant contact with the media to answer questions about medicines, health products, the agency's activities, its method of operation, and its decision-making process.

In 2018, ANSM responded to 860 requests from the media (an average of 71 per month).

Compared to the previous year, ANSM's media coverage decreased 26% with a total of nearly 7,340 mentions (written press as well as online, radio, and TV media). The written press accounted for nearly 40% of all media coverage, while the online press accounted for 49%.

In 2018, ANSM representatives spoke out more often: 36% of media mentions quoted an ANSM employee (vs. 31% in 2017), and the number of times managers spoke out increased significantly.

In addition, ANSM organised regular events with the press, including press conferences and breakfasts as well as meetings with various editorial boards in order to strengthen its relationship with journalists.

### HIGHLIGHTS IN 2018

- **Participation in two press conferences** with the French Ministry of Health and Solidarity regarding the increase in the number of mandatory vaccines (January 2018) and the seasonal flu vaccine campaign (October 2018).
- **Organisation of a press meeting** during the visit of the French Minister of Health and Solidarity to ANSM to publicise the report on improving the information provided to users and healthcare professionals about medicines (September 2018).
- **Organisation of four press breakfasts** with an update on topical issues and an explanation of ANSM's activities:
  - in February regarding the action plan to ensure the continuity of treatment of patients taking Cytotec (misoprostol) ahead of its withdrawal from the market, the evaluation of the marketing authorisation (MA) for baclofen for the treatment of alcohol addiction, and medication shortages,
  - in June regarding the new European regulations for medical devices and *in vitro* diagnostic medical devices as well as the stricter risk reduction measures for valproate, the evaluation of the baclofen MA, the enhanced surveillance measures for Prolia, and recommendations for the names and labels of medications,
  - in September regarding medicines containing valsartan, cyproterone acetate (Androcur and its generics), the risk of meningioma, and the creation of a TSSC expert committee entitled "Evaluation of the relevance and feasibility of making medical cannabis available in France"<sup>47</sup>,
  - in October regarding the issuance of a market authorisation for the use of baclofen in the treatment of alcohol addiction<sup>48</sup> and apheresis devices manufactured by Haemonetics.

### 2018 DATA

- **860** media requests, an average **71** each month
- **7,340** media mentions

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<sup>47</sup> See also the focus entitled "Evaluation of the relevance and feasibility of making medical cannabis available in France", page 104.

<sup>48</sup> See also the focus entitled "Issuance of MA for the use of baclofen in the treatment of alcohol addiction", page 107.

## Information for parliamentary representatives

Three senators and three deputies have a seat on ANSM's Board of Executives<sup>49</sup>. The agency also contributes to discussions with parliamentary representatives via the responses it provides to letters and written questions submitted to the Health Minister or directly to the agency.

### 2018 DATA

In 2018, the agency responded to 67 written questions and 22 letters from parliamentary representatives. The main questions submitted by parliamentary representatives related to:

- stock shortages for certain medicines/vaccines and supply problems,
- the medications Levothyrox and Androcur,
- the safety of plasma donations (apheresis machines manufactured by Haemonetics),
- breast implants and the risk of anaplastic large-cell lymphomas,
- access to rare disease treatments and innovative treatments,
- biosimilar medicines,
- the renewal of the certification of certain medical devices.

## Patient information and patient involvement in the agency's work

The relevance and effectiveness of the agency's decisions are based on its ability to keep patients informed and involve patient representatives in ANSM's work.

The agency increased its involvement with patient associations in 2018 by organising meetings and calls to answer their questions and, increasingly, to alert and mobilise them with respect to sensitive issues. In 2018, ANSM had over one hundred exchanges with patient representatives.

### SUPPORT FOR ASSOCIATION PROJECTS

In 2018, ANSM launched its seventh competitive call for proposals aimed at patient associations. The objective of this call was to promote initiatives encouraging the proper and safe use of medicines and other health products. Of the 15 eligible projects, two were chosen as a result of the selection process; these projects reflected the agency's main priorities, which include:

- optimising patient information,
- collecting data on practical difficulties encountered by patients using certain categories of health products,
- promoting the correct use of and adherence with treatments.

A total of €30,000 was allocated in subsidies.

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<sup>49</sup> See also "Governance bodies", page 11.

## Discussions within the Interface Committees

Interface committees work with patient groups, the College of General Practitioners, 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 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 7 full members representing patient or health system consumer associations and seven full members representing the agency. It also has 14 deputies. Its members were reappointed in 2016 for a period of three years.

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.

A working group dedicated to patient information was created in 2014. Its goal is to suggest ways to optimise the information the agency provides to patients and the general public.

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

Committee	Number of meetings in 2018
Interface committee working with accredited patient or health system consumer associations involved in the health products sector	3

### THE COLLEGE OF GENERAL PRACTITIONERS INTERFACE COMMITTEE

The College of General Practitioners (CGP) and ANSM share a common objective—to ensure patient safety. To achieve this goal, 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 College of General Practitioners in 2016. Its goal is to create a space for discussion in order to best anticipate actions and decisions that could impact general practitioners and their patients.

#### Its goals:

- better understand and take into account the needs of general practitioners,
- make ANSM's activities more transparent,
- increase the contribution of general practitioners to the agency's activities and missions,
- inform physicians early on to help them provide better patient care,
- optimise the collection and assessment of information to detect and monitor risks.

#### In practice:

- discuss the feasibility of the proposed measures and the readability of the information on a case-by-case basis,
- develop "key messages" and tools about actions impacting practices,
- help monitor a medicine's effectiveness and safe use after its put on the market,
- share information about health policy decision, proper use information, investigations, and more.

The Interface Committee met three times in 2018. Throughout the year, it worked on the topic of "Medication errors". This collaboration resulted in the organisation of a discussion day between ANSM and the CGP.

## HIGHLIGHTS IN 2018

- **Organisation of an ANSM-College of General Practitioners discussion day on Medication errors in high-street pharmacies** (November 2018)<sup>50</sup>.

## INTERFACE COMMITTEES AND MANUFACTURER REPRESENTATIVES

These committees serve as an interface between ANSM and manufacturers concerning questions of general interest in accordance with the agency's transparency rules. They were created and formed in 2013, with equal numbers of manufacturing representatives and agency representatives.

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

The composition of these committees, their agendas, and meeting minutes are published on ANSM's website.

Committee	Number of committee meetings in 2018	List of working groups	Total number of working group meetings in 2018
Medical industry representative interface committee	4	<ul style="list-style-type: none"> <li>• Publicity/information/communications</li> <li>• Early access to innovation</li> <li>• Monitoring</li> <li>• Industrial practices</li> <li>• Process improvement/MA and MA amendment request process optimisation</li> </ul>	16
Interface committee working with representatives from medical device and <i>in vitro</i> diagnostic medical device industries	1	<ul style="list-style-type: none"> <li>• Industrial practices</li> <li>• Vigilance</li> <li>• Access to innovation</li> <li>• European regulations regarding MDs and IVDMDs</li> <li>• National quality control relations</li> </ul>	5

<sup>50</sup> See also the focus entitled "An ANSM-College of General Practitioners discussion day on medication errors in high-street pharmacies", page 144.

## FOCUS ON: An ANSM-CGP discussion day on medication errors in high-street pharmacies

During Patient Safety Week, the theme of which was “Using Medications Wisely”, the CGP and ANSM organised a day dedicated to medication errors in high-street pharmacies on 28 November 2018. The goal of this day was to raise awareness among private-practice healthcare professionals about the issue of medication errors and to encourage experience sharing by giving the floor to general practitioners and all high-street stakeholders, including pharmacists, nurses, and patients.

The day, which included both speeches and debates with the audience, was centred around three areas of focus:

- a review of medication errors and high-risk situations,
- a summary of regional and national experiences,
- a round-table discussion with stakeholders from the healthcare industry to gather feedback and ideas for preventing medication errors.

The event underscored the need to share information and adopt a concerted, global approach while raising awareness among every stakeholder in the healthcare industry. Providing the patient with support plays a key role in helping patients comply with their treatment, following the directions for their prescription, and preventing medication errors.

After the day's meetings, the CGP and ANSM developed a common action plan that included the following:

- A decision to include medication error management in the introductory and continuous training programme for all healthcare professionals (pharmacists, doctors, nurses, etc.).
- The implementation of a methodological assistance system for teams operating in the field that would like to better identify medication errors.
- A competition, such as a hackathon, during the second half of 2019 to help develop digital tools that would make it easier to report, analyse, and receive feedback about medication errors. To make this possible, ANSM is offering to share its medication error reporting data.
- The creation of informational documents or communication activities to raise awareness among all actors (general practitioners, pharmacists, nurses, and the general public): offering widespread access to patient information documents to help them switch to a new medication or creating guides for each stakeholder, etc.
- The improvement of the support system for patients released from hospital through the systematic use of documents that provide patients with all the information they need for the next step in their treatment (end of prescriptions, change of dose during hospitalisation, etc.).
- The promotion of the use of the pharmaceutical file containing the patient's prescription and dispensing history, which is key for properly following up on a patient.
- The organisation of a plenary session on medication errors during the CGP conference in April 2019.

**For more information, watch the video about the day on ANSM's YouTube channel:**

[https://www.youtube.com/channel/UCLwzdfn\\_TDPGx7pv7nbDryQ](https://www.youtube.com/channel/UCLwzdfn_TDPGx7pv7nbDryQ)



## FOCUS ON: ANSM creates a strategy for opening up its data to the public

In 2018, ANSM made it a priority to develop a strategy and establish the necessary conditions for publishing its data.

Making its data available to the public is a new key step in ANSM's openness policy and is the continuation of the actions it has been taking since 2017, which include the launch of public hearings, and 2018, namely the development of a digital strategy. It meets the goals featured in the second Objectives and Performance Contract for 2019-2023, the first half of which is dedicated to opening up the agency to stakeholders and making its work more transparent. Publishing the agency's data is part of ANSM's data and information systems master plan. Finally, it aligns with the agency's broader governmental policy of promoting the use of data with, in the healthcare sector, the creation of the Health Data Hub.

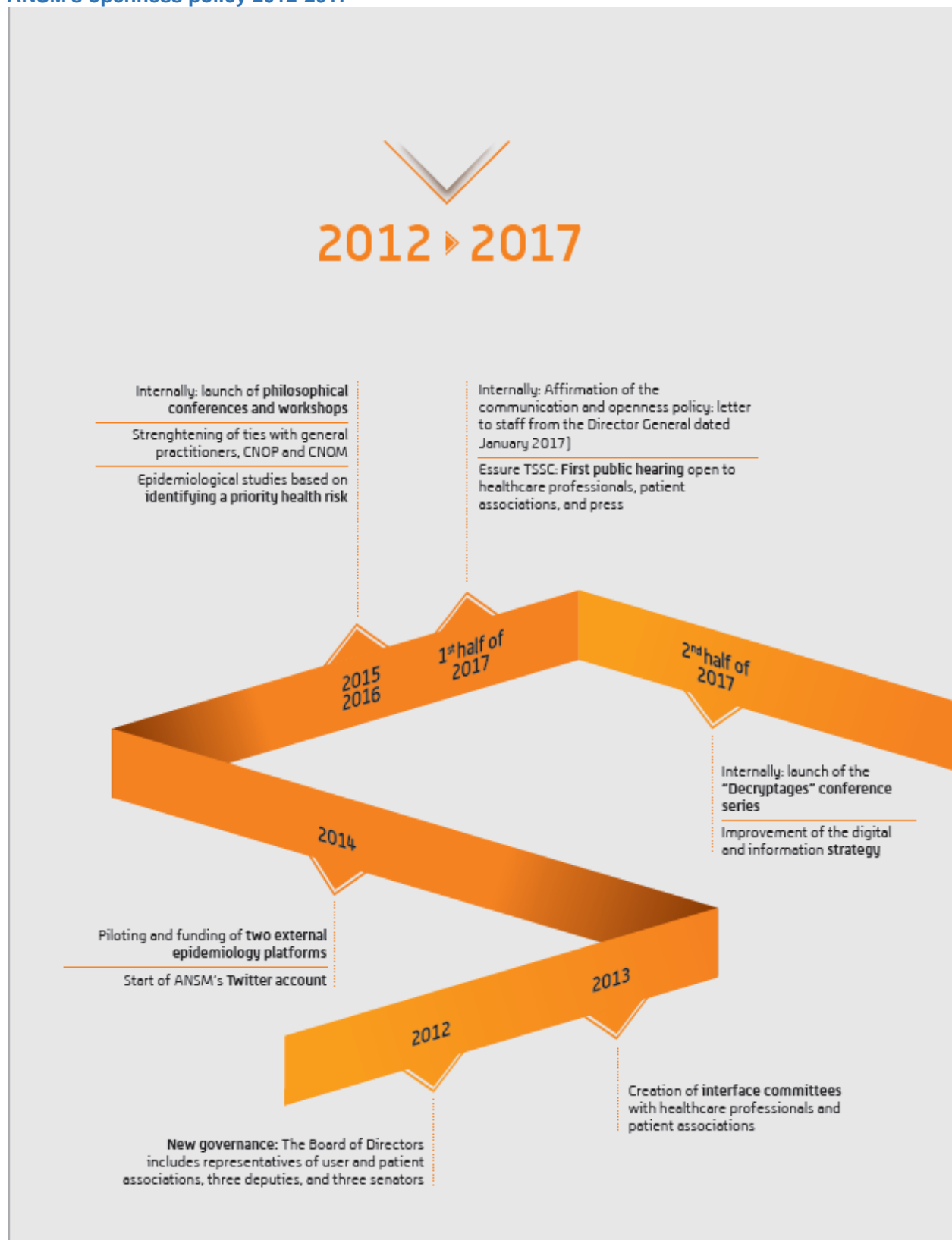
The data openness strategy, which will be start to be rolled out in 2019, seeks to achieve the following goals:

- Publishing documents required by law, starting with administrative documents that are requested through the administrative document access law, also known as CADA requests;
- Gradually publishing the agency's databases on data.gouv.fr (publication of "raw data");
- Communicating with the public about the content of the dossiers managed by the agency by publishing its evaluation documents.

This data will be made available without violating confidentiality or legally protected rights, be they personal or collective.

ANSM is receiving assistance from external experts. Etalab (from the Prime Minister's departments) is helping with the method, and CADA is consulting with the agency on any legal questions.

## ANSM's openness policy 2012-2017





# NATIONAL INTEGRATION OF HEALTH AND MEDICAL RESEARCH PROFESSIONALS

## Promoting independent research to support ANSM's missions

In 2018, ANSM launched its seventh 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.

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.

### HIGHLIGHTS IN 2018

- **Publication of a second summary report** on research projects funded by ANSM since 2012 regarding the safety of health products (December 2018).
- **Funding of two national academic networks:** “Health products and pregnancy” and “New translational approaches in clinical toxicology”.

### 2018 DATA

In 2018, ANSM decided to re-focus its call for proposals on three major challenges facing the agency. ANSM offered **to fund a national structured network** for each of the following themes:

- “Health products and pregnancy”
- “New translational approaches in clinical toxicology”
- “Society and health products”

For the seventh edition of the agency’s call for proposals, two applications for the creation of a national “Health products and pregnancy” network and two applications for the creation of a national “New translational approaches in clinical toxicology” network were submitted. No applications for the “Society and health products” category were submitted.

For each topic, a jury made up of independent scientists evaluated the applications and interviewed the project leaders. At the end of the selection process, ANSM funded the “Health products and pregnancy” network run by Isabelle Lacroix (Toulouse University Hospital) and the “New translational approaches in clinical toxicology” network piloted by Bruno Clément (Inserm).

At the same time, the agency followed up with selected projects from 2012 to 2017. 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 used properly. Each project's funding convention requires the regular submission of scientific reports, budget reports, and a presentation of interim results halfway through the project's term. Around fifty projects are regularly monitored in this way.

## Focus on: ANSM publications in international scientific journals in 2018

### Scientific publications of the health product epidemiology department

- Bouillon K, Bertrand M, Bader G, Lucot JP, Dray-Spira R, Zureik M. Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes. *JAMA* 2018;319(4):375-387. doi:10.1001/jama.2017.21269.
- Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel MF, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018;155(2):337-346.e10. doi: 10.1053/j.gastro.2018.04.012.
- Lassalle M, Colas S, Rudnichi A, Zureik M, Dray-Spira R. Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res* 2018 doi: 10.1097/01.blo.0000533617.64678.69. [Epub ahead of print].
- Blotière PO, Weill A, Dalichampt M, Billionnet C, Mezzarobba M, Raguideau F, Dray-Spira R, Zureik M, Coste J, Alla F. Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: An application to antiepileptic drug use in 4.9 million pregnant women in France. *Pharmacoepidemiol Drug Saf* 2018. DOI: 10.1002/pds.4556.
- Coste J, Billionnet C, Rudnichi A, Pouchot J, Dray-Spira R, Giral P, Zureik M. Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France. *Eur J Prev Cardio*. 2018. doi: 10.1177/2047487318776831. [Epub ahead of print].
- Bouyer B, Rudnichi A, Dray-Spira R, Zureik M, Coste J. Thromboembolic risk after lumbar spine surgery: a cohort study of 325,000 French patients. *J Thromb Haemost* 2018 Jun 12. doi: 10.1111/jth.14205. [Epub ahead of print].
- Billioti de Gage S, Collin C, Le-Tri T, Pariente A, Bégaud B, Verdoux H, Dray-Spira R, Zureik M. Antidepressants and Hepatotoxicity: A Cohort Study among 5 Million Individuals Registered in the French National Health Insurance Database. *CNS Drugs* 2018; 32(7):673-684. doi: 10.1007/s40263-018-0537-1.
- Chaignot C, Zureik M, Rey G, Dray-Spira R, Coste J, Weill A. Risk of hospitalisation and death related to baclofen for alcohol use disorders: comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165,334 patients between 2009 and 2015 in France. *Pharmacoepidemiol Drug Saf* 2018; 27:1239-1248. DOI: 10.1002/pds.4635.
- Lassalle M, Colas S, Zureik M, Dray-Spira R. Reply to the Letter to the Editor: Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res* 2018;476(12):2462-2463. doi: 10.1097/CORR.0000000000000525.

### Scientific publications of the controls Division

- Morgeaux S, Koy A, Manniam I, Regourd E, Variot P, Costanzo A. Establishment of detection antibodies BRRs batch 4 for in vitro potency assay of hepatitis A vaccines by ELISA. *Pharmeur Bio Sci Notes*. 2018; 2018:1-11.
- Identification and quantification of ethylene oxide in sterilized medical devices using multiple headspace GC/MS measurement. Gimeno P, Auguste ML, Handlos V, Nielsen AM, Schmidt S, Lassu N, Vogel M, Fischer A, Brenier C, Duperray F. *J Pharm Biomed Anal*. 2018 Sep 5;158:119-127. doi: 10.1016/j.jpba.2018.05.035. Epub 2018 May 22.

## Relations with other health system operators

### PARTNERSHIPS 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 through 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 Solidarity. 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.

ANSM participates in steering and monitoring committees and provides its expertise with respect to health products (chemical medicines, biological medicines, diagnostic tests, etc.), their methods of use, and the preparation of health alerts (heat wave plan).

### PARTICIPATION IN HEALTH THREAT MANAGEMENT

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). ANSM is involved in the Biotox (biological risk), Piratox (chemical risk) and Piratome (radiological risk) parts of the plan.

The agency is a member of the Biotox-Piratox Laboratories, responsible for analysing the event of a malicious act. implement the exercise in and identification of various

#### ANSM helps prepare the health system for large-scale health threats

Scientific Board of the National Network of which brings together laboratories human, animal, or environmental samples in ANSM helped organise the network and November 2018 concerning the detection highly pathogenic microorganisms.

In addition, ANSM contributes certain medicines that are included in the government's strategic medication inventory as part of a three-part convention with the French Ministry of Health and Santé publique France. ANSM is in charge of a programme that tests the quality, stability, and safety of health products included in France's strategic inventories. The goal is to ensure the medicines in these inventories remain compliant. ANSM develops the control strategy that must be followed and adapts it to suit the timing of the controls. This strategy complies with the recommendations in the European guidelines regarding the monitoring of strategic medicine inventories.

its expertise in monitoring the quality of

### HIGHLIGHTS IN 2018

- **As part of its preparation for exceptional health situations, ANSM is a member of the “Regional health resources during exceptional health situations” commission, which was created by Santé publique France.** This commission write opinions, develops technical and operational recommendations, identifies the necessary resources, and creates standards. It oversees working groups such as the “Evolution of mobile health centres” working group, which is tasked with improving the capacities of emergency medical staff in the event of terrorist attacks and natural or accidental catastrophes.

## Focus on: ANSM in its environment: A sociological study co-funded by the CNRS and ANSM

ANSM and the laboratory of the CNRS organisation sociology centre decided to conduct a research project on surveillance practices for health products outside of crisis situations (vigilance systems, media, social networks) given that the healthcare system is changing, society is evolving, and ANSM is having to adopt new strategies to cope with new social challenges.

The study began in September 2018 and will last for 30 months. It is run by four research sociologists specialising in organisations and health issues. They are supported by a group of seven students completing their master's degree in sociology at Sciences Po.

The study includes three phases:

- an exploratory research phase led by researchers from September to December 2018,
- a collective research phase conducted by Master's students from January to June 2019,
- a more in-depth research phase and analysis overseen by researchers from June 2019 to February 2020.

At the end of the study, a report in the form of an organisational diagnostic will be written and made public.

## Legal and regulatory activities

### ANSM'S ROLE IN REVISING LEGISLATION

ANSM helps develop legislation and regulations on both a national and European level<sup>51</sup>.

In 2018, the agency helped write several European texts (e.g. Texts on biosimilar medicines, herbal medicines, medical devices, and substances used in cosmetic products).

On a national level, the agency helped write and publish over thirty texts on medicines (including best practice guidelines for pharmacovigilance and icons on medicine packaging), biologics, medical devices, *in vitro* diagnostic medical devices, and cosmetics.

### LITIGATION AND RULINGS

In 2018, ANSM received 101 new requests related to its decisions.

Fifty-five decisions were delivered by the administrative judge. One hundred and twenty-seven decisions were issued in 2017. The vast majority of disputes submitted to the courts of law were rejected (52 rejections, withdrawals or dismissals).

### FINANCIAL SANCTIONS

Since the start of the process at the end of 2015, ANSM initiated 46 financial sanction procedures, 21 of which led to sanctions against the operators of a medicine or medical device.

### HIGHLIGHTS IN 2018

- **First financial sanction for non-compliance with regulatory provisions regarding medicine shortages (€348,623).**

### 2018 DATA

- **9 health policy rulings, most of which involved medical devices**
- **16 financial sanction procedures initiated**
- **10 financial sanctions issued**

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<sup>51</sup> See also the "Overview of major French and European texts published in 2018" in Appendix 5, page 199.



**Combined records of all disputes**

All disputes	2015	2016	2017	2018
Rejections/withdrawals/dismissals	46	37	122	52
Cancellation/conviction	2	3	5	3

**Summary of sanctions issued since the process was implemented**

Sector	Area of activity	2016	2017	2018
Medical device	Advertising	2	0	3
	Marketing	0	4	0
	Medical device vigilance	0	0	0
Pharmaceutical company	Distribution best practices	1	0	0
	Public service obligations	0	0	5
Medicine	Advertising	0	4	1
	Shortage	0	0	1
Total		3	8	10
Total amount (euros)		58,102	526,983	989,123

# EUROPEAN WORK

## European strategy

The agency's European strategy was put in place in 2016. It aims to make ANSM's actions more efficient with respect to the European issues for which France decides to serve as the rapporteur or co-rapporteur by identifying the therapeutic topics that are most important to the agency and ranking them in terms of their strategic interest according to set criteria.

For each level of priority, a quantitative target has been set (70% of high-priority, level-1 topics, 20% of moderate-priority, level-2 topics, and 10% of low-priority, level-3 topics).

In 2018, the EMA had to prepare for the possibility that the United Kingdom would not only leave the European Union in 2019, but that it would also stop participating in the work of the EMA. With respect to centralised procedures, the United Kingdom is the rapporteur or co-rapporteur within the CHMP for around 20% of applications assigned through 2018.

Like all other national agencies, ANSM was asked to take over a portion of the United Kingdom's assignments and volunteered to become the rapporteur or co-rapporteur for 21 applications, which represents 95% of the total applications proposed.

To keep up with its normal duties and continue to play an active role in new procedures, ANSM was granted 10 new employees not covered by the cap to not only maintain but also increase its presence in the centralised procedure.

These ten employees, who were recruited between September 2018 and January 2019, made it possible for ANSM to achieve and even exceed the targets that were assigned to the agency to ensure the sustainability of the recruitment campaign: 16 new CHMP applications were assigned to France in 2018 (the target total was 14, compared to 12 in 2017). Similarly, the number of European scientific opinions processed in France rose from 57 in 2017 to 79 in 2018<sup>52</sup>.

ANSM decided to task a new structure that reports to the agency's executive managers, the European Strategy Piloting Centre, with overseeing the European strategy and any related activities.

The centre coordinates the activity of the ten new recruits, the three employees assigned to the topic in 2017, and the CHMP and PRAC delegates and is overseen by a Centre Manager with help from a coordinator and assistant managers.

### HIGHLIGHTS IN 2018

- **Creation of the European Strategy Piloting Centre** (preparation in December 2018 and installation in January 2019).

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<sup>52</sup> See also the chapter entitled "Scientific opinions", p. 94.

## Focus on: Preparing for Brexit

In preparation for the United Kingdom's exit from the European Union, ANSM and the French Health Minister began meeting in October 2018 to assess the impact of a hard Brexit on medications and identify the necessary measures within their sphere of influence that could be put in place to prevent shortages in France, especially with respect to ensuring marketing authorisations for medicines complied with the law.

### Several steps were taken:

- Creation of a webpage about Brexit on ANSM's website.
- Identification of medicines that could be impacted (namely medicines with MAs that would no longer comply with European regulations).
- A letter campaign in December 2017 aimed at MA holders to remind them of their obligation to have a marketing authorisation that was valid in the EU-27 at the time when Brexit was scheduled to take place (initially scheduled for 30/03/2019).
- Letter campaign in January 2019 to all owners and operators of medicines marketed in France reminding them of their responsibility to provide an adequate and continuous supply for the national market and informing them of issues with transporting goods through the United Kingdom due to the possibility of the reintroduction of border controls. They were asked to report any issues with supplying the French market and plan to implement temporary alternative sources or additional stock outside of the United Kingdom as soon as possible if needed.
- A letter campaign in February 2019 for all clinical trial sponsors in France.
- Organisation of regular updates with union representatives of pharmaceutical companies regarding previous and future actions as well as any issues that have been identified.
- Discussions with customs and the publication of information on future customs procedures on the ANSM website.

For each medicine that was found to be at risk of a shortage, ANSM contacted each laboratory concerned to verify this risk and identify on a case-by-case basis the solutions that could be implemented to make the MA compliant once again and avoid any supply disruptions due to regulatory concerns.

Similar steps were taken for medical devices and *in vitro* diagnostic medical devices. In this case, the problem was caused by the post-Brexit validity of CE compliance certificates issued by a notified body located in the United Kingdom. However, given the limited amount of data available and the specificity of the sector, as seen in the wide variety of medical devices and the diverse manufacturing steps and processes used to make them, it is difficult to establish an exhaustive list of products that will be affected by Brexit.

It is important to note that regulatory concerns for medicines registered through the centralised procedure are handled by the EMA.

Nevertheless, despite the agency's efforts to prepare for Brexit, it is difficult to anticipate all the health product safety risks that could be created due to this event. To this point, and especially with respect to medicines, ANSM does not have the authority to require pharmaceutical manufacturers to carry out all the regulatory processes necessary to ensure the compliance of their MAs and continue marketing their products in France.

In addition, as part of its work to prepare for Brexit, the agency established priorities with respect to risks to patient health. ANSM decided to prioritise the principle of a patient's lost opportunity.

When it identifies a supply issue for a given medicine, ANSM plans on delivering an import authorisation (IA) in replacement of the non-compliant MA. Import authorisations are covered by both European and national regulations. This approach is a typical response to a shortage. As such, additional national measures are not necessary. In addition, as indicated by the European Commission in its statement on 21 February 2019, a country's competent authorities can authorise, under certain conditions and when the circumstances are justified, an MA holder to keep a quality control site in the United Kingdom no later than 31 December 2019. ANSM, with the approval of European authorities, organised the implementation of these exceptions with respect to pharmaceutical companies.

With respect to medical devices, ANSM's Director General can issue a decision on a case-by-case basis to guarantee the continued availability of certain devices that are essential for patient health or public health.

In addition, special attention must be paid to the physical flows of products and customs procedures when products are transported across borders. For example, if a product is bulky and difficult to transport, it could take longer to reach patients.

## Representation of ANSM within European bodies

### EUROPEAN MEDICINES AGENCY (EMA)

ANSM represents France on the Executive Board of the EMA (European Medicines Agency). 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.

ANSM is also a stakeholder in the EMA's various committees for the assessment and surveillance of medicines, namely:

- **The Committee for Medicinal Products for Human Use (CHMP):** the 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 comprises representatives from all member states, meets every month 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<sup>53</sup>.
- **The European Pharmacovigilance Assessment Committee (PRAC),** created as part of Europe's pharmacovigilance law in July 2012, strengthens 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<sup>54</sup>.

### HEADS OF MEDICINES AGENCIES (HMA)

ANSM actively took part in meetings of the Heads of Medicines Agencies (HMA) during the rotating presidencies of the Council of the European Union, which took place in Bulgaria and Austria, and pursued a wide variety of projects aimed at facilitating the implementation of its strategy.

ANSM worked with the EMA and the European Commission to monitor the efforts of MA-owning companies to bring the marketing authorisations for their medicines into compliance following Brexit<sup>55</sup>.

ANSM oversees the development of an efficient, effective, and collaborative approach to inspections as part of the agency network's goal to use resources more efficiently while promoting mutual trust and a fair division of labour in an effort to help change the global regulatory environment. To help achieve this goal, ANSM supported international collaborative initiatives regarding inspections of manufacturing best practices of the International Coalition of Medicines Regulatory Authorities (ICMRA) and Pharmaceutical Inspection Co-operation Scheme (PIC/S).

### EUROPEAN NETWORK OF COMPETENT AUTHORITIES FOR MEDICAL DEVICES (CAMD)

The network met twice in 2018. Discussions on its attributions, some of which are now governed by new regulations (post-market surveillance and supervision of notified bodies), are underway. Several task forces have been put in place to help member states implement new regulations.

As stipulated by new European regulations, the Medical device coordination group (MDCG) was created in November 2017. Two representatives from ANSM and two representatives from the Ministry of Health represent France. This group met six times in 2018. Its responsibilities are described in article 105 of UE regulation 2017/745. The group helped evaluate the first notified body (NB) under current regulations.

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<sup>53</sup> See also the chapter entitled "Marketing authorisations (MAs) for medicines", p. 105.

<sup>54</sup> See also the chapter entitled "France's contribution to European pharmacovigilance", p. 26.

<sup>55</sup> See also the focus on "Preparing for Brexit", page 155.

The MDCG comprises eleven sub-working groups: NBO (supervision of NB), Standards, CIE (WG on Clinical Investigation and Evaluation), PMSV (WG on Post-Market Surveillance and Vigilance), MS (Market Surveillance), B and C (classification/qualification), NET (New Technologies), Eudamed, UDI (Unique Device ID), International Matters (along with IMDRF), and IVD (In-Vitro Diagnostic MD). ANSM is represented in each of these groups, which will be led by the Commission. Some groups will also be co-led by a member state.

## 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 of the European Union.

Based on the area in question, ANSM takes part in the various entities within the EMA, European Commission, Council of Europe, and the OECD.

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

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 Healthcare (EDQM).

With respect to medical devices and *in vitro* diagnostic medical devices, ANSM is a member of the Notified Body Operations Group (NBOG) within the European Commission. As a member of this group, the agency designates notified compliance certification bodies.

With respect to cosmetic products, ANSM participates in the work of the Platform of European Market Surveillance Authorities (PEMSAC), the European Commission's European market surveillance network for cosmetic products.

As regards safety trials, ANSM is a member of European and international authorities (the EMA, European Commission, and the OECD) that establish the rules for inspections with respect to laboratory best practices.

## HIGHLIGHTS IN 2018

**The Bulgarian and Austrian presidencies continued the work of previous presidencies by focusing on the following topics:**

- redirecting the agenda in light of Brexit,
- optimising the network's regulatory operations,
- the availability of authorised medicines and access to new medicines,
- helping national agencies to apply the Clinical Trials Regulation,
- increasing surveillance.

# INTERNATIONAL COOPERATION ACTIVITIES

## Multilateral cooperation activities

### COOPERATION BETWEEN INTERNATIONAL AGENCIES

The activities of the ICMRA (International Coalition of Medicines Regulatory Authorities) continued in 2018 during two meetings in Basel and Washington.

Several topics were discussed, especially with respect to pharmaceutical innovation and pharmacovigilance. The ICMRA Innovation project examined prospective analysis methodologies that could be used to identify trends and evaluated how the results of the prospective analysis could be used to identify innovative products and regulatory opportunities and challenges. A working group was created to examine gaps in current pharmacovigilance practices. It was tasked with studying the opportunities and challenges presented by the use of real world data (RWD) initiatives in healthcare and to facilitate international collaboration in this field. A position paper and a list of related initiatives was created.

**In March 2018, ANSM participated, as it does every year, in the UN's Commission for Narcotics and Psychotropics**

As the national authority in charge of supervising the use of narcotic and psychotropic products, ANSM participated, as it does every year, in the United Nation's Commission for Narcotics and Psychotropics in March 2018. It also drew up an annual report for the International Narcotics Control Board (INCB). In addition, on 4–7 June 2018, the INCB visited France in an effort to improve dialogue between the board and competent French authorities and meet with the main authorities responsible for implementing international drug control treaties and civil society representatives. The agency met with the members of this delegation on 6 June 2018.

### INTERNATIONAL COOPERATION ACTIVITIES

Several trainees from medicine control laboratories in Africa (namely Côte d'Ivoire, Burkina Faso, and South Africa) received training. This type of training helps develop and implement new laboratory techniques aimed at increasing market surveillance in each trainee's country.

A delegation from the new authorities under the Chinese medicines agency (NMPA) met with ANSM senior management to explore opportunities to work together on shared interests.

As part of its cooperation agreement with Lebanon, the agency continued to provide technical assistance to support developments in the field of generics and medical devices.

ANSM's Director General took part in a demonstration to celebrate the 10-year anniversary of the agency's cooperation with Lebanon with respect to the quality of medicines and medical device traceability.

### TECHNICAL AND SCIENTIFIC MULTILATERAL COOPERATION

ANSM continued to play a significant role in the activities of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) with respect to technical issues related to manufacturing best practices (especially regarding advanced therapy medicinal products), the training of inspectors (presidency of the PIC/S Inspection Academy sub-committee for training and development), and the evaluation of membership requests/re-evaluation of participating authorities (Saudi Arabia, Argentina, and Russia). By the end of 2018, the PIC/S included 52 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), which comprises 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 2018, ANSM's laboratories participated in 22 collaborative studies, including 10 performance studies. ANSM also participated in four joint quality audits with other OMCLs in Belgium, Bulgaria, Serbia, and Morocco.

## **Cooperation activities with agencies within the European network**

Several benchmarking visits were conducted in Sweden, Spain, Germany, and Belgium to discuss best practices for evaluating clinical trials, medication registration applications, and their organisational structures with the goal of identifying ways to make them more efficient.

## **Bilateral cooperation activities**

The agency continued its bilateral activities with the competent national authorities of third countries under current bilateral conventions and further strengthened these relationships by sharing information on multiple occasions, especially with the United States, Japan, Brazil, and Canada, regarding health products (inspection reports, batch recalls, compassionate use of medicines, imports, regulatory information, etc.).





## **Part 4**

### **Reinforcing ANSM's efficiency and pursuing its modernisation**

## Reinforcing ANSM's efficiency and pursuing its modernisation

### Optimising internal processes and the integrated management system

**p. 164**

- Adopting a quality policy p. 164
- Process mapping p. 166
- The agency's modernisation policy p. 167
- Internal auditing activity p. 167

### Implementing the Information System Master Plan (ISMP)

**p. 169**

### Human resources

**p. 171**

- The HR policy is based on the jobs and skills master plan p. 171
- Employment changes p. 172
- Training and career design by business line p. 173
- Measures to improve the quality of life at work p. 174
- Dialogue between management and employees p. 176
- Internal communications: providing support and creating meaning p. 177

### The agency's budget

**p. 178**

- Revenue p. 178
- Expenditure p. 180
- Contracts p. 182
- Strengthening purchasing procedures p. 183
- Rolling out internal accounting and budgetary controls p. 184

# OPTIMISING INTERNAL PROCESSES AND THE INTEGRATED MANAGEMENT SYSTEM

## Adopting a quality policy

The actions carried out in 2018 were aimed at preparing the agency's Management and Quality System for 2015 ISO 9001 certification with respect to the "Managing risk" macro process. This includes the "Monitoring health products" processes, "Managing high-risk situations" processes, "Inspecting" and "Controlling health products" processes, and the key steering and support processes that make up the macro process road map established in 2018.

The roll-out and management of the agency quality management system was based on the ISO 9001 standard. This standard identifies risks and opportunities at every level of the organisation.

With the implementation of its committed to better managing its a continuous improvement process organisation, and results.

**At the end of 2017, ANSM created the CASAR to make it easier to manage the most sensitive alerts**

quality policy, the agency risks and promoting and developing with respect to its practices,

To help managers and agents fully associated with this quality policy goals, a support plan was created and conferences were organised throughout the year to support the internal roll-out of the quality management system.

understand the challenges and break it down into operational in March. Meetings, workshops,

## RISK MANAGEMENT

Risk management makes up the core of ANSM's quality policy. The agency incorporates it into all of its decisions to reduce the risks faced by any patient exposed to health products.

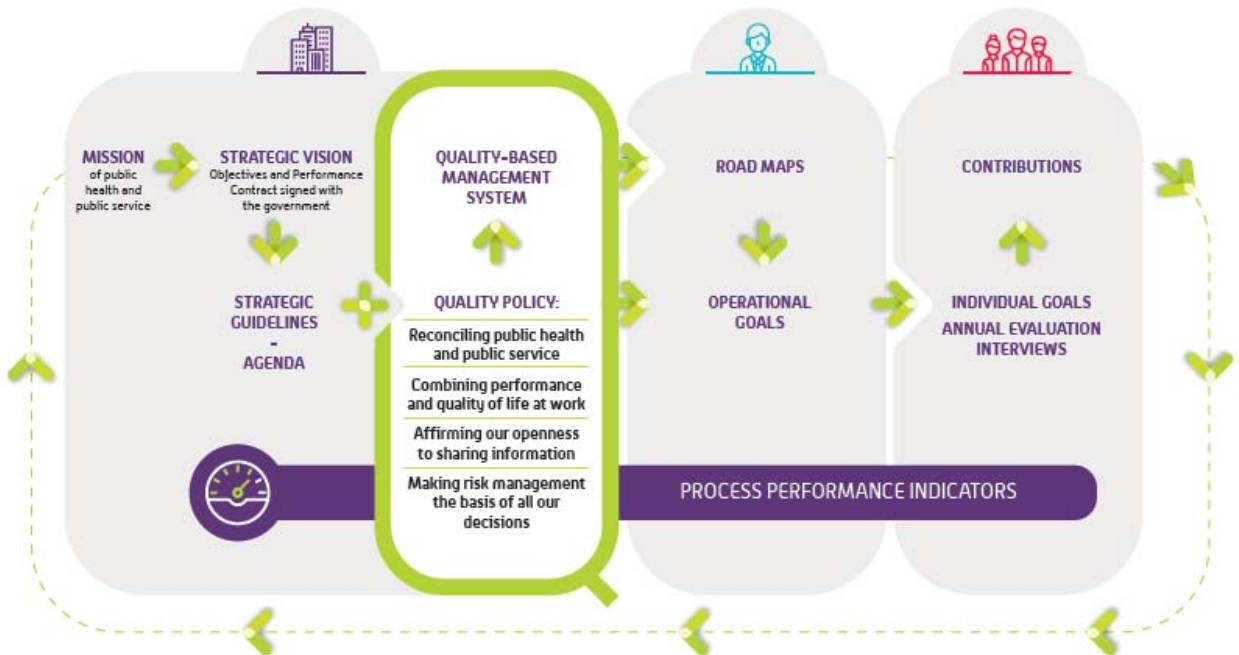
To address this new concern, ANSM created a Support Centre for emergency situations, health alerts, and risk management at the end of 2017 to make it easier to manage the most sensitive alerts and to strengthen ANSM's response capacities both internally and externally, especially given the agency's growing exposure to a national and European health environment that is in the midst of monumental change.<sup>56</sup>

## HIGHLIGHTS IN 2018

- **ISO 9001 certification** (January 2019)
- **Certification audit on risk management** (17-20 December 2018)
- **Adopting a quality policy** (March 2018)

<sup>56</sup> See the chapter entitled "Risk management", p. 15.

**QUALITY** FROM STRATEGY TO THE ANNUAL EVALUATION INTERVIEW



## Process mapping

The quality management system is based on nine macro-processes (steering, business line, and support macro-processes) and 23 processes that are included on the same quality management map.

The areas of focus included in the quality policy are applied through the operational goals and performance indicators that are supported by these processes, which are based on steering, business lines, and resources.

The 23 processes were finalised and adopted in 2018.

### EVOLUTION OF THE MACRO-PROCESSES MAPPING 14/03/2018

#### STEERING MACRO-PROCESSES

ESTABLISH STRATEGY AND STEER THE INSTITUTION	ENSURE LEGAL, REGULATORY, AND ETHICAL SECURITY	STEER THE AGENCY'S COMMUNICATION AND INFORMATION POLICY
Establish the agency's strategic orientations (Steering and Internal Control Mission)	Ensure legal and regulatory security (Legal and Regulatory Affairs Division)	Steer the communication policy (Communications Division)
Steer the institution (Steering and Internal Control Mission)	Make sure ethical concerns are included in processes (Ethics of Expertise Department)	
Steer the agency's scientific policy (Scientific and European Strategy Division)		
Steer the agency's European policy (Scientific and European Strategy Division)		

#### BUSINESS LINE MACRO-PROCESSES

MANAGE FLOWS	AUTHORISE AND/OR REGISTER AND/OR ISSUE OPINIONS	MANAGE RISK
Steer and prioritise flows (Repository and Flow Management Division)	Authorise clinical trials (Innovation and Authorisation Policy Division)	Monitor health products (Surveillance Division)
Safeguard information (Repository and Flow Management Division)	Authorise new requests and modifications and/or register products and/or issue opinions (Innovation and Authorisation Policy Division)	Manage high-risk situations (Scientific and European Strategy Division)
	Authorise institutions (Inspection Division)	Control health products (Laboratory Controls Division)
		Inspect (Inspection Division)

#### SUPPORT MACRO-PROCESSES

MANAGE RESOURCES	MANAGE INFORMATION SYSTEMS	ENSURE SAFETY AND SECURITY
Manage human resources (HR)	Urbanise information systems (Information Technology Division)	Ensure site safety and security (Finance and Administration Division)
Manage technical resources (Finance and Administration Division)	Build and maintain information systems (Information Technology Division)	Ensure information security (Information Technology Division)
Manage finances (Finance and Administration Division)		

## The agency's modernisation policy

The agency's modernisation policy, which was launched in 2015, continued in 2018 with the extension of certain priority projects and the launch of new projects. The priority projects are aimed at securing the agency's working processes. They harmonise practices between departments, improve the traceability of applications, and create better working conditions.

The 2018 portfolio included **nine priority projects**, four of which were from previous portfolios:

Priority projects	Status	
Optimising processes for new MA requests	Launched in August 2017	Continued in 2019
Optimising pharmacovigilance processes	Launched in 2015	Project closed
Optimising medical device surveillance processes	Launched in 2016	Project closed
Optimising the use of external expertise	Launched in 2015	Continued in 2019
Centralising the processing of named-patient TAUs	Launched in October 2017	Project closed
Organising the processing of clinical trials	Launched in 2015, suspended in 2016, and relaunched in 2018	Project closed
Pooling administrative support	New 2018 project	Project closed
Management of whistleblowers	New 2018 project	Project closed
Scientific/technical/regulatory opinions: interactions with operators	New 2018 project	Project closed

## Internal auditing activity

ANSM's internal auditing activity has covered organisational issues and work and business line processes as well as financial, budgetary, and accounting topics since 2018. That is why a new governance structure, the Internal Auditing Committee, was created to oversee the agency's internal audits. The committee will be chaired by the Director General and is scheduled to come into effect in 2019. The Internal Audit Committee approves and regularly reviews how the annual internal auditing programme is being implemented.

The activity is based on an annual programme that includes all of the internal audits conducted within the agency and is managed through two monitoring and performance indicators:

- the internal audit activity completion rate
- the recommendation implementation rate

The internal audit activity completion rate for 2018 was 60% with three reports and one audit that was initially not included in the programme:

- MA modification stock process
- TSSC process
- General Services contract and purchasing management process
- Crisis management process: report in 2019 following the IGAS audit
- Organisation of the management of European activities: report in 2019 following the resizing of the European activity in response to Brexit
- Organisation of the DPAI: report in 2020 following the ongoing MA project

A management plan for monitoring audit action plans, which started to be created in 2016, was implemented in 2018. The action plans for 75% of audits conducted since 2016 are now being monitored.

## Focus on: ISO 9001 certification regarding the “Risk Management” macro-process



In 2018, ANSM launched a process to certify its quality management system.

This certification allows an independent and competent third party to assess that its quality management system is compliant with the business line requirements set by the agency and the chosen standard.

For ANSM, this is the 2015 version of the international ISO 9001 standard. The certifying body was AFNOR Certification, and the certification process is voluntary.

The risk management certification audit took place from 17 to 20 December 2018 and mobilised 110 agents in total. It involved the 20 processes included in the “Risk Management” macro-process. The results of the audit were very positive. At the Saint Denis and Montpellier sites, which were both audited, zero major or minor cases of non-compliance were found. Eight strong areas, eight areas for improvement, and two sensitive areas were identified.

The auditors determined that senior management’s commitment to quality management was clearly expressed and demonstrated and that this commitment was shared by every level in the organisation.

ANSM obtained its initial ISO 9001 certification in January 2019 for the “Risk Management” macro-process.



This certification attests to the quality of services that ANSM provides the users and stakeholders of the healthcare system as part of its surveillance and control activities regarding health products, the management of high-risk situations, and its inspection missions. It demonstrates its ability to secure and control its processes and continue to transform into an even more effective organisation. Certification marks an important, positive, and promising step for the agency and aligns with its policy regarding modernisation, innovation, and openness towards the challenges facing public health and civil society.



# IMPLEMENTING THE INFORMATION SYSTEM MASTER PLAN (ISMP)

The 2014-2018 Information System Master Plan (ISMP) was a major area of focus in 2018.

A new project management governance system, information system project portfolio, was created to prepare for the new master plan.

This project portfolio made it possible to carry out all of our projects with a success rate of over 80%.

Significant changes have been made to for external services, and new formulated to allow the Information respond to three major challenges,

- agility, which lets the agency better the business lines while also service on a day-to-day basis and reducing the risk of production problems as much as possible,
- robustness, to achieve highly effective and secure information systems while also reducing the agency's technology debt,
- a user-centred focus, to continue to pay more and more attention to users and provide a level of high-quality service and responsiveness that takes into account all the needs of the agency's business lines, both in terms of resources and operations.

## Agility, robustness and a user-centred focus are the major challenges of the IT division

the management process agreements have been Technology Division to namely:

respond to the needs of providing high-quality

## IMPROVING INFRASTRUCTURE SECURITY

Steps were taken to make sure equipment rooms were up to standard in order to uphold the commitments the agency made to the National Information System Security Agency (ANSSI).

As part of these actions and in an effort to improve information system security, the agency has rolled out solutions, which were first launched by the MODIS (Modernisation of infrastructure and services) project, to adequately protect its infrastructure given the current climate.

A new agreement was made to render the various external hosting sites more effective in order to comply with security rules for applications hosted outside of the agency and facilitate their operations.

## DEVELOPING A NEW ISMP

The year 2018 was a transitional year. The agency developed a new ISMP and presented it to the Board of Executives during their meeting in March 2019. This new ISMP will continue the agency's efforts to modernise and change to a paper-free system in the coming years while also incorporating all aspects of the Objectives and Performance Contract, to which it is attached.

## HIGHLIGHTS IN 2018

### The most important milestones from 2018 include:

- updated version of the Cross-Cutting Input-Output Tool. This tool is used to monitor the agency's flows and boost the traceability of inputs and outputs,
- new developments with E-saturne, a tool aimed at dematerialising named-patient temporary authorisations for use,
- updated version of the Hermès module from Dimedia (medical device vigilance tool),
- SIRHIUS (Information system for receiving, ranking, and managing emergencies),
- several business line reporting projects on the Qlikview tool,
- PHENICS (Programme to harmonise and digitally record inspections through centralised management),
- a badge printing and digitisation tool,
- an update to the CIRIL payment tool that added withholding capabilities,
- an update to the medicine database,
- version 3 of the Cross-Cutting Dossier Tracking system and the creation of a tracking system specifically created to manage MA variations and automate authorisation-related decisions (automatic close of applications once the regulatory deadline has passed).
- **the creation of portable workstations** to help promote remote working at the agency.

## 2018 DATA

- **Over 80 milestones achieved**
- **Over 180 applications used each day across 200 servers**
- **Over 1,400 user workstations maintained**
- **Over 10,000 user help tickets served throughout the year**

# HUMAN RESOURCES

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

Since 2015, the agency has followed its Human Resources Master Plan (HRMP), which was designed to bridge the gap between ANSM's major strategic areas of focus, especially those listed in the Goal and Performance Contract (COP), and its human resource policy.

The goal is to help each employee take part in the agency's collective environment to better serve health and health safety consumers.

Voted on by the Board of Directors on 12 May 2016, it includes four strategic areas of focus:

- **Priority 1:** make collaborative work one of the agency's strengths
- **Priority 2:** consolidate managerial practices and orient them towards helping to promote individual and collective professional effectiveness
- **Priority 3:** support individual and collective professional development and anticipate business line changes, both in terms of quality and number
- **Priority 4:** promote the development of a respectful working environment that fosters individual and collective professionalism

Throughout 2018, ANSM made progress on all of these fronts.

### HIGHLIGHTS IN 2018

- **Supported the priority projects of the agency**, its employees, and its managers
- **Developed a managerial culture and harmonised practices**
- **Created and improved a professionalisation track** that helps new arrivals build their skills
- **Consolidated human resource steering skills** to better ensure the agency has the resources to fulfil its missions
- Continued to pursue the trainee host policy
- **Implemented stricter measures** to prevent ethics risks
- **Secured the human resource management processes** to simplify and improve the quality of service provided to employees
- **Formalised HR policies** as part of the agency's quality policy
- **Implemented an action plan** to combat psychological and social risks
- **Rolled out the remote working policy**
- **Improved the employee-manager dialogue** and increased discussion time with employee representatives

## Employment changes

To fulfil its health product safety missions, ANSM was supported by a workforce of 927.2 full-time equivalents (FTEs) in 2018. Temporary workers represented 1% of the total workforce in 2018.

It also employed 20.2 full-time equivalents not covered by the cap. This portion of the agency's workforce includes trainees, work support contracts, and a team dedicated to improving European activity.

### 2018 DATA

#### Changes in jobs authorised between 2015 and 2018

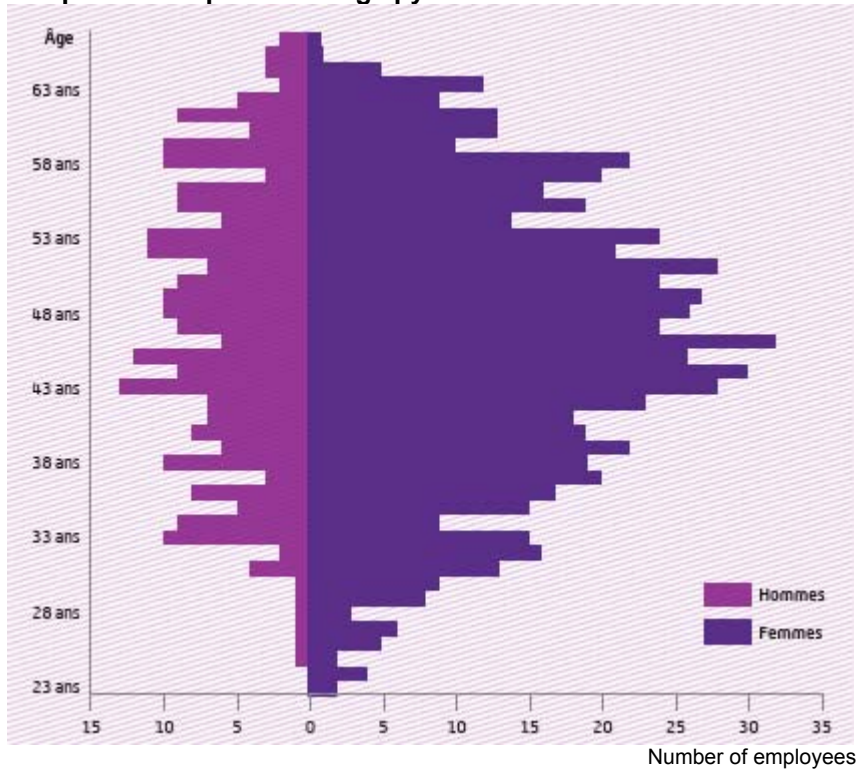
Authorised FTEs	2015	2016	2017	2018
Below cap	993	969.5	956.75	<b>935</b>
+/-	-10.00	-23.50	-12.75	<b>-21.75</b>

Sixty-eight FTEs were eliminated from ANSM's workforce in four years. In 2018, in light of its increasingly limited budgetary context, ANSM continued to pursue its transformation programme by structuring its activity and prioritising projects. To help adapt its operations to the available positions, the agency continued to closely manage its activities through the following:

- a portfolio of priority projects based on a structural overhaul of its business line processes and organisation in order to become more efficient and improve decision-making times with respect to dossiers that are important to public health or have significant economic implications,
- the implementation of an integrated management system (performance, quality, risks, audits, urbanisation) in support of the agency's ISO 9001 certification, which it obtained at the end of 2018,
- the application of an approach aimed at structuring and prioritising the agency's activities with the goal of overhauling its activity management methods,
- an analysis of the resources affected by all activities through a project that launched in 2017 and continued into 2018 aimed at objectively allocating resources to each of the agency's activities before activating a cost-performance accounting system,
- the optimisation of support processes to maintain the agency's staff and scientific skills as much as possible,
- an update to ANSM's organisation in 2018 by simplifying current modes of operations and making them more efficient.

During the same period, the number of positions not covered by the cap rose from 6 jobs in 2015 to 36 jobs in 2018. As a result, the agency was able to recruit trainees and increase its funding for European activities. In 2018, ten positions dedicated to evaluating European applications were created for a period of two years to represent the agency on strategic European issues, especially with respect to Brexit.

## The permanent personnel age pyramid



Men   
Women 

## 2018 DATA

- **90% of agents are contract employees, and 10% are civil servants.**
- **The average age of an employee at ANSM is 46.2 years.**
- **The agency's workforce is 72% female, which has remained constant over the past three years.**
- **Increase in the number of women** in senior management roles: in 2015, 56% of managers were male and 44% were female. In 2018, this proportion was reversed. **Women now occupy 56% of management roles**, i.e. an increase of 12 percentage points over this period.
- **The average retirement age is 63.5 for contracted employees and 62.2 for civil servants.**

## Training and career design by business line

The 2018 training plan was created in line with the 2015-2018 OPC and HRMP. It has helped improve the agency's steering and modernisation efforts and boost its managerial capacities. It has also helped improve the quality of life at work.

With respect to skill development, the agency created 17 career design programmes organised by business line, six of which are currently being rolled out.

These programmes include the baseline training and support policies offered in real-life conditions when an employee joins a new department and when an employee is undergoing professional development. Each employee can follow a training programme that is adapted to both his/her needs and ANSM's expectations.

## 2018 DATA

- 36 agents assisted during their onboarding process
- 17 programmes developed or underway
- 72%: employee access rate to training
- 2,976 days of training
- 4.13 days of training on average per every trained employee

## Measures to improve the quality of life at work

### CREATION OF AN ACTION PLAN TO PREVENT AND COMBAT PSYCHOLOGICAL AND SOCIAL RISKS (PSR)

Following the “Quality of life at work and prevention of PSRs” study in October 2017, an action plan was created based on three main areas of focus:

- governance and strategy,
- employees and management line,
- organisation of work, roles, and responsibilities.

The Health and Safety Committee, prevention network, and union organisers all contributed to the project by submitting their ideas and suggestions.

To monitor the application of the action plan, a Psychological and Social Risk Observatory was created. This structure is overseen by ANSM's Director General. The group met for the first time in December 2018 and comprises stakeholders from the internal prevention network, doctors specialising in prevention and occupational psychologists, human resources senior management, ANSM senior management, and union organisations.

The purpose of the Psychological and Social Risk Observatory is to develop and regularly monitor the progress of the action plan in an effort to reduce psychological and social risks and improve the quality of life at work. It also analyses a range of indicators associated with these risks.

### IMPLEMENTING A REMOTE WORKING POLICY

To lay the groundwork for the roll-out of the remote working policy in 2019, a review of a pilot phase that has already been conducted within ANSM was done with help from remote workers and their managers. The goal of this review was to identify the system's strong points and areas for improvement.

The positive results of this review prompted senior managers to roll out the remote working policy to the entire agency starting in 2019. A provisional roll-out schedule was approved before the end of 2018.

### PROVIDING BETTER SUPPORT TO PEOPLE WITH DISABILITIES

In 2018, the agency continued its efforts to implement a proactive policy for hiring and retaining people with disabilities or serious health problems. To this end, it works closely with the prevention department (prevention medicine, nurse's office, occupational psychologist, social assistance), the primary goal of which is to improve employees' working conditions.

To do so, several steps have been taken:

- commuting assistance,
- adaptive workstations,
- adaptive equipment.

Through these various actions, the agency is pursuing a participating policy of inclusion of people with disabilities.

## CONTINUED RENOVATION OF THE AGENCY'S FACILITIES

At its Saint Denis site, ANSM continued the work it began at the end of 2017 on the essential maintenance of its facilities and equipment. The construction continued in 2019 with the replacement of four lifts and two freight lifts.

The agency gained ownership over the property development at the Montpellier-Vendargues site. Given the end of the lease in 2024 and after informing and receiving the approval of regulatory authorities, the operation concluded in December 2018. A renovation plan for the site will be launched in 2019.

At the Lyon site, ANSM continued to work with ANSES on the plan to build new laboratories that will be shared by both agencies. The first step is to get the approval of local communities and secure funding assistance.

## HEIGHTENED SECURITY AND SAFETY AT ANSM

The agency maintained its heightened safety and security measures in 2018.

The Montpellier-Vendargues site signed a contract to improve the security of the site's physical access points. The work will be finished in early 2019.

At the Saint-Denis site, an inspection by the General Directorate for Internal Security helped ANSM improve its security system. Some recommendations were put in place in 2018, while others are scheduled for 2019 and 2020, primarily due to the amount of funding they require.

## HIGHLIGHTS IN 2018

- **Organisation of awareness-raising actions regarding disabilities** during the 22nd European Disability Employment Week (EDEW). Videos featuring ANSM employees with disabilities were shared online. Employees were able to take an introductory class on sign language and receive testing to raise awareness about auditory disabilities (November 2018)
- **Purchase of the facilities at ANSM's Montpellier-Vendargues site** (14 December 2018)
- **Safety and security audit of the Saint-Denis Site by the General Directorate for Internal Security** (5-7 February 2018)

## Dialogue between management and employees

Improving the dialogue between management and employees is an essential part of the agency's approach.

After the majority union boycotted the Technical Committee for almost an entire year, both parties decided to foster a more productive collaboration, and the group returned to the committee.

A schedule of talks between management and unions was started in 2018. Remote working was the first topic of discussion. Many other themes will be discussed in 2019.

In 2018, for the first time, the agency decided to use an electronic voting system during the elections for the employee representatives on the Board of Directors and during the professional elections in December 2018.

These elections were both successful.

The five representative unions within ANSM are:

- SPAPS - UNSA: 50.44% of votes cast
- C2A: 19.89% of votes cast
- CGT-Ansm / SUD-Ansm Solidaires Fonction Publique (joint list): 16.70% of votes cast
- SNPASS FO: 12.97% of votes cast

The employee representatives elected to the Board of Directors are Renaud Kiesgen de Richter (45.19%), Laurent Decuyper (26.92%), and Sylvie Morgeaux (16.73%).

At its first professional election within ANSM, the union C2A received representative union status based on the election results.

### HIGHLIGHTS IN 2018

- **Elections for employee representatives on the Board of Directors** (October 2018)
- **Professional elections** (CTE/CAP/CCP) (December 2018)

### 2018 DATA

#### 58 meetings in 2018:

- **29 committee meetings** (CTE, CHSCT, CCP, CAP, training commission, catering commission, observatory of psychological and social risks, loans and aid commission)
- **18 working, discussion, and/or collaboration meetings between employees and management outside of ANSM's committees.**



## Internal communications: providing support and creating meaning

The agency's internal communications strategy is based on four major institutional areas:

- making ANSM's strategy meaningful and further strengthening the ownership of its challenges,
- promoting the agency's managerial approach to foster employee-manager dialogue,
- increasing discussion time, promoting feedback, and helping employees gain a new perspective,
- supporting quality of life at work and bringing people together as a team.

The agency continued its cycle of in-house conferences to promote strategic or sensitive topics internally. To this end, it organised a conference and educational workshops to promote its quality policy, reviewed events that marked the year, and hosted philosophical conferences and workshops on risk and mistrust to help attendees gain a new perspective.

### HIGHLIGHTS IN 2018

The year 2018 was marked by two major milestones:

- **the promotion of the quality policy and the agency's transformation** with support from managers, especially with respect to the certification the agency obtained at the end of 2018,
- **the organisation of the agency's 25th anniversary celebration** for its staff (September 2018).

## THE AGENCY'S BUDGET

Following three budget revisions, ANSM's 2018 budget amounted to nearly €123 million in terms of commitment authorisations and €123.5 million in payment appropriations. The budget was implemented at 93% in commitment authorisations (€117.7 million) and 94% in payment appropriations (€119.1 million).

In response to the continued decrease in the budgets allocated to state operators, the agency implemented a number of actions starting in 2016, including a proactive savings plan that was necessary to manage its expenses and limit the deterioration of its working capital fund. In preparation for the 2018 budget and given the significant effort that had been made, the state decided to help maintain the agency's financial situation by increasing its resources. The initial 2018 budget was based on a significantly higher level of public service cost subsidies. The state increased this amount by €6.8 million, which resulted in a vote on a balanced budget.

The fiscal year ended with a surplus budget of nearly €7 million, which added €6 million to the working capital fund. This development is the result of implementing cost-savings measures throughout the year. These measures affected all budgetary envelopes, and current operations in particular.

### HIGHLIGHTS IN 2018

- A €6.8 million increase to the public service cost subsidy.
- Restoration of the working capital fund (€6 million by the end of the fiscal year).
- Increase in the agency's ability to oversee European activities with the creation of 10 jobs not covered by the cap that are dedicated to these activities.

## Revenue

The subsidy for public service costs is paid by the French government and represented **92.4%** of ANSM's operating income. It amounted to **€116.6 million** in 2018, i.e. a substantial increase of €6.8 million.

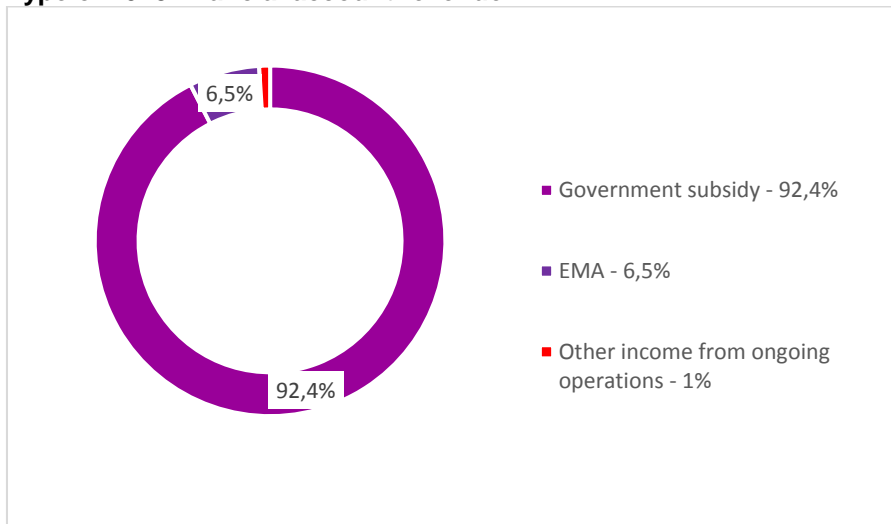
Own-source revenue primarily consisted of revenue paid by the EMA in exchange for work done by ANSM. In 2018, the agency continued to pursue its strategy of increasing its activities with EMA regarding topics of key importance to France, including oncology, haematology, neurology, and infectious diseases, especially viral diseases and vaccines. This partnership with the EMA will generate additional and long-lasting revenue through variations and annual taxes.

### 2018 DATA

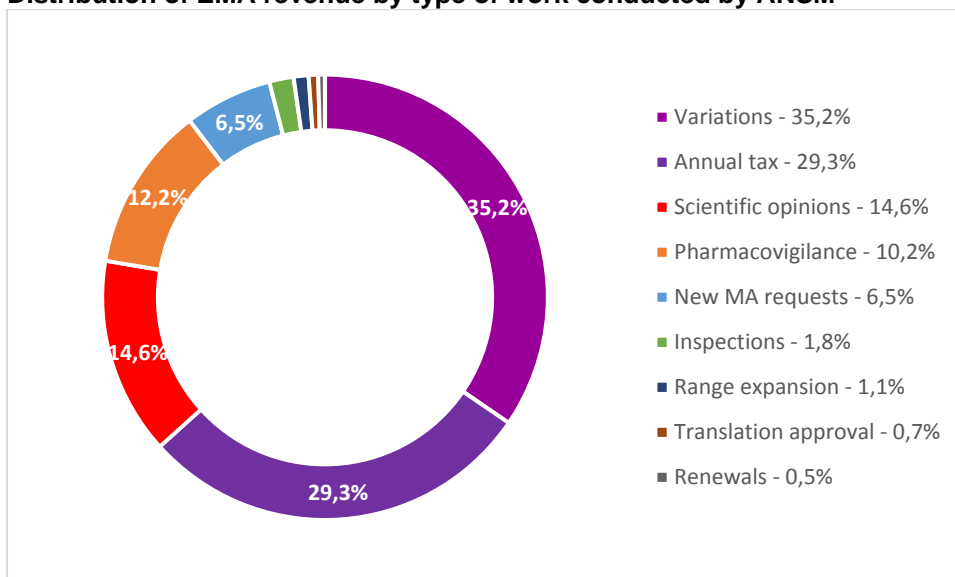
#### Change in ANSM revenue since 2013 (in thousands of €)

	2013	2014	2015	2016	2017	2018
Government subsidy	116,359	103,176	113,160	111,786	109,807	<b>116,598</b>
EMA	7,286	8,597	8,198	4,270	8,564	<b>8,200</b>
Other taxes and fees	595	4,937	849			
Other income from ongoing operations	4,161	5,640	3,750	319	1,162	<b>1,321</b>
Total operating revenue	128,401	122,350	125,957	116,375	119,533	<b>126,119</b>

### Type of 2018 financial account revenue



### Distribution of EMA revenue by type of work conducted by ANSM



## Expenditure

### EXPENDITURE BY DESTINATION

Since 2016, the agency has been using the strategic guidelines included in the 2015-2018 Objectives and Performance Contract to determine its budgetary goals:

Guaranteeing a high level of safety for health products throughout their life cycle	38%
To promote rapid, closely monitored, and broad access to all health products	22%
Consolidating ANSM's relationships with stakeholders and increasing their involvement	12%
Making ANSM more efficient and modern	28%

The year 2018 was the final year of the 2015-2018 OPC. During this time, the agency consolidated the measures it had already taken and laid the groundwork for the actions that will address the major goals included in the 2019-2023 OPC.

### EXPENDITURE BY ENVELOPE

Change in ANSM's expenditures since 2013 (in millions of €)

	2013	2014	2015	2016	2017	2018
Staff	80.6	79.1	79.7	79.6	79.6	<b>79.9</b>
Operation	32	34.1	33.7	23	23.3	<b>23</b>
Intervention	17.3	16.6	12.7	12.7	10.6	<b>9.3</b>
Investment	9.4	9.3	10.9	8.1	7.2	<b>6.9</b>
<b>Total payment appropriations spending</b>	<b>139.3</b>	<b>139.1</b>	<b>137</b>	<b>123.4</b>	<b>120.7</b>	<b>119.1</b>

#### STAFF: €79.9 million

The staff budget was implemented at €79.9 million, i.e. 97.5% of the initial budget.

It includes:

- payroll: €78.6 million (€78.3 million in 2017),
- social actions: €1.3 million.

Employment authorisations were implemented as follows:

Jobs	2018 authorisations		2018 implementation		Rate of implementation	
	FTE	WFTE	FTE	WFTE	FTE	WFTE
Below cap	935	935	922.6	927.2	98.67%	99.17%
Beyond cap	36	21.6	26	20.2	72.22%	93.52%
<b>Total</b>	<b>971</b>	<b>956.6</b>	<b>948.6</b>	<b>947.4</b>	<b>97.69%</b>	<b>99.00%</b>

#### OPERATION: €23 million

The operations envelope used €22.6 million in CA and €23 million in PA during the 2018 financial year.

In 2018, to increase the openness of stakeholders and improve the transparency of its work and data, the agency took the first steps towards implementing its digital strategy. The first concrete results of the project are expected in 2019 with the creation of a new website.

ANSM also created three freephone numbers (Levothyrox, Valsartan, and Androcur) to provide users and healthcare professionals with information and support.

It invested heavily in the development of its Quality Management System, leading to a certification that attests to the quality of the services it provides healthcare system users and stakeholders as part of its activities regarding health product surveillance and control, the management of high-risk situations, and inspections.

Finally, the agency continued its efforts to make some of its expenditures more efficient through the renewal of several contracts and the signing of a contract with UGAP, which led to substantial savings, especially with respect to the agency's information systems and expenditures on third-party application management.

### INTERVENTION: €9.3 million

With respect to intervention expenses, ANSM continued to fund vigilance network and research activities, spending €9.3 million in CA and PA.

ANSM is currently working with the authorities to reform its vigilance networks. Against this backdrop, the Regional Pharmacovigilance Centres, Drug Dependence Evaluation and Information Centres, and regional medical device and reagent vigilance centres used nearly 100% of their budgets.

Moreover, €1 million in credit was granted to fund two pharmaco-epidemiological platforms (PEPS - Rennes University Hospital and Drugs Safe - Bordeaux University) at the end of 2014 to support their work on the safety of health products in France. An epidemiological study programme will be launched in 2019 as part of the EPI-PHARE scientific interest group, which is overseen by both CNAM and ANSM<sup>57</sup>.

Finally, a call for high-level scientific research proposals made it possible to fund studies on two topics: "health products and pregnancy" and "new approaches in clinical toxicology". In 2018, funding for one-off scientific studies was also granted as part of an association-led call for proposals and as part of an effort that was separate from a call for proposals.

### INVESTMENT: €6.9 million

With respect to IT investments, the update of the 2018 project portfolio revealed that some IT projects needed to be rescheduled in 2019 or cancelled. During the update, which took place in the last few months of 2018, the agency decided to prioritise certain projects based on the resources (and particularly human resources) that were available. Several projects were cancelled and will be incorporated at a later date through new tools included in the 2019-2023 Information Systems Master Plan.

With respect to other investment expenditures, outside of spending aimed at improving property and updating laboratory equipment, which are recurrent expenses that are part of specific equipment plans, the largest expense in 2018 was the purchase of the Vendargues site for a total of €2.57 million.

Costs	Initial 2017 budget	Financial accounts for 2017	Initial 2018 budget	Receipts	Initial 2017 budget	Financial accounts for 2017	Initial 2018 budget
Staff	80.9	79.6	82	Subsidy for service costs	109.8	109.8	116.6
Operation	26.5	23.3	26.5				
Intervention	10.1	10.6	10.8	EMA revenue	8.2	8.6	8.6
Investment	7.3	7.2	7	Other resources	1.1	1.1	1.1
<b>Total costs</b>	<b>124.8</b>	<b>120.7</b>	<b>126.3</b>	<b>Total receipts</b>	<b>119.1</b>	<b>119.5</b>	<b>126.3</b>
Budget surplus	0	0	0	Budgetary deficit	6.3	1.2	0

<sup>57</sup> See also the focus entitled "ANSM and CNAM join forces to create EPI-PHARE, a public expertise body specialising in health product epidemiology", page 37.

## Contracts

ANSM's total number of active contracts is 374 (compared to 382 in 2017), including 18 construction contracts (5%), 74 supply contracts (20%), and 282 service contracts (75%).

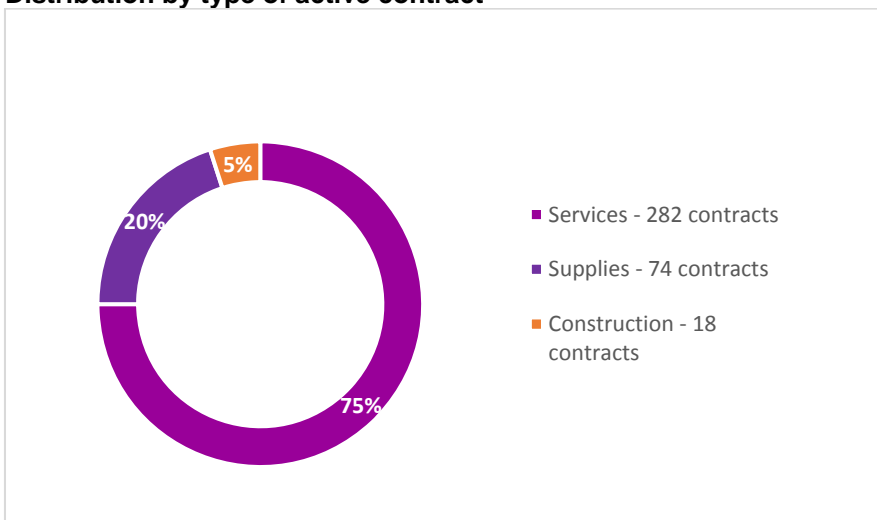
As in previous years, the six main user branches are:

- CTROL (103 active contracts in 2018),
- DAF (including general and security services - 89 active contracts in 2018),
- DRH (54 active contracts in 2018),
- DSI (48 active contracts in 2018),
- DIRCOM (25 active contracts in 2018),
- DMFR (15 active contracts in 2018),

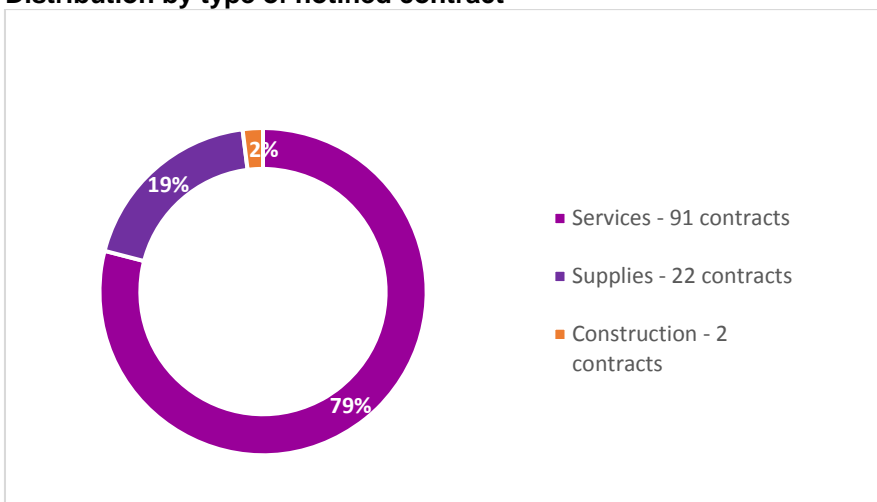
These six branches alone account for 334 active contracts, or 89% of the total number of active contracts.

The number of notified contracts in 2018 was 115, including 91 service contracts.

### Distribution by type of active contract



### Distribution by type of notified contract



### HIGHLIGHTS IN 2018

- **With respect to supply contracts, a consultation involving 16 batches was made for laboratory reagents and consumables (July 2018).**

## Strengthening purchasing procedures

In 2018, ANSM continued its work with the French Procurement Department to align its needs with those of other operators as much as possible. ANSM entered into framework agreements with the French Procurement Department for the provision of electricity and gas and the optimisation of property lease agreements.

Also in 2018, ANSM decided to join the Hospital IT Purchasing Office (CAIH) to address the following needs:

- services to ensure the digital security and conformity of information systems (IS) and, more specifically, provide IT project management support with respect to IS security and dedicated training sessions,
- Supply of micro-IT equipment,

In addition, an agreement between ANSM and ABM to pool orders was signed in November 2017 for a period of four years. This agreement concerns managerial support services (support for change, steering, collaborative work practices, and HR issues within teams).

Based on this agreement, a multi-beneficiary framework agreement involving two batches was signed between the two agencies in 2018. ANSM was the coordinator.

It laid the groundwork for two inter-agency health agreements concerning HR and IS purchases presented to and approved by the Board of Directors on 8 March 2018.

Based on these agreements, several inter-agency contracts are being drawn up and will be signed in 2019 (IT project management support for IS projects with ANSM as the coordinator, training in foreign languages and office equipment).

### HIGHLIGHTS IN 2018

- **ANSM joined the Hospital IT Purchasing Office** (November 2018).
- **Multi-beneficiary, two-batch framework-agreement between ANSM and ABM** during the second half of 2018, notified in January 2019.

## Rolling out internal accounting and budgetary controls

The summary of the measures taken as part of the internal budgetary and accounting control process was presented to the Board of Directors on 8 March 2018.

It includes two branches: internal accounting controls aimed at ensuring the quality of the accounts, and internal budgetary controls, aimed at scheduling the budget and ensuring its sustainability. During 2018, the agency completed a series of actions it began in 2017, namely an update of its deliverables, including the risk map, the action plan presented to the Board of Directors for deliberation on 8 March 2018, the control plan, etc.

The roll-out of ANSM's internal budgetary and accounting control process in 2018 resulted in:

- wider coverage of budgetary and accounting issues,
- more integrated risk management through the addition of the quality management system,
- education regarding risk management and the traceability of actions, controls, and evaluations.

The risk map covers 23 risks. To manage these risks, 25 actions have been identified.

The implementation of audits of subsidy recipients, which is one of these actions, represented a key development in 2018.

The system was 90% rolled out in 2018, three years after the application of the Budgetary and Public Accounting Management decree.

By gradually bringing this process in line with the Quality Management System, the agency will be able to more fully manage risks by incorporating risks associated with the work environment (risks related to IT, legal, and business line concerns).





## Glossary

<b>A</b>	
AAP	Appel à projets—Call for proposals
ABM	Agence de la biomédecine—Biomedicines agency
AE	Autorisations d'engagement—Commitment authorisations
AIP	Autorisation d'importation parallèle—Parallel import authorisation
AMM	Autorisation de mise sur le marché—Marketing authorisation
AMOA	Assistance à maîtrise d'ouvrage—Project management assistance
AMOE	Assistance à maîtrise d'œuvre—Project ownership assistance
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail—French Agency for Food, Environmental, and Occupational Health Safety
ANSSI	Agence nationale de sécurité des systèmes d'information de l'Etat—French National Information System Security Agency
AP-HP	Assistance Publique – Hôpitaux de Paris—Public Assistance – Hospitals of Paris
ARS	Agence régionale de santé—Regional Health Agency
ASIP Santé	Agence des systèmes d'information Santé partagés de santé—Shared Health Information Systems Agency
ASMR	Amélioration du service médical rendu—Improved medical service
ASN	Autorité de sûreté nucléaire—Nuclear Safety Authority
ATEV	Accidents thromboemboliques veineux—Venous thromboembolic events
ATNC	Agents transmissibles non conventionnels—Non-conventional transmissible agents
ATU	Autorisation temporaire d'utilisation—Temporary Authorisation for Use
ATUn	Autorisation temporaire d'utilisation nominative—Named-Patient Temporary Authorisation for Use
ATUc	Autorisation temporaire d'utilisation de cohorte—Cohort Temporary Authorisation for Use
<b>B</b>	
BEAC	Protocol (carmustine, etoposide, cytarabine, cyclophosphamide, and mesna)
BNPV	Base nationale de pharmacovigilance—National pharmacovigilance database
BPC	Bonnes pratiques cliniques—Clinical best practices
BPD	Bonnes pratiques de distribution—Distribution best practices
BPDG	Bonnes pratiques de distribution en gros—Wholesale distribution best practices
BPF	Bonnes pratiques de fabrication—Manufacturing best practices
BPL	Bonnes pratiques de laboratoire—Laboratory best practices
BPPV	Bonnes pratiques de pharmacovigilance—Pharmacovigilance best practices
BRN	Blood regulators network
BWP	Biologic working party (within the EMA)
<b>C</b>	
CA	Conseil d'administration—Board of Directors
CAD	Cellule d'aide à la décision—Decision-making assistance unit
CAIH	Centrale d'achat de l'informatique hospitalière—Hospital IT Purchasing Office
CAP	Centrally authorised products
CASAR	Centre d'Appui aux Situations d'urgence, aux Alertes sanitaires et à la gestion des Risques (ANSM)—Support centre for emergency situations, health alerts and risk management
CAT	Committee for advanced therapies (EMA committee)
CEN	Comité Européen de Normalisation—European Committee for Standardisation
CEIP	Centre d'évaluation et d'information sur la pharmacodépendance—Technical Committee for Drug Dependence Evaluation and Information Centres
CESP	Common European Submission Platform
CHMP	Committee for medicinal products for human use (EMA committee)
CHSCT	Comité d'hygiène, de sécurité et des conditions de travail—Hygiene, Safety, and Working Conditions Committee
CHU	Centre hospitalier universitaire—University hospital
CIB	Contrôle interne budgétaire—Internal budgetary control
CIC	Contrôle interne comptable—Internal accounting control
CICF	Contrôle interne comptable et financier—Internal accounting and financial control

CMDh	Coordination group for mutual recognition and decentralised procedures – Human (EMA committee)
CMG	Collège de la médecine générale—College of General Practitioners
CNAMTS	Caisse nationale de l'assurance maladie des travailleurs salariés—French salaried workers health insurance fund
CNGE	Collège national des généralistes enseignants—French National College of Generalists in Medical Education
CNGOF	Collège national des gynécologues et obstétriciens français—National College of French Gynaecologists and Obstetricians
CNOM	Conseil national de l'Ordre des médecins – French National College of the Board of Physicians
CNOP	Conseil national de l'Ordre des pharmaciens—French National College of the Board of Pharmacists
CNQ	Contrôle national de qualité—National quality control
CNRS	Centre national de la recherche scientifique—National Scientific Research Centre
COFRAC	Comité français d'accréditation—French Accreditation Committee
COMP	Committee for Orphan Medicinal Products (EMA committee)
COP	Contrat d'objectifs et de performance—Objectives and Performance Contract
CORUSS	Centre opérationnel de réception et de régulation des alertes sanitaires et sociales—Operational Centre for the Reception and Regulation of Health and Social Alerts
CP	Crédits paiement—Payment appropriations
CPP	Comité de protection des personnes—Ethics Committee
CQDM	Contrôle de Qualité des dispositifs médicaux—Quality control of medical devices
CRAT	Centre de référence sur les agents tératogène—Teratogenic agent reference centre
CRMRV	Centre régional de matériovigilance—Regional Medical Device Vigilance Centre
CRO	Contract Research Organisation
CRPV	Centre Régional de Pharmacovigilance—Regional pharmacovigilance centre
CSP	Code de la Santé publique—French Public Health Code
CSST	Comité scientifique spécialisé temporaire—Temporary Specialist Scientific Committee
CTMRV	Comité technique de matériovigilance et de réactovigilance—Technical Committee for Medical Device Vigilance and Reagent Vigilance
CTPV	Comité technique de pharmacovigilance—Technical pharmacovigilance committee
CTROL	Direction des contrôles—Laboratory Controls Division

## D

DAE	Défibrillateurs automatisés externes—Automated external defibrillators
DAE	Direction des achats de l'Etat—Department of Government Procurement
DCI	Dénomination commune internationale—International Common Denomination
DCP	Procédure décentralisée—Decentralised procedure
DEHP	di (2-ethylhexyl) phtalate
DEQM	Direction européenne de la qualité du médicament—European Directorate for the Quality of Medicines
DGCCRF	Direction générale de la concurrence, de la consommation et de la répression des fraudes—Directorate General for Fair Trade, Consumer Affairs, and Fraud Control
DGDDI	Direction générale des douanes et des droits indirects—Directorate General of Customs and Excise Duties
DGOS	Direction générale de l'organisation des soins—Directorate General of Healthcare Organisation
DGS	Direction générale de la Santé—Ministry of Health
DINSIC	Direction interministérielle du numérique et du système d'information et de communication de l'Etat—Inter-Ministerial Department of State Digital Technologies, Information Systems, and Communications
DIRCOM	Direction de la communication et de l'information—Department of Communications and Information
DM	Dispositif médical—Medical device
DMDIV	Dispositif médical de diagnostic <i>in vitro</i> — <i>In-vitro</i> diagnostic medical device
DMLA	Dégénérescence maculaire liée à l'âge—Age-related macular degeneration
DP	Dossier pharmaceutique—Pharmaceutical dossier
DPI	Déclaration publique d'intérêts—Public conflict of interest statement
DU	Diplôme universitaire—University diploma

DSI Direction des systèmes d'information—Information system security

## E

EDQM Direction européenne de la qualité du médicament—European Directorate for the Quality of Medicines  
EFS Etablissement français du sang—French National Blood Service  
EGFR Epidermal growth factor receptor  
EHESP Ecole des hautes études en santé publique—School of Public Health  
EI Effet indésirable—Adverse effect  
EMA European Medicines Agency  
EST Encéphalopathies spongiformes transmissibles—Transmissible spongiform encephalopathies  
Etalab share it Etalab is part of the DINSIC. Its main purpose is to manage the accessibility of public data and  
ETP Equivalents temps plein—Full-time equivalents  
ETPT Equivalent temps plein travaillé—Worked full-time equivalents  
EUCALB European union concerted action on Lyme borreliosis  
EUDAMED Base de données des dispositifs médicaux—Medical devices database

## F

FAAH Fatty acid amide hydrolase  
FDA Food and Drug Administration (US FDA)

## G

GBCP Gestion Budgétaire et Comptable Publique—Budgetary and Public Accounting Management  
GCDM Groupe de coordination des dispositifs médicaux—Medical devices coordination group  
GIS Groupement d'intérêt scientifique—Scientific Interest Group  
GT Groupe de travail—Working group

## H

HAP Hors appel à projet—Outside of calls for proposals  
HAS Haute autorité de santé—French National Health Authority  
HCSP Haut Conseil de la santé publique—French High Council for Public Health  
HMA Heads of Medicines Agencies  
HPS Hors produits de santé—Excluding health products  
HTA Health technology assessment

## I

ICH International Conference on Harmonisation  
ICMRA International coalition of medicines regulatory authorities  
INCa Institut national du cancer—National Cancer Institute  
INSERM Institut national de la santé et de la recherche médicale—French national institute of health and medical research  
IRISA Institut de recherche en informatique et système aléatoire—Research Institute of Computer Science and Random Systems  
ISRS Inhibiteur sélectif de la recapture de sérotonine—Selective serotonin reuptake inhibitor  
ITMO Institut thématique multi-organismes—Multi-Body Topical Institute

## J

JAMA Journal of the American Medical Association

## L

LAGC-AIM Lymphome Anaplasique à Grandes Cellules associé aux implants mammaires—Breast-implant-associated anaplastic large-cell lymphoma  
LF Lymphome folliculaire—Follicular lymphoma  
LFB Laboratoire français du fractionnement et des biotechnologies—French blood fractionation and biotechnology laboratory  
LLC Leucémie lymphoïde chronique—Chronic lymphoid leukaemia  
LPM Loi de Programmation Militaire—Military Programming Law

LTSI Laboratoire du traitement du signal et de l'image—Signal and Image Processing Laboratory

## M

MCJ Maladie de Creutzfeldt-Jakob—Creutzfeldt-Jakob Disease  
MDEG Medical devices expert group  
MDS Médicaments dérivés du sang—Blood-derived medicines  
MFM Myofasciite à macrophages—Macrophagic myofasciitis  
MICI Maladie inflammatoire chronique de l'intestin—Chronic inflammatory bowel disease  
MITM Médicament d'intérêt thérapeutique majeur—Medicine of major therapeutic interest  
MOA Maitrise d'ouvrage—Project management  
MODIS Modernisation des infrastructures et services—Modernisation of Infrastructure and Services  
MOE Maitrise d'oeuvre—Project ownership  
MOT Micro-organismes et toxines—Microorganisms and toxins  
MPUP Matière première à usage pharmaceutique—Pharmaceutical starting material  
MRP Procédure de reconnaissance mutuelle—Mutual recognition procedure  
MSA Modification substantielle soumise à l'ANSM pour autorisation—Substantial modification submitted to ANSM for authorisation  
MTI Médicament de thérapie innovante—Advanced therapy medicinal product  
MTI-PP Médicament de thérapie innovante préparé ponctuellement—Innovative therapy medicines prepared on a one-off basis

## N

NBOG Notified Body Operations Group  
NDS National Drug Control System

## O

OCDE Organisation de coopération et de développement économiques—OECD  
Organisation for Economic Co-operation and Development  
OCLAESP Office central de lutte contre les atteintes à l'environnement et à la santé publique—  
Central Office for the Prevention of Damage to the Environment and Public Health  
OEDT Observatoire européen des drogues et des toxicomanies—European Monitoring Centre  
for Drugs and Drug Addiction  
OEEQ Organisme d'évaluation externe de la qualité—External quality evaluation body  
OFDT Observatoire français des drogues et des toxicomanies—French Monitoring Centre for  
Drugs and Drug Addiction  
OICS Organe International de contrôle des Stupéfiants—International Narcotics Control Board  
OMCLs Official medicines control laboratories  
OMS Organisation mondiale de la santé—WHO World Health Organisation  
ON Organisme notifié—Notified body  
OTES Outil de Traçabilité Entrant Sortant—Input-Output Traceability Tool

## P

PBRER Periodic benefit-risk evaluation report  
PCA Plan de continuité des activités—Activity continuity plan  
PCR Polymerase chain reaction  
PDCO Paediatric committee (EMA committee)  
PEMSAC Plateforme européenne de surveillance des cosmétiques—European cosmetic  
surveillance platform  
PEPs Pharmaco-épidémiologie des produits de santé—Health Product Pharmaco-Epidemiology  
PGR Plan de gestion des risques (Risk management plan)  
PIC/s Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation  
PIP Plan d'investigation pédiatrique—Paediatric investigation plan  
PMF Prescription médicale facultative—Optional medical prescription  
PMR Plan de maîtrise de risques par processus—Risk management by process plan  
PMSI Programme de médicalisation des systèmes d'information—Information system  
medicalisation programme  
PRAC Pharmacovigilance risk assessment committee (EMA committee)  
PSL Produits sanguins labiles—Labile blood products

PSP	Protocole Standard Prion—Prion standard protocol
PSUR	Periodic safety update report
PSUSA	Periodic safety update single assessment
PTA	Produits thérapeutiques annexes—Related therapeutic products
PTT	Protocole temporaire de traitement—Temporary treatment protocol
PUI	Pharmacie à usage intérieur—Hospital pharmacy
PUT	Protocole d'utilisation thérapeutique et de recueil d'information—Information collection and therapeutic use protocol

## R

RCP	Résumé des caractéristiques produit—Summary of product characteristics
REACH	Enregistrement, évaluation et autorisation des produits chimiques—Registration, evaluation, and authorisation of chemicals
RIPH	Recherche impliquant la personne humaine—Human research
RNLBP	Réseau national des laboratoires biotox-piratox—National Network of Biotox-Piratox Laboratories
RPS	Risque psycho-sociaux—Psycho-social risks
RSSI	Responsable de la sécurité des systèmes d'information—Information system security manager
RTU	Recommandation temporaire d'utilisation—Temporary Recommendation for Use

## S

SATT	Sociétés d'accélération du transfert de technologies—Companies accelerating technology transfer
SAWP	Scientific advice working party
SCL	Service commun des laboratoires—Joint laboratory service
SCENIHR	Scientific committee on emerging and newly identified health risks (part of the European Commission)
SDRH	Schéma directeur des ressources humaines—Human Resources Master Plan
SDSI	Schéma directeur des systèmes d'information—Information Systems Master Plan
SDSID	Schéma directeur des systèmes d'information et de la donnée—Information and Data Systems Master Plan
SEEPH	Semaine européenne pour l'emploi des personnes handicapées—European Disability Employment Plan
SGDSN	Secrétariat général de la défense et de la sécurité national—French Department of Defence and National Security
SI	Système d'information—Information system
SMI	Système de management intégré—Integrated management system
SMQ	Système de management de la qualité—Quality management system
SMR	Service médical rendu—Medical service
SNDS	Système national des données de santé (formerly SNIIRAM)—National Health Database
SNIIRAM	Système national d'informations inter régimes d'assurance maladie (replaced by SNDS)—National Health Insurance Inter-Scheme Information System
SRE	Situation à risque élevé—High-Risk Situation
SSI	Sécurité des Systèmes d'information—Information system security
STD	Suivi transverse des dossiers—Cross-Cutting Dossier Tracking

## T

TAVI	Transcatheter Aortic Valve Implantation
TROD	Test de diagnostic rapide—Rapid diagnostic test
TSH	Thyroid-stimulating hormone
TSO	Traitement de substitution aux opiacés—Opioid replacement therapy

## U

UGAP	Union des groupements d'achats publics—Government-owned organisation that procures public merchandising services
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## V

VHB	Virus de l'hépatite B—Hepatitis B virus
VHP	Voluntary harmonisation procedure

# Appendix 1

## Members of ANSM's Board of Directors as of April 2019

**Chair of the Board of Directors:** Catherine de Salins

**Vice Chair:** H  l  ne Berrue-Gaillard

### **PERMANENT MEMBERS REPRESENTING THE GOVERNMENT:**

#### **Representatives of the Health and Social Action Minister**

- Chair: Anne-Claire Amprou / Deputy member: J  r  me Salomon
- Chair: Dominique Felten / Deputy member: Emmanuelle Cohn
- Chair: Sabine Fourcade / Deputy member:   ric Ginesy

#### **Representatives of the Social Security Minister**

- Chair: Sophie Casanova / Deputy member: Edouard Hatton

#### **Representatives of the Budget Minister**

- Chair: Antoine Letiers / Deputy member: Marie Chanchole

#### **Representatives of the Research Minister**

- Chair: Beno  t Lavallart / Deputy member: Anne Paoletti

#### **Representatives of the Economy and Finances Minister**

- Chair:   ric Cuziat / Deputy member: Catherine Argoyti
- Chair: Julie Galland / Deputy member: Alain-Yves Bregent

#### **Representatives of the Foreign Affairs Minister**

- Chair: Florence Chambon / Deputy member: Akcal Fatih

### **MEMBERS OF PARLIAMENT APPOINTED BY THE PRESIDENT OF THEIR ASSEMBLY**

#### **Deputy Members**

- Julien Borowczyk
- Josiane Corneloup
- H  l  ne Vainqueur-Christophe

#### **Senators**

- St  phane Artano
- Laurence Cohen
- G  rard Deriot

### **REPRESENTATIVES OF BASIC MANDATORY HEALTH INSURANCE PROGRAMMES**

- Chair: Olivier Lyon-Caen / Deputy member: Anne Fagot-Campagna
- Chair: Sandrine Far   / Deputy member: Philippe Labatut

### **REPRESENTATIVES OF THE NATIONAL BOARD OF PHARMACISTS AND PHYSICIANS**

#### **French Medical Board**

- Chair: Jacques Morali / Deputy member: Fran  oise Stoven

#### **National Board of Pharmacists**

- Chair: Carine Wolf-Thal / Deputy member: Fr  d  ric Lahiani

### **REPRESENTATIVES OF HEALTH SYSTEM CONSUMER ASSOCIATIONS**

- Chair: H  l  ne Berrue-Gaillard / Deputy member: Philippe Schneider
- Chair: Yann Mazens / Deputy member: Sophie Le Pallec

#### **QUALIFIED EXPERTS IN THE AGENCY'S SCOPE**

- Xavier De Cuyper
- Mady Denantes

#### **REPRESENTATIVES OF THE AGENCY'S STAFF**

- Chair: Renaud Kiesgen de Richter / Deputy member: Wahiba Oualikene-Gonin
- Chair: Laurent Decuyper / Deputy member: Lynda Arnaud-Boissel
- Chair: Sylvie Morgeaux / Deputy member: Abdoul-Aziz Diop

#### **MEMBERS WITH AN ADVISORY CAPACITY**

- Dominique Martin, Director General of ANSM
- Marie-Thérèse Cocqueel, ANSM Budget Controller
- Jean-Michel Pugnère, Agency Accountant
- XXXXXX, Chair of ANSM's Scientific Council



## Appendix 2

### Referral procedures sent to the CHMP and PRAC<sup>58</sup>

Name of the procedure (International Common Denomination [ICD] or common name)	Start of procedure	End of procedure	Referral type
<b>REFERRALS SENT TO CHMP</b>			
Scandonest and associated commercial names (mepivacaine)	14/09/2017	31/05/2018	Article 30 of Directive 2001/83/EC
Oral medications used as a secondary prevention measure after a myocardial infarction containing omega 3 acid ethyl esters	22/03/2018	18/10/2018 <sup>59</sup>	Article 31 of Directive 2001/83/EC
Diclofenac Sodium Spray Gel 4% Cutaneous Spray, Solution and associated commercial names (diclofenac sodium)	26/04/2018	15/11/2018	Article 29(4) of Directive 2001/83/EC
Paclitaxel Hetero and associated commercial names (paclitaxel)	26/04/2018	18/10/2018	Article 29(4) of Directive 2001/83/EC
Gentamicin (solution for infusion/solution for injection) (gentamicin)	30/04/2018	15/11/2018	Article 5(3) of Regulation (EC) no. 726/2004
Medicines containing metamizole (metamizole sodium)	31/05/2018	13/12/2018	Article 31 of Directive 2001/83/EC
Medicines containing norethisterone and ethinylestradiol (norethisterone and ethinylestradiol)	31/05/2018	18/10/2018	Article 5(3) of Regulation (EC) no. 726/2004
Medicines for respiratory diseases containing bacteriophages	28/06/2018	Ongoing	Article 31 of Directive 2001/83/EC
Angiotensin II receptor blockers (sartans) containing a tetrazole group	16/07/2018	Ongoing	Article 31 of Directive 2001/83/EC
Septanest and associated commercial names (articaine (hydrochloride)/ adrenaline (tartrate))	26/07/2018	Ongoing	Article 30 of Directive 2001/83/EC
Syner-Kinase and associated commercial names (urokinase)	26/07/2018	Ongoing	Article 29(4) of Directive 2001/83/EC
Perlinring and associated commercial names (etonogestrel/ethinylestradiol)	23/08/2018	18/10/2018	Article 29(4) of Directive 2001/83/EC
Diotop 75 mg/20 mg modified-release gel capsules and associated commercial names (diclofenac/omeprazole)	18/10/2018	15/11/2018	Article 29(4) of Directive 2001/83/EC
Basiron AC and associated commercial names (benzoyl peroxide)	13/12/2018	Ongoing	Article 13 of Regulation (CE) no. 1234/2008
Medicines containing fosfomycin (fosfomycin calcium, fosfomycin disodium, fosfomycin sodium, fosfomycin trometamol)	13/12/2018	Ongoing	Article 31 of Directive 2001/83/EC

<sup>58</sup> Source: Annual Report 2018, EMA, Annex 17.

<sup>59</sup> A new re-assessment is underway.

Medicines containing norethisterone/ethinylestradiol (norethisterone and ethinylestradiol)	13/12/2018	Ongoing	Article 5(3) of Regulation (EC) no. 726/2004
<b>REFERRALS SENT TO THE PRAC</b>			
Medicines containing retinoids (acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tretinoin, tazarotene)	07/07/2016	22/03/2018	Article 31 of Directive 2001/83/EC based on pharmacovigilance data
Oral, injectable, or inhaled medicines containing quinolones and fluoroquinolones (nalidixic acid, pipemidic acid, cinoxacin, enoxacin, pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin, flumequine)	09/02/2017	15/11/2018	Article 31 of Directive 2001/83/EC based on pharmacovigilance data
Medicines containing valproate-related substances	09/03/2017	21/03/2018	Article 31 of Directive 2001/83/EC based on pharmacovigilance data
Medicines containing flupirtine (flupirtine)	26/10/2017	21/03/2018	Article 31 of Directive 2001/83/EC based on pharmacovigilance data
Medicines containing hydroxyethyl starch (HES (hydroxyethyl starch)	26/10/2017	27/06/2018 <sup>60</sup>	Article 107i of Directive 2001/83/EC
Xofigo (radium Ra223 dichloride)	30/11/2017	26/07/2018	Article 20 of Regulation no. 726/2004 based on pharmacovigilance data
Esmya (ulipristal acetate)	30/11/2017	31/05/2018	Article 20 of Regulation no. 726/2004 based on pharmacovigilance data
Zinbryta (daclizumab beta)	08/03/2018	31/05/2018	Article 20 of Regulation no. 726/2004 based on pharmacovigilance data
Medicines containing methotrexate (methotrexate)	12/04/2018	Ongoing	Article 31 of Directive 2001/83/EC based on pharmacovigilance data

<sup>60</sup> Date of the revision of the position of the CMDh. The initial position was adopted on 24/01/2018.

## Appendix 3

### Opinions issued by the Commission for monitoring the risk/benefit ratio of healthcare products in 2018

SUBJECT	OPINION OF THE COMMISSION
<p><b>Revision of the risk-benefit ratio of the medication Baume Arôme, cream (methyl salicylate, clove essential oil, and allspice essential oil)</b></p>	<p>The commission declined to launch a re-evaluation of the risk-benefit ratio but approved the modification of the summary of product characteristics (SPC) and the equivalent sections of the package leaflet:</p> <ul style="list-style-type: none"> <li>- <b>Section 4.1 “Therapeutic indications”:</b> Modification of the indication label to ensure it complies with rules for self-medications, i.e. the treatment of benign pathologies by the patient. Restriction of the indication to the following: “Local symptomatic treatment of minor wounds (bruises, contusions, etc.)”</li> <li>- <b>Section 4.2 “Posology and method of administration”:</b> Addition of treatment period and quantity of product to apply. Because it is a self-medication, limiting the treatment period to 3-5 days is recommended, The laboratory should recommend a specific amount of cream for each application;</li> <li>- <b>Section 4.3 “Contraindications” and 4.6 “Fertility, pregnancy, and breastfeeding”:</b> Adjustment of labels regarding pregnancy in compliance with the label previously approved for topical agents containing NSAIDS.</li> <li>- <b>Section 4.8 “Adverse effects”:</b> Update in compliance with current guidelines (SOCs and frequency).</li> <li>- <b>Section 4.9 “Overdose”:</b> Update to add symptoms of a salicylate overdose and appropriate treatment.</li> <li>- <b>Section 5.1 “Pharmacodynamic properties” and 5.2 “Pharmacokinetic properties”:</b> The laboratory must offer labels that explain the medicine’s pharmacodynamic and pharmacokinetic properties and provide supporting data.</li> </ul> <p><b>Package leaflet:</b> Add the sentence: “Keep medicine out of reach of children” at the start of the package leaflet.</p> <p><b>The packaging</b> must be changed in the following ways:</p> <ul style="list-style-type: none"> <li>- Improve the visibility of the sentence “Keep out of the sight and reach of children”;</li> <li>- Add the sentence “Do not swallow”.</li> </ul>

<p><b>Re-evaluation of the risk-benefit ratio of medicines containing alpha-amylase (Maxilase, Mégamylase, Alfa-amylase Biogaran conseil, and Drill maux de gorge alfa-amylase)</b></p>	<p>The commission came to an unfavourable ruling on the medicine's risk-benefit ratio for the indications listed in its marketing authorisation.</p>
<p><b>Re-evaluation of the risk-benefit ratio for the medicine Vectarion, lyophilisate and solution for injection preparation (almitrine mesylate)</b></p>	<p>The commission issued a favourable ruling on the medicine's risk-benefit ratio for the indication "Adjuvant therapy for mechanical ventilation in the most serious cases of acute respiratory distress syndrome (ARDS) in the event of refractory hypoxaemia and hypercapnia despite optimal artificial respiratory assistance (protective ventilation, prone position, etc.) and/or the absence of another adapted and accessible respiratory device (CO2 purification, venous oxygen, etc.)."</p> <p>The commission also found that section 4.1 of the summary of product characteristics (SPC) and the equivalent section in the leaflet of the medicine Vectarion needed to be revised as follows:</p> <p><b>deletion of the following indications:</b>  "Hypoxaemia and hypercapnia caused by alveolar hypoventilation in the following situations:</p> <ul style="list-style-type: none"> <li>- episodes of acute respiratory decompensation complicating cases of chronic obstructive pulmonary disease</li> <li>- withdrawal of artificial respiratory assistance</li> <li>- momentary respiratory depression caused by central analgesics, neuroleptics, fluothane".</li> </ul>
<p><b>National re-evaluation of the risk-benefit ratio of the medicine Curaspotaqua 5%, gel (benzoyl peroxide)</b></p>	<p>The commission decided that the medicine's current prescription and dispensing conditions (optional medical prescription, available over the counter) needed to be made more strict. A medical prescription is still optional to purchase this medicine, but it is no longer available over the counter.</p> <p>It also recommended the medicine's commercial name be changed to avoid:</p> <ul style="list-style-type: none"> <li>- any confusion with cosmetic products with a name similar to "curapost"</li> <li>- that patients think it is made of water due to the term "aqua"</li> <li>- Finally, the commission issued a favourable ruling on the following recommendations to improve the information provided about methods of administration:</li> <li>- verify the application time based on the clinical study on Curaspotaqua specifically;</li> <li>- make the instructions for use more visible in the package leaflet (use an inset);</li> <li>- include information about application period and rinsing instructions on the tube;</li> <li>- modify the packaging of the box and tube: indicate in red the sentence "rinse off with water after 1-5 minutes".</li> </ul>
<p><b>Re-evaluation of the risk-benefit ratio of the medicines Phenergan syrup, cream, solution for injection, and tablet (promethazine)</b></p>	<p>The commission issued the following rulings:</p> <ul style="list-style-type: none"> <li>- <b>unfavourable risk-benefit ratio for the medicine Phenergan 2% cream</b> for the indication listed in the marketing authorisation, specifically "local symptomatic treatment for itching, especially due to insect bites". However, pending the referral decision of the European Medicines Agency, the commission recommended that the topical form be restricted to a prescription-only medicine.</li> </ul>

	<p>- <b>unfavourable risk-benefit ratio for the medicines Phenergan 0.1% syrup and Phenergan 25 mg tablet</b> for the following indication listed in the marketing authorisation: “symptomatic treatment of various allergy symptoms: runny nose, itchy eyes, and hives”. However, pending the referral decision of the European Medicines Agency, the commission recommended that the syrup and tablet forms be restricted to prescription-only medicines.</p> <p>- <b>favourable risk-benefit ratio for the medicine Phenergan 25 mg tablet</b> for the following indication listed in the marketing authorisation: “occasional insomnia and temporary insomnia”.</p> <p>- <b>unfavourable risk-benefit ratio for the medicines Phenergan 2.5% solution for injection</b> for the following indication listed in the marketing authorisation: “symptomatic treatment of acute hives”.</p> <p>- <b>favourable ruling regarding the following modifications</b> to the summary of product characteristics (SPC) for the oral forms of the medicine Phenergan:</p> <ul style="list-style-type: none"> <li>- modify the number of tablets per box: reduction to 5 tablets per box (instead of the current 20 tablets per box);</li> <li>- improve the information about adverse effects by including extrapyramidal effects such as tardive dyskinesia, akathisia, and abnormal movements (section 4.8);</li> <li>- improve the warnings section by adding the risk of the loss of intestinal peristalsis that could lead to intestinal occlusion or ischaemic colitis (sections 4.4 and 4.8);</li> <li>- improve warnings for patients aged 75 and over by adding a recommendation to not use the product (section 4.4);</li> <li>- improve information on interactions with other medicines and other types of interactions to comply with the latest version of ANSM's Thesaurus of Medicine Interactions (section 4.5);</li> <li>- improve information on pharmacodynamic properties by including the medicine’s dopamine antagonist properties (section 5.1).</li> </ul>
<p><b>Revision of the risk-benefit ratio of the medicine Tilcotil 20 mg, scored film-coated tablet (tenoxicam)</b></p>	<p>The commission recommended that the summary of product characteristics (SPC) for the medicine Tilcotil be modified to include the medicine's risk to the skin, which was found to be excessive due to the seriousness and frequency of the effects.</p>

## Appendix 4

List of the active substances and proprietary medicines whose risk-benefit ratio was being revised or reassessed in 2018

- Tenoxicam/Tilcotil
- Methyl salicylate + clove (essential oil) + allspice (essential oil)/Baume Aroma
- Chloraminophene 2 mg, gel (chlorambucil)
- Alpha-amylase/Maxilase
- Benzoyl peroxide/Curaspotaqua 5%, gel
- Promethazine/Phenergan syrup, cream, solution for injection, and tablet
- Methocarbamol/Lumirelax

# Appendix 5

## Overview of major French and European texts published in 2018 (excluding health policy decisions, individual decisions, and agency organisation)

### MEDICINES

#### EUROPEAN TEXTS

Commission implementation decision (EU) 2018/134 of 24 January 2018 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

Commission implementation decision (EU) 2018/133 of 24 January 2018 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

Regulation (EU) 2018/781 of the Commission of 29 May 2018 amending regulation (EC) no. 847/2000 with respect to the definition of the concept of "similar medicine"

#### FRENCH TEXTS

Decree no. 2018-291 of 20 April 2018 regarding the security of the medicine supply chain

Order of 30 January 2018 regarding the content and methods for presenting information at the end of a research project mentioned in paragraph 1 of article L. 1121-1 of the French Public Health Code regarding medicines for human use

Order of 16 February 2018 amending the order of 12 December 2017 regarding the approval of regional pharmacovigilance centres

Order of 12 April 2018 establishing the research list stipulated in paragraph 3 of article L. 1121-1 of the French Public Health Code

Order of 22 June 2018 modifying the order of 5 May 2017 relating to the display of a symbol on the outer packaging of certain medicines or products

Order of 21 December 2018 establishing the format of the summary of a research protocol involving humans mentioned in paragraph 3 of article L. 1121-1 of the French Public Health Code that only includes questionnaires or interviews

Decision of 2 February 2018 regarding pharmacovigilance best practices

### BIOLOGICAL PRODUCTS

#### FRENCH TEXTS

Decree no. 2018-810 of 25 September 2018 extending and adapting various bioethics provisions of the French Public Health Code to New Caledonia and French Polynesia

Decree no. 2018-1223 of 24 December 2018 amending biological analyses and screening tests carried out while screening donated blood

Order of 1 February 2018 regarding best practice for the use of tissues by doctors and surgeons-dentists outside of healthcare facilities

Order of 1 February 2018 regarding the list of tissues that can be used by doctors and surgeons-dentists outside of healthcare facilities

Order of 30 March 2018 establishing the technical conditions for authorising blood banks managed by a health cooperative group in application of article R. 1221-19-1 of the French Public Health Code

Order of 12 April 2018 establishing the research list stipulated in paragraph 2 of article L. 1121-1 of the French Public Health Code

Order of 12 April 2018 establishing the research list stipulated in paragraph 3 of article L. 1121-1 of the French Public Health Code

Order of 18 December 2018 modifying the amended order of 5 April 2016 establishing the selection criteria for blood donors

Decision of 8 February 2018 involving the list and characteristics of labile blood products

Decision of 17/04/2018 amending the decision of 27/04/2016 establishing the style and content of the survey completed by each blood donor in application of article R. 1221-5 of the French Public Health Code

Decision of 3 May 2018 amending the decision of 8 February 2018 establishing the list and characteristics of labile blood products

Decision of 10/07/2018 defining the best practices established in article L. 1222-12 of the French Public Health Code

Explanatory notice regarding the decision of 10/07/2018 defining the best practices established article L. 1222-12 of the French Public Health Code

## MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

### FRENCH TEXTS

Decree no. 2018-436 of 4 June 2018 regarding the simplification of the maintenance and quality control procedure for certain medical devices

Order of 25 January 2018 establishing the best practice recommendations for prescribing, conducting, and sharing the results of medical laboratory tests included in prenatal blood diagnostics

Order of 6 March 2018 amending the order of 25 January 2018 establishing the best practice recommendations for prescribing, conducting, and sharing the results of medical laboratory tests included in prenatal blood diagnostics

Order of 20 April 2018 establishing the best practice recommendations for conducting imaging examinations included in prenatal diagnostics and caring for pregnant women and couples during these exams

Order of 15 May 2018 establishing the conditions for conducting immunological tests and red blood cell counts

Order of 20 December 2018 amending the 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

Order of 21 December 2018 establishing the format of the summary of a research protocol involving humans mentioned in paragraph 3 of article L. 1121-1 of the French Public Health Code that only includes questionnaires or interviews

## COSMETIC AND TATTOO PRODUCTS

### EUROPEAN TEXTS

Commission report to the European Parliament and Council regarding the development, certification, and legal approval of substitutes to animal testing in the cosmetics industry (2015-2017)

Commission regulation (EU) 2018/885 of 20 June 2018 amending Appendix VI of regulation (EC) 1223/2009 of the European Parliament and Council on cosmetic products



[Commission regulation \(EU\) no. 2018/978 of 9 July 2018 \(and amendment\) amending Appendices II and II to regulation \(EC\) no. 1223/2009 of the European Parliament and Council on cosmetic products](#)

[COMMISSION REPORT TO THE EUROPEAN PARLIAMENT AND COUNCIL - Revision of regulation \(EC\) no. 1223/2009 of the European Parliament and Council regarding cosmetic products and substances with properties that can disrupt the endocrine system](#)

[Commission regulation \(EU\) 2018/1847 of 26 November 2018 amending Appendix V of regulation \(EC\) no. 1223/2009 of the European Parliament and Council on cosmetic products](#)

## FRENCH TEXTS

[Order of 12 April 2018 establishing the research list stipulated in paragraph 2 of article L. 1121-1 of the French Public Health Code](#)

[Order of 12 April 2018 establishing the research list stipulated in paragraph 3 of article L. 1121-1 of the French Public Health Code](#)

[Order of 21 December 2018 establishing the format of the summary of a research protocol involving humans mentioned in paragraph 3 of article L. 1121-1 of the French Public Health Code that only includes questionnaires or interviews](#)

## CROSS-CUTTING TEXTS

## EUROPEAN TEXTS

[Regulation \(EU\) 2018/1725 of the European Parliament and Council of 23 October 2018 regarding the protection of physical persons with respect to the processing of personal data by institutions, bodies, and organisations within the European Union and the free circulation of these data and repealing regulation \(EC\) no. 45/2001 and decision no. 1247/2002/EC \(GDPR\)](#)

[Commission directive \(EU\) no. 2018/350 of 8 March 2018 amending directive 2001/18/EC of the European Parliament and Council regarding the evaluation of environmental risks presented by genetically modified organisms](#)

## FRENCH TEXTS

[Law no. 2018-493 of 20 June 2018 regarding the protection of personal data \(GDPR\)](#)

[Ordinance no. 2018-1125 of 12 December 2018 in application of article 32 of law no 2018-493 of 20 June 2018 regarding the protection of personal data and amending law no. 78-17 of 6 January 1978 regarding information technology, files, and freedoms and various provisions regarding the protection of personal data](#)

[Decree no. 2018-687 of 1 August 2018 in application of law no. 78-17 of 6 January 1978 regarding information technology, files, and freedoms, amended by law no. 2018-493 of 20 June 2018 regarding the protection of personal data \(GDPR\)](#)

[Decree no. 2018-811 of 25 September 2018 regarding various provisions intended to ensure consistency in the regulatory texts regarding general administration topics in the health sector with respect to the provisions of law no. 2016-41 of 26 January 2016, which modernised our healthcare system](#)

[Order of 12 April 2018 establishing the research list stipulated in paragraph 2 of article L. 1121-1 of the French Public Health Code](#)

[Order of 12 April 2018 establishing the research list stipulated in paragraph 3 of article L. 1121-1 of the French Public Health Code](#)

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