ansm

French National Agency for
Medicines and Health Products Safety

ANNUAL REPORT 2019

EDITORIAL

A committed Agency attentive to its users' needs

2019 was the first year of the Agency's new Objectives and Performance Contract (COP), signed with the Minister for Solidarity and Health in May 2019. It sets out the Agency's strategic areas of focus up to 2023, the most important of which include openness to stakeholders and increased transparency.

The continuation and acceleration of this outreach strategy designed to address society's expectations had a very concrete impact on the Agency's activity and operations throughout the year.
The reform of the ANSM's advisory bodies is the cornerstone of this commitment, aimed at taking into account the plurality of expertise and, in particular, the patient experience, in a more systematic and integrated way. Health system users are now an integral part of the 15 permanent scientific committees created in July 2019 and whose work began in September 2019. Of the 291 members appointed, 40 represent user associations. The same applies to the "healthcare products information" committee, specifically dedicated to information and communication issues and which held its first meeting in October 2019.

Other initiatives testify to the Agency's openness towards informed decision-making based on a plurality of perspectives: for example, seven public consultation processes were organised in 2019 on topics that strongly mobilise public opinion, such textured breast implants, as well as numerous consultation meetings with stakeholders. The very close partnership with the College of General Medicine (CMG), hinged around regular meetings, has also made it possible to get general practitioners involved in the Agency's actions and decisions and for the Agency to address practitioners at the French Congress of General Medicine (CMGF). The advice and expertise of pharmacists is also sought whenever a recommendation impacts their practices and their relationship with patients. There are therefore frequent discussions between the Agency, the French National College of the Board of Pharmacists and pharmacists' union representatives.

This open approach ties in very closely with the Agency's communication and information policy and the dissemination of the risk management (RM) culture. Supported by the COP, this approach focuses all the ANSM's actions and decisions on the safety of the patients who use healthcare products and not only on the safety of healthcare products themselves. It is gradually permeating all of the Agency's activities.

The outreach strategy also reflects the Agency's development plan launched in 2019, which aims to implement an organisation that is even more open to the outside world in order to better integrate professionals and users in its activities. In-house, conferences led by sociologists and philosophers throughout the year aimed to more effectively share with teams the issues at stake in this major change within the Agency, to provide objectivity and help employees better understand the transformations under way within the Agency's environment and in the public health landscape as a whole.

In addition to its "traditional" activities, the Agency is increasingly involved in public health priorities. An example of this in 2019 concerned the issue of medication errors, approached in an innovative way through the first Hackathon dedicated to the topic, in partnership with the CMG, the University of Paris-Est Créteil, the Regional Pharmacovigilance Centres and ASIP-Santé.

At the same time, a shift towards a proactive policy with respect to publication of the Agency's data began in 2019. This policy is largely reflected in the Information and Data Systems Master Plan (SDSID), appended to the COP 2019-2023. The ultimate objective is to put the Agency's data and documents online proactively and progressively, in accordance with what is legally allowed to be divulged, in order to raise awareness of the Agency's actions, promote its expertise and encourage the use of its data. To enable them to be understood by all publics, the data are accompanied by educational information. Hence more than 100 releasable documents were published between April and December 2019 and preparatory work for the publication of raw pharmacovigilance, haemovigilance, medication error and clinical trial data was carried out in 2019.

Access to innovation is also one of the Agency's major focuses, mainly through its European activities, which have been further strengthened, both in terms of human resources and the improvement of procedures. The Agency is developing a proactive policy that is both quantitative (the number of European dossiers examined by the Agency) and qualitative (the weight of our opinions in the European debate). The ANSM is the first European agency to have set up a pilot phase concerning the initial application for authorisation for clinical investigations relating to medical devices.

In order to improve the service provided to users and, in particular, reduce the time taken to process applications, the ANSM has made changes to some of its procedures. For example, 2019 saw the arrival of new "fast track" procedures for clinical trial authorisations, the e-saturne system for named-patient temporary authorisations for use (ATUs) and the implementation of a "simplified procedures" platform for pharmaceutical sites.
With a view to further optimising its services and responsiveness to stakeholders, the ANSM has once again demonstrated its commitment to its Quality approach and obtained renewal of its ISO 9001 certification in January 2020 for "Risk Management".

The wide-scale roll-out of teleworking processes in 2019 has had a significant impact on the Agency's ability to ensure the continuity of its missions in the recent situations facing the country, including the public transport strike at the end of 2019.

2019 was also marked by the Médiator trial at the Paris High Court, held from 23 September 2019 to 6 July 2020. Through its Director General, the ANSM participated in the judicial debates throughout the trial with the utmost transparency, helping to uncover the truth and assuming its responsibility as a public institution.

The ANSM and its employees demonstrate a constant and ongoing commitment to ensuring patient safety. The high level of expertise of the Agency's teams and their ability to deal with crisis situations that often generate new expectations, while continuing to fulfil all of the ANSM's missions, must be applauded. These teams are key players in the far-reaching changes under way designed to open up the Agency to different publics and adapt to new challenges related to public health and the safety of healthcare products.

Catherine de Salins

Dominique Martin

HIGHLIGHTS IN 2019

- ISO 9001 certification for the scope of risk management (January)
- Implementation of the e-Saturne application for the computerised processing of requests for personal temporary authorisations for use (TAUs) (March)
- Withdrawal of textured-shell breast implants from the market (April)
- Signature of the 2019-2023 Objectives and Performance Contract (May)
- Medical cannabis: the Agency endorsed the recommendations of the Temporary Scientific Committee (July) – The authorisation of medical use of cannabis was written into law (Article 43 of Law n°2019-1446 on financing social security)
- Reform of bodies: establishment of the new scientific committees and the Healthcare Products Information Committee (July and September)
- Organization of a hackathon on medication errors with the CMG (College of General Medicine) and UPEC (September)
- Proper use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs): end of free access (December)

KEY FIGURES IN 2019

OUR INTERACTIONS WITH OUR ENVIRONMENT

- 1,537 conflicts of interest investigated as part of an internal ethics compliance report
- 2,394 ethics contributions and analyses
- 11 Temporary Specialised Scientific Committees (CSSTs) created
- 138 updates and 13 press releases published
- 3.7 million unique visitors to the ANSM website
- 22,722 Twitter subscribers and 40,085 LinkedIn subscribers

ENSURING THE SAFETY OF HEALTH PRODUCTS

37 new high-risk risk situations (HRS) dealt with in 2019, with an average of 42 HRS in progress

Medicines

- 59,177 cases of adverse effects were collected and registered by the Centres Régionaux de Pharmacovigilance (Regional Pharmacovigilance Centres – RPCs), including 7,802 adverse effects reported by patients
- 51,807 cases of adverse effects were reported through pharmaceutical companies
- 86 pharmacovigilance studies were in progress in 2019, and 6 new studies were begun
- 2,180 medication error or risk of medication error reports were transmitted to the ANSM
- 1,504 reports of shortages or risks of shortages were managed by the ANSM, as were strategies for finding medicinal alternatives for critical products
- 2,102 quality defect reports were submitted

Blood products

- 6,838 adverse effects related to haemovigilance were reported among donors of labile blood products
- 7,700 adverse effects related to haemovigilance were reported among recipients of labile blood products

Medical devices (MD) and in vitro diagnostic medical devices (IVDMD)

- 18,994 adverse effects related to medical device vigilance were reported, 553 of which were received from patients and patient associations
- 1,628 adverse effects were reported in reagent vigilance

Laboratory tests and inspections

- 660 inspections were carried out in 2019, of which:
- 10% were random inspections,
- 6% were inspections conducted outside France.
- 4,387 test reports based on laboratory studies were produced

FACILITATING ACCESS TO THERAPEUTIC INNOVATION

- 813 clinical trials authorised for medicines and 99 for MDs and IVDMDs
- 20 new cohort TAUs granted and 3,766 patients newly included in the scheme
- 26,528 registered TAUs granted
- 1,016 MAs and registrations issued by the ANSM in 2019 (national procedure and decentralised European and mutual recognition procedures)
- 19 MA applications under a centralised procedure assigned to France
- France rapporteur or co-rapporteur for 88 PIPs (Paediatric Investigation Plans)
- France releases more batches of vaccines to French and European markets than any other Member State

OUR RESOURCES

- 912 WFTEs
- €120.55 million budget

1 OUR ESTABLISHMENT

The ANSM in brief

The French National Agency for Medicines and Health Products (ANSM) is a public establishment under the authority of the French Ministry of Health. On behalf of the French State, it is responsible for the safety of health products and promotes access to therapeutic innovation. It acts on behalf of patients, alongside health professionals and in consultation with their respective representatives in all the Agency's bodies.

Through its evaluation, expertise and monitoring policy, the ANSM ensures that health products available in France are safe, effective, accessible and properly used.

It has the following missions:

- authorising the marketing of medicines and biological products,
- monitoring all health products throughout their life cycle
- studying the impacts of their use,
- collecting and analysing adverse effect reports,
- controlling product quality in its laboratories,
- inspecting manufacturing and distribution sites

Its priorities for action are set out in the Objectives and Performance Contracts that it enters into with the State.[1]

The ANSM is actively involved in European and international activities. Its activities are very much in line with European procedures and its activities are carried out in coordination with the European Medicines Agency, the European Commission and the other national agencies of the European Union. It also collaborates with international health organisations.[2]

The ANSM has a Board of Directors,[3] a Scientific Board[4] and Advisory Commissions.[5] It is also backed by an Ethics of Expertise Committee and Department[6], which help guarantee the independence and impartiality of the agency's decisions.

It has three sites: in Saint-Denis (headquarters), Lyon and Vendargues (laboratories).

Health products under the responsibility of the 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
Micro-organisms and toxins
Breast milk collected, tested, processed and preserved by breast milk banks

Medical devices (MD) and in vitro diagnostic medical devices (IVDMD)

[1] See the "2019-2023 Objectives and Performance Contract", page 12.
[2] See "European and international interactions", p 42.
[3] See "Governance Bodies" on page 11.
[4] See "Governance Bodies" on page 11.
[5] See "Activities of advisory bodies", page 17.
[6] See "Independence and impartiality: ethical obligations", page 22.

Therapeutic diagnostic and in vitro diagnostic devices, technical platforms, and medical software

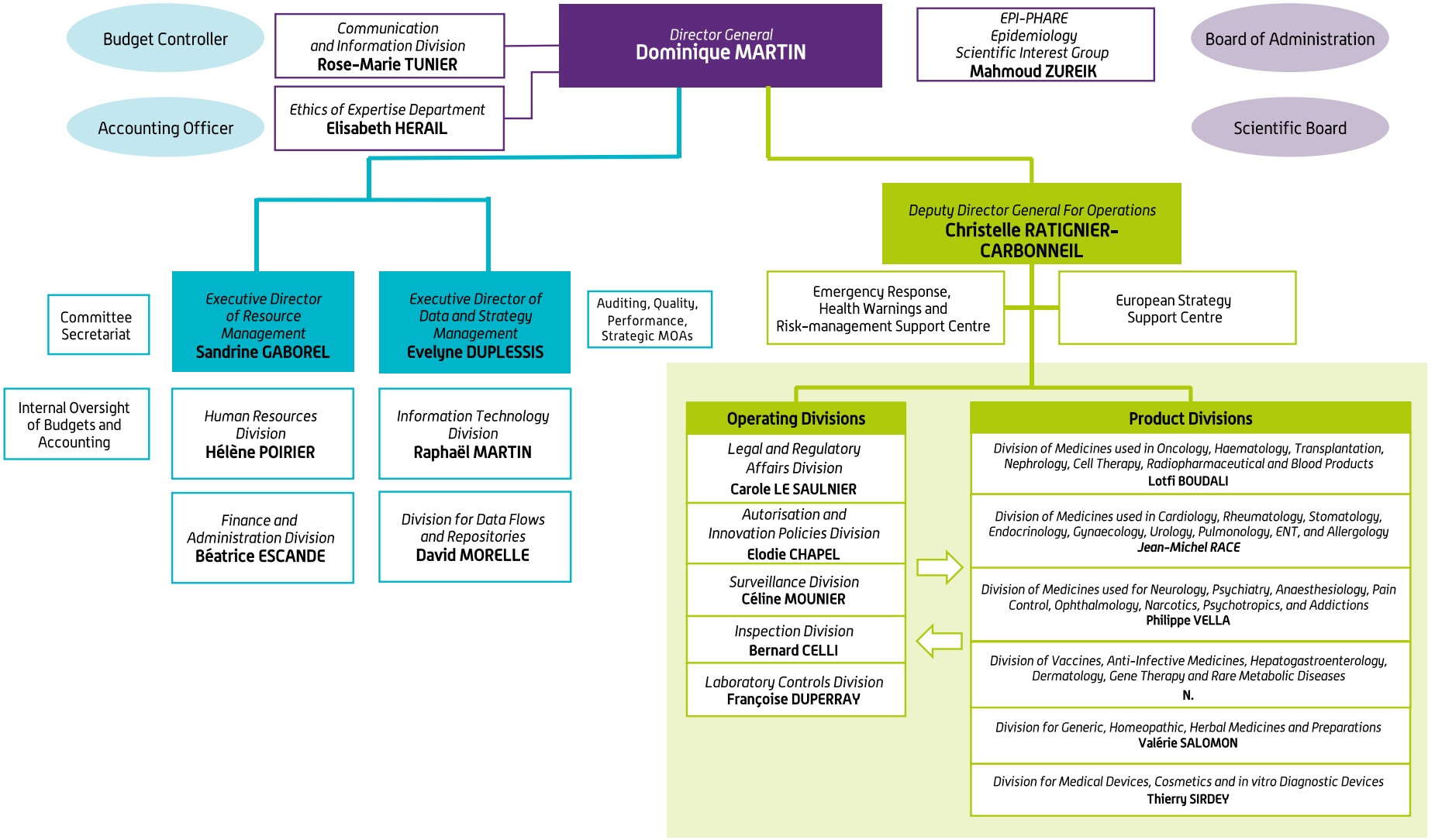
Cosmetic and tattoo products

An ISO 9001:2015-certified Agency since January 2019 for the following activities

- Monitoring Health Products
- Dealing with high-risk situations
- Testing health products
- Inspecting
- Tackling shortages of medicines

The ANSM's role in the health system

Organisation chart as of September 2020



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 President is Ms Catherine de Salins.

It comprises 27 members, most of whom are members of Parliament, healthcare professionals, and patient representatives.[1]
Votes are evenly distributed between government representatives (9 members, 18 votes) and the 18 other members, each of whom has one vote.

Apart from the representatives of the Agency's personnel, who are elected, the members of the Board of Directors are appointed by the Minister for Health. Except for 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 2019 in March, June, and November.

Scientific Board

The ANSM Scientific Board was created in 2012 and renewed in 2015 for a three-year term.
Its term of office ended in September 2018, and is currently being renewed.

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 the ANSM's Director General are appointed by order of the Health Minister for a renewable three-year period; these members are chosen on the basis of their scientific expertise in the field of health products.
- Six scientific experts proposed by the Minister for Research are appointed by decree of the Minister for Health for a renewable, three-year period, based on their expertise in health products.

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

[1] A complete list of members can be found in Appendix 1, page 201.

Objectives and Performance Contract 2019-2023

The second Objectives and Performance Contract (*Contrat d'Objectifs et de Performance* – COP), entered into by the Ministry of Solidarity and Health and the ANSM, defines the Agency's main strategic orientations for the next five years (2019 to 2023). It is part of the implementation of the National Health Strategy (SNS), defined by the Government for the 2018-2022 period and contributes to the first priority commitment of the "My Health 2022" project: "Promoting quality and refocusing care on the patient".

The COP highlights four strategic areas divided into 21 major objectives, which are in turn broken down into operational actions. Twenty-four monitoring indicators, of a qualitative or quantitative nature, are used to monitor implementation.

The objectives and actions have been developed with various central government bodies, under the guidance of the French Ministry of Health and with support from the Inspectorate General of Social Affairs (IGAS). Stakeholders were also consulted with regard to the main strategic priorities.

An assessment report on the implementation of the COP will be presented to the ANSM Board of Directors and published on an annual basis.

Strategic priority 1: Develop the Agency's openness to stakeholders and increase the transparency of its activities

The new framework of the National Health Strategy (2018-2022) and the "Ma Santé 2022" (My Health 2022) collective commitment project reinforce the ANSM's major policy of placing the patient at the heart of its safety measures. Within this framework and in consultation with the Ministry of Health, the Agency must continue to build constructive, trusting and long-term relationships with its users, i.e. patients, health professionals and manufacturers.

Strategic priority 2: Make risk management a common operating principle for all the Agency's missions

The ANSM is establishing a risk management approach that permeates all its actions and decisions. This approach, applied to health safety and based on paying particular attention to users, aims to prevent the occurrence of adverse events associated with treatments, and with health products in particular, or, failing that, to reduce their risks to an acceptable level.

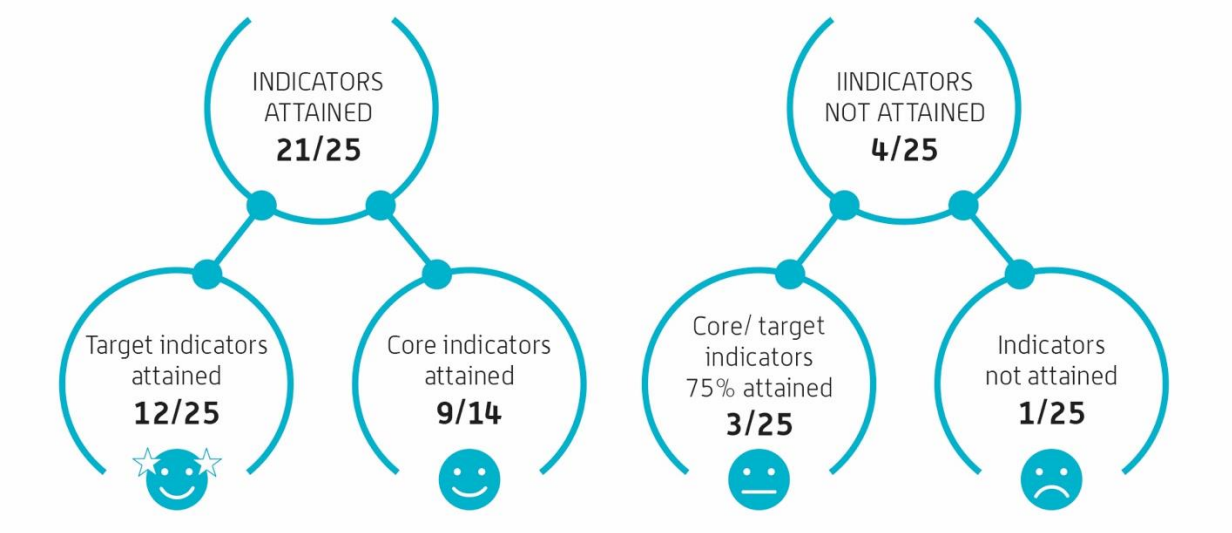
Strategic priority 3: Reinforce and stabilise the Agency's positioning to facilitate access to innovation in the European environment

The ANSM is an essential link in supporting the development of innovative healthcare products and facilitating their availability under conditions that ensure patient safety. Today, innovation-support activities are very much in line with European procedures. In this context, the Agency must strengthen its European positioning to enable early and secure access to innovation.

Strategic priority 4: Stabilise the institution's performance and efficiency

The Agency must meet the public service performance requirement of providing safer and more efficient services that satisfy the expectations of the audiences they serve. The aim is to guarantee the quality and safety of health products for all citizens, and fast access to the most recent products that improve patients' lives. To achieve these goals, the ANSM is committed to carrying out numerous activities.

In 2019:



The complete 2019 review of monitoring indicators can be found in Appendix 2, page 208 (results on 31 December 2019).

The indicators classified per activity can also be found in the report, bearing the following wording: "COP 2019-2023 indicator"

2 OUR INTERACTIONS WITH OUR ENVIRONMENT

Three-way interview

Paul Frappé, President of the Collège de la Médecine Générale
Christelle Ratignier-Carbonneil, Deputy Director General of the ANSM
Gérard Raymond, President of France Assos Santé

What changes did you note in 2019 in terms of the way the Agency works with patient/healthcare professional representatives?

Paul Frappé: First of all, we observe that the ANSM is becoming an important vector for dialogue between healthcare professionals and patients, via associations. Thanks to the meetings it organises, we get the opportunity to meet one another and exchange information.
In addition, the College of General Medicine has seen an increase in the number of requests from the ANSM over the last three years. The nature of these requests has changed too. It is now less a question of asking us for specific opinions than of collaborating together and jointly constructing the most appropriate response.

Gérard Raymond: Over the last few years, we have also observed the ANSM's willingness to be open and, in particular, its willingness to develop dialogue with patients. The introduction of a patient representative in all its bodies since 2019 is a perfect illustration of this.
However, difficulties sometimes arise when it comes to understanding everyone's roles. It is necessary for each of the stakeholders to know their respective expectations and roles, and what characterises and differentiates them from each other. This will allow for better collaboration.

Christelle Ratignier-Carbonneil: It is important to be able to bring all stakeholders together within a single entity to aid this mutual understanding. All viewpoints are important and complementary, and enable us to learn from one other.
In this respect, the evolution of bodies[1], especially the permanent scientific committees (CSP), is an important process.
And I am pleased to see that, within the Agency, exchanges with healthcare professionals and patients are increasingly systematic. Despite the difficulties, we are managing to move forward and reach decisions together concerning effective safety measures. Beyond the safety of healthcare products, it is patient safety that matters.

On which dossiers in particular did you work together in 2019?

Paul Frappé: Some of the key dossiers we handled in 2019 included sartans,[2] therapeutic cannabis,[3] breast implants[4] and medicinal products containing clay. The participation of doctors' representatives on the ANSM's Board of Directors and the ANSM's participation in the French General Medicine Congress and regional meetings are also highlights of our collaboration. Finally, the hackathon,[5] organised by the ANSM, the CMG and Paris-Est Créteil University in September 2019, is an excellent reflection of the dynamism of our exchanges, with the mobilisation of a great diversity of profiles and age groups.

Gérard Raymond: We have collaborated on cross-disciplinary issues but also on specific issues, in order to provide the patients' perspective, concerning Levothyrox for example. More generally, we have been working on drug supply pressures.
In addition, we have played an important two-way relay role: transmitting feedback from the field to the ANSM and, conversely, disseminating the ANSM's warning or risk minimisation messages to the field.

[1] Also read "Activities of advisory bodies", page17.
[2] Also read "Evaluation of the risk of nitrosamine impurities in chemical medicines", page 134.
[3] Also read "Decision to implement a trial on cannabis for therapeutic purposes", page 138
[4] Also read "Textured breast implants are withdrawn from the market" page 103.
[5] Also read "Organisation of a hackathon in partnership with the CMG and Paris-Est Créteil University on medication errors in the community setting", page 36.

Christelle Ratignier-Carbonneil: One example we can mention is the dialysate[1] issue, which needed to be dealt with urgently with important implications in terms of continuity of care. The key to dealing with the situation quickly was to bring together all the players, healthcare professionals and patient associations.
The supply pressures for corticosteroids,[2] which lasted several months, are another example. Despite a real scarcity of supply, our exchanges have enabled us to make progress.
The Medtronic pump[3] dossier, as well as the Sinemet dossier, in which the France Parkinson association was closely involved, were also important areas of collaboration in 2019.
These examples show that we are now shifting away from specific, one-off collaborations with our stakeholders towards a joint construction approach, albeit respecting our respective perimeters. This allows us to adopt positions that are more appropriate and easier for our publics to understand.

What changes do you foresee and would you like to see in the way the Agency works with stakeholders?

Gérard Raymond: The last few years have been spent setting up this collaboration. The challenge over the next few years will be to consolidate and improve our working methods. We still need to get to know each other better in order to reduce any lingering questions and misunderstandings. We also need to learn how to work together in a more in-depth manner and not just in urgent situations. We should be able to collaborate more efficiently in the coming years. Finally, a third challenge is that of opening up to civic society. The ANSM's initiatives enable mutual knowledge of stakeholders, but it is important that citizens are familiar with the ANSM too.

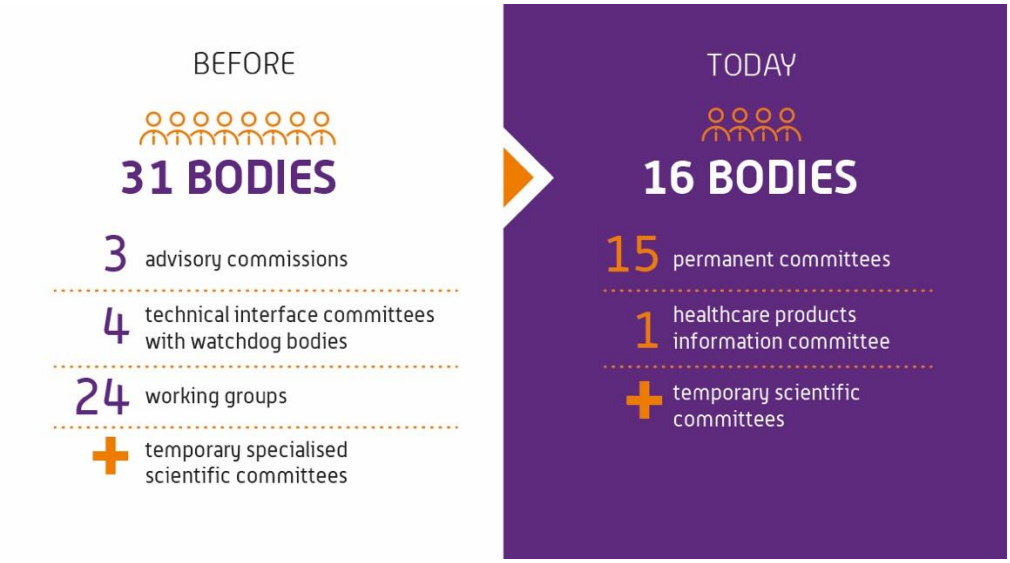
Paul Frappé: It is crucial, in fact, that each party can properly fulfil their respective roles. We generalists must remain generalists. Faced with the multiplication of requests, we need to be able to organise ourselves better, in a spirit of continuity, rather than in fits and starts and in response to urgent situations. Obviously, there will always be urgent opinions to be given, but it should be possible to programme the work more effectively. More concretely, we could work on building a network of regional correspondents or holding a new hackathon.

Christelle Ratignier-Carbonneil: It's true that we need to become more adept at anticipating. Having said that, we are a health authority that is required to handle emergencies, and that will always be the case. But, in order to better structure our work, we could consider setting up a joint meeting of the two interface committees[4] once a year, for example.
I think that we are moving in the right direction, towards a collaboration that respects our respective positions and missions. This approach has become an important component of the Agency's culture. I cannot perceive of our mission without the involvement of patients and healthcare professionals. So we need to continue our collaboration, onwards and upwards.

[1] Also read "Discussion meetings and investigations concerning the use of citrate-based dialysate in haemodialysis patients", page 32.
[2] Also read "Supply shortages concerning prednisone-based proprietary medicines and oral prednisolone", page 52.
[3] Also read "Organisation of a first institutional meeting with all the stakeholders concerned by the discontinuation of manufacturing of the Medtronic MiniMed implantable insulin pump", page 32.
[4] Also read "Reinforced consultation with stakeholders", page 30.

Activities of advisory bodies

The terms of the 3 advisory commissions, 24 working groups and 4 technical committees with the vigilance networks created in 2016 ended in June 2019. These bodies were replaced by 15 permanent scientific committees established in July 2019 whose work began in September 2019 and one Healthcare Products Information Committee whose first meeting was held in October 2019.
The reform of the ANSM's consultative bodies is part of its strategy of opening itself up to civil society and embracing multiple sources of expertise. The users of the health system are now incorporated into all consultative bodies of expertise.



The **15 permanent scientific committees** may be consulted by the Director General of the ANSM when the appraisal of a case or question requires a collegial expert opinion in addition to the internal evaluation, notably due to the innovative nature of the products, any major public health impacts associated with them, or when there is a need for better knowledge of practices or of the actual conditions in which products are used.

They are each composed of 10 to 20 members. Each committee now has at least 1 to 3 representatives of user associations. Members of permanent committees are appointed for 4-year terms and are all subject to the ANSM’s ethics requirements.

The **Healthcare Products Information Committee (CIPS)** focuses specifically on information and communication issues concerning health products. Its mission, in conjunction with ANSM teams, is to propose innovative solutions for the ANSM and then participate in their roll-out.

This multidisciplinary committee meets four times a year and brings together representatives of patient associations, health professionals, foreign agencies and social scientists.

Temporary Scientific Committees are external expert groups, specifically established to address a given issue. A limited number of meetings are held over a fixed period of time.

Establishment of Permanent Scientific Committees and initial activities

- Launch of a call for applicants on 27 February 2019.
- 291 appointed members including 40 representatives of user associations.
- The work of the 15 permanent committees began in September 2019.
- 31 meetings were held during the last four months of 2019.
- An initial satisfaction survey was conducted at the end of 2019 among committee members to assess the establishment and operation of these new committees.

Decision to implement an experiment with medical cannabis

The ANSM began its activities related to medical cannabis in September 2018 with the creation of a temporary specialised scientific committee (CSST) to evaluate the relevance and feasibility of making cannabis available for therapeutic use in France. This committee reviewed the converging scientific evidence demonstrating the benefits of cannabis for the treatment of certain symptoms of different pathologies, growing demand from patients and health professionals, and the fact that many countries worldwide and in Europe have already introduced cannabis for medical use.
In December 2018, the CSST considered it relevant to authorise the use of medical cannabis for patients under certain clinical situations (epilepsy, pain, palliative care, painful spasticity, support treatment in cancer care). The ANSM concurred with these conclusions and expressed the desire to see an experiment put in place in order to evaluate the provision of cannabis for medical purposes in real situations, and thus determine whether this provision could subsequently be generalised.

The testing of the medical use of cannabis in France is provided for in the Social Security Financing Act of 24 December 2019, effective in 2020.

On 15 October 2019, the Director General of the ANSM appointed a new Temporary Scientific Committee (CST) for the “Implementation of Medical Cannabis Testing in France”, composed of 23 people, health professionals and patients who were tasked with clarifying the conditions of the experiment and ensuring optimal safety. The CST is also responsible for listing the reference centres that will include patients, located throughout France, in connection with the different learned societies and the indications for the experiment.
Several aspects will ensure the quality of the drugs used: they must conform to precise terms and conditions governing product specifications and quality; production and distribution sites can be controlled by the ANSM, and product testing will be carried out by ANSM laboratories.
The safety of prescription will be ensured: treatment can only be initiated by physicians who have volunteered for the scheme. They must undergo mandatory preliminary training, and practise in reference structures supporting the chosen indications. Any general practitioner in the non-hospital sector will be able to renew prescriptions.
The safety of the dispensing procedure will also be ensured: pharmacists in the hospital and non-hospital sectors, also trained in advance, will dispense cannabis as part of the experiment. Medical cannabis, like any narcotic drug, will be prescribed on secure prescriptions and stored in locked safes.
With regard to the monitoring of the experiment, all participating patients will be monitored in an electronic log kept up to date by health professionals. This log will be used to assess the feasibility of the circuit and its acceptability to patients, and will also centralise data on doses administered, the efficacy, adverse effects and impact on quality of life.

The experiment on medical cannabis is expected to begin in late 2020/early 2021. It is scheduled to last 18 months during which 3,000 patients should be monitored for at least 6 months.

In addition

- **Inaugural meeting of the CIPS on 18 October 2019.** This first session of the Healthcare Products Information Committee (CIPS) provided an opportunity to reiterate the key communication issues for the ANSM and define the themes of the Committee's programme for 2020.

- Public hearing on reinforcing risk reduction measures related to in utero exposure to anti-epileptics (May).
  Following the publication of the ANSM report on the risks of malformations and neuro-developmental disorders in children exposed to anti-epileptic drugs during pregnancy, the ANSM convened a committee of experts to issue an opinion on the reinforcement of the risk reduction measures required for each anti-epileptic marketed in France. In a public hearing with a live webcast, members heard representatives of health professionals and representatives of associations of patients at risk.
  Following these hearings and taking account of the Agency's report and the measures already implemented for valproate, the Committee was asked to propose a series of recommendations for the reinforcement of risk-reduction measures for anti-epileptics other than valproate, including:
  - introducing a monitoring record for patients with epilepsy starting at 10 years of age,
  - implementing specific measures for anti-epileptics with a proven risk of birth defects.

- CSST: "Public consultation on the role and use of textured breast implants in cosmetic and reconstructive surgery" (February)[1]

2019 DATA

- 272 individuals were appointed as ad hoc external experts to the Agency in 2019
- **5 meetings held for all French pharmacopoeia committees**

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 target	Attained
1	Number of public hearings per year	≥ 6	7
4	Rate of increase in satisfaction of stakeholders in permanent and temporary committees	Survey no.1 and creation of the scale	Survey completed The score is stabilising
21	Rate of reduction in recourse to external individual expertise	Reference year	2019 reference: pending consolidated data

[1] See "Textured-shell breast implants are withdrawn from the market" on page 103.

Permanent Scientific Committees

Permanent Scientific Committee	Creation date and appointment of members	Number of meetings in 2019
Labile blood products and blood donors	29/07/2019	2
Therapy and cardiovascular risk	12/07/2019	2
Dermatology drugs	29/07/2019	1
Diagnostic and nuclear medicine drugs	29/07/2019	3
Oncology and haematology	29/07/2019	4
Drug safety and quality	12/07/2019	0
Promotion of safe use of medicines	12/07/2019	3
Reproduction, pregnancy and lactation	12/07/2019	1
Paediatrics	29/07/2019	1
Psychotropics, narcotics and addictions	12/07/2019	1
Monitoring and pharmacovigilance	12/07/2019	7
Haemovigilance	29/07/2019	2
Medical device vigilance and reagent vigilance	12/07/2019	2
Interface with the toxicovigilance network	12/07/2019	1
Quality control of medical devices	29/07/2019	1

Temporary Scientific Committees (CST)

Temporary Specialised Scientific Committee (CSST)	Creation date	Number of meetings in 2019
Public consultation on the role and use of textured breast implants in cosmetic and reconstructive surgery	05/02/2019	1 meeting held over 2 days
Ranking of indications for polyvalent immunoglobulins during shortages	08/01/2019	1
Extension of CSST on "Physical restraint medical devices"	31/01/2019	0
Phagotherapy – feedback and outlook	01/02/2019	1
Regulations for micro-organisms and toxins (MOT): bacteria, toxins and viruses listed under Article L. 5139-1 of the French Public Health Code	12/02/2019	5
Evaluation of the relevance and feasibility of making medical cannabis available in France	10/09/2018	4
Public hearing on reinforcing risk-reduction measures related to in utero exposure to anti-epileptics	25/04/2019	1
Microbiological controls of breast milk from lactaria	05/06/2019	4
Meningioma and cyproterone acetate – further work	23/10/2019	1
CSST on “Evaluation of the relevance and feasibility of making medical cannabis available in France”.	28/09/2018	4
CST on “Implementation of medical cannabis testing in France"	15/10/2019	7
Review of Best Preparation Practices - Finalisation of activities	04/11/2019	8
Medical device cybersecurity and new information technology challenges	29/11/2019	0
Inclusion in clinical trials of asymptomatic patients at risk of developing Alzheimer's disease	16/03/2018	1

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 organisational system adopted by the ANSM to implement its ethics policy and monitor its application relies on a department especially designed for this purpose and run by the agency's ethics officer, and on 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 2019, the 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.

ANSM personnel

As part of the agency's recruitment and appointment process, any of the candidates' possible links and relationships 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 conducted; 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. It should be noted that as from 1st February 2020, the provisions of Law No. 2019-828 of 6 August 2019 on the transformation of the public service have changed these procedures and obligations for public officials in the event of their departure to the private sector, including the transfer of the Public Service Ethics Commission to the High Authority for the Transparency of Public Life.

Recourse to external collegial expertise

Appointments to an ANSM collegial body (commission, working group, or temporary specialised scientific committee) are first examined by the Ethics Department, which studies the links and relationships reported by each member on their CV and their public declaration of interests form, as well as those listed in the public Health Transparency Database. The aim is to identify any activity that might be incompatible with the mandate of the body in question and any risks of conflicts of interest that should be avoided.

2019 DATA

Cases that led to an ethics risk analysis by the Ethics Department

- 31 applicants' applications during the pre-recruitment phase
- 20 pharmacy interns' or trainees' applications
- 34 cases of agents leaving the ANSM
- 421 experts' applications

HIGHLIGHTS IN 2019

Implementation of internal monitoring procedures relative to the application of ethical rules on expertise (April)

The recommendations made, both by the Agency's Ethics Committee at its meeting on 28 February 2018, and by the General Inspectorate for Social Affairs (IGAS) as part of the audit of the management of health risks by the ANSM that was carried out by the Agency in 2018, led to the modification of the organisation of internal monitoring, as from 1st April 2019, with a view to ensuring compliance with ethics rules at the ANSM.

As a result of these recommendations, the relevant departments must now ensure the traceability of all auditing operations they carry out (internal "first-level" audits). The purpose of this approach is to ensure that their experts fulfil their reporting requirements, to verify that any conflicts of interest have been analysed, and that appropriate measures to address such conflicts have been put in place before any bodies meet or any expert missions have been assigned.

The Ethics Department will conduct audits ("second-level" sampling audits) to verify the proper performance of first-level audits by departments, and to ensure that the conflict-of-interest prevention and management system is functioning properly.

To help them apply these new audit procedures, the Ethics Department has established a set of operating procedures and traceability documents for all departments in charge of health expertise.

To this end, training modules were put in place in 2019 with a view to ensuring the proper appropriation of these resources by managers of bodies, or by people who regularly use the services of external experts. For example, ten training sessions involving a total of 63 people were run by the Ethics Department between April and June 2019.

Integration of risks of breaches of probity into the ANSM Charter Of Ethics (December)

An Ethics Charter specific to the ANSM was issued in May 2016, then updated in March 2017 and August 2018. Based on the Agency's prior experience, it sets out all of the rules and behaviours to be adopted by ANSM staff and associates in the context of their assigned tasks. This charter has been appended to the ANSM's Rules of Procedure since January 2018.

In addition, in accordance with the French Anti-Corruption Agency's recommendations, drawn up pursuant to the Law of 9 December 2016 on transparency, the fight against corruption and the modernisation of public life, (known as the Sapin 2 Law), a revision of this charter was initiated in the second half of 2019 in order to include the procedures for preventing risks of breaches of probity, such as corruption, influence peddling, illegal acquisition of equity stakes, favouritism, misappropriation of public funds, embezzlement, and insider trading. A series of practical information sheets accompany this charter which, for each type of breach of probity, state the article of the French Criminal Code (or of the Monetary and Financial Code) relating to it, examples of such situations applied to the context of the ANSM, and the conduct required to prevent their occurrence.

This update of the Ethics Charter, presented to the ANSM Ethics Committee in December 2019, was adopted by the staff representative bodies and by the Board of Directors in March 2020.

Internal auditing of the application of ethical rules with regard to expertise

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

In 2019, these auditing operations focused on:

- the compliance of the declarations of interests of Agency staff subject with these statutory reporting obligations,
- the obligation to develop a classification table listing the interests of members of bodies prior to holding committee meetings (permanent scientific committees),
- the obligation to draw up an assessment sheet listing any links of interest prior to the solicitation of any external expert whose services are used on an ad hoc basis.

2019 DATA

- 5 compliance-auditing operations
- 3 audits of decision-making processes relating to clinical trials on medicines

In total, these audits covered 1,537 public conflict-of-interest statements (DPIs), including 421 applications from experts, 342 of which were received at the time of the renewal of expert assessment bodies.

- 2,394 contributions and analyses

Ethics Committee

The Ethics Committee is an advisory body that reports to the Director General and issues opinions on all issues related to the ethics of expertise, notably with a view to preventing risks of conflicts of interest, and particularly with regard to the most sensitive and complex cases.

This committee comprises the Chairs of the Board of Directors and the Scientific Board (or their representatives), an external personality, and the representatives of organisations of health professionals and associations 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. The ANSM's Ethics Officer attends committee meetings in an advisory capacity.

2019 DATA

The Ethics Committee was consulted twice in 2019:

- In February, an opinion was expressed on the application of the Director General's note of 28 August 2018 concerning financial assets held by ANSM staff.
- In December, it was consulted on the incorporation of procedures for preventing risks of breaches of probity into the Agency's Ethics Charter, and on the practical information sheets accompanying this charter,

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 core	2019 target	Attained
22	Compliance rate derived from internal audit (Staff / collegial expertise/ individual expertise)	95%	100%	Staff: 97% Collegial expertise: 100%

Dialogue and sharing of information with stakeholders

As an agency responsible for providing expertise and supporting decision-making, the ANSM acts in the interest of patients every day by ensuring the safety of drugs and health products. Promoting dialogue and the sharing of information with stakeholders, health professionals, patients and the general public are part of its mission to make its activities and decisions known to all.

The Agency's commitment to consolidating and strengthening its long-standing relationships with stakeholders was highly apparent in 2019. The ANSM aspires to foster increasingly constructive and trusting relationships with patients and users, but also with health professionals who prescribe or dispense health products. They must be permanently integrated into all of the Agency's working practices.

These relationships are forged by adopting a two-pronged approach:

- encouraging the active involvement of stakeholders in the Agency's expertise and decision-making processes in order to mobilise multi-stakeholder expertise and optimise decision-making, which also improves the understanding and monitoring of these decisions.
- providing instructive and exhaustive information and documentation about the Agency's procedures, in real time.

In line with its new COP, the Agency was actively engaged in maintaining its commitments to its target groups throughout 2019. In particular, it developed a more educational approach to its communications, pursued an increasingly proactive information strategy especially through its relations with the press, and strengthened its commitment to its stakeholders. The ANSM has increased its presence on social networks and made preparations to redesign its website in order to provide better responses to the needs of its different audiences.

Improving educational measures to ensure the safety of health products

The ANSM's different activities (including evaluations, decisions, studies, actions to protect patient safety, etc.) facilitate its production of reference documentation pertaining to health product safety for its audiences: patients, the general public, health professionals, the scientific community, and manufacturers. The goal of this work is to share knowledge and support the implementation of the many decisions made by the Agency.

The expertise of patients and professionals in the field is sought on a regular basis in order to improve the understanding and effectiveness of the information produced by the Agency.

HIGHLIGHTS IN 2019

The birth of a revamped website

As part of its new communication policy, the ANSM is committed to ensuring that its audiences are better informed. This policy of openness and transparency is particularly apparent in the Agency's redesigned website, which improves access to information for its audiences in terms of the browsing experience and content.

The future site, whose redesign began in 2019, sets out to better inform Internet users about decisions, and to give them an improved understanding of the Agency's missions and decisions.

Designed as an information site, the future website is intended to be more accessible, in terms of how it conveys the latest information, and also by adopting a new approach to communication.
The information will be presented in such a way as to be understandable by all Internet users, regardless of their level of knowledge. To this end, a new, more inclusive, educational and accessible editorial line will be adopted.

The future website will benefit from a smoother and more intuitive browsing experience. Content will be more attractive, in accordance with internet users' new information consumption habits. Interactive tools, videos and infographics will feature prominently, for example.

The website also aims to inform audiences, health professionals, patients and the general public about safety alerts in real time. ANSM data (e.g. on drug availability) will also be made available (in accordance with our transparency commitments.

In 2019, in order to achieve these objectives and fully satisfy all internal and stakeholder expectations, workshops were organised to gather the opinions of agents, representatives of patient associations, health professionals, watchdog members and industry representatives.

Following this first phase, devoted to auditing and identifying needs, the first prototypes were launched in the autumn of 2019.

In addition

- **Finasteride 1 mg used to prevent hair loss**: publication of an information sheet (December)[1]
- **Human fibrinogen-based proprietary medicines**: publication of a guide to proper use developed to facilitate the identification of medicines of major therapeutic value, and thus limit the risk of confusion and medication error in the context of supply shortages (September).
- **Sinemet (levodopa/carbidopa)**: publication of an information document describing the consequences of the modification of tablets following a change in the manufacturing process (May).
- **Chemotherapeutic drugs based on 5-fluorouracil (5-FU) or capecitabine for dihydropyrimidine dehydrogenase enzyme deficiency (DPD deficiency)**: publication of a document to inform patients, prior to starting treatment, of the existence of DPD deficiency and the dosage to be taken, in order to investigate any possible partial or total deficiency (April).

2019 DATA

- Publication of 138 updates and 13 press releases
- Dissemination of 8 "ANSM Actu" newsletters
- 3,710,808 unique visitors to ansm.sante.fr, i.e. nearly 818,946 more than in 2018

[1] See "ANSM improves information on Finasteride 1 mg used to prevent hair loss", p. 76.

Change in the number of different visitors[1] to the ANSM website

Number of different visitors *	2017	2018	2019
January	280,151	245,736	339,968
February	234,770	224,603	291,605
March	283,107	232,338	288,563
April	227,344	255,681	315,315
May	243,130	204,675	302,681
June	230,285	210,248	304,458
July	230,373	263,880	287,225
August	301,690	135,397	257,573
September	318,102	246,331	305,968
October	211,863	275,500	330,257
November	240,249	311,732	366,798
December	210,284	285,741	320,397

[1] One different visitor = one IP address

An increasingly proactive information strategy

2019 was a busy year for media events. Numerous events were organised to support and explain the actions carried out by the ANSM. The provision of support in several sequences helped to improve interactions with journalists, and facilitated long-term monitoring.

Compared to the previous year, the number of media mentions for the ANSM increased by 4%. The ANSM also raised its profile on audiovisual media (TV and radio).

Several ANSM actions received particular attention, such as:

- the posting of a warning message on paracetamol boxes to improve the prevention of risks of overdose-related liver damage,
- approval to proceed with medical cannabis experimentation,[1]
- the discontinuation of a clinical trial conducted illegally by the "Josefa Fund" among patients with Parkinson's and Alzheimer's disease in particular,[2]
- notice to physicians and pharmacists about medication shortage problems,[3]
- the prohibition of macrotextured breast implants as a precautionary measure in order to reduce women's exposure to the risk of large-cell anaplastic lymphoma.[4]

HIGHLIGHTS IN 2019

Experimentation with medical cannabis

The Communication Department paid significant attention to the ANSM's work on medicinal cannabis. The societal dimension of these activities attracted the general public's attention. Media support was provided at each stage, from the confirmation of the relevance of cannabis use for medical purposes in certain therapeutic situations, to the validation of the practical framework for access to medical cannabis for experimentation in France, followed by the creation in late 2019 of the committee responsible for establishing the practical conditions for this experiment (products used, training of health professionals and conditions for monitoring patients).

2019 DATA

- More than 7,500 media mentions
- More than 1,000 requests from journalists
- More than 200 interviews given

[1] See "Decision to implement an experiment with medical cannabis", page 18.
[2] See "ANSM prohibits an unauthorised clinical trial among patients with Parkinson's and Alzheimer's disease", page 122.
[3] See "Securing the Supply of Drugs of Major Therapeutic Value" on page 81.
[4] See "Textured-shell breast implants are withdrawn from the market" on page 103.

Increased consultation with stakeholders

The diversification of working arrangements with stakeholders continued in 2019.

Public hearings held before the consultative bodies, broadcast live, were organised to give access, on a specific health safety issue, to the multiple points of view that inform the consultative bodies' reflection and debates.

Similarly, **consultation meetings**, in advance or to support decision-making on sensitive issues, were held with stakeholders to alert them, share information, answer their questions and also to involve them in devising messages for ANSM audiences.

The ANSM has regular interactions with **professional organisations**, and has established **partnerships** with them in order to transmit its information to specific audiences – especially health professionals – as efficiently as possible.

Partnership with the College of General Medicine

The College of General Medicine (Collège de la médecine générale – CGP) and ANSM share a common objective: to ensure patient safety.

To achieve this goal, the closest possible collaboration with the general medicine sector is required. 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.
As the representative of the profession, the College is the ANSM's preferred interlocutor.

In addition, since 2016, a partnership has been established between the ANSM and the College. This partnership takes different forms: an interface committee, participation in conferences (national and regional), the organisation of themed days or events on specific fields of activity (medication errors, pregnancies and medicines, analgesics, etc.).

The interface committee

The interface committee, consisting of representatives of the College and the ANSM, aims to create a forum for discussion in order to best anticipate actions and decisions that could impact general practitioners and their patients. It meets three to four times a year.

Its goals:

- better understand and take account of the needs of general practitioners,
- make the 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 in order to detect and monitor risks.

In practice:

- discuss the feasibility of the proposed measures and the clarity of information on a case-by-case basis,
- develop "key messages" and tools to inform actions impacting practices,
- help monitor a medicine's effectiveness and safe use after its market launch,
- share information about health policy decisions, information about proper use, investigations, etc.

The interface committee met three times in 2019. During these committee meetings and discussions of the various topics, the issues of proper use of medicines and overprescription were regularly raised. They will be the new focus of activities for the next few years.

The French General Medicine Congress

Each year, the ANSM takes part in the National Congress organised by the College, which brings together nearly 5,000 general practitioners. Present on a stand enabling direct interaction with delegates, the ANSM also participates in plenary sessions. In 2019, the ANSM co-organised a session with the College on the prevention of medication errors.

Regional meetings of the College of General Medicine

In parallel with its annual congress, the College organises regional meetings. These meetings offer general practitioners opportunities to discuss professional issues raised by the College in partnership with the institutions. In this context, the ANSM co-organises with the College one of the four sessions held during the day. In 2019, the theme of this session was pain management: "*Même pas mal : le patient douloureux et les médicaments" (*No Pain: the Painful Patient and Medication). The ANSM's intervention focused on the prescription, consumption and misuse of analgesics in France.

Real-time interactions

The ANSM enjoys a special relationship with the College, which enables it to hear the College's opinion on cases that may have an impact on general practitioners, and then implement measures that have the greatest possible relevance to the realities encountered in the field.

Partnership with the National Board of Pharmacists

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

Partnership with patient associations

The Patient Interface Committee met twice in 2019. During these meetings, a discussion was initiated in consultation with members of the Committee in order to adapt its actions in line with the Agency's policy of openness towards its stakeholders.

HIGHLIGHTS IN 2019

Integration of patient associations into expert bodies

As part of its strategy of openness towards users and health professionals, the ANSM decided to implement a reform of its advisory bodies,[1] which was approved by a resolution of its Board of Directors. More specifically, the new system of expert advisory bodies is based on:

- A Healthcare Products Information Committee; this body was created in direct response to the report on improving information about medication for users and health professionals, submitted to the French Minister for Health by the information task force chaired by Dr. Gérald Kierzek and Magali Léo in September 2018, which addresses the difficulties encountered due to the change of Levothyrox formula.
- Fifteen permanent scientific committees, which can be consulted when the investigation of a case requires a collegial opinion in addition to an internal evaluation, on all issues and products falling within the scope of the Agency's competence. In general, two representatives of patient associations sit on these committees.
- Temporary scientific committees tasked with addressing one-off or specific subjects;

[1] Also see "Activities of advisory bodies", page 17.

The ANSM also decided that committees should more systematically incorporate public hearings of stakeholders, particularly patients or patient associations.

Discussion meetings and investigations on the use of citrate-based dialysate in haemodialysis patients

On five occasions between 2018 and 2019, the ANSM brought together all stakeholders (health professionals, learned societies, patient associations, INSERM, and ABM) to analyse the possible impact of citrate-based dialysates on the mortality of haemodialysis patients in France.

In October 2018, the presentation, at a congress, of the results of an observational study suggesting that citrate-based dialysates negatively impact haemodialysis mortality in France, led dialysis centres to abandon citrate haemodialysis on a massive scale. Further independent investigations on the available data were deemed necessary. The Biomedicine Agency therefore conducted three observational studies using REIN (French Renal Epidemiology and Information Network) data collected over a very long period of time (January 2010 to December 2017) and concerning more than 100,000 patients.

The final ABM report concludes that the use of citric acid in dialysates does not pose a risk of excess mortality for patients.

The extensive mobilisation of stakeholders and the investigations carried out have improved the knowledge of dialysates. Clearer information has now been made available to haemodialysis patients via a user guide for haemodialysis patients and their families, and to health professionals through clarifications on the use of dialysates published by the French Nephrology, Dialysis and Transplantation Society (SFNDT). All stakeholders also agreed on the need to keep furthering this knowledge of dialysates.

Organisation of a first institutional meeting with all stakeholders affected by the production stoppage of the Medtronic MiniMed insulin pump (MIP) (September)

The MIP implantable insulin pump is a medical device that mimics the physiological mechanism of the pancreas and enables intraperitoneal insulin administration in adult type 1 diabetic patients who cannot tolerate subcutaneous administrations (including by means of a pump) and who suffer from frequent, or otherwise unexplained, hyperglycaemia and/or severe hypoglycaemia. Around 250 patients use the MIP pump in France.
On 12 September 2019, in light of the scheduled withdrawal of this pump from the market in July 2020 (stoppage of production postponed until December 2020), the ANSM brought together all relevant stakeholders to share the available data and discuss possible short- and medium-term solutions to enable the continued treatment of patients. Representatives of diabetic patients, diabetologists, Medtronic and Sanofi, the French Ministry of Health and the French National Health Authority (Haute Autorité de Santé – HAS) participated in this discussion meeting.
The patients present had the opportunity to testify to the improvement in both their quality of life and the management of their diabetes by this implantable pump.

Mindful of the difficulties encountered by patients fitted with the MIP pump at this meeting, the ANSM asked health professionals to develop protocols for the care of the patients concerned. The ANSM also reminded attendees that it does not have the authority to compel manufacturers to manufacture products, but that it encourages innovation and can support projects designed to make a new implantable insulin pump available to patients once again.

In addition

- Participation in the 19th Annual Congress of the National College of General Teachers (CNGE): Round table on “Opioids: analgesia and addiction” (November).
- Information meeting on the pilot phase for clinical investigations of medical devices in the framework of the application of the new European Regulation on 4 July.
- Information and discussion meeting for prescription support software (PAS) and dispensing assistance software (DAS) publishers on April 15.
- Public hearings of patients and health professionals on the role and use of textured breast implants in cosmetic and reconstructive surgery (February).[1]
- Information meeting for patients and health professionals on medical devices for the treatment of pelvic organ prolapse and urinary incontinence (January).[2]

[1] See "Textured-shell breast implants are withdrawn from the market" on page 103.
[2] See “Mesh implants for the treatment of urinary incontinence and pelvic organ prolapse”, page 110.

Reinforcing the role of social networks

Social networks are essential tools for understanding the environment and the audiences concerned by the Agency's decisions

Throughout the year, the ANSM has conducted a number of campaigns on the safety of health products (paracetamol, anti-epileptics, sartans, etc.) on social networks, and has also participated in national and European campaigns such as European Vaccination Week in April and World Week for the Proper Use of Antibiotics in November.

Social networks are also considered a channel enabling direct interaction with our audiences. When it comes to combating health-related fake news and rumours, detecting the first signs of supply shortages, and recommending the proper use of medicines to patients and healthcare professionals, our presence on social networks helps improve the safety of healthcare products.

In addition, when there are no associations representing patients for given pathologies, social networks can facilitate the identification of contacts or communities that express the points of view and expectations of the patients concerned. In this way, interactions with the ANSM's audiences on social networks have enabled the inclusion of informal groups of patients and collectives in consultation meetings, which have led to the adoption of information or risk reduction measures in collaboration with health professionals. This includes consultation meetings on the treatment of pelvic prolapse and urinary incontinence,[1] and those on textured breast implants in cosmetic and reconstructive surgery.[2]

They also enable interventions, if necessary, in response to false information endangering public health.

2019 DATA

- Twitter: 22,722 subscribers (+ 6,105 new subscribers, up 37% compared to 2018)
- LinkedIn: 40,085 subscribers (+26,019 new subscribers, up 185% compared to 2018)
- Youtube: 728 subscribers (+ 530 new subscribers, up 270% compared to 2018)

An integrated approach to internal and external communication

The Agency's internal communication activities have strongly supported the Agency's strategy of openness. For example, staff conferences have been held throughout the year to improve awareness of the challenges of this major change to the Agency, and to help employees take a step back and better understand the transformations taking place in the Agency's environment and in public health. This led to 11 philosophical conferences and workshops, jointly presented with a team of sociologists from Sciences Po/CNRS, Sorbonne-University and Etalab, on the publication of data.

Partnerships and agreements

In 2019, the ANSM continued its partnership policy with institutional players in the health sector, notably by renewing the collaboration agreement with the French Agency for Food, Environmental, and Occupational Health Safety (ANSES), to enable enhanced cooperation in common scientific fields, areas of expertise and inspections. In addition, the ANSM and the French National Cancer Institute (INCA) have also decided to step up their collaboration in the fields of early access to anti-cancer drugs, and in monitoring the proper use of medicines, which includes examining the expediency of establishing temporary recommendations for use (RTU),with the support of the CNIB. This heightened collaboration also extends to the field of medical devices (e.g. medical tests, and imaging in cancer care).

[1] Also see "Mesh implants for the treatment of urinary incontinence and pelvic organ prolapse", page 110.
[2] Also see "Textured-shell breast implants are withdrawn from the market", page 103.

Information for parliamentary representatives

Three senators and three members of parliament sit on the ANSM Board of Directors. The agency also contributes to discussions with parliamentary representatives via the responses it provides to letters and written questions submitted to the Health Minister or directly to the agency.

In 2019, the agency responded to 40 written questions and 34 letters from parliamentary representatives. The main questions submitted by parliamentary representatives related to:

- stock shortages for certain medicines, and supply problems,
- the proprietary medicines Levothyrox and Androcur,
- the safety of plasma donations (apheresis machines),
- access to rare disease treatments and innovative treatments,
- experimentation with medical cannabis.

Interface Committees with manufacturers

The Interface Committee for professional organisations representing the pharmaceutical industry met once in plenary session. In addition, several working groups of this committee met to consider industrial practices, process innovations or improvements, and supply shortages.

The Interface Committee for professional organisations representing the medical device (MD) and in vitro diagnostic medical device (IVDMD) industries met twice in plenary session. The activities of the committee and its working groups focused on issues related to the implementation of the two new regulations for MDs and IVDMDs, and the supply shortages of MDs.

Availability of Agency data

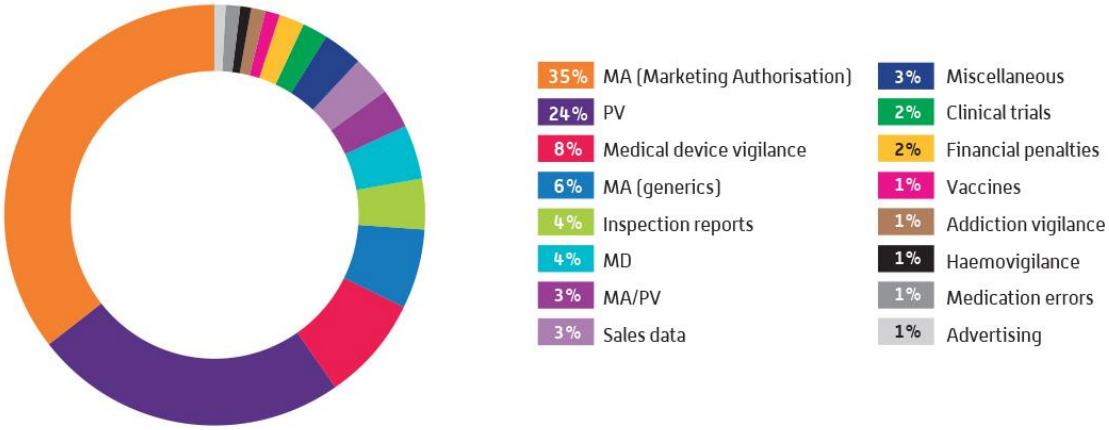
The implementation of a proactive publication policy for the Agency's data is consistent with its policy of openness and its Information and Data Systems Master Plan (SDSID).[1] The objective is to ensure the proactive and progressive online availability of the Agency's data and documents, in compliance with legal secrecy requirements, in order to improve awareness of the Agency's actions, promote its expertise and facilitate the exploitation of its data. To this end, the data will be accompanied by educational content.

External experts are assisting the ANSM with this process. Etalab (associated with Prime Minister's Office) is helping with methodological aspects, while the CNIL (French Data Protection Authority) and CADA (Commission for Access to Administrative Documents) are assisting with legal questions.

Requests for access to the Agency's administrative documents

Concerning the application of the provisions of the Code of Relations between the public and the administration, the agency received 169 requests for administrative documents. The number of requests remains stable compared to 2018. However, the Agency has observed an increase in requests over the last few years, with requests relating to increasingly large volumes of documents.

FIELDS CONCERNED BY REQUESTS FOR ADMINISTRATIVE DOCUMENTS



HIGHLIGHTS IN 2019

Organisation of a hackathon in partnership with Paris-Est Créteil University (UPEC) on "Medication errors in the non-hospital sector" (September 2019)

In continuation of the Interface Committee's work on medication errors, the ANSM, the CMG and UPEC organised the first hackathon dedicated to medication errors.

Divided into 18 teams, 110 candidates – medical and pharmacy students, nursing students and engineering students from the Ecole Supérieure d'Ingénieurs Paris-Est Créteil (ESIPE-Créteil) – worked non-stop for 30 hours on innovative digital services or applications for patients, healthcare professionals, healthcare institutions and public authorities.

Using data from the ANSM medication error database, the projects had to meet one of three challenges: facilitate the reporting of cases of medication error; assist within the analysis of reports; inform

[1] Also see "Implementation of the Information and Data Systems and Data Master Plan", page 182.

healthcare professionals and patients with the common goal of preventing medication errors in the non-hospital and hospital sectors.

The participants were accompanied by mentors from the ANSM, the Regional Pharmacovigilance Centres (RPCs) and ASIP-santé, as well as general practitioners, pharmacists, representatives of patient associations, and young companies who contributed their experience.

At the end of the challenge, 9 winning teams were pre-selected by intermediate juries composed of members with multidisciplinary backgrounds (doctors, patient associations, CRPV, ASIP-santé, ANSM and UPEC).

The Grand Jury, whose members were the President of UPEC, the President of the College, the Director General of the ANSM, and representatives of patients' associations, the French network of RPCs, the French Ministry of Health, the High Authority for Health, the CNAM, the DREES and ETALAB, ranked the three best projects and rewarded the winners. Prizes worth a total of €12,000 were awarded.

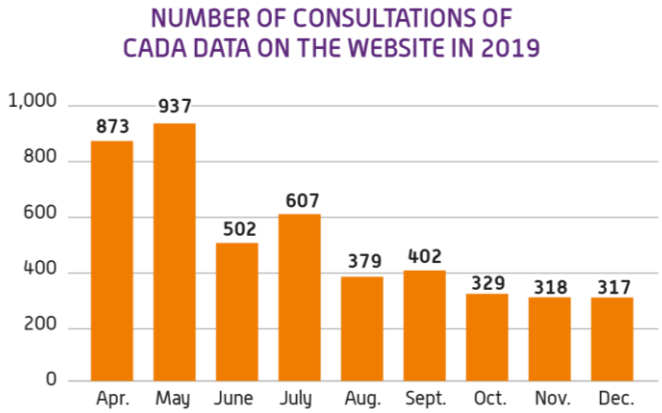
First prize: "QRShare Project", which aims to incorporate a QR code on the patient's prescription that contains all the information about the prescription. This technology secures the dispensing of medication and facilitates reporting while raising patient awareness of the reporting of medication errors.
The pharmacist will scan the QR code to check that the prescription corresponds to the dispensed medication. If a medication error occurs, the patient can scan the QR code and will be immediately redirected to the pre-completed form on the “signalement.social-sante.gouv.fr” reporting portal.

Second prize: "Symbiosis Project", which is designed to increase the number of reports from patients and healthcare professionals. This project is based on the exploitation of a new data-gathering source: the SICAP database belonging to the Poison Control and Toxicovigilance Centres.
The Symbiosis tool selects and automatically extracts cases of medication errors before importing them into the national pharmacovigilance database, and then into the medication error database, using a relevance-sorting operation based on an algorithm incorporating three criteria (severity, frequency, and population type). Offering guaranteed data quality, Symbiosis provides an interface for the validation of collected medication errors dedicated to the Regional Pharmacovigilance Centres.
The project meets the challenges of "facilitating reporting" and "assisting analysis".

Third prize: “AlertMed Project”, which is designed to simplify reporting by healthcare professionals and patients via a voice-assisted mobile application and a chatbot. The application provides an identical reporting form to that on the "signalement.social-sante.gouv.fr" reporting portal, and enables monitoring of the status of the report.
The project meets the challenges of "facilitating reporting" and "facilitating information for health professionals and patients".

Publication of CADA documents

Between April and December 2019, more than 100 CADA documents were published on the ANSM website.



Preparation for publication of vigilance and monitoring data

Preparatory work for the publication of raw pharmacovigilance, haemovigilance and medication error data on the data.gouv.fr website and on the Agency's website, was carried out in 2019. The question of publishing data from the National Pharmacovigilance Database (BNPV) was referred to CADA and the CNIL. An audit of the Agency's databases was carried out in conjunction with Etalab, as well as the benchmarking of publications produced abroad.

Preparations for the publication of clinical trial data were also made in 2019 and several stages were completed:

- consensus on the format of the evaluation report and non-publishable data,
- consultation with patient representatives,
- an IT project relating to the Agency's new website.

In 2020, these different activities should lead to:

- Online publications on vigilance
  - Publication of vigilance data and scoreboards
- Creation of a clinical trials register on the Agency's new website
  - Publication of data and evaluation reports from clinical trials of medicines and non-health products (HPS)
- Publication of inspection reports and inspection databases
- Information about stock-outs
  - Publication of raw data on stock-outs
  - Creation of a medication availability portal

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 core	2019 target	Attained
5	Implementation rate of the data publication work programme	75%	100%	80%

Legal and regulatory activities

The ANSM carries out a substantial amount of legal activity, producing more than 80,000 rulings each year, some of them of an individual or regulatory in nature, which is a noteworthy characteristic for a public administrative body. It also participates in the drafting of texts relating to its field of competence in support of the Ministry of Health.

Participation in the revision of legislation

The ANSM helps to develop legislation and regulations on both the national and European levels.[1]
In 2019, the Agency was involved in the drafting and publication of more than 50 texts, including on vigilance for all health products, medicines, biological products and medical devices.

Litigation and rulings

In 2019, the ANSM received 98 new requests related to its decisions.
In addition, 66 decisions were handed down by the administrative court, up from the 55 decisions handed down in 2018. The vast majority of disputes brought before courts of law were rejected (57).

Financial sanctions

Since the start of the process at the end of 2015, the ANSM initiated 62 financial sanction procedures, 24 of which led to sanctions against the operators of a medicine or a medical device.

HIGHLIGHTS IN 2019

Recommendations for applicants and holders of marketing authorisations and registrations relating to the names of medicinal products: an initial review, 2 years after their publication

The ANSM regularly receives reports of medication errors, which may occur during the dispensing, preparation or administration of medicines. Approximately 30% of these reports are related to packaging (labelling), and around 3% are related to the name of the drug.

In this context, the ANSM must ensure that a medicine, by virtue of its presentation or name, is not likely to pose a risk to public health, linked to confusion with other medicines or other health or consumer products.

To this end, after a broad public consultation, the ANSM published recommendations on its website, in February 2018, with a view to reducing the risk of medication errors induced by the choice of name or the presentation of the outer packaging of medicines.

In its recommendations entitled "Recommendations for applicants and holders of marketing authorisations and registrations relating to the names of medicinal products", the ANSM particularly prohibits the use of an “umbrella brand”, i.e. the designation, under a single invented name, of several medicines with different qualitative compositions in terms of their active substances and/or indications, or even of several products of different status, medicines and other health products (medical devices, cosmetic products or food supplements). It has been estimated that the proliferation of such product ranges, particularly in a self-medication context, creates a particular risk of confusion and error for patients when taking medicines.

[1] Also read the "Overview of major French and European texts published in 2019", Appendix 3, p. 207.

After two years of implementation, an initial encouraging observation can be made, bearing witness to the industry's gradual adoption and implementation of the principles derived from the recommendations on names of medicines. In particular, there was a 50% reduction in the number of proposals for names under "umbrella brands" examined by the ANSM during the year following the publication of these recommendations, compared to the previous year.

The ANSM, supported by the Conseil d'Etat (French Council of State) ruling of 21 October 2019 (see below), intends to continue its actions in this in this vein and encourages all manufacturers to follow suit.

In this respect, it should also be noted that during the same period, several manufacturers informed the ANSM of voluntary steps taken to improve the marketing of certain ranges of self-medication products sold under umbrella brands. Their stated objectives included: clarifying the ranges, refocusing them on the medicine, choosing different names according to the composition of the medicines or the status of the products concerned, and ensuring greater differentiation between products (particularly between medicines and other products).
These changes were initially submitted to the ANSM in the framework of requests to modify marketing authorisations (name-change requests), generally accompanied by proposals for changes to the outer packaging (presentation of information, content of information).

Consequently, while the ANSM recommendations are indeed intended to be applied to any new medicine placed on the market, or at the time of a name change, they are also consistent with the more generalised context of voluntary implementation by pharmaceutical companies. The ANSM draws attention to the actions taken by certain manufacturers in this regard, with patient safety in mind, and strongly recommends that all manufacturers adopt the same approach and seize every opportunity to proactively improve the packaging of medicines available on the market.

Recommendations reinforced by the Conseil d'Etat ruling of 21 October 2019

After rejecting the summary suspension proceedings in May 2018, the Conseil d'Etat (French Council of State) session of 21 October 2019 rejected the applications submitted by the French Association for Responsible Self-Medication (AFIPA) to annul the ANSM recommendations published in February 2018, relating to the labelling of the packaging of certain medicines and to the use of a "single-status umbrella brand".

After reiterating that the recommendations are intended to stamp out medication errors and avoid any confusion between medicines, and that they were issued with legitimate concern for the protection of public health, the Conseil d'Etat concurred with the ANSM by finding that it had not infringed the provisions of the French Public Health Code and had not committed a manifest error of appreciation or a legal error.

Like the ANSM, the Conseil d'Etat considers above all that the use of umbrella brands is likely to promote confusion between medicines with different compositions in terms of their active substances, and different indications, and may thus be misleading vis-à-vis their quality or properties, which is prohibited by Article R. 5121-3 of the Code.

2016-2019 Financial sanctions led by ANSM

Sector	Field of activity	2016	2017	2018	2019
Medical devices	Advertising	2	0	3	0
	Marketing	0	4	0	0
	Medical device vigilance	0	0	0	0
Pharmaceutical site	Best distribution practices	1	0	0	0
	Public service obligations	0	0	5	0
Medicine	Advertising	0	4	1	1
	Stock shortages	0	0	1	2
Total		3	8	10	3
Total amount (€)		58,102	526,983	989,123	264,175

European and international interactions

Cooperation activities with agencies in the European network

Cooperation is continuing between the agencies in the European regulatory network (HMA - Heads of Medicines Agencies), the European Medicines Agency (EMA) now based in Amsterdam, and the European Commission.

The ANSM is represented on the following EMA committees: Committee for Medicinal Products for Human Use (CHMP), Committee for Advanced Therapies (CAT), Pharmacovigilance Risk Assessment Committee (PRAC),[1] Committee for Orphan Medicinal Products (COMP), Committee on Herbal Medicinal Products (HMPC) and the Paediatric Committee (PDCO),[2] as well as on numerous scientific and regulatory working groups.

The ANSM is represented on the HMA network's Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

The ANSM attends the plenary meetings of the EMA Board and the HMA network organised on a rotating basis by the Presidency of the Council of the European Union.

All of these activities are coordinated under the aegis of the ANSM's Senior Management within a structure dedicated to coordinating European strategy (CPSE).

Further reading

- **Participation of ANSM laboratories in the work of the European Directorate for the Quality of Medicines (EDQM) (page 138).**
- **Integration of the ANSM into the European Commission's STARS (Strengthening Training of Academia in Regulatory Sciences and supporting regulatory scientific advice) consortium (page 148).**

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 target	Attained
17	Ratio of revenue and expenditure on European activity	≥ 1.0	1.38

[1] Also read "France's contribution to European pharmacovigilance", page 65.
[2] Also read “Access to orphan and paediatric medicines”, page 160.

Two-way interview

Pierre Démolis and Vincent Gazin (CPSE)

How did the new COP affect the implementation of your activity in 2019?

V.G.: The COP has consolidated the ANSM's European positioning by giving it at a high level of priority, particularly with regard to centralised activity. It has promoted the visibility of European activity in the Agency's processes and enabled an even greater mobilisation of teams.

P.D.: We can also take the opposite perspective and consider that the establishment of the CPSE had an impact on the goals set out in the new COP, which take account of the Agency's enhanced capabilities, not simply in terms of human resources but also in an improved organisation of procedures and a proactive policy of improvement, both quantitatively (number of cases) and qualitatively (importance of our opinions in the European debate).

In what way is improving the ANSM's European positioning one of the cornerstones of the Agency's actions?

P.D.: Marketing innovations are mainly happening in Europe. The most crucial discussions on safety take place at the European Pharmacovigilance Risk Assessment Committee – the PRAC. We are bound to show solidarity with Community decisions. Relinquishing our influence would be disastrous; we would become passive spectators with regard to an essential aspect of health policy which, in certain areas, is decided entirely by Europe. Of course, essential work still needs to be done at the national level, such as early or compassionate access to treatment, the regulation of clinical trials, relations with our local interlocutors and partners, and all aspects of national monitoring.

V.G. The Agency is obviously a key interlocutor at the national level, but it is also a member of a European network. On this subject, we must not forget that our communications must also target the European Union as a whole. Being able to share the results of our work and debate the issues covered at the European level is what reinforces our European positioning. This is all the more important as certain issues are only dealt with at the European level. Strengthening the Agency's European positioning is consistent with what we are doing at the national level, in terms of access to innovation, for example.

How does reinforcing the ANSM's European positioning benefit patients in France and public health in general?

P.D.: Medicines are far from being a primarily commercial commodity. They are health goods, and as such, it must be recognised that they have cultural, and sometimes national, specificities. Perceptions of contraceptives in Poland or Malta on the one hand, and in the Netherlands or France on the other, are shaped by culture. This caricatural example shows how important it is to remain indispensable. Differences in Europe include a rather Nordic tendency towards liberalism and very flexible regulation that leaves considerable leeway to individual decisions, including those related to risks, while France and Germany, for example, adopt a somewhat sovereign position. It is impossible to strike a fair and acceptable balance if we remain silent and take no responsibility in the debate. It is a question of safety and access to innovation. France must have its say.

V.G.: It would be a pity to invest substantially at the national level, particularly in clinical trials, without completing the entire process, i.e. continuing through to the marketing authorisation stage which is carried out at European level. French expertise, nurtured by all our stakeholders (Committees, RPCs, patient representatives, and the Agency) must be promoted at the European level. Only by pursuing this goal will our work and investments at the national level make sense. The example of screening for dihydropyrimidine dehydrogenase enzyme deficiency (DPD deficiency) before initiating 5-fluorouracil-

based treatments in order to identify patients at increased risk of developing toxicity is a good example of the role played by the ANSM at the European level.[1]

Which of the activities/issues that you addressed in 2019 made the biggest impression on you, either because of the workload involved, the novelty or unexpected nature, or the consequences for the Agency's work?

P.D.: In terms of marketing authorisations (MAs), France was co-rapporteur for Vitrakvi, the first anti-cancer drug approved in Europe with an indication that refers to a mechanism of action rather than to an anatomical location or the morphology of the tumour. This revolution will have a profound impact on the treatment of rare cancers in particular.

In your opinion, which of the orientations embarked on in 2019 will be the most important for the Agency's future? And why?

V.G.: A major development that was glimpsed in 2019, and which is expected to become more important in 2020, is the introduction of multinational evaluations. For the examination of an MA application, for example, one Member State may ask another Member State to act as a "service provider" in order to carry out part of the evaluation (pharmaceutical quality, clinical, non-clinical, etc.). France and Portugal engaged in this type of collaboration this year. This practice of pooling expertise holds promise and creates links between teams in different countries instead of each working on an entire application.[2]
The ANSM's international collaboration projects are not limited to Europe. In 2019, the Agency signed an agreement with the South Korean and Brazilian national agencies. These agreements are essential for sharing information with non-EU countries.

[1] Also read "Fluoropyrimidines and DPD deficiency: France publishes a pharmaco-epidemiology study and initiates a referral procedure", page 69.
[2] Also read "Assessment of centralised procedures by multinational teams", page 157.

European coordination in the field of medical devices

The ANSM is participating in European activities to implement the European regulations on medical devices through its membership of the MDCG (Medical Device Coordination Group) whose missions are laid down in Art. 105 of EU Regulation 2017/745. Six 1- or 2-day meetings were held in 2019, some of which were open to stakeholders. Fifteen guidelines developed by the MDCG sub-groups were adopted.

The MDCG comprises 13 sub-working groups:

- NBO (supervision of notified bodies),
- Standards,
- CIE (WG on Clinical Investigation and Evaluation),
- PMSV (WG on Post Market Surveillance and vigilance),
- MS (Market Surveillance),
- Borderline and Classification,
- NET (New technologies),
- Eudamed,
- UDI (Unique Device Identifier),
- International Matters (in connection with IMDRF),
- IVD (in vitro diagnostic MD),
- Nomenclature
- Annex XVI.

The ANSM is represented in each of these groups chaired by the Commission and co-chaired by a Member State in certain cases. The ANSM co-chairs the IVD group.
Several of the Agency's directorates are involved in these activities.
Cooperation between competent authorities for MDs and IVDDs also occurs within the network of European Competent Authorities for Medical Devices (CAMD) – of which the ANSM is an active member, notably sitting on its executive committee. Two plenary meetings were held in Denmark and Finland in 2019.

Several CAMD Task Forces have been set up to help Member States and the Commission implement the new regulations, with the prioritisation of actions to be implemented in the short and medium term. A Task Force in preparation for a no-deal Brexit has also been established.

HIGHLIGHTS IN 2019

Pilot Phase of Clinical Trials[1]

The application of EU Regulation 2017/745 (for the clinical investigation section) imposes new working arrangements for the competent authorities and Ethics Committees of the Member States.
The ANSM has introduced a "pilot phase" in preparation for these changes, which simulates the application of the provisions of this regulation while conforming to the current regulations. The project, led by the ANSM, has been carried out since November 2018 by representatives of all stakeholders: academic and industrial sponsors, CPP, CNRIPH, French Ministry of Health, the ANSM.
This pilot phase concerns the application for initial authorisation for clinical investigations (CIs) for medical devices meeting the following criteria, irrespective of the sponsor: Class III MDs, or an implantable or invasive Class IIa or IIb MDs without the CE Mark, or bearing the CE Mark but used in a CI in a manner not conforming to their intended purpose.

France is the first country to have implemented such a pilot phase.
Six CI applications were submitted under these terms between September and December 2019 (i.e. 50% of eligible applications).

[1] Also read "Application of the European Regulation on medical devices: ANSM introduces a pilot phase for the clinical investigations part", page 146.

Voluntary “denotifications” or terminations of NBs' activities

As some Notified Bodies (NBs) have lost their notification under Directive 93/42/EEC, or have ceased their activities, the certificates for medical devices that were originally issued by these Notified Bodies have been invalidated.

The ANSM has implemented a procedure enabling manufacturers of such devices to obtain an extension of their EC certificates, under certain conditions, for a limited period of time. This procedure has been established in line with the European consensus on this issue.

The actions carried out, and in particular, the extensions granted by the ANSM, have prevented interruptions to the continuity of care, while guaranteeing patient safety.

Preparing for Brexit

A CAMD Task Force has been established in order to anticipate the consequences of the United Kingdom leaving Europe, avoid disruptions to the supply of certain devices and ensure continuity of care. Co-chaired by the ANSM, it met several times in 2019 with a view to adopting a common position and defining and preparing the tools to be implemented in response to Brexit, with regard to medical devices, and especially devices covered by an EC certificate of conformity issued by a British notified body.

In addition

- The European “**Joint Action on Market Surveillance of Medical Devices**” (JAMS) project[1]

[1] See "European JAMS project", page 123.

Multilateral cooperation activities

Cooperation between international agencies

The ANSM is a member of the International Coalition of Medicines Regulatory Authorities (ICMRA), which is an international collective of heads of drug regulatory agencies. It began meeting annually under the impetus of the US-FDA in 2006 as part of a policy of developing openness, in order to share experience of common issues and pool approaches to global health challenges and public health protection issues.

ICMRA aims to facilitate interactions, identify synergies, and optimise the benefits of existing initiatives, tools and resources in order to enable regulators of medicines to exercise collective and collaborative strategic leadership in international bodies such as the **ICH** (International Council on Harmonization), **IPRP** (International Pharmaceutical Regulators Programme), **IMDRF** (International Medical Device Regulators Forum), **PIC/S** (Pharmaceutical Inspection Co-operation Scheme), and the **APEC** (Asia-Pacific Economic Cooperation) forum.

In 2019, the ANSM participated in the plenary meeting held in Rome, covering digital health, regenerative medicine, prevention of medication shortage problems, combating antibiotic resistance, and therapeutic cannabis.

International cooperation activities

Some ten collaboration protocols have been signed by the ANSM and its international counterparts on the exchange of information covering all regulated products. The latest protocols were signed with the competent authorities for South Korea and Brazil in 2019.

3 OUR ACTIVITY

Every health product provides benefits but also poses risks. The ANSM's role is to assess whether the benefits for the patient outweigh the risks: this is known as a positive benefit-risk balance. This concept is fundamental to the assessment of the efficacy and safety of a health product throughout its life cycle.

The benefit-risk balance is assessed at the development stage of a therapeutic innovation in order to facilitate early and safe access for patients. A continuous process then begins, which is designed to verify that the efficacy and safety data originally presented in the marketing dossier are still valid in real life, when the health product is widely used by the population. This reassessment may lead to changes in use, or decisions to suspend or withdraw a product from the market, for example.

The ANSM therefore constantly monitors health products and also intervenes in various ways to support innovation and supervise measures to ensure its early, safe and fair implementation.

ENSURING THE SAFETY OF HEALTH PRODUCTS

Two-way interview

Rose-Marie Tunier (DIRCOM) and Nicolas Thévenet (CASAR)

In what way is risk management (RM) one of the cornerstones of the Agency's actions?

R.-M.T.: As a public health player, our role is not only to manage risks when they arise, but above all, to anticipate their occurrence, with the sole aim of ensuring patient safety. This predictive management at the service of everyone's health requires detailed knowledge of our environment and the ability to take it into account. Central to all the ANSM's activities, RM is apparent at two levels of the Agency: firstly, in terms of organisational structure, we promote the reporting of information by including patient representatives in our bodies and by actively listening to public opinion, for example; secondly, in terms of its corporate culture, the Agency draws its strength from its expertise in multiple fields – medical, legal, scientific and even communications – all of which enable a global analysis of risks.

N. T.: Our health environment is constantly changing, and we must relate our decision-making projects – most often based on scientific data – to the players in this environment.
In this respect, we have established an RM system based on 3 pillars: prioritisation and ranking of incoming signals and cases, situational analysis integrating all components of the environment, and collegial consultation.
In this sense, RM encourages us to define internal management methods adapted to health situations, reduce the risks identified by appropriate action plans and relate our opinions to the environment. The ANSM is now fully committed to this approach even if much remains to be done in order to cover all the Agency's fields of competence.

How has the new COP (2019-2023) impacted the implementation of your activity in 2019, and more specifically the field of risk management?

N. T.: The notion of a risk-based approach integrating all the elements of our environment is central to CASAR. The COP's focus on risk management is a major factor in the internal dissemination of a risk culture. It plays a key role in mobilising teams, and in promoting adherence to RM principles and their implementation. The RM approach promoted by the COP is therefore a long-term strategy. It must eventually be integrated into all health-related activities and will involve iterative developments over several years.

R.-M.T.: DIRCOM has developed a vision and adopts a cross-cutting approach: its missions relate to several areas of the COP, including RM. Information strategy and risk management come together in the permanent link that the Agency has established with its stakeholders and through the opinion monitoring that we carry out. The way we address the public has changed: it now takes the form of what we hope will be a permanent dialogue, in order to provide the best possible response to the concerns of patients and healthcare professionals. The COP has also formalised activities that we were already undertaking, and in particular, it has strengthened the links with CASAR, which coordinates RM in high-risk situations with all the directorates concerned, especially DIRCOM.

In your opinion, which of the orientations embarked on in 2019 will be the most important for the Agency's future? And why?

N. T.: Our ability to interact internally on the basis of shared data within a defined and structured framework is a key issue.
The Openness Project[1] launched by the ANSM in 2019, will enable the establishment of collegial teams to facilitate the integration of all these elements related to scientific analysis, which contribute to effective decision-making and to reducing impacts through anticipation.

[1] This is the Agency's development project, which proposes an even more outward-looking organisational structure, in order to better integrate its audiences – professionals and users – into its activities.

In addition, 2019 saw the pursuit of activities designed to improve our ability to exploit our databases. This is a major issue in the health field and concerns the detection of "low" health risks. The pursuit of these activities plays an essential role in ensuring that the ANSM remains in touch with its realities during this century in which digital ecology has become an overriding concern.

R.-M.T.: The Agency is indeed facing a twofold challenge in the field of data sharing. It needs to use this data to increase its risk analysis capabilities, while also meeting transparency requirements with regard to this data. Exploiting and sharing the data in our possession is therefore a key issue for the future.
One of the other major projects in progress since 2019 is the redesign of our website. The new site will provide the Agency with better information and response capabilities. It will be one of the tools enabling the Agency to pursue its cultural drive towards openness and dialogue with stakeholders and the population as a whole.
Finally, I would like to reaffirm the importance of the principle of collegiality. As I see it, risk management is first and foremost based on collegiality, both internally and externally, and requires new ways of working. It is this ability to understand the issues at stake in their entirety, and to support decisions with the help of different players possessing diverse expertise, that enables us to carry out our missions successfully. And it is this collegiality that is the real strength of the Agency today.

Risk Management

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

More specifically, this new principle involves the following actions:

- prioritising all health security activities based on a process of risk analysis,
- expanding epidemiological studies,
- developing a monitoring and planning strategy,
- implementing a coordination plan for heightened risk situations (HRS) and health crisis situations.

The ANSM's Support Centre for Emergency Situations, Health Alerts and Risk Management (CASAR) aims to facilitate the management of the most sensitive alerts and thus enhance the Agency's response capacity. CASAR is thus responsible for coordinating the management of any events likely to become HRSs.

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.

CASAR conducts a risk analysis including social impact, the acceptability of the situation, and 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.

HIGHLIGHTS IN 2019

Supply shortages concerning prednisone-based proprietary medicines and oral prednisolone (May)

At the beginning of the year, the ANSM was informed of supply shortages lasting from several weeks to several months concerning prednisolone-based proprietary medicines and prednisone marketed by some ten distributing pharmaceutical companies. From the end of April onwards, health professionals started reporting concerns over increasingly serious supply problems, with impacts on patients' care pathways.

These supply problems stemmed from a combination of factors: a shortage of betamethasone at the end of 2018 with a delay to the introduction of prednisone- and prenisolone-based proprietary medicines, problems with the effervescent form of prednisolone at one of the manufacturing sites located in Greece, production delays following various difficulties at the other sites, and the delayed implementation of an additional packaging line at one of the manufacturing sites.

In response to the identified shortages, various actions were carried out by pharmaceutical companies at the request of the ANSM:

- all pharmaceutical companies producing or exploiting prednisone and prednisolone-based medicinal products for the French market, as well as representatives of the LEEM and GEMME professional unions were summoned to a meeting by the Director General of the ANSM, and a joint letter was sent to all the companies, reminding them of their obligations to supply the French market (copied to LEEM and GEMME),
- a quantitative quota via allocations to wholesaler-distributors was introduced by pharmaceutical companies as quickly as possible, with a stock held in reserve to meet requests for emergency supplies,
- requests for reallocation of stocks originally intended for other countries (imports) were sent to pharmaceutical companies,
- regular updates carried out with patient associations and health professionals,

- the available stocks of proprietary medicines were closely monitored by the ANSM and a table showing the availability of these proprietary medicines was updated on a weekly basis,
- information was published and regularly updated on the ANSM website in order to inform patients and healthcare professionals as regularly as possible.

All of these actions began to alleviate some of the shortages in the summer of 2019, and then enabled supplies to return to their normal levels from October 2019 onwards.

Monitoring of several medical devices used as medical device disinfectants (October)

In October 2019, the ANSM was informed of the presence of bacteria in the water system of the production plant operated by the manufacturer Anios, in Sainghin-en-Mélantois. Bacterial identification tests revealed the presence of “opportunistic” bacteria, with a very low risk of infection for the general population, but which are likely to cause infection in immunocompromised people. This contamination led the manufacturer to interrupt its production of medical devices in order to carry out decontamination operations and modify the installation of its water supply system. Production was gradually resumed in November 2019, returning to normal production capacity in early 2020.

In this context, the health authorities, in conjunction with learned societies, took action to ensure the safety of these products and the continuity of care. In particular, the ANSM carried out inspections and its laboratories conducted microbiological tests on certain products as part of the investigations. In addition, the ANSM launched its procedure for managing “exceptional health situations” (*Situations Sanitaires Exceptionnelles* – SSE) and worked closely with the Ministry of Solidarity and Health’s crisis centre.

To guarantee the safety and conformity of marketed products, the ANSM made a health policy decision in November 2019 requiring, inter alia, the performance of microbiological analyses of the production water system, and the microbiological testing of medical devices before they are marketed. Non-compliant batches were recalled by the manufacturer.

Since the gradual resumption of production, the ANSM has put in place more stringent procedures to monitor the steps taken by Laboratoires Anios to guarantee microbiological safety and supply capacity.

The measures implemented at the Sainghin-en-Mélantois plant, the monitoring of microbiological analyses, and medical device vigilance data, showed that the risk of bacterial presence in the plant's water system was under control by the end of May 2020. Batches with non-compliant microbiological results were not released to market.
No Burkholderia cepacia complex infections were reported in any inpatients in connection with the contamination identified in October 2019.

In addition, Laboratoires Anios agreed to maintain a long-term microbiological testing protocol and sampling plan to ensure the microbiological safety of medical devices manufactured at the Sainghin-en-Mélantois production site before they are released to market. On 26 May 2020, the ANSM decided to cancel the health policy decision made in November.

At the same time, the ANSM issued an injunction to DMD, a subsidiary of Laboratoires Anios, following several regulatory breaches identified during an inspection. The ANSM will continue to monitor the implementation of all measures required within the time frames stipulated by the injunction.

In addition

- Prohibition of a clinical trial conducted without authorisation by the “Josefa Fund” among patients suffering from Parkinson's and Alzheimer’s[1] diseases (September)
- Pursuit of actions to reduce the risk of meningioma associated with the use of Androcur[2] (June)
- Accompanying the decision to prohibit macrotextured-shell breast Implants and polyurethane[3] breast implants (April)
- Continuation of and support for European initiatives concerning the presence of nitrosamine impurities (NDMA) in medicines[4] (2019)
- Excessive-risk alert related to the use of citrate-based dialysate in dialysis patients[5] (from the end of 2018 and throughout 2019)
- Securing supplies to the French market in view of Brexit (year 2019)

2019 DATA

- 37 new high-risk risk situations (HRS) dealt with in 2019, with an average of 42 HRS in progress

- A high proportion of HRSs concern stock shortages of medicines, medical devices, and cardiology medication.

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 core	2019 target	Attained
2	Rate of high-risk situations (HRS) involving stakeholders in the case-management process	> 50	75%	95%
6	Implementation rate of emergency action plans for high-risk situations (HRS)	70%	100%	95%

[1] See “ANSM prohibits an unauthorised clinical trial among patients suffering from Parkinson’s and Alzheimer’s disease”, page 122.
[2] See “Androcur (cyproterone acetate) and risk of meningiomas: France publishes a pharmaco-epidemiological study and initiates a referral procedure”, page 68.
[3] See “Textured-shell breast implants are withdrawn from the market” on page 103.
[4] See "Evaluation of the risk of nitrosamine impurities in chemical medicines" on page 134.
[4] See “Discussion meetings and investigations on the use of citrate-based dialysate in haemodialysis patients” on page 32.

Surveillance of medicines

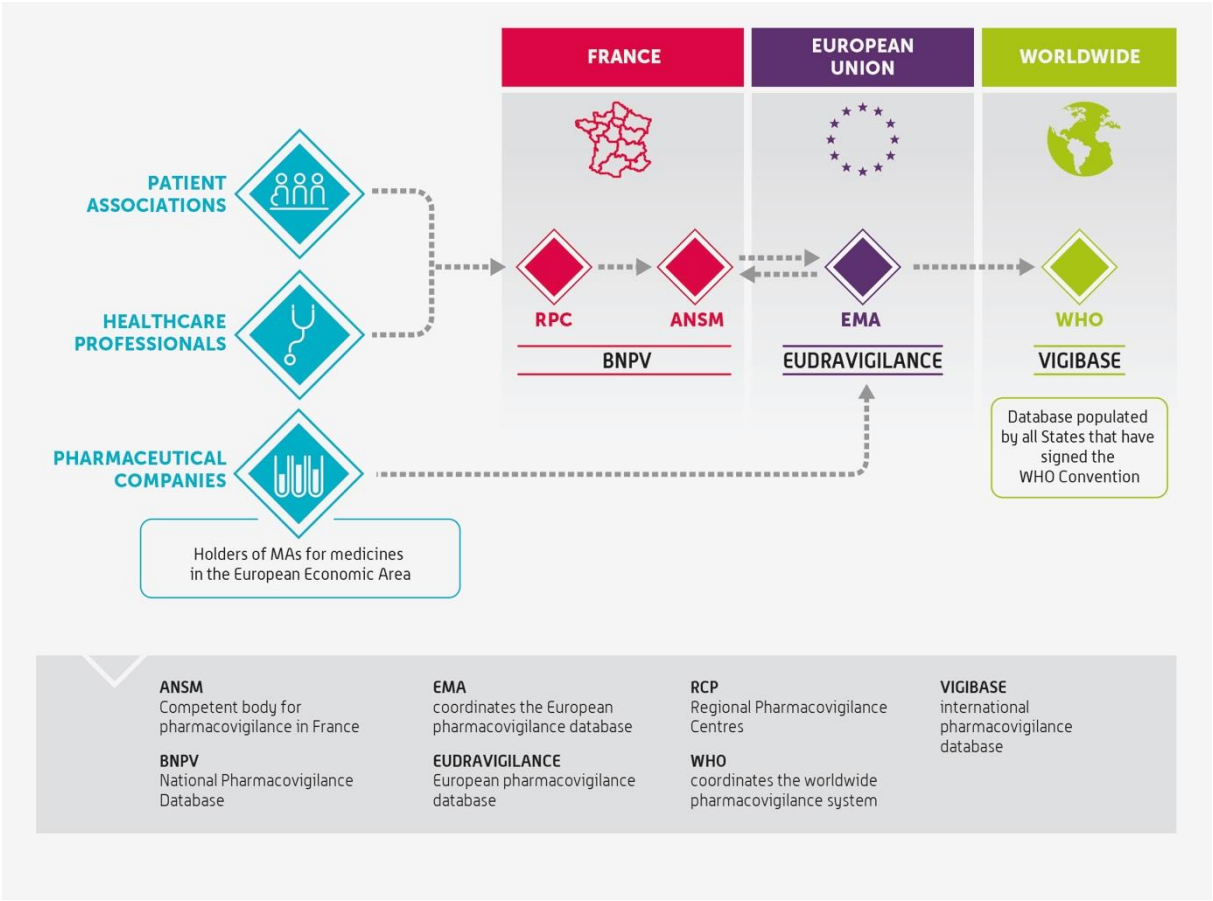
Pharmacovigilance

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).

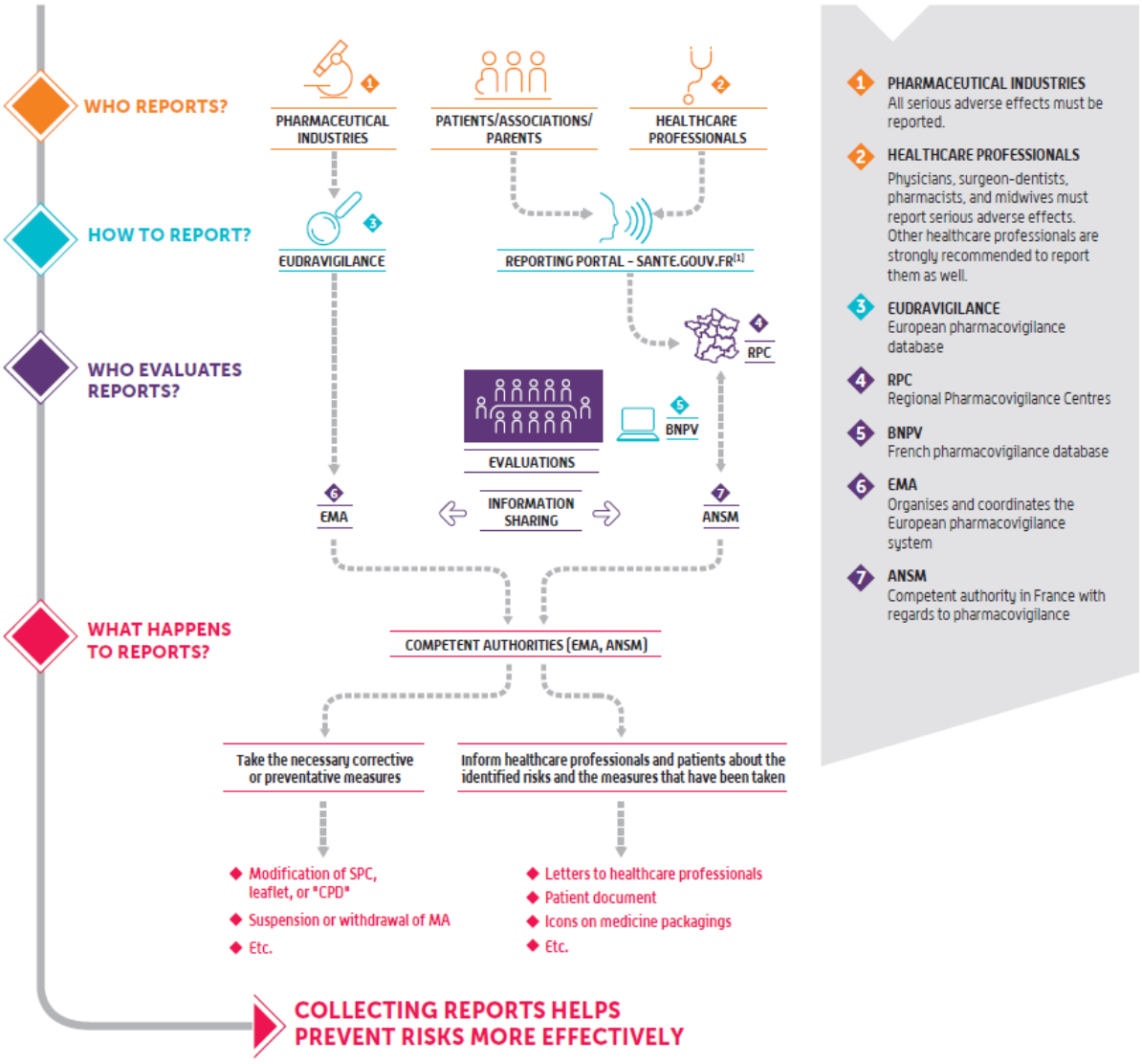
Pharmacovigilance examines adverse effects that occur under normal conditions of use as well as those that arise due to medication errors, abuse, misuse, overdose, and professional exposure.

Pharmacovigilance is active at the regional level through France's 31 regional pharmacovigilance centres, at the national level through the ANSM, and at the European level through the European Medicines Agency and Member States.

REPORTING AND MONITORING OF ADVERSE EFFECTS OF MEDICATION FRANCE/EUROPE/WORLD



REPORTING AND MONITORING OF ADVERSE EFFECTS OF MEDICATION IN FRANCE AND EUROPE



French pharmacovigilance

Healthcare professionals and health system users report any adverse effects that come to their attention.
An online reporting portal for adverse health events, www.signalement-sante.gouv.fr, has been available since 2017 thanks to a partnership between the French Minister of Health and healthcare agencies, including the ANSM.
This portal is designed to increase health safety vigilance while also simplifying the reporting process. It is accessible to everyone, including both healthcare professionals and users.

Regional Pharmacovigilance Centres (RPCs) collect reports from healthcare professionals and users. They record them in the national pharmacovigilance database (BNPV) and analyse them.
RPCs play a critical role by drawing the ANSM's attention to potential signals in the form of noteworthy cases and by performing expert assessments. These assessments make it possible to confirm, dismiss, and, where necessary, characterise signals and risks.

Pharmaceutical companies must put in place a pharmacovigilance system under the responsibility of a designated coordinator who is responsible for the implementation and management of the distributor's pharmacovigilance system and for ensuring compliance with all of its pharmacovigilance obligations.
Distributors submit the medicine-related adverse-effect reports they collect directly to the European pharmacovigilance database (EudraVigilance).

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

The ANSM can initiate pharmaco-epidemiological studies to obtain an overall view of a health product's profile of use in real life, confirm a signal or quantify a risk[1]. It also encourages and facilitates the performance of safety studies by academic authorities after a medicine has received marketing authorisation.

The ANSM examines and implements measures aimed at preventing or reducing risks in order to ensure the safe use of medicines.[2]

Further information and resources: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Pharmacovigilance/Organisation-de-la-pharmacovigilance-nationale/(offset)/0

HIGHLIGHTS IN 2019

The ANSM publishes a report confirming the safety of compulsory vaccines for children under 2 years of age (June)

In order to reduce cases of infectious diseases, prevent epidemics and increase vaccination coverage, the Law of 30 December 2017 increased the number of compulsory vaccinations for infants. Children

[1] To find out more, visit the EPI-PHARE, GIS (scientific interest group) website, created in late 2018 by ANSM and CNAM. EPI-PHARE carries out, manages and coordinates pharmaco-epidemiological studies based on complex big data from the National Health Data System (SNDS), in order to inform the decision-making of public authorities (https://www.epi-phare.fr/)
[2] See "Risk-reduction measures", page 75.

born on or after 1st January 2018 must therefore be vaccinated at the ages specified in the vaccination schedule against diphtheria, tetanus, polio, whooping cough, type b *Haemophilus influenzae* infections, hepatitis B virus, invasive pneumococcal infections, invasive meningococcal C infections, measles, rubella and mumps.

To address the concerns of healthcare professionals and the general public regarding the safety of mandatory vaccines in the optimal manner, the ANSM established a public consultation of the stakeholders concerned, in the form of a temporary specialised scientific committee (CSST) in July 2018, which enabled the formulation of opinions on the type of information and presentation to be provided.

The ANSM published an initial report on the safety of these vaccines in June 2019. All adverse event or effect reports transmitted to the national network of Regional Pharmacovigilance Centres over the 2012-2017 period preceding the extension of the mandatory vaccines, and over the first 6 months of its implementation, were analysed. An analysis of French cases of adverse events reported to pharmaceutical companies was also carried out.
The dissemination of this information was accompanied by a presentation to stakeholders prior to the publication and an announcement transmitted by the media.

In total, between 2012 and 2017, for nearly 38 million doses of vaccine administered, 962 infants vaccinated between 0 and 23 months of age who had exhibited one or more adverse events or effects were reported to the national pharmacovigilance system. This concerned 75 children for vaccinations carried out in the first half of 2018.
The adverse effects reported were mainly known, transient adverse effects described in the Summary of Product Characteristics (SmPC) for the different vaccines involved. In addition to these data, a specific analysis of certain effects and events of particular interest, some of which are referred to as “sensitive” due to concerns expressed by health professionals or users, did not reveal any new safety signals.

The updates for these data for children vaccinated throughout 2018 and again in 2019 consolidate these observations.

In addition

- Bradykinic angioedema (November)
  Following reports of bradykinic angioedema in patients treated with angiotensin-converting enzyme (ACE) inhibitors (ACE inhibitors), but also with angiotensin II receptor blockers (ARB II) and gliptins, the ANSM has invited healthcare professionals and patients to be particularly attentive to signs of this type of angioedema when taking these medicines.

- Ifosfamide: a study requested by the ANSM shows a higher risk of encephalopathy with the medicine in solution form (Ifosfamide EG) (October)
  According to a pharmacovigilance study carried out by the Montpellier and Clermont Ferrand Regional Pharmacovigilance Centres at the ANSM’s request, the risk of encephalopathy in patients taking ifosfamide appears to be greater with the proprietary medicine in solution form (Ifosfamide EG), compared to the proprietary medicine in powder form (Holoxan). As a result, the ANSM decided to refer the matter to the EMA[1] to enable the reassessment of this known risk. Pending the conclusions, the ANSM recommends that doctors take this excess risk into account when treating their patients and managing any encephalopathies.

- Domperidone (Motilium and generics): discontinue use in children under 12 years of age (June)
  As part of the reassessment of the benefit-risk ratio for domperidone conducted by the EMA in 2014, an efficacy study in children under 12 years of age had been requested. The results of this study, presented this year, showed no difference in efficacy compared to placebo. Due to this lack of efficacy and its side effects, the use of domperidone is now restricted to adults and adolescents over 12 years of age and weighing more than 35 kg.

[1] Also read: "Ifosfamide: the ANSM alerts other Member States to an increased risk of encephalopathy with the pharmaceutical form in solution", page 65.

- **Suspension of MA and recall of Pneumorel medicines (February)**
  Following the identification of a potential effect of the active ingredient – fenspiride – on the occurrence of arrhythmias, the ANSM decided to suspend the marketing authorisations for Pneumorel (tablet and syrup), used to treat coughing and expectoration in bronchopneumonia sufferers, after discussions with the European authorities and Servier, the pharmaceutical company that markets the medicine in France.

- **Daratumumab (Darzalex) and risk of hepatitis B virus reactivation (July)**
  Following cases reported during the first 6 months of treatment with this targeted therapy for the multiple myeloma indication (several with fatal outcomes), all patients prescribed this treatment are now required to be screened for hepatitis B virus (HBV) infection (screening of patients currently undergoing treatment must also be carried out). For HBV-positive patients, clinical and biological monitoring for signs of reactivation should be performed during treatment and for at least six months after the stoppage of treatment. In the event of HBV reactivation, treatment with daratumumab should be discontinued and a doctor specialising in the treatment of this type of infection should be consulted.

- **Pharmacovigilance monitoring of Levothyrox**
  2019 was notable for the pharmacovigilance monitoring of adverse effects related to the new Levothyrox formula and the diversification of the therapies available on the French market. The new formula is distributed in more than 18 EC countries with no significant effects reported. The 2019 PSUSA for levothyroxine confirmed this safety data.
  In addition, the ANSM, in collaboration with the DGS, has drawn up and distributed of a booklet to accompany the end of the availability of Euthirox in September 2020 and to assist with the transition to other alternatives.

2019 DATA

Adverse effect reports submitted to the national pharmacovigilance system

Month	Total Cases	of which patient cases
January	4,734	567
February	6,794	1,206
March	5,207	603
April	4,583	631
May	4,657	703
June	4,290	561
July	5,668	616
August	4,564	522
September	4,133	574
October	4,654	605
November	4,052	498
December	5,841	716
Total 2019	**59,177**	**7,802**
Total 2018	71,130	20,192

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

Adverse effects reported to the ANSM	2015	2016	2017	2018	2019
Total number of cases received and recorded by Regional Pharmacovigilance Centres (RPCs) (1)	47,089	55,761	82,077[1]	71,130	59,177
• of which cases of serious adverse effects	30,412	35,622	42,715	34,387	34,237
• of which cases of adverse effects reported by patients	2,331	3,061	31,798	20,192	7,802
Number of cases of serious adverse effect reports from pharmaceutical companies(2)	-	-	-	59,371	51,807
• of which cases of serious adverse effects	15,411	17,109	23,433	18,436	17,192

(1) The number of cases of adverse effects includes initial and follow-up cases
(2) The number of cases of adverse effects includes initial cases

Profile of reporters reporting adverse effects recorded in the National Pharmacovigilance Database (BNPV)

Reporter profile	%
Specialist doctors	54.76%
Patients	13.18%
Pharmacists	22.65%
General practitioners	5.95%
Other health professionals	1.89%
Nurses	1.50%
Dentists	0.06%
Legal professionals	0.01%

[1] The trend is towards a steady increase in the number of reported cases of adverse effects. The sharp rise in 2017 and 2018 was mainly due to the numerous reports submitted for the new Levothyrox formula.

National pharmacovigilance surveys

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, Europe-wide survey.

The decision to launch a national survey is made by the ANSM's Director General. The Director General appoints one or more expert rapporteurs and an expert editor from the RPCs in compliance with rules of general ethics and rules for managing conflicts of interest, and according to the relevant field of expertise.
The pharmaceutical manufacturer(s) involved in the survey are informed by the 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 at the ANSM's request to one of its advisory bodies, either for information or to formulate recommendations.

According to the conclusions of the survey, the Director General of the ANSM can decide to end or continue the survey, and implements appropriate measures to prevent and reduce any identified risk(s).

HIGHLIGHTS IN 2019

Pharmacovigilance survey on the safety profile of decongestant vasoconstrictors in the ENT sector (March)

Decongestant vasoconstrictor medicines (indirect and direct sympathomimetics) in the ENT field are used to treat common cold symptoms. Those used orally contain pseudoephedrine in combination with paracetamol, ibuprofen or cetirizine. They are not prescription-only medicines, unlike those administered nasally (List II).

Adverse neurological and cardiovascular effects associated with vasoconstrictor use have been identified and have been monitored by surveys presented to the Technical Pharmacovigilance Committee (CTPV) on a regular basis since 2001.

In 2016, a pharmaco-epidemiology study conducted by the AFIPA did not reveal any links between the use of these medicines in individuals without a cardiovascular history and the occurrence of myocardial infarction (MI) and strokes. However, the method used did not address the risk of these products in the population that is specifically at cardiovascular risk, nor did it answer the question of the risk of rare and/or disabling or even lethal events in the population without cardiovascular co-morbidity.

In December 2017, advertising to the general public was banned by the ANSM.

In March 2019, a new national pharmacovigilance survey on central neurological and cardiovascular effects was presented to the CTPV. The purpose of the survey was to update the data from the previous survey in 2012.

This survey demonstrated the persistence of adverse cardiovascular and neurological effects (stroke, myocardial infarction, seizures, cerebral vasoconstriction syndromes) associated with oral and nasal vasoconstrictor use in patients with and without associated risk factors. Other adverse ischemic effects were identified through this analysis (ischemic colitis, ischemic optic neuropathies). In addition, significant misuse was found (prolonged use beyond 5 days, association with another vasoconstrictor by the oral or nasal route, or failure to comply with contra-indications), in particular with nasal forms,

which is partly explained by the widespread use of these drugs in the general population and their presence in family medicine cabinets.

The ANSM has implemented various actions to reduce the identified risks associated with taking these products. The various players concerned (patients, healthcare professionals, manufacturers) were asked to engage in discussions on the subject, which led to the production of a dispensing assistance sheet and an information sheet on proper use in mid-February 2020, and their dissemination to dispensing pharmacists and patients, respectively. In addition, several announcements were published on the Agency's website to warn of this risk of adverse effects and misuse. A significant decrease in sales of these proprietary medicines has been observed since the various measures implemented by the ANSM between 2012 and 2020 (sales have declined by one third).

In addition, the ANSM transmitted the opinion of the Toulouse RPC – the rapporteur of the survey – to the EMA in order to mention the risk of ischemic optic neuropathy in the product information for pseudoephedrine-based proprietary medicines.

Pharmacovigilance survey on the risk of migration of the Nexplanon (etonorgestrel) contraceptive implant into the pulmonary artery (February)

Nexplanon is a contraceptive drug containing etonogestrel in the form of a small stick inserted just under the skin of the inner arm. Approximately 200,000 women use Nexplanon each year. It was initially marketed as Implanon (non-radiopaque) in 2001, and was subsequently marketed as Nexplanon when a radiopaque version was released in 2011. It is the only contraceptive implant marketed in France.

In 2016, the first pharmacovigilance reports on the migration of this implant, particularly into the pulmonary artery, led to the introduction of several measures to reduce this risk at the national and European levels. At that time, an information letter had been sent out to healthcare professionals, in order to inform them of the risk and remind them of the obligation to be trained in the insertion and removal of this type of implant, giving priority to face-to-face training with an opportunity for hands-on practice.

In February 2019, two pharmacovigilance surveys conducted by the Tours RPC on the risk of pulmonary artery migration and neurovascular damage at the insertion site, showed that despite these measures, the number of reports of migration into the pulmonary artery in 2017 was approximately 3.17 per 100,000 insertions (around 30 cases since the start of marketing). Moreover, there appeared to be little awareness of the risk of implant migration among the women and professionals concerned. These cases of migration into the pulmonary artery are rare but can have serious consequences. In most cases, it was possible to remove the implant by endovascular surgery after further examinations (imaging), but in approximately 20% of the patients (6/27) a thoracoscopy or thoracotomy was required, some of which were complicated. The treatment can therefore be complex, especially when the implant is found belatedly. It is therefore essential to remove it quickly after migration.

On the basis of these reports, the ANSM initiated a European referral procedure in July 2019, which was finalised in October 2019. The conclusions of this European discussion led to the reinforcement of measures to reduce this risk, including the provision of information about the implant insertion/removal procedure to health professionals and to women who are already fitted with an implant, or for whom insertion is envisaged.

A letter was therefore sent to healthcare professionals in January 2020, reminding them of the existence of a risk of neurovascular damage at the insertion site (which may be manifested by tingling or sensitivity problems in the hand), and of migration of the implant, particularly into the pulmonary artery, potentially linked to the deep or incorrect insertion of Nexplanon.
This letter states that the insertion site has been modified and indicated with greater anatomical precision. In addition, physicians are asked to inform patients of this risk before and at the time of insertion. When the implant is fitted, women will be given a patient card with the instruction leaflet, inviting them to check on the presence of the implant once or twice a month by delicate palpation, and to contact their doctor or midwife quickly if they can no longer feel the implant.

In addition, the ANSM strongly recommends that healthcare professionals receive face-to-face training for the fitting of these implants.

The French National Health Authority (HAS) and the national public health agency (Santé Publique France – SPF) have been informed of the risk of migration of the implant and the contraception memo sheet has been updated by the HAS for this risk.

The exact cause of these migrations has not yet been identified. One of the causes could be excessively deep insertion when the implant is fitted, causing it to be placed directly in a blood vessel. Another hypothesis is that the implant migrates a certain distance from the insertion site, following an impact to the arm or the repetition of certain movements, although anatomical peculiarities have not been ruled out, either.

The ANSM is therefore maintaining increased surveillance of the Nexplanon implant, particularly with regard to the risk of migration and the effectiveness of the risk-reduction measures implemented at the end of 2019.

In June 2019, the ANSM co-authored an article on Nexplanon in the medical journal "Contraception" with the RPC in charge of the case.[1]

In addition

- **Pharmacovigilance survey by the Fernand Widal RPC on the risk of meningioma associated with the use of cyproterone acetate (Androcur and generics)[2] (June)**

- **Pharmacovigilance survey by the Tours and Marseille RPCs - Non-steroidal anti-inflammatory drugs (NSAIDs) and serious infectious complications[3] (April)**

- **Monitoring of the safety profile of docetaxel and paclitaxel-based proprietary medicines by the Rouen and Grenoble, Toulouse and Lille RPCs (March)**
  Following the occurrence of cases of enterocolitis in a neutropenic context, in patients treated with docetaxel, a national investigation was initiated in September 2016. Initial results were presented at the March 2017 session of the CTPV (Technical Pharmacovigilance Committee). Although it had been concluded that the taxane profile was known (no new signals identified), a recent increase in the reporting rates of serious effects for both substances had prompted the CNIB and ANSM to jointly propose recommendations for health professionals and patients (October 2017). The findings of this survey presented at the March 2019 session of the CTPV suggest a decline in the incidence of the reporting rate for effects of interest, probably following the spike in reports from the previous pharmacovigilance alert, and with the ANSM and INCa recommendations perhaps also leading to better prevention and monitoring. The monitoring is now closed.

[1] Publication in the journal *Contraception*: C. Simon, A. Maurier, L. Gaboriau, L. Vrignaud, P. Dayani, T. Vaillant, M. Andrée Bos-thompson, A. Pierre Jonville-bera, Incidence and characteristics of intravascular pulmonary migration of etonogestrel implants: a French nationwide study, Contraception (2020), doi: https://doi.org/10.1016/j.contraception.2020.05.006.
[2] Also read “Androcur (cyproterone acetate) and risk of meningiomas: France publishes a pharmaco-epidemiological study and initiates a referral procedure”, page 68.
[3] Also read “Non-steroidal anti-inflammatory drugs (NSAIDs) and serious infectious complications: ANSM shares a national survey and issues a European signal”, page 65.

2019 DATA

- **86** ongoing national pharmacovigilance surveys
- **6** new investigations opened
- **8** Technical Pharmacovigilance Committee (CTPV) meetings with collective expertise from 36 national pharmacovigilance surveys

Number of new national pharmacovigilance surveys

2015	2016	2017	2018	2019
14	21	8	17	6

France's contribution to European pharmacovigilance

The French national pharmacovigilance system is part of the European pharmacovigilance system. France therefore works closely with the EMA and the other Member States to monitor and ensure the safe use of medicines in France and the rest of the European Union. The ANSM actively participates in European pharmacovigilance working groups, especially the Pharmacovigilance Risk Assessment Committee (PRAC).[1]

The ANSM is involved on a daily basis in the common European evaluation procedures enabling monitoring and responses to changes in the benefit-risk ratio of medicines: referrals, signals, PSUSA, risk-management plan, post-marketing safety studies, etc. This participation particularly entails producing reports (when France is rapporteur) or commenting on reports from other countries. The ANSM is also actively involved in the development of best pharmacovigilance practices impacting many aspects of drug safety.

In addition, the national pharmacovigilance system France transmits data to EudraVigilance, the European Medicines Agency (EMA) database, on a daily basis. This database is the sole collection site in Europe for all serious adverse effects and, since November 2017, non-serious adverse effects occurring in Europe, reported by the relevant national authorities or by pharmaceutical companies. 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 the ANSM forwards to EudraVigilance daily,
- pharmaceutical companies; this data is transmitted directly to EudraVigilance.

Further information and resources: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Pharmacovigilance/Organisation-de-la-pharmacovigilance-europeenne/(offset)/1

HIGHLIGHTS IN 2019

Also read "Non-steroidal anti-inflammatory drugs (NSAIDs) and serious infectious complications: the ANSM shares a national survey and issues a European signal" (April)

Following reports of serious infectious complications with NSAIDs used in cases of fever or pain, the ANSM asked the regional pharmacovigilance centres in Tours and Marseille to conduct a national pharmacovigilance survey in June 2018, covering the two NSAIDs most commonly used in these indications: ibuprofen and ketoprofen. The objective of this investigation was to determine whether these serious infectious complications were promoted by use of NSAIDs or whether they reflected the natural progression of the original infectious disease.

Based on the conclusions of the survey, which pointed towards these NSAIDs playing an aggravating role in the event of infection, the PRAC analysed all available data on the risk of infectious complications and the use of these two NSAIDs at the ANSM's request. In April 2020, the PRAC confirmed that the use of ibuprofen or ketoprofen may, in the case of certain infections, mask symptoms such as fever or pain, leading to a delay in the patient's treatment with an associated risk of complications from the infection. The PRAC also concluded that this risk was observed for bacterial infections in the context of chickenpox and pneumonia.

To reduce this risk, the PRAC recommended providing further information about proprietary medicines containing ibuprofen or ketoprofen in patient information leaflets and/or summaries of product characteristics.

Ifosfamide: the ANSM alerts other Member States to an increased risk of encephalopathy with the pharmaceutical form in solution (December)

[1] Also read "European and international interactions", page 42.

Ifosfamide is indicated for the treatment of several cancers in adults and children, including soft-tissue sarcomas and lymphomas. Two ifosfamide-based proprietary medicines are available in France: Ifosfamide EG 40 mg/ml in solution to be diluted for infusion, and Holoxan, a powder to be reconstituted, for injectable solutions (1,000mg and 2,000 mg).

The occurrence of encephalopathies under ifosfamide has been known about since 1993 and is included in drug information documentation (package leaflets, SmPCs). In 2015, pharmacovigilance data suggested an increase in cases of encephalopathy in the paediatric population with the proprietary medicine Ifosfamide EG, marketed in France since 2012. One hypothesis was the formation of neurotoxic impurities due to the degradation of the product during the storage period. The ANSM then decided as a precautionary measure to reduce the shelf life of Ifosfamide EG from 18 months to 7 months. To evaluate the effectiveness of this measure, the ANSM had requested the implementation of a pharmacovigilance study at the Montpellier and Clermont Ferrand Regional Pharmacovigilance Centres.

This study concluded that the risk of encephalopathy under Ifosfamide appears to be greater with the proprietary medicine in solution (Ifosfamide EG), compared to the proprietary medicine in powder form (Holoxan), despite the reduction in shelf life. The ANSM has therefore referred the matter to the EMA so that a review of all available data can be carried out. This review was initiated at the PRAC session in December 2019.

In addition

- **Drafting of best pharmacovigilance practices for pregnant and breastfeeding women[1] (December)**

- **Gilenya (fingolimod 0.25 mg and 0.5 mg gel capsule): new contraindication for pregnant women and women of childbearing age not using effective contraception[2] (July)**

- **Modafinil (Modiodal and generics): do not use during pregnancy (July)**
  After assessing the risk in children exposed to modafinil during pregnancy, the EMA requested that the risk of birth defects be added to the package leaflet for the medicine, and it is now specified that modafinil should not be used during pregnancy. Similarly, women of childbearing age treated with modafinil must use effective contraception.

- **Nitrosamines: assessing the risk of impurities in chemical medicines[3]**

- **Opioid safety: establishment of a pan-European task force**
  In the context of the health crisis in North America caused by the increase in deaths related to opioid consumption, the EMA decided to set up a pan-European task force in order, inter alia, to monitor the situation, exchange information and coordinate actions to prevent the risk of abuse, misuse, overdose and dependence. The ANSM has been actively involved in the creation of this task force and is actively participating in it.[4]

[1] Also read "Drafting of Best Pharmacovigilance Practices specific to pregnancy", page 91.
[2] Also read "Contraindications to the use of fingolimod during pregnancy and for women of childbearing age who are not using effective contraception" on page 91.
[3] Also read "Assessing the risk of nitrosamine impurities in chemical medicines" on page 134.
[4] Also read “ANSM's role in the prevention of addictive behaviours, and its interactions with other organisations”, page 93.

2019 DATA

In 2019, over 2 million adverse effect reports (2,002,814), including around 160,000 (159,860) reports submitted by patients (-7% compared to 2018), were transmitted to the European database (EudraVigilance). This figure has dropped very slightly (0.7%) compared with the previous year.

The total number of reports from French RPCs accounts for around 18% (59,177) of the reports from EU Member States (327,889); the French population represents 13% of the EU population.

Number of cases recorded in PRAC agendas

Number of cases recorded in PRAC agendas	2015	2016	2017	2018	2019
Number of cases recorded in PRAC agendas	1,932	2,164	2,259	2,702	2,391
of which France is rapporteur	224	187	165	162	184

Breakdown by type of procedure (France as rapporteur)

Referrals	Signals	Risk Management Plan (RMP)	Periodic Safety Update Report (PSUR)	Post-Authorisation Safety Study (PASS)	Renewal of Marketing Authorisation (MA)	Total 2019
1	1	38	64	23	6	138[1]

- **Risk management plans**: 12% of the RMPs evaluated were RMPs submitted as part of an initial MA procedure. The remainder were assessed in a post-MA procedure.
- **Periodic safety update reports**: 44% of the PSURs concerned active substances present in products authorised only under the centralised procedure. The others were also (14%) or exclusively (42%) authorised under national procedures.
- **Post-authorisation safety studies**: 26% of the evaluations focused on study protocols and 56% on results of the studies.

[1] Lower than the number of cases on the PRAC agenda in 2019 (184) because a procedure can be scheduled at several PRAC sessions.

Review of referral procedures

Referral procedures address major concerns regarding a medicine's safety or benefit-risk ratio. They can also be used to settle a disagreement between Member States concerning a medicine's use.

During a referral, rapporteurs belonging to competent authorities (including the ANSM) are asked to carry out a scientific evaluation 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. Member States that are not rapporteurs participate by commenting on the rapporteurs' reports and participating in discussions in European working groups.

The recommendation becomes legally binding once the decision is issued by the European Commission or the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

HIGHLIGHTS IN 2019

Androcur (cyproterone acetate) and risk of meningiomas: France publishes a pharmaco-epidemiological study and initiates a referral procedure (July)

The risk of meningioma associated with the use of cyproterone acetate has been known since 2009 and mentioned in the SmPC/package leaflet following the evaluation of a European signal issued by France.

A pharmaco-epidemiological study conducted by the ANSM/CNAMTS, in collaboration with the neurosurgery team at Lariboisière Hospital, showed a significant increase in the risk of meningioma in patients exposed to high doses of cyproterone acetate over a long period of time. This study quantified this risk and demonstrated the strength of the link between treatment with cyproterone acetate and the risk of meningioma.

Following the publication of these results, and in addition to the risk reduction actions carried out by the ANSM, a pharmacovigilance survey was set up under the responsibility of the Fernand-Widal RPC. The aim of this survey was to improve the characterisation of meningioma risk associated with the use of cyproterone acetate-based proprietary medicines, on the basis of spontaneous adverse effect reports collected and documented by the RPC network.

The results of the pharmacovigilance survey were confirmed and supplemented by those of the epidemiological study. In particular, they revealed significant off-label prescription for acne and/or contraceptive indications, a preferential location of meningiomas on the base of the skull and a long exposure time of 14.7 years on average.

This survey also enables the improved characterisation of certain aspects: progression, surgical treatment rate, specificity related to pregnancy.

A European benefit-risk reassessment was then initiated by the ANSM in July 2019, in addition to the improvement of product information, announcements intended to promote proper use and reduce risk (such as MRI monitoring), and the introduction of a consent form as a requirement for the prescription and dispensing of Androcur and its generics.

At the end of the review, the PRAC’s recommendations included restricting the indications of proprietary medicines containing high doses of cyproterone acetate to uses only after the failure of alternatives, and contraindicating low doses (in association with an oestrogen) in case of the existence or a history of meningioma.

The SmPCs/package leaflets for CPA-based proprietary medicines have been amended accordingly.

Activities will continue in 2020 with the quantification of the meningioma risk related to macro-progestogens (lutenyl/luteran).

Fluoropyrimidines and DPD deficiency: France publishes a pharmaco-epidemiological study and initiates a referral procedure (March)

Fluorouracil (administered by injection), capecitabine and tegafur are anti-cancer drugs, while topical fluorouracil (applied to the skin) is used for various skin conditions and flucytosine is a drug used for serious fungal infections. Severe toxicities, sometimes fatal, have been reported in association with overexposure to a drug whose metabolism and breakdown in the body depends on an enzyme called dihydropyrimidine dehydrogenase (DPD). Indeed, some patients present what may be a partial or total DPD enzymatic deficiency (the percentage is estimated at between 3% and 10% and 0.1% and 0.5%, respectively, in the Caucasian population).

Noting the lack of consensus on screening methods, the ANSM shared with other European authorities the national recommendations drawn up as part of the joint work with the French National Health Authority (HAS) and the National Cancer Institute (INCa), on the methods for detecting dihydropyrimidine dehydrogenase (DPD) deficiency in the context of chemotherapies containing fluoropyrimidines. On this basis, the ANSM initiated a referral procedure in order to supplement the information in the SmPCs and package leaflets on the risks of severe and sometimes fatal toxicity linked to DPD deficiency.

To reduce this risk, the PRAC recommended a contraindication for patients with known complete DPD deficiency, and an adjusted starting dose for patients with partial deficiency. Testing for DPD deficiency is also recommended prior to the start of treatment. The PRAC considered genotyping and phenotyping (and measuring uracilemia) to be the most appropriate screening methods, based on current knowledge. The SmPCs for products containing 5-fluorouracil (i.v.), capecitabine and tegafur should therefore contain information about both these screening methods, taking account of the applicable clinical guidelines.

In addition

- **Restriction of Xeljanz (tofacitinib) use (November)**
  Following the observation of an increased risk of pulmonary embolism and death in rheumatoid arthritis patients treated with Xeljanz (tofacitinib) at high doses (10mg twice daily) in a clinical trial, the PRAC concluded that Xeljanz should be used with caution in patients at high risk of thrombosis (blood clots). In patients over 65 years of age, Xeljanz should be used only if no alternative therapy is available. As a maintenance therapy for ulcerative colitis, a 10 mg dose twice daily is not recommended in high-risk patients unless there is no adequate alternative.

- **Lemtrada (alemtuzumab): new measures to reduce the risk of serious cardiac problems and autoimmune diseases (November)**
  Following the observation of new cases (including fatalities) of disorders linked to immune responses and cardiovascular reactions, the PRAC has restricted the indications, introduced new contraindications, implemented new measures to rapidly identify and treat adverse events, and updated the "guidelines for physicians" and the "patient information pack".

- **Picato (ingenol mebutate): start of a European review procedure (September)**
  Following new data pointing towards an excessive risk of skin cancer in patients treated with ingenol mebutate compared to patients treated with placebo or other drugs, particularly in patients with a history of skin cancer, a referral procedure was initiated by the European Commission, for which France was co-rapporteur.

- **Methotrexate: new measures to reduce the risk of medication errors (July)**
  Since 2007, errors in oral methotrexate use (daily instead of weekly use) have been reported, most of them associated with serious and sometimes fatal adverse effects. Although this risk of medication error with methotrexate has been known for many years, and despite measures taken to reduce this risk in some countries (including France), cases of overdose are still being reported.

As a result, a safety referral procedure (according to Article 31 of European Directive 2001/83/EC) was initiated at the European level in April 2018 in order to analyse the reasons for these errors and discuss the implementation of measures to reduce the risk.
The PRAC completed its evaluation and concluded, at its July 2019 session, that further risk reduction measures are required.
These risk reduction measures include restricting the prescription of these medicines to experienced healthcare professionals, issuing stronger warnings on packaging, providing educational material for patients/caregivers and health professionals, introducing a patient card attached to the packaging, and generalising blister packaging.

- **Pneumorel (fenspiride): cancellation of MAs in Europe following the ANSM alert (May)**
  In February, the ANSM had suspended the MA for Pneumorel. This suspension had triggered a European referral procedure, for which France was co-Rapporteur. PRAC recommended by consensus the cancellation of all marketing authorisations for medicines containing fenspiride, considering that these medicines, used to treat mild coughs, can lead to serious and unpredictable arrhythmias, and that in practice, at-risk patients cannot be identified in advance.

- **Leuprorelin: start of a European review procedure (April)**
  A referral procedure was initiated following reports of handling errors during product preparation that may lead to situations in which some patients receive an insufficient quantity of the medicine, which may reduce the benefit of the treatment.

2019 DATA

- Twelve referral procedures were finalised in 2019[1]
- Eight of these referral proceedings were related to pharmacovigilance (according to Articles 31, 20, and 107i of the legislation on pharmacovigilance).

The eight other referral procedures were initiated to address concerns regarding the effectiveness or quality of certain medicines, to harmonise the legal notices for medicines at the European level, and to resolve inconsistencies between different Member States during decentralised mutual recognition procedures.

[1] Source EMA, Annual Report 2019, on page 72. See “Summary of referral procedures in 2019” Appendix 4, on page 211.

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 sixth-largest contributor, providing approximately 4% of the total number of adverse effect reports received.

2019 DATA

856,346 cases taken from the National Pharmacovigilance Database and submitted by France as of 31 December 2019.

Contributor countries in VigiBase	ICSR:[1] cumulative data as of 31/12/2019
United States	10,159,968
Korea	1,603,253
China	1,111,302
United Kingdom	1,014,278
Germany	856,580
France	**856,346**
Canada	710,422
Italy	548,611
Japan	468,072
India	414,885
Other	3,940,683
Total	**21,684,400**

[1] ICSR: individual case safety report.

Medicine use surveillance

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 (misuse) that does not comply with the terms of a medication's MA or TRU.

Signals 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 healthcare system users, as well as organisations representing healthcare professionals (learned societies, organisations, etc.), and special sources of information about real-life practices,
- the ANSM's discussions with its institutional partners, especially the French health insurance system,
- ANSM monitoring and evaluation activities,
- manufacturers, who must monitor and collect information on use for the medicines under their responsibility, especially through educational and pharmacovigilance activities, and pass on this information to the ANSM.

For manufacturers, the legislation stipulates that a company that manufactures a proprietary medicine must help ensure that it is used properly and implement every educational measure deemed necessary to inform healthcare professionals when it observes prescriptions that are non-compliant with the proper use of the medication. It must also notify the ANSM without delay.

The ANSM collects and analyses reports of non-compliant use transmitted by the manufacturers of proprietary medicines.
In order to facilitate their approach, a guide has been published for these manufacturers: *Reporting of non-compliant prescription drug use by companies - A guide for proprietary medicine manufacturers* https://ansm.sante.fr/var/ansm_site/storage/original/application/d36d6dd7055c0ac1281bd1f75a62184c.pdf

The purpose is to identify cases of non-compliant use and collect the information needed to evaluate the public health impact of these practices and implement appropriate measures to prevent or reduce non-compliant use, as necessary.[1]

Non-compliant uses are a major concern for the ANSM, both because they are a major source of side effects, but also because the intervention methods are complex and often hard to implement.

HIGHLIGHTS IN 2019

- **The use of nifuroxazide (Ercefuryl and its generics) must be discontinued in children and adolescents under 18 years of age and is now available only on prescription (July)**
  Due to the risks associated with nifuroxazide – mainly of an immuno-allergic nature – and to significant misuse, this intestinal anti-infective agent indicated for the treatment of acute diarrhoea of presumed bacterial origin, is now available on prescription only. In addition, its use must be discontinued in children and adolescents under 18 years of age.

- **SmPC update for Ondansetron[2] (July)**

[1] See "Risk-reduction measures", p. 75.
[2] See "SmPC update for Ondansetron", p. 90.

2019 DATA

- **40** cases of use were identified that did not comply with the medicine's marketing authorisation and exposed patients to a potential or proven risk.
- During the year, risk reduction measures or actions were implemented for **75**% of these cases.
- The remaining cases were still being evaluated as of 31 December 2019.

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 core	2019 target	Attained
9	Consumption rates of intervention credits allocated to pharmacoepidemiology	50%	100%	90%
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an inter-operator approach	-	Implementation of the work programme	Implementation of the work programme

Medicines undergoing revision and review of their benefit-risk ratio

Reviewing the benefit-risk 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 when the marketing authorisation (MA) was granted, and the safety data initially reported during clinical trials, remain 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 consistent with the requirements for efficacy and safe use.

A national procedure to review or revise the benefit-risk (BR) ratio can be initiated in different risk-management contexts:

- following a signal of a risk of adverse effects,
- following a signal of loss of benefit,
- after an assessment of the latest data, especially during the MA renewal process which occurs every five years.

The systematic national BR review/revision programme based on selection criteria defined in 2011, has now been completed.

Reviewing the benefit-risk ratio of medicinal products is a continuous process and involves "traditional" national and European surveillance/vigilance methods, leading to the adoption of risk-reduction measures.[1]

HIGHLIGHTS IN 2019

Decontractyl (mephenesin): withdrawal of marketing authorisations (June)

A review of the benefit-risk ratio of proprietary medicines containing mephenesin was initiated by the ANSM following the reporting of several cases of adverse effects.

Concerning Decontractyl 500 mg, in tablet form, an increase in cases of abuse and dependence has been observed in recent years. Discomfort, dizziness and anaphylactic reactions have also been reported. Concerning Décontractyl Baume (balm form), burning sensations and erythema have been reported. Some of these events have occurred in children through skin-to-skin transfer of the drug applied to adults.

The available data on the effectiveness of these treatments remain limited. Therapeutic alternatives, both drug and non-drug based, are also available.

In light of all these factors, the ANSM considered that the benefit-risk ratio of the proprietary medicines Décontractyl 500 mg (tablet form) and Décontractyl Baume was now unfavourable and decided to withdraw their marketing authorisation as of 28 June 2019.

2019 DATA

Over the course of 2019, the benefit-risk ratio of seven active substances was revised as part of a revision or review procedure.

- Lumirelax 500 mg, in tablet and 10% cream form (methocarbamol)
- Stresam gel capsule (etifoxine hydrochloride)
- Estracyt 140 mg, capsule (estramustine phosphate)

[1] See “Risk-reduction measures”, p. 75.

Risk-reduction measures

Systematic measures regulate the proper use of the medicine as soon as it is released to market. This includes the information contained in the Summary of Product Characteristics (SmPC) (for healthcare professionals) or in the package leaflet (for patients), as well as the packaging of the medicinal product, or the introduction of specific prescribing and dispensing conditions.

When these guidelines are found to be insufficient to ensure safe and effective use of the medicine, additional risk-reduction measures can be put in place:

- letters to healthcare professionals,
- information documentation for healthcare professionals and/or patients that is disseminated via different media, including letters, guides, check-lists, brochures, patient cards, training slides, etc.)
- restricted-access programmes: product access is restricted by specific measures pertaining to prescription conditions, dispensation, and use (controlled distribution, pregnancy-prevention programme, etc.).

These measures may be combined.

Special case: Additional risk-reduction measures
Additional risk reduction measures are created to prevent or reduce the probability of adverse effects, their seriousness, and/or their impact on the patient.
The application of these measures is the responsibility of the MA holder and is overseen by the ANSM, which 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.

Further information and resources: https://www.ansm.sante.fr/Activites/Surveillance-des-medicaments/Mesures-additionnelles-de-reduction-du-risque/(offset)/1

HIGHLIGHTS IN 2019

Proper use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs): these medicines can no longer be sold as over-the-counter drugs (December)

Paracetamol and some NSAIDs (ibuprofen and aspirin) are the most commonly used painkilling and antipyretic medicines used by adults and children on a self-medication basis.

These drugs are safe and effective when used properly, but pose risks when used improperly. Indeed, paracetamol can cause serious liver damage in certain cases of overdose, which can lead to liver transplants (leading cause of liver transplants of drug origin in France). In particular, NSAIDs are likely to cause renal complications and serious infectious complications, and are toxic to the foetus in the event of exposure from the start of the sixth month of pregnancy (beyond 24 weeks of amenorrhea).

However, it was possible for pharmacies to present some of them, available without a prescription, for sale on a self-service basis.

Consequently, to promote the proper and safe use of these commonly used medicines containing paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), the ANSM wanted to end their availability as over-the-counter drugs and require them to be kept behind the counter, thus reinforcing the pharmacist's advisory role at the time of dispensing, vis-à-vis patients who wish to use them, especially without a prescription.

This measure was introduced on 15 January 2020, since when these medicines can no longer be sold on a self-service basis in pharmacies, i.e. "over the counter", but remain available without a prescription.

This measure is consistent with the Agency's efforts to improve the safety of the use of these medicinal products, including by posting a message on boxes of medicinal products containing paracetamol to warn of the risk of liver damage in the event of an overdose.

The ANSM improves information on finasteride 1 mg used to prevent hair loss (December)

The ANSM has repeatedly informed patients and healthcare professionals about the risks of psychiatric disorders and sexual dysfunction during treatment with finasteride, and about what to do if these adverse events occur. This medicine, used to treat hair loss, is closely monitored at both European and national levels.

In October 2019, the ANSM brought together patient representatives and healthcare professionals to develop an information document for men who are currently taking finasteride for hair loss or for whom a prescription is being considered.

This sheet, in addition to the package leaflet contained in the boxes of finasteride 1 mg, lists:

- the expected benefits in relation to the risks associated with taking this drug, such as psychiatric disorders and/or sexual dysfunction,
- the benefit of granting oneself time to reflect before starting this long-term treatment,
- what to do in the event of adverse effects, including the stoppage of treatment in the event of mood changes.

This form is intended to be handed to the patient by the physician during consultation and by the pharmacist when the product is dispensed, and is intended to facilitate dialogue between patients and health professionals.

This information sheet has been sent by mail to all dermatologists, general practitioners and dispensing pharmacists in France. It can also be downloaded from the ANSM's website. At the same time, the ANSM has also informed the RPCs and professional organisations / learned societies of urology, andrology, sexology / sexual medicine, endocrinology, neurology, psychiatry and dermatology, the French National Board of Pharmacists (CNOP) and the College of General Medicine (CMG).*

The ANSM is also continuing its investigations with the dual objective of improving knowledge of the adverse effects of finasteride and improving the safety of its use.

In addition

- **Reinforcement of information on the risks associated with vasoconstrictors**[1]

- **Alpha-amylase-based medicines: only available on request from pharmacists as of 15 January 2020 (December)**
  To ensure the safe use of medicines containing alpha-amylase that present a known risk of allergic reactions, which are very rare but can be serious, the ANSM has removed these pharmaceutical specialities from the list of medicines available in pharmacies on a self-service basis as of 15 January 2020. The ANSM thus wishes to reinforce the pharmacist's advisory role, and therefore the information provided to patients, when these non-prescription drugs are dispensed.

- **Modification of conditions for prescribing and dispensing certain biotherapies used in the treatment of chronic inflammatory diseases in rheumatology, gastroenterology, dermatology, and ophthalmology (July)**
  The conditions for prescribing and dispensing certain biotherapies, namely the proprietary medicines adalimumab, etanercept, golimumab, certolizumabpegol and anakinra, have been

[1] Also read "Pharmacovigilance survey on the safety profile of decongestant vasoconstrictors in the ENT sector", page 61.

modified. From now on, although the initiation of treatment with these proprietary medicines remains restricted to a hospital physician specialising in the pathology concerned, it no longer appears necessary for the treatment to be reassessed in hospital by this same specialist on an annual basis. This measure is intended to facilitate the patient's care pathway by allowing them to be treated in the non-hospital sector after treatment has been started in hospital for certain proprietary biotherapy medicines. By promoting collegiality in decision-making, it also helps to reinforce the proper use of treatments, while limiting the risks inherent to their use and including patients in therapeutic education programmes.

- **Cyproterone acetate in 50 or 100 mg tablets (Androcur and its generics): measures to improve information about the risk of meningioma[1] (June)**

- **Chemotherapies based on 5-FU or capecitabine: mandatory testing for DPD deficiency before any treatment[2] (April)**

- **Alemtuzumab: implementation of restrictive measures (April)**
  Following reports of serious cardiovascular reactions, newly identified autoimmune hepatitis and haemophagocytic lymphohistiocytoses, measures to restrict use were put in place until the completion of the European review of the benefit-risk ratio of Lemtrada for the treatment of multiple sclerosis.

- **Clay-based drugs in the symptomatic treatment of acute diarrhoea in children: restriction of use in children under 2 years of age (March)**
  Medicines based on clay extracted from the soil, such as Smecta (diosmeticte), may contain trace amounts of lead. As a precautionary measure, the ANSM has restricted the use of these drugs in children under 2 years of age, even for short-term treatment.
  In the context of the dissemination of this measure, the ANSM recalled that the treatment of acute diarrhoea is based primarily on hygieno-dietary measures, and that if the symptoms persist in infants and children under 2 years of age, the reference treatment is the administration of an oral rehydration solution.

2019 DATA

Additional risk reduction measures:

- **44** letters to healthcare professionals sent out
- New measures put in place for **21** active substances (52 documents)
- Updates on **65** active substances (152 documents)

[1] See “Androcur (cyproterone acetate) and risk of meningiomas: France publishes a pharmaco-epidemiological study and initiates a referral procedure”, page 68.
[2] See “Fluoropyrimidines and DPD deficiency: France publishes a pharmaco-epidemiological study and initiates a referral procedure”, page 69.

Managing medication errors

Since 2005, the ANSM, in collaboration with the RPC network, has been organising the collection and processing of the reporting 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).
This work focuses on errors without adverse effects (potential errors, risks of medication errors, and latent errors), and on medication errors resulting in adverse effects (in coordination with pharmacovigilance).

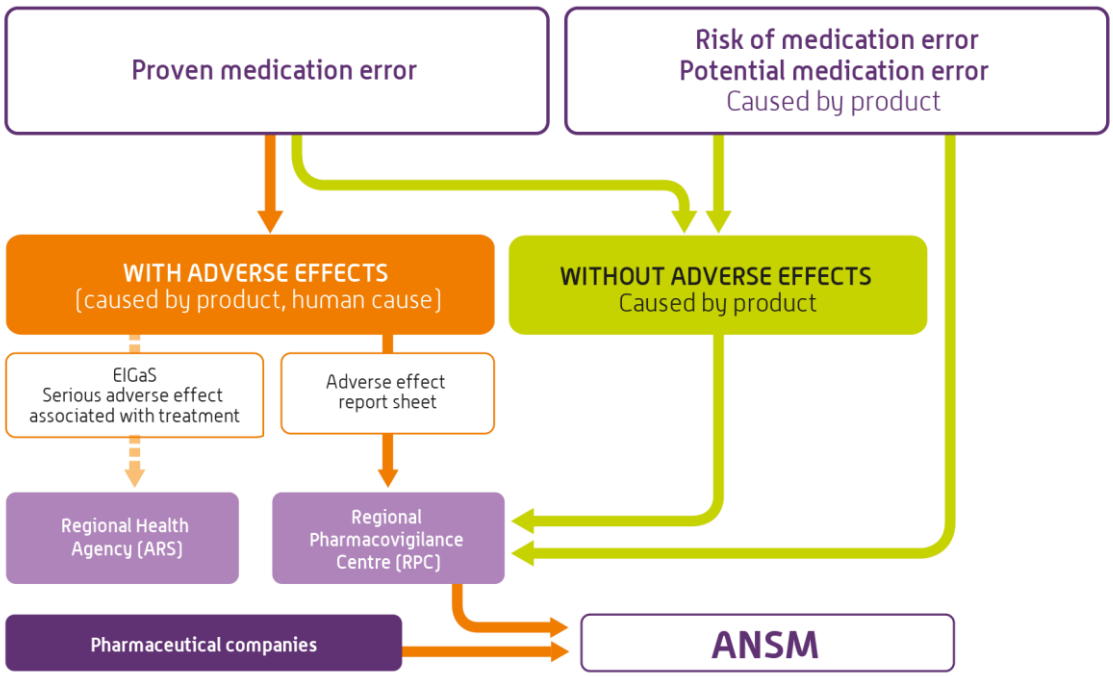
In 2019, there were two major developments in the management of error reports. RPCs now receive and process reports of errors without adverse effects, as well as errors with adverse effects. These RPCs then draw the ANSM's attention to potential signals, in the form of noteworthy medication errors. The Agency evaluates and analyses them as potential signals.

It can put in place measures to ensure that the error does not happen again:

- 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); announcement to healthcare professionals or the public; etc.
- an action in the context of a more overarching discussion about medicines (e.g. improved and harmonised labelling of injectable solutions in small volumes, recommendations and information campaigns regarding means of administration for oral solutions, etc.).

Furthermore, in view of the increasing number of shortages of medicines and the resulting risk of medication errors, the ANSM wished to reinforce the existing procedure for managing stock shortages by implementing a framework of analysis for the risk of medication errors in the context of medication shortages requiring substitution, particularly vis-à-vis the importation of proprietary medicines.

Further information https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Erreurs-medicamenteuses/Qu-est-ce-qu-une-erreur-medicamenteuse/(offset)/0 **and watch our infographic video entitled "What is a medication error?"**



Death by lomustine overdose in the context of a shortage of the proprietary medicine Belustine (August)

Following a shortage of the proprietary medicine Belustine (lomustine: bottles of five 40 mg gel capsules), this proprietary medicine was replaced by the German proprietary medicine Cecenu (lomustine: bottles of twenty 40 mg gel capsules). Information about this substitution was sent to hospital pharmacists by the laboratory at the request of the ANSM, which disseminated it on its website.

One patient, a glioblastoma sufferer who was treated with lomustine, died following an overdose after previously receiving several courses of treatment with Belustine.[1] Due to a shortage of the proprietary medicine Belustine, packaged in bottles of five 40 mg gel capsules, a bottle of Cecenu containing twenty 40 mg gel capsules had been dispensed to the patient as fall-back medicine. Despite the information provided by the doctors, nurses and the pharmacist, the patient took the entire bottle of 20 capsules at home and received a dose of 800 mg instead of the 160 mg prescribed. The patient's death occurred due to multiple organ failure following hospitalization.

Analysis of pharmacovigilance and medication error databases revealed three serious cases of lomustine overdose with severe pancytopenia that occurred after administration of the proprietary medicine Cecenu imported to replace out-of-stock Belustine.

The ANSM then asked:

- the lab to send a letter to hospital pharmacies, notifying them about:
  - the occurrence of serious cases, one of which was fatal,
  - the need for pharmacists to be particularly vigilant when dispensing (writing the number of capsules to be taken on the box, provision of clear information to patients, etc.)
  - the need for prescribers to convert the dosage in mg into the number of gel capsules per dose on the prescription.
- the need for hospital pharmacies to repackage the boxes of Cecenu containing 20 gel capsules, into four boxes of five capsules, with the pharmaceutical company sending pharmacies four boxes with safety lids, four stickers and four package leaflets for each box of Cecenu delivered.

This particularly serious situation confirmed the need for the Agency to reinforce the existing procedure for managing stock shortages by implementing a framework of analysis for the risk of medication errors in the context of medication shortages requiring substitution, particularly in the context of the importation of proprietary medicines. This procedure is being finalised.

Confusion between Siklos 100 mg and Siklos 1,000 mg (April)

A case of medication error during dispensation between the proprietary medicine Silkos in 100 mg and 1,000 mg form was reported in relation to a child with major sickle-cell syndrome without G6PD deficiency taking 400 mg of Siklos per day (clear and unambiguous prescription). 1,000 mg instead of 100 mg tablets had been dispensed to the child at a non-hospital pharmacy. His parents then gave him four tablets a day, i.e. 4,000 mg/day instead of 400 mg/day for a period of fifteen days. The parents stopped the treatment when the child started feeling unwell (gastric pain, fatigue, etc.) . The dosing error was detected at the hospital and the child was hospitalised suffering from aplasia.
Other reports of the same problem were found in the medication error database.

The ANSM then put in place a communication plan including:

- an information update posted on its website,
- a letter sent to dispensing pharmacists, reminding them of the need for vigilance when dispensing the proprietary medicine Siklos,
- a reminder of existing risk-reduction documentation (doctor's guide, patient's guide, prescription support sheet).

[1] Note that the dosage regimen is a single dose every 6 weeks.

In addition

- **Zymaduo drops (Vitamin D) and Objectif Zeroverrue (wart-remover): risk of confusion (November)**
  Following several reports of medication errors related to confusion between vials of Objectif zeroverrue (wart-remover in drop form) and ZymaD (Vitamin D), during administration, with serious medical consequences in infants, the ANSM requested a change in the colour of the cap of Objectif zeroverrue (from white to orange) with a batch recall of the old vials.

- **Organisation of a hackathon on medication errors by the ANSM, the Collège de la médecine générale and Paris-Est Créteil University (September)[1]**

- **Lytos (sodium clodronate tetrahydrate) and Lithos (potassium and magnesium citrate): risk of confusion (June)**
  Following the report of a new case of confusion between the drug Lytos and the dietary supplement Lithos, the ANSM reiterated its recommendations of 25/07/2017 aimed at health professionals and patients.

- **Sinemet (levodopa/carbidopa): modification of 100 mg/10 mg and 250 mg/25 mg tablets (May)**
  Following a change of manufacturing plant, the composition and appearance of Sinemet 100 mg/10 mg and Sinemet 250 mg/25 mg tablets have been modified. An information document for patients has been produced by the ANSM, in conjunction with patient representatives and healthcare professionals, for distribution by pharmacists when dispensing the new boxes of Sinemet.

2019 DATA

- **2,180** reports were submitted to the ANSM, including **1,993** proven errors, **74** potential errors and **113** potential medication errors (or latent errors).
- **62%** of reports of proven errors led to an adverse effect (half of which were considered serious in terms of pharmacovigilance criteria).
- **34%** of reports of proven errors did not lead to an adverse effect.
- The description did not specify whether the error led to an adverse reaction for the remaining **4%**.

Evolution of medication error reports

2015	2016	2017	2018	2019
2,741	2,414	2,234	2,197	**2,180**

[1] See “Organisation of a hackathon on medication errors by ANSM, the Collège de la médecine générale (College of General Medicine) and Paris-Est Créteil University”, page 36.

Monitoring the coverage of patients' health needs

Securing the supply of drugs of major therapeutic value

When there are risks of medicine stocks being in short supply, the ANSM focuses its efforts on securing the supply of “essential” medicines, referred to as “medicines of major therapeutic value”, and those whose unavailability would pose a public health risk.

The 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.

The ANSM interacts with patients and healthcare professionals in the early stages of stock shortages and limited-supply situations by:

- communicating regularly about the supply situation of certain essential proprietary medicines.
- including patient and healthcare professional representatives in discussions about the risk of supply shortages,
- organising discussion meetings with healthcare representatives, patients, and manufacturers about certain situations involving limited supplies or shortages.

Further information: https://www.ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments/Risque-de-rupture-de-stock-et-ruptures-de-stock-des-medicaments-d-interet-majeur

HIGHLIGHTS IN 2019

Tackling shortages and improving the availability of medicines in France - Ministerial roadmap (July)

On 8 July 2019, the Minister of Solidarity and Health presented 28 measures to combat shortages and improve the availability of medicines in France. This roadmap revolves around four main priorities:

- promoting transparency and quality of information in order to restore trust and the fluidity of interactions between all stakeholders, from health professionals to patients,
- tackling drug shortages through new prevention and management actions implemented throughout the medication circuit,
- reinforcing national coordination and European cooperation to improve the prevention of medication shortages,
- putting in place a new national governance system.

The ANSM is fully committed implementing this roadmap with the Ministry of Health and in partnership with all stakeholders. In this context, it participates in the various working groups. The ANSM is particularly active in the "Transparency and quality of information for health professionals and patients" and "Prevention and regulation of shortages" groups, which it leads or jointly leads with the Ministry of Health, and in the "Strengthening European cooperation" group.

Mitomycin C: the imported drug should be reserved for priority indications (October)

On 11 April 2019, Kyowa Kirin Pharma France declared a shortage of the proprietary medicine Ametycin 40 mg – a powder for bladder irrigation solution – for a two-month period. On 7 May 2019, the laboratory announced a total stockout. The pharmaceutical company was summoned to a meeting with the ANSM and solutions were implemented to provision the French market, which remained in short supply.

On 30 September 2019, Kyowa Kirin Laboratory informed the ANSM of a quality issue at their production site for the active substance Mitomycin C in Japan. A batch recall was performed. The proprietary medicines Ametycin 10 mg in powder form for injectable solution, and Ametycin 40 mg powder for bladder irrigation solution (mitomycin C) were out of stock for an indefinite period.

Units originally intended for the Scandinavian markets were then imported.

At the end of October, in order to address this supply shortage, the ANSM, in consultation with the learned societies of urology and ophthalmology and the French Ministry of Health, recommended reserving the various imported proprietary medicines for priority indications.

These recommendations were regularly updated in the following months according to the availability of products, and this case continued to be monitored throughout the first half of 2020.

In addition

- **Supply shortages of the proprietary medicines Depamide and Depakote (December)**
  The ANSM advises against initiating valproate-based treatments in adult patients exhibiting manic episodes of bipolar disorder, and recommends initiating treatment with lithium (unless contraindicated), or carbamazepine, or with the antipsychotic medicines indicated in this situation.

- **Prolonged shortage of the proprietary medicines** Spironolactone Altizide 25 mg/15 mg (Aldactazine and some generics) (December)
  Following the extension by several months of the stock-out period for proprietary medicines containing spironolactone and altizide (diuretic drugs used to treat high blood pressure and oedemas of renal, cardiac and hepatic origin), the ANSM reminded patients of the procedures for modifying their treatment.

- **Bladder tumours: update of the BCG Medac / Oncotice treatment recommendations (November)**
  Following shortages in supplies of the proprietary medicines BCG Medac and Oncotice (imported proprietary medicines), the ANSM, in consultation with the Oncology Committee of the French Urology Association (CCAFU), has updated the patient treatment recommendations.

- **Cellcept (Mycophenolatemofetil) 500 mg and 250 mg: information on localised supply problems (July)**
  Following shortages in supplies of the proprietary medicines Cellcept 500 mg (film-coated tablet) and Cellcept 250 mg (gel capsule) encountered locally, the ANSM has been in regular contact with representatives of patient associations and healthcare professionals in order to share the information at its disposal.

- **Supply shortages concerning prednisone-based proprietary medicines and oral prednisolone (May)**[1]

[1] See “Supply shortages concerning prednisone-based proprietary medicines and oral prednisolone”, page 52.

Changes in limited-supply and supply-shortage reports (2015-2019)

Changes in supply-shortage and limited-supply reports	2015	2016	2017	2018	2019
	391	405	538	871	**1,504**

Changes in limited-supply and supply-shortage reports per therapeutic category

Therapeutic category	Proportion		Number of reports		Proportion of therapeutic category
	2018	2019	2018	2019	
Digestive system and metabolism	3.89%	**7.38%**	34	**111**	12.64%
Blood and haematopoietic organs	12.69%	**6.58%**	111	**99**	5.33%
Cardiovascular system	21.71%	**22.61%**	190	**340**	15.47%
Dermatology	1.71%	**0.73%**	15	**11**	3.57%
Genitourinary system and sex hormones	2.40%	**2.86%**	21	**43**	3.89%
Systemic hormones, excluding sex hormones and insulins	3.09%	**5.72%**	27	**86**	1.55%
Anti-infective agents (systemic use)	13.49%	**15.29%**	118	**230**	10.87%
Antineoplastic and immunomodulating agents	8.23%	**9.38%**	72	**141**	5.30%
Musculoskeletal system	3.20%	**3.26%**	28	**49**	3.94%
Nervous system	18.97%	**18.28%**	166	**275**	19.19%
Parasiticides, insecticides and repellents	1.14%	**0.80%**	10	**12**	0.53%
Respiratory system	2.74%	**1.46%**	24	**22**	6.65%
Sensory organs	4.23%	**3.59%**	37	**54**	2.23%
Miscellaneous	2.51%	**2.06%**	22	**31**	8.83%

COP 2019-2023 indicator

No. of indicator	Title of indicator	2019 core	2019 target	Attained
7	Percentage of cases in which a measure to reduce the risk of shortage was proposed on time	70%	80%	80%
8	Increase in the proportion of stock shortages in cases leading to financial sanctions implemented at the Agency	-	≥ 10%	50%

Managing quality defects

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

Solutions are formulated in response to each report, according to different criteria and always taking account of the associated patient risk.

Several measures may be implemented:

- **Batch Recall**: in cases such as stability defects, cross-contamination or non-compliance with product specifications.
  Batch recalls are then carried out by the laboratory, in consultation with the ANSM.
- **Quarantine**: when batches not yet distributed are affected by a quality defect, a quarantine procedure may be requested pending the results of the investigations.
- **Alerts to potential users**: if necessary, the ANSM can issue an alert to patients and healthcare professionals.
- ***"Rapid Alerts"***: the ANSM may issue Rapid Alerts about quality defects to inform the competent authorities in other countries about the assessments and decisions made with respect to a report.

Further information:https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Votre-declaration-concerne-un-medicament/Votre-declaration-concerne-un-medicament/Votre-declaration-concerne-un-medicament-Vous#defaut

HIGHLIGHTS IN 2019

Emerade injectable adrenaline pens (August)

At the end of August, the ANSM was informed of two quality defects in Emerade adrenaline injection pens (auto-injectors):

- a risk of failure to activate – some patients have observed a blockage of the needle in the pen at the time of use,
- an out-of-specification result for a stable batch in which two particles (corrosion particles) in solution were observed after the activation of the pen.

Following these reports, the laboratory decided to suspend production of Emerade in order to investigate the cause of the malfunctioning of certain pens. Deliveries of Emerade pens to pharmacies were therefore suspended for several months while the laboratory investigated the problem.

As alternatives were not available in sufficient quantities to be exchanged for the Emerade pens already in patients' possession, the ANSM decided not to recall the batches of Emerade already on the market in order to avoid leaving patients without adrenaline pens.

The ANSM, in consultation with patient associations and learned societies, then issued several announcements to:

- patients and parents, giving instructions on how to use these potentially defective pens (laboratory investigations showed that all pens could be activated but may require more pressure than normal),
- health professionals, asking them to:
  - stop prescribing Emerade and fall back on alternatives,
  - reserve the use of adrenaline pens in general (the other proprietary products being Anapen, Epipen and Jext) for use by the patient themselves because of their ease of administration.

The pharmaceutical company's investigation identified the causes of these defects, several corrective actions were then proposed, and variations will be submitted during the year 2020.

Depamide (valpromide) 300 mg, gastro-resistant film-coated tablet (June)

At the end of June 2019, Sanofi-Aventis informed the ANSM of a quality defect related to a problem with the dissolution of 300 mg Depamide (valpromide) tablets that concerned 12 batches produced at a new manufacturing site. The patient risk was a potential risk of decreased efficacy of the product due to reduced bioavailability.

In response to this report, a number of measures were implemented, including:

- a recall of the batches concerned,
- an announcement issued to health professionals, recommending in particular that treatment should no longer be initiated and mentioning alternatives,
- a statement sent to patient associations,
- the implementation of close monitoring of stocks of medicines based on *valproate* or its derivatives.

The ANSM closely monitored the corrective actions proposed by the pharmaceutical company and reviewed the various modifications to the manufacturing process. In view of the company's difficulties in producing sufficient quantities of compliant batches, the laboratory was asked to restart production at the former manufacturing site.
The ANSM will continue to monitor the situation of these proprietary medicines and the progress of corrective actions throughout 2020.

In addition

- **As a precautionary measure, replacement of vials of water for injection (WFI) used for the reconstitution of Tegelin 2.5 g and Alfalastin 1 g (September)**
  Due to the random presence of visible and translucent particles inside the vials, the vials of water for injection supplied with Tegelin 2.5 g and Alfalastin 1 g lyophilisates (reconstitution powder) were withdrawn from use.

- **Recall of ranitidine-based tablets (Azantac and generics) (September)**
  Following the presence of an impurity (NDMA) in certain batches of ranitidine, a recall from pharmacies of medicines in tablet form containing ranitidine was organised as a precautionary measure.

- **Recall of Losartan Accord 50 mg, scored film-coated tablets, batch PW00369 (March)**
  As part of ongoing investigations into the quality defects of certain drugs in the sartan class, an impurity – NMBA – was identified in a batch of Losartan Accord 50 mg, scored film-coated tablets. This batch was recalled.

- **Recall of batch nos T3829 and T9703 of the proprietary medicine UPFEN 200 mg (ibuprofen) (February)**
  An error was found in the package insert of certain boxes regarding the dosage for the paediatric population (children weighing 20-30 kg): the maximum dose indicated in mg per day (1,200 mg) was double the normally permitted dose (600 mg).
  As this error could have led to a risk of overdose, a recall of the batches was carried out.

- **Recall of batch no. 5430717 of the proprietary medicine Pecfent 400 micrograms/spray, nasal spray solution (fentanyl) (January)**
  Following the identification of a vial closure defect, the proprietary medicine Pecfent 400 microgram/spray was subject to a batch recall.

- **Recall of batch no. 013097 Depakine 200mg/ml and Zentiva Sodium Valproate 200 mg/ml (January)**

Due to the discovery, in a box, of a pipette intended for another dosage (300 mg/ml instead of 200 mg/ml), a batch common to the proprietary medicines Depakine 200 mg/ml (oral solution), and Zentiva Sodium Valproate 200 mg/ml (oral solution), was recalled.

- **Recall of batches of the Sandoz proprietary medicines amoxicillin/clavulanic acid in powder form for oral suspension (infant and pediatric dosage) due to an inconsistency in the package leaflet (January)**

- **Batch recall of Irbesartan-based medicines (January)**
  Due to the identification of NDEA at levels above the EMA limits in Irbesartan batches, a recall of the batches concerned was organised.

2019 DATA

The number of medication quality defect reports rises every year, from 624 reports in 2004 to 2,102 in 2019.

641 reports were the subject of an in-depth investigation, and 70 batch recalls were issued.

Change in the number of quality-defect reports (20042019)

	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
2018	1,987	52
2019	2,102	70

Number of recalls following a quality defect
Comparison of the data from 2018 and 2019

	Number of recalls following a quality defect – 2018	Number of recalls following a quality defect – 2019
January	7	4
February	7	5
March	9	6
April	3	8
May	1	6
June	3	4
July	3	5
August	6	7
September	1	6
October	7	11
November	1	5
December	4	2

Control over advertising

All promotional documents intended for health professionals and the public are subject to prior control by the ANSM. The ANSM's role is to ensure the safety of promotional messages; advertisements must not encourage poor prescribing habits and must be consistent with the health authorities' evaluations and communications.

The legislation sets 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.

For advertising that targets health professionals, the recipient of the advertisement must be able to clearly identify the medicine's target population and understand the expected benefit-risk 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).

For advertising that targets the general public (self-medication products and certain vaccines), the goal is for patients to understand the conditions under which they should use the treatment. Patients should understand the need to follow their pharmacist's advice and to take into account certain safety messages regarding medicines or therapeutic classes that require special attention (for example: paracetamol and medicines contraindicated for pregnant women, etc.).
Consumer advertising is subject to submission periods (8 per year), and applications are processed in less than 2 months (regulatory deadline).

Further information: https://www.ansm.sante.fr/Activites/Publicite-pour-les-medicaments/Modalites-de-controle-de-la-publicite/(offset)/0

HIGHLIGHTS IN 2019

Formal notice vis-à-vis GSK's vaccination information campaign

This draft public information campaign, carried out by GSK for meningococcal meningitis vaccines, focused on the lack of information about the disease. It presented the pathology and symptoms, and urged the protection of children against all serotypes of meningococcus. It did not mention any vaccine trade names.

However, this campaign used terms such as "vaccination" or "vaccines" and aimed to promote vaccination against meningococcus serotypes for which consumer advertising is not authorised (not included in the list of vaccines mentioned in Article L 5122-6 of the CSP).
In this way, the campaign aimed to indirectly promote the vaccines marketed by the pharmaceutical company, which corresponds to the definition of advertising for medicinal products as defined by Article L 5122-1 of the CPMP.

This project was therefore considered by the Agency as advertising for vaccines for which no application for approval had been made, and for vaccines for which consumer advertising is not authorised. The ANSM therefore decided to issue a formal notice vis-à-vis the campaign, which was confirmed by the Ministry of Health. The Agency therefore rejected this draft campaign.

In addition

- **Formal notice following the unauthorised publication of the** https://www.stoplameningite.fr/ **website (October)**.
  This meningitis campaign, conducted by the Pzifer laboratory on this website, promoted vaccination. Formal notice was issued against it but no financial penalties were imposed.

- **Ban on native advertising (March).**
  As it is not always clear whether this type of presentation is a form of advertising, native advertising is not compatible with the provisions of Article R.5122-3 1° of the French Public Health Code.

- **Ban on a "drug samples" tab on the Abbvie pro website (December).**
  This is a website on which the pharmaceutical company advertises its medicines. Despite a reminder of the regulatory principles on the website, the presence of a specific "drug samples" tab with a sample request form can be considered as an incentive to demand. This tab was therefore rejected by the ANSM.

2019 DATA

Applications for approval of advertisements targeting healthcare professionals (MP approvals)

- **8,407** applications for approval (around 570 more than in 2018)
  - 10.9% of these applications were declined

Applications for approval of consumer advertisements (GP apppprovals)

- **1,232** applications for approval
  - 56.7% of these applications were subject to requests for corrections
  - 7.8% of these applications were declined

Medicines and pregnancy

Activities aimed at monitoring and evaluating the risks of exposure to medicines during pregnancy and breastfeeding, as well as risks to reproduction, are carried out by the “Reproduction – Pregnancy – Breastfeeding” (RGA) 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 activities.

The RGA unit is mainly responsible for:

- an evaluation activity for new MAs, requests for changes to MA information, periodic safety reports, and signals at both national and European level,
- monitoring of products likely to present teratogenic or foetotoxic risks, in particular through regularly updated risk mapping, harmonisation of information relating to pregnancy, breastfeeding and fertility in SmPCs and package leaflets, literature monitoring, and the performance of meta-analyses and systematic reviews of data in the scientific literature on the risks associated with use during pregnancy or breastfeeding, in conjunction with networks specifically dedicated to pregnancy,
- a cross-disciplinary activity to address more global issues such as communication on "medicines and pregnancy", the provision of general documents for healthcare professionals and patients, the drafting of scientific reports reflecting the present state of knowledge for a category of medication, and the management of networks and/or partners specialising in RGA.

HIGHLIGHTS IN 2019

SmPC update for Ondansetron (July)

Ondansetron is an antiemetic indicated for the prevention and treatment of nausea and vomiting induced by certain chemotherapies and radiotherapy, which is used off-label for the treatment of uncontrollable nausea and vomiting (or hyperemesis gravidarum) during pregnancy.
In December 2018, a European signal was issued by the United Kingdom on the basis of 2 major publications showing an increased risk of congenital malformations following exposure to ondansetron during pregnancy.

The ANSM has been actively involved in evaluating the signal, including by providing the results of a meta-analysis showing an increased risk of oral clefts and cardiac malformations.

In July 2019, the PRAC decided to update section 4.6 of the SmPC for ondansetron-based proprietary medicines. These now indicate that ondansetron is likely to cause orofacial malformations in the first trimester of pregnancy and that the available epidemiological studies of heart defects show conflicting results.
Therefore, ondansetron should not be used during the first trimester of pregnancy.

The ANSM also liaised with learned societies and met with patient-support associations dedicated to fighting hyperemesis gravidarum in order to discuss the implications of this European decision with them.

Also read "Contraindications to the use of fingolimod during pregnancy and for women of childbearing age who are not using effective contraception" (July)

Fingolimod is indicated as a maintenance therapy for highly active, relapsing-remitting forms of multiple sclerosis (MS). The target receptor for fingolimod (sphingosine 1-phosphate receptor) is involved in the formation of the vascular system during embryogenesis.

France, via the ANSM, was appointed as rapporteur by the PRAC to evaluate the post-authorisation data for fingolimod.

After evaluating the 2018 data, the ANSM shared its conclusions with the other Member States that post-marketing data reported in humans suggest that the use of fingolimod during pregnancy is associated with twice the risk of congenital malformation compared to the rate observed in the general population.

In light of these data, the PRAC recommended contraindicating the use of fingolimod during pregnancy and for women of childbearing age who are not using effective contraception. These measures reinforce the pre-existing recommendations.

The SmPCs for specialties containing fingolimod have been updated to prevent the risk of pregnancy less than two months before the discontinuation of treatment.

Drafting of Best Pharmacovigilance Practices specific to pregnancy

In 2019, the EMA began drafting Best Pharmacovigilance Practices specific to pregnancy in order to take better account of the specificities related to risk assessment during this particular period (including those related to fertility and breastfeeding).

The ANSM's Reproduction, Pregnancy and Breastfeeding Unit has contributed actively to the drafting of these Best Practices by participating in numerous discussions with the EMA and Member States. It has made the document available to its network by publishing it on its website for public consultation.

A very large number of comments were received during the public consultation phase and are currently being analysed by the EMA. Work will continue in 2020.

In addition

- **Modafinil (Modiodal and generics): do not use during pregnancy (July)**
  After assessing the risk in children exposed to modafinil during pregnancy, the EMA requested that the risk of birth defects be added to the package leaflet for the medicine, and it is now specified that modafinil should not be used during pregnancy. Similarly, women of childbearing age treated with modafinil must use effective contraception.

- **Publication of the expert committee's opinion on reinforcing risk-reduction measures related to exposure to antiepileptic drugs during pregnancy (July)**

- **Publication of the report "Antiepileptics in Pregnancy: Current state of knowledge on the risks of malformations and neurodevelopmental disorders" (April)**

- **Aubagio (teriflunomide): reminder of the contraindication during pregnancy (January)**

2019 DATA

- **108** evaluations regarding section 46 (pregnancy, breastfeeding, fertility) and/or section 53 (non-clinical–reproductive toxicity) of SmPCs and package leaflets
- **33** signals transmitted by Regional Pharmacovigilance Centres, one third (n=12) of which had an action in progress or led to new measures
- **21** signals from the literature were received and processed, 19% of which concerned signals with actions already finalised (n=2) or being processed (n=2)
- **19** analyses of paediatric investigation plans
- **8** MA applications studied
- **9** participations in meetings of ICH S5 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Safety and Reproductive Toxicology)
- **9** participations in PDCO (Paediatric Committee) meetings
- **6** participations in SWP (Safety Working Party) meetings

The ANSM's role in the prevention of addictive behaviours and its interactions with other organisations

The ANSM is the designated national authority for monitoring the use of psycho-active products, both medicines and non-medicines.

The ANSM controls the legal trade and movement of narcotics and psychotropic substances in France. With respect to regulatory matters, the ANSM monitors the production, manufacture, importation, exportation, 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). France is one of the largest legal opioid-producing countries in the world.
In 2019, more than 12,500 import and export authorisations and approximately 1,150 business authorisations for narcotic drugs and psychotropic substances were issued to the various operators.

The 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 proper use of medicines, 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. The ANSM manages the national addiction vigilance system with help from a network of 13 Centres for Evaluation and Information on Pharmacodependence - Addiction Vigilance (CEIP-A), based in university hospitals located in each region.

To detect and assess abuse, drug dependence, and misuse of medicines or psychoactive substances, the ANSM and CEIP-As have introduced specific data collection and assessment studies. Hence, in addition to collecting spontaneous notifications concerning cases of abuse, drug dependence, and misuse transmitted by healthcare professionals (healthcare professionals are required to report severe cases of abuse and dependence), annual surveys are conducted with entities specialising in addiction care (OPPIDUM[1]), community pharmacists (OSIAP[2] and ASOS[3]), toxicology experts (DRAMES,[4] DTA,[5] and the French national survey on chemical dependence). The ANSM also makes sure that patients and healthcare professionals are kept informed of any changes in the safety profile of these medicines and substances.

In addition, the ANSM 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). The ANSM also transmits its studies to the European Monitoring Centre for Drugs and Drug Addiction (OEDT/EMCDDA), especially data concerning deaths from fatal overdoses.

Further information: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Pharmacodependance-Addictovigilance/Pharmacodependance-Addictovigilance/(offset)/0

[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] OSIAP (Ordonnances Suspectes, Indicateur d'Abus Possible – Suspect prescriptions, an indicator of possible abuse).
[3] ASOS (Antalgiques stupéfiants et ordonnances sécurisées—Narcotic analgesics and secure prescriptions).
[4] DRAMES (Décès en Relation avec l'Abus de Médicaments et de Substances – Deaths related to medicine and substance abuse).
[5] DTA (Décès Toxiques par Antalgiques – Drug-poisoning deaths involving analgesics).

Expert assessments

In September 2019, the Commission for Narcotics and Psychotropics was replaced by the Permanent Scientific Committee on Psychotropics, Narcotics and Addictions, composed of health professionals, representatives of the addiction vigilance network, and benefiting from the presence of two representatives of patients and users.[1] Its missions include:

- assessing the risks of drug dependence, abuse and misuse of psychoactive products, and the management of addictions (except for treatment for tobacco or alcohol addiction),
- proposing surveys and studies to the ANSM Director General, which it considers to be relevant to the performance of its missions,
- advising the Director General on measures to promote the appropriate use of psychoactive medicines or non-medicinal psychoactive products, to prevent and reduce their misappropriation and abuse, or to address the risks associated with the use of such products.

This committee may be consulted and issue opinions on applications pertaining to psychoactive medicines and substances in order to:

- propose the addition of these substances to the list of narcotic or psychotropic agents,
- determine (at the time of the MA application submission) or modify the prescription and dispensation conditions (after marketing),
- reassess the benefit-risk ratio of psychoactive medicines,
- participate in the implementation or modification of risk management plans for psychoactive medicines,
- propose general measures designed to promote proper use, reduce the misuse and abuse of psychotropic medicines, and prevent, reduce the risks or manage the consequences of using non-medicinal psychoactive substances.

HIGHLIGHTS IN 2019

Opioid analgesics: the ANSM publishes an overview of opioid consumption in France (February)

In France, improving pain management is a public health priority, through action plans that have been implemented since 1998. The wider availability and use of opioid drugs has contributed greatly to the improvement of this care. However, although these drugs are used properly most of the time, their high potential for abuse and dependence means that they are subject to misuse associated with significant damage to health.
For example, since 1990, North America has faced an unprecedented health crisis with an epidemic of fatal overdoses due to the overuse of opioid analgesic drugs.

In this context, on 11 May 2017, the ANSM organised a day of partnership-based discussions with healthcare professionals, patient associations and health authorities in order to obtain a comprehensive overview of consumption data in France and of the associated issues. A report entitled "Review of the consumption of opioid analgesics and their problematic uses" was then published by the ANSM in February 2019.

Although the situation is not comparable to that in the United States, a number of indicators call for increased vigilance on the part of health authorities. For example, the number of hospital admissions related to prescription opioid use is increasing: between 2000 and 2017, the number of hospital admissions related to prescription opioid use rose from 15 to 40 per million inhabitants. The notification rate for opioid intoxication cases recorded in the National Pharmacovigilance Database (BNPV) has doubled in 10 years, and the cases of abuse and dependence recorded by the addiction vigilance network have also doubled. Deaths involving opioids also rose from 1.3 per million people in 2000 to 3.4 per million people in 2015.

[1] Also see the chapter on “Activities of advisory bodies”, page 17.

In the United States, strong opioids, particularly oxycodone, are responsible for this crisis. In France, they account for only 2% of the consumption of analgesics. However, their consumption has increased considerably in 10 years: + 738% for oxycodone, and 338% for fentanyl. The growth is therefore spectacular, even if the absolute number remains moderate because the starting point is very low. In France, “weak” opioids are the most widely consumed analgesics. They account for 20% of analgesic consumption (behind paracetamol and ibuprofen), and tramadol is the most commonly prescribed. Tramadol is also the most frequently misused drug, and increasingly so, despite its consumption levelling off since 2013. Very fast-onset withdrawal syndromes are also increasingly reported. Finally, tramadol is the leading analgesic involved in analgesic-related deaths. Codeine is also widely consumed. However, its use fell by 30 per cent between 2016 and 2017 as a result of it becoming a prescription-only medicine in response to an increase in cases of abuse by adolescents, which had led to deaths.

Since the publication of that report, a number of measures have been adopted to improve the proper use of opioid analgesics:

- The 2019-2022 "Preventing and tackling opioid overdoses" roadmap has been published by the Ministry of Health, following work carried out jointly with the various stakeholders involved. In particular, this roadmap calls for the widest possible use of ready-to-use naloxone for patients treated with opioids.
- In April, the EMA, actively supported by France, created a working group specifically dedicated to opioid surveillance.[1]
- At the proposal of the ANSM, it was decided to limit the validity period of prescriptions containing tramadol-based medicines. Prescriptions will now only be valid for 12 weeks (instead of one year previously).[2]

The surveillance of these drugs will be carried out by all of the ANSM’s vigilance networks.

Change in the prescribing and dispensing conditions for tramadol

Tramadol is the most widely used opioid analgesic in France. Several surveys by the addictovigilance network (CEIP-A) have shown increasing misuse of tramadol in recent years:

- the most frequently mentioned opioid analgesic in a 2018 survey on problematic use both among drug users and in the general population for treating pain. In particular, dependence is observed with signs of withdrawal occurring even when the product is taken at recommended doses and over a short period of time, which leads to persistent use by patients who are no longer suffering from pain.
- The analgesic involved in the most deaths related to the use of analgesics, ahead of morphine (DTA survey).
- The second-most frequently found analgesic on falsified prescriptions presented in pharmacies, behind codeine (OSIAP survey).

At the proposal of the Director General of the ANSM, the maximum prescription period for analgesics containing tramadol (oral route) has been reduced from 12 to 3 months, in order to limit their misuse and risks of dependence. This measure will come into force on 15 April 2020. Beyond 3 months, a new prescription will be required for continued treatment with oral tramadol.

[1] Also read “Opioid safety: establishment of a pan-European working group”, page 66.
[2] Order of 13 January 2020, effective on 15 April 2020.

Rising use and increase in the number of serious cases linked to nitrous oxide consumption, particularly among young adults

For many years, nitrous oxide was only consumed for festive purposes. However, the addiction vigilance network now reports cases of daily consumption of hundreds of nitrous oxide cartridges (normally intended for whipped cream siphons) over several months.
In 2016, the first misappropriations of nitrous oxide with serious health consequences were observed, with two cases of dependence and one death (in a context of polydrug use). In early 2018, a serious case of acute cervical myelitis was reported following daily consumption of pure nitrous oxide. Since 2019, serious cases with neurological complications have been reported.
The addiction vigilance investigation into nitrous oxide (medical and non-medical) has been maintained.

Increase in the number of cases of kratom consumption

Kratom is a plant native to South-East Asia that contains many alkaloids with opioid properties. Its "recreational" use is spreading, particularly among drug users, especially in the United States and France,
who claim that they want to use kratom as a replacement for alcohol or opiates, as a provider of antidepressant effects (2 cases) or as a stimulant (1 case).
Twenty cases of adverse reactions have been reported to the addiction vigilance network in France since 2007, with an increase seen since 2016.
Reported cases include addiction, withdrawal syndrome, anorexia/weight loss and psychotic decompensation. One serious case of toxic hepatitis and one death in a poly-drug use context have also been reported.

In this context, at the proposal of the ANSM, kratom, mitragynine and 7-hydroxymitragynine were classified on the list of psychotropic drugs by order of 23 December 2019.

In addition

- **Publication of an information update alerting patients, parents of children with epilepsy and healthcare professionals about the dangers of using products containing cannabidiol, particularly those sold on the Internet (January).**

- **Implementation of a specific system for reporting and investigating serious pneumopathies occurring among electronic cigarette users ("vapers") by the Ministry of Health**, in conjunction with health agencies, including the ANSM. This follows a health alert in the United States about cases of severe pneumonia in vapers.

2019 DATA

In 2019, the Commission for Narcotics and Psychotropics met three times and the Permanent Scientific Committee on Psychotropics, Narcotics and Addictions met once.

Opinions were issued on the following subjects:

- inclusion of kratom, mitragynine and 7-hydroxymitragynine on the list of psychotropic drugs,
- limitation of the maximum duration of tramadol prescription to 12 weeks,
- limitation of the maximum duration of pregabalin prescription to 12 weeks,
- conditions for prescribing and dispensing the first long-acting, injectable opioid substitution drug (Buvidal, buprenorphine).

Overall assessment of the work of the Commission on Narcotic Drugs 2016-2019

Powers of the Commission for Narcotics and Psychotropics (CSP)	Number of cases (opinions & information)				Number of cases with opinions issued				
	2016	2017	2018	2019	2016	2017	2018	2019	TOTAL
Assessment of the risks of drug dependence, abuse and misuse of psychoactive products (including substances, plants or medicines), and of the measures to be taken to safeguard public health (including conditions for prescribing and dispensing (CPD))	3	9	7	4	1	6	4	2	**13**
Evaluation of psychoactive products with a view to their classification on the list of narcotic drugs or psychotropic substances	2	5	0	1	1	4	0	1	**6**
Drugs within the scope of addiction management	0	1	2	0	0	1	1	0	**2**
General measures to promote the appropriate use of psychoactive medicines or non-medicinal psychoactive products, to prevent and reduce their misappropriation and abuse, or to address the risks associated with the use of such products.	0	3	3	4	0	0	0	1	**1**
TOTAL	**5**	**18**	**12**	**9**	**2**	**11**	**5**	**4**	**22**
No. of sessions/year	2	5	4	3	2	5	4	3	**14**
Day of partnership-based discussions involving the Commission for Narcotics and Psychotics	0	1	1	0	0	0	0	0	**2**

Surveillance of blood products

The ANSM is involved in the collection, analysis and monitoring of:

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

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.

Haemovigilance is supported by the network of regional haemovigilance and transfusion safety coordinators (CRH-ST) and haemovigilance and transfusion safety correspondents (CHV-ST) in healthcare institutions (ES) and blood transfusion establishments (ETS) and the e-FIT[1] national electronic reporting system.
This database enables members of the network (CRH-ST, CHV-ST, Vigilance Division of the Etablissement français du Sang (EFS) [French National Blood Service], Haemovigilance Department of the Military Blood Transfusion Centre (CTSA), and ANSM) to intervene rapidly and share information about any potentially significant event that could impact the safety of the blood transfusion chain, LBPs, and blood donors.

In addition, until March 2019, the ANSM managed the Decision-Making Assistance (CAD) Unit, an inter-institutional structure responsible for issuing recommendations on the preventive measures to be implemented to avoid the transmission of infectious agents (mainly arboviruses: West Nile virus, chikungunya, dengue, zika) through transfusion or transplantation, following epidemiological alerts in France and abroad.
This activity was transferred to the French High Council for Public Health (HCSP) in March 2019. Since then, the ANSM has contributed to this activity within the HCSP's "Safety of Human Body Products" group (SECPROCH).

Further information: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Hemovigilance/L-hemovigilance-et-son-organisation/(offset)/0

[1] E-Fit is the database for the reporting of serious transfusion chain reactions, serious adverse effects arising in blood donors, post-blood-donation information, and adverse effects in recipients, in addition to transfusion activity data.

HIGHLIGHTS IN 2019

- **Publication of the 16th Haemovigilance Annual Report 2018 (December)**
  Analysis of the reports shows that the majority of the adverse effects that occurred in recipients or donors were of the non-severe variety. In addition, new actions for the prevention of undesirable effects aimed at making transfusion safer and measuring their impact have been put in place.

- **Lifting of the injunction against LFB[1] (November)**
  On 19 November 2019, the ANSM lifted the injunction it had issued in May 2018 against the pharmaceutical group LFB. The latest inspections have established the laboratory's regulatory compliance.

- **Human Fibrinogen: the ANSM has developed a practical guide to promote the proper use of available products (September)**
  Following periods of supply difficulties and repeated stock shortages, the ANSM has developed a practical guide for healthcare professionals who use three human fibrinogen-based proprietary medicines.

- **Presentation of the review of the CAD for the 2015-2018 period at the Congress of the French Blood Transfusion Society (SFTS) (September)**
  For several years, this Decision-Making Assistance (CAD) unit has enabled the deployment of rapid responses to various alerts, as well as the involvement and provision of information to all French and European health institutions involved in the protection of recipients of labile blood products and transplants

- **Prioritisation of indications for human polyvalent immunoglobulins (Ig) in a context of limited supplies: update on actions implemented and updating of the current prioritisation (April)**
  The implementation of alternative solutions by the ANSM and the prioritisation of indications applied in the field with the involvement of all stakeholders have enabled the resumption of more satisfactory Ig supplies. However, the availability of Ig remains a concern and the prioritisation list is still in effect.

- **Recommendation to the ABM to raise awareness among organ, tissue and cell procurement teams of the "chikungunya" risk for donors returning from Thailand (February).**
  Indeed, the CAD had been notified following the Chikungunya epidemic in Thailand since late 2018 and the unusual number of imported cases involving travellers returning from Thailand.

- **Haemonetics apheresis devices:[2] update on ongoing investigations (January)**
  As part of the investigations carried out on Haemonetics apheresis devices, the ANSM has continued its inspections of several EFS and CTSA sites.

[1] See "Lifting the injunction against LFB", page 128.
[2] See "Apheresis medical devices used to collect certain blood components from a donor" on page 111.

Haemovigilance reports of serious adverse effects among donors
(2019 cumulative data)

	Number of adverse effects among donors	Severe adverse effects
January	451	104
February	969	225
March	1,585	369
April	2,205	520
May	2,713	649
June	3,334	801
July	4,069	1,038
August	4,625	1,199
September	5,144	1,348
October	5,773	1,510
November	6,314	1,665
December	6,838	1,801

Haemovigilance reports of serious adverse effects among receivers
(2019 cumulative data)

	Number of adverse effects among receivers	Severe adverse effects
January	727	20
February	1,317	26
March	1,924	37
April	2,577	47
May	3,172	53
June	3,705	68
July	4,474	82
August	5,074	91
September	5,565	101
October	6,195	108
November	6,777	118
December	7,700	128

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, nearly 75% 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.

Monitoring of medical devices and in vitro diagnostic medical devices

A medical device is an instrument, material, apparatus, appliance, implant, or software that is used for medical purposes in humans and which does not achieve its principal intended action by pharmacological, immunological or metabolic means.
[1]

The medical device market is extremely vast and the sector is a highly innovative one. The GMDN identifies over 20,000 types of products, including single-use or reusable consumables, implants and biological-derived devices, designed and marketed by various manufacturers, from major multinationals to micro-companies.

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.

Marketing

The marketing conditions for medical devices (MDs) and in vitro diagnostic medical devices (IVDMDs) are exactly the same.

It is not the ANSM that grants the marketing authorisation: this is governed by three European directives, known as the "New Approach" directives.
These directives set the “essential requirements” related to health and safety that the design and use of the MD must comply with and require manufacturers to identify their product with the CE mark, guaranteeing conformity of the MD, prior to marketing.

To be able to place the CE mark on their product and market it in Europe, manufacturers must have received a certificate of conformity, issued by an accredited body (known as the “notified body”).
According to the procedures described in the directives, this body assesses the manufacturer’s quality system and the conformity of all devices, excluding class I devices (class I without a measuring function and supplied in a non-sterile condition).
For class III devices, or for active implantable medical devices, the design dossier is also systematically examined.
All other products that are subsequently put on the market must comply with the product that obtained the certificate of conformity permitting CE marking.

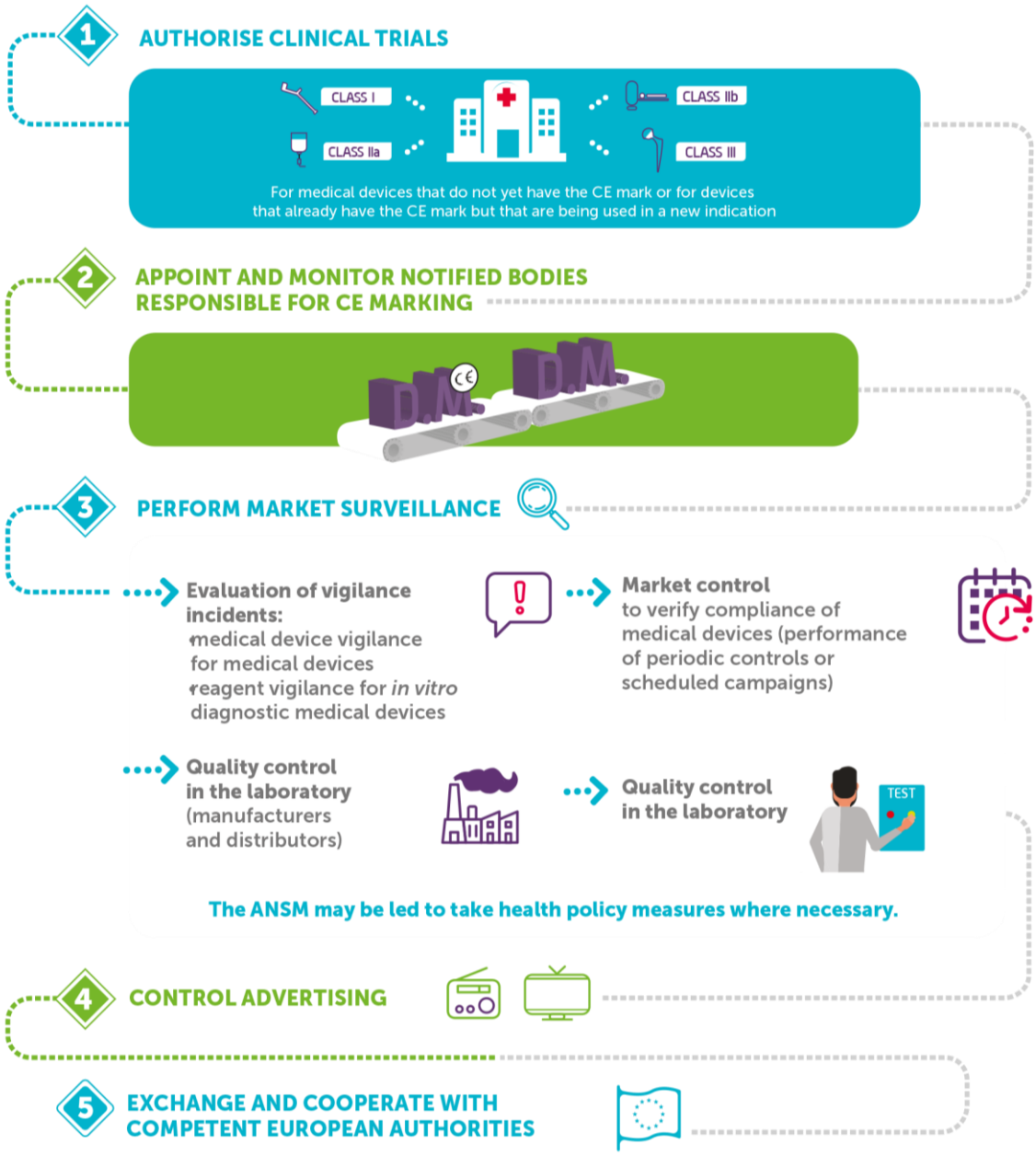
Once on the market, the MD is the responsibility of the manufacturer marketing it. The manufacturer must carry out tests to ensure no problems occur during its use and take preventive or corrective measures if necessary.

CE marking is renewed periodically.
The notified body performs regular audits: its decisions are valid for a maximum period of five years and can be renewed for a maximum period of five years.

[1] Global Medical Device Nomenclature

The role of the ANSM

The Agency is responsible for effective, active market surveillance in France and intervenes at several levels throughout the control chain.



Find out more: https://www.ansm.sante.fr/Produits-de-sante/Dispositifs-medicaux
And https://www.ansm.sante.fr/Produits-de-sante/Dispositifs-medicaux-de-diagnostic-in-vitro

Watch our 3 educational videos:

What is a medical device?

Bringing a medical device to market

The ANSM's role in the life cycle of medical devices

HIGHLIGHTS IN 2019

Textured breast implants are withdrawn from the market (April)

Since 2011, when the first cases of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) were reported, the ANSM has carried out numerous investigations examining the link between the occurrence of BIA-ALCL and the texture of breast implants.
Several expert committee meetings have been held at the ANSM since 2015 highlighting the predominance of ALCL cases with textured breast implants.
The ANSM has also continued to closely monitor medical device vigilance cases, in coordination with other health authorities, particularly European ones.
Since the notification of BIA-ALCL cases linked to textured breast implants has continued since then, the ANSM convened a Temporary Specialist Scientific Committee (CSST) on 7 and 8 February 2019. This group consulted patients, healthcare professionals, European and international health authorities and manufacturers. The objective was to issue an opinion with respect to the role of textured breast implants in cosmetic and reconstructive surgery in the context of the development of BIA-ALCL.
The hearings with stakeholders were accessible to the public since they were broadcast live on the internet.
The expert group issued its opinion on 8 February 2019, recommending, in particular: *"In the context of the ANSM's recommendation to preferentially use smooth implants in view of the doubts raised by healthcare professionals, it is necessary to prohibit the use of Allergan's Biocell texture. The greatest caution is required with equivalent textured breast implants and polyurethane implants. However, the committee does not recommend preventive removal of these textured implants."*
In view of this opinion and all the information it had on the use of breast implants in France, the ANSM considered that the more textured and rough an implant is, the greater the risk of the development of BIA-ALCL.
As a precaution, and in order to reduce women's exposure to the risk of BIA-ALCL, the ANSM took the decision on 2 April 2019 to withdraw certain macro-textured implants of an equivalent texture to Allergan brand implants with a Biocell-type shell and implants with a polyurethane shell. The ANSM did not recommend preventive removal for women already fitted with these types of implants.
Several international health authorities also made similar decisions.
In addition to this decision, concise information documents were produced aimed at women wishing to have breast implants for reconstructive or cosmetic purposes.

For the treatment of peripheral arterial disease (PAD) of the lower extremities, the use of Paclitaxel-coated medical devices (stents or balloons) should be reserved for the most severely affected patients (May)

A meta-analysis[1] published in December 2018 suggested a possible excess mortality in patients with peripheral arterial disease (PAD) of the lower extremities treated with paclitaxel-coated medical devices (balloons or stents) from two years following application of this medical device compared to the mortality in patients treated with devices without this substance (uncoated balloons or bare metal stents).

In order to provide advice to the healthcare professionals concerned, in February 2019, the ANSM mobilised an expert group and consulted several learned societies involved in the treatment of PAD (in particular, in the fields of cardiology, vascular medicine and surgery, vascular interventional radiology, etc.), in order to determine whether or not there are long-term risks associated with the use of these paclitaxel-coated devices.

Based on the opinion returned by the experts, the ANSM considered that the potential risk of long-term mortality needed to be taken into consideration when deciding on the treatment of PAD and, in May 2019, recommended that healthcare professionals should:

- Preferably use alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents.
- Reserve the use of these devices to patients at particularly high risk of restenosis, in whom the practitioner can estimate that the benefits of using a paclitaxel-coated product outweigh the medium-term risk identified by the meta-analysis. In this case, patients must be given prior information about the advantages of this choice compared to the increased risk of death observed in the study and systematically be involved in the decision-making process.
- Maintain monitoring of patients treated with paclitaxel-coated devices. In the absence of data concerning the origin of the potential risk of excess mortality and pending additional data, this monitoring should focus specifically on cardiovascular follow-up.

The ANSM also worked in liaison with the European and international competent authorities on this topic. A further meeting bringing together patient representatives, healthcare professionals and institutional partners (DGS, HAS, DGOS) was held in March 2020 to draw up an inventory of all the available data. In the light of this new assessment, the recommendations published in May 2019 were confirmed.

[1] Katsanos et al. “Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials” (J Am Heart Assoc. 2018).

In addition

- **Discussion meetings and investigations concerning the use of citrate dialysate in haemodialysis patients.**
  The ANSM met with all the stakeholders involved (healthcare professionals, learned societies, patient associations, INSERM, ABM) five times in 2018 and 2019 to study the possible impact of citrate dialysates on haemodialysis patient mortality in France.[1]

- **Withdrawal of Telefunken and HeartReset automated external defibrillators (AEDs) made by Dutch company GGT Holding B.V (November).**
  These products had been put on the market between 2014 and 2019 without a valid CE certificate of conformity.

- **Contamination of several medical devices used as medical device disinfectants[2] (October).**

- **Interference with maltose in the event of peritoneal dialysis with icodextrin: market control of blood glucose monitoring systems (October).**

- **Organisation of a first institutional meeting with all the stakeholders concerned by the discontinuation of manufacturing of the Medtronic MiniMed implantable insulin pump (MIP)[3] (September).**

- **Interference of Biotin in certain laboratory tests: market control of the in vitro diagnostic medical devices impacted (July).**

- **Banning of a menopause self-testing device (May).**
  The data provided by the manufacturer in terms of demonstration of the device performance were inadequate to certify its efficacy.

- **Banning and market withdrawal of dental implants marketed by French company Cortical (April).**
  Following an inspection by the ANSM, it emerged that this distributor did not have a valid CE certificate.

- **Withdrawal of peripheral vascular stent and balloon catheter medical devices marketed by the company Pan Medical (March)**.
  They did not have a valid certificate of conformity.

- **Banning of female condoms made by the company Tianjin CondomBao Medical Polyurethane Tech.co and distributed by Bong France (January).**
  Breaches of the legislative and regulatory requirements were identified.

- **Information meeting on medical devices to treat pelvic organ prolapse and urinary incontinence[4] (January).**

- **Withdrawal of "Andrastent L, XL and XXL" peripheral stents made by Andramed GmbH (April).**
  This withdrawal follows the absence of a CE certificate of conformity for the XXL model since 26 September 2017.

[1] See "Discussion meetings and investigations concerning the use of citrate dialysate in haemodialysis patients", page 32.
[2] See "Monitoring of several medical devices used as medical device disinfectants", page 53.
[3] See: "Organisation of a first institutional meeting with all the stakeholders concerned by the discontinuation of manufacturing of the Medtronic MiniMed implantable insulin pump", page 32.
[4] See "Mesh implants for the treatment of urinary incontinence and pelvic organ prolapse", page 110.

Monitoring of incidents and risks of incidents

Medical device vigilance

Medical device vigilance evaluates incidents and risks of incident 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 vigilance 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 the ANSM.

Find out more: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Materiovigilance/Qu-est-ce-que-la-materiovigilance/(offset)/0

Reagent vigilance

Reagent vigilance evaluates incidents and risks of incident related to the use of *in vitro* diagnostic medical devices.
The reagent vigilance system is structured around a national tier (ANSM) and a local tier managed by local reagent vigilance 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 the ANSM.

Find out more: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Reactovigilance/Reactovigilance/(offset)/0

For 5 years, the ANSM has been funding a regional medical device/reagent vigilance tier as part of a trial to be made permanent in the context of the ministerial reform relative to vigilance (decree of 6 December 2019). The main objectives of this regional organisation are to:

- reinforce the medical device and reagent vigilance system by consolidating the organisation of vigilance networks,
- improve the transmission and quality of reports,
- develop regional expertise in terms of medical devices and implement preliminary assessment of the risk level of notifications as locally as possible,
- facilitate information-sharing between healthcare professionals,
- coordinate the local correspondent network,
- promote the bottom-up and top-down transmission of information between the local, regional and national levels,
- participate in addressing the training and information needs of local correspondents.

HIGHLIGHTS IN 2019

Banning of and market withdrawal of Ancora and Novaplus intrauterine devices (November)

The ANSM has taken a health policy decision that the Ancora and Novaplus intrauterine devices (IUDs) made by the manufacturer Eurogine (IUD also included in some Sethygyn sets marketed by Euromedial, when delivered with an insertion kit) are no longer to be used in France. This decision follows an increase in the number of rupture incidents during the removal of these IUDs by healthcare professionals, as well as reports of spontaneous expulsions of part or all of these IUDs.

Since 2018, numerous incidents have been reported by healthcare professionals or directly by women fitted with Ancora and Novaplus IUDs. The manufacturer had indicated the risk of rupture when removing these IUDs in 2018. At the time, this information was accompanied by a recommendation to follow up

women using these IUDs and a recall of the Ancora and Novaplus batches concerned and already on the market.
More than a third of the vigilance reports received by the ANSM concerned a spontaneous expulsion of the IUD.

Taking into account the data provided by the manufacturer and the studies carried out by the ANSM, failings were identified, in particular as concerns demonstration of the IUDs' stability over time and the information available to women fitted with them.

Consequently, on 28 November 2019, the ANSM took a health policy decision that the Ancora and Novaplus IUDs made by the manufacturer Eurogine (IUD also included in some Sethygyn sets marketed by Euromedial) could no longer to be fitted in France.

This decision was accompanied by two recommendations, validated by several healthcare professional organisations: one aimed at healthcare professionals and the other at women fitted with these IUDs. They are invited to make sure they are aware of the symptoms that may suggest expulsion of the IUD and the measures to be taken in this event (consultation of a healthcare professional) and to regularly check that the IUD strings are present.

Suspension of the use of software used in radiotherapy (July)

In its decision of 9 July 2019, the ANSM suspended the marketing, commissioning and distribution of three "prescription", "positioning" and "patient follow-up sheet" modules of the Onchronos/Oncorus software packages manufactured by Deuxtec until they were brought into line with the applicable regulations.

These software solutions are used in radiotherapy centres for transferring and archiving administrative and prescription-related data. They are designed to ensure centralised access to patient data and hence facilitate the prescription of treatments.

The ANSM received a medical device vigilance notification related to these software solutions, reporting an incident risk. This concerned a prescription error that had been detected before administration to the patient. No known incidents have been reported to the ANSM.

The French Nuclear Safety Authority (ASN), in the context of its radiotherapy centre inspection missions, observed that the safety of the software ultimately depended on the vigilance of its users, with the software itself not providing a demonstrated guarantee in its operation.

The suspension decided on by the ANSM aims to put an end to the use of software modules that have medical functions despite not having been developed in accordance with medical device requirements. The radiotherapy equipment can still be used without these software solutions, which do not interact directly with its operation. An adaptation of procedures and practices may be necessary in user centres.

In addition

- **Banning of two wart and verruca products - "Expert 1.2.3 Verrues Cutafilm" and "Steripan Traitement Verrues" - and recall of bottles due to a risk of accidental 2nd-degree burns (October).**
  After investigation, it was observed that the packaging of these corrosive solutions in bottles did not prevent the risk of spillage.
  In addition, due to the risk of confusion with other products, bottles of "Objectif ZeroVerrue Original" with a white cap were the subject of a recall from patients and should also be taken back to pharmacies, parapharmacies or supermarkets.

- **Recall of batches of the Advance – Herdegen bi-material walking stick following several incident reports (June)**

- **Monitoring of FreeStyle Libre devices following the availability of modified Abbott sensors (May).**
  In view of the numerous reports relative to skin reactions (allergic reactions, irritation, redness, lesions, purulent wounds, etc.) occurring in patients using FreeStyle Libre, with some patients having required medical treatment, the manufacturer modified an internal component of the sensors. The modified sensors were put on the market in May 2019. The ANSM is closely monitoring this dossier and has been regularly analysing the safety reports transmitted by the manufacturer. A decrease in notifications concerning these skin reactions has been observed since August 2019 in France and around the world.

2019 DATA

Medical device vigilance reports

Medical device vigilance	2015	2016	2017	2018	2019
Number of reports	15,783	15,961	18,208	18,838	**18,994**
• of which serious	825	749	1,015	1,133	**1,206**
• of which received from patients and patient associations	34	129	1,432	682	**553**

Origin of medical device vigilance reports

	%
Manufacturers	47
Healthcare institutions	36
Other players (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions)	17

Reagent vigilance reports

Reagent vigilance	2015	2016	2017	2018	2019
Number of reports	1,355	1,474	1,366	1,344	**1,628**

Origin of reagent vigilance reports

	%
Manufacturers	47
Healthcare institutions	36
Others	17

Reinforced monitoring for certain categories of medical devices

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, also called “mesh implants”, are presented in the form of strips and implantable pelvic mesh implants.

The ANSM has been monitoring these implantable devices for several years.

The ANSM's reinforced monitoring 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, made it possible to identify the implants sold in France and perform a clinical evaluation on these implants. Around 50,000 implants from approximately one hundred marketed brands are sold every year in France. Over this period, the number of products sold increased. For some devices, the investigation into the quality of the clinical evaluation will continue.
  - Along with its European counterparts, the ANSM is also part of a task force overseeing these devices. The objective is to ensure that manufacturers continue to monitor their product after it has been put on the market, as they are required to do.

- **Medical device vigilance:**
  - Medical device vigilance reports are closely followed up.
  - The results of the medical device vigilance survey conducted by the ANSM in 2016 were published in 2018: the complication rate observed over the period 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, the ANSM funded the Vigi-mesh clinical study coordinated by Poitiers University Hospital. The purpose of this monitoring study is to collect reports from several healthcare facilities of short- and long-term complications after surgery, without or without implants. The first inclusions began in February 2017. The study has been extended for a period of 3 years and patient recruitment will continue until February 2022. The increase in the number of patients will enable more in-depth analyses to be performed, in particular on the basis of type of surgery, type of complication or the implants inserted.

In view of these data, on 22 January 2019, the ANSM organised a review meeting on the treatment of pelvic organ prolapse and urinary incontinence, bringing together patients, healthcare professionals (urologists, gynaecologists, general practitioners, nurses, midwives, etc.) and health authorities (Ministry of Health (DGS), National Authority for Health (HAS), Directorate General of Health Care Provision (DGOS)). The objective of this meeting was to discuss the benefit of these medical devices and the risks related to their use. It led to the development of an action plan tailored to the situation in France, aimed at improved oversight of the use of these implantable medical devices and the treatment of pelvic organ prolapse and urinary incontinence, more generally, and hence guaranteeing patient safety throughout the care pathway.

One of the action avenues to emerge from this meeting was the continuation of the Vigi-mesh, study coordinated by Poitiers University Hospital (Prof. Xavier Fritel). The aim of this study is to identify the short and long-term complications following pelvic repair surgery, with or without the use of implants, in several hospital centres. The ANSM therefore decided to continue its funding, the first funding period

coming to an end in December 2019. This extension of the study for a period of 3 years will make it possible, in particular, to collect more clinical information, including long-term data, and to compare the outcomes of women after surgery for the treatment of urinary incontinence and/or pelvic organ prolapse, with or without the insertion of a mesh implant.

Another action avenue identified was individual evaluation of these device categories by the HAS. In accordance with the orders of 22 February 2019 and 26 November 2019, this evaluation began with implantable devices for the treatment of pelvic organ prolapse by the vaginal route. The ANSM responded to the requests made by the HAS to complete its action.

In addition, follow-up of the incidents reported to the ANSM in the context of medical device vigilance is continuing.

On a European level, the ANSM is actively taking part in a task-force to monitor these medical devices, the objective being to ensure that manufacturers continue to monitor their product after it has been put on the market, as they are required to do. In this context, a review of some of the technical documentation for the devices (clinical evaluation, post-market surveillance, risk management, instructions for use, etc.) has been initiated by the competent European authorities. The ANSM has evaluated several devices. Where deficiencies were identified in the dossiers evaluated, these were shared with the manufacturers and their notified body. They were requested to take them into account for updating of the technical documentation. Pooling of the results of evaluations within the European task-force led to the drafting of recommendations with respect to what is expected in terms of the clinical evaluation and post-market surveillance of these devices. These recommendations have been distributed to all European notified bodies, which have also been encouraged to schedule reassessment of manufacturers' technical dossiers as soon as possible.

In the USA, the FDA published a statement on its website in April 2019, requesting all manufacturers of implants for the treatment of pelvic organ prolapse by the vaginal route to stop selling and distributing these products. The only two manufacturers concerned in the USA - Boston Scientific and Coloplast - took the decision to stop marketing these devices in Europe too, despite the fact that they had a CE mark.

Find out more: https://www.ansm.sante.fr/Activites/Surveillance-des-dispositifs-medicaux-implantables/Surveillance-des-bandelettes-sous-uretrales-et-implants-de-renfort-pelvien/(offset)/3#dm

Apheresis medical devices used to collect certain blood components from a donor

As a follow-on from the re-evaluation of the risk-benefit ratios of apheresis procedures begun in 2017, the ANSM recommended a certain number of measures designed, firstly, to continue closely monitoring medical devices used to collect and separate blood components from a donor and, secondly, to supplement the general information donors receive about apheresis by including the risks related to the presence of particles.

The ANSM ensures that the safety of plasma and platelet donors is guaranteed during the use of apheresis machines and implements all necessary to measures to ensure recipients have access to the blood products they need.

Hence, the ANSM periodically monitors medical device vigilance reports concerning the presence of particles in apheresis circuits.

Apheresis machine manufacturers have undertaken to implement actions to improve their machines and supplement their studies as requested by the ANSM.

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

During the course of this reinforced monitoring, several medical device vigilance incidents were reported to the ANSM at the end of August 2018 involving apheresis machines made by 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 also inside 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 in Tarbes was taken on 30 August 2018 by the 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 the ANSM. This incident was also without repercussions for the donor and led to a new inspection being conducted by the ANSM.

In the light of these incidents and the lack of any explanation from the manufacturer, Haemonetics, with respect to the possible causes, on 12 September 2018, the 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.

The ANSM continued to investigate devices manufactured by Haemonetics, in particular through additional inspections, and, in collaboration with the French Atomic Energy and Alternative Energy Commission (CEA), through analyses of the apheresis products concerned by these incidents in an effort to determine the source of the particles found. The objective of the analyses was to identify and characterise the particles present and sampled during the incidents.

The CEA performed analyses to determine the size and morphologies of the particles found during these incidents. Qualitative elementary analyses were also performed, as well as molecular analyses using a mass spectrometer to compare the particles with the sections of a seal of an SUMD with the reference number 782HS-P-SL.

An organic origin of the particles generated during these incidents, probably related to the various blood components contained in the device, is likely based on all the analyses performed by the ANSM and CEA laboratories.

No particles from a seal in the device or any other part of the device were identified. These reports are available on the ANSM's website.

The ANSM also consulted all the relevant European authorities to determine, in particular, whether they had received any medical device vigilance reports involving Haemonetics apheresis machine malfunctions with the release of particles. The responses 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, nor for patients receiving these products or for the professionals handling the machines.

Nevertheless, the ANSM is continuing to investigate the Haemonetics devices in order to determine the source of the malfunctions observed. They are probably multifactorial in origin, and related to the machines' maintenance schedule and frequency of use, in particular. The ANSM is also continuing to monitor the corrective actions undertaken by Haemonetics relating to the manufacturing and control processes for these devices and within the context of the health policy decision of 12 September 2018.

ESSURE permanent contraceptive device

Although the Essure medical device for tubal sterilisation has no longer been marketed in France since August 2017, the ANSM is maintaining the reinforced monitoring it had put in place for this device, via:

- monthly trend-tracking of medical device vigilance incidents reported. Hence, between January 2013 and December 2019, the ANSM received a total of 3,323 reports concerning Essure. Of these reports, 2,234 described the development of multiple symptoms.
- monitoring of the scientific literature and of the general and social media concerning the topic in order to assess the quality of life of women following the removal of the Essure implant and to have histological analyses of tissues following removal with a view to obtaining data concerning the evolution over time of the Essure implant.
- maintenance of the close links with associations representing women currently or previously fitted with an Essure implant in order to listen to their concerns and take into account their needs.

Breast implants: reinforced monitoring maintained, particularly as concerns the risk of the development of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)

- See “Textured breast implants are withdrawn from the market” page 103.

Market control activities

The objective of product evaluation and control activities is to verify the compliance of devices with European directive essential requirements relative to health and safety.

These activities are conducted on devices marketed in France and are based, in particular, on the CE declaration of conformity and the technical documentation produced by the manufacturer.

They are implemented following an analysis of:

- data derived from the compulsory declarations and communications submitted by manufacturers, agents or distributors
- referrals received from third parties (institution, manufacturer, healthcare professional, other health authorities, etc.) by the ANSM.

These market control operations concern either:

- a specific device,
- a set of devices on the market with a specific issue

Find out more: https://www.ansm.sante.fr/Activites/Surveillance-du-marche-des-dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro-DM-DMDIV/Dispositifs-medicaux-Operations-d-evaluation-et-de-controle-du-marche/(offset)/3
and https://www.ansm.sante.fr/Activites/Surveillance-du-marche-des-dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro-DM-DMDIV/Dispositifs-medicaux-de-diagnostic-in-vitro-Operations-d-evaluations-et-de-controle-du-marche/(offset)/1

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

Each year, the ANSM monitors the arrival of new medical devices on 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 of devices belonging to other classes must also notify the ANSM.
This notification prior to marketing in France provides information on the devices used in the country, as well as the market players.

Themed campaigns by product range launched and/or continued in 2019

The ANSM may proactively conduct an assessment of the regulatory conformity and the risk-benefit ratio of a medical device, at any point in its life cycle, as part of its market surveillance and in addition to its vigilance report management activities.

To this end, the Agency carries out product range control activities aimed at verifying demonstration of 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.

Quality control of radiation-emitting medical devices

Quality control of medical devices is designed to ensure that medical devices maintain their performance throughout the duration of their use.
This control may be applied to all medical devices as soon as they are included on a list approved by the 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 the ANSM, which currently relies on 13 accredited independent bodies responsible for verifying on-site compliance with the control standards defined by the Agency. Seventy accreditations were valid at the end of 2019.

Furthermore, supervisory bodies and users must report any non-conformities observed during quality controls to the ANSM. In the event of a serious non-conformity, the ANSM notifies site operators of the need to cease activities until they are brought into compliance.
In 2019, 923 non-conformity reports were received and processed by the ANSM.

National quality control of medical laboratory tests

National quality control of medical laboratory 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 performance of a test. It also makes it possible to monitor the *in vitro* diagnostic medical devices used in laboratories.

Find out more: https://www.ansm.sante.fr/Activites/Controle-national-de-qualite-des-analyses-de-biologie-medicale-CNQ/Controle-national-de-la-qualite-des-resultats-des-examens-de-biologie-medicale/(offset)/0#div

HIGHLIGHTS IN 2019

Public consultation process relating to a project concerning guidelines for medical device cybersecurity (July)

In July 2019, the ANSM launched a public consultation process relating to a project concerning guidelines for medical device cybersecurity.
The objective is to draw up guidelines aimed at the manufacturers of medical devices incorporating software to ensure that cybersecurity aspects are taken into account during the development process and hence minimise the risk of a cyber-attack.
This is the first time that guidelines have been developed in this field in Europe. The ANSM shared its research with the European Commission so that the regulations relating to medical devices could evolve to incorporate this security issue.

This public consultation process follows on from the work conducted by the Agency in the area of medical device cybersecurity, which led to the creation of a specialised expert committee for this subject in 2017.

While the marketing of medical devices is tightly regulated, the cybersecurity culture remains very heterogeneous between medical device manufacturers. Overall, cybersecurity issues are still inadequately understood, little consideration is given to them during the medical device design and development process and they are little covered in regulations or specific recommendations.

Yet, if medical devices integrating software are more and more connected (wifi, radiofrequency, bluetooth, etc.), they will have to face new threats generated by technological advances, in particular computer malware.

After its expert committee has completed its work, the ANSM will propose recommendations aimed at medical device manufacturers so that they can take the necessary measures to prevent any malicious attacks on their medical devices and thus prevent data compromise and misuse.

Rapid diagnostic tests for streptococcal throat infections (RDTs): publication of practical information aimed at pharmacists (November)

In the context of the battle against antibiotic resistance, in November 2019, the ANSM published a report on rapid oropharyngeal tests to detect group A beta-haemolytic streptococcal throat infections. Available in pharmacies, these medical devices, and their characteristics, were listed in this report in order to enable pharmacists to make informed choices.

Tackling antibiotic resistance is a global public health challenge. It is directly related to the over-consumption and misuse of antibiotics. WHO considers it to be one of the most serious threats to world health.

As part of the interministerial road map to control antibiotic resistance launched in France in 2016, the use of rapid tests was encouraged, in particular for rapid diagnostic tests (RDTs) for throat infections, differentiating between viral and bacterial infections.
This test is able to detect group A beta-haemolytic streptococcal throat infections that may require antibiotic therapy. Most sore throats (around 80%) are viral and antibiotic treatment is pointless in these cases. The use of an RDT for throat infections therefore helps reduce unnecessary antibiotic therapy.

The report published by the ANSM presents an inventory of the devices available in France that comply with current regulations.

A study of the actual performance of these RDTs, particularly with respect to the analytical sensitivity of all the tests present in this inventory, will be performed by the end of the first quarter of 2020. This inventory will be supplemented by a report presenting the study protocol and the results.

Since January 2020 RDTs for throat infections have been reimbursed by the French national health insurance system if they are performed in the pharmacy setting.

Publication of guidelines for the management of medical device alarms in healthcare institutions (November)

In the context of its medical device vigilance activities, the ANSM receives a large number of reports of incidents or risks of incidents related to medical device alarm malfunctions. These reports mainly concern cardiorespiratory monitors, central monitors and intensive care ventilators. They report situations generating important risks that are sometimes life-threatening to patients.
Correct alarm management in the context of patient monitoring is the responsibility of healthcare professionals.

The ANSM's work, conducted in collaboration with experts, consisted of:

- an analysis of medical device vigilance data and, more specifically, reports of deaths related to alarm malfunctions, and the analysis of half-yearly periodic safety update reports transmitted by monitoring device manufacturers,
- a survey of 631 hospital departments in collaboration with the regional medical device vigilance network,
- a study of the standards-related and scientific literature and collection of information from manufacturers.

Analysis of signals concerning monitoring devices shows that a significant share of these cases are related to the conditions of use and not a technical failure of the device. Hence, ensuring that users understand how the alarms work, as well as the precautions to be taken, could reduce the number of incidents.

Following the recommendations made by the Afssaps in 2005 and the publication of studies and articles on the topic since then, on 28 November 2019, the ANSM published:

- an audit document relating to the management of the most important alarms,

- a training guide for alarm users,
- a guide for newly purchased devices.

These guides and annexes are aimed at providing operators with avenues for improving their alarm management, applicable to all medical devices and hospital departments requiring assistance, incorporating risks resulting from the development of alarm transferral and concentration solutions.

2019 DATA

Registration of medical devices	2015	2016	2017[1]	2018	2019
Class I medical devices	4,251	3,591	7,772	1,703	**4,316**
Class IIa, IIb, III medical devices and AIMDs	5,583	8,094	6,723	7,265	**9,734**
Custom-made medical devices	693	536	375	165	**371**
In vitro diagnostic medical devices	531	863	423	284	**609**

Quality control of medical devices	2015	2016	2017	2018	2019
Number of new standards	2	2	0	**0**	**1**
Number of certifications granted	25	12	14	**9**	**0**[2]
Number of non-conformities declared	1,335	1,176	726	**730**	**923**

[1] A high number of notifications - around 4,000 MDs - were received in 2017. In these notifications, all versions in the range were entered individually, contributing to a significant increase in the registration figures. Range versions are now registered together, counting for a single registration.
In 2018, the ANSM received and registered fewer notifications and the number of MDs per notification was lower.

[2] Since 21/02/2019, quality control bodies have no longer been accredited by the ANSM but nonetheless remain accredited.

Discipline	Operation	Month	Test controlled	Maximum number of laboratories / experts controlled per operation
DNA profiling	19IEG1	April	- IEGAS1, IEGAS2, IEGAS3, IEGAS4: DNA profile	**88**
Neonatal screening	19DNN1	May	- T191-T192: TSH - H191-H192: 17 OH-progesterone - P191-P192: Phenylalanine - M191-192: IR trypsin - D191-D192: Neonatal screening for sickle cell disease	**20**
Measurement of blood lead levels	19PLO1	July	- PLO-19-01, PLO-19-02, PLO-19-03, PLO-19-04, PLO-19-05: Blood lead levels	**25**
Screening for Trisomy 21	19T21	July	- 19TA-2T: MSM2T screening (AFP, hCG, hCGB, free estriol) - 19TB-1: MSM1T first-semester combined screening (PAPP-A, hCGB)	**88**
DNA profiling	19IEG2	October	- IEGAT1, IEGAT2, IEGAT3, IEGAT4: DNA profile	**94**

Control of advertising

Since 2011, the scope of application of advertising control has been extended to include medical devices and *in vitro* diagnostic medical devices. This is an additional tool to help manage their safe use.

The advertisement must present the MD/IVDMD in an objective manner, particularly in terms of performance or compliance with essential safety requirements, and promote its correct use. In addition, advertising aimed at the general public is prohibited for reimbursable class IIb and III MDs.

Prior control of advertisements applies for certain categories of medical devices (presenting a high risk to human health), the list of which is defined by a ministerial decree. Advertising for other MDs/IVDMDs is subject to *a posteriori* control, without systematic submission to the ANSM.

Find out more: https://www.ansm.sante.fr/Activites/Publicite-pour-des-dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Modalites-encadrant-la-publicite-pour-les-dispositifs-medicaux/(offset)/0

2019 DATA

Control of advertisements for medical devices and *in vitro* diagnostic medical devices	2015	2016	2017	2018	2019
Number of applications submitted	405	506	339	396	371
Of which rejected	63	49	26	43	0

Monitoring of other health products

Monitoring of cosmetic products

Cosmetic products are governed by a European regulatory framework stipulating the conditions for their marketing. They are marketed:

- under the responsibility of the manufacturer or its representative,
- without requiring prior authorisation,
- providing that they are safe for human health when used under normal or reasonably foreseeable conditions of use,
- with indication 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 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.

The 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.

Monitoring of cosmetic products is carried out by both the ANSM and the DGCCRF (French Department for Fair Trading, Consumer Affairs and Fraud Control).

The 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 the European authorities for use in the updating of European regulations. In collaboration with the French Ministry of Health, the ANSM 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 may be a health concern when they relate to substances that may be endocrine disruptors or CMR[1]-type substances.

Cosmetic product vigilance

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

The cosmetic product vigilance system 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 the ANSM and the application of corrective measures when necessary.

The ANSM also serves as a platform for liaison between the competent European authorities, manufacturers and end-users.

[1]Chemical substances that are carcinogenic, mutagenic or toxic to reproduction in humans.

Control of the cosmetics products market

The 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 the ANSES.

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

Find out more: https://www.ansm.sante.fr/Activites/Surveillance-du-marche-des-produits-cosmetiques/Surveillance-du-marche-des-produits-cosmetiques-les-metiers-de-l-ANSM/(offset)/0

Monitoring of tattooing products

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

The ANSM is responsible for monitoring adverse effects occurring with the use of these products and taking the necessary measures designed to better control their use and the substances they include in their composition. It coordinates its actions with the DGCCRF.

Find out more: https://www.ansm.sante.fr/Activites/Surveillance-du-marche-des-produits-de-tatouage/Surveillance-du-marche-des-produits-de-tatouage/(offset)/0

HIGHLIGHTS IN 2019

Non-rinse cosmetic products containing phenoxyethanol must not be used on the nappy area of children aged 3 years or under (December)

Phenoxyethanol is a preservative used in a variety of cosmetic products and, in particular, those used when changing babies. Various toxicological studies suggest toxicity causing systemic effects, such as haematotoxicity, as well as a potential toxicity of phenoxyethanol at high doses for reproduction and development in animals.

The ANSM has been monitoring and investigating this substance used as a preservative in cosmetic products for a number of years.
As a precaution, back in 2012 the ANSM recommended that this preservative not be used in cosmetic products intended for use on the nappy area of babies and that its maximum concentration be set at 0.4% for other products intended for use in children under 3 years of age.

The European Scientific Committee on Consumer Safety (SCCS), on the other hand, in its opinion of October 2016, considered that phenoxyethanol used at a concentration of 1% in cosmetic products is safe, regardless of age group.

Following this opinion, the ANSM continued its investigations and, at the end of 2017, it put together a temporary specialist scientific committee (CSST) composed of toxicology, epidemiology, expology, dermatology and allergology experts, tasked with assessing whether the 2012 recommendations should be maintained. The experts concluded that “the recommendation of 26 January 2012 for non-use of phenoxyethanol in cosmetic products intended for the nappy area” should be maintained. This committee also specified that it would be preferable to extend it to include wipes, which are very widely used to cleanse the nappy area of young children. In all other cosmetic products intended for children aged 3 years or under, the maximum phenoxyethanol concentration may remain at 1%".

On the basis of this opinion, the ANSM therefore took a precautionary health policy decision requiring responsible persons marketing “non-rinse” cosmetic products (excluding deodorants, hairstyling products and make-up) containing the preservative phenoxyethanol to make sure that it is stated on the labelling, at the latest 9 months from the date of publication of this decision, that they may not be used on the nappy area of children aged 3 years or under. For other products intended for children aged 3 years or under, the concentration of 1% phenoxyethanol is applicable, in accordance with the European regulations relative to cosmetic products.

Hence, non-rinse cosmetic products containing phenoxyethanol must no longer be used on the nappy area of children aged 3 years or under, since 20 December 2019. In order to protect the health of young children in view of the toxicity of this ingredient found in certain wipes, talc, liniments and lotions, the wording “do not use on the nappy area of children aged 3 years or under” has been compulsory on the labels of the products concerned since 20 December 2019.

Furthermore, in application of the Council of State decision of 4 December 2019, the ANSM’s recommendation of 26 January 2012 to no longer use phenoxyethanol in cosmetic products intended for the nappy area of children under 3 years of age and to limit its concentration to 0.4% in all other types of products intended for children aged under 3 years is no longer applicable.

On a national level, a petition requesting cancellation of the health policy decision is still in the process of being examined.

On a Community level, discussions with the Commission and the SCCS are under way in order to provide clarification and ensure mutual understanding of the rationales and the different scientific points involved in this case between the ANSM and the SCCS.

Cosmetic peel/Apiskin health policy decision (February)

Following a report and notification of an adverse reaction following the use of a cosmetic peel product containing trichloroacetic acid (TCA) purchased online, a health policy decision was taken by the ANSM on 25 February 2019 against the company ApY Skin Solution. This decision suspended the manufacturing and packaging, wholesale distribution and marketing, in return for payment or free of charge, holding for sale or distribution free of charge, advertising and use of certain skin peel and/or lightening products.

The ANSM is regularly consulted about skin peel products sold as cosmetics. Only peels designed to remove superficial dead skin without significantly impacting either the normal physiology of the epidermis or its barrier function may be given the status of cosmetic product. Cosmetic product regulations prohibit substances such as trichloroacetic acid and phenol, which cannot therefore be used as ingredients in cosmetic products.

The ANSM reiterates that a cosmetic product must be safe for human health when used under normal or reasonably foreseeable conditions of use and calls on consumers to be vigilant with respect to these cosmetic products, which may be illegal.

2019 DATA

- **228** cosmetic product reports processed by the ANSM (compared to 231 in 2018), nearly half of which were classified as serious.

Inspection to ensure compliance of the quality of practices and health products

The ANSM oversees the quality of the practices that culminate in the marketing and monitoring of health products by:

- helping to define enforceable regulatory frameworks (especially good practices and applicable standards),
- managing the corresponding sites (authorisations, accreditations, declarations, sanctions, etc.),
- ensuring that the enforceable regulatory provisions are implemented, via random on-site inspections or in the context of the annual inspection programme.

Inspections make it possible to establish a degree of confidence in the quality of the practices of the players involved (manufacturers, operators, importers, distributors, trial sponsors, investigators, etc.), who are responsible for these practices, as well as the quality and safety of the health products they put on the market, including their starting materials.

The purpose of these inspections is to:

- evaluate compliance with the good practices or standards that apply for a given activity or product or clinical or non-clinical trial,
- ensure the capacity to produce high-quality data and/or healthcare products,
- carry out technical investigations in response to a report,
- gather the necessary information for administrative actions (technical opinions, certificates, injunctions, health policy decisions relating to health products or activities that result in a risk).

The annual inspection programme is organised according to a risk-based approach, which combines:

- regulatory requirements,
- the intrinsic risk related to the activities conducted,
- the inspection history,
- reports received by the ANSM,
- internal or external referrals,
- campaigns relating to a specific topic,
- administrative action follow-up.

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

Find out more: https://www.ansm.sante.fr/Activites/Processus-d-inspection/Processus-et-rapports-d-inspection/(offset)/0

HIGHLIGHTS IN 2019

The ANSM bans an unauthorised clinical trial conducted in Parkinson's and Alzheimer's patients (September)

In June 2019, the ANSM was informed that patients had been approached by a fund called the "JOSEFA fund", claiming that a skin patch containing two substances said to be melatonin derivatives - valentonin and 6-methoxy-harmalan (6-MH) - was effective. This information indicated that a clinical trial had been set up using these transdermal patches claiming pharmacological actions to treat sleep disorders and neurodegenerative diseases, in particular Parkinson's and Alzheimer's diseases.

As part of its health safety missions, the ANSM carried out investigations that revealed that no human research study concerning these patches had been submitted to the ANSM.

On 28 June 2019, the ANSM referred the matter to the competent Public Prosecutor, in accordance with article 40 of the French code of criminal procedure, and transferred the investigation report relating the facts and providing all the information collected by the ANSM's services following this report.

In July 2019, additional data was transmitted to the ANSM and verified during an inspection, enabling collection of information concerning the implementation of an unauthorised human trial. The collaboration between the ANSM and the Aquitaine regional health agency (ARS) enabled more in-depth investigation, with the performance of a further inspection. This demonstrated that at least 350 people had been recruited by the "Josefa Fund" to take part in this trial aimed at testing transdermal patches containing substances presented as melatonin derivatives (valentonin and 6-methoxy-harmalan). Biological samples were then taken from the individuals recruited, in particular to measure concentrations of the substances contained in these patches.

Before it can be implemented, a clinical trial in humans needs to have been approved by an ethics committee and authorised by the ANSM (in accordance with article L. 1121-4 of the French Public Health Code). Since this approval and authorisation had not been sought by the "Josefa Fund", the ANSM took the decision on 19 September 2019 to ban the trial, in accordance with the health policy powers granted to it by the French Public Health Code.

This decision was accompanied by an information update to inform the individuals having been recruited for the trial. The latter were invited to rapidly consult their general practitioner to inform him/her about the situation, have a general health check-up and ensure they were receiving appropriate treatment for their disease. The ANSM also set up a toll-free number to answer questions from patients or their families. In the absence of any elements from the "Josefa Fund" confirming that patients had been informed that the clinical trial had been banned and that patients had stopped using the patches, on 27 September 2019 the ANSM took a second health policy decision, ordering the "Josefa Fund" to immediately cease all distribution, prescription, advertising and use of these patches.

The regulatory framework governing the implementation of human research is designed to protect individuals taking part in trials. In the absence of the ANSM's authorisation and the approval of an ethics committee, the safety of individuals cannot be guaranteed, which is what led the ANSM to make the administrative decisions aimed at stopping this unauthorised trial. The production of the patches has been totally halted and they may no longer be distributed.

Furthermore, non-compliance with the legal framework for human research is a criminal offence. Hence the ANSM has referred the matter to the courts for possible criminal proceedings. The case is currently being investigated by the judicial authorities.

European JAMS project

The European "Joint Action on Market Surveillance of medical devices" project (JAMS) helps to reinforce the medical device market surveillance system by improving coordination between European Union (EU) members. Jointly funded by partner member states and the European Commission, the project concerns the harmonisation of practices in the field of inspection and the development of clinical assessment training and coordination tools.

The ANSM has been particularly involved in the technical studies conducted since the start of the project in 2016, in particular as co-leader of the joint inspections of manufacturers working group. In the spring of 2019, the British authority (MHRA) withdrew from the JAMS project, for which it had been responsible for administrative and financial coordination. It was in this context that the ANSM decided to take over the role of coordinator in April 2019 in order to complete the project in collaboration with the other 17 participating member states.

The project was responsible for two major achievements:
the setting up of a group of inspectors on a European scale with a view to joint inspection of medical device manufacturers,

- the creation of an exchange platform between member states to promote real-time coordination with respect to emerging issues related to medical devices, in particular sensitive medical devices such as implants.

In December 2019, the ANSM organised the final conference for the JAMS project at the European Commission in Brussels, in the presence of the Union's 23 member states, the Commission (DG GROW, DG SANTE, CHAFEA), the French Ministry of health, patient and consumer associations, healthcare professional and industry representatives.

Management of pharmaceutical sites: the ANSM sets up a 'fast-track" process for innovative products and computerises procedures (October)

In order to simplify authorisation procedures for pharmaceutical sites manufacturing novel or innovative medicines in France, the ANSM has introduced a procedure designed to reduce the application examination period from 90 to 60 days. In addition, it made available on its website a portal for the computerised submission of administrative applications relative to the management of pharmaceutical sites and brokers.[1]

2019 DATA

- The ANSM conducted 660 inspections (677 in 2018), including:
  - **10%** random inspections,
  - **6%** inspections outside of France.

- The year was marked by a confirmation of the number of administrative decisions resulting from observations made during inspections:
  - **50** injunctions issued by the ANSM (65 in 2018), with 7.5% of inspections leading to this type of measure
  - **8** health policy decisions (5 in 2018),
  - **2** financial sanctions
  - **7** procedures sent to the public prosecutor

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
11	Rate of sensitive inspection follow-ups controlled	85%	100%	92%

[1] Also read "Computerisation of administrative procedures relative to pharmaceutical sites", page 126.

Inspection of clinical and non-clinical trials

Inspection of preclinical trials

The principles of Good Laboratory Practice (GLP) are the framework applied by all trial facilities in OECD member countries to ensure the quality and mutual acceptance of data from non-clinical safety studies.

The ANSM verifies the degree of GLP compliance of trial facilities responsible for conducting safety studies on medicines for human use, cosmetics, tattooing products, and, following referrals, medical devices.

Inspection of clinical trials

The ANSM inspects sites where clinical trials are conducted, as well as the sponsors of these studies or their subcontractors (CROs). These inspections concern the safety and rights of the individuals participating in the trials and verification of the quality and credibility of the data obtained.

Medicinal product trials are conducted within the framework of Good Clinical Practice guidelines.

HIGHLIGHTS IN 2019

ANSM GLP inspection audit (March)

The ANSM GLP inspection audit was performed from 11 to 15 March 2019. This 10-year audit gives international recognition to the ANSM's preclinical inspections. It was conducted by auditors from three OECD member countries.

No **non-conformities were identified by the OECD auditors and the Agency's mastery of Good Laboratory Practice and the quality of its inspections were highlighted.**

In March 2020, the results of this audit were presented to the OECD's GLP working group, made up of all member countries (36 countries, 50 authorities), in order to **validate compliance of the ANSM GLP inspection with the organisation's guidelines** and, consequently, confirm the international value of the results of the Agency's GLP inspections.

2019 DATA

- **30** preclinical trial inspections conducted by the ANSM in France and internationally (i.e., 4% of the total number of inspections).
- **33** clinical trial inspections conducted by the ANSM in France and internationally (i.e., 5% of the total number of inspections).

Inspection of medicinal products and their starting materials

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

The inspection of pharmaceutical sites makes it possible to verify their compliance with good manufacturing practice (GMP), good wholesale distribution practice (GDP) for medicinal products, as well as compliance with good pharmacovigilance practice (GVP).

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

The aim of these inspections is to verify the site's compliance with GMP and GDP.

HIGHLIGHTS IN 2019

Computerisation of administrative procedures relative to pharmaceutical sites (October)

All administrative applications relative to pharmaceutical sites (opening, closure, technical variations, administrative changes, etc.) were previously submitted to the ANSM by the responsible pharmacist in paper format.

The ANSM undertook a project to computerise these procedures, opting for exclusively online submissions: “Simplified procedures”.

The various applications are now sent to the ANSM exclusively via online submission of a dossier via a dedicated platform. It includes online data entry and submission of supporting documents in PDF format. An acknowledgement of receipt is sent electronically following the submission.

Submission templates are also available to site operators so they can prepare their application before logging on to the platform. These submission templates summarise all the information and the supporting documents to be supplied with the application.

Via this “Simplified procedures” application, the ANSM can:

- manage and assess applications submitted to the Agency by applicants,
- exchange with applicants via a dedicated messaging system,
- process the application, ruling on its outcome: accepted, dropped or rejected,

This platform was put in place on 1 October 2019 for a transition period of 3 months. Since 1 January, all applications have been submitted via the “Simplified procedures” platform only. Applications are no longer accepted in paper format.

2019 DATA

- **930** pharmaceutical sites recorded by the ANSM in France, including:[1]
  - 426 manufacturers and/or importers
  - 271 operators
  - 408 wholesale distributors

- **740** pharmaceutical starting material manufacturing, distribution, and import sites recorded by the ANSM in France.

[1] Some sites with several statuses.

- **227** medicinal product-related inspections conducted by the ANSM in France and internationally (i.e., **34%** of the total number of inspections).

- **105** pharmaceutical starting material-related inspections conducted by the ANSM in France and internationally (i.e., **16%** of the total number of inspections).

Inspection of starting material operators

	2015	2016	2017	2018	2019
On-site inspections	87	96	98	110	**105**
• of which in France	70	81	81	90	**84**
• of which outside of France	17	15	17	20	**21**
Injunctions	3	2	3	3	**7**
Health policy decisions or GMP non-conformity notices	5	2	0	2	**1**
Dossiers passed on to the judicial authorities	0	0	0	0	**0**

Pharmaceutical site inspection
(operators, manufacturers, importers and distributors)

	2015	2016	2017	2018	2019
On-site inspections	201	209	231	238	**227**
• of which in France	186	191	211	227	**213**
• of which outside of France	15	18	20	11	**14**
Injunctions	10	19	19	24	**19**
Health policy decisions/suspensions	6	4	1	1	**2**
Dossiers passed on to the judicial authorities	2	5	4	1	**1**

Administrative management of sites

	2015	2016	2017	2018	2019
Pharmaceutical sites					
Operating licences	56	59	48	43	**57**
Closure decisions	72	70	60	44	**43**
Variation authorisations	-	-	-	110	**130**
Certificates of compliance with GMP for medicinal products issued following inspection	168	267	288	197	**228**
"Starting material" sites					
Certificates of compliance with GMP for pharmaceutical starting materials issued following inspection	93	61	111	79	**65**

Inspection of pharmacovigilance systems

	2015	2016	2017	2018	2019
On-site inspections	7	27	29	**27**	**32**
• of which in France	7	27	29	**27**	**31**
• of which outside of France	0	0	0	**0**	**1**
Injunctions	3	5	0	**3**	**3**
Dossiers passed on to the judicial authorities	0	0	0	**0**	**0**

Inspection of blood products and other biological products

The preparation, import, and storage of products derived from the human body (blood products, tissue, cells, 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.

Breast milk for therapeutic use

Since September 2005, the ANSM has been the competent authority in charge of breast milk collected and treated by breast milk banks and prescribed by a doctor as a healthcare product to care for very premature infants.

The ANSM oversees the technical appraisal of breast milk bank operating authorisation applications, which are issued by regional health agencies. It also carries out inspections aimed at assessing compliance with good practice guidelines.

The authorisation scheme for microorganisms and toxins

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, inter-site transfer, import and export of certain agents responsible for infectious diseases, pathogenic microorganisms and toxins (MOTs) require authorisation by the ANSM. Authorisations are granted once the biological safety and security risks have been evaluated.

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

The ANSM also monitors licensed representatives who are authorised to store and handle MOTs, and collects administrative reports and notifications of any events that could potentially result in the spread of MOTs.

HIGHLIGHTS IN 2019

Lifting of the injunction against LFB (November)

Following the injunction announced in January 2017 requiring LFB Biomédicaments to bring into line some of its industrial practices with respect to Good Manufacturing Practice (GMP) and marketing authorisation applications, in January 2018, the ANSM carried out a follow-up inspection that was the subject of a new injunction.

On 19 November 2019, the ANSM lifted the injunction that it had announced in May 2018 against the pharmaceutical group LFB, since the latest inspections had established its regulatory compliance.

As part of its missions, the ANSM carries out additional monitoring of the manufacture of medicinal products derived from human blood and ensures they are available to patients. These are medicinal products that are particularly complex to manufacture and are of major therapeutic value, for which few alternatives exist.

LFB Biomédicaments is one of the main operators producing medicinal products derived from human blood marketed in France. It is regularly inspected by the ANSM.

During inspections in November 2016 and January 2018, some significant non-conformities with respect to the current regulations were observed. These led the ANSM to issue a first injunction in January 2017, which was replaced by a second one in May 2018.

During this period, supply of the French market for medicinal products derived from human blood was secured and continued. In fact, medicinal products derived from human blood are subject to a "dual release" process, which means that they may only be put on the market following the approval of both the manufacturer's responsible pharmacist and an official medicines control laboratory (OMCL). For LFB, the ANSM is the OMCL. This procedure ensures that, even in the event of an injunction, the quality and safety of medicinal products can be guaranteed, for the benefit of patients.

The most recent follow-up inspections demonstrated that LFB's pharmaceutical sites had been brought back into line with the regulations and therefore made it possible to lift the injunction in November 2019.

The ANSM will verify that the corrective measures put in place by LFB are maintained. It will also continue its regular follow-up of stocks of medicinal products derived from human blood in order to guarantee optimal cover of patients' needs.

In addition

- **Breast milk treated by breast milk banks: launch of studies to update the regulations (June)**
  In liaison with the Ministry of Health and the Directorate General of Health Care Provision (DGOS), the ANSM has launched studies to update the regulations concerning breast milk banks. To this end, a temporary scientific committee was created to re-examine microbiological control methods applied to pasteurised breast milk.

- **Launch of studies to update the regulations concerning microorganisms and toxins (February)**
  In liaison with the Ministry of Health and the French Department of Defence and National Security (SGDSN), the ANSM has launched studies to update the regulations concerning microorganisms and toxins (MOTs). To this end, the ANSM will firstly convene an independent expert committee to re-examine the list of MOTs posing risks to public health.

2019 DATA

- 70 blood products and other biological products-related inspections conducted by the ANSM in France and internationally (i.e., around 10% of the total number of inspections).

Inspection of blood products and other biological products	2015	2016	2017	2018	2019
Inspections of cell therapy units and tissue banks	22	37	28	26	**24**
Inspections of labile blood products	38	26	17	27	**32**
Inspections of breast milk banks	16	15	7	10	**14**
Injunctions	1	5	5	6	**2**
Health policy decisions/suspensions	1	0	0	2	**0**

Management of sites producing and distributing labile blood products	2015	2016	2017	2018	2019
Authorisations and renewals	2	0	3	13	**0**
Variations	32	30	36	50	**42**
Closures	0	0	0	0	**0**

Monitoring of breast milk banks	2015	2016	2017	2018	2019
Number of dossiers examined	1	26	3	3	**2**

Microorganisms and toxins	2015	2016	2017	2018	2019
Examination of authorisation applications					
Total number of MOT authorisations granted during the year	1,236	662[1]	827	1,069	**983**
Number of applications received to hold MOTs (excluding temporary storage for inter-laboratory operations)	43	41	44	50	**50**
Authorisation suspensions	0	0	0	0	**0**
Health policy decisions	1	0	0	0	**0**
Laboratories and sites					
Number of sites	ND	110	109	112	**103**
Number of MOT authorisation holders (excluding temporary storage for inter-laboratory operations)	161	152	146	129	**120**
Total number of inspections performed per year	28	32	30	33	**30**
Number of dossiers forwarded to the judicial authorities (excluding consignments)	2	1	1	0	**1**

Inspection of OTC sites	2019
On-site inspections	**24**
• of which tissue banks	**12**
• of which cell therapy	**12**
Injunctions	**1**
Dossiers passed on to the judicial authorities	**0**

Administrative management of healthcare institutions, EFS (non EP), associations, private bodies (MTIpp, MTI ex, TC)	2015	2016	2017	2018	2019
Pharmaceutical sites					
Operating licences	9	31	37	5	**4**
Closure decisions	5	2	6	0	**4**
Variation authorisations	19	24	66	110	**118**

1The granting of multiple authorisations (allowing several operations) was made routine practice in 2016, notably for MOT transfers (sales/transfers, imports, exports).

Inspection of medical devices and in vitro diagnostic medical devices

The ANSM inspects the various stakeholders involved in the medical device and *in vitro* diagnostic medical device sector: notified bodies, manufacturers, agents and distributors, to ensure they comply with the applicable regulatory requirements. There are approximately 3,500 of these companies in France.

Given the very large number of products and sites, an annual or multi-year themed inspection campaign schedule is defined. In 2019, it concerned high-risk class I MDs, software considered to be MDs and class IIb and III MDs for which the manufacturer operates in France.

HIGHLIGHTS IN 2019

Signature of a cooperation protocol between the ANSM and the DGCCRF (February)

The Agency has been cooperating for a number of years with the French Department for Fair Trading, Consumer Affairs and Fraud Control (DGCCRF), these two bodies having jurisdiction over patient safety and consumer protection.

A cooperation protocol governs the numerous exchanges between the ANSM and the DGCCRF, in particular concerning medical devices and *in vitro* diagnostic medical devices, but also cosmetic products, essential oils, herbal medicines, non-corrective contact lenses and tattooing products. The protocol also concerns the qualification of products presented as nutritional supplements. This collaboration is hinged around the complementarity of the two bodies' actions in several fields: survey, inspection, control, product analysis, adverse event reports, product qualification and health policy measures against operators involved in the manufacturing and supply chain for healthcare products, cosmetics and tattooing products.

The consultation work carried out 2019 culminated in an updated protocol signed on 14 February 2020 by the two Directors General.

2019 DATA

- 111 inspections related to MDs, medical device vigilance, and IVDMDs were performed in France and internationally, i.e., 17% of the total number of inspections.
- In addition to inspecting industrial operators, the ANSM also oversees and monitors the notified body in France: 4 inspections of GMED (medical certification body) were conducted in 2019. ANSM inspectors participated in the joint evaluation of another European notified body.
- Publication of the "Synopsis of the dental implant campaign" (14/11/2019).

Inspection of manufacturers

	2015	2016	2017	2018	2019
Medical devices (excluding medical device vigilance)					
Inspections	77	79	79	73	**78**
• of which in France	63	68	69	64	**76**
• of which outside of France	14	11	10	9	**2**
Injunctions	7	9	9	8	**6**
Health policy decisions	7	2	4	3	**4**
Dossiers passed on to the judicial authorities	0	1	0	0	**4**
***In vitro* diagnostic medical devices**					
Inspections	39	44	33	19	**26**
• of which in France	37	44	32	18	**26**
• of which outside of France	2	0	1	1	**0**
Injunctions	7	8	7	3	**5**
Health policy decisions	3	0	0	0	**0**
Dossiers passed on to the judicial authorities	2	0	0	0	**0**

Inspection of medical device vigilance systems

	2015	2016	2017	2018	2019
On-site inspections	15	17	20	14	**7**
• of which in France	12	17	19	13	**7**
• of which outside of France	3	0	1	1	**0**
Injunctions	3	2	0	2	**1**
Dossiers passed on to the judicial authorities	0	0	0	0	**0**

Inspection of cosmetic products

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

The ANSM inspects cosmetic product manufacturers and responsible persons in charge of marketing these products in order to verify compliance:

- of documents supporting marketing of these products (product information file),
- of product manufacturing, distribution, import and export practices with European cosmetics regulations.

Given the very large number of products and sites, an annual or multi-year themed inspection campaign schedule is defined. In 2019, it concerned compliance of cosmetic products with Good Manufacturing Practice (GMP).

In the field of cosmetic products, the ANSM works alongside the DGCCRF in the context of a cooperation protocol.

2019 DATA

- 22 medicinal product-related inspections conducted by the ANSM in France and internationally (i.e., 3.5% of the total number of inspections).

Inspection of cosmetic product sites

	2015	2016	2017	2018	2019
Inspections	32	36	26	32	**22**
Injunctions	9	8	9	16	**5**
Health policy decisions	1	1	1	0	**1**
Dossiers passed on to the judicial authorities	0	1	0	0	**0**

Quality control of healthcare products in the laboratory

Laboratory control conducted by ANSM teams provides an independent technical and scientific expert assessment of the quality of healthcare products and their safety of use.

The controls are conducted in a national or coordinated European context. They concern all healthcare products.

The objective of these controls is to:

- confirm the quality of products,
- prevent batches of imperfect quality being released onto the market,
- detect quality defects and undertake corrective or preventive actions,
- contribute to the handling of public health alerts,
- detect falsified healthcare products.

The results of controls are used for numerous purposes: release of vaccine and blood-derived medicine batches before marketing,[1] market surveillance in a scheduled context or for "urgent" requests that may result from various inputs (within or outside the ANSM), marketing authorisation decision-making aid, corrective or preventive actions, review of applications, health policy decisions, etc.

In addition, the ANSM plays a major role within the European network of official medicines control laboratories (OMCLs) led by the EDQM.

Find out more: https://www.ansm.sante.fr/Activites/Controle-en-laboratoire/Le-controle-des-produits-de-sante-en-laboratoire/(offset)/0

HIGHLIGHTS IN 2019

Evaluation of the risk of the presence of nitrosamine impurities in chemical medicinal products

In June 2018, the genotoxic impurities NDMA & NDEA belonging to the nitrosamine group of chemicals were detected in medicinal products containing valsartan. A European evaluation of all drugs belonging to the sartan class presenting a risk of nitrosamine formation was then performed by triggering a referral procedure for this class of medicines. In July 2019, the presence of nitrosamines was identified in medicinal products containing ranitidine, and once again a European re-evaluation of the risk-benefit ratio was conducted via the referral procedure.

In September 2019, considering that a multitude of referral procedures might therefore be triggered, the European Medicines Agency (EMA) and the national competent authorities (NCA) coordinated via the CMDh, anticipated this, asking all marketing authorisation (MA) holders to conduct a risk assessment related to the presence of nitrosamines as a precautionary measure. This process was begun at the end of 2019 and is likely to last at least 4 months.

In parallel, the EMA made a self-referral by triggering Article 5(3) in order to draw up guidelines relative to the detection of nitrosamines, risk assessment and minimisation of their impact aimed at holders and competent authorities in collaboration with various scientific committees and stakeholders. These guidelines are expected to be published in 2020.
This European procedure concerns all chemical or chemically synthesised medicines with an MA in Europe. In France, this procedure will affect 13,000 MAs and around 565 MA holders.

At the ANSM, assessment of the nitrosamines 5(3) guidelines is mobilising a team composed of representatives on European committees (CHMP, PRAC, CMDh) and internal and external experts in

[1] Also read "Release of batches of vaccines and blood-derived medicinal products", page 170.

pharmaceutical quality, epidemiology and genotoxicology, as well as the implementation of an internal unit within the ANSM's control laboratory department. On an international level, the ANSM participated in meetings with stakeholders such as LEEM/GEEM/AFIPA and international players, including the FDA, Health Canada and Swiss Medic. An ANSM web page and a dedicated web platform have been created. The results of the different analysis phases are to be submitted by French MA holders on this platform. The deadline for the submission of the results of the 1st phase of this process - assessment of the risk of contamination during synthesis and manufacture of the medicinal product - has been postponed until 1 October 2020 following site closures related to the COVID crisis.

2019 DATA

Laboratory controls

	Starting materials and chemical medicinal products / plants	Starting materials, medicinal products and biological products	Other healthcare products	Total
January	38	252	0	**290**
February	16	520	103	**639**
March	38	249	0	**287**
April	104	389	4	**497**
May	13	249	0	**262**
June	16	309	3	**328**
July	45	331	0	**376**
August	31	184	1	**216**
September	60	284	0	**344**
October	42	424	0	**466**
November	44	267	0	**311**
December	20	311	40	**371**
TOTAL	467	3,769	151	**4,387**

Analytical certificates

Comparison of cumulative data for 2018 vs 2019 (all certificates combined)

	Cumulative total for analytical certificates in 2018	Cumulative total for analytical certificates in 2019
January	329	290
February	656	929
March	1,001	1,216
April	1,299	1,713
May	1,561	1,975
June	1,904	2,303
July	2,281	2,679
August	2,650	2,895
September	2,963	3,239
October	3,441	3,705
November	3,820	4,016
December	4,225	4,387

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	100%

Quality control of medicinal products and biological products

Laboratory controls conducted in the context of market surveillance for medicines and biological products take two forms: scheduled surveys, which are based on a prior risk analysis, and controls that are performed urgently.

Scheduled surveys

Prior risk analyses are conducted using a tool developed by the European network of 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 surveys concern both medicines authorised on a European level (in which case the results are shared between European countries) and medicines only authorised in France.
The samples come directly from pharmaceutical companies at the request of the ANSM or are taken by ANSM inspectors at the premises of a finished product or starting material manufacturer (in France or outside France).

Urgent controls

Urgent controls are conducted in response to a suspected quality defect reported via inspections, referrals from judicial authorities or reports by healthcare professionals or users.

HIGHLIGHTS IN 2019

Renewal of Pharmacopoeia experts

The European Pharmacopoeia Commission renewed its experts in November 2019.

The experts are appointed to a European Pharmacopoeia working group or expert group by the European Pharmacopoeia Commission following submission of their applications by the French Pharmacopoeia Authority (NPA = National Pharmacopoeia Authority).
Experts may be ANSM employees or external to the ANSM.

The expert contributes to the work of the group to which he/she belongs, including, if applicable, via the production of experimental results, technical verification and validation of control methods, with a view to drafting, revising or deleting a monograph or other general text in the Pharmacopoeia.

The role of group chair is different: he/she is a member of the Pharmacopoeia Commission and works closely with the scientific secretary of his/her working group at the EDQM. The group chair ensures that any comments received following publication in Pharmeuropa are taken into account where they are relevant. The reasons for their rejection must be clearly formulated. He/she ensures the good scientific level of the monographs, the impartiality of the comments and compliance with the Pharmacopoeia's editorial rules. His/her role is described in the European Pharmacopoeia technical guides published by the EDQM.

Following the process to renew the mandates of European experts in European Pharmacopoeia groups (EDQM), France is well represented:

- 58 experts appointed to 60 European groups (5 as chair),
- including 18 experts from the ANSM (2 chairs), 8 university or academic experts, 2 experts from the ANSES and 30 industrial experts.

In addition

- The ANSM was involved in numerous collaborative studies on a European and international level (with WHO):
  - Strong participation in the chemical CAP and generic CAP programmes, with control of the generic series for capecitabine, and inhalers (20 CAP products in total),
  - Participation in the mutual or decentralised products exchange programme (93 products controlled),
  - Participation in the collaborative study organised by WHO, which enabled the introduction of the first international reference standard for Adalimumab.
  - Performance of the first tests in the study of etanercept biosimilars (project leader: ANSM Control department).

- Concerning biological products, in the context of market surveillance of CAP products organised by the EDQM, participation in the control of four products: Elocta, Obizur, Praluent and Tecentriq.

- In the context of national market surveillance, finalising of control of three monoclonal antibodies: Adcetris, Blyncyto and Darzalex.

- The Pharmacopoeia and the ANSM participated in the studies on the use of therapeutic cannabis in France.[1] Firstly, it presented the Pharmacopoeia requirements with respect to the quality of cannabis and its preparations. This presentation took place in the context of the temporary specialist scientific committee (CSST) aimed at evaluating the relevance and feasibility of making therapeutic cannabis available in France. On the same occasion, it also presented the work under way at the European Pharmacopoeia concerning the cannabis flower monograph.
  Then the Pharmacopoeia participated in the development of the “Products” specifications concerning the medicinal products that will be used during the medical cannabis trial in France. This work was the subject of a specific temporary scientific committee (CST) and the specifications were unanimously adopted on 8 January 2020.

[1] Also read “Decision to implement an experiment with medical cannabis”, page 18.

2019 DATA

In 2019, the total non-conformity rate detected with chemical medicinal products was around 6% for controls conducted as part of the scheduled programme (including those related to the wording on the labelling) and also 6% for controls conducted urgently. Appropriate follow-up is systematically initiated for every non-conformity detected.

Laboratory controls in a European context

	European centralised procedure medicinal products	Of which controls conducted for the EDQM	European decentralised or mutual recognition procedure medicinal products	Controls conducted urgently	Total
Chemical medicinal products	28	20	93	0	**121**

Detection of non-conformities

	Controls conducted in a scheduled context	Controls conducted urgently
Chemical medicinal products	21/346[1]	2/33
Chemical starting materials	3/77	0/17

Pharmacopoeia

	2015	2016	2017	2018	2019
Monograph studies for the French Pharmacopoeia	28	64	45	44	**65**
Monograph studies for the European Pharmacopoeia	554	402	601[2]	648	**498**

[1] 5 of which linked with labelling
[2] This number includes not only monographs studied in the context of Pharmeuropa surveys, but also those studied before being submitted to the European Commission for approval (data not included in previous years).

Laboratory control campaigns for medical devices

Laboratory controls on medical devices are conducted as part of targeted surveys requested by ANSM departments (Inspection department and Product departments) or when there is a suspected quality defect (especially following an inspection).

HIGHLIGHTS IN 2019

Initiation of collaboration with the LMGC

In the context of reinforcement of monitoring of medical devices (MDs), a collaboration was initiated with a joint research unit (*Laboratoire de Mécanique et Génie Civil* (Mechanical and Civil Engineering Laboratory), Montpellier, LMGC) in order to expand the analytical capacities of the ANSM's Control department, in particular for mechanical and functionality testing.

The diversity of the medical devices on the market is such that control methods are extremely varied. Nonetheless, numerous devices, due to their nature and function, require mechanical methods (such as tensile strength, mechanism trigger level, wear, abrasion, etc.) for their control. The LMGC has both the technical capacities (apparatus) and the skills to perform this type of control.
During 2019, the first conclusive tests were conducted on IUDs and self-dosing pens. Furthermore, an audit was performed to ensure compliance with the required quality framework. It should also be noted that this collaboration may concern medicinal products (case of pens or patches, for example).

This project also has a European dimension, with the need to have an official medicines control laboratory (OMCL) specialised in this type of technique having been expressed within the European network of OMCLs.

Hence, from 2020 several surveys concerning MDs will be launched (as well as concerning medicinal products) following an appropriate risk analysis.

This collaboration should make it possible to significantly extend the ANSM's analytical arsenal, particularly for mechanical tests applied to MDs, and, consequently, to contribute more generally to reinforcing the monitoring of these healthcare products.

2019 DATA

Laboratory controls on medical devices

	2015	2016	2017	2018	2019
Medical devices controlled	80	61	116	**51**	**40**
Non-conformities detected	3	0	0	**10**	**2**

FACILITATING ACCESS TO INNOVATION AND DEVELOPMENT

Joint interview

Elodie Chapel (Authorisation and Innovation Policies Department (DPAI)) and Gaëlle Guyader (Oncology and Haematology Unit (ONCOH))

What impact has the new objectives and performance contract (COP) had on your activities in 2019?

E.C.: It has led to the *Ouverture*[1] project being made one of the Agency's priorities for the coming years, creating a reciprocal commitment between the Agency and its supervisory bodies, as well as with user associations and healthcare professionals.
More specifically, in the area of innovation, this has helped us speed up the implementation of the innovation service.
Finally, this COP confirms our intentions to step up the ANSM's participation in scientific opinions and clinical trials, which are major tools for the development of innovative products, on both a European and national level.

G.G.: The objective of opening up to stakeholders has effectively changed the way we work and the way we approach dossiers. This focus has reinforced and structured the collegial nature of our exchanges with our key contacts: doctors, pharmacists, patients and patient associations.
The new COP, which is a natural follow-on from our previous strategy, further consolidates our actions, in terms of modernisation and innovation in particular. Concretely, for a "product" department such as ours, its objectives are translated into reality every day via the earlier and more secure access to innovative medicines to treat patients with serious and/or rare diseases.

In what way is "facilitating access to innovation" one of the cornerstones of Agency life?

G.G.: Innovation is a major public health challenge and is one of the greatest expectations of our various stakeholders and, in particular, the patients who stand to benefit from it.
It is one of the Agency's main missions and the one that demands the greatest responsiveness as well as the greatest vigilance. This balance is in our DNA and also implies a proactive vision aligned with national systems on the one hand and competitiveness and European strategy on the other.

E.C.: Globally, creating a momentum hinged around innovation helps develop and root the risk management culture in our practices and make the patient's interests the central concern of teams when they are examining dossiers. More broadly, innovation is also the capacity to take risks - always measured - because we believe in medical and scientific progress. We believe in having a positive vision of the future, in not looking inward and being stuck in our ways.

What does "early access to innovation" bring to patients nationally and to public health more broadly?

G.G.: Early access means enabling patients for whom all therapeutic options have been exhausted to receive appropriate, safe and effective treatment, following rigorous and proportionate scientific assessment. This translates into very short (infra-regulatory) timeframes for the authorisation of clinical trials, the fluidity and flexibility of the invaluable mechanisms represented by named-patient and cohort temporary authorisations for use (ATUs), and also our mobilisation and the contribution of France within the European landscape. Our solid presence at all the different stages of a drug's life cycle and our capacity to anticipate are crucial, the ultimate goal being to serve patients. Our in-depth and cutting-edge knowledge of medicinal products in the development pipeline and of scientific advances is essential in order to be able to offer treatments within a secure framework well ahead of their future marketing.

[1] That is the name of the Agency's development project aimed at creating an even more outward-looking organisation, in order to more effectively integrate its various publics, professionals and users in its activities.

E.C.: This has a strong patient impact: providing access to treatments for patients with few or no alternatives. An effective authorisation system, of which the Agency is part, also makes it possible to have strong national research, both public and private. And research is one of the markers of French medical excellence. Enabling research to flourish throughout France creates the conditions for an ecosystem in which the very best practitioners want to remain in the country to carry out their projects. This gives it a second major interest in terms of public health.
Finally, for the Agency, it is chance to see dossiers concerning innovative healthcare products at the earliest possible stage and hence to express its safety and quality requirements as soon as possible.

Among the activities/dossiers that you have handled in 2019, which stand out most for you, either because of the workload involved, their new or unexpected nature, or their repercussions for the Agency's work?

E.C.: Without doubt the *Ouverture* project, but it's still too soon to draw conclusions! Because it affects the way we operate at the Agency and has enabled us to work all together to reflect on the major themes for our future: the risk management culture, cross-functionality and a collegiate approach to dossiers, in particular. Also the project to evolve ethics committees that we are working on with the Ministry of the Health and ethics committee representatives. This is an important project because ethics committees are essential and key partners when it comes to ensuring a successful transition to a European scale for clinical trials.

G.G.: One example is the number of "indication extension"[1] cohort temporary authorisation for use projects that have been evaluated, and the speed at which this was done, representing an opportunity in terms of innovation implemented following the work of the CSIS.[2] One of the highlights was the first indication extension cohort ATU for the treatment of advanced ovarian cancer, which was granted whenever the regulatory texts were applied, with immediate access to the product for these patients with a serious disease who had not responded to previous therapies and for whom all existing treatment options had been exhausted.
With respect to this aspect, it is important to highlight the major contribution of the CPOH (permanent scientific committee for oncology/haematology) and its experts, whose commitment and skills made it possible to examine a large number of applications in optimal conditions and with very short timeframes, for the benefit of patients.

In your view, which of the approaches launched in 2019 will be most important for the Agency's future? And why?

E.C.: The *Ouverture* project and, more broadly, our capacity to project a positive vision of ourselves in the future, as an Agency that regulates, of course, but also one that creates: science, value for patients, links with healthcare professionals and associations.

G.G.: The fundamental trio: the transparency of our work, which is a guarantee of confidence and trust, our outward-looking approach, which represents an avenue for dialogue and sharing, and innovation, which is the basis for fairness of treatment and management. All these approaches place the Agency on a trajectory of modernisation and performance, the ultimate goal being to serve and ensure the safety of the users of our healthcare system.

[1] i.e., for a medicinal product that already has an MA in a different indication.
[2] CSIS: *Conseil Stratégique des Industries de Santé* (French Strategic Council for the Healthcare Industries).

Early access to healthcare products

Scientific opinions

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

The purpose of the ANSM's scientific opinions is to facilitate rapid access for patients to products that are innovative, represent a major therapeutic advance or address an unmet medical need, especially with respect to rare diseases or paediatric developments. This access is free.

Find out more: https://www.ansm.sante.fr/L-ANSM/Avis-scientifique-de-medicament/Avis-scientifique-de-medicament/(offset)/0

HIGHLIGHTS IN 2019

Inclusion of the ANSM in the STARS consortium (February)

In 2019, the ANSM mobilised to support access to innovation for patients and reinforce academic research. Hence, for example, the ANSM joined the European Commission's STARS (Strengthening Training of Academia in Regulatory Sciences and supporting regulatory scientific advice) consortium in order to develop medical research in France.

This European project aims to prepare and advise academics with respect to medical research regulations. The goal is to facilitate the successful completion of academic research and ensure easier access to marketing authorisations for medicinal products.
The STARS consortium brings together 19 European Union countries and promotes the development of regulatory science on a European level, including research studies on practices, the promotion of training for academic partners and concerted actions designed to support innovation.

The consortium began its work with a survey of all member states to evaluate the level of regulatory knowledge of academics. The survey was coordinated by the ANSM in France. The survey response rate was particularly high in France, demonstrating a high level of regulatory knowledge in the country. The survey also demonstrated a need for regulatory and scientific support on the part of academic sponsors.

On a European level, the consortium will coordinate work between the national authorities, European institutions and the academic research community for a period of 3 years. The work will now involve the development of a joint strategy aimed at reinforcing knowledge of regulatory requirements via training and support actions.

On a national level, the ANSM is continuing to work with both academic and industrial sponsors to more effectively incorporate regulatory imperatives into the construction of research projects, facilitate the development of innovative new products and boost the number of clinical studies successfully completed.

2019 DATA

National scientific opinions issued for medicinal products

	2015	2016	2017	2018	2019
National opinions	8	9	17	8	**11**

Of the 11 national opinions issued by the ANSM:

- **3** opinions concerned advanced therapy medicinal products (gene therapy or cell therapy),
- **7** opinions concerned rare diseases in the field of paediatrics,
- **4** opinions concerned major therapeutic advances

European scientific opinions issued for medicinal products

	2015	2016	2017	2018	2019
European opinions issued by the EMA	510	578	630	634	**674**
Of which opinions coordinated by the ANSM	66	76	57	79	**76**
	12.9%	13.2%	9%	12.4%	**11.3%**

Of the 76 European opinions in which the ANSM participated:

- **41** opinions concerned the oncology/haematology field
- **11** opinions concerned rare genetic diseases
- **13** opinions concerned ophthalmology
- out of all the opinions, **13** opinions concerned paediatrics.

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	Target 2019	Attained
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	84[1]
16	Growth rate in the number of applications treated by the health innovation service	-	Creation of the Innovation Service at the ANSM	75% of the action plan attained

[1] Higher than the number of European scientific opinions issued (76) due to withdrawal or postponement until 2020 of certain opinions attributed in 2019.

Clinical trials

The ANSM is the competent authority to authorise clinical trials in France. Irrespective of the health product concerned, the ANSM's evaluation of clinical trial authorisation applications covers the safety and quality of the products used during the clinical trial, as well as the safety of the individuals taking part in these studies.

The Agency also inspects certain clinical trial sites. These inspections mainly concern the trial implementation practices, including the protection of patients taking part, and verification of the robustness of the data produced as a result of these trials.

Find out more: https://www.ansm.sante.fr/Activites/Essais-cliniques/Recherches-impliquant-la-personne-humaine-RIPH/(offset)/0

HIGHLIGHTS IN 2019

The ANSM reduces all clinical trial processing times

As part of the 8th French Strategic Council for the Healthcare Industries (CSIS), the ANSM has initiated a resolutely active process to speed up access to innovation for patients. The various mechanisms include two fast track processes implemented at the end of 2018 (Fast Track 1 and Fast Track 2) for clinical trial authorisations for innovative medicines.
In February 2019, in view of the success of this system in terms of very efficient timeframes, the ANSM expanded its scope to include trials with a complex design and on advanced therapy medicinal products. In addition to the success of the Fast-Track procedure, which was therefore extended in October, 2019 also saw an overall reduction in processing times.

Application of the European regulation regarding medical devices: the ANSM introduces a pilot phase for the clinical investigations part (September)

Application of EU Regulation 2017/745 (for the clinical investigation part) requires new working methods for the competent authorities and Ethics Committees of member states. It is scheduled to come into force on 26 May 2021. To prepare for application of the European regulation provisions, in September 2019 the ANSM introduced a pilot phase, in liaison with the stakeholders concerned (academic and industrial sponsors, Ethics Committees, CNRIPH (French National Commission for human research), Ministry of Health).
This pilot phase concerns the initial application for authorisation for clinical investigations (CI) relating to medical devices meeting the following criteria, irrespective of sponsor:

- MD types concerned: class III devices or classes IIa or IIb implantable or invasive devices,
- MD statuses concerned: without CE mark or with CE mark and use in the CI non-compliant with their intended use,
- all therapeutic areas are concerned.

6 applications were submitted in accordance with these conditions between September and December 2019 (i.e., 50% of eligible dossiers).

Clinical trials, all medicinal products

	2017	2018	2019
Number of applications submitted	838	940	**938**
Number of authorisations	741	830	**813**
Number of refusals	4	19	**12**
Including early-phase clinical trials			
Number of applications submitted	36	144	**145**
Number of authorisations	NA[1]	125	**124**
Number of refusals	NA	11	**8**
Including clinical trials on advanced therapy medicinal products (ATMPs)			
Number of applications submitted	30	40	**40**
Number of authorisations	14	36	**26**
Number of refusals	0	0	**0**

13 clinical trials authorised for “organs, tissues, cell preparations” trials and one trial refused

The assessment timeframes were particularly efficient in 2019 and well below the regulatory timeframes, as the ANSM had undertaken:

- Average time for Fast-Tracks (excluding ATMPs): 29 days
- Average time for all medicinal product trials: 51 days
  - Trials authorised in one round: 29 days
  - Trials subject to an interim letter: 55 days

Clinical trials on "non-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.

	2017	2018	2019
Number of applications submitted	217	240	**203**
Number of authorisations	165	201	**168**
Number of refusals	0	1	**1**

The average assessment times were also very good for these trials in 2019:

- Trials authorised in one round: 30 days
- Trials subject to an interim letter: 40 days

Clinical trials on medical devices and in vitro diagnostic medical devices

These are primarily subject to authorisation by the ANSM when they concern medical devices that do not yet have the CE mark or medical devices that already have this mark but are being used in a new indication. They may also concern clinical trials that require investigations involving a not insignificant risk. The number of applications submitted includes both applications for clinical investigation authorisation for MDs/IVDMDs and MD/IVDMD opinions issued in the context of clinical trials on medicinal products.

[1] Not applicable: creation of the early trials unit in December 2017.

	2017	2018	2019
Number of applications submitted	216	190	**177**[1]
Number of authorisations	97	93	**99**
Number of refusals	2	2	**9**
MD/IVDMD favourable opinions in clinical trials on medicinal products	12	10	**20**
MD/IVDMD unfavourable opinions in clinical trials on medicinal products	0	0	**3**

The average assessment times were also very good for these trials in 2019: 46.2 days.

99 clinical trial authorisations for medical devices issued, including 6 for IVDMDs

- 57% are industrial sponsors
- 43% are institutional sponsors

Breakdown of medical device clinical trials by therapeutic area

Therapeutic area	%
Cardiology	17
Dermatology	10
Anaesthesia/Resuscitation	1.5
Orthopaedics	6.8
Ophthalmology	7.8
Others	11.8
Imaging/Diagnostics	3.3
Gastroenterology	5
Oncology	5.5
Endocrinology/Diabetology	3.4
Neurology	10.6
Gynaecology	6.2
ENT	2.3
Pulmonology	2.7
Urology/Nephrology	4
Hepatology	1.6
Neurosurgery	0.5
Not stated	0

[1]N.B.: There was no fall in clinical trial applications. However, given the entry into force of the Jardé law on human research at the end of 2016, several submissions did not fall within the scope of the clinical trials handled by the Agency.
The requalification rate fell: 2017: 28.8%, 2018: 22.3% and 2019: 12.2%,

Clinical trial substantial amendment authorisation applications

SUBSTANTIAL AMENDMENT APPLICATIONS FOR TRIALS, ALL MEDICINAL PRODUCTS	2017	2018	2019
Number of applications submitted	2,682	3,022	**3,863**
Number of applications granted	2,632	2,885	**3,700**
Number of applications refused	2	6	**13**

21 substantial amendment applications authorised for “organs, tissues, cell preparations”

The average processing time is: 25 days

- Trials authorised in one round: 21 days
- Trials subject to an interim letter: 45 days

SUBSTANTIAL AMENDMENTS FOR TRIALS ON "NON-HEALTH PRODUCTS"	2017	2018	2019
Number of applications submitted	681	495	**384**
Number of applications granted	636	475	**371**
Number of applications refused	0	5	**2**

The average processing time is:

- Trials authorised in one round: 15 days
- Trials subject to an interim letter: 26 days

SUBSTANTIAL AMENDMENTS FOR TRIALS ON MDs and IVDMDs	2017	2018	2019
Number of applications submitted	222	161	**188**
Number of applications granted	217	169	**184**
Number of applications refused	0	1	**0**

The average processing time is: 22 days

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
14a	Difference between the management times and the regulatory timeframes for clinical trial authorisations [MED, Non-health products, MDs]	-	≥ 15 days	Average: 14.4 days
14b	Difference between the management times and the regulatory timeframes for clinical trial authorisations [ATMPs]	-	≥ 70 days	Average: 43.4 days
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	0%	50%	100%

Temporary authorisations of use

A temporary authorisation for use (ATU) is an exceptional, special early-access procedure, which, since 1994, has given numerous patients for whom there is no available alternative treatment access to medicines in indications that are not authorised in France.

ATUs are granted by the ANSM in the following conditions:

- the medicinal products are intended for the diagnosis, prevention or treatment of rare or serious conditions,
- there are no other appropriate treatments available on the market,
- their efficacy and safety of use are assumed on the basis of the available scientific data and the implementation of treatment cannot be delayed.

They may be named-patient temporary authorisations for use (ATUn), i.e., granted for a specific named patient, or concern a group of patients (cohort temporary authorisation for use, ATUc).

Find out more: https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Qu-est-ce-qu-une-autorisation-temporaire-d-utilisation/(offset)/0

HIGHLIGHTS IN 2019

Implementation of a teleservice: e-Saturne (March)

The e-Saturne web application was launched nationally in March 2019 with the objective of replacing "paper" ATUn requests - previously mostly handwritten and sent by fax - with a fully computerised process.

The ANSM developed and produced a web application aimed at healthcare professionals to enable computerisation at source and in a structured format of named-patient temporary authorisation for use requests. The requests are initiated by hospital prescribers and relayed by internal hospital pharmacists, who transmit them to the ANSM via a secure environment. If the request meets the granting criteria published in the ATUn reference framework, a favourable opinion is granted in real time. If the request does not comply with the granting criteria, it follows a specific assessment circuit. Following evaluation by the ANSM department in charge of the product, the named-patient temporary authorisation for use unit issues the decision in the form of an electronic document that can be downloaded by the applicant.

The launch of the application has been a great success. Healthcare professionals increasingly adopted the new system up until December 2019. The scheduled discontinuation of faxed applications took place as scheduled on 31/12/2019 and all ATUn requests are now submitted via this application.

Amendment of the regulations: possibility of granting extension ATUs

Following the amendment of the regulations concerning temporary authorisations for use introduced by the 2019 French Social Security budget act, it is now possible to grant "indication extension" temporary authorisations for use. These ATUs enable early access to innovative medicines that already have an MA but in a new indication in the process of being authorised or to come.

Over the course of 2019, the ANSM granted 6 indication extension ATUs, primarily in the oncology/haematology field.

In addition

- **Breast cancer: the ANSM authorises access to two innovative new treatments (August)**
  The ANSM has granted two cohort temporary authorisations for use for two medicinal products: Atezolizumab in the treatment of triple-negative breast cancer and Trastuzumabemtansine in the adjuvant treatment of patients with HER2-positive breast cancer who have residual invasive disease.

- **The ANSM grants an indication extension cohort ATU for the use of Tecentriq (atezolizumab) in small cell lung cancer (May)**
  The ANSM granted a cohort ATU to the proprietary medicinal product Tecentriq (1200 mg) concentrate for solution for infusion in the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), in combination with carboplatin and etoposide.

- **Indication extension cohort ATU for the use of Lynparza 100 mg and 150 mg tablets (olaparib) in certain gynaecological cancers (March)**
  The ANSM granted the first cohort ATU for a medicinal product that already has an MA in a different indication. Thanks to this first specific cohort temporary authorisation for use, some patients with advanced ovarian cancer will be able to benefit from maintenance therapy with Lynparza (olaparib) following first-line platinum-based chemotherapy.

2019 DATA

Summary of named-patient ATUs

	2015	2016	2017	2018	2019
Named-patient ATUs granted	24,791	27,095	22,295	21,633	**26,528**
Medicinal products (or active substances) made available per year	219	205	253	217	**227**
Patients included	17,829 including 12,175 treatment initiations	19,625 including 14,029 treatment initiations	16,621 including 11,390 treatment initiations	15,987 including 11,342 treatment initiations	**NA**[1]

Summary of cohort ATUs

	2015	2016	2017	2018	2019
New cohort ATUs	13	10	11	20	**20**
Medicinal products under cohort ATUs having obtained an MA	12	9	8	16	**14**
Newly included patients	10,216	11,909	8,250	5,642	**3,766**

[1] Year the ATUn unit was created, data not available

Proprietary medicinal products that were granted a cohort ATU in 2019

20 cohort ATUs granted in 2019 (19 different active substances), the great majority in the haematology and oncology field.

PROPRIETARY MEDICINAL PRODUCT	Active substance
Libtayo 350 mg concentrate for solution for infusion	Cemiplimab
Alpelisib 50 mg film-coated tablets Alpelisib 200 mg film-coated tablets	Alpelisib
Atezolizumab 840 mg concentrate for solution for infusion	Atezolizumab
Leukotac 1 mg/ml concentrate for solution for infusion	Inolimomab
Kadcyla 160 mg powder for concentrate for solution for infusion	Trastuzumabemtansine
Larotrectinib 25 mg hard capsules Larotrectinib 100 mg hard capsules Larotrectinib 20 mg/ml oral solution	Larotrectinib
Lynparza 100 mg film-coated tablets Lynparza 150 mg film-coated tablets	Olaparib
Polatuzumab Vedotin 140 mg powder for concentrate for solution for infusion	Polatuzumabvedotin
Sarclisa 20 mg/ml concentrate for solution for infusion	Isatuximab
Tecentriq 1,200 mg concentrate for solution for infusion	Atezolizumab
Xtandi 40 mg film-coated tablets	Enzalutamide
Osilodrostat 1 mg film-coated tablets Osilodrostat 5 mg film-coated tablets Osilodrostat 10 mg film-coated tablets	Osildrostat
Gilteritinib 40 mg film-coated tablets	Gilteritinib
Waylivra 285 mg solution for injection in pre-filled syringe	Volanesorsen
Esketamine Janssen 28 mg nasal spray, solution	Esketamine
Sunosi 75 mg and 150 mg film-coated tablets	Solriamfetol hydrochloride
Dupixent 200 mg and 300 mg solution for injection in pre-filled syringe	Dupilumab
Trogarzo 200 mg concentrate for solution for infusion	Ibalizumab

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
15	Rate of cohort ATU requests constituting an indication extension	30%	60%	30%

Temporary recommendations for use

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

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

RTUs last for a period of three years. They can be renewed and are accompanied by patient monitoring implemented by the pharmaceutical companies.

Since the programme was created, the ANSM has granted 28 RTUs.

Find out more: https://www.ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/(offset)/0

HIGHLIGHTS IN 2019

2 RTUs were granted in 2019:

- **Berinert 500 IU powder and solvent for solution for injection** in the salvage therapy of episodes of antibody-mediated rejection refractory to standard treatment in heart, kidney or lung transplant patients who cannot take part in clinical trial NCT03221842, and in combination with standard intravenous immunoglobulin (IgIV) therapy and plasma exchange.

- **Xalkori 200 mg and 250 mg capsules** in the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with a c-MET exon 14 mutation, following at least one line of double-platinum therapy combined or otherwise with chemotherapy.

Marketing authorisation of medicinal products

Marketing authorisation and registration applications for medicinal products

There are four marketing authorisation procedures for medicinal products: three European procedures and one national procedure.

On a European level:

- **The centralised procedure** is compulsory for advanced therapy medicinal products, medicinal products derived from biotechnologies, innovative medicinal products containing a new active substance and for which the therapeutic indication is the treatment of certain diseases (AIDS, cancer, neurodegenerative disease, diabetes, auto-immune diseases and viral diseases), as well as for orphan medicinal products indicated in the treatment of rare diseases. For other diseases, it remains optional.
  This procedure may also be considered if the medicinal product presents a major benefit for European Union patients.
  After the procedure, the MA is issued by the European Commission for all member states.

- **The decentralised procedure** applies to medicinal products that are not yet authorised in the European Union and that are destined for 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 already granted in one of the member states of the European Union, known as the "reference state" by other member states designated by the pharmaceutical company holding the MA.

- At the end of the European phase of these last two procedures (decentralised and mutual recognition), the competent national authorities then grant the MAs in their national language along with their annexes (summary of product characteristics, annex II, package leaflet and labelling).

On a national level:

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

The ANSM thus issues MAs for medicines authorised under the national procedure and medicines authorised under European decentralised and mutual recognition procedures. The decisions also specify the prescribing and dispensing conditions for the medicine, which are specific to each country.

In addition, the ANSM also issues registration decisions: these are simplified authorisation procedures that may apply to certain herbal and homeopathic medicines in accordance with specific conditions.[1]

Once an MA or registration has been granted, they may be the subject of variations, which need to be authorised before they can be implemented.

The different variation categories are:

- Minor type-IA variation: a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned,

[1] Also read "Herbal medicines" page 167 and "Homeopathic medicines", page 169.

- Minor type-IB variation: a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension,
- Major type-II variation: a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned,
- MA extensions,
- Urgent safety restrictions for safety reasons: any interim change to the terms of a marketing authorisation due to new information having a bearing on the safe use of the medicinal product.

Finally, the marketing authorisation or registration is granted for an initial duration of 5 years. It may then be renewed for an unlimited period, unless the Commission decides, on justified grounds relating to pharmacovigilance, to proceed with one additional 5-year renewal.

Find out more: https://www.ansm.sante.fr/Activites/Autorisations-de-Mise-sur-le-Marche-AMM/L-AMM-et-le-parcours-du-medicament/(offset)/0

HIGHLIGHTS IN 2019

Acceleration of the processing of marketing authorisations

The ANSM has put in place a new process for the treatment of MA applications designed to streamline their processing in liaison with applicants and reduce the timeframes previously involved. In particular, the aim is to align national MA calendars with those for decentralised MAs, with the same clock-stop times.

The new process has been applied to new national MA applications since 1 October 2019.

It has also resulted in faster processing of several hundreds of national MA applications already submitted in the first half of 2019 as part of the ANSM's undertaking at the 8th French Strategic Council for the Healthcare Industries (CSIS). Over this period, 95% of the 357 MA applications concerned resulted in a decision issued by the ANSM.

Assessment of centralised procedures by multinational teams

Centralised procedure MA applications are coordinated by the EMA and assessed by national competent authority (NCA) assessors. Each month, based on notifications of application submissions announced to the EMA by pharmaceutical companies for the coming months, the NCAs apply to be the CHMP rapporteur or co-rapporteur. The NCAs then propose a preliminary assessment team made up of quality, non-clinical and clinical specialists. A centralised MA assessment team is generally composed of 5 to 8 members.

Since 2015, the EMA has allowed assessment teams to be made up of assessors from different NCAs. Consequently, a centralised MA application will have its quality part reviewed by assessors from one NCA, while the non-clinical and clinical parts will be examined by assessors from another NCA. However, only one of the NCAs will be the official (co-)rapporteur to the EMA (lead NCA), with the other acting as a service provider (participating NCA). Both NCAs will be paid by the EMA on a prorata basis for their involvement in the expert assessment of the application.

In 2019, 24 centralised MA procedures were proposed in multinational teams, i.e., around 15% of all procedures. Between 2015 and July 2019, the ANSM assessed 13 procedures in this context, 10 as lead NCA. It is one of the member state authorities most frequently implementing a multinational team assessment procedure, with Germany (22 of which 10 as participating NCA), Austria (16; 3), Sweden (14; 11), the Netherlands (14; 4), Ireland (13; 6), Norway (13; 9) and Portugal (13; 9).

Multinational team assessments offer the advantage of maintaining the active participation of the ANSM in procedures of medical and scientific interest that are priorities for the Agency while offering flexibility in terms of the expert assessments being conducted at the same time as part of the Agency's other activities (clinical trials, safety procedures, etc.). A second advantage is the consolidation of interactions between teams from different NCAs, enabling increased consideration of the European context and the sharing of practices. The trade-off is an increase in the complexity of procedure management, involving multiple milestones, multiple stakeholders, contractualisation of the distribution of responsibilities and remuneration, which require rigorous management of procedures.

The EMA continues to support multinational assessments and has extended them to post-MA procedures.

Marketing authorisations

1,016 marketing authorisations and registration granted by the ANSM in 2019 (national procedure and European decentralised and mutual recognition procedures) versus 1,256 in 2018.

CENTRALISED PROCEDURES	2015	2016	2017	2018	2019
Number of MA applications submitted	111	114	90	84	**117**
Number of MAs[1] granted	94	82	92	85	**66**
Number of MA applications refused	4	0	11	5	**4**
Number of applications assigned to France (rapporteur, co-rapporteur)	9	14	10	14	**19**

MUTUAL RECOGNITION PROCEDURES	2015	2016	2017	2018	2019
Number of MA applications submitted	ND	ND	495	159	**78**
Number of MAs granted	40	32	44	64	**77**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	3	7	2	1	**0**

DECENTRALISED PROCEDURES	2015	2016	2017	2018	2019
Number of MA applications submitted	ND	ND	638	552	**546**
Number of MAs granted	298	295	607	789	**404**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	21	9	30	33	**21**

NATIONAL PROCEDURES	2015	2016	2017	2018	2019
Number of MA applications submitted	ND	ND	183	145	**154**
Number of MAs granted	168	239	303	343	**265**
Number of MA applications refused	31	6	5	15	**20**
Number of herbal medicine registration applications submitted	ND	ND	0	0	**1**
Number of herbal medicine registrations granted	8	10	30	5	**16**
Number of herbal medicine registration applications refused	0	0	0	0	**0**
Number of homeopathic medicine registration applications submitted	ND	ND	32	5	**16**
Number of homeopathic medicine registrations granted	23	58	61	55	**254**
Number of homeopathic medicine registration applications refused	1	0	1	1	**1**

[1] Data expressed in number of medicinal products

MA variations[1]

MUTUAL RECOGNITION PROCEDURES (France as reference member state)	2015	2016	2017	2018	2019
Number of type IA applications submitted	ND	ND	220	207	**278**
Number of type IA applications granted	ND	ND	214	192	**248**
Number of type IA applications refused	ND	ND	2	4	**3**
Number of type IB applications submitted	ND	ND	194	226	**200**
Number of type IB applications granted	ND	ND	185	205	**131**
Number of type IB applications refused	ND	ND	0	5	**2**
Number of type II applications submitted	ND	ND	91	70	**97**
Number of type II applications granted	ND	ND	87	55	**41**
Number of type II applications refused	ND	ND	0	2	**0**

NATIONAL PROCEDURES	2015	2016	2017	2018	2019
Number of type IA applications submitted	ND	ND	2,326	2,745	**3,427**
Number of type IA applications granted	ND	ND	2,076	2,609	**3,232**
Number of type IA applications refused	ND	ND	32	89	**121**
Number of type IB applications submitted	ND	ND	1,478	2,522	**2,305**
Number of type IB applications granted	ND	ND	1,424	2,417	**2,165**
Number of type IB applications refused	ND	ND	35	63	**38**
Number of type II applications submitted	ND	ND	781	850	**739**
Number of type II applications granted	ND	ND	433[2]	706	**465**
Number of type II applications refused	ND	ND	43	104	**39**

Average processing times:[3]

- for national type IA applications: 18 days
- for national type IB applications: 26 days
- for national type II applications: 84 days

The average times for notification of national decisions for MA variations resulting from European procedures (MRP/DCP) are: 18 days.

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	50%	100%	63%
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infra-regulatory timeframes	90%	100%	91%

[1] Abandoned applications are not counted.
[2] Applications processed as part of the ad hoc MA update mechanism (MA update) are not counted.
[3] The times are calculated between confirmation of an application deemed to comply (D0) and notification of a decision.

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 via the centralised procedure.

The role of the ANSM on a national level

Since 2005, France has implemented three rare diseases plans. These plans play a key role for the stimulation, development and marketing of medicines for rare diseases in France, particularly in terms of promoting early access to medicines, research and innovation.
The third plan, which was launched in July 2018, covers the period between 2018 and 2024.
The ANSM is involved in this last plan via participation in the reflection processes relative to priorities 4 and 5, aimed, respectively, at promoting access to treatments in rare diseases and driving the momentum of research in the field of rare diseases.

The role of the ANSM on a European level

The ANSM participates in the EMA's Paediatric Committee (PDCO), which includes representatives from each European Union member state, as well as physician and patient associations. This committee is responsible for coordinating activities relative to paediatric medicines within the EMA. It assesses and follows up Paediatric Investigation Plan dossiers (PIPs), as well as other paediatric issues, including European scientific opinions.

Paediatric Investigation Plans

The ANSM plays an important role in the assessment of PIPs, which detail the therapeutic need, the resulting partial or complete development waivers, including clinical and preclinical development strategy, with the paediatric formulation, depending on the ages of the children and adolescents.

PIPs have been compulsory since the European Paediatric Regulation came into force in 2007. They must be submitted prior to any new MA or MA extension application, irrespective of procedure type, except in the event of PIP waivers (determined on the basis of indication) and deferrals of certain clinical trials granted by the PDCO, before submission of a marketing authorisation application for a medicinal product in Europe.

Participation in European working groups

The ANSM 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".

It also takes part in working groups associated with the PDCO and the EMA that focus on neurology, paediatric oncology and neonatology. It helps draft the general recommendations and scientific opinions on a European level, relative to paediatrics, as well as scientific or regulatory recommendations, required for the development of paediatric medicines.

Find out more: https://www.ansm.sante.fr/Activites/Medicaments-en-pediatrie/Medicaments-en-pediatrie/(offset)/0

Paediatric medicines

France was the rapporteur or co-rapporteur for 88 PIPs and their variations, including 32 new applications (+60% compared to 2018). The involvement of France increased significantly in 2019 following the United Kingdom's withdrawal from the EU. In Europe, France is 4th in terms of evaluating PIP developments. This confirms a national determination to make paediatrics a public health priority.

	2015	2016	2017	2018	2019
Number of Paediatric Investigation Plan (PIP) applications for which France was the rapporteur or peer-reviewer	55	64	61	70	**88**
Percentage relative to the total number of PIPs	6.3%	6.5%	5.6%	6.1%	**7.3%**

Orphan medicinal products

Five orphan medicines were authorised, i.e., 5% of the medicines authorised as part of the European centralised procedure.

	2015	2016	2017	2018	2019
MAs granted for orphan medicinal products out of the total number of MAs granted via the centralised procedure	15/93	14/114	14/92	22/164	**5/111**

Generic medicines

A generic medicine is created using the same drug substance as a medicine that has already been authorised (referred to as the "originator") for which the 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 in order to demonstrate the same therapeutic efficacy.

It can differ in some respects as compared to the reference medicine, 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.

Marketing generic medicines

A generic medicine is governed by the same rules as the “original” medicine: same procedures for obtaining a marketing authorisation (national or European MAs), same requirements in terms of quality, reproducibility from one batch to another, stability of physicochemical characteristics, etc.

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

Generic and reference medicines are subject to the same prescribing and dispensing rules and monitoring conditions.

The list of generic medicines is available in a "directory” of generic groups. This is updated monthly, taking into account new marketing authorisations granted and variations made to medicinal products already listed.
https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Le-repertoire-des-generiques/(offset)/5

Generic medicines and bioequivalence inspections

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

Generic medicines and laboratory control

The purpose of laboratory control is to verify the purity of the active ingredient, the quality of the finished product and compliance with specifications until expiry. The Agency has organised annual generic medicine testing in its laboratories since 1999.

This programme is also conducted on a 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).

The ANSM is also involved in the European programme, developed by the EMA in collaboration with the EDQM, concerning the control of generics with a centralised MA. Since 2013, two drugs have been controlled each year in accordance with a joint protocol. The ANSM contributes regularly, as both a scientific advisor and a product controller.

Find out more: https://www.ansm.sante.fr/Dossiers/Medicaments-generiques/Qu-est-ce-qu-un-medicament-generique/(offset)/0

HIGHLIGHTS IN 2019

- **Management of ongoing new MA applications in the context of CSIS[1] recommendations**
- **Evaluation of the risk of the presence of nitrosamine impurities in chemical medicinal products[2]**

[1] See “Acceleration of the processing of marketing authorisations”, page 157.
[2] See “Evaluation of the risk of the presence of nitrosamine impurities in chemical medicinal products”, page 134.

2019 DATA

SUMMARY OF GENERIC MEDICINE AUTHORISATIONS	2015	2016	2017	2018	2019
MAs granted for generic medicines	339	406	803	932	**539**
Number of generic groups included in the directory	1,077	1,130	1,232	1,333	**1,432**

SCHEDULED CONTROLS	2019 summary	
	Batches controlled	**% Non-conformities detected**
Non-generic medicines	158*	5, i.e., 3%
Generic medicines	155	11, i.e., 7% (+3% labelling)
Generic starting materials*	74	3, i.e., 4%

*+ 33 Hospital preparations (0 non-conformities)

In 2019, the average non-conformity rate was 7% for generics and 5 % for all medicines controlled in 2019 (excluding labelling).

All these non-conformities are followed up by the ANSM in liaison with the pharmaceutical companies concerned.

MAIN GENERIC GROUPS CONTROLLED IN 2019
Aripiprazole
Bisoprolol
Brinzolamide
Busulfan
Capecitabine
Captopril/HTZ
Dexpanthenol
Dutasteride
Entecavir
Epirubicin
Eplerenone
Valganciclovir

Biosimilar medicines

A biosimilar medicine is similar to a "reference" biological medicinal product that has already obtained a marketing authorisation. Any biological medicinal product for which the patent has fallen into the public domain may be copied. This copy is called a biosimilar. Since biosimilar products cannot be strictly identical to the reference product, they cannot be used in the same way as generics of chemical medicinal products.

Marketing and monitoring biosimilar medicines

The MA is granted on the basis of quality and safety data, as well as 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 request of the health authorities and in accordance with recommendations tailored to each medicine. This system must include the same measures as for the reference biological medicine, as well as monitoring of the immunological profile of the biosimilar product.

In principle, biosimilar medicines are authorised to treat the same diseases as the reference medicine. If a clinical similarity between a reference biological product and a biosimilar product can be demonstrated in an indication considered to be representative, the efficacy and safety data can potentially be extrapolated to other indications approved for the reference biological product under certain conditions. However, a biosimilar medicine can have fewer indications than the reference medicine, usually due to a lack of conclusive 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.

Interchangeability of biosimilar medicines

Although prescribers are free to choose between two biological medicines in the absence of an identified prior treatment, it is nonetheless preferable not to change the original prescription by replacing one medicine with another, for reasons of safety and traceability, which are not guaranteed. Nevertheless, in view of new knowledge and the continuous analysis of safety and efficacy data relative to biosimilar medicines within the European Union, it may be possible to envisage replacing a medicine 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 appropriate clinical monitoring during treatment,
- the traceability of the products concerned must be guaranteed.

As for any medicine, it is necessary to ensure constant traceability of products and medicine batches in order to guarantee their follow-up. This concept is particularly important for biological products due to their greater variability. It is therefore crucial that different products with the same international non-proprietary name or containing the same active substance be easily identifiable in order to detect and evaluate any safety or immunogenicity problems potentially associated with the product.

Monitoring

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

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 12 years.

List of biosimilar medicines

The list of biosimilar medicines authorised in Europe is published on the ANSM's website.[1] This list makes it possible to clearly match the dose and pharmaceutical form of a reference biological product to a corresponding biosimilar medicine, if applicable (or the reverse).

The medicines included on this list are categorised by similar biological group. These groups are themselves organised by active substance. For each medicine, the reference list indicates its name and, for all the information regarding its presentations, dose, pharmaceutical form, the name of the marketing authorisation holder, the name of the company or organisation operating the medicine (if not the MA holder), as well as its therapeutic indications and dosage, provides a link to the data contained in the public medicines database, including, in particular, the medicine's SmPC and package leaflet.

Find out more: https://www.ansm.sante.fr/Activites/Medicaments-biosimilaires/Les-medicaments-biosimilaires/(offset)/0#dm

HIGHLIGHTS IN 2019

Four new biosimilar medicines were authorised in the EU in 2019. A total of 55 are now available.

Medicinal products authorised in the EU are not necessarily marketed in every member state. In the EU, the biosimilars market cannot be compared to the generics market because, unlike the latter, biosimilar products cannot be substituted at present. These products are, on average, 20 to 30% less expensive than the reference products but currently only account for a minority of prescriptions including all the reference medicines. However, there has been a significant growth in biosimilar sales in the past ten years. The penetration rate of biosimilars naturally remains dependent on the products, the indications and the various alternatives available to patients and prescribers.

[1] Also read the list of “Biosimilar products authorised in Europe (December 2019)”, Appendix 5, page 214.

Herbal medicines

A herbal medicine is a medicine for which the active substance is composed exclusively of one or more herbal substances, a plant-based preparation or a combination of several herbal substances or plant-based preparations.[1]
It may take the form of a pharmaceutical product, a pharmaceutical preparation (pharmacy-compounded or pharmacy-prepared) or a herbal drug substance.

The ANSM has been publishing a list of groups of generic herbal medicine groups since 2017. These groups concern seven herbal active substances: ginkgo, ispaghul, common ivy, St. John's Wort, saw palmetto, Alexandrian senna, and the common grape vine and are included in the directory of generic groups published on the ANSM website (annex II).

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

Find out more: https://www.ansm.sante.fr/Activites/Medicaments-a-base-de-plantes/Les-medicaments-a-base-de-plantes/(offset)/0#dm

Medicine preparations

The French Public Health Code defines three categories of medicine preparations: hospital preparations, pharmacy-compounded preparations and pharmacy-prepared preparations. Unlike proprietary medicinal products, these preparations are not subject to authorisation by the ANSM, which is responsible for ensuring their regulation and safety.

For hospital preparations, the ANSM manages an e-filing database for these preparations created by pharmacies for internal use and pharmaceutical sites authorised to manufacture medicinal products. In particular, this database allows the ANSM to monitor the status of activities in France or study alternatives in the event of stock shortages of marketed proprietary medicinal products.

The ANSM also monitors and helps answer the technical and regulatory questions of the various stakeholders (regional health agencies, hospital pharmacies, pharmaceutical sites, healthcare professionals, patient associations, etc.).

Find out more: https://www.ansm.sante.fr/Activites/Preparations-hospitalieres-magistrales-et-officinales/Preparations-hospitalieres-magistrales-et-officinales/(offset)/0

[1] Also read “Marketing authorisation and registration applications for medicinal products”, page 155.

HIGHLIGHTS IN 2019

Good preparation practices (GPP) for medicinal products for retail pharmacies and hospital pharmacies: continuation of revision work and public consultation

A revision of the 2007 edition of GPP for medicinal products for retail pharmacies and hospital pharmacies is in progress. The work is being carried out within a temporary specialist scientific committee tasked with performing a scientific expert assessment. The committee met nine times in 2019 and its members' mandate was renewed in November 2019 to enable revision of the good practices to be finalised.

All the revised chapters aimed at retail pharmacies and hospital pharmacies, as well as guidelines on the preparation of sterile medicines, were published on the ANSM's website in July 2019 for the purpose of public consultation. Numerous contributions were received, demonstrating the high level of interest among the profession for guidelines of this type. The contributions will be examined and the last guidelines finalised in 2020.

Parenteral nutrition: implementation of stability studies on standardised paediatric formulas

In liaison with a neonatal intensive care working group from the Ministry of Solidarity and Health tasked with defining standardised paediatric parenteral nutrition formulas, the ANSM conducted stability studies on a dozen formulas. These studies will enable them to be listed in the national formulary of the French Pharmacopoeia in order to harmonise practices.
The ANSM is thus improving access to hospital preparations destined for children, particularly in the field of neonatal care, guaranteeing their safe use.

In addition

- **Mitomycin C (October–December).** Support for hospital pharmacies following a total stock-out of medicinal products used to make ophthalmological preparations (glaucoma surgery and cancer of the eyeball).[1]

- **Faecal microbiota transplants (September)**. An inventory of pharmacy-compounded preparations and hospital preparations was conducted, identifying the hospital pharmacies making this type of preparation in France, their practices and the controls performed before they are dispensed.

[1] Also read "Mitomycin C: the imported medicine should be reserved for priority indications", page 82.

Homeopathic medicines

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

There are two authorisation procedures:[1]

- a marketing authorisation procedure that concerns medicines for which an indication, a dosage, a target population, a duration of treatment and method of administration are claimed,
- a specific registration procedure for medicines that meet the following conditions: oral or external administration, lack of a specific therapeutic indication on the label or in any of the product information and a degree of dilution that guarantees the medicine's safety.

Furthermore, all homeopathic medicines with authorisations granted prior to 18 January 1994 (i.e., 1,163 stocks) are currently being reassessed by the ANSM.
The re-evaluation focuses more specifically on aspects related to safety and quality based on an assessment of the risks related to the composition of the starting material included in each stock. The non-clinical assessment makes it possible to estimate the safety of the stock by defining a suitable dilution level that does not pose a risk to human health. Recognition of the homeopathic tradition must also be justified. After the evaluation, a registration decision or marketing authorisation is granted based on the requirements of the current regulations.

Once the validation process is complete, the medicines have a specific label and package leaflet aimed at reinforcing patient safety and information.

As they are granted, the ANSM publishes the following:

- marketing authorisations for homoeopathic medicines,
- registration decisions.

Registration decisions may include, for each homeopathic stock, all the authorised dilutions and the various pharmaceutical forms authorised (granules, granules in a single-dose container, tablets, oral solutions in an ampoule, oral drop solutions, ointments and oral powder).

These authorisations (registrations and MAs) can be consulted in the directory of pharmaceutical products or the public medicines database on the ANSM website.

[1] Also read "Marketing authorisation and registration applications for medicinal products", page 155.

Release of batches of vaccines and blood-derived medicinal products

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

This system requires control of 100% of vaccine and blood-derived medicinal product batches before they are marketed. Batches released by an independent national authority in this way may circulate freely within the European area.

This release, conducted by the 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 medicinal product 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 the member states and avoids unnecessary duplication of tests.

Find out more: https://www.ansm.sante.fr/Activites/Liberation-de-lots-et-de-vaccins/Liberation-de-lots-de-vaccins-et-de-medicaments/(offset)/0

HIGHLIGHTS IN 2019

France is the leading country in terms of the release of vaccine doses in Europe

For several years, France has been one of the most prolific vaccine batch-releasing countries in Europe. This dominant role can be explained by its expertise, recognised throughout Europe and internationally, and its responsiveness. Depending on the years, it releases 35 to 40% of all vaccine doses used in Europe and around 40% of the vaccine doses used in France.

For blood-derived medicinal products, the ANSM is extensively involved in control of the national market, with it being responsible, in particular, for release of all products of the main national manufacturer (LFB). It is also well positioned in Europe.

Implementation of controls for release of the new Mosquirix vaccine

The ANSM was selected by the pharmaceutical company GSK to handle the release of its new malaria vaccine, Mosquirix, jointly with the Belgian OMCL. GSK had initially chosen the NIBSC, but decided to seek a different OMCL due to Brexit.

The Mosquirix vaccine is produced as a result of expression by *S. cerevisiae* of hybrid “particles” containing Circumsporozoite (RTS) antigens and the hepatitis B virus surface antigen.

Controls need to be performed on the bulk products and the finished products. The following three methods have been tested:

- identity and protein purity on bulk batches by SDS page,
- identity and quantification of the RTS antigen (malaria) by ELISA on the finished product,
- identity and quantification of the S antigen (Hepatitis B) by ELISA on the finished product.

The test to detect bacterial endotoxins is also performed on the finished product.

Feasibility tests were conducted during which the three methods were put in place in the laboratory and adapted to the ANSM's operating conditions.
The three methods were then validated with the aim of studying repeatability, defining the precision of the method and establishing control cards. Next, an equivalence test was conducted, with comparison of the values of the three batches supplied by GSK.

Ultimately, the three methods were validated in 2019 and GSK appointed the ANSM as the OMCL in charge of batch release in its MA dossier. The first three batches of finished products for control and release were received at the end of 2019.

"3Rs" approach: Development of a serological method (MIA) as an alternative to the challenge method for combined Diphtheria / Tetanus/ Acellular Pertussis vaccines

As part of the approach to reduce animal experimentation (3Rs rule), over the past few years the ANSM has developed a serological method on guinea pigs based on the simultaneous assay of four antibodies in the serum of the same animal: anti-diphtheria, anti-tetanus, anti-PT and anti-FHA for the acellular pertussis valence (MIA assay). This assay is performed on Luminex equipment.

The results obtained on three different batches of Tetravac vaccine were presented at the Strasbourg workshop on 11 December 2019 in the presence of the EDQM and several OMCLs. These results demonstrate an equivalence between the challenge method and the ANSM's serological method for the three valences. A good level of reproducibility between the three operators was also demonstrated.

A collaboration with the PEI, the only OMCL along with the ANSM that uses a multiplex method, is envisaged in order to assess the robustness of the method and its applicability to any type of combined vaccine.

2019 DATA

Release of batches of vaccines and blood-derived medicinal products

Indicators	2017 total	2018 total	2019 total
Batches certified:	3,104	2,947	**2,934**
- of which vaccines	1,518	1,714	**1,589**
- of which blood-derived medicinal products and plasma pools	1,586	1,233	**1,345**

Involvement of member states in the release of vaccine batches in Europe
France is the leader.

	%
France	35.1
Belgium	25.1
Germany	14.4
Netherlands	11.0
Austria	4.8
Italy	3.0
United Kingdom	2.7
Norway	1.6
Poland	0.9
Switzerland	0.8
Bulgaria	0.4
Denmark	0.2

Breakdown of vaccine doses circulating in France released by OMCLs
France is the leader in terms of the release of vaccine doses circulating in France.

	%
France	36.2
Netherlands	25.8
Belgium	16.6
Germany	14.9
Austria	5.4
United Kingdom	0.6
Norway	0.31
Denmark	0.1
Italy	0.05
Poland	0.04

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, breast milk for therapeutic use. They also include products, formerly known as ancillary therapeutic products (ATPs), which come into contact with biological products for their storage, preparation, processing, packaging or transport prior to any therapeutic use in humans.

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

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

Labile blood products (LBPs) are products derived from the blood of a donor, intended for transfusion into a patient. In particular, these concern red 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. The ANSM is involved in the evaluation of labile blood products and the monitoring of adverse reactions that may occur either in blood donors or in the recipients of labile blood products, post-donation information and transfusion chain incidents.[1]

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

2019 DATA

Opinions issued for labile blood products

	2015	2016	2017	2018	2019
Favourable opinions for new applications	4	4	4	6	**6**
Favourable opinions for variations	4	3	13	16	**14**
Updating of the list and characteristics of LBPs	2	1	0	2	**1**

[1] Also read “Surveillance of blood products”, page 98.

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4 OUR RESOURCES

Joint interview

Hélène Poirier (HR Department) and Raphael Martin (Information Systems Department)

What impact has the new objectives and performance contract (COP) had on your activities in 2019?

R.M.: The Information Systems and Data Master Plan (SDSID) was prepared at the same time as the Objectives and Performance Contract (COP). In fact, it is appended to the COP and so the IS and Data Strategy really does mirror the goals of the COP. Monitoring the annual project portfolio - one of the COP follow-up indicators - makes official something that we had actually been doing for several years.

H.P.: The objective of improving quality of work life for the benefit of the establishment's performance was already included in the previous COP. It has been fine-tuned, with new indicators, particularly relating to the prevention of psychosocial risks and reinforcement of the managerial community.

In what way is "stabilising the establishment's performance and efficiency" one of the cornerstones of Agency life?

H.P.: In a context of increasingly constrained resources and more and more missions, it is essential to reinforce all the efficiency improvements that can be achieved. Since the Agency is, above all, an intellectual production establishment, the internal performance of those who work there is crucial. Processes, work organisation and distribution of roles obviously contribute to an ever better performance. But, most of all, we are absolutely convinced that if the quality of work life of our employees continues to improve, then so will their performance.

R.M.: We need to reinforce all the tools used to meet these performance and efficiency objectives. And, of course, Human Resources and Information Systems are the main two tools to be highlighted. Optimising procurement processes and better steering of activities are also key components in terms of optimising costs.

Among the activities/dossiers that you have handled in 2019, which stand out most for you, either because of the workload involved, their new or unexpected nature, or their repercussions for the Agency's work?

H.P.: 2019 was clearly a year of wide-scale roll-out of teleworking processes within the Agency, with almost 60% of employees teleworking at the end of 2019. Within a very short period of time, the Agency successfully provided employees with the tools required, adapted its processes to enable some of their work to be carried out remotely and evolved its management methods accordingly. This enabled us to work almost normally at the end of 2019 despite the strikes: employees were very largely able to work from home and continue to fulfil their roles.

R.M.: That's right. The implementation of teleworking for an additional 300 employees, the result of collaborative work with the HR Department, is a major milestone in the Agency's remote working policy. The implementation of an electronic submission process for named-patient premarket approval applications (ATUn), which represent 25,000 applications per year was another of the year's highlights. Finally, we must remember the reinforced security of applications exposed outside the Agency, following the recommendations of the French National Information System Security Agency (ANSSI).

During the course of 2019 did you lay the groundwork for any actions for which concrete results will only be visible in 2020 and, if so, what were they?

H.P.: In terms of qualify of work life, the Agency began the roll-out of two ambitious action plans. The first is an action plan to prevent and reduce psychosocial risks, consisting of 51 actions. Developed on the basis of various social diagnoses and barometers carried out in recent years, it aims to put in place a series of very concrete measures relating to communication, management, work organisation, etc. designed to reduce these risks and, ultimately, improve quality of working life. These actions will be particularly visible in 2020.
The second is an action plan to address the issue of disability, both in terms of welcoming new employees with disabilities to the Agency and improving the working conditions of employees with disabilities or those in the process of being recognised as disabled. We can still greatly improve the way in which disability is taken into account at the Agency and our proactive plan demonstrates our determination to do so. We began to lay the foundations for this with our participation in Duoday in 2019.

R.M.: Changes in the Information Systems Department's organisation and the rationalisation of our service providers should enable us to provide better service both internally and externally.

In your view, which of the approaches launched in 2019 will be most important for the Agency's future? And why?

R.M.: In light of current events, the progress in teleworking begun in 2019 is a real advantage for the Agency's ability to operate in crisis situations and in line with new lifestyles. This has a significant impact on quality of working life.

H.P.: I agree with Raphaël. The fact that the vast majority of our employees can work from home is a major advantage to us. Eliminating travel time significantly reduces fatigue. But teleworking also allows us to experiment with new ways of working, to recruit employees who are further away from the Agency's three sites, to rethink our workspaces, the relations between employees and the Agency, etc. This way of organising work, which will continue to be ramped up in the years to come, is particularly constructive for our operations.

Optimising internal processes and the integrated management system

The quality policy, an offshoot of the 2019-2023 Objectives and Performance Contract

The 2019 Quality policy was aligned with the four strategic priorities of COP 2019-2023. It includes four strategies, which are applied to processes through operational objectives and performance indicators:

- **Continuing the institution's outreach policy and public data access**, in order to strengthen our ties with healthcare professionals and patients and establish a constructive dialogue,
- **Placing the patient at the centre of risk management processes**, to reduce the risks associated with health products,
- **Reinforcing the Agency's European positioning**, in particular to facilitate and accelerate patient access to therapeutic innovations governed by European regulations,
- **Combining performance and quality of work life**, in order to continuously improve the quality of service to users.

HIGHLIGHTS IN 2019

An evolving process map

Process mapping was optimised in 2019, in particular through the creation of the "Combating drug shortages" process. This evolution is representative of the Agency's commitment to ensuring access to care for patients. Each of the 23 processes is led by a pilot, who ensures that the process is properly implemented and guarantees its performance and improvement.

A quality audit programme

A quality audit programme was implemented in 2019 for all processes falling within the scope of "Risk management" certification, by a network of 34 Quality auditors trained in the ISO 9001 standard and audit methodology.

The objectives of this programme were to:

- Verify that the orientations of the Quality policy and the strategic priorities of the Objectives and Performance Contract are deployed for the processes.
- Evaluate process performance and identify opportunities for improvement.
- Ensure that the Agency's Quality Management System complies with business requirements and the requirements of the ISO 9001 version 2015 standard.

Renewal of ISO 9001 certification for “Risk Management”

The ANSM has once again demonstrated its commitment to its Quality approach and obtained renewal of its ISO 9001 certification in January 2020 for "Risk Management".
No non-conformities or sensitive points were identified.

The strong points identified during the audit are:

- the "patient" focus, the Agency has adopted an approach that seeks to favour openness to users,
- the permanent adaptation of the organisation to its environment, to the needs and demands of users and authorities,
- the importance placed on the steering of processes through the monitoring of performance indicators,

- the robustness of processes, underpinned by the experience of employees.

These findings demonstrate the close relationship between the institution's strategy and day-to-day activities.

Maintaining high risk management standards in terms of ethics and anti-corruption

In order to improve risk management (business, ethics and dishonesty) in accordance with the recommendations of audit bodies, the Agency has implemented an internal control policy based on the following methodology:

- identification of operational risks in each process in the Agency's overall process map,
- identification of appropriate levels of control (1, 2), including the implementation of internal audits (level 3 control),
- implementation and evaluation of the results scheduled for 2020 to verify that the risks identified are adequately covered, in particular within the framework of the quality policy.

The implementation of this policy will need to be accompanied by a reflection process with respect to its governance and appropriate dimensioning.

User satisfaction surveys

In order to assess the satisfaction level of ANSM users and to gather information concerning their expectations, a first series of qualitative surveys was carried out in 2019.
This general customer focus mechanism is a genuine steering tool for its outreach strategy and helps the Agency meet the objectives of ISO 9001 certification in the context of its quality process.

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 target	Attained
3	Overall stakeholder satisfaction rate	Survey No. 1 and scale creation	Survey partially conducted

Launch of the “Users’ welcome” project

The “Users’ welcome” project was launched in 2019.

The project challenges are as follows:
to guarantee a level of public service in line with users' expectations in terms of quality and response times to their requests (Public Action 2022),
to guarantee a continuous improvement in the quality of the service provided to users.

The project objectives are as follows:

to propose optimisation levers (processes, tools, organisation) enabling optimised, differentiated and efficient management of requests received (collection, referral, follow-up/traceability, processing, distribution),
be able to assess user satisfaction (response times and quality of the ANSM's responses), within the framework of the Agency's Quality Process (ISO 9001 Certification).

Implementation of the “Whistleblower” system

To facilitate the reporting of alerts issued by whistleblowers and reinforce their follow-up, in February 2019 the Agency out in place a procedure via a specific address: lanceur.alerte@ansm.sante.fr. This procedure falls within the scope of law No. 2016-1691 of 9 December 2016 relating to transparency, the fight against corruption and the modernisation of economic life (known as the “Sapin 2” law).

The lanceur.alerte@ansm.sante.fr address, which can be accessed from the homepage of the ANSM’s website, enables any person who is personally aware of it to easily report any serious violation of a law or regulation or any serious threat to the general interest, concerning health or cosmetic products intended for human use or activities falling within the scope of the ANSM's competence. This may include, for example, non-compliant practices of a site carrying out operations concerning these products (e.g. manufacturer, distributor) or any serious threat to public health related to a healthcare product.

A variety of actions may be taken by the Agency in response to these reports: triggering of an inspection, analysis of a product by the Agency's control laboratories, verification of the dossiers initially submitted by operators, etc.

2019 DATA

In 2019, the ANSM received 221 reports, more than half of which were processed under the "whistleblower" procedure, while the others fell within the scope of other procedures (vigilance, stock-out, in particular) or were outside the jurisdiction of the ANSM and were therefore forwarded to the relevant authorities.

PRODUCT CATEGORIES CONCERNED BY THE REPORTS REVIEWED

45% Medicinal products
24% MD - MD/IVDMD
21% Cosmetics
7% Other (excluding AMM)
3% Other (ANSM)

SOURCE OF ALERTS

40% Employee/subcontractor/service-provider
26% Private individual
23% Healthcare professional
8% Other
3% Association

The Agency's modernisation policy

The Agency's modernisation policy, launched in 2015, continued in 2019, as reflected by the composition of the product portfolio.

Priority projects
Data office
Publication of data
Computerisation
Archiving policy
Citizen mail /Users' welcome
Openness of the Agency to users
Risk analysis reinforcement
Innovation and referral service
Reinforcement of expertise

These nine priority projects are in line with the Agency's major objectives.

Priority projects are now identified in the work programme in order to simplify the institution's management system, leading to the elimination of the project portfolio as of 2020.

Internal audit activities

The following 2019 annual program was voted on by the Internal Audit Committee and the Board of Directors:

- organisational audit of the IS infrastructure unit,
- organisational audit relative to securing the ethical risk,

- organisational audit of crisis management,
- European follow-up audit relative to the pharmacovigilance process,
- audit of the ID update control process,
- organisational audit of European activities,
- audit of the internal budget and accounting control system.

The implementation of this annual programme is monitored via a performance indicator, for which the result was 100% in 2019.

In addition, the recommendations resulting from the audits are followed up through action plans steered by the departments and validated by the internal audit department.

These plans thus contribute to the concrete implementation of changes and participate in the continuous improvement of the Agency.

Implementation of the Information Systems and Data Master Plan (SDSID)

A strategic vision of the evolution of information systems over the next 5 years

The 2019-2023 Information Systems and Data Master Plan (SDSID) was adopted by the Board of Directors on 14 March 2019 and signed on 14 March 2019 between the state, represented by Agnès Buzyn, Minister for Solidarity and Health, and Dominique Martin, ANSM Director General.

The 2019-2023 SDSID is a scoping document appended to the 2019-2023 Objectives and Performance Contract (COP). It sets out priority courses of action in line with the Agency's strategic vision and its drive to modernise and enhance the value of the data it has at its disposal for its missions.

It also meets the objectives of the French law promoting the Digital Republic of 7 October 2016 and the Public Action 2022 program to improve the quality of public services, provide a modernised working environment and optimise resources.

The SDSID is built around five strategic objectives:

- **Making data central to health and public health issues**, for the benefit of users, businesses and the ecosystem,
- **Ensuring mastery of the IS and data** to address the needs of all users and stakeholders,
- **Correlating the effectiveness and efficiency of the IS function** to meet the Agency's ambitions,
- **Incorporating information systems and data within an innovation dynamic** in order to support the evolution of digital and societal practices,
- **Promoting the Agency and its public health actions via the IS and data uses** as part of a collaborative approach that is open to external partners.

These five strategic objectives are broken down into 13 operational objectives, 29 actions and 16 monitoring indicators, of a qualitative or quantitative nature, enabling its implementation to be monitored and progress to be reported.

HIGHLIGHTS IN 2019

Setting up of a secure hosting area for the information system

Following an audit by the ANSSI (French National Information System Security Agency), the decision was taken to revise part of the ANSM's hosting infrastructure to protect applications accessible on the Internet. A reflection process was conducted in order to find the best compromise between security and the cost of implementing this secure space, also known as the DMZ (Demilitarized zone). This infrastructure reinforcement is technically complex and innovative. Based on new-generation hardware and software, it ensures a perfect seal between our servers visible from the Internet and the central servers.
Operating conditions go beyond ANSSI recommendations and security is increased. This operation makes it possible to present an application service that is reinforced in terms of network protection, with alert and monitoring tools.

Updating of the “Public medicines database”

The public medicines database allows both the public and healthcare professionals to consult data and reference documents on the medicinal products currently marketed in France or which have been marketed in the past five years.

It was created in 2013 to provide a unique and free source of information on medicines.
It is fed by data from the ANSM, the French National Health Authority (HAS) and the French national health insurance system under the supervision of the Ministry of Health. The ANSM is responsible for its operational and technical coordination.
Until now, it was possible to search for a medicine via its name or its active ingredient.

Changes to the new version in 2019 have added a search feature by diseases associated with the medicines. This development responds to a request from the Minister of Solidarity and Health, who had announced this measure when the information report on medicinal products was submitted in September 2018.

In parallel with the construction of functional specifications, extensive information-sharing and exchanges were implemented between the ANSM and the French national health insurance fund (CNAM) (Thesorimed repository) in order to define the hundred or so diseases to be put on line initially and to link medicines with them.

The ANSM was able to meet the expectations of the supervisory authority as well as the users of the application. This illustrates the Agency's ability to mobilise an entire project team, to propose reinforced communication and to set up a daily steering system to stick to a schedule.

Work to reduce technical debt and control its obsolescence

Several projects were launched in 2019 aimed at reducing the technical debt.

Upgrades to the directory, network filtering equipment and secure access software were the most significant projects.

The implementation of the first building blocks of a tool to list all infrastructure hardware and their state of obsolescence (CMDB) now makes it possible to better anticipate obsolescence projects.

Finally, choices driven by application strategy, which favour Saas (Software As A Service) or "Low Code" type applications (configuration rather than development), avoid recreating debt and control the obsolescence of these applications (Chronos, Sirhius, etc.).

Continued roll-out of teleworking

Following the successful 2018 deployment of teleworking, 2019 saw the continued roll-out of new teleworking posts, ultimately doubling the number of teleworkers by the end of the year.

Between April and October 2019, the ANSM and the IS Department deployed:

- 270 new laptop computers,
- 300 new access accounts to the Agency for secure teleworking (VPN).

The continued roll-out of teleworking has proceeded to plan and has improved quality of working life, as well as developing the collective capacity to deal with crisis situations by enabling employees to fulfil the Agency's missions when they are unable to access ANSM premises.

At the end of 2019, 600 employees were capable of working from home.

Laying the groundwork for a new Information Systems Department organisation

The review of implementation of the 2018 IS project portfolio and the internal audits carried out demonstrated the need to improve the IS project portfolio implementation rate. These different reflections led the IS Department to propose a new organisation that enables the resources associated with projects to be separated from those associated with maintenance and IT services, and to secure reflection processes relating to the main architecture of systems.

The first measure was to put in place a technology strategy manager post to provide an advisory role to the IS Department in relation to Information Systems and Data Master Plan strategy.

The second action was to launch the preparation of a new organisation for the "Studies and projects" and "Cross-functional project and architecture" units, which will make it possible to secure project portfolio implementation and industrialise the management of live system support. The preparations led to a proposed organisation as 2 units – “Project Management” and “Maintenance and Services” – scheduled to be implemented for the first quarter of 2020.

The various preparatory studies have been praised for their quality and the incorporation of the constraints and objectives of General Management and the IS Department.

In addition

The most noteworthy launches of the year include:

- The launch of an electronic submission application for named-patient premarket approval applications (ATUn), called E-Saturne, enabling computerisation of named ATU applications
- Launch of the CHRONOS leave management application
- Implementation of the first double authentication on an ANSM application, in this case on the SIRHIUS application used by the Support Centre for Emergency Situations, Health Alerts and Risk Management (CASAR).
- Deployment of multiple data mining and business indicator applications with the QlikView tool that aggregates relevant data from different business applications into a single application
- Deployment of a new version of the EURS application, a computer application used to receive electronic submissions of MA dossiers from pharmaceutical sites

2019 DATA

- > 24 launches at the ANSM (excluding external hosting)
- > 130 applications used each day across 366 virtual servers (90 physical ones)
- > 1,500 user workstations maintained
- > 9,000 support tickets and 3,600 user requests throughout the year.

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 baseline	2019 target	Attained
19	IS project annual portfolio implementation rate	80%	100%	80%

Human Resources

Since 2015, the Agency has implemented a Human Resources Master Plan (SDRH), which links the ANSM's major areas of focus, particularly those indicated in the Objectives and Performance Contract (COP), with its human resources policy.

The goal is to help each employee fulfil their role within the Agency's collective environment in order to address public health issues for the benefit of healthcare users and the safety of healthcare products.

Adopted by the Board of Directors on 12 May 2016, it includes four strategic priorities:

- Priority 1: making collaborative work one of the Agency's strengths
- Priority 2: consolidating managerial practices and focusing them towards supporting collective and individual professional efficiency
- Priority 3: supporting individual and collective professional development and anticipating business line changes (in terms of quality and number)
- Priority 4: promoting the development of a respectful working environment that fosters individual and collective professionalism

Throughout 2019, the ANSM implemented concrete projects in all of these areas.

HIGHLIGHTS IN 2019

Wide-scale roll-out of teleworking in 2019

A teleworking experiment in place since 2018, with about a hundred employees, had demonstrated the effectiveness of this method of organisation within the Agency. In 2019, in close consultation with personnel representatives, General Management decided to roll out the system very widely, as part of priority 4 of the COP. This approach enabled all employees who wished to do so to work from home for an average of one day per week, provided that their activities could be conducted remotely. The 2019 campaign was a great success, with 55% of personnel (i.e., 551 employees) teleworking at the end of the year.

This new mode of organisation offers multiple benefits for both the Agency and employees. Questionnaires completed by employees and managers confirm an improvement in the quality of work life for employees, leading to increased efficiency. So far, not a single employee has wanted to opt back out of this system! The main benefit expressed is, of course, the elimination of travel time, but positive changes in working relationships and increased motivation are also highlighted.

Moreover, this is an important factor in terms of making the Agency an attractive employer, as evidenced by the recruitment of a few employees from outside the Agency's usual catchment area this year, who can work in Saint-Denis, Lyon or Vendargues a few days a week.

The deployment of teleworking has been made possible by replacing desktop computers with laptops for employees working from home. This mobility facilitates interactions and working methods within the Agency itself. While the Agency has encouraged rapid access to teleworking for as many employees as possible, the roll-out is gradual in terms of the number of days worked from home. A maximum of one set teleworking day per week enables the gradual adjustment of our organisational and management methods. Inspectors, already mobile and accustomed to working remotely, can telework up to 5 days a month, in a more flexible way. In 2019, Monday was chosen as a non-telework day, which made it possible to maintain times when everyone was present on site, in order to foster cross-functional work. Awareness-raising actions were proposed to all teleworkers and their managers. Although it may all appear quite straightforward, it is always good to remind people about the importance of correct posture and the right reflexes, to encourage disconnection, etc.

The system was also very popular internally and proved very useful to those who were able to benefit from it, particularly in December, during the public transport strikes. With a large proportion of employees travelling to the Saint-Denis site by public transport, the Agency authorised up to 3 days of teleworking per week during this period, which made day-to-day life easier for a large proportion of employees and enabled missions to be carried out under almost normal conditions. In this context, good cooperation

between human resources and information systems made it possible to equip new employees within very short timeframes in order to facilitate the working conditions of as many people as possible.
This is a big step forward in terms of quality of work life. The odds are high that new employees who did not apply in 2019 will want to become teleworkers in 2020. And we already know that some employees are eagerly awaiting an even wider-scale roll-out of the system, with an increase in the number of teleworking days per week.

Introduction and roll-out of a disability action plan

In order to extend its support for people with disabilities, the Agency wanted to set up a disability action plan.
Approved by the health and safety committee, the purpose of this action plan is to continue and expand measures designed to keep people with disabilities in employment, as well as to guide recruitment policy in order to encourage the hiring of employees with disabilities. This translates into concrete actions aimed, for example, at supporting employees with disabilities in their disability recognition process, entering into partnerships with CAP Emploi (specialised recruitment service for people with disabilities) or identifying opportunities to improve the accessibility of our premises.

In addition, awareness-raising initiatives for all employees were carried out as part of European Disability Employment Week. After having put videos of volunteer employees online in 2018, this year's week was dedicated to "DYS" disabilities, with awareness-raising about dyslexia, dyspraxia, dyscalculia, dysphasia and attention deficit disorders.

In May, the Agency also participated in Duoday, welcoming people with disabilities and getting them to form duos with volunteer employees. Pairs were formed at the ANSM for this day of exchange, to help overcome prejudices related to disability, promote inclusion and share skills.

Aware that the integration of diversity is everyone's business, it is important to continue communicating about the issue with employees.

Implementation of an action plan to combat psychosocial risks

Improving quality of work life and preventing psychosocial risks are key objectives in view of the regulatory and organisational changes resulting from the Objectives and Performance Contract (COP) and the Agency's work programme. In this context, a PSR action plan was developed jointly with social partners and approved by the health and safety committee in July in order to address internal issues and thus improve the quality of work life at the Agency. Comprised of 51 actions, and hinged around six themes (communication, organisation of health and prevention players, work organisation, management, meaning and values, aggression and violence), it aims to reduce and prevent the occurrence of psychosocial risks at the ANSM.

Extension of the prevention network

The extension of the Agency's prevention network is precisely one of the actions that has been put in place as part of the roll-out of the PSR prevention plan. In consultation with union organisations, the choice was made to increase the number of staff dedicated to the prevention network in order to ensure that the various risks are better taken into account at all ANSM sites. It is now made up of 8 prevention assistants (10% of their working time), coordinated by a prevention advisor (20% of working time), which therefore represents 1 full-time equivalent dedicated to occupational risk prevention. In particular, this network is responsible for updating the single occupational risk assessment document and plays an advisory role to senior management.

Internal communication: supporting change and giving meaning

The Agency's internal communication strategy is hinged around four major institutional priorities:

- Giving meaning and inspiring pride
- Supporting the ANSM's modernisation policy and upholding its values
- Promoting understanding and aiding objectivity
- Supporting quality of life and bringing people together as a team

In connection with the adoption of the Objectives and Performance Contract and the Information Systems and Data Master Plan appended to it, an action plan has been deployed to explain the institution's strategy and how it can be best translated into day-to-day activities, with a view to the surveillance audit for the renewal of ISO 9001 certification.
As part of this dynamic, all projects related to the institution's outreach strategy were supported: openness to users, reform of scientific bodies, open access to data, hackathon on medication errors, which rallied strong support from ANSM employees in their capacity as mentors supporting students.

The Agency also continued its cycle of in-house conferences to support strategic or sensitive topics. To this end, it reviewed news items that had particularly marked the year.

There was also a particular focus on promoting the Agency's business lines and archives, with the discovery of historic archives dating back to the 19th and 20th centuries. An exhibition coinciding with the 2020 New Year ceremony was dedicated to these archives.

Continued renovation of the Agency's premises

The real estate renovation operations on the Saint-Denis - Pleyel site consist of:

- the installation of air-conditioning throughout the premises to protect against noise pollution generated by the work on the tower and, more broadly, in the Pleyel district as a whole, which will make it difficult to open the windows,
- creation of a new emergency staircase to enable the Agency to continue operating its meeting rooms on the ground floor of building C-D, the previous one having been rendered unusable due to the infrastructure demolition work on the Pleyel Tower site,
- improvement of the road surface in the inner courtyard,
- the fitting-out work on the 1st and 3rd floors of the main building for the installation of the European Strategy Steering Centre (CPSE) on the one hand, and the Communication Department and CASAR on the other.

As regards the Vendargues site, the acquisition of this site in 2018 meant that an investment plan had to be put in place in 2019 to deal with the most urgent initial work to renovate the premises, such as:

- HVAC engineering works, in particular the supply and installation of fan convectors in meeting rooms, which no longer complied with current regulations,
- upgrading of the fire safety system and securing the perimeter of the site and its premises,
- asbestos removal work in the administrative building,
- removal of floor and wall coverings and repainting of the ground floor of the administration building.

Finally, as regards the Lyon site, work continued along with the ANSES to complete the financing plan with the local authorities for the construction of new laboratories, shared by the two agencies, on the ANSES site in Lyon.

In addition

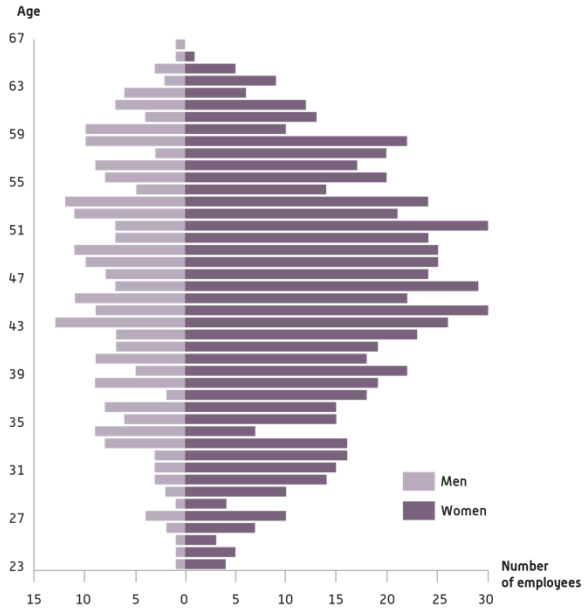
- Development of a managerial culture and harmonisation of practices
- Improvement of professional development programmes to help new arrivals build their skills
- Continuation of the apprentice intake policy, with 14 apprentices in 2019
- Reinforcement of measures designed to prevent ethics risks
- Securing of human resources management processes to simplify and improve the quality of service provided to employees
- Formalising of HR policies as part of the Agency's quality policy
- Enhancing the quality of employee-manager dialogue and increasing discussion time with employee representatives
- Computerisation of absence management

2019 DATA

Evolution of jobs authorised over 3 years

FTEs authorised	2017	2018	2019
Within ceiling	956.75	935	912
+/-	-12.75	-21.75	-23

The age pyramid of personnel within ceiling at 31 December 2019



- 91% of employees are contract employees, and 9% are civil servants
- The average age of ANSM employees is 46.5 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 2019, 51% of managers were women
- The average retirement age is 63.9 years for contracted employees and 63.3 for civil servants

Training

- 87% employee access rate to training
- 3,613 training days
- 3.66 days of training on average per trained employee
- 14 apprentices were hosted

COP 2019-2023 indicator

Indicator No.	Indicator title	2019 target	Attained
23	PSR action plan implementation rate	50%	61%
24	Teleworking employee percentage	25%	55%

Budget

For 2019 the public service subsidy remained stable compared to 2018, with an amount of nearly €116.5 million, i.e., a decrease limited to €105,855. This public service subsidy made it possible to approve a balanced budget and therefore without drawing on working capital.

There was no modification in the initial approved budget in 2019. The 2019 budget execution amounts to €123.70 million in commitment authorisations (CA) and €120.55 million in payment appropriations (PA) for an initial budget of €126.58 million in CA and €127.13 million in PA, i.e., a consumption rate of 98% in CA and 95% in PA, resulting in a positive budget balance of €5.714 million, i.e., 4.5% of the available budget.

In the 2019 financial year, working capital continued to be replenished, amounting to €31.11 million. This brings the monthly expense coverage ratio to 3.3 months.

HIGHLIGHTS IN 2019

Towards a multi-year funding trajectory for the Agency

Several audits and controls were performed at the start of 2019, including the survey carried out by the Court of Auditors at the request of the Chairman of the Senate's Social Affairs Committee.
In her conclusions, she specifically noted that the ANSM's model of financing by means of a public service subsidy for nearly 92% of its income *"differentiates it from most other European health safety agencies, whose budgets are mainly based, not on a subsidy, but on fees and royalties paid by industrial players and/or on their own resources".*

She suggests that *"to remedy the unpredictability of its resources and avoid any attrition effect on its activity, it is necessary to define a multi-year trajectory for the State subsidy to the ANSM, in line with strategic objectives, particularly in terms of growth in activity. This multi-year resource trajectory could be discussed by Parliament when it examines the national health insurance spending target (ONDAM), as provided for in the social security finance and financing bills for 2020 currently under discussion. The strategic objectives for defining this trajectory could, for their part, be defined in the Agency's Objectives and Performance contract (COP), based on the objectives and management agreements for the social security branches. This change must be accompanied by the continuation and realignment of the savings efforts undertaken by the ANSM."*

In line with these recommendations, the finance law for 2020 provided for the transfer of ANSM funding from the State budget (Health mission, programme 204) to that of the Health Insurance system. In addition, the Agency's COP 2019 - 2023 incorporates the objectives to be attained and sets out the actions to achieve them.

2019 DATA

Revenue

Evolution in ANSM revenue since 2014 (in thousands of €)

	2014	2015	2016	2017	2018	2019
State subsidy	103,176	113,160	111,786	109,807	116,598	**116,481**
EMA	8,597	8,198	4,270	8,564	8,200	**8,550**
Clearance of taxes and fees	4,937	849				
Other income from ongoing operations	5,640	3,750	319	1,162	1,321	**1,237**
Total operating revenue	122,350	125,957	116,375	119,533	126119	**126,268**

The public service subsidy received from the State accounted for 92% of the ANSM's operating income. It amounted to €116,481,029 in 2019, i.e., an amount equivalent to the subsidy allocated in 2018.

The Agency's own revenues were mainly made up of revenues paid by the EMA in return for work carried out by the ANSM.

Types of revenue in the 2019 financial account

	%
State subsidy	92%
EMA	7%
Other income from ongoing operations	1%

Distribution of EMA revenue by type of work conducted by the ANSM

	%
Scientific opinions	12.4%
New MA applications	12.6%
Variations	34.0%
Range extensions	0.3%
Annual tax	25.7%
Renewals	0.7%
Inspections	1.9%
Validation of translations	0.6%
PSUR and PASS Pharmacovigilance	11.7%

In 2019, in the context of European centralised activities, the Agency evaluated 19 new MA or MA extension applications (+ 73% compared to 2018), 84 type II variation or MA renewal applications (+ 5%), 64 PRAC procedure applications (- 9%) and issued 76 scientific opinions (+ 7%). The position of France was reinforced, with 9.2% of the portfolio of centralised procedures, mainly in oncology, infectiology and neurology.

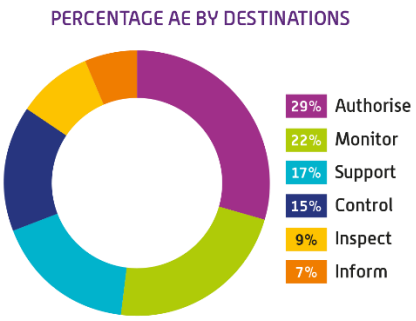
The number of new requests each year leads to a linear increase in maintenance procedures (range extensions, PSUR and PASS pharmacovigilance) in the years that follow, a concept that is incorporated into the economic model in order to anticipate the increase in human resources required over the next 10 years.

Expenditure

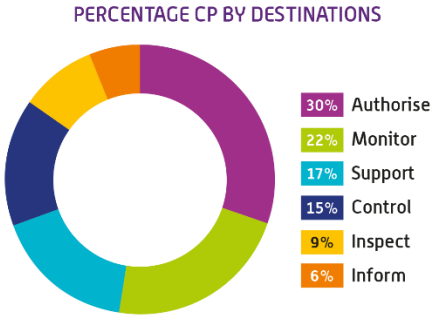
Expenditure by destination

The expenditures by destination are broken down for 2019 taking into account the ANSM's major missions. This presentation is based on the business framework implemented since 2017, which has changed slightly over the period. This framework is the basis for the implementation of a cost-performance accounting system capable of covering all activities and missions, on the one hand, and aimed at an exhaustive breakdown of expenses and revenues, on the other hand.

% CA



% PA



Expenditure by envelope

Evolution in ANSM expenditure since 2014 (in millions of €)

	2014	2015	2016	2017	2018	2019
Personnel	79.1	79.7	79.6	79.6	79.9	**80**
Operation	34.1	33.7	23	23.3	23	**22.8**
Intervention	16.6	12.7	12.7	10.6	9.3	**9.6**
Investment	9.3	10.9	8.1	7.2	6.9	**8.1**
Total payment appropriations spending	139.1	137	123.4	120.7	119.1	**120.5**

Personnel €80 million

The personnel envelope was implemented to the tune of €80 million, i.e., 98% of the initial budget provision.
It includes:

- payroll: €78.7 million (€78.6 million in 2018),
- social actions: €1.24 million

The execution of employment authorisations can be broken down as follows:

Jobs	2019 authorisations		2019 execution		Execution rate	
	FTE	WFTE	FTE	WFTE	FTE	WFTE
Within ceiling	912	912	912	912	100%	100%
Outside ceiling	36	33	28.6	28.9	79%	88%
Total	**948**	**945**	**940.6**	**940.9**	**99.2%**	**99.6%**

Operation: €22.8 million

The operations envelope used €25.9 million in CA and €22.8 million in PA during the 2019 financial year. Compared to 2018, the commitment rate for the initial budget has increased by 14 points to 98% and the payment rate by one point to 88%.

In line with the 2018 financial year, the Agency continued its work on the implementation of its digital strategy aimed at increasing openness to stakeholders and improving the transparency of its work and data. In addition, the Agency has communicated extensively with healthcare professionals and patient associations, with the introduction of six toll-free numbers to respond to external requests.

In 2019, the Agency worked hard to improve its management, in particular by extending its quality policy via confirmation of the ISO 9001 certification obtained at the end of 2018 and the organisation of internal and external audits. In this context, it was necessary to support the managerial community and to train employees in quality standards.

The significant development of teleworking (nearly half of employees teleworking by the end of 2019) also required support, with training of both staff and managers.

Intervention: €9.3 million

With respect to intervention expenses, the ANSM continued to fund vigilance network and research activities, spending €9.3 million in CA and €9.6 million in PA.

The budgets relating to the operation of the vigilance networks, which account for nearly 68% of the Agency's intervention expenses, remained stable compared to 2018 and were used to the tune of 96%.

At the end of 2018, the directors general of the ANSM and the CNAM, signed an agreement to create a scientific interest group (SIG) made up of the epidemiologist teams from both institutions. From 2019, the creation of this scientific expertise unit required the internal deployment within the ANSM of both personnel competent in the field of epidemiology and operational credits to enable the partnership to be negotiated and studies for the EPI-PHARE scientific interest group to be carried out. In this context, a call for applications was launched to fund partner centres to conduct a research program in the field of pharmaco-epidemiology, targeted epidemiological studies and partnership agreements with universities to host academic teams as part of a research programme.

Finally, 2019 was marked by the organisation of a hackathon on the theme of "medication errors" organised jointly by the Agency, the Collège de Médecine Générale (CMG) and the Paris-Est Créteil University (UPEC).

Investment: €8.1 million

The 2019 investments were committed to the tune of €7.8 million and executed to the tune of €8.1 million (taking into account balances from previous years), i.e., a respective implementation rate of 99% and 95%, respectively, compared to the initial budget.

IT investments enabled the completion of the priority IS projects programmed as part of the 2019 project portfolio. They amounted to €3 million in CA and €3.2 million in PA. New projects were also launched, such as EUDAMED (European Medical Devices Database) and VDI (Virtual Desktop Infrastructure), contributing to the development of network solutions for teleworking, for which VPN accesses were doubled by the end of 2019.

Real estate investments amounted to €4.4 million in CA and nearly €4.5 million in PA. They mainly concerned Saint-Denis - Pleyel, with the installation of an air-conditioning system in all the premises to improve the well-being of employees in anticipation of noise pollution due to the start of work on the Pleyel Tower and potential further heat waves. In addition, following the acquisition of the Vendargues site in 2018, the first urgent renovation work on the premises was carried out as part of an investment plan.

Expenses	2019 initial budget	2019 financial accounts	2020 initial budget	Income	2019 initial budget	2019 financial accounts	2020 initial budget
Personnel	81.6	80	82.1	Public service subsidy	116.5	116.5	115.8
Operation	25.9	22.8	24.8				
Intervention	11.1	9.6	11.6	EMA income	9.6	8.6	9.7
Investment	8.5	8.1	7.9	Other resources	1	1.2	1
Total expenses	**127.1**	**120.5**	**126.5**	**Total revenue**	**127.1**	**126.3**	**126.5**
Budget surplus	0	5.7	0	Budget deficit	0	0	0

Contracts

The ANSM's **total number of active contracts** is 317 (compared to 374 in 2018). This decrease can be explained by the Agency's consolidation efforts (for example, the number of batches for the Vendargues laboratories was reduced from 13 to 6 when the contract was renewed), the use of public purchasing groups (for example for the purchase of computer licenses), and the non-renewal of certain one-off requirements.
Six departments account for 285 active contracts, i.e., 89% of the total number. The Laboratory Controls Department generates the most activity, with 87 contracts, i.e., more than the Maintenance Services Department (85).
The total number contracts notified by the ANSM in 2019 was 110. This number is stable compared to 2018.

Three procedures concluded in 2019 alone represent 24% of the total amount:

- Air conditioning installation work on the ANSM site in St-Denis, for €2.5 million
- Support for the ANSM's digital communication with strategic consulting, web and social media operational support and website redesign, for €1.16 million
- User rights, maintenance, support, purchase of licenses from Microfocus and Suse, for €1.89 million.

Breakdown by type of active contract

	%
Services (247 contracts)	78%
Supplies (53 contracts)	17%
Construction work (17 contracts)	5%

Breakdown by type of notified contract

	%
Services (85 contracts)	77%
Supplies (15 contracts)	14%
Construction work (10 contracts)	9%

Reinforcement of purchasing procedures

Continued pooling of the Agency's purchases:

- within the framework of central purchasing groups, such as the UGAP as part of the "Health" operator agreement for a group of purchasing families: computer hardware and software, intellectual services, services (security - reception - photocopier rental, etc.),
- by subscribing to the framework agreements of the State Procurements Department (DAE) for the supply of fluids (gas and electricity),
- by joining the RESAH (hospital purchasing network) in order to benefit, in particular, from telecommunications contracts,
- within the framework of agreements with other health agencies, such as for training (managerial support training) or IT services (project management assistance).

Deployment of internal accounting and budget control

Internal accounting and budget control consists of two areas: internal accounting controls aimed at ensuring the quality of the accounts, and internal budget controls, aimed at scheduling the budget and ensuring its sustainability.

A summary of the measures taken as part of the internal accounting and budget control process was presented to the Board of Directors on 14 March 2019.

The risk map covers 23 risks. To manage these risks, 25 actions have been identified.

1. The internal accounting and budget control mechanism was audited between mid-April and June by the General Economic and Financial Control (CGEFI) mission. The CGEFI mission made nine recommendations designed to enable the ANSM to reinforce its control of budget management risks and the internal financial system:

- improvement of overall budget management via monitoring of execution and the incorporation of the programme within a multi-year approach,
- the further development of the internal accounting and budget control process, in particular via improved formalisation of controls and follow-up of corrective actions following financial audits,
- the continuation of work to integrate quality and internal financial control processes.

2. For the year 2019, the Financial Risk Management Office (BMRfin) evaluated the deployment rate of the internal accounting and budget control system at 100%. The main areas being worked on four years after the implementation of the budget management and public accounting system were:

- broader coverage of the budget and accounting perimeter,
- more integrated risk control via linking with the quality management system (QMS),[1]
- education regarding risk management and the traceability of actions, controls, and evaluations.
- description of level 1 and level 2 controls in the procedures.

3. The workshops relating to the integration work on the two QMS-internal accounting and budget control systems implemented since 2018 and consolidated in 2019, will continue in 2020. This enables process pilots to assimilate the two systems. This work helps define new shared control standards and contributes to the legibility of the approach.

[1] Piloted by the internal control steering mission (MPCI) in 2018 via methodological support for a community of players mobilised within the framework of ISO9001 certification.

GLOSSARY

CPA	Cyproterone acetate
ABM	*Agence de la biomédecine* - French Biomedicines Agency
AE	*Autorisations d'engagement* - Commitment authorisations (CA)
NSAID	Nonsteroidal anti-inflammatory drugs
AFAQ	*Association française pour l'assurance de la qualité* - French Quality Assurance Association
MA	Marketing authorisation
NPA	National Pharmacopoeia Authority
ANS	*Agence du numérique en santé* - French Digital Healthcare Agency
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
PAD	Peripheral arterial disease
APEC	Asia-Pacific economic cooperation
ARS	*Agence régionale de santé* - Regional health agency
ASIP Santé	*Agence des systèmes d'information partagés de santé* (French shared health information systems agency), now the ANS
ASN	*Autorité de sûreté nucléaire* - French Nuclear Safety Authority
ASOS	*Antalgiques, stupéfiants et ordonnances spécialisées* - Narcotic analgesics and secure prescriptions
ATU	*Autorisation Temporaire d'Utilisation* - Temporary Authorisation for Use, a French early access programme
ATUc	*Autorisation temporaire d'utilisation de cohorte* - Cohort Temporary Authorisation for Use
ATUn	*Autorisation temporaire d'utilisation nominative* - Named-Patient Temporary Authorisation for Use
IS	Ischaemic Stroke
BMRFIN	*Bureau de la maîtrise des risques financiers* - Financial Risk Management Office
BNPV	*Base Nationale de Pharmacovigilance* - French national pharmacovigilance database
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GWDP	Good Wholesale Distribution Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
GPP	Good Preparation Practice
GVP	Good Pharmacovigilance Practice
CA	*Conseil d'administration* - Board of Directors
CAD	*Cellule d'aide à la décision* - Decision-making assistance unit
CADA	*Commission d'accès aux documents administratifs* - Commission for access to administrative documents
CAMD	Competent authorities for medical devices
CAP	Centrally authorised products
CASAR	*Centre d'Appui aux Situations d'urgence, aux Alertes sanitaires et à la gestion des Risques* - Support centre for emergency situations, health alerts and risk management (ANSM)
CAT	Committee for advanced therapies (EMA committee)
SCLC	Small cell lung cancer
CCAFU	*Comité de cancérologie de l'association française d'urologie* - French Urology Association Oncology committee
EC	European Commission
CEIP	*Centre d'Evaluation et d'Information sur la Pharmacodépendance* - French Centre for Evaluation and Information on Pharmaceutical Drug Dependence

CEPS	*Comité économique des produits de santé* - French Healthcare Products Pricing Committee
CHAFEA	Consumers health, agriculture and food executive agency (reporting to the European Commission)
CHMP	Committee for medicinal products for human use (EMA committee)
CHSCT	*Comité d'hygiène, de sécurité et des conditions de travail* - Health and Safety committee
CIB	*Contrôle interne budgétaire* - Internal budget control
CIC	*Contrôle interne comptable* - Internal accounting control
CICB	*Contrôle interne comptable et budgétaire* - Internal accounting and budget control
CIPS	*Comité d'information des produits de santé* - French Healthcare Products Information Committee
CGEFI	*Contrôle général économique et financier* - General Economic and Financial Control
CMDH	Coordination group for mutual recognition and decentralised procedures - Human (EMA committee)
CMG	*Collège de la médecine générale* - French College of General Medicine
CMR	Carcinogenic, mutagenic or toxic to reproduction
CNAM	*Caisse nationale d'assurance maladie* - French National Health Insurance Fund
CNAMTS	*Caisse nationale de l'assurance maladie des travailleurs salariés* - French National Health Insurance Fund for Salaried Workers
CNIL	*Commission nationale de l'informatique et des libertés* - French Data Protection Authority
CNGE	*Collège national des généralistes enseignants* - French National College of Generalists in Medical Education
CNOP	*Conseil national de l'Ordre des pharmaciens* - French National College of the Board of Pharmacists
CNQ	*Contrôle national de qualité* - National quality control
CNRIPH	*Commission nationale des recherches impliquant la personne humaine* - French National Commission for human research
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
CPD	*Conditions de precriptions et de délivrance* - Prescribing and dispensing conditions (PDC)
CPOH	*Comité scientique permanent oncologie/hématologie* - Permanent scientific committee for oncology/haematology
CPP	*Comité de protection des personnes* - Ethics Committee
CPSE	*Centre de pilotage de la stratégie européenne* (ANSM) - European Strategy Steering Centre (ANSM)
CQDM	*Contrôle de Qualité des dispositifs médicaux* - Quality control of medical devices
CRAT	*Centre de référence sur les agents tératogènes* - 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
CSIS	*Conseil Stratégique des Industries de Santé* - French Strategic Council for the Healthcare Industries
CSP	*Code de la Santé Publique* - French Public Health Code
CSP	*Comité scientifique permanent* - Permanent scientific committee
CST	*Comité scientifique temporaire* - Temporary scientific committee
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 committee for pharmacovigilance
CTSA	*Centre de transfusion sanguine de l'armée* - French military blood transfusion centre

AED	Automated external defibrillators
DAE	*Direction des achats de l'Etat* - French State Procurements Department
INN	International Non-proprietary Name
DCP	Decentralised procedure
EDQM	European Directorate for the Quality of Medicines and HealthCare
DGCCRF	*Direction générale de la concurrence, de la consommation et de la répression des fraudes* - French Directorate General for Fair Trade, Consumer Affairs, and Fraud Control
DGOS	*Direction générale de l'organisation des soins* - French Directorate General of Healthcare Organisation
DGS	*Direction générale de la Santé* - French Ministry of Health
IUD	Intrauterine device
MD	Medical device
IVDMD	In-vitro diagnostic medical device
PD	Pharmaceutical dossier
DPD	Dihydropyrimidine dehydrogenase
DPI	*Déclaration publique d'intérêts* - Public conflict of interest statement
DPS	*Décision de police sanitaire* - Health policy decision
DRAMES	*Décès en Relation avec l'Abus de Médicaments et de Substances* - Death related to medicine and substance abuse
DREES	*Direction de la recherche, des études, de l'évaluation et des statistiques* - French Department for Research, Studies, Evaluation and Statistics (Ministry of Health)
DTA	*Décès toxique par antalgique* - drug-poisoning death involving analgesics
CT	Clinical trial
EDQM	European Directorate for the Quality of Medicines and HealthCare
EFS	*Etablissement français du sang* - French National Blood Service
AE	Adverse effect
TEAE	Treatment-emergent serious adverse event
EMA	European Medicines Agency
ETALAB	Etalab is part of the DINSIC. Its main purpose is to manage the outreach policy and the sharing of public data.
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FTE	Full-time equivalents
WFTE	Worked full-time equivalents
EUDAMED	Medical devices database
FDA	Food and Drug Administration (US FDA)
GBCP	*Gestion Budgétaire et Comptable Publique* - Budget and Public Accounting Management
GCDM	*Groupe de coordination des dispositifs médicaux* - Medical devices coordination group
RM	Risk management
GIS	*Groupement d'intérêt scientifique* - Scientific Interest Group (SIG)
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
HMPC	Committee on Herbal Medicinal Products (EMA committee)
HPS	*Hors produits de santé* - Non-health products
CI	Cinical Investigations
ICH	International Conference on Harmonisation
ICMRA	International coalition of medicines regulatory authorities
ICSR	Individual case safety report
ACE INHIBITORS	Angiotensin converting enzyme inhibitors
IGAS	*Inspection générale des affaires sociales* - Inspectorate General of Social Affairs
IMDRF	International medical devices regulators forum
INCA	*Institut national du cancer* - French National Cancer Institute
INSERM	*Institut national de la santé et de la recherche médicale* - French National Institute of Health and Medical Research

IPRP	International pharmaceutical regulators programme
IRSN	*Institut de radioprotection et de sûreté nucléaire* - French Institute for Radiation Protection and Nuclear Safety
MRI	Magnetic Resonance Imaging
JAMS	Joint action on market surveillance of medical devices
LAD	*Logiciels d'aide à la dispensation* - Software to aid dispensing
BIA-ALCL	Breast-implant-associated anaplastic large-cell lymphoma
LAP	*Logiciels d'aide à la prescription* - Software to aid prescribing
LFB	*Laboratoire français du fractionnement et des biotechnologies* - French blood fractionation and biotechnology laboratory
LMGC	*Laboratoire de Mécanique et génie civil* - Mechanical and Civil Engineering Laboratory (University of Montpellier)
ARMM	Additional risk minimisation measures
MDS	*Médicaments dérivés du sang* - Medicinal products derived from blood or plasma
MILDECA	*Mission interministérielle de lutte contre les drogues et les conduites addictives* - French inter-ministerial mission for drug and addictive behaviour control
MITM	*Médicament d'intérêt thérapeutique majeur* - Medicine of major therapeutic interest
MOT	Microorganisms and toxins
MRP	Mutual recognition procedure
MSA	*Modification substantielle soumise à l'ANSM pour autorisation* - Substantial variation submitted to the ANSM for authorisation
ATMP	Advanced therapy medicinal product
MTI-PP	*Médicament de thérapie innovante préparé ponctuellement* - Advanced therapy medicinal product prepared on a one-off basis
NCA	National competent authority
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NDS	National drug control system
NIBSC	National Institute for Biological Standards and Control (part of the UK Medicines and Healthcare Products Regulatory Agency)
OECD	Organisation for Economic Cooperation and Development
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
OFDT	*Observatoire français des drogues et des toxicomanies* - French Monitoring Centre for Drugs and Drug Addiction
INCB	International Narcotics Control Board
OMCLs	Official medicines control laboratories
WHO	World Health Organisation
NB	Notified body
OPPIDUM	*Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse* - French programme to monitor illicit psychotropic products or misuse of psychotropic medicinal products
OSIAP	*Ordonnances suspectes, indicateur d'abus possible* - Suspect prescriptions, indicator of possible abuse
PASS	Post-authorisation safety studies
PDCO	Paediatric committee (EMA committee)
RMP	Risk Management Plan
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation
PIP	Paediatric Investigation Plan
FI	For injection
PRAC	Pharmacovigilance risk assessment committee (EMA committee)
LBP	Labile blood products
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
ATP	Ancillary therapeutic products
PUI	*Pharmacie à usage intérieur* - Hospital pharmacy
SmPC	Summary of Product Characteristics
RESAH	*Réseau des acheteurs hospitaliers* - French hospital purchasing network

RIPH	*Recherche impliquant la personne humaine* - Human research
RMP	Risk Management Plan
PSR	Psychosocial risks
RTU	*Recommendation Temporaire d'Utilisation* - Temporary recommendation for use, a French early access programme
SAWP	Scientific Advice Working Party
SCCS	Scientific Committee on Consumer Safety
SECPROH	*Sécurité des produits du corps humain* - Safety of products from the human body (HCSP group)
SDRH	*Schéma directeur des ressources humaines* - Human Resources Master Plan
SDSID	*Schéma directeur des systèmes d'information et de la donnée* - Information and Data Systems Master Plan
IS	Information system
QMS	Quality Management System
SNDS	*Système national des données de santé* - National Health Database (formerly SNIIRAM)
SNS	*Stratégie nationale de la santé* - French National Health Strategy
SPF	*Santé publique france* - French National Public Health Agency
SRE	*Situation à risque élevé* - High-Risk Situation
STARS	Strengthening training of academia in regulatory sciences and supporting regulatory scientific advice
SWP	Safety Working Party
TCA	Trichloroacetic acid
RDT	Rapid diagnostic test
ORT	Opioid replacement therapy
EU	European Union
UGAP	*Union des groupements d'achats publics* - French Government-owned organisation that procures public merchandising services
VDI	Virtual desktop infrastructure
HBV	Hepatitis B virus
VPN	Virtual private network

APPENDICES

Appendix 1

Members of the ANSM's Board of Directors as of April 2020

Chair of the Board of Directors: Catherine de SALINS
Vice Chair: Hélène BERRUE-GAILLARD

Permanent members representing the government:
Representatives of the Health and Social Action Minister
Titular member: Véronique DEFFRASNES / Deputy: Maurice-Pierre PLANEL
Titular member: Pierre CHARESTAN / Deputy: Emmanuelle COHN
Titular member: Béatrice TRAN / Deputy: Jean-Martin DELORME

Representatives of the Social Security Minister
Titular member: Sophie CASANOVA / Deputy: Timothée MANTZ

Representatives of the Budget Minister
Titular member: David BONNOIT / Deputy: Marie CHANCHOLE

Representatives of the Research Minister
Titular member: Benoît LAVALLART / Deputy: Anne PAOLETTI

Representatives of the Economy and Finances Minister
Titular member: Éric CUZIAT / Deputy: Catherine ARGOYTI
Titular member: Julie GALLAND / Deputy: Alain-Yves BREGENT

Representatives of the Foreign Affairs Minister
Titular member: Florence CHAMBON / Deputy: Nicolas THIRIET

Members of parliament appointed by the president of their assembly
Deputies (members of parliament)
Julien BOROWCZYK
Josiane CORNELOUP
Hélène VAINQUEUR-CHRISTOPHE

Senators
Stéphane ARTANO
Laurence COHEN
Gérard DERIOT

Representatives of basic mandatory French health care insurance schemes
Titular member: Olivier LYON-CAEN / Deputy: Geneviève MOTYKA
Titular member: Sandrine FARÉ / Deputy: Philippe LABATUT

Representatives of the national board of pharmacists and physicians
French Medical Board
Titular member: Jacques MORALI / Deputy: Françoise STOVEN

National Board of Pharmacists
Titular member: Carine WOLF-THAL / Deputy: Xavier DESMAS

Representatives of health system consumer associations
Titular member: Hélène BERRUE-GAILLARD / Deputy: Philippe SCHNEIDER
Titular member: Gérard RAYMOND / Deputy: Sophie LE PALLEC

Qualified individuals in the Agency's area of expertise

Xavier DE CUYPER
Mady DENANTES

Representatives of the Agency's personnel

Titular member: Renaud KIESGEN DE RICHTER / Deputy: Wahiba OUALIKENE-GONIN
Titular member: Laurent DECUYPER / Deputy: Lynda ARNAUD-BOISSEL
Titular member: Sylvie MORGEAUX / Deputy: Abdoul-Aziz DIOP

Members with an advisory capacity

Dominique MARTIN, ANSM Director General
Marie-Thérèse COCQUEEL, ANSM Budget Controller
Jean-Michel PUGNIÈRE, Agency Accountant
N.N., Chair of the Agency's Scientific Council

Appendix 2

2019/2023 Objectives and Performance Contract - 2019 Results

Priority 1 - Develop the Agency's openness to stakeholders and reinforce the transparency of its work

Objective: reinforce the public nature of decision-making processes

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
1	Number of public hearings per year	-	≥ 6	7	

Objective: diversify partnership-based working methods in order to adapt to the variety of situations and expectations of stakeholders

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
2	Rate of high-risk situations (HRS) involving stakeholders in application management processes	> 50	75%	95%	
3	Overall stakeholder satisfaction rate	-	Survey No. 1 and scale creation	Survey partially conducted	

Objective: reinforce stakeholder involvement in decision development processes

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
4	Progress rate for satisfaction of stakeholders in permanent and temporary committees	-	Survey No. 1 and scale creation	Survey conducted Rate in the process of stabilising	

Objective: guarantee an improvement in public access to our data

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
5	Completion rate for the data publication work programme	75%	100%	80%	

Priority 2 – Incorporate risk management as an action principle shared by all the Agency's missions

Objective: ensure reinforced management of high-risk situations throughout the life cycle of healthcare products

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
6	Completion rate for urgent action plans for high-risk situations (HRS)	70%	100%	95%	

Objective: secure the coverage of patients' health needs for healthcare products of major therapeutic interest

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
7	Rate of dossiers for which a stock-out risk minimisation measure was proposed within the timeframe	70%	80%	80%	
8	Progression of the share of stock-outs in causes having led the agency to take financial sanctions	-	≥ 10%	50%	

Objective: Reinforce the ANSM's position in Europe in order to facilitate early access to innovative healthcare products for patients

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
9	Rate of consumption of operational credits allocated to pharmacoepidemiology	50%	100%	90%	
10	Rate of completion of the annual work programme on coverage of misuses identified in the context of an inter-operator approach	-	Implementation of the work programme	Implementation of the work programme	
11	Rate of sensitive inspection follow-ups controlled	85%	100%	92%	
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	100%	

Priority 3 - Reinforce and stabilise the Agency's position for access to innovation in the European environment

OBJECTIF : Renforcer le positionnement européen de l'ANSM pour faciliter l'accès précoce des patients aux produits de santé innovants

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	84	
14a	Difference between the management times and the regulatory timeframes for clinical trial authorisations (MED, Non-health products, MDs)	-	≥ 15 days	Average: 14.4 days	
14b	Difference between the management times and the regulatory timeframes for clinical trial authorisations (ATMPs)	-	≥ 70 days	Average: 43.4 days	

Indicators 14a and 14b: the management lead times remain below the regulatory authorisation times.

Objective: reinforce mechanisms for early access to innovations (Temporary Authorisation for Use ATU)

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
15	Rate of cohort ATU requests constituting an indication extension	30%	60%	30%	

Objective: help ensure active early support for sponsors in the field of health innovation

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
16	Growth rate in the number of applications treated by the health innovation service	-	Creation of the Innovation Service at the ANSM	75% of the action plan attained	

Objective: guarantee the European sustainability strategy

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
17	Ratio of income and spending allocated to European activities	-	≥ 1,0	1,38	

Objective: reinforce the ANSM's European position in the field of MDs and IVDMDs

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	0%	50%	100%	

Priority 4 – Stabilise the institution's performance and efficiency

Objective: adapt the organisation to improve performance

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
19	IS project annual portfolio implementation rate	80%	100%	80%	

Objective: ensure compliance of authorisation processes with regulatory timeframes and implement target infra-regulatory timeframes for priority products

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
20a	Rate of national and European procedures examined for all MA submissions, New applications within regulatory timeframes	50%	100%	63%	
20b	Rate of national and European procedures examined for all MA submissions variations and translation within infra-regulatory timeframes	90%	100%	91%	

Objective: Secure the expertise resources required to perform the Agency's missions

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
21	Rate of reduction in use of external individual expertise	-	Reference year	Reference 2019: pending consolidated data	

Objective: Maintain high risk management standards in terms of ethics and anti-corruption

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
22	Rate of compliance derived from internal control (Personnel / collegial expertise / individual expertise)	95%	100%	Personnel: 97% Collegial expertise: 100%	

Objective: Improve quality of work life to reinforce internal performance

Indicator N°	Indicator title	Baseline	Target	Attained	End 2019
23	PSR action plan implementation rate	-	50%	61%	
24	Teleworking employee percentage	-	25%	55%	

Appendix 3

Overview of major French and European texts published in 2019 (excluding health policy decisions, individual decisions, PIs, MAs and excluding Agency organisation)

Cross-disciplinary healthcare products

FRENCH TEXTS

Decree No. 2019-1306 of 6 December 2019 concerning vigilance procedures relative to healthcare products and treatment-emergent adverse events

Medicinal products

EUROPEAN TEXTS

Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No. 469/2009 concerning the supplementary protection certificate for medicinal products
Commission Implementing Decision (EU) 2019/769 of 14 May 2019 amending Implementing Decision 2012/715/EU establishing a list of third countries with a regulatory framework applicable to active substances for medicinal products for human use and the respective control and enforcement activities ensuring a level of protection of public health equivalent to that in the Union

FRENCH TEXTS

Decree No. 2019-1192 of 19 November 2019 relative to the generics directory, the hybrid groups registry and the elimination of the tobacco control fund
Decree No. 2019-592 of 14 June 2019 relative to the deactivation for a third party of the unique identifiers appearing on the boxes of medicines for human use mentioned in article R. 5121-138-2 of the Public Health Code
Decree No. 2019-278 of 5 April 2019 relating to the modification of the conditions for registration of medicines on the list of pharmacy-prepared medication mentioned in article R. 5121-202 of the Public Health Code
Order of 2 December 2019 amending the Order of 12 November 2019 specifying, pursuant to Article L. 5125-23 of the Public Health Code, the medical situations in which the substitution of a proprietary medicinal product from the same published generic group for the prescribed medicinal product may be excluded
Order of 12 November 2019 specifying, pursuant to Article L. 5125-23 of the Public Health Code, the medical situations in which the substitution of a proprietary medicinal product from the same generic group for the prescribed medicinal product may be excluded
Order of 5 November 2019 amending the amended order of 20 September 1999 stipulating the list of medicinal products classed as narcotics for which the maximum prescription duration is limited to fourteen or seven days
Orders amending the decree of 22 February 1990 stipulating the list of medicinal products classed as narcotics: of 20 December of 14 October 2019
Order of 30 September 2019 amending the Order of 22 August 1990 in application of article R. 5121-86 of the Public Health Code for cannabis
Order of 29 May 2019 relating to the efficiency and pertinence of hospital prescription of biosimilar medicines dispensed in the community
Order of 19 February 2019 on the date of publication of the last of the delegated acts adopted by the European Commission on the basis of Article 54a of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
Orders classifying the list of poisonous substances of 26 September 2019 of 1 July 2019 of 6 May 2019

of 11 February 2019
Orders modifying the exemptions to the regulation of poisonous substances and classifying them on the lists of poisonous substances: of 4 July 2019 of 21 May 2019 of 20 May 2019 of 24 April 2019
Decision of 18 October 2019 establishing the 2020 calendar and submission periods and the form and content of advertising authorisation requests for medicinal products for human use (18/10/2019)
Decision of 06/05/2019 amending the amended Decision of 29/12/2015 on good manufacturing practice for medicinal products (06/05/2019)
Temporary Recommendations for Use (RTU) decisions: of 16/09/2019 renewing the RTU for Baclofen in the treatment of alcohol dependence of 26/08/2019 renewing the RTU for Thalidomide Celgene 50 mg capsules of 16/07/2019 authorising a Temporary Recommendation for Use (RTU) for BERINERT 500 IU mg powder and solvent for solution for injection/infusion of 04/03/2019 amending the Temporary Recommendation for Use (RTU) for RITUXIMAB medicinal products in the treatment of severe primary immune thrombocytopenia (ITP) refractory to other treatments
NPP (named patient products, allergens specifically prepared for an individual) decision of 29 July 2019 - STALLERGENES company (19/08/2019)
Decision of 31/07/2019 withdrawing the MA for: PNEUMOREL 0.2 PERCENT syrup PNEUMOREL 80 mg coated tablets
Decision of 08/02/2019 suspending the MA for: PNEUMOREL 80 mg coated tablets PNEUMOREL 0.2 PERCENT syrup
Decision amending the list of medicinal products for pharmacy-prepared medication stipulated in article R.5121-202 of the Public Health Code: of 19/12/2019 (2) of 17/12/2019 of 31/10/2019 of 26/07/2019 of 11/06/2019 of 01/02/2019
Decision of 30 December 2019 authorising additive No. 117 to the Pharmacopoeia (30/12/2019)
Generic medicines – Decisions: of 21/11/2019 of 25/10/2019 of 18/09/2019 of 16/09/2019 of 30/07/2019 of 20/06/2019 of 28/05/2019 of 18/04/2019 of 27/03/2019 of 26/02/2019 of 25/01/2019

Biological products

FRENCH TEXTS

Order of 17 December 2019 stipulating the selection criteria for blood donors
Order of 17 April 2019 amending Annex 1 of the Order of 16 August 2007 stipulating the dossier template supporting declarations and applications for authorisation to store and prepare components from the human body for scientific purposes

Decision of 18/10/2019 setting the calendar of submission periods for the year 2020 for applications for authorisation to communicate for promotional purposes on the plasmas stipulated in Article L 1223-3 of the Public Health Code (18/10/2019)
Decisions amending the reference list of biosimilar groups stipulated in article R.5121-9-1 of the Public Health Code: of 24/09/2019 of 23/08/2019 of 28/06/2019 of 28/05/2019 of 15/03/2019

Medical devices and in vitro diagnostic medical devices

EUROPEAN TEXTS

Commission Implementing Decision (EU) 2019/1396 of 10 September 2019 laying down the rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the designation of expert panels in the field of medical devices (Text with EEA relevance.)
Commission Implementing Decision (EU) 2019/1244 of 1 July 2019 amending Decision 2002/364/EC as regards requirements for HIV and HCV antigen and antibody combined tests and as regards requirements for nucleic acid amplification techniques with respect to reference materials and qualitative HIV assays (notified under document C(2019) 4632)
Amendment to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117 of 5.5.2017)
Amendment to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117 of 5.5.2017)
Commission Implementing Decision (EU) 2019/939 of 6 June 2019 designating issuing entities designated to operate a system for the assignment of Unique Device Identifiers (UDIs) in the field of medical devices

FRENCH TEXTS

Orders amending the Order of 15 March 2010 laying down the conditions of enforcement of the essential requirements applicable to medical devices, implementing Article R.5211-24 of the Public Health Code: of 29 November 2019 of 4 October 2019
Order of 13 February 2019 issued pursuant to Article R. 5212-29 of the Public Health Code and specifying the conditions for the accreditation of external quality control bodies

Cosmetic and tattooing products

EUROPEAN TEXTS

Commission Regulations (EU) amending the Annexes to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products: 2019/1966 of 27 November 2019: II, III and V 2019/1858 of 6 November 2019: v 2019/1857 of 6 November 2019: VI 2019/831 of 22 May 2019: II, III and V 2019/698 of 30 April 2019: III and V 2019/681 of 30 April 2019: II 2019/680 of 30 April 2019: VI
Commission Decision (EU) 2019/701 of 5 April 2019 establishing a glossary of common ingredient names for use in the labelling of cosmetic products

Cross-disciplinary texts

FRENCH TEXTS

Decree No. 2019-1189 of 15 November 2019 relating to the fees levied on applications to change the name or address of the marketing authorisation holder submitted to the French National Agency for Medicines and Health Products Safety
Decree No. 2019-389 of 30 April 2019 applying article 1635 bis AE of the general taxation code relative to fees levied for applications submitted to the French National Agency for Medicines and Health Products Safety
Decree No. 2019-388 of 30 April 2019 relating to minor type IA changes to the terms of a marketing authorisation that are not subject to payment of the fee provided for in Article 1635 bis AE of the General Tax Code

Appendix 4

Summary of referral procedures in 2019

Referrals submitted to the CHMP

Name of the procedure (international non-proprietary name (INN) or common name)	Start of procedure	End of procedure	Type of referral
Omega-3 acid ethyl esters – containing medicinal products for oral use in secondary prevention after myocardial infarction (various)	22/03/2018	28/03/2019	Article 31 of directive 2001/83/EC
Septanest and associated names (articaine (hydrochloride)/ adrenaline (tartrate))	28/06/2018	28/03/2019	Article 30 of directive 2001/83/EC
Bacterial lysates-containing medicinal products for respiratory conditions (Haemophilus influenzae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus mitis / Streptococcus pneumoniae / Streptococcus pyogenes, Haemophilus influenzae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus pneumoniae / Streptococcus pyogenes, Streptococcus pneumoniae / Streptococcus agalactiae / Staphylococcus aureus / Haemophilus influenzae, Haemophilus influenzae / Klebsiella ozaenae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus pneumoniae / Streptococcus pyogenes / Streptococcus viridans, Haemophilus influenzae / membrane fraction of Klebsiella pneumoniae / ribosomal fractions of Klebsiella pneumoniae / Streptococcus pneumoniae / Streptococcus pyogenes, Escherichia Coli/ Klebsiella pneumoniae / Staphylococcus Aureus / Staphylococcus epidermidis / Streptococcus salivarius / Streptococcus pneumoniae/ Streptococcus pyogenes / Haemophilus influenzae / Corynebacterium pseudodiphtheriticum / Moraxella catarrhalis	28/06/2018	27/06/2019	Article 31 of directive 2001/83/EC
Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan)	16/07/2018	31/01/2019	Article 31 of directive 2001/83/EC
Syner-Kinase and associated names (urokinase)	26/07/2018	28/02/2019	Article 29(4) of directive 2001/83/EC
Basiron AC and associated names (benzoyl peroxide)	15/11/2018	28/03/2019	Article 13 of Commission Regulation (EC) No. 1234/2008
Norethisterone and ethinylestradiol (norethisterone and ethinylestradiol)	13/12/2018	26/04/2019	Article 5(3) of Commission

			Regulation (EC) No. 726/2004
Direct Oral Anticoagulants (DOACs)	31/01/2019	Ongoing	Article 5(3) of Commission Regulation (EC) No. 726/2004
Lartruvo (olaratumab)	31/01/2019	26/04/2019	Article 20 of Commission Regulation (EC) No. 726/2004 l
Methocarbamol/paracetamol-containing medicinal products (methocarbamol/paracetamol)	29/05/2019	Ongoing	Article 31 of Commission Regulation 2001/83/EC
Flurbiprofen Geiser (flurbiprofen)	27/06/2019	17/10/2019	Article 29(4) of Commission Regulation 2001/83/EC
Nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients	19/09/2019	Ongoing	Article 5(3) of Commission Regulation (EC) No. 726/2004
Ranitidine-containing medicinal products (ranitidine)	19/09/2019	Ongoing	Article 31 of Commission Regulation 2001/83/EC
Budesonide SUN and associated names (budesonide)	17/10/2019	Ongoing	Article 29(4) of Commission Regulation 2001/83/EC

Referrals submitted to the PRAC

Name of the procedure (international non-proprietary name (INN) or common name)	Start of procedure	End of procedure	Type of referral
Methotrexate containing medicinal products (methotrexate)	12/04/2018	22/08/2019	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Fenspiride-containing medicinal products (fenspiride)	14/02/2019	29/05/2019	Article 107i of Directive 2001/83/EC
Fluorouracil and fluorouracil related substances (capecitabine, fluorouracil, tegafur, flucytosine)	15/03/2019	Ongoing	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Estradiol-containing (0.01% w/w) medicinal products for topical use (estradiol)	11/04/2019	Ongoing	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Lemtrada (alemtuzumab)	11/04/2019	14/11/2019	Article 20 of Commission Regulation (CE) No. 726/2004 resulting from pharmacovigilance data
Xeljanz (tofacitinib)	16/05/2019	14/11/2019	Article 20 of Commission Regulation (CE) No. 726/2004 resulting from pharmacovigilance data
Leuprorelin-containing depot medicinal products (leuprorelin)	14/06/2019	Ongoing	Article 31 of Commission Regulation 2001/83/EC resulting from pharmacovigilance data
Cyproterone-containing medicinal products (cyproterone)	11/07/2019	Ongoing	Article 31 of Commission Regulation 2001/83/EC resulting from pharmacovigilance data
Picato (ingenol mebutate)	05/09/2019	Ongoing	Article 20 of Commission Regulation (CE) No. 726/2004 resulting from pharmacovigilance data

Appendix 5

Biosimilar products authorised in Europe (December 2019)

Reference medicinal product	Biosimilar medicinal product	Active substance	Pharmaceutical company	Authorisation date
Genotropin	Omnitrope	somatropin	Sandoz GmBH	12/04/2006
Eprex	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
Neupogen	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
Remicade	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
GONAL-f	Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013
	Bemfola		Finox Biotech AG	27/03/2014
Lantus	Abasaglar	insulin glargine	Eli Lilly Regional Operations	09/09/2014
	Semglee		Mylan S.A.S	22/03/2018
Enbrel	Benepali	etanercept	Samsung Bioepis UK Limited	14/01/2016
	Erelzi		Sandoz GmBH	23/06/2017
Humira	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
	Idacio		Fresenius Kabi Deutschland GmbH	02/04/2019

Clexane	Inhixa	enoxaparin	Techdow Europe AB	15/09/2016
	Thorinane		Pharmathen S.A.	15/09/2016
Forsteo	Terrosa	teriparatide	Gedeon Richter Plc.	04/01/2017
	Movymia		STADA Arzneimittel AG	11/01/2017
Humalog	Insulin lispro Sanofi	insulin lispro	Sanofi Aventis France	19/07/2017
Mabthera	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
Herceptin	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
Avastin	Mvasi	Bevacizumab	Amgen Europe B.V.	14/01/2018
	Zirabev		Pfizer Europe MA EEIG	14/02/2019
Neulasta	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
	Cegfila		Mundipharma Corporation (Ireland) Limited	19/12/2019
	Grasustek		Juta Pharma GmbH	20/06/2019

The penetration of biosimilar products in the EU is currently not comparable to that of generic chemical medicines. These products are new on the market and their efficacy and safety profiles are less well known to prescribers. The list of biosimilar medicines published on the ANSM website is regularly updated.

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